e-ISSN:2602-2079

Volume 4
Issue 12
2020

JOURNAL of Surgery and Medicine

International Medical Journal

JOSAM

Volume: 4 - Issue: 12

Contents

Case report

J Surg Med. 2020;4(12):1101-1103.
DOI: 10.28982/josam.816697

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Melatonin prevents post-traumatic ischemic damage in rats

Melatonin ratlarda post-travmatik iskemik beyin hasarını önlemektedir

Cengiz Gölçek [1], Mehmet Arif Aladağ [2], Harika Gözükara [3]

[1] Department of Neurosurgery, Malatya Education Research Hospital Malatya, Turkey
[2] Department of Neurosurgery, Medical Faculty, İnönü University, Malatya, Turkey
[3] Department of Biostatistics, Medical Faculty, İnönü University, Malatya, Turkey

ORCID ID of the author(s)
CG: 0000-0002-1969-9080
MAA: 0000-0003-3872-3741
HG: 0000-0003-1208-4072

Corresponding author / Sorumlu yazar:
Cengiz Gölçek
Address / Adres: Malatya Eğitim Araştırma Hastanesi, Nöroşirürji Kliniği, Malatya, Türkiye
E-mail: cengizgolcek@gmail.com

Ethics Committee Approval: This study was carried out in the experimental research laboratories of Medical Faculty of İnonu University in accordance with the Ethical Committee's guidelines on the maintenance and usage of rats (2011/A-85).
Etik Kurul Onayı: Bu çalışma, İnönü Üniversitesi Tıp Fakültesi deneysel araştırma laboratuvarlarında, Etik Kurul'un sıçanların bakımı ve kullanımına ilişkin yönergeleri çerçevesinde gerçekleştirilmiştir (2011/A-85).

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/21/2020
Yayın Tarihi: 21.12.2020

Abstract

Aim: Brain trauma is among the leading causes of mortality and long-term disability in the world. Studies suggested that cerebral ischemia is an important mechanism of secondary neuronal injury in traumatic brain injury (TBI), and that melatonin has protective effects on the brain after trauma. It was also shown that melatonin alleviates the formation of cerebral ischemia and ischemic brain damage in many cerebral pathophysiological processes. However, there is no study which investigates the effects of melatonin on cerebral ischemia after brain trauma. Therefore, we aimed to induce experimental focal brain trauma in rats and assess the effects of melatonin on posttraumatic cerebral ischemia.

Methods: The animals used in this research were divided into four groups as follows: Control group (Group 1), Traumatic Brain Injury (TBI) group (Group 2), TBI plus Placebo group (Group 3), and TBI plus Melatonin group (Group 4). Brain trauma was induced using the weight drop technique in all groups except the Control group (Group 1). The groups with induced brain trauma were separated into five sub-groups to be sacrificed at the given times (12, 24, 72, 120 and 168 hours). Hematoxylin and eosin (H&E) staining was applied to count the number of red neurons, which indicate the grade of cerebral ischemia.

Results: Our results showed that the number of red neurons was significantly less ($P<0.05$) in the melatonin-treated groups compared to those in the trauma and placebo groups within the same amount of time.

Conclusion: The present study found that melatonin markedly inhibits the progression of cerebral ischemia after brain trauma. Therefore, melatonin can be used as a potential therapeutic agent to prevent posttraumatic secondary cerebral injuries. However, further studies are needed to investigate the mechanism of its effect.

Keywords: Melatonin, Traumatic brain damage, Secondary injury, Ischemic injury

Öz

Amaç: Beyin travması, dünyadaki ölümlerin ve uzun süreli sakatlığın önde gelen nedenleri arasındadır. Çalışmalar, serebral iskeminin travmatik beyin hasarında (TBH) sekonder nöronal hasarın önemli bir mekanizması olduğunu göstermiştir. Bilimsel araştırmalar, melatoninin travma sonrası beyin üzerinde koruyucu bir etkiye sahip olduğunu göstermiştir. Ayrıca melatoninin birçok serebral patofizyolojik süreçte beyin iskemik beyin hasarını hafiflettiği gösterilmiştir. Bununla birlikte, melatoninin beyin travması sonrası serebral iskeminin oluşması üzerine olan etkisini araştıran herhangi bir çalışma yoktur. Bu nedenle, sıçanlarda deneysel fokal beyin travması oluşturduk ve zamansal seyri içinde melatoninin travma sonrası serebral iskemi oluşumu üzerindeki etkisini araştırdık.

Yöntem: Hayvanlar dört gruba ayrıldı: kontrol (Grup 1), Travmatik Beyin Hasarı (TBH) (Grup 2), TBH artı plasebo (Grup 3) ve TBH artı melatonin (Grup 4). Beyin travması, ağırlık bırakma tekniği ile kontrol grubu dışındaki tüm gruplarda oluşturuldu. Beyin travması oluşturulan grupların her biri belirli zamanlarda (12, 24, 72, 120 ve 168 saatlerde) sakrifiye edilecek şekilde beş alt gruba ayrıldı. İskeminin derecesini göstermede kırmızı nöronların sayısını belirlemek için hematoksilin-eozin (H&E) boyama kullanıldı.

Bulgular: Sonuçlarımız, melatonin ile tedavi edilen gruplarda travma ve plasebo gruplarına kıyasla kırmızı nöron sayısının anlamlı bir şekilde azaldığını ($P<0.05$) gösterdi.

Sonuç: Bu çalışma, melatoninin beyin travması sonrasında oluşan iskemiyi azaltığını desteklemektedir. Bu yüzden, melatonin travma sonrası oluşan ikincil serebral yaralanmaları önlemek için potansiyel bir terapötik ajan olarak kullanılabilir. Ancak onun bu etkisinin mekanizmalarını araştırmak için daha ileri çalışmalar gerekmektedir.

Anahtar kelimeler: Melatonin, Travmatik beyin hasarı, İkincil hasar, İskemik hasar

How to cite/Atıf için: Gölçek C, Aladağ MA, Gözükara H. Melatonin prevents post-traumatic ischemic damage in rats. J Surg Med. 2020;4(12):1101-1103.

Introduction

Although it is not possible to treat post-traumatic primary cerebral damage caused by direct mechanical factors, post-traumatic secondary injuries brought about by multidimensional processes beginning after the primary injury are likely to respond to treatment [1,2].

One of the most common causes of post-traumatic secondary damage is ischemia [3-5]. Further research on this topic found that pathophysiological processes leading to posttraumatic secondary damage are similar to those leading to ischemic damage [6,7].

Melatonin, a natural agent, has a protective effect on neurons in post-traumatic injuries [8]. Melatonin can prevent the formation of both ischemia and ischemic damage after subarachnoid hemorrhage and ischemia reperfusion injury [9,10]. However, to the best of our knowledge, there is no study on the effect of melatonin on ischemia formation after brain trauma.

Due to all the above-mentioned reasons, we investigated the effect of melatonin on post-traumatic cerebral ischemia formation in experimentally induced head trauma in rats.

Materials and methods

Ethical statement

This study was carried out in the experimental research laboratories of Medical Faculty of İnonu University in accordance with the Ethical Committee's guidelines on the maintenance and usage of rats (2011/A-85-Analysis of the temporal development of secondary injury in head injuries).

Experimental procedure

The experiment was performed on eighteen, 15-week-old Wistar albino rats weighing between 200 and 250g. The animals were kept under the standard conditions of 12-hour light and dark cycles, at a 20^0C steady room temperature, with a humidity ranging from 40% to 60%. The lab rats had free access to standard dry pellets and tap water throughout the study.

The rats were divided into four groups: Group 1: Control (n=5), Group 2: Trauma (n=25), Group 3: Trauma plus Placebo (n=25), and Group 4: Trauma plus Melatonin (n=25). The rats in Group 1 were sacrificed under anesthesia and their data were considered the basal level for comparison. To determine the change with time, groups 2-4 were further divided into 5 subgroups (A-E), containing 5 rats each.

One day before the operation, the rats were starved and given Enrofloxacin (Baytril, 2.27 mg/kg, Bayer) subcutaneously for prophylactic purposes. The rats were anesthetized with ketamine hydrochloride (50mg/kg) and Xylazine (10mg/kg) for the operation. To stabilize their body temperature, they were set on operation tables pre-heated to 37℃. Anesthesia was maintained with additional ketamine injections, as needed.

The rats in the control group were sacrificed without performing any procedures. The surgical sites of the rats in trauma, trauma plus placebo and, trauma plus melatonin groups were shaved and antiseptically cleaned. A midline longitudinal scalp incision, and periosteal and muscular dissection were made to expose the surface of the skull. A craniotomy (10 mm x 15 mm), centered over the right parietal bone, was performed using a dental drill. For the induction of brain injury, we used the weight drop technique modified by Feeney et al. [11], which included a 9 g weight dropped from a height of 50 cm onto a 10 mm diameter piston resting on the exposed dura. Thus a head trauma was created by applying 450 g/cm force according to the formula of $EP=m.g.h$.

To explore changes with time, trauma, trauma plus placebo and, trauma plus melatonin groups were divided into 5 subgroups (A-E), with 5 rats in each. Each group was sacrificed at specified time points after the injury, as follows: Subgroup A: Sacrificed at the 12^{th} hour, B: Sacrificed at the 24^{th} hour, C: Sacrificed at the 72^{nd} hour, D: Sacrificed at the 120^{th} hour, and E: Sacrificed at the 168^{th} hour after injury. Six hours after procedure, 1 ml 2.5% alcohol and 20 mg/kg/day melatonin (Sigma) in 1 ml 2.5% alcohol solution were injected intraperitoneally in the trauma plus placebo and trauma plus melatonin groups respectively, while Group 2 received no medications. Intraperitoneal melatonin or alcohol injections (warmed at 37^0C) were continued until sacrifice.

Sample collection and sacrifice of rats

At the end of periods mentioned above for each subgroup, the animals were re-anesthetized, and the ascending aorta was cannulated retrogradely through a thoracotomy. The cranio-cervical circulation was perfused with 200 ml of heparinized iso-osmotic phosphate buffer saline (0.1M, pH 7.4) at a physiological mean arterial pressure (80–90mmHg) via a peristaltic pump (May=PRS9508=991129-1). The perfusion was followed by 200ml of 0.1M phosphate buffer saline containing 4% paraformaldehyde at a physiological mean arterial pressure as above. Brains were rapidly resected and right and left hemispheres were separated. The right hemispheres, which contained the contusion epicenter, were post-fixed in 4% formalin and processed for paraffin embedding. Representative sections were sliced into 5 μm thick sections and stained with hematoxylin-eosin (H&E) for the evaluation of the degree of ischemia. The number of red-stained neurons typically observed in early injuries were counted [12] in 10 different areas on a light microscope (Olympus, BX400) and added.

Statistical analysis

The data of the control group represented the basal level of all parameters. The distribution of the data was analyzed with the Shapiro-Wilk test. Data was presented as median (min-max). Kruskal Wallis H test was performed for comparison of groups. Multiple comparisons were carried out with the Conover test. A P-value <0.05 was considered statistically significant.

Results

The images of samples from Groups 2 and 4 under light microscopy are shown in Figures 1A and 1B. The distribution of pink acidophilic neurons (ischemic red neurons) by groups is shown in Table 1.

The number of red neurons in sub-groups (A-E) of Trauma (Group 2), Trauma plus Placebo (Group 3) and Trauma plus Melatonin (Group 4) groups were 10 (7-18), 15 (5-18), 15 (13-18), 16 (14-18), 16 (14-17), and 10 (8-17), 14 (5-16), 15 (14-17), 15 (14-18), 16 (15-18) and, 6 (6-7), 5 (4-5), 7 (6-8), 7 (6-8), 6 (5-8), respectively.

While the number of red neurons in Trauma and Trauma plus Placebo groups significantly increased at 12, 24, 72,

120, 168 hours, there was no significant difference between Trauma and Trauma plus Placebo groups. In all of subgroups of Trauma and Trauma plus Placebo groups, the number of red neurons were significantly higher than that of the control group. Significant elevation in the number of these neurons over time in the post-traumatic brain indicates cerebral ischemia.

Table 1: Comparison of the number of pink acidophilic dead neurons (red neurons) between the groups and subgroups (RN: Red Neuron)

Subgroup (Time) Group	A (12. S) RN(n) median (min-max)	B (24.S) RN(n) median (min-max)	C (72. S) RN(n) median (min-max)	D (120. S) RN(n) median (min-max)	E (168. S) RN(n) median (min-max)	*P*-value
1.Basal level	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1.000
2.Trauma	10 (7-18)	15 (5-18)	15(13-18)	16(14-18)	16 (14-17)	<0.001
3.Trauma+Placebo	10 (8-17)	14(5-16)	15(14-17)	15(14-18)	16(15-18)	<0.001
4.Trauma+Melatonin	6 (6-7)	5 (4-5)	7 (6-8)	7 (6-8)	6 (5-8)	<0.001
P-value	<0.001	0.002	<0.001	<0.001	<0.001	

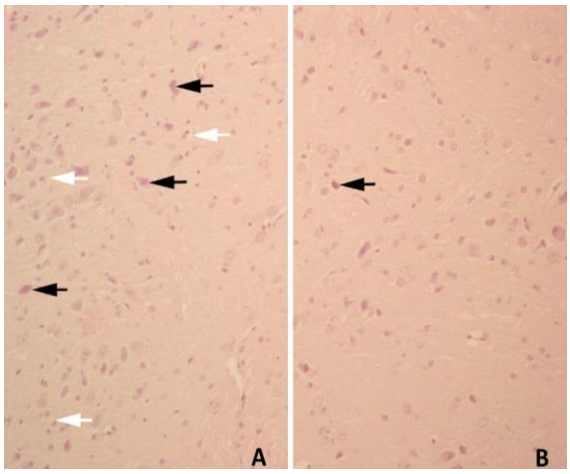


Figure 1: Pink acidophilic dead neurons "red neurons" (black arrows) and moderate glial proliferation (white arrows) in the subcortical area of trauma-induced cerebral hemisphere. HE, x 90 (A. Trauma, B. Trauma+melatonin group)

The number of red neurons in the Melatonin group was significantly lower than that in the Trauma and Trauma plus Placebo groups. The administration of melatonin prevented the formation of ischemia.

Discussion

Red neurons that exhibit homogeneous eosinophilic cytoplasm and, pyknosis, karyorrhexis and karyolysis of the nuclei are known to indicate neurons exposed to ischemia [12]. Therefore, we used the number of red neurons to show the grade of ischemic damage in our study. Based on our results, ischemia began right after trauma and showed gradual increase, and melatonin administration significantly alleviated the formation of cerebral ischemia.

Post-traumatic cerebral ischemic damages are characterized by an imbalance between cerebral oxygen supply and consumption. It was indicated that the major mechanisms causing cerebral ischemic damage are cerebral perfusion impairment, related to second phase arterial vasospasm together with the extravasation of blood due to structural damage in the intracerebral arteries resulting from mechanical trauma, and the increase in focal glucose metabolism [7,13-16].

Melatonin, an endogenous indolamine produced in the pineal gland from an amino acid, tryptophan, is a natural agent that has very beneficial effects. Various studies have shown that melatonin prevents vasospasm in cerebral arteries, reduces ischemic damage after trauma and reduces neuronal damage in cerebral traumas with its protective/preserving effect on neurons [8,9,17,18]).

These data suggested that the protective effect of melatonin on secondary brain injury might be due to its preventive effect on ischemia formation, by stopping the progress of posttraumatic ischemic process.

Limitations

We investigated the histopathological parameters and ischemic findings only. These parameters do not directly demonstrate a link between melatonin's protective and anti-ischemic effects. Therefore, further, larger studies including other parameters are required to reach definite conclusions.

Conclusion

Melatonin, a well-tolerated agent which can overcome the morpho-physiological barriers such as the blood-brain barrier, can be used as a potential therapeutic agent to prevent posttraumatic secondary brain injury by reducing ischemic injury. However, further studies with other parameters are required to demonstrate the direct links between melatonin's protective effect on secondary cerebral injury and preventive effect on ischemia formation.

Acknowledgements

The authors thank Nusret Akpolat for histopathological preparations and analysis.

References

1. Cunningham AS, Salvador R, Coles JP, Chatfield DA, Bradley PG, Johnston AJ, et al. Physiological thresholds for irreversible tissue damage in contusional regions following traumatic brain injury. Brain. 2005;128:1931–42. doi: 10.1093/brain/awh536
2. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. Br J Anaesth. 2007;99:4–9. doi:10.1093/bja/aem131
3. Coles JP, Fryer TD, Smielewski P, Rice K, Clark JC, Pickard JD, et al. Defining ischemic burden after traumatic brain injury using 15O PET imaging of cerebral physiology. J Cereb Blood Flow Metab. 2004;24:191–201. doi: 10.1097/01.WCB.0000100045.07481.DE.
4. Coles JP, Fryer TD, Smielewski P, Chatfield DA, Steiner LA, Johnston AJ, et al. Incidence and mechanisms of cerebral ischemia in early clinical head injury. J Cereb Blood Flow Metab. 2004;24:202–11. doi: 10.1097/01.WCB.0000103022.98348.24.
5. Oertel M, Boscardin WJ, Obrist WD, Glenn TC, McArthur DL, Gravori T, et al. Posttraumatic vasospasm: the epidemiology, severity, and time course of an underestimated phenomenon: a prospective study performed in 229 patients. J Neurosurg. 2005;103:812–24. doi: 10.3171/jns.2005.103.5.0812
6. Bramlett HM, Dietrich WD. Pathophysiology of cerebral ischemia and brain trauma: similarities and differences. J Cereb Blood Flow Metab. 2004;24:133–50. doi: 10.1097/01.WCB.0000111614.19196.04.
7. Kunz A, Dirnagl U, Mergenthaler P. Acute pathophysiological processes after ischaemic and traumatic brain injury. Best Pract Res Clin Anaesthesiol. 2010;24(4):495-509. doi: 10.1016/j.bpa.2010.10.001.
8. Tsai MC, Chen WJ, Tsai MS, Ching CH, Chuang JI. Melatonin attenuates brain contusion-induced oxidative insult, inactivation of signal transducers and activators of transcription 1, and upregulation of suppressor of cytokine signaling-3 in rats. J Pineal Res. 2011;51:233-45. doi: 10.1111/j.1600-079X.2011.00885.
9. Aladag MA, Turkoz Y, Parlakpinar H, Ozen H, Egri M, Unal S C .Melatonin Ameliorates Cerebral Vasospasm After Experimental Subarachnoidal Haemorrhage Correcting Imbalance of Nitric Oxide Levels in Rats. Neurochem Res. 2009 Nov;34(11):1935-44. doi: 10.1007/s11064-009-9979-7.
10. Ramos E, Patiño P, Reiter RJ, Gil-Martín E, Marco-Contelles J, Parada E, et al. Ischemic brain injury: New insights on the protective role of melatonin. Free Radic Biol Med. 2017;104:32-53. doi: 10.1016/j.freeradbiomed.2017.01.005.
11. Feeney DM, Boyeson MG, Linn RT, Murray HM, Dail WG. Responses to cortical injury: I. Methodology and local effects of contusions in the rat. Brain Res. 1981;211:67-77.
12. Leesta JE. The anemic pole infarction in forensic neuropathology. Second Edition.2009. CRC Press. Taylor&Francis group. USA. pp. 115-117. ISBN-13-978-0-8493-9167-5
13. Sun L, Kuroiwa T, Ishibashi S, Katsumata N, Endo S, Mizusawa H. Transition of areas of eosinophilic neurons and reactive astrocytes to delayed cortical infarcts after transient unilateral forebrain ischemia in Mongolian gerbils. Acta Neuropathol. 2006;111:21–8. doi: 10.1007/s00401-005-1081-x.
14. Ginsberg MD, Zhao W, Alonso OF, Loor-Estades JY, Dietrich WD, Busto R. Uncoupling of local cerebral glucose metabolism and blood flow after acute fluid-percussion injury in rats. The Am J Physiol. 1997;272(6 Pt 2):H2859–68. doi: 10.1152/ajpheart.1997.272.6.H2859.
15. Inoue Y, Shiozaki T, Tasaki O, Hayakata T, Ikegawa H, Yoshiya K, et al. Changes in cerebral blood flow from the acute to the chronic phase of severe head injury. J Neurotrauma. 2005;22:1411–8. doi: 10.1089/neu.2005.22.1411.
16. Tavazzi B, Signoretti S, Lazzarino G, Amorini AM, Delfini R, Cimatti M, et al. Cerebral oxidative stress and depression of energy metabolism correlate with severity of diffuse brain injury in rats. Neurosurgery. 2005;56:582–9. doi: 10.1227/01.neu.0000156715.04900.e6.
17. Ramos E, Patiño P, Reiter RJ, Gil-Martín E, Marco-Contelles J, Parada E, et al. Ischemic brain injury: New insights on the protective role of melatonin. Free Radic Biol Med. 2017;104:32-53. doi: 10.1016/j.freeradbiomed.2017.01.005.
18. Beni SM, Kohen R, Reiter RJ, Tan DX, Shohami E. Melatonin-induced neuroprotection after closed head injury is associated with increased brain antioxidants and attenuated late-phase activation of NF-kappaB and AP-1. FASEB J. 2004;18:149-51. doi: 10.1096/fj.03-0323fje

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1104-1107.
DOI: 10.28982/josam.820913

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Can ischemia modified albumin (IMA) and total sulfhydryl level (TSH) be used as a biomarker in the diagnosis of bladder tumor? A prospective case-control study

İskemi modifiye albümin (İMA) ve toplam sülfhidril seviyesi (TSH) mesane tümörü tanısında biyobelirteç olarak kullanılabilir mi? İleriye dönük vaka kontrol çalışması

Recep Eryılmaz [1], Canan Demir [2], Rahmi Aslan [1], Halit Demir [3], Kerem Taken [1]

[1] Department of Urology, Yuzuncu Yil University, School of Medicine, Van, Turkey
[2] Van Yuzuncu Yıl University, Vocational School of Health Services, Tuşba-Van, Turkey
[3] Van Yuzuncu Yıl University, Department of Biochemistry, Tuşba-Van, Turkey

ORCID ID of the author(s)
RE: 0000-0002-4506-8784
CD: 0000-0002-4204-9756
RA: 0000-0002-4563-0386
HD: 0000-0002-2746-7941
KT: 0000-0002-4370-4222

Corresponding author / Sorumlu yazar:
Recep Eryılmaz
Address / Adres: Yüzüncü Yıl Üniversitesi, Tıp Fakültesi, Üroloji Kliniği, Van, Türkiye
E-mail: recepuro@hotmail.com

Ethics Committee Approval: The approval for the research was received from the interventional ethics committee of Van Yuzuncu Yıl University on 3/4/2020 with the decision number 2020/09. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Van Yüzüncü Yıl Üniversitesi müdahale etik kurulundan 04.03.2020 tarih ve 2020/09 sayılı kararla araştırma onayı alındı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/21/2020
Yayın Tarihi: 21.12.2020

Abstract

Aim: Bladder tumor is one of the most common cancers. Cystoscopy, which is an invasive procedure, is used in its diagnosis. We conducted a study to determine whether a more non-invasive method can be used for this purpose. In this study, the uses of Ischemia Modified Albumin (IMA) and total sulfhydryl level (TSH), which are both antioxidant markers, were investigated for the diagnosis of bladder tumor.

Methods: Ischemia Modified Albumin (IMA) and total sulfhydryl level (TSH) were identified by the spectrophotometric method. Patients with primary bladder tumors who did not receive any prior treatments or undergo any interventions were included in this prospective case control study. Those with severe cardiac and neurological diseases, other malignancies, acute and chronic infectious diseases, active organ failure, chronic obstructive pulmonary diseases, and other ischemic immunosuppressive diseases, along with individuals with severely low or high serum albumin levels (<20 or >55 g/L) were excluded from the study.

Results: Forty-two primary bladder tumors and 45 healthy volunteers were included in the study. Serum IMA and TSH levels of the patient and control groups were compared. Patients with bladder tumors had high serum IMA (P=0.045) levels and low TSH levels (P=0.033).

Conclusion: Both IMA and total TSH can be considered non-invasive biomarkers in the diagnosis of bladder tumor. Since there are few studies on this subject in the literature, further, larger studies are needed.

Keywords: Bladder tumor, IMA, Total TSH

Öz

Amaç: Mesane tümörü en yaygın görülen kanserlerden biridir.Tanısında sistoskopi gibi invazif bir yöntem kullanılmaktadır.Bu çalışmada, mesane tümörü tanısında kulanılmak üzere daha non invaziv bir yöntem belirlemek için bir oksidan belirteç olan İskemi Modifiye Albümin (İMA) ve yeni bir antioksidan belirteç olan total sülfhidril (TSH) düzeyinin mesane tümörlü hastalarda bir biyobelirteç olup olamayacağını araştırmayı amaçladık.

Yöntemler: İskemik Modifiye Albümin (İMA) ve total sülfhidril seviyesi (TSH) spektrofotometrik yöntemle belirlendi. Çalışmaya, primer mesane tümörü olan ve daha önce herhangi bir tedavi almayan aynı zamanda herhangi bir cerrahi müdahalesi olmayan hastalar dahil edilirken, ağır kalp ve nörolojik hastalıkları, diğer maligniteleri, akut ve kronik enfeksiyon hastalıkları, aktif organ yetmezliği, kronik obstrüktif akciğer hastalığı olan ve diğer iskemik immünsüpresif hastalıkları olan hastalar çalışma dışı bırakıldı. Ciddi derecede düşük veya yüksek serum albumin seviyeleri (<20 veya >55 g/L) olan kişiler de çalışmadan çıkarıldı.

Bulgular: 42 primer mesane tümörü ve 45 sağlıklı gönüllü çalışmaya dahil edildi. Hasta ve gönüllü gruplarının serum İMA ve total TSH düzeyleri karşılaştırıldı. Kontrol grubuna göre mesane tümörü olan hastaların serum İMA (P=0,045) düzeyleri yüksek ve total TSH düzeyleri düşük (P=0,033) izlendi.

Sonuç: Hem İMA hemde Total TSH düzeyi, mesane tümörü tanısında daha noninvaziv bir biyobelirteç olarak düşünülebilir. Literatürde bu konuda çok fazla çalışma bulunmadığından daha geniş çaplı çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Mesane tümörü, İMA, Total TSH

How to cite/Atıf için: Eryılmaz R, Demir C, Aslan R, Demir H, Taken K. Can ischemia modified albumin (IMA) and total sulfhydryl level (TSH) be used as a biomarker in the diagnosis of bladder tumor? A prospective case-control study. J Surg Med. 2020;4(12):1104-1107.

Introduction

Bladder tumor is the most common type of cancer among individuals above the age of 65 years; and it constitutes 7% of all cancers. Its etiology includes tobacco dependence, schistosomiasis, eating and drinking habits and lifestyle changes. Lifestyle, eating and drinking habits are particularly effective on the oxidant-antioxidant balance [1]. Recently, research on the role of free radicals in cancer development and the protective effects of antioxidants has increased. Oxidative stress (OS) occurs during cell proliferation due to both hydrogen peroxide and superoxide [2].

Ischemia Modified Albumin (IMA), a systemic marker of oxidative stress, and total sulfhydryl, an antioxidant marker, are among the new biochemical markers [3,4].

Albumin is a protein consisting of 585 aminoacids. The last amino acid terminal in the albumin structure is capable of binding heavy transition metals (nickel, cobalt) [5]. It reversibly binds the drugs in blood, bilirubin, hormone, fatty acids, cations (Ca^{+2}, Na^{+2} and K^{+}) and other ligands [6]. Amino end (N terminal) of albumin molecule is the primary binding site of transitive metal ions, especially the aspartyl-alanyl-histidyl-lysine amino acid sequence, which binds cobalt (Co^{+2}), nickel (Ni^{+2}), copper (Cu^{+2}) [7]. Free radical damage and disruption of cell membrane integrity cause the formation of damaged albumin by reducing the binding of these heavy metals to the N-terminal of albumin. This modified form of albumin is called Ischemia Modified Albumin (IMA) and measured spectrophotometrically by albumin cobalt binding test [8]. It was examined in different diseases such as pulmonary embolism, cancer, paralysis, and particularly, ischemic heart diseases, all of which yielded IMA levels above the normal range [9,10]. Plasma proteins are highly sensitive to oxidation due to the free sulfhydryl groups in serum albumin structure. Therefore, it is stated that measuring sulfhydryl groups bound to proteins is a significant indicator to identify oxidative stress [11,12].

We herein investigated the use of IMA level, which is an oxidant marker, and total sulfhydryl level, which is a new antioxidant, as biomarkers in diagnosing bladder tumors in patients.

Materials and methods

This prospective study includes 42 patients with primary bladder cancer, who were diagnosed in our urology clinic in a tertiary university hospital between 04/03/2020-10/10/20 and 45 healthy individuals. No sample selection was made from the universe. All patients enrolled in the study had primary bladder tumors which were diagnosed during cystoscopy and none had received any previous treatments or interventions. Patients with severe cardiac and neurological diseases, other malignancies, acute and chronic infectious diseases, active organ failure, chronic obstructive pulmonary diseases, other ischemic immunosuppressive diseases, and severely low or high serum albumin levels (<20 or >55 g/L) were excluded from the study. Since the formation of ischemia modified albumin is related to disruption of the cell membrane and normal albumin in serum, too high or low albumin levels would affect its levels.

The control group comprised completely healthy volunteers who did not have any disease or history of drug use and had not undergone any surgeries.

Demographic, clinical, and biochemical data of both groups were recorded and analyzed comparatively. Written consents were obtained from patients and volunteers.

The approval for this research was received from the interventional ethics committee of Van Yuzuncu Yıl University on 04/03/2020 with the decision no 2020/09.

Sampling and analysis

Blood samples were drawn from the antecubital vein into serum biochemistry tubes and centrifuged at 5000 rpm for 10 minutes. The obtained serum samples were stored at -80 ° C until biochemical analysis.

IMA measurement

Serum IMA level was measured by colorimetric analysis developed by Bar-Or. To measure IMA, 50 ml of cobalt chloride was added to 200 ul of serum, shaken slightly, and the mixture solution was incubated for 10 minutes to ensure proper binding of cobalt to albumin. Then, coloring substance 50 uL of 1.5 mg/ ml dithiothreithol (DTT) (Sigma-Germany) was added and binding reaction was stopped by adding 1.0 ml% 0.9 NaCl after 2 minutes. A colorimetric control was prepared for each sample. 50 uL distilled water was used instead of 50 uL 1.5 mg/ml DTT for control samples. The obtained color complex was measured by spectrophotometric method at 470 nm. The results were reported as absorbance unit (ABSU).

Total sulfhydryl groups (SH) were measured by the methods described initially by Elmman (Ellman, 1959) and total sulfhydryl level was identified with the method developed by Hu (Hu, 1984). Here, thiols react with 5, 5'-dithiobis- (2-nitrobenzoic acid) (DTNB). It then gives the maximum peak at 412nm. 25uL of serum was added to 1 mL of Tris-EDTA buffer (0.25 mmol / L Tris base, 20 mmol / L EDTA, pH 8.2) and absorbance was read at 412 nm (A1). After that, a 25L aliquot of DTNB stock solution (10mmol/L in absolute methanol) was added to the primary solution. After 15 minutes at ambient temperature, the absorbance was read again (A2) together with a DTNB blank (B). The concentration of sulfhydryl groups was calculated by using reduced glutathione as sulfhydryl group standard and the result was expressed in mmol/L.

Statistical analysis

The descriptive statistics for the features mentioned are Mean and Standard Deviation. Kolmogorov-Smirnov test was used to verify that continuous variables were normally distributed. Normally and non-normally distributed binary groups were compared with the T-test and Mann Whitney U test, respectively. ROC curve analysis was performed to evaluate the performance of the biomarkers in distinguishing the patient group from the control group. The statistical significance level was 5%. SPSS statistical packaged software was used for all calculations.

Results

The mean age of the patients and the control group were 63.2 (3.22) years and 60.66 (4.15) years, respectively. There were 26 males (62%) in the patient group and 30 males (67%) in the control group. The mean tumor size was 3.27 (1, 35) cm.

None of our patients had muscle invasion and all were papillary urothelial tumors. The size of the tumor was larger than 3 cm in 24 patients while it was smaller in 18. Eighteen patients had low-grade and 24 patients had high-grade bladder tumors. The demographic characteristics of the patient and control groups were similar (Table 1). The diagnostic features of the patients are presented in Table 2.

Table 1: Demographic characteristics of the patient and control groups

Variable	Bladder cancer(n=42)	Control group(n=45)
Mean Age/year	63.2 (3.22)	60.66 (4.15)
Male	26	30
Female	16	15
Body Mass Index (BMI) kg/m^2	25.32 (6.45)	26.55 (4.63)
Smoker	30	33

Table 2: The diagnostic properties of patients

Variable	Bladder cancer(n=42)
Tumor size	
<3cm	18
>3cm	24
Grade	
Low grade	18
High grade	24
Pathology	
Papillary urothelial tumor	34
Carcinoma in situ	8
Other pathologies	0
Detrusor invasion -	42
Detrusor invasion +	0
TNM Stage	
Ta	24
Tis	8
T1	10

The descriptive statistics and comparison results of both IMA and TSH levels are shown in Table 3. The differences between the means of patient and control groups in terms of both IMA and TSH levels were statistically significant ($p<0.05$). Serum IMA levels were higher and serum TSH levels were lower in patients with tumors larger than 3 cm compared to those with smaller tumors. Likewise, patients with high-grade tumors had higher serum IMA levels and lower serum TSH levels compared to those with low-grade tumors ($p<0.05$ for both). While the mean IMA level of the patient group was significantly higher than that of the control group (Figure 1), the mean TSH of the patient group was significantly lower (Figure 2).

Table 3: Descriptive statistics and comparison results

	Group	n	Mean (SD)	P-value
IMA (Absorbance unit)	Control	45	0.962 (0.090)	<0.05
	Patient	42	3.1976 (0.977)	
TSH (nmol/mg protein)	Control	45	0.203 (0.065)	<0.05
	Patient	42	0.031 (0.022)	
IMA	>3cm	24	4.0187 (0.06033)	<0.05
	<3cm	18	2.1483 (0.40493)	
IMA	High Grade	24	4.0058 (0.08632)	<0.05
	Low Grade	18	2.0565 (0.11324)	
TSH	>3cm	24	0.0142 (0.00504)	<0.05
	<3cm	18	0.0535 (0.01367)	
TSH	High Grade	24	0.0142 (0.00504)	<0.05
	Low Grade	18	0.0535 (0.01367)	

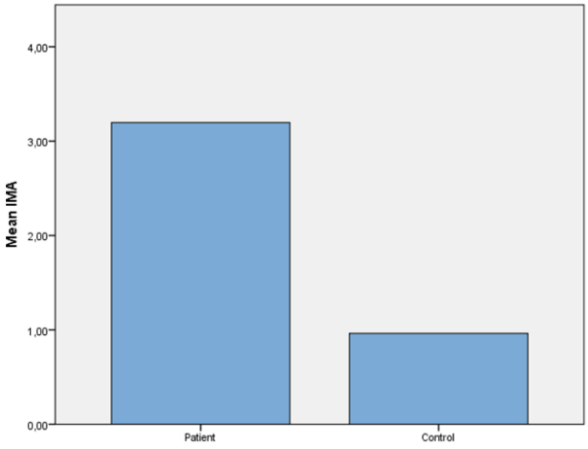


Figure 1: Serum IMA levels in patients and controls

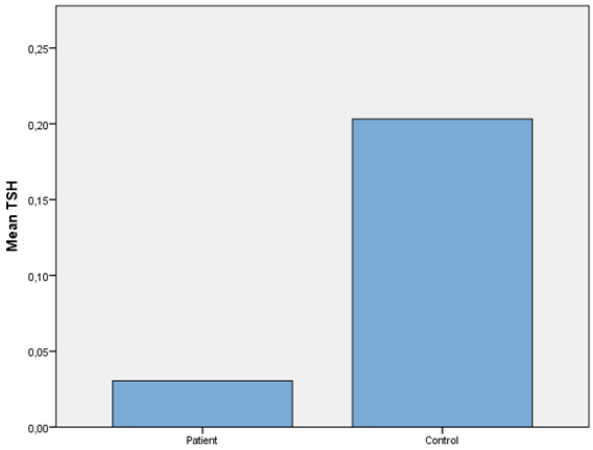


Figure 2: Serum TSH levels in patients and controls

Discussion

Oxidative stress may play a role in the development of many cancers. Discussions continue about whether oxidative stress is a factor in tumor progression or cancer pathophysiology. Some results show that ROS is a mutagenic factor causing DNA damage, suppressing apoptosis, and triggering proliferation, invasion, and metastasis [13].

Oxidative stress causes cancer development by stimulating tissue protein denaturation, DNA damage, lipid peroxidation and altering normal metabolic activity [9]. Reactive oxygen species (ROS) forming oxidative stress cause cancer by stimulating DNA damage and genetic mutation. Excessive ROS production leads to formation of ischemia modified albumin (IMA) by modifying serum albumin with oxidation [10].

In a study regarding the correlation between antioxidants and bladder cancer performed by Islam et al. [14], there was a decrease in the activity of antioxidant enzymes (superoxide dismutase, catalase, glutathione and paraoxonase) in the tissues of patients with bladder cancer. As a result, imbalance occurs between oxidizers and antioxidants. It shows that the imbalance has a potential role in etiology and progress of bladder cancer.

How oxidant-antioxidant balance plays a role in cancer pathogenesis has been mentioned in detail in the studies above. Therefore, we think that IMA and serum total sulfhydryl levels, both of which are antioxidant markers, can be used as biomarkers to diagnose bladder tumors. In this study, there is a statistical significance in the parameters of both patient and control groups when serum IMA and total sulfhydryl level were compared. No previous study has been conducted regarding serum total sulfhydryl level in patients with bladder tumor. In this sense, our study is a first.

There are many studies revealing the correlation between serum IMA level and cancer. In a study by Qing-Xing Huangai et al. [15], serum IMA levels strongly correlated with serum albumin levels in patients with advanced gastric cancer. Serum IMA level in patients with pre-operative advanced gastric cancer was indicated as an independent prognostic factor for operation.

Erkut et al. [16] identified that IMA could be used as a hypoxic indicator in acute leukemias.

In another study, Da Silveria RA et al. [17] found that both inflammatory and oxidative processes increased in prostate

cancer, and accordingly, serum IMA level was high while antioxidant defense decreased.

In the study of Ellidag et al. [18], total antioxidant status (TAS) level was lower compared to the control group, and total antioxidant status (TOS) and IMA levels were higher. Also, serum albumin levels were significantly low in these patients.

Currently, there is no strong non-invasive test to diagnose bladder tumors early. Early diagnosis is significant for the patients at risk of bladder tumor. When bladder tumor is diagnosed with the current diagnostic techniques, more than 70% of the cases are non-muscle invasive and 30% have already invaded the muscle or are metastatic. The 5-year survival rate of early bladder tumor is 94%, while it is lower than 50% in muscle-invasive stage and lower than 20% if metastatic [19].

Studies have reported that serum IMA levels are high in diverse types of cancer and hypoxic diseases. These studies state that serum IMA level is directly related to cancer. It can be also used as a biomarker in some types of cancer and as a prognostic factor in others. In the studies of Wong et al. [19], the importance of early diagnosis of bladder tumor was indicated in detail on the survey.

In our study, serum IMA levels were significantly higher in the bladder tumor patient group compared to the controls, and especially higher among patients with a tumor size greater than 3 cm and high-grade tumors. According to these results, serum IMA level can be used as a biomarker in patients with bladder tumors. Although the specificity of serum IMA level is lower than cystoscopy in bladder tumor, it is a more non-invasive method.

Total sulfhydryl groups are a significant part of the antioxidant defense against free radicals [20]. Another target of free radical attacks is sulfhydryl groups bound to proteins. Compounds with sulfhydryl have a significant role in protecting cells against particularly reduced glutathione free radical damage [21]. Total sulfhydryl would be a protective biomarker against cancer as an antioxidant, which is why serum total sulfhydryl level was measured in patients with bladder tumors in this study. It was significantly lower in the overall patient group, in those with tumor sizes greater than 3 cm and high-grade tumors.

Limitations

The limitations of our study are the small number of our patients and the fact that IMA and total TSH levels were not checked in the follow-up of patients after primary surgery.

There is a need for large-scale studies which investigate the use of IMA and total TSH levels in patients with bladder tumors.

Conclusions

We determined that serum IMA level is high, and serum total sulfhydryl level is low in bladder tumors. Both parameters are non-invasive biomarkers in the diagnosis of bladder tumor. The results were more significant in high grade tumors and those larger than 3 cm in size. In addition, IMA and TSH may play key roles in the etiopathogenesis of bladder tumors. Therefore, the measurement of total sulfhydryl level, especially in bladder tumors, is a first in the literature. There is a need for further, comprehensive studies on the subject.

References

1. Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder cancer incidence and mortality: a global overview and recent trends. European Urology. 2017;71(1):96–108.
2. Sawicka E, Kratz EM, Szymańska B, Guzik A, Wesołowski A, Kowal P, et al. Preliminary Study on Selected Markers of Oxidative Stress, Inflammation and Angiogenesis in Patients with Bladder Cancer. Pathol Oncol Res. 2019 Mar 4. doi: 10.1007/s12253-019-00620-5.
3. Awadallah SM, Atoum MF, Nimer NA. Ischemia modified albumin: an oxidative stress marker in beta-thalassemia major. Clin Chim Acta 2012; 413(9-10):907-10.
4. Uzar E, Tamam Y, Evliyaoglu O, Tuzcu A, Beyaz C, Acar A, et al. Serum prolidase activity and oxidative status in patients with diabetic neuropathy. Neurol Sci. 2012;33(4):875-80.
5. Chawla R, Goyal N, Calton R, Goyal S. Ischemia modified albumin: A novel marker for acute coronary syndrome. Indian J Clin Biochem. 2006;21:77-82.
6. Lee E, Eom JE, Jeon KH, Kim TH, Kim E, Jhon GJ, et al. Evaluation of albumin structural modifications through cobalt-albumin binding (CAB) assay. J Pharm Biomed Anal. 2014;91:17-23.
7. Sbarouni E, Georgiadou P, Voudris V. Ischemia modified albumin changes review and clinical implications. Clin Chem Lab Med 2011;49:177-84.
8. Zurawska-Płaksej E, Grzebyk E, Marciniak D, Szymańska-Chabowska A, Piwowar A. Oxidatively modified forms of albumin in patients with risk factors of metabolic syndrome. J Endocrinol Invest. 2014;37:819-27.
9. Sbarouni E, Georgiadou P, Voudris V. Ischemia modified albumin changes - review and clinical implications. Clin Chem Lab Med. 2011; 49(2):177-84.
10. Cakir M, Karahan SC, Mentese A, Sag E, Cobanoglu U, Polat TB, et al. Ischemia modified albumin levels in children with chronic liver disease. Gut Liver 2012;6(1):92-7.
11. Hu ML. Measurement of protein thiol groups and glutathione in plasma. Meîhod Enzymol. 233:380(S994).
12. Stockcr R, Frei B. Endogenous antioxidant defences İn human blood plasma,"Oxidative Stress: Oxidants and Antioxidants, editör: Sies H, Acedemic Press, London (1991):213.
13. Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Interact. 2006;160:1–40.
14. Islam MO, Bacchetti T, Ferretti G. Alterations of Antioxidant Enzymes and Biomarkers of Nitro-oxidative Stress in Tissues of Bladder Cancer. Oxid Med Cell Longev. 2019 May 5;2019:2730896. doi: 10.1155/2019/2730896. eCollection 2019
15. Huang QX, Ma J, Wang YS. Significance of preoperative ischemia-modified albumin in operable and advanced gastric cancer. Cancer Biomark. 2018;22(3):477-85.
16. Erkut N, Mentese A, Ozbas HM, Sumer A, Orem A, Topbas M, et al. The indicator of hypoxia in acute leukemia: Ischemia-modified albumin. Cancer Biomark. 2015;15(5):559-65.
17. Da Silveira RA, Hermes CL, Almeida TC, Bochi GV, De Bona KS, Moretto MB. et al. Ischemia-modified albumin and inflammatory biomarkers in patients with prostate cancer Clin Lab. 2014;60(10):1703-8.
18. Ellidag HY, Eren E, Aydin O, Akgol E, Yalcinkaya S, Sezer C, et al. Ischemia modified albumin levels and oxidative stress in patients with bladder cancer Asian Pac J Cancer Prev. 2013;14(5):2759-63.
19. Wong R, Rosser CJ. UroSEEK gene panel for bladder cancer surveillance Transl Androl Urol. 2019 Dec;8(Suppl 5):S546-9.
20. Ryrfeldt A, Bannenberg G, Moldeus P. Free radicals and lung disease. British Med Bull. 1993;49(3):588-603.
21. Cotgreave IA, Johansson U, Moldeus P, Brattsand R. The effect of acute cigarette smoke inhalation on pulmonary and systemic cysteine and glutathione redox states in the rat. Toxicology. 1987;45:203-12.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1108-1111.
DOI: 10.28982/josam.827657

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Evaluation of the effects of antiepileptic drugs on complete blood count parameters

Antiepileptiklerin kan sayımı üzerine etkilerinin değerlendirilmesi

Haticenur Kırar [1], Emine Türkkan [1], Tuğçe Aksu Uzunhan [1], Alper Kaçar [1], Soner Sazak [1], Okan Dikker [2], Hüseyin Dağ [1]

[1] University of Health Sciences, Istanbul Prof.Dr. Cemil Taşçıoğlu City Hospital, Department of Pediatrics, Istanbul, Turkey
[2] University of Health Sciences, Istanbul Prof.Dr. Cemil Taşçıoğlu City Hospital, Department of Medical Biochemistry, Istanbul, Turkey

ORCID ID of the author(s)
HK: 0000-0002-7549-6886
ET: 0000-0002-5126-7843
TAU: 0000-0003-0596-2690
AK: 0000-0001-7577-5386
SS: 0000-0003-0233-6950
OD: 0000-0002-9153-6139
HD: 0000-0001-7596-7687

Corresponding author/Sorumlu yazar:
Hüseyin Dağ
Address/Adres: Sağlık Bilimleri Üniversitesi, İstanbul Prof.Dr. Cemil Taşçıoğlu Şehir Hastanesi, Çocuk Sağlığı ve Hastalıkları Bölümü, Darülaceze sokağı, No: 27, Sisli, İstanbul, Türkiye
E-mail: huseyindag2003@gmail.com

Ethics Committee Approval: The study was approved by the Ministry of Health Okmeydani Training and Research Hospital Ethics Committee (date: 07.02.2018 and number: 4396). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma Sağlık Bakanlığı Okmeydanı Eğitim ve Araştırma Hastanesi Etik Kurulu tarafından onaylandı (tarih: 07.02.2018 ve sayı: 4396). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: The incidence of pediatric epilepsy ranges between 1-3%, and various anticonvulsant drugs are used in its treatment. Seizure type, effectiveness and side effects are important in drug selection. Various hematological side effects of anticonvulsants have been reported. This study aims to determine the hematological side effects of the anticonvulsants used in our clinic.

Methods: A total of 87 epilepsy patients between the ages of 1 and 15 years, who were diagnosed and followed up in the Pediatric Neurology Outpatient Clinic of Health Sciences University, Okmeydanı Training and Research Hospital between January 2017-2018 and who received anticonvulsant medication for at least 3 months were included in this study. The blood values and hematological side effects of the anticonvulsants were noted from the patient files. The statistical analyses were performed with IBM SPSS Statistics v.22 (SPSS IBM, Turkey).

Results: Among all, 44.8% of the patients were using Valproic acid (VPA), 28.7%, Levetiracetam (LEV), 12.6%, Oxcarbazepine (OXC), 8%, Phenobarbital (PB), and 4.6%, Carbamazepine (CBZ). Platelet values were below 150,000/ul in 7.6% of VPA users and 14.2% of PB users. The hemoglobin value fell below 10 g/dl in 2.5% of VPA users, 14.2% of PB users, and 8% of LEV users. Absolute neutrophil count fell below 1500/ul in 9% of the patients using OXC and 14.2% of those using PB. The decrease in platelet values before and after anticonvulsant use was statistically significant (P=0.039), while the decrease in hemoglobin and neutrophil values were not.

Conclusion: In patients using antiepileptic drugs, complete blood count may be affected. Periodic monitoring of blood parameters is important in the close follow-up of patients. It is not known exactly how and how often the hematological side effects of antiepileptic drugs take place. Future studies on this subject are necessary.

Keywords: Antiepileptic drug, Child, Complete blood count

Öz

Amaç: Çocukluk çağında epilepsi görülme oranı %1-3 arasındadır. Epilepsi tedavisinde çeşitli antikonvülzan ilaçlar kullanılmaktadır. İlaç seçiminde nöbet tipi, ilacın etkinliği ve ilacın yan etkileri önemlidir. Antikonvülzan kullanımının çeşitli hematolojik yan etkileri bildirilmiştir. Bu çalışmanın amacı kliniğimizde kullanılan antikonvülzanlara bağlı hematolojik yan etkileri ve bu etkilerin sıklığını saptamaktır.

Yöntemler: Ocak 2017 - Ocak 2018 tarihleri arasında Sağlık Bilimleri Üniversitesi Okmeydanı Eğitim ve Araştırma Hastanesi Çocuk Nöroloji polikliniğinde epilepsi tanısı almış ve en az 3 aydır antikonvülzan tedavi verilmiş, 1 - 15 yaş arasındaki 87 hastanın dosyalarından kan değerleri ve ilaçların hematolojik yan etkileri kaydedildi. Çalışmada elde edilen bulgular değerlendirilirken, istatistiksel analizler için IBM SPSS Statistics 22 (IBM SPSS, Türkiye) programı kullanıldı.

Bulgular: Çalışmamızda hastaların %44,8'i Valproik asit (VPA), %28,7'si Levatiresetam (LEV), %12,6'sı Okskarbazepin (OXC), %8'i Fenobarbital (PB), %4,6'sı Karbamazepin (CBZ) kullanıyordu. VPA kullananların %7,6'sında, PB kullananların %14,2'sinde trombosit değerinin 150.000/ul altına düştüğü saptandı. VPA kullananların %2,5'inde, PB kullananların %14.2 'sinde, LEV kullananların %8'inde hemoglobin değerinin 10 g/dl altına düştüğü saptandı. OXC kullanan hastaların %9'unda, PB kullananların %14,2'sinde mutlak nötrofil sayısının 1500/ul altına düştüğü saptandı. İlaç öncesi ve sonrası değerler karşılaştırıldığında, hemoglobin ve nötrofil değerlerindeki düşüş anlamlı bulunmazken, trombosit değerlerindeki düşüş istatistiksel olarak anlamlı bulundu (P=0,039).

Sonuç: Anti epileptik ilaç kullanan hastaların kan sayımı etkilenebilmektedir. Hastaların takibinde kan parametrelerinin periyodik olarak yakından izlenmesi önemlidir. Antiepileptik ilaçların hematolojik yan etkisinin nasıl ve ne sıklıkta olduğu tam olarak bilinmemektedir. Bu konuda yapılacak çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Antiepileptik ilaç, Çocuk, Kan sayımı

How to cite/Atıf için: Kırar H, Türkkan E, Uzunhan TA, Kaçar A, Sazak S, Dikker O, Dağ H. Evaluation of the effects of antiepileptic drugs on complete blood count parameters. J Surg Med. 2020;4(12):1108-1111.

Introduction

Epilepsy is associated with persistent dysregulation of brain functions and a predisposition to recurrent seizures. The International League Against Epilepsy (ILAE) defines epilepsy as having at least two unprovoked seizures, at least 24 hours apart. It can be caused by various genetic, structural, metabolic, immune, and infectious reasons [1,2]. It is a common neurological problem in children and adolescents, whose frequency varies between 1-3%. There are few studies on the side effect profile of antiepileptic drugs used in the treatment of epilepsy in children, and their safety profile is not completely known. Only 13 of the 34 drugs used have the Food and Drug Administration (FDA) approval for children [3].

Most epileptic seizures can be treated with antiepileptic drugs (AEDs). When choosing an AED, physicians should pay attention that it is a highly effective, safe, and well-tolerated drug for the seizure type. The main goal in epilepsy treatment should be monotherapy. However, if seizures cannot be controlled despite the first two monotherapy treatments, drug combinations should be tried. The list of drugs used in epilepsy is gradually increasing. Drugs are primarily used in partial seizures in adults and, when effective, they can be used in other seizure types and children [4,5].

Many side effects of antiepileptic drugs have been described, and their hematological side effects are given particular attention in the literature. Many AEDs are associated with hematological disorders ranging from mild thrombocytopenia or neutropenia to anemia, from red cell aplasia to bone marrow failure. Fortunately, potentially fatal hematological disorders such as aplastic anemia are exceedingly rare. Children are more frequently affected by the side effects of AEDs than adults because they are treated more frequently and at higher doses. Although there are many studies and publications on the side effects of AEDs, there is no consensus on which drug causes which hematological side effect and how often [6].

In this study, we aimed to discuss the hematological side effects of AEDs in children, which are rarely seen, in light of the literature by evaluating our patients who were followed up in our clinic.

Materials and methods

Research method and study population

Patients diagnosed with epilepsy who were admitted to the Pediatric Neurology outpatient clinic of Health Sciences University Okmeydanı Training and Research Hospital between January 2017 and January 2018 were included in our study. The study was approved by the Ministry of Health Okmeydani Training and Research Hospital Ethics Committee (date: 07.02.2018 and number: 4396) and carried out in accordance with the Helsinki Declaration. Patients aged between 1-15 years who were given anticonvulsant therapy for at least 3 months, and whose hospital records were complete, were included in the study. The hospital records of patients with an infection or known hematological disease, using drugs other than antiepileptic therapies, and having any other systemic diseases were excluded. Gender, date of birth, age, diagnosis date, drugs used, drug initiation date, drug doses, duration of use, hemoglobin in blood count (HGB), hematocrit (HCT), leukocyte (WBC), thrombocyte (PLT), absolute neutrophil count (ANC), absolute lymphocyte count (ALC) and absolute monocyte count (AMC) were recorded on patient forms. How often and which anticonvulsant was causing hematological side effects were evaluated. This information was then transferred to the electronic program to analyze the statistical data.

Statistical analysis

When evaluating the findings obtained in the study, IBM SPSS Statistics 22 (SPSS IBM, Turkey) program was used. The normality of distribution of the parameters was evaluated with the Shapiro Wilks test. Descriptive statistical methods (mean, standard deviation, frequency), as well as One-way ANOVA test were used to compare normally distributed parameters between groups for quantitative data. Kruskal Wallis test was used for intergroup comparisons of non-normally distributed parameters. Paired Sample t-test and Wilcoxon Signed Ranks test were used to compare the normally and non-normally distributed quantitative data, respectively, before and after drug use. $P<0.05$ was considered statistically significant.

Results

The study was conducted with 87 patients, 50 (57.5%) males and 37 (42.5%) females, aged between 1 and 15 years. The mean age of the patients was 8.51 (4.09) years. Among them, 44.8% (n=39) were using VPA, 28.7% (n=25) were using LEV, 12.6% (n=11), OXC, 8% (n=7), phenobarbital, 4.6% (n=4) CBZ and 1.1% (n=1) was using ethosuximide.

In this study, the most used anti-epileptic drug was VPA. In 7.6% (n=3) of VPA users, the PLT value fell below 150,000 /ul, and in 2.5% (n=1), the HGB value fell below 10 g/dl. In 8% of the patients using LEV (n=2), HGB value was below 10 g/dl. Nine percent of OXC (n=1) users had ANC below 1500 /ul. In 14.2% of the patients using PB (n=1), the HGB value fell below 10 g/dl, in 14.2% (n=1), PLT count fell below 150,000 /ul, and in 14.2% (n=1), neutrophil count was <1500 /ul. When the pre- and post-drug values summarized in Table 1 were compared, the decrease in HGB and ANC values were not statistically significant, while the decrease in PLT count was ($P=0.039$). No statistically significant difference was found among the drug groups in terms of percentage change in blood count values measured during the pre- and post-drug periods ($P>0.05$) (Table 2).

Table 1: The Effects of Antiepileptics on Complete Blood Count

	Pre-drug		Post-drug		
	Min-Max	Mean (SD)	Min-Max	Mean (SD)	*P*-value
HGB	10.2-14.6	12.32 (0.99)	9.4-15.8	12.33 (1.28)	[1]0.884
HCT	30.2-43.1	36.54 (2.79)	29.5-46.7	36.71 (3.11)	[1]0.488
WBC	3760-17450	7976.43 (2309.36)	4680-16600	8019.42 (2289.81)	[1]0.886
PLT	156000-478000	296206.90 (74858.8)	125000-489000	279678.16 (76622.22)	[1]0.039*
ANC (median)	1210-13020	4087.24 (2154.70) (3380)	550-11580	3982.64 (1899.65) (3540)	[2]0.906
ALC (median)	890-7400	3035.75 (1234.62) (2870)	1130-7200	3181.61 (1254.91) (2960)	[2]0.349
AMC (median)	220-1880	621.49 (282.61) (580)	250-1710	597.70 (218.89) (600)	[2]0.942

[1] Paired samples t-test, [2] Wilcoxon sign test, * $P<0.05$

Table 2: Percentage Changes in Complete Blood Count Parameters by Antiepileptic Drug Group

Percentage Changes	Medications used					*P*-value
	Levetiracetam	Oxcarbazepine	Valproic acid	Phenobarbital	Carbamazepine	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
HGB	0.31 (7.29)	1.58 (6.24)	-0.28 (5.67)	-1.79 (10.22)	2.59 (5.71)	[1]0.832
HCT	0.85 (7.26)	1.93 (6.08)	0.45 (5.94)	-1.24 (6.88)	-0.44 (6.75)	[1]0.936
WBC	10.63 (47.59)	-3.29 (30.21)	4.61 (29.03)	18.48 (45.29)	9.76 (31.03)	[1]0.813
PLT	2.59 (26.38)	7.22 (22.57)	-9.46 (23.62)	-1.24 (38.43)	1.83 (8.55)	[1]0.253
ANC (median)	18.22 (86.68)	-0.57 (56.03)	8.73 (50.66)	75.33 (107.58)	45.43 (79.7)	[2]0.382
	(-12.23)	(-19.85)	(-0.51)	(36.96)	(22.93)	
ALC (median)	29.72 (75.37)	5.38 (25.8)	18.27 (68.46)	-1.86 (48.82)	-4.67 (40.98)	[2]0.727
	(8.73)	(4.56)	(6.7)	(-25.58)	(-13.02)	
AMC (median)	-7.12 (38.96)	1.66 (38.23)	22.01 (51.65)	12.41 (73.98	12.96 (50.3)	[2]0.191
	(-5.19)	(0)	(16.13)	(7.14)	(27.45)	

[1] One-way ANOVA test, [2] Kruskal Wallis test, Note: It was excluded from the analysis due to 1 child using ethosuximide

Discussion

Epilepsy is a common neurological disorder seen in the pediatric age group and AEDs constitute the basis of treatment. The new generation AEDs are gradually added to the old generation antiepileptics [7, 8]. The choice of AEDs for epilepsy treatment in infants and children depends not only on the effectiveness of the agent, but also on its safety, toxicity potential, tolerability, its effect on behavior and learning, and existing patient comorbidities [9-11].

BDZs (Benzodiazepines), clonazepam, diazepam, and lorazepam, which have been used frequently in the treatment of epilepsy, act on the GABA (Gamma Amino Butyric Acid) -BDZ receptor complex [12,13]. Few cases of lorazepam and clonazepam-induced pancytopenia, thrombocytopenia caused by clonazepam, and acute granulocytopenia, acute thrombocytopenic purpura, and active antiplatelet antibodies during treatment with diazepam were reported [14-18]. In this study, we also had patients using BDZ, but these patients were not included in the study because they were using multiple AEDs.

CBZ is widely used as an antiepileptic, which rarely causes hematological diseases such as aplastic anemia, thrombocytopenia, and leukopenia [19,20]. The rate of aplastic anemia due to CBZ ranges between 1/50000 and 1/200.000 [21]. In a cohort study by Blackburn et al. among 29,357 patients receiving AED, the frequency of severe blood dyscrasias, including aplastic anemia was investigated. They found only one case of aplastic anemia and did not find any relationship between the use of antiepileptic agents and aplastic anemia [22]. However, cases of thrombocytopenia related to CBZ have been reported in the literature [23-26]. In our study, 4.6% of the patients (4 patients) were using CBZ. No hematological side effects were encountered due to this drug.

Levetiracetam is another commonly used AED, and there are a few case reports about thrombocytopenia associated with LEV use [27-29]. To estimate the rate of LEV-induced thrombocytopenia, Sahaya et al. published a retrospective study in 2010. Accordingly, the medical records of 758 patients aged 18 years and older who received LEV during their hospital stay from June 2006 to December 2008 were reviewed. Thrombocytopenia was detected in 29 of 758 patients during LEV treatment. A secondary factor causing thrombocytopenia was determined in 23 patients, pre-existing thrombocytopenia was detected in 4 patients, and a clear relationship between LEV therapy and thrombocytopenia was reported in one patient [30]. In our study, 28.7% of the patients (n=25) were using LEV, HGB value fell below 10 g/dl in 8% (n=2), and no patient developed thrombocytopenia. Changes in hemoglobin values were not statistically significant.

Oxcarbazepine (OXC) is used in monotherapy or combination therapy in adults and children with partial and secondary generalized tonic-clonic seizures. Although OXC treatment has rare hematological side effects, thrombocytopenia, neutropenia, pancytopenia, and hemolytic anemia have been reported, especially at higher doses [31-34]. In our study, 12.6% of the patients (11 patients) were using OXC, and ANC was below 1500 /ul in 9% (1 patient). However, this decrease was not statistically significant.

Phenobarbital (PB) acts through GABA-dependent chloride channels and is an effective anticonvulsant for many seizure types such as tonic-clonic and focal seizures, and some clinical epilepsy sub-syndromes [35]. Megaloblastic anemia, leukopenia, agranulocytosis, and thrombocytopenia were associated with PB treatment [36]. In our study, 8% of the patients (7 patients) were using PB and among those, 14.2% (n=1) had HGB values below 10 g/dl, 14.2% (n=1) had PLT counts below 150,000 /ul, and the neutrophil count of 14.2% (1 patient) fell under 1,500 /ul. Patients should be followed up in terms of side effects related to phenobarbital use.

Thrombocytopenia is observed in 12-18% of patients using VPA and it is the most common hematological side effect of this drug [37]. Studies in pediatric patients have shown that blood loss and administration of blood products during surgical procedures are significantly increased in children on VPA monotherapy. Patients who received VPA treatment had a 23-fold relative risk of increased blood loss compared to those who did not receive VPA treatment, and a significant difference was observed in bleeding times and PT/aPTT values. Generally, thrombocytopenia was not severe, and no bleeding symptoms were encountered. Platelets have been found to increase within a few days after VPA dosage adjustments or ceases. Nevertheless, very rarely, fatal subarachnoid and pulmonary hemorrhage and pancytopenia have been reported [38]. In our patient group, in 7.6% of the patients (3 patients) using VPA, the PLT value fell below 150,000/ul, but no patients had severe thrombocytopenia (PLT count <100,000/ul). Platelet depletion was significantly lower when other antiepileptics were considered. Besides, coagulation disorders were not observed. Very few cases of factor XIII deficiency were reported during VPA treatment in adults and children. The rarity of homozygous factor XIII deficiency and the return of factor XIII activity to the normal range after VPA dose reduction support the effect of VPA on factor XIII levels. It is especially important to evaluate the platelet count, PT, aPTT, TT, fibrinogen, vWF, and factor XIII before surgical procedures in patients using VPA. Bleeding, hematomas, petechiae, bruising and prolonged bleeding are the alarm signs for dose reduction or cessation of treatment [39].

Besides, there are also publications indicating that VPA use causes neutropenia, although it is not as common as thrombocytopenia [40]. In our study, this rare side effect of VPA use was not encountered. Neutropenia usually occurs during the

first weeks of drug exposure and resolves within the first days after stopping the drug. VPA should be discontinued if the absolute neutrophil count (ANC) drops to <500 cells/mm [41].

Limitations

Our study is retrospective, and the number of our cases is relatively low, which are its two major limitations.

Conclusion

Considering the increasing number of pediatric patients diagnosed with epilepsy and the increasing use of AEDs, the hematological side effects of antiepileptic drugs should not be overlooked. It is seen in our study that the use of AEDs caused a significant decrease in the platelet value. In line with these results, blood count results of AED users must be followed up periodically. The mechanisms through which antiepileptic drugs cause hematological side effects and how often they occur are not known yet. There is a need for larger series and multi-center studies on this subject.

References

1. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014 Apr;55(4):475-82. doi: 10.1111/epi.12550. Epub 2014 Apr 14. PMID: 24730690.
2. Fisher RS, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia. 2017 Apr;58(4):531-42.
3. Cormier J, Chu CJ, Safety and efficacy of levetiracetam for the treatment of partial onset seizures in children from one month of age. Neuropsychiatr Dis Treat. 2013;9:295-306.
4. Bialer M, Johannessen SI, Koepp MJ, Levy RH, Perucca E, Tomson T, et al. Fourteenth Eilat Conference on new antiepileptic drugs and devices (EILAT XIV). I. Drugs in preclinical and early clinical development. Epilepsia. 2018;59:1811-41.
5. Perry MS. New and Emerging Medications for Treatment of Pediatric Epilepsy. Pediatr Neurol 2020;107:24.
6. Asadipooya AA, Sperling MR. Antiepileptic drugs and hematological disorders. Antiepileptic drugs: a clinician's manual. Oxford University Press, New York. 2009;165-170.
7. Guerrini R, Zaccara G, la Marca G, Rosati A. Safety and tolerability of antiepileptic drug treatment in children with epilepsy. Drug Saf. 2012;35(7):519-33.
8. Weijenberg A, Brouwer OF, Callenbach PM. Levetiracetam Monotherapy in Children with Epilepsy: A Systematic Review. CNS Drugs 2015;29(5):371–82.
9. Sankar R. Selecting appropriate pharmacotherapy for the child with epilepsy. Adv. Stud. Med 2005;5464–9.
10. Füsun Ferda Erdoğan. New Antiepileptic Drugs. Epilepsi. 2014; 20(Ek-1):56-8.
11. Sema saltık. Çocukluk Epilepsilerinde Tıbbi Tedavi. Epilepsi 2014;20(Ek 1):50-5.
12. Verrotti A, Coppola G, Parisi P. Bone and calcium metabolism and antiepileptic drugs. Clin Neurol Neurosurg. 2010;112:1-10.
13. Asadi-Pooya AA, Sperling MR. Mechanisms of actions and pharmacokinetic properties of antiepileptic drugs. Antiepileptic drugs: a clinician's manual. Oxford University Press, New York. 2009;69-148.
14. El-Sayed S, Symonds RP Lorazepam induced pancytopenia. Brit Med J. 1988;296:1332.
15. Bautista-Quach MA, Liao YM, Hsueh CT Pancytopenia associated with clonazepam. J Hematology Oncology. 2010;3:24.
16. Veall RM, Hogarth HC. Letter: Thrombocytopenia during treatment with clonazepam. Br Med J. 1975;4(5994):462.
17. Bussien R. Acute granulocytopenia after simultaneous administration of gentamicin and diazepam. Nouv Presse Med. 1974;3:1236.
18. Baumes RM. Drug induced cytopenia: acute thrombopenic purpura and active antiplatelet antibodies in the presence of valium. Maroc Med. 1971;546:321-4.
19. Handoko KB, Souverein PC, van Staa TP, Meyboom RH, Leufkens HG, Egberts TC, et al. Risk of aplastic anemia in patients using antiepileptic drugs. Epilepsia. 2006 Jul;47(7):1232-6.
20. Andres E, Maloisel F. Idiosyncratic drug-induced agranulocytosis or acute neutropenia. Curr Opin Hematol. 2008;15:15–21.
21. Zaccara G, Franciotta D, Perucca E. Idiosyncratic adverse reactions to antiepileptic drugs. Epilepsia. 2007;48:1223–44.
22. Blackburn SC, Oliart AD, Garcia Rodriguez LA, Pérez Gutthann S. Antiepileptics and blood dyscrasias: a cohort study. Pharmacotherapy. 1998;18:1277–83.
23. Tichy E, Lam S, Militano U, Bessmertny O. A case of severe thrombocytopenia and antiepileptic hypersensitivity syndrome. J Pediatr Pharmacol Ther. 2003 Jan;8(1):29-33.
24. Tohen M, Castillo J, Cole JO, Miller MG, Heros R, Farrer RJ. Thrombocytopenia associated with carbamazepine: A case series. J Clin Psychiatry. 1991;52:496
25. Abate MV, Stocco G, Devescovi R, Carrozzi M, Pierobon C, Valencic E, et al. Carbamazepine-induced thrombocytopenic purpura in a child: Insights from a genomic analysis. Blood Cells Mol Dis. 2016 Jul;59:97-9.
26. Kumar R, Chivukula S, Katukuri GR, Chandrasekhar UK, Shivashankar KN. Carbamazepine Induced Thrombocytopenia. J Clin Diagn Res. 2017;11(9):OD12-3.
27. Kimland E, Höjeberg B, von Euler M. Levetiracetam-induced thrombocytopenia. Epilepsia. 2004;45:877–8.
28. Meschede A, Runge U, Sabolek M. Thrombocytopenia during levetiracetam therapy. Epilepsy. 2008;80:91–2.
29. Oghlakian R, Nock C, Koubeissi M. A case of levetiracetam-induced thrombocytopenia. Epileptic Disord. 2010;12:335–7.
30. Sahaya K, Goyal MK, Sarwal A, Singh NN. Levetiracetam-induced thrombocytopenia among inpatients: a retrospective study. Epilepsia. 2010;51(12):2492-5.
31. Mahmud J, Mathews M, Verma S, Basil B. Oxcarbazepine-induced thrombocytopenia. Psychosomatics. 2006;47:73-4.
32. Hsiao YT, Wei IH, Huang CC. Oxcarbazepine-related neutropenia: a case report. J Clin Psychopharmacol. 2010;30:94-5.
33. Calamaras MR, Stowe ZN, Newport DJ. Pancytopenia associated with the introduction of oxcarbazepine. J Clin Psychopharmacol. 2007;27:217-8.
34. Chaudhry MM, Abrar M, Mutahir K, Mendoza C. Oxcarbazepine-induced hemolytic anemia in a geriatric patient. Am J Ther. 2008;15:187-9.
35. Suddock JT, Cain MD. Barbiturate Toxicity. 2020 Jul 2. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan–. PMID: 29763050.
36. Asadipooya AA, Sperling MR. Antiepileptic drugs and hematological disorders. Antiepileptic drugs: a clinician's manual. Oxford University Press, New York. 2009;165-70.
37. Buoli M, Serati M, Botturi A, Altamura AC. The Risk of Thrombocytopenia During Valproic Acid Therapy: A Critical Summary of Available Clinical Data. Drugs R D. 2018;18(1):1-5.
38. Gerstner T, Teich M, Bell N. Valproate-associated coagulopathies are frequent and variable in children. Epilepsia. 2006;47:1136-43.
39. Teich M, Longin E, Dempfle CE, Konig S. Factor XIII deficiency associated with valproate treatment. Epilepsia. 2004;45:187-9.
40. Watts RG, Emanuel PD, Zuckerman KS, Howard TH. Valproic acid-induced cytopenias: evidence for a dose-related suppression of hematopoiesis. J Pediatr. 1990;117:495-9.
41. Curnutte JT, Coates TD. Disorders of phagocyte function and number. Hematology: basic principles and practice, 3rd edn. Churchill Livingstone, New York. 2000;743-5.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1112-1115.
DOI: 10.28982/josam.836439

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Role of anesthesia type on cognitive functions in adults undergoing cataract surgery

Katarakt cerrahisi geçiren yetişkinlerde anestezi tipinin bilişsel işlevler üzerindeki rolü

Yeliz Kılıç [1], Mustafa Değer Bilgeç [2], Burak Taha Sarıoğlan [1], Gülay Erdoğan Kayhan [1], Mehmet Sacit Güleç [1], Ahmet Özer [2]

[1] Department of Anesthesiology and Reanimation, Faculty of Medicine, Osmangazi University, Eskişehir, Turkey
[2] Department of Ophthalmology, Faculty of Medicine, Osmangazi University, Eskişehir, Turkey

ORCID ID of the author(s)
YK: 0000-0003-1446-7747
MDB: 0000-0002-9972-2147
BTS: 0000-0002-9043-1685
GEK: 0000-0002-2635-9295
MSG: 0000-0002-7107-3798
AÖ: 0000-0002-8509-6982

Corresponding author/Sorumlu yazar:
Yeliz Kılıç
Address/Adres: Osmangazi Üniversitesi Tıp Fakültesi Anesteziyoloji Reanimasyon Anabilim Dalı, Büyükdere Mh., 26040, Odunpazarı, Eskişehir, Türkiye
E-mail: yeliz_kilic3@hotmail.com

Ethics Committee Approval: The approval for this study was obtained from Osmangazi University Ethical Committee (no: 24; 10.10.2019). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma için onay Osmangazi Üniversitesi Etik Kurulu'ndan alınmıştır (no: 24; 10.10.2019). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: Postoperative cognitive dysfunction (POCD) is a major concern for anesthesiologists and surgeons. However, the relationship between anesthesia type and postoperative cognitive functions has not been clearly identified. The aim of this study is to compare the impact of three anesthetic methods, local, topical, and general anesthesia, on the development of POCD in patients undergoing cataract surgery.

Methods: Patients aged between 19-64 years who underwent cataract surgery were enrolled in this prospective observational study. All patients were assigned to one of three anesthesia groups: General (n=27), local (n=23), and topical (n=27). Cognitive status was assessed preoperatively and postoperatively (1st hour, 1st day, 1st week), using Blessed Orientation-Memory-Concentration (BOMC) test.

Results: Except age, the three anesthesia groups were similar in baseline patient characteristics and hemodynamic data (P>0.05). Age was significantly different between the groups: Patients in general anesthesia group were the youngest and those in local anesthesia group were the oldest (P<0.001). All postanesthetic BOMC scores in local and topical groups decreased compared to baseline values (P>0.05). However, the 1st hour BOMC score showed an insignificant increase in the general anesthesia group (P=0.554). Baseline mean BOMC score was higher in local anesthesia group than in other groups (P=0.037), whereas postoperative BOMC scores were similar between the three groups (P>0.05).

Conclusions: Local, topical, and general anesthesia had no different effects on postoperative cognitive functions in adult patients undergoing cataract surgery. There was also no statistical difference in postoperative BOMC scores between the three anesthesia methods.

Keywords: Anesthesia, Cataract surgery, Postoperative cognitive dysfunction

Öz

Amaç: Postoperatif bilişsel işlev bozukluğu (POCD), anesteziyologlar ve cerrahlar için büyük bir endişe kaynağıdır. Ancak anestezi tipi ile postoperatif bilişsel işlevler arasındaki ilişki net olarak belirlenememiştir. Katarakt cerrahisi geçiren hastalarda POBD gelişimi üzerine üç anestezi yönteminin (lokal, topikal ve genel anestezi) etkisini karşılaştırmak.

Yöntemler: Bu prospektif gözlemsel çalışmaya katarakt ameliyatı geçiren 19 ve 64 yaşlarındaki hastalar alındı. Tüm hastalar üç anestezi grubundan birine atandı; genel (n=27), yerel (n=23) ve topikal (n=27). Bilişsel durum ameliyat öncesi ve sonrası (1. saat, 1. gün, 1. hafta) Blessed Orientation-Memory-Concentration (BOMC) testi kullanılarak değerlendirildi.

Bulgular: Üç anestezi grubu, yaş hariç, temel hasta özellikleri ve hemodinamik veriler açısından benzerdi (P>0,05). Yaş, gruplar arasında anlamlı olarak farklıydı ki bunlar arasında genel anestezi grubundaki hastalar en genç, lokal anestezi grubundakiler ise en yaşlılardı (P<0,001). Lokal ve topikal gruplarda tüm anestezi sonrası BOMC skorları başlangıç değerlerine göre azaldı (P>0,05). Ancak 1. saat BOMC skoru genel anestezi grubunda istatistiksel olarak anlamlı olmayan bir artış gösterdi (P=0,554). Lokal anestezi grubunda bazal ortalama BOMC skoru diğer gruplara göre daha yüksekti (P=0,037), postoperatif BOMC skorları ise üç grup arasında benzerdi (P>0,05).

Sonuç: Katarakt cerrahisi geçiren yetişkin hastalarda lokal, topikal ve genel anestezinin postoperatif bilişsel işlevler üzerinde farklı bir etkisi yoktu. Üç anestezi yöntemi arasında postoperatif BOMC skorlarında da istatistiksel bir fark yoktu.

Anahtar kelimeler: Anestezi, Katarakt cerrahisi, Postoperatif bilişsel işlev bozukluğu

How to cite/Atıf için: Kılıç Y, Bilgeç MD, Sarıoğlan BT, Kayhan GE, Güleç MS, Özer A. Role of anesthesia type on cognitive functions in adults undergoing cataract surgery. J Surg Med. 2020;4(12):1112-1115.

Introduction

Postoperative cognitive dysfunction (POCD) is a clinical entity characterized by progressive hypomnesia, personality changes, impaired orientation, attention, perception, consciousness, and judgment [1]. The severity of this phenomenon ranges from mild disease to a serious life-threatening form, with a reported incidence of up to 60% [2]. Therefore, POCD has become one of the most important criteria in the selection of anesthesia type in surgical patients.

In general, the incidence of POCD is higher in patients undergoing general anesthesia than those receiving other types of anesthesia. Li et al. explained this with the cholinergic disturbance related to inhalation anesthetics whereas other authors pointed out the dose of anesthesia agents [3-5]. In recent studies, some local anesthetic agents (e.g., lidocaine) have been shown to cause cognitive dysfunction due to their neurotoxic effects [6,7]. However, the impact of anesthesia type on cognitive functions has not been clearly identified yet.

Cataract surgery is one of the most frequently performed surgeries in routine practice, and can be performed under local, topical, or general anesthesia. Few studies investigated the effect of anesthesia type on POCD in patients undergoing cataract surgery in the literature, with most reporting conflicting results [8,9]. In this context, determining the impact of anesthesia type on cognitive functions following cataract surgery is of foremost importance for the accurate perioperative management of these patients.

This study aimed to investigate the impact of three anesthetic methods, including local, topical, and general anesthesia, on the development of POCD in adult patients undergoing cataract surgery.

Materials and methods

General data

Following the approval from the Ethics Committee of the Eskişehir Osmangazi University (number 24, 10 September 2019), patients who underwent elective cataract surgery at Osmangazi University between September 2019 and March 2020 were enrolled in this prospective observational study. All patients were preoperatively informed about the steps of the procedures. Written informed consent was obtained from each participant. All patients were routinely evaluated before the operation. Demographic characteristics including age, gender, and educational level, American Society of Anesthesiologist (ASA) physical status, procedural data, anesthetic techniques, and perioperative anesthesia-related complications were recorded.

Inclusion and exclusion criteria

The inclusion criteria were as follows: ASA physical status I-III, aged between 18 and 65 years, and a sufficient level of education for completion of neuropsychological tests. Patients with significant cardiovascular, respiratory, renal, hepatic, neurological disorders, serious hearing, or visual impairment, those using psychiatric drug (benzodiazepine, antidepressant, etc.) or alcohol, and allergic to the drugs involved in the study were excluded.

Anesthetic techniques

The fasting time was at least 8 hours before the operation. Patients did not have any premedication. Standard monitoring included five-lead electrocardiogram, noninvasive blood pressure measurement, pulse oximetry, and monitoring inspiratory/expiratory gas concentrations. Preanesthetic heart rate (HR) and mean arterial pressure (MAP) were noted. Patients were assigned to one of three anesthesia groups: General anesthesia (Group G), local (retrobulbar) anesthesia (Group L), and topical anesthesia (Group T).

General anesthesia was induced by propofol (2-3 mg kg^{-1}) and remifentanil (0.5 µg kg^{-1}). Following adequate loss of consciousness, airway control was provided by laryngeal mask airway (LMA). The patients received sevoflurane inhalation (2-3%) in 4 L min^{-1} medical air (50%) and oxygen (50%) and remifentanil infusion (0.1-0.2 µg kg^{-1}) to maintain anesthesia. Minimal alveolar concentration value was set at 1-1.2 throughout the surgery.

Local (retrobulbar) anesthesia was performed by the surgeon. In supine position, the inferolateral point of the inferior orbital margin was palpated while the patient's nose pointed towards the ceiling of the room. Thereafter, a blunt 25-gauge needle was inserted into subcutaneous tissue at the junction of the middle and lateral third of the orbit in the lower eyelid. While the patient was looking supranasally perpendicularly, the needle was inserted 35 mm towards the apex of the muscle cone. After aspiration to prevent intravascular injection, 3-4 ml of local anesthetic (equal mixture of 2% lidocaine and 0.5% bupivacaine) were injected. For proper distribution of the local anesthetic, the injection site was patted for 2-5 minutes.

Topical anesthesia was performed in supine position by the surgeon. Proparacaine hydrochloride (0.5%, single dose) was dropped into the conjunctival sac. Subsequently, 1% lidocaine (without additive) was applied into the anterior chamber.

HR, MAP, peripheral oxygen saturation, and end-tidal carbon dioxide were monitored continuously during the surgical procedure. Intraoperative HR and MAP values were recorded at 10^{th}, 15^{th}, and 30^{th} minutes. After the procedure, all patients were followed up in the recovery room for at least 30 minutes.

Evaluation of cognitive function

Cognitive status was evaluated by Blessed Orientation-Memory-Concentration test (BOMC), with scores ranging from 0 to 28 [10]. Each wrong answer scored one point, meaning that higher scores were associated with worse cognitive levels. The BOMC is a short cognitive screening tool, available in the public domain, which can be completed in a few minutes. This diagnostic tool consists of three main items: *Orientation* is evaluated with patient report of the current year, month, and time of day. *Concentration* is evaluated by having the patient count backward from twenty to one and say the months in reverse order. *Memory* is evaluated through delayed recall of a brief phrase. A Turkish version of BOMC test was used in the study population [11]. The patients were evaluated by BOMC test four times throughout the study: Preoperatively (baseline), and at the 1^{st} postoperative hour, day, and week.

Statistical analysis

A power analysis (G power 3.01) showed that a sample size of 15 patients per group was required to achieve 90% power

with a 5% significance level and moderate effect size (0.25) to evaluate the differences in BOMC scores between the groups. The standard version of the Statistical Package for the Social Sciences (SPSS 23.0 software, IL-Chicago-USA) was used for statistical analysis. Descriptive data were presented as number (%) and mean (SD) for categorical and continuous variables, respectively. Kruskal-Wallis and one-way ANOVA tests were used to evaluate the differences between the three groups. A *P*-value of <0.05 was considered statistically significant.

Results

A total of 77 patients with a mean age of 50.9 years (19-64 years) were included in the study. There were 42 (54.5%) females and 35 (45.5%) males. All patients were classified into three groups according to the type of anesthesia: General anesthesia group (Group G, n=27), local (retrobulbar) anesthesia group (Group L, n=23), and topical anesthesia group (Group T, n=27).

Statistically, the three patient groups were similar in gender, ASA physical status, and educational level ($P>0.05$). However, age was significantly different between the groups. Patients in the general anesthesia group were the youngest and those in the local anesthesia group were the oldest ($P<0.001$). The comparison of baseline patient characteristics is presented in Table 1.

Table 1: Comparison of baseline characteristics between the groups

	Group G (n=27)	Group L (n=23)	Group T (n=27)	*P*-value
Age (year)	42.1 (11.5)	57.6 (5.5)	54 (7.9)	<0.001
Gender				0.665
female	13 (48.1%)	14 (60.9%)	15 (55.6%)	
male	14 (51.9%)	9 (39.1%)	12 (44.4%)	
ASA status				0.282
ASA 1	10 (37%)	4 (17.4%)	12 (44.4%)	
ASA 2	16 (59.3%)	18 (78.3%)	15 (55.6%)	
ASA 3	1 (3.7%)	1 (4.3%)	0	
Educational status				0.252
elementary	15 (55.5%)	18 (69.6%)	17 (63%)	
high school	8 (29.6%)	2 (8.7%)	4 (14.8%)	
university	4 (14.8%)	3 (13%)	5 (18.5%)	
missing	0	0	1 (3.7%)	

Data are presented as mean (standard deviation) for age, n (%) for other variables

All postoperative BOMC scores in local and topical anesthesia groups were less than the baseline values. However, the postoperative 1st hour BOMC score in the general anesthesia group was insignificantly higher compared to baseline value ($P=0.554$, Wilcoxon test). A graphical representation of the mean preoperative (baseline) and postoperative BOMC scores among the three anesthesia groups is presented in Figure 1.

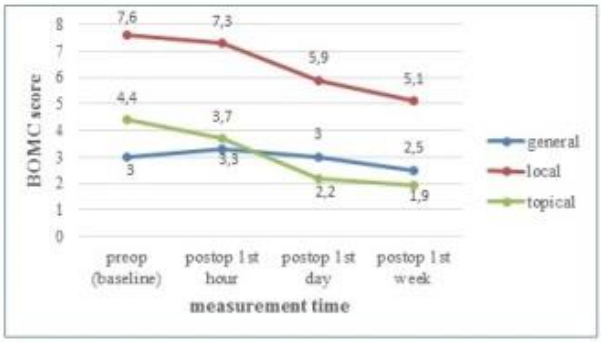


Figure 1: The mean preoperative (baseline) and postoperative (1st hour, 1st day, and 1st week) BOMC scores in three anesthesia groups

The three groups were compared with each other in terms of all HR values, MAP values, and BOMC sores (Table 2). No significant differences in baseline HR and MAP values were found between the patient groups ($P>0.05$). On the other hand, intraoperative HR and MAP values at 10th, 15th, and 30th minutes were significantly lower in general anesthesia patients compared to those in local and topical groups ($P<0.05$). Baseline mean BOMC score was higher in local anesthesia patients than in other groups ($P=0.037$) whereas postoperative BOMC scores were similar between the three groups ($P>0.05$).

Table 2: Comparison of intraoperative hemodynamic data and BOMC scores between the groups

	Group G (n=27)	Group L (n=23)	Group T (n=27)	*P*-value
HR (baseline)	74.6 (13.8)	82.8 (13.9)	80.5 (14.2)	0.083
HR (10th min)	65.4 (9.7)	78.9 (12.7)	75.3 (11.7)	<0.001
HR (15th min)	65.1 (9.8)	78.6 (13.6)	74.5 (11.1)	<0.001
HR (30th min)	65.8 (10.2)	78.6 (12.6)	73.3 (11.3)	0.001
MAP (baseline)	101.5 (17.7)	108.8 (20.1)	105.8 (11.5)	0.359
MAP (10th min)	70.2 (11.1)	105.2 (16.2)	103 (12.7)	<0.001
MAP (15th min)	69.6 (10.7)	105.1 (17.4)	101.2 (12.4)	<0.001
MAP (30th min)	68.5 (11)	106.1 (17.3)	102.1 (12.3)	<0.001
BOMC (baseline)	3 (3.9)	7.6 (6.7)	4.4 (4)	0.037
BOMC (1st hour)	3.3 (3.8)	7.3 (6.5)	3.7 (3.7)	0.050
BOMC (1st day)	3 (3.7)	5.9 (5.9)	2.2 (2.6)	0.079
BOMC (1st week)	2.5 (3.8)	5.1 (6)	1.9 (2.5)	0.219

Data are presented as mean (standard deviation) for all variables

Discussion

The present study showed that three anesthesia methods, general, local, and topical anesthesia, did not significantly affect cognitive functions in adult patients undergoing cataract surgery. Despite some methodological differences, this result was consistent with the study by Campbell et al. [9]. In another study conducted on patients undergoing cataract surgery, no differences in most cognitive testing results were found between general and local anesthesia. However, the authors showed a generalized reduction in memory performance across both anesthesia groups, contrary to our results [8]. In addition to that study, there are a limited number of studies indicating the worse effect of general anesthesia on cognitive functions in comparison to other anesthesia methods [12-14]. On the other hand, most clinical studies comparing general anesthesia with regional anesthesia types in terms of developing POCD showed no significant differences [15].

Although there is some evidence that supports the potential relationship between exposure to general anesthesia and development of neurocognitive impairment, the differences between the methodologies of the studies, including patient characteristics, variable POCD definitions, and non-standardized diagnostic tests, were the major limitations to reaching a definitive judgment on this subject [16-18]. In routine practice, the diagnosis of POCD is made by psychometric evaluation using specific neuropsychological scales such as the short BOMC test. This diagnostic scale is known to be superior to other similar tests because it is short, easy-to-understand, and based on simple scoring system [11]. It has been also shown that BOMC test has a high sensitivity rate in detecting cognitive dysfunction [19]. The other potential pitfall of the previous studies is the variable demographic characteristics of the patient cohorts. To us, pediatrics and geriatrics should differ from adults due to their special cognitive status. In the present study, patients aged between 18 and 65 years old were included to avoid possible age-related effects. We also tried to provide homogeneity of the patient groups. For this reason, anesthesia protocols were standard in each study group. Statistically, all anesthesia groups were similar in basic characteristics including gender, educational level, preoperative ASA status, preoperative HR, and MAP values. However, patients who received general

anesthesia were statistically younger than those in the other two groups. This can be explained by the traditional tendency of general anesthesia in younger and healthy individuals. In parallel to this statistical significance in age distribution, preanesthetic BOMC score was lower in general anesthesia group while the local anesthesia patients had higher scores. The fact that almost all postoperative BOMC scores were less than preoperative values was one of the most important results obtained from the present study, indicating that type of anesthesia did not have any significant effect on early postoperative cognitive status. It should be noted here that there was a mild increase in postoperative 1st hour BOMC score in the general anesthesia group, probably due to the early anesthetic effect of inhalation agents. This mild impairment in cognitive status was expected and consistent with the previous reports [20,21]. In our opinion, lower postoperative BOMC scores can be explained by the increased attention of the patients to the test questions and the absence of geriatric and pediatric patients in the study population.

In general, no sufficient evidence to recommend the use of non-general anesthesia instead of general anesthesia has been reported in a current guideline for perioperative brain health [22]. In daily practice, non-general anesthesia techniques such as local and topical anesthesia are frequently used for many surgical procedures including cataract surgery, especially in elderly or comorbid patients. The geriatric patients were beyond the scope of the present study. However, the fact that patients with general anesthesia were statistically younger than those who received topical or local anesthesia was consistent with this general approach. Indeed, the main reason for excluding patients over 65 years of age was the low preference of general anesthesia for cataract surgery in this age group due to the potential anesthesia-related morbidities, as well as providing a homogenous study cohort.

Limitations

Several limitations of the present study should be noted. First, the study was conducted in a single center, which may limit the generalization of the statistical results. Second, the relatively small number of patient groups may make it difficult to interpret subgroup findings. However, considering the limited data regarding the impact of anesthesia type on POCD in patients undergoing cataract surgery, we hope that the results obtained from the present study can contribute to the current literature. In addition, the standard anesthesia protocols and homogeneity of the patient groups were the strengths of the present study, because cognitive dysfunction following surgery is not only associated with anesthetic factors. Patient- and surgery-related factors may also contribute to this complicated entity. Finally, future large-scale studies may be required to validate the results obtained from the present study.

Conclusion

The present study showed that local, topical, and general anesthesia had no different effect on cognitive functions in adult patients undergoing cataract surgery. There was also no statistical difference in postoperative BOMC scores between the three anesthesia methods.

References

1. Fong HK, Sands LP, Leung JM. The role of postoperative analgesia in delirium and cognitive decline in elderly patients: a systematic review. Anesth Analg. 2006;102:1255-66.
2. Vatter H, Konczalla J, Seifert V. Endothelin related pathophysiology in cerebral vasospasm: what happens to the cerebral vessels? Acta Neurochir. 2011;110:177-80.
3. Casati A, Aldegheri G, Vinciguerra E, Marsan A, Fraschini G, Torri G. Randomized comparison between sevoflurane anaesthesia and unilateral spinal anaesthesia in elderly patients undergoing orthopaedic surgery. Eur J Anaesthesiol. 2003;20:640-6.
4. Li HT, Cao QJ, Qi XJ, Lu WL. Effect of anesthesia on cognitive status and MMP-2 expression in rats. Asian Pac J Trop Med. 2014;7:333-6.
5. Zywiel MG, Prabhu A, Perruccio AV, Gandhi R. The influence of anesthesia and pain management on cognitive dysfunction after joint arthroplasty: a systematic review. Clin Orthop Relat Res. 2014;472:1453-66.
6. Rundshagen I. Postoperative cognitive dysfunction. Dtsch Arztebl Int. 2014;111:119-25.
7. Fathy W, Hussein M, Khalil H. Effect of local anesthesia (with lidocaine vs bupivacaine) on cognitive function in patients undergoing elective cataract surgery. Local Reg Anesth. 2019;12:1-6.
8. Karhunen U, Jönn G. A comparison of memory function following local and general anaesthesia for extraction of senile cataract. Acta Anaesthesiol Scand. 1982;26:291-6.
9. Campbell DN, Lim M, Muir MK, O'Sullivan G, Falcon M, Fison P, et al. A prospective randomised study of local versus general anaesthesia for cataract surgery. Anaesthesia. 1993;48:422-8.
10. Upadhyaya AK, Rajagopal M, Gale TM. The Six Item Cognitive Impairment Test (6-CIT) as a screening test for dementia: comparison with Mini-Mental State Examination (MMSE). Curr Aging Sci. 2010;3:138-42.
11. Kalem ŞA, Öktem Ö, Emre M. [Kısa Blessed Oryantasyon-Bellek-Konsantrasyon Test (BOMC) ve Standardize Mini Mental Test (SMMT) betimsel istatistik değerlerinin bir normal erişkin Türk örnekleminde saptanması]. In Turkish. Arch Neuropsychiatry. 2002;39:95-102.
12. Hole A, Terjesen T, Breivik H. Epidural versus general anaesthesia for total hip arthroplasty in elderly patients. Acta Anaesthesiol Scand. 1980;24:279-87.
13. Jones MJ, Piggott SE, Vaughan RS, Bayer AJ, Newcombe RG, Twining TC, et al. Cognitive and functional competence after anaesthesia in patients aged over 60: controlled trial of general and regional anaesthesia for elective hip or knee replacement. BMJ. 1990;300:1683-7.
14. Mandal S, Basu M, Kirtania J, Sarbapalli D, Pal R, Kar S, et al. Impact of general versus epidural anesthesia on early postoperative cognitive dysfunction following hip and knee surgery. J Emerg Trauma Shock. 2011;4:23-8.
15. Davis N, Lee M, Lin AY, Lynch L, Monteleone M, Falzon L, et al. Postoperative cognitive function following general versus regional anesthesia, a systematic review. J Neurosurg Anesthesiol. 2014;26:369-76.
16. Mason SE, Noel-Storr A, Ritchie CW. The impact of general and regional anesthesia on the incidence of postoperative cognitive dysfunction and postoperative delirium: a systematic review with meta-analysis. J Alzheimers Dis. 2010;22:67-79.
17. Silbert BS, Evered LA, Scott DA. Incidence of postoperative cognitive dysfunction after general or spinal anaesthesia for extracorporeal shock wave lithotripsy. Br J Anaesth. 2014;113:784-91.
18. Belrose JC, Noppens RR. Anesthesiology and cognitive impairment: a narrative review of current clinical literature. BMC Anesthesiol. 2019;19:241.
19. Aranake-Chrisinger A, Cheng JZ, Muench MR, Tang R, Mickle A, Maybrier H, et al. Ability of postoperative delirium to predict intermediate-term postoperative cognitive function in patients undergoing elective surgery at an academic medical centre: protocol for a prospective cohort study. BMJ Open. 2018;8:e017079.
20. Meineke M, Applegate RL, Rasmussen T, Anderson D, Azer S, Mehdizadeh A, et al. Cognitive dysfunction following desflurane versus sevoflurane general anesthesia in elderly patients: a randomized controlled trial. Med Gas Res. 2014;4:6.
21. Poorzamany Nejat Kermany M, Dahi M, Yamini Sharif R, Radpay B. Comparison of the effects of dexmedetomidine and remifentanil on cognition state after cataract surgery. Anesth Pain Med. 2016;6:e33448.
22. Berger M, Schenning KJ, Brown CH, Deiner SG, Whittington RA, Eckenhoff RG, et al. Best practices for postoperative brain health: recommendations from the fifth international perioperative neurotoxicity working group. Anesth Analg. 2018;127:1406-13.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1116-1119.
DOI: 10.28982/josam.839908

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Retropharyngeal approach in cervical disc hernias

Servikal disk hernilerinde retrofarengeal yaklaşım

Şükrü Oral [1]

[1] **Department of Neurosurgery, Kayseri City Hospital Kocasinan, Kayseri, Turkey**

ORCID ID of the author(s)
ŞO: 0000-0003-4328-0690

Corresponding author/Sorumlu yazar:
Şükrü Oral
Address/Adres: Kayseri Şehir Hastanesi Nöroşirurji Kliniği, Kocasinan, Kayseri, Türkiye
E-mail: sukruor@yahoo.com

Ethics Committee Approval: Kayseri City Hospital Ethics Committee approval (Decision number: 213, Approval date: 15.10.2020) was obtained. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Kayseri Şehir Hastanesi Etik Kurul onayı (Karar no: 213, Onay tarihi: 15.10.2020) alındı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: High-level disc hernias are rare pathologies encountered in clinical practice. Treatment is more difficult than other cervical disc hernias. In this study, we aimed to convey our clinical experience in C2-3 and C3-4 disc herniations, also presenting the complications we encountered during surgical treatment.

Methods: In this retrospective cohort study, we reviewed the clinical and radiological records of 42 patients we operated between 2010-2019. Magnetic resonance imaging, computed tomography and direct radiographs were utilized as imaging modalities. Anterior retropharyngeal approach was the preferred surgical method. The modified Japanese Orthopedic Association (mJOA) score and Nurick Scale were used in clinical follow-up and physical examination of these patients.

Results: Among all patients, the most common symptom was severe pain radiating from the neck to the occipital region. The mean age was 54.14 years. The average mJOA scores were 15.1 in the preoperative period and 17 in the postoperative sixth month. We observed that 83.3% of our patients had an mJOA recovery rate of fifty percent and above. All but seven patients' complaints improved well after treatment. There was a negative correlation between symptom duration and recovery rate (P=0.003, Correlation Coefficient r=-0.449). The rate of recovery was lower in patients with a longer duration of symptoms. Three of our patients developed difficulty in swallowing after the operation and recovered within four weeks with diet and exercise.

Conclusion: We determined that retropharyngeal approach is a safe option for disc hernias at the upper cervical level. However, long operation time and excessive retraction during surgery may lead to complications such as difficulty in swallowing due to the stretching of the neural structures.

Keywords: Cervical disc hernia, Anterior retropharyngeal approach, Dysphagia

Öz

Amaç: Bilindiği gibi yüksek düzey disk hernileri klinik pratikte karşılaştığımız nadir patolojilerdir. Tedavisi diğer boyun fıtıklarına göre daha zordur. Bu çalışmada üst düzey servikal disk hernilerindeki (C2-3 ve C3-4) klinik deneyimlerimizi aktarmak istedik. Ayrıca, cerrahi yaklaşımda karşılaştığımız komplikasyonları da anlattık.

Yöntemler: Çalışmamızda geçmiş yıllarda (2010-2019) ameliyat ettiğimiz kırk iki hastanın klinik ve radyolojik kayıtlarını geriye dönük olarak gözden geçirdik. Hastaların görüntüleme testlerinde manyetik rezonans görüntüleme, bilgisayarlı tomografi ve direkt radyografilerden yararlanıldı. Cerrahi yöntem olarak anterior retrofarengeal yaklaşım kullanıldı. Hastaların değerlendirmelerinde klinik takip ve fizik muayenede modifiye Japon Ortopedi Derneği (mJOA) skoru ve Nurick Skalası kullanıldı.

Bulgular: Hastalarda en sık görülen semptom, boyundan oksipital bölgeye yayılan şiddetli ağrıdır. Hastaların ortalama yaşı 54,14 idi. Hastalarımızın ortalama mJOA skoru preoperatif dönemde 15,1, postoperatif altıncı ayda 17 olarak ölçüldü. Hastalarımızın %83,3'ünde mJOA iyileşme oranının yüzde elli ve üzerinde olduğu, %16,7'sinin ise yüzde 50'nin altında olduğu görüldü. Yedi hasta dışında hastaların şikayetleri tedaviden sonra düzeldi. Semptom süresi ile iyileşme oranı arasında negatif korelasyon vardı (P=0.003, Korelasyon Katsayısı r=-0.449). Semptom süresi daha uzun olan hastalarda iyileşme oranının daha düşük olduğu görüldü. Ameliyattan sonra üç hastamız yutma güçlüğü geliştirdi. Hastamız diyet ve egzersizle dört hafta içinde iyileşti.

Sonuçlar: Çalışmamız sonucunda retrofaringeal yaklaşımın üst servikal seviyedeki disk hernileri için güvenli bir seçenek olduğunu bulduk. Ancak ameliyat sırasında uzun ameliyat süresinden ve aşırı geri çekilmeden kaçınmazsak, sinir yapılarının gerilmesinden dolayı yutma güçlüğü gibi komplikasyonlarla karşılaşabiliriz.

Anahtar kelimeler: Servikal disk hernisi, Anterior retrofarengeal yaklaşım, Yutma güçlüğü

How to cite/Atıf için: Oral Ş. Retropharyngeal approach in cervical disc hernias. J Surg Med. 2020;4(12):1116-1119.

Introduction

A herniated disc in the cervical spine is usually located at C5-6 and C6-7 levels. However, the cervical herniated disc at the C2-3 segment is extremely rare [1], and usually occurs in elderly patients. Similarly, disc herniation at C3-4 level is an uncommon pathology and constitutes between 4-8% of all cervical disc hernias. The approach to the upper cervical region is highly challenging because of the mandible and the complex anatomy [2-4]. Several techniques have been described for approaching this region, such as anterolateral extradural, trans-corporeal, posterior extradural, transoral, anterior retropharyngeal and submandibular parapharyngeal approaches [5-9]. In this study, we shared our experience with 42 patients who were operated for cervical disc hernia at the C2-3 and C3-4 levels between June 2010-June 2019. Anterior retropharyngeal approach was our preferred technique. Our research in the literature showed that there are small case series about upper cervical disc hernias or a small section among larger cervical disc hernia series. Accordingly, our study includes the largest case series ever written on this subject.

Materials and methods

We operated forty-two patients who underwent surgical treatment due to C2-3 and C3-4 level disc herniation from June 2010 to June 2019 in our department. The patients' data were collected retrospectively from hospital records, including patients' demographic information, operative details, clinical outcomes, and radiological images (Table 1). All patients were evaluated with magnetic resonance imaging (MRI), cervical roentgenograms and computerized tomography (CT) (Figure 1). The modified Japanese Orthopedic Association (mJOA) score and Nurick Scale were used in the clinical follow-up and physical examination of the patients. The improvement rate of mJOA was calculated using the Hirabayashi method ((postoperative mJOA-preoperative mJOA)/(18-preoperative mJOA) x 100) [10]. The mJOA recovery rate of 50 percent or more was considered satisfactory. We used a sub-axial anterior retropharyngeal approach to remove the herniated disc from C2-3 and C3-4 disc space. Sample cases in our series are shown in Figure 1, 2 and Figure 3. A cervical collar was prescribed to the patients for use during the first four postoperative weeks. Exercise and diet program were applied to patients who had difficulty swallowing. Shaker exercise was taught to the patients and prescribed as a home program for four weeks every other day, 3 days a week and once a day. It was suggested that the amount of food intake at each meal be reduced. The clinical and radiographic outcomes were recorded and analyzed.

Surgical technique

All patients were operated under general anesthesia. The patient was placed in the supine position with hyperextension of the neck. A transverse incision was made from the anterior margin of the sternocleidomastoid muscle and extended until the anterior cervical midline of the C3 level. Then, the platysma and superficial fascia was incised horizontally. The facial artery and submandibular gland were retracted supero-laterally. The deep cervical fascia was divided, the pre-tracheal fascia was bluntly dissected, and carotid pulse was palpated. The prevertebral fascia was incised. A plane was created to reveal the cervical spine by cutting the prevertebral fascia between the medial border of the carotid sheath and the midline of the spinal column. After this stage, the vascular and neural structures at high cervical levels were dissected and retracted, and C2-3 and C3-4 disc spaces were reached. In two of our patients, the facial vein was ligated because it narrowed the surgical area. The disc contents and endplates were removed. The cervical Polyetheretherketone (PEEK) cage and auto graft were implanted.

Statistical analysis

Frequency and percentage, mean value, standard deviation, min-max are used for descriptive statistics. Shapiro-Wilk test was used to evaluate the normality of distribution of the quantitative variables, unpaired and paired T tests were utilized for comparison of normally distributed independent and dependent variables, respectively. Pearson Correlation Coefficient was used to show the relationship between variables. $P<0.05$ was considered statistically significant.

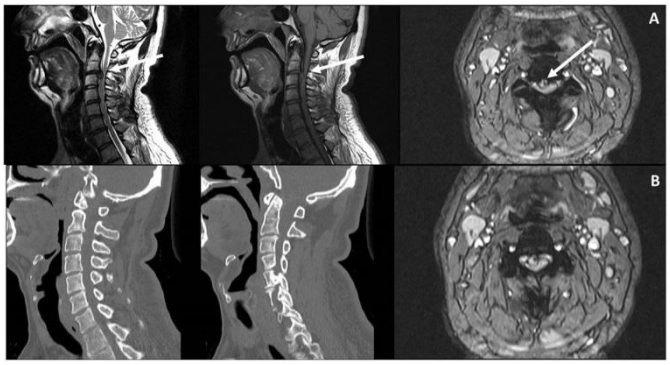


Figure 1: 38 /M He had severe pain in the right arm and suboccipital area for three months, no loss of motor function and a positive Hofmann reflex. A-In the preoperative period, C2-3 level discs are shown on the sagittal T1-T2 weighted MRI and axial-T2 MRI. B-Sagittal CT images and axial-T2 MRI show the C2-3 level disc.

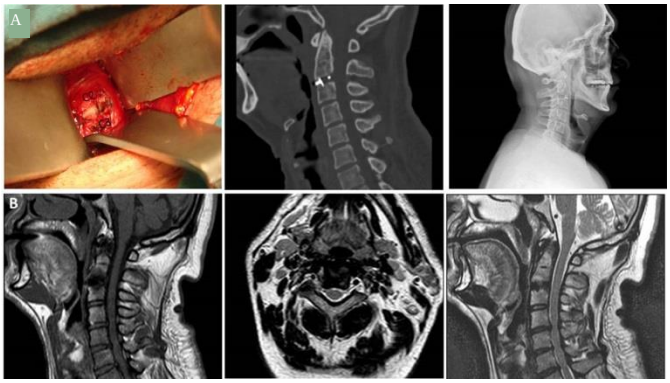


Figure 2: A- The intraoperative photograph of the C2-3 level is shown in the first box, followed by its postoperative images in sagittal CT and Lateral Cervical Spine Radiograph. B-In the postoperative period, C2-3 level disc was removed, which is demonstrated on the T1-sagittal, T2-axial and T2- Sagittal MRI images.

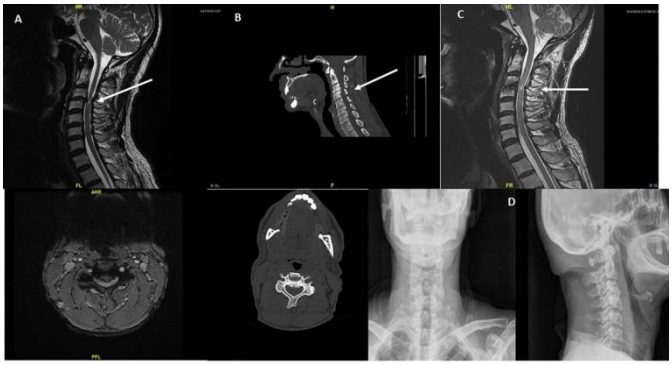


Figure 3: 51/M He complained of neck pain and had mild difficulty in buttoning and walking but could perform these without help. A- T2 sagittal and axial MRI sequence showing C3-4 disk herniation B- Sagittal and Axial CT scan of the spine revealed the C3-4 level C- Postoperative T2 sagittal MRI showing decompression D- Postoperative X-ray images revealed the peek cage

Results

In this study, 42 patients, 32 males and 10 females, were operated during a nine-year period. The mean age of all patients was 54.14 years. Suboccipital and neck pain was the most common symptom. Nine patients presented with signs of myelopathy, including gait difficulty and motor loss in the distal muscle groups of the upper extremities. In addition, their hand skills were severely reduced, and Hoffman's Sign was positive in physical examination. The mean duration of symptoms was 7.4 months. The patients were followed up for 23.1 months. Clinical symptoms and signs in the patients improved in the postoperative period except for seven patients. The mean preoperative Nurick score was 0.73. The average mJOA score of our patients was 15.1 in the preoperative period and 17 in the postoperative sixth month. Among all, 83.3% of our patients had a mJOA recovery rate of fifty percent and above. The mean mJOA recovery rate was 69.9%. There was a negative correlation between duration of symptoms and recovery rate (P=0.003, Correlation Coefficient=-0.449). The rate of recovery was lower in patients with a longer duration of symptoms (P=0.003). The mean duration of operation was 135.9 minutes, with 148 minutes for repair of hernias at C2-3, and 133.9 minutes for those at C3-4 (P=0.093). Mild dysphagia developed in three patients, who recovered in four weeks. The mean operative time of patients with postoperative swallowing difficulties was 184 minutes, while it was 132.2 minutes in patients without complications. This difference was statistically significant and there was a significant relationship between dysphagia and duration of surgery (P=0.004) (Table 2). Superficial wound infection developed in two patients, whose wounds healed within two weeks with antibiotic treatment and wound care.

Table 1: Demographic and clinical information of the patients

	Number of Patients	Minimum	Maximum	Mean	SD
Age	42	38	76	54.14	9.67
Follow-up Time (Month)	42	8	48	23.12	11.10
Preoperative Modified JOA Score	42	12	16	15.17	1.32
Postoperative Modified JOA Score	42	15	18	17.00	1.01
Preoperative Nurick Score	42	0	2	0.74	0.79
Recovery Rate of Modified (JOA	42	33.33	100	69.9	25.30
Duration of Symptoms (Month)	42	4	17	7.38	3.49
OperationTime(Minute)	42	110	190	135.98	18.90

Table 2: Statistical outcomes

Values		Number of Patients	Mean/SD	*P*-value
Modified JOA Score	Preoperative	42	15.17 (1.32)	0.001
	Postoperative	42	17.00 (1.01)	
Operation Time(minute)	Dysphagia	3	184.00 (7.21)	0.001**
	Other Patients	39	132.28 (13.66)	
Operation Time(minute)	C2-3 Level	6	148.00 (18.64)	0.093**
	C3-4 Level	36	133.97 (18.44)	
Duration of Symptoms (Month)	Complications	7	10.71 (3.59)	0.004**
	No complications	35	6.71 (3.11)	

* Paired t-Test, ** Unpaired t-test (Student t-Test)

Discussion

Cervical disc herniations are one of the stages of the spinal degeneration and often occur in the third and fourth decades. C5-6 and C6-7 levels are the most frequently affected segments. Anterior cervical discectomy and fusion is a method in which spinal cord and roots are relieved with decompressive surgery [1]. Fusion and sagittal balance are achieved using a cage [1,9]. Spine surgeons often prefer this method in cervical disc pathologies.

C2-3 and C3-4 level disc herniations are usually seen in the elderly population. Etiology is still unclear. However, there are some opinions in the elderly population that upper cervical level disc hernia develops because of the increase in upper segments due to spondylosis, which develops over time at C5-6 and C6-7 levels. It is less common in the younger population [3]. In our series, the mean age was in harmony with the literature. The side approach to the cervical spine involves surgical difficulties due to vertebral artery and nerve roots [8]. Anterior approach to the cervical spine is commonly preferred by surgeons during cervical disc surgery, because of anatomic orientation [4,5,7]. Since high level hernia is exceedingly rare, there are a limited number of studies in the literature about this subject. Various techniques for approaching C2-3 and C3-4 discs are defined, including posterolateral intradural, anterolateral extradural, trans-corporeal, anterior retropharyngeal, and submandibular approaches [6,8,11]. We preferred the anterior retropharyngeal approach, which is almost identical to the submandibular approach. This method is mostly preferred in clinical trials, as reported in the literature [4, 5, 7]. In this approach, many surgeons emphasized that the head should be tilted at least 30 degrees to the opposite side [2, 4, 5], so that the mandible does not prevent performing the surgery comfortably [4,5]. Undeniably, all approaches have their own risks. Russo et al. stated that the C2-3 level disc was an obstacle in the standard anterior approach, as the internal branch of the superior laryngeal nerve enters the thyroid membrane just below the C3 vertebra. Superior laryngeal nerve damage leads to permanent change in phonation and increases the risk of aspiration [4]. In our study, there was no related complication. Nishizawa et al. performed C2-3 discectomy using posterolateral intradural approach in 3 elderly patients and did not encounter any complications in their follow-up. However, since C1-C3 laminectomy and suboccipital craniectomy are performed in this technique, it is likely that it may cause instability in the long term, especially in young patients. Again, there is a risk of developing cerebrospinal fluid fistula and meningitis because the dura mater is opened. There are no such risks in the anterior approach we use.

Anterior approaches are not without complications, as well. Finn et al. used an anterior retropharyngeal approach in their series, which included 11 cases. They stated that 4 patients developed dysphagia, of which three resolved, and one patient developed mild permanent dysphonia [9]. Structural pharyngoesophageal lesions, which are among the causes of oropharyngeal dysphagia, include oropharyngeal and esophageal carcinoma, benign tumors, esophageal web, Zenker's diverticulum, inflammatory diseases, postoperative changes, foreign bodies, thyroid enlargements, vertebral spur, cervical lymphadenopathy, and vascular anomalies. Anterior cervical spinal fusion surgery may temporarily impair pharyngeal swallowing function. It has been reported many times in the literature that anterior interventions in cervical spine surgery can temporarily impair swallowing function. Behavioral changes, postural changes, swallowing exercises and diet programs

constitute the basis of treatment in oropharyngeal swallowing difficulties [12,13]. In our series, three patients had difficulty swallowing and recovered within four weeks with exercise and diet.

The most common complications in the anterior retropharyngeal approach are dysphonia and difficulty swallowing [9,14]. To prevent these complications, it was recommended that the skin incision be performed at least 2 cm below the mandible and excessive retraction of trachea and esophagus during the operation be avoided [5,14,15]. Anderson et al. made a number of recommendations to prevent the development of postoperative dysphagia, some of which include keeping the operation time under one hundred seventy-five minutes, and the endotracheal tube pressure below 20 mm Hg, using small and smooth surface retractors, local steroid injection to the retropharyngeal area (triamcinolone 40 mg), and working with speech therapists and otolaryngologists in high risk cases [12]. According to our results, the longer the operation time, the higher the risk of developing dysphagia.

In their cadaveric study, Fard and his colleagues indicated that some anatomical structures blocking the surgical corridor can be divided, such as ascending pharyngeal artery and vein, lingual artery and vein, facial artery vein, retromandibular vein (temporo-maxillary vein, posterior facial vein) and digastric tendinous junction [16]. In our study, we had to ligate the facial vein in two patients with no complications.

Limitations

The surgical method we used in the study is unfortunately exceedingly difficult to apply in short-necked and obese patients. Therefore, these patients were not included in the study. Also, since disc hernias at the C2-3 and C3-4 levels are rare, they cannot be compared with other surgical methods. A larger number of patients and longer follow-up periods could improve the quality of the study, which may take many years, based on the low incidence of this disease.

Conclusion

Compared to other approaches, less complications occur in the anterior retropharyngeal approach. Since most complications are due to excessive retraction and long operation time, we suggest avoiding both, if possible. In addition, the benefit from surgery decreases as the duration of symptom increases. We think this result will help us better inform our patients about surgical treatment and its results. Likewise, it would be more appropriate to choose posterior approaches in patients with short necks.

References

1. Jomin M, Lesoin F, Lozes G, Thomas CE 3rd, Rousseaux M, Clarisse J. Herniated cervical discs. Analysis of a series of 230 cases. Acta Neurochir (Wien). 1986;79(2-4):107-13.
2. McAfee PC, Bohlman HH, Riley LH Jr, Robinson RA, Southwick WO, Nachlas NE. The anterior retropharyngeal approach to the upper part of the cervical spine. J Bone Joint Surg Am. 1987 Dec;69(9):1371-83.
3. Nishizawa S, Yokoyama T, Yokota N, Kaneko M. High cervical disc lesions in elderly patients--presentation and surgical approach. Acta Neurochir (Wien). 1999;141(2):119-26.
4. Russo A, Albanese E, Quiroga M, Ulm AJ. Submandibular approach to the C2-3 disc level: microsurgical anatomy with clinical application. J Neurosurg Spine. 2009 Apr;10(4):380-9.
5. Park SA, Lee JH, Nam YS, An X, Han SH, Ha KY. Topographical anatomy of the anterior cervical approach for c2-3 level. Eur Spine J. 2013 Jul;22(7):1497-503.
6. Shim CS, Jung TG, Lee SH. Transcorporeal approach for disc herniation at the C2-C3 level: a technical case report. J Spinal Disord Tech. 2009 Aug;22(6):459-62.
7. Skaf GS, Sabbagh AS, Hadi U. The advantages of submandibular gland resection in anterior retropharyngeal approach to the upper cervical spine. Eur Spine J. 2007 Apr;16(4):469-77.
8. Türe U, Güçlü B, Naderi S. Anterolateral extradural approach for C2-C3 disc herniation: technical case report. Neurosurg Rev. 2008 Jan;31(1):117-21; discussion 121.
9. Finn MA, MacDonald JD. C2-C3 Anterior Cervical Fusion: Technical Report. Clin Spine Surg. 2016 Dec;29(10): E536-E541.
10. Hirabayashi K, Satomi K. Operative procedure and results of expansive open-door laminoplasty. Spine (Phila Pa 1976). 1988 Jul;13(7):870-6.
11. Kotil K, Sengoz A. The management in the C2-C3 disc herniations: a clinical study. Turk Neurosurg. 2011 Jan;21(1):15-21.
12. Anderson KK, Arnold PM. Oropharyngeal Dysphagia after anterior cervical spine surgery: a review. Global Spine J. 2013 Dec;3(4):273-86.
13. Logemann JA, Larsen K. Oropharyngeal dysphagia: pathophysiology and diagnosis for the anniversary issue of Diseases of the Esophagus. Dis Esophagus. 2012 May;25(4):299-304.
14. Orestes MI, Chhetri DK. Superior laryngeal nerve injury: effects, clinical findings, prognosis, and management options. Curr Opin Otolaryngol Head Neck Surg. 2014 Dec;22(6):439-43.
15. Park SH, Sung JK, Lee SH, Park J, Hwang JH, Hwang SK. High anterior cervical approach to the upper cervical spine. Surg Neurol. 2007 Nov;68(5):519-24; discussion 524.
16. Fard SA, Patel AS, Avila MJ, Sattarov KV, Walter CM, Skoch J, et al. Anatomic considerations of the anterior upper cervical spine during decompression and instrumentation: a cadaveric based study. J Clin Neurosci. 2015 Nov;22(11):1810-5.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1120-1123.
DOI: 10.28982/josam.833018

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Can systemic inflammation markers obtained from complete blood count in the first trimester play a role in predicting early pregnancy loss?

İlk trimesterde tam kan sayımından elde edilen sistemik inflamasyon belirteçleri erken gebelik kaybını tahmin etmede rol oynayabilir mi?

Derya Kanza Gül [1]

[1] **Department of Gynecology and Obstetrics, Medipol University School of Medicine Health, Istanbul, Turkey**

ORCID ID of the author(s)
DKG: 0000-0001-8879-9299

Corresponding author/Sorumlu yazar:
Derya Kanza Gül
Address/Adres: Medipol Üniversitesi Tıp Fakültesi Sağlık Kadın Hastalıkları ve Doğum Anabilim Dalı, İstanbul, Türkiye
E-mail: deryakanza@yahoo.com

Ethics Committee Approval: The study was approved by the Istanbul Medipol University Clinical Research Ethics Committee (Reference number: 10840098-772.02-E.58403 Date: 16/10/2020). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma, İstanbul Medipol Üniversitesi Klinik Araştırmalar Etik Kurulu tarafından onaylandı (Referans numarası: 10840098-772.02-E.58403 Tarih: 16/10/2020). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: Ten percent of pregnancies result in early pregnancy loss, and in 40%, the cause is unknown. The purpose of this study is to evaluate the relationship between first trimester hematological inflammatory markers and early pregnancy loss.

Methods: This retrospective case-control study was conducted at Department of Obstetrics and Gynecology at The Private Nisa Hospital between 1 January 2015 and 1 October 2020. A total of 611 patients were evaluated, including 310 patients with early pregnancy loss, and 301 patients, who were included in the study as the healthy control group. Sociodemographic data and complete blood count results of the groups were obtained by scanning hospital files and computer registration systems.

Results: No statistically significant differences were detected between the two groups in terms of Red Cell Distribution Width (RDW), plateletcrit (PCT), Eosinophil and NLR (Neutrophil Lymphocyte Ratio) values (P>0.05 for all). In the early pregnancy loss group, PLT(P=0.004), MPV(P<0.001), PDW(P=0.005), PLR (platelet lymphocyte ratio) (P<0.001), ELR (eosinophil lymphocyte ratio) (P<0.001), and ENR (eosinophil neutrophil ratio) (P=0.004) values were higher, while WCB (P<0.001), Hemoglobin (P=0.007), Neutrophil (P<0.001), and Lymphocyte (P<0.001) values were lower, compared to the healthy control group.

Conclusions: PLT, MPV, PDW, PLR, ELR and ENR were related with early pregnancy loss. Inflammation markers, thrombocyte activation markers and allergy markers obtained from Complete Blood Count (CBC) in the first trimester pregnancy constitute a cost-effective, and easy method to predict early pregnancy loss.

Keywords: Early pregnancy loss, Systemic inflammation, Inflammatory markers, Thrombocyte activation markers, Allergy markers

Öz

Amaç: Tüm gebeliklerin %10'u erken gebelik kaybıyla sonuçlanır ve % 40'ında neden bilinmemektedir. Bu çalışmanın amacı ilk trimester hematolojik inflamatuar belirteçleri ile erken gebelik kaybının arasındaki ilişkiyi değerlendirmektir

Yöntemler: Bu retrospektif vaka kontrol çalışması 1 Ocak 2015- 1 Ekim 2020 tarihleri arasında Özel Nisa Hastanesi Kadın Hastalıkları ve Doğum Anabilim Dalı'nda yapılmıştır. Erken gebelik kaybı olan 310 hasta ve sağlıklı kontrol grubu olarak 301 hasta olmak üzere toplamda 611 hasta değerlendirildi. Grupların sosyodemografik verilerine ve tam kan sayımı sonuçları hastane dosyaları ve bilgisayar kayıt sistemleri taranarak elde edildi.

Bulgular: Her iki grup arasında RDW, PCT, Eosinofil ve NLR düzeylerinde açısından istatistiksel olarak anlamlı fark yoktu (tümü için P>0,05). Erken gebelik kayıplı grupta sağlıklı kontrol grubuna kıyasla WCB (P<0,001), hemoglobin (P=0,007), Nötrofil (P<0,001) ve Lenfosit (P<0,001) değerleri daha düşük iken PLT (P=0,004), MPV (P<0,001), PDW (P=0,005), PLO (platelet lenfosit oranı) (P<0,001), ELO (eosinofil lenfosit oranı) (P<0,001) ve ENO (eosinofil nötrofil oranları) (P=0,004), değerleri istatistiksel olarak anlamlı düzeyde yüksek olduğu saptandı (P<0,05).

Sonuç: PLT, MPV, PDW, PLO, ELO ve ENO erken gebelik kaybı ile güçlü bir şekilde ilişkiliydi. İlk trimesterde yapılan Tam kan sayımından den elde edilen trombosit ve alerji belirteçleri fetal kayıpları tahmin etmek için kullanılabilecek ekonomik ve güvenli bir yöntemdir.

Anahtar kelimeler: Erken gebelik kaybı, Sistemik inflamasyon, İnflamasyon belirteçleri, Trombosit aktivasyon belirteçleri, Alerji belirteçleri

How to cite/Atıf için: Gül DK. Can systemic inflammation markers obtained from complete blood count in the first trimester play a role in predicting early pregnancy loss? J Surg Med. 2020;4(12):1120-1123.

Introduction

Early pregnancy loss is the absence of the embryo or heartbeat in the gestational sac in the first trimester of pregnancy [1]. Ten percent of all pregnancies result in early pregnancy loss. A total of 80 % of pregnancy losses are detected within the first twelve gestational weeks [1,2]. Genetic, infectious, endocrinologic, anatomical, and immunologic implantation abnormalities are known causes in its etiology. The cause is unknown in 40% of early pregnancy losses [3,4].

In the literature, it has been stated that systemic inflammatory markers are important in pathogenesis [5]. The aim of this study was to compare systemic inflammation markers obtained from the complete blood counts (CBC) of pregnant women in their first trimester, including white blood cell count (WBC), hemoglobin (Hb), neutrophil, lymphocyte, platelet distribution width (PDW), platelet count (PLT), mean platelet volume (MPV), neutrophil to lymphocyte ratio (NLR), eosinophil to lymphocyte ratio (ELR), platelet to lymphocyte ratio (PLR), and eosinophil to neutrophil ratio (ENR), to predict early pregnancy loss. All the above-mentioned markers are easy to obtain and cost-effective [6,7]. They are used to predict inflammatory diseases, complicated pregnancies, gynecological cancers [8], ovarian hyperstimulation syndrome [9], early ovarian failure [10], endometriosis [11], hyperemesis gravidarum [12], gestational diabetes [13], preeclampsia [14], intrahepatic pregnancy cholestasis [15] in numerous studies in the literature.

Materials and methods

The study was approved by Istanbul Medipol University Clinical Research Ethics Committee and conducted in accordance with the 1964 Helsinki Declaration and local guidelines regarding studies with human participants. Written approval was obtained from Private Nisa Hospital before the data collection phase (Reference number: 10840098-772.02-E.58403 Date: 16/10/2020).

This retrospective case control study reviewed the data of the pregnant patients who were followed up in Yenibosna Private Nisa Hospital Maternity Outpatient Clinic between January 1, 2017 and October 1, 2020, which were obtained from the hospital files and hospital registry.

Patients between the ages of 18-35 years with pregnancy losses in the first trimester were included in the study group, while those within the same age range who gave live births at ≥37 gestational weeks were included in the control group.

Patients with insufficient data, multiple pregnancy, a history of recurrent miscarriage or infertility, any other medical conditions, known thrombophilia, complicated pregnancy, and congenital uterine anomalies, smokers, along with those requiring chronic drug treatment, were excluded from the study.

The study was based on chart review. Among 8937 patients, a total of 611 patients were evaluated in the present study, including 310 patients with early pregnancy loss who met the inclusion and exclusion criteria, and 301 patients as the healthy control group.

The medical data of the patients were examined, and the age, gravida, parity, gestational week, Body Mass Index (BMI=Weight (kg) Height^{-2} (m)) of the patients were recorded.

The basal complete blood count values of patients with early pregnancy loss were obtained as they first visited our clinic, when fetal heart beats were observed, and that of patients who carried healthy pregnancies to term were obtained during their first visit for routine pregnancy follow-up. The blood samples were drawn into tripotassium ethylene diamine tetra acetic acid (EDTA) tubes. All hematological parameters were analyzed with a Beckman Coulter Blood Count Analyzer (XT2000i, Sysmex, Osaka, Japan) 15 minutes after drawing blood.

Statistical analysis

Numbers (n), percentages (%), mean, Standard Deviation (SD), Standard Error (SE), median, Interquartile Range (IQR), minimum (Min) and maximum (Max) values were used in the analysis of the data. The fitness of the data to normal distribution was tested with Kolmogorov-Smirnov Test. Mann Whitney-U test was used to compare intergroup mean values. ROC Analysis was performed to determine the cut-off values. Statistical significance level was $P<0.05$. The data were analyzed with SPSS 22.0 Statistical Package Program.

Results

The two groups were similar in terms of age, BMI, gravida, and parity, and both groups were homogenous with regards to these characteristics ($P>0.05$ for all) (Table 1).

Table 1: Demographic and clinical features

Variables	Control group (n=301) Mean (SD)	Median	Min-Max	Early pregnancy loss group (n=310) Mean (SD)	Median	Min-Max	*P*-value
Age (year)	31.96 (5.59)	32	17-40	32.29 (5.15)	33	17-42	0.478
BMI (kg/m^2)	28.43 (2.96)	28.04	22.04-40.15	28.81 (3.38)	28.58	22.03-40.15	0.418
Gravida(number)	1.98 (0.99)	2	1-6	1.90 (0.93)	2	1-6	0.469
Parity(number)	0.98 (0.99)	1	0-5	0.90 (0.92)	1	0-5	0.445

Mann-Whitney U, BMI: Body mass index

The comparison of laboratory results of the groups is shown in Table 2. There were significant differences between the groups in terms of WBC ($P<0.001$), hemoglobin ($P=0.007$), PLT ($P=0.004$), MPV ($P<0.001$), PDW ($P=0.005$), neutrophil ($P<0.001$) and lymphocyte ($P<0.001$) values. PLR ($P<0.001$), ELR ($P<0.001$), and ENR ($P=0.004$) were significantly higher in patients with early pregnancy loss.

The ROC analysis of the predictive performance of PLR for early pregnancy loss is shown in Figure 1. The area under the curve was 0.681 (0.022) (95% Confidence Interval (CI), 0.639-0.723). The best PLR cut-off value was 113.71, with 68.1% sensitivity, and 42.7% specificity for early pregnancy loss prediction.

The ROC analysis of the predictive performance of ELR for early pregnancy loss is presented in Figure 2. The area under the curve was 0.591(0.023) (95% CI, 0.545-0.636). The best ELR cut-off value was 0.04, with 59.0% sensitivity and 45.3% specificity for early pregnancy loss prediction.

The ROC analysis of the predictive performance of ENR for early pregnancy loss is shown in Figure 3. The area under the curve was 0.567(0.023) (95% CI, 0.522-0.613). The

best ENR cut-off value was 0.01, with 56.8% sensitivity, and 43.2% specificity for early pregnancy loss prediction.

Table 2: Laboratory values of the groups

Parameters	Control group (n=301) Mean (SD)	Median	Min-Max	IQR	Early pregnancy loss group (n=310) Mean (SD)	Median	Min-Max	IQR	*P*-value*
WBC(/mm³×10³)	9.45 (2.73)	9.14	2.48-27.40	3.30	8.38 (2.71)	7.89	0.16-21.60	2.81	<0.001
HB(g/dL)	11.76 (1.18)	11.80	8.30-17.20	1.60	11.96 (1.24)	12.10	8.00-14.80	1.53	0.007
RDW(%)	14.29 (7.16)	13.40	3.20-134.00	1.80	13.97 (2.46)	13.20	11.10-32.30	2.50	0.051
PLT(/mm³×10³)	230.24 (65.90)	222.00	91.00-551.00	79.00	241.56 (61.68)	235.50	13.10-480.00	80.25	0.004
MPV(fL)	10.68 (1.15)	10.60	5.40-14.80	1.50	10.17 (1.14)	10.20	0.80-13.20	1.30	<0.001
PDW(%)	13.39 (2.64)	12.90	8.50-24.70	3.30	12.93 (2.79)	12.20	7.90-22.30	3.93	0.005
PCT(%)	0.24 (0.06)	0.23	0.11-0.50	0.08	0.24 (0.06)	0.24	0.07-0.47	0.07	0.511
N(×10³/uL)	6.45 (2.25)	6.25	1.05-18.03	2.72	5.95 (2.34)	5.46	2.26-18.50	2.30	<0.001
L(×10³/uL)	2.18 (0.71)	2.13	0.31-6.10	0.79	1.84 (0.57)	1.77	0.12-4.18	0.67	<0.001
E(×10³/uL)	0.09 (0.09)	0.07	0.00-0.78	0.08	0.11 (0.10)	0.09	0.00-0.75	0.10	0.065
NLR	3.31 (1.99)	2.90	0.89-21.32	1.52	3.68 (3.28)	3.01	1.06-48.00	1.68	0.141
PLR	115.25 (52.48)	106.94	36.80-606.45	49.39	145.72 (102.50)	132.34	6.52-1700.00	54.16	<0.001
ELR	0.05 (0.05)	0.04	0.00-0.48	0.04	0.06 (0.09)	0.05	0.00-1.31	0.05	<0.001
ENR	0.02 (0.02)	0.01	0.00-0.08	0.02	0.02 (0.02)	0.06	0.00-0.16	0.02	0.004

**Mann-Whitney U, HB: Hemoglobin, WBC: white blood cell count, RDW: red cell distribution width, PLT: platelet, PDW: count platelet distribution width, MPV: mean platelet volume, PCT: plateletcrit, N: Neutrophil, L: Lymphocyte, E: Eosinophil, NLR (Neutrophil/Lymphocyte), PLR: PLT / Lymphocyte, ELR: Eosinophil / Lymphocyte, ENR: Eosinophil / Neutrophil

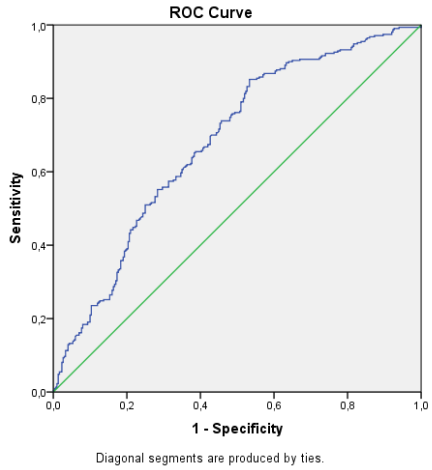


Figure 1: ROC analysis performed to examine the role of PLR in preedicting early pregnancy loss (AUC=0.681, *P*<0.001).

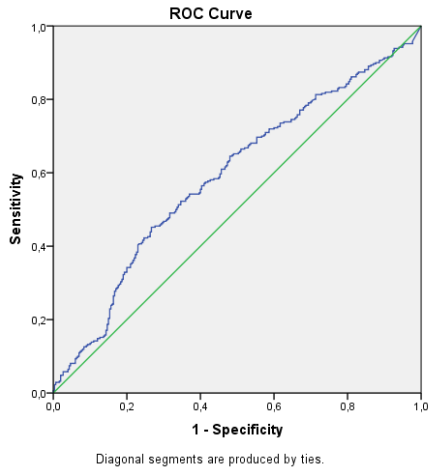


Figure 2: ROC analysis performed to examine the role of ELR in predicting early pregnancy loss (AUC=0.591 (0.023), *P*<0.001)

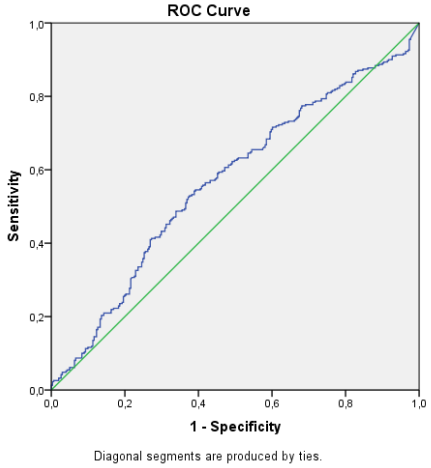


Figure 3: ROC analysis performed to examine the role of ENR in predicting early pregnancy loss (AUC=0.567 (0.023), *P*=0.004).

Discussion

The implantation of the embryo into the endometrium depends on the harmonious interaction between the placenta, fetus, and maternal circulation [16]. An imbalance between the physiological regulation of immune response, physiologically increased inflammation and the semi-allogenic fetus during pregnancy may result in spontaneous or recurrent miscarriage, preeclampsia, premature birth, and intrauterine growth restriction [17,18].

Many studies show that maternal circulation is responsible for the immune mechanism, and the pathogenesis of early pregnancy loss includes oxidative inflammation caused by thrombosis [18,19]. MPV, PDW, and PCT are considered platelet activation markers. Large platelets with high MPV values decrease placental perfusion, leading to pregnancy loss [18,20]. Platelets also have roles in strong immune modulation. In the study of Aynioglu et al. [21], PLT, PCT and RDW were significantly higher in patients with pregnancy loss. In this study, we found that PLT, MPV, PDW levels were higher in the early pregnancy loss group.

Based on increased immune response, neutrophils increase, and lymphocytes decrease in number. NLR is an important marker in the diagnosis of inflammatory diseases. It increases in many inflammatory diseases like Hyperemesis gravidarum [12], gestational diabetes [13], preeclampsia [14], intrahepatic pregnancy cholestasis [15], and in complicated pregnancies. In the literature, there were a small number of studies in which NRL was evaluated in early pregnancy loss, reporting differing results. In the studies conducted by Oglak et al. [6] to evaluate 285 patients, NLR was higher in patients with early pregnancy loss than in healthy controls' and no statistical difference was detected in other studies [7,22]. In this study, we found that NLR values were similar among the two groups.

In recent years, PLR was reported to predict chronic inflammatory diseases and malignancies, in addition to thromboembolic diseases [23,24]. It was researched in early membrane rupture, preeclampsia, gestational diabetes, and pancreatitis [14,25,26]. Platelet activation and elevated PLR values cause damage, especially to the endothelia of spiral arterioles, and thrombosis and impaired implantation ensue [27]. There are a few studies in which high PLR values were detected in early pregnancy loss [6,7]. In the study of Ata et al. [7], AUC

was 0.686 for PLR in EPL (P<0.001), with a sensitivity and specificity of 78% and 50%, respectively at >115.41 threshold. Similarly, in this study, we found that PLR values were higher in early pregnancy loss. In EPL group, the PLR cut-off value was 113.71. Any value above this had 68.1% sensitivity and 42.7% specificity for the prediction of miscarriage (Area Under Curve: 0.681 (0.022), 95% Confidence Interval (CI): 0.639-0.723).

Eosinophil, Eosinophil to Neutrophil Ratio (ENR) and Eosinophil to Lymphocyte Ratio (ELR) values, which can be easily calculated with CBC, are hematological allergy markers. Among the causes of eosinophilia (high number of eosinophils) are allergies, parasitic infections, leukemia, and polyarthritis nodosa autoimmune disease [28]. Eosinopenia does not have any specific cause, 0% eosinophil is considered normal [29]. Eosinophil decreases physiologically with gestational age [30]. Allergic markers were evaluated in preeclampsia in a small number of studies [31,32]. However, there is no study that evaluates allergic markers in early pregnancy loss. In this study, ELR and ENR values were higher at statistically significant levels in the EPL group compared to the healthy controls. In the EPL group, the cut-off value of ELR was 0.04, with 59.0% sensitivity and 45.3% specificity for early pregnancy loss prediction. The ENR cut-off value was 0.01 and had 56.8% sensitivity and 43.2% specificity.

As a major strength, this is the first study which evaluates almost all inflammation markers obtained from CBC, such as neutrophils, lymphocytes, NLR, PLR, thrombocyte activation markers such as PLT, MPV, PDW, and allergy markers such as ELR and ENR in the prediction of early pregnancy loss. The limitations of this study include the use of a retrospective design, small sample size, and the lack of generalizability of data.

Conclusion

PLR, MPV, PDW, ELR, ENR values are cheap and easily obtainable markers in predicting early pregnancy loss. Further randomized, prospective, controlled trials with high number of subjects are warranted to evaluate allergy markers together with inflammatory markers.

References

1. American College of Obstetricians and Gynecologists' Committee on Practice Bulletin Gynecology ACOG Practice Bulletin No. 200. Early Pregnancy Loss. Obstet Gynecol. 2018;132(5):197–207.
2. Kolte AM, Bernardi LA, Christiansen OB, Quenbay S, Farquharson RG, Goddijn M et al. Terminology for pregnancy loss prior to viability: a consensus statement from the ESHRE early pregnancy special interest group. ESHRE Special Interest Group, Early Pregnancy. Hum Reprod. 2015;30(3):495-8.
3. Shorter JM, Atrio JM, Schreiber CA. Management of early pregnancy loss, with a focus on patient centered care. Semin Perinatol. 2019;43(2):84-94.
4. Pinar MH, Gibbins k, He M, Kostadinov S, Silver R. Early Pregnancy Losses: Review of Nomenclature, Histopathology, and Possible Etiologies. Fetal Pediatr Pathol. 2018;37(3):191–209.
5. Calleja-Agius J, Jauniaux E, Pizzey AR, Muttikrishna S et al. Investigation of systemic inflammatory response in first trimester pregnancy failure. Hum Reprod. 2012;27(2): 349–57.
6. Oğlak SC, Aydın MF. Are neutrophil to lymphocyte ratio and platelet to lymphocyte ratio clinically useful for the prediction of early pregnancy loss? Ginekologia Polska. 2020;30(9):524–7.
7. Ata N, Kulhan M, Kulhan NG, Turkler C. Can neutrophil-lymphocyte and platelet-lymphocyte ratios predict threatened abortion and early pregnancy loss? Ginekologia Polska. 2020;91(4): 210–5.
8. Ethier JL, Desautels DN, Templeton AJ, Oza A, Amir E, Lheureux S. Is the neutrophil-to-lymphocyte ratio prognostic of survival outcomes in gynecologic cancers? A systematic review and meta-analysis. Gynecol Oncol. 2017;145(3): 584–94.
9. Verit FF, Cetin O, Yildirim O, Keskin S, Yucel O, Yalcinkaya S. Neutrophil to lymphocyte ratio is superior to platelet to lymphocyte ratio as an early predictor of moderate/ severe ovarian hyperstimulation syndrome. J Obstet Gynaecol. 2014;34(7):639–43.
10. Ilhan G, Verit FF, Altan E, Zebitay AG, Sozen H, Akyol H, Eken M. Evaluation of Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio and Red Blood Cell Distribution Width-Platelet Ratio for Diagnosis of Premature Ovarian Insufficiency. J Family Reprod Health. 2016;10(4):211–6.
11. Cho S, Cho H, Nam A, Kim HY, Choi YS, Park KH, Cho DJ, Lee BS. Neutrophil-to-lymphocyte ratio as an adjunct to CA-125 for the diagnosis of endometriosis. Fertil Steril. 2008;90(6):2073–9.
12. Caglayan EK, Ustun YE, Gocmen AY, Sarı N, Seckin L, Kara M, et al. Is there any relationshipbetween serum sirtuin-1 level and neutrophil-lymphocyte ratio in hyperemesis gravidarum? J Perinat Med. 2016;44(3):315–20.
13. Colak E , Ozcimen EE, CeranMU , Tohma YA , Kulaksızoglu S. Role of mean platelet volume in pregnancy to predict gestational diabetes mellitus in the first trimester. J Matern Fetal Neonatal Med. 2020;33(21):3689-94.
14. Serin S, Avcı F, Ercan O, Köstü B, Bakacak M, Kıranet H. Is neutrophil/lymphocyte ratio a useful marker to predict the severity of pre-eclampsia? Pregnancy Hypertens. 2016;6(1):22-5.
15. Abide Ç, Vural F, Kılıççı Ç, Ergen EB, Yenidede I, Eser A, Pekinet O. Can we predict severity of intrahepatic cholestasis of pregnancy using inflammatory markers? Turk J Obstet Gynecol. 2017;14:160-5.
16. Akdemir N, Cevrioglu AS, Ozden S, Kuru B, Bilir F, Bilir C Platelet Indices and Blood Groups in Early Recurrent Miscarriage: A Study in Pregnant Women J Clin Gynecol Obstet. 2013;2(1):27-30.
17. Challis JR Lockwood CJ, Myatt L, Norman JE, Strauss JF, Petragliaet F. Inflammation and pregnancy. Reprod Sci. 2019;16(2):206–15.
18. Yiyenoğlu OB. Uğur MG, Özcan HÇ, Can G, Öztürk E, Balat Ö, et al. Assessment of oxidative stress markers in recurrent pregnancy loss: a prospective study. Arch Gynecol Obstet. 2014;289(6):1337-40.
19. Kim KJ, Yang KM, Sachs AG. Recurrent pregnancy loss: A disease of inflammation and coagulation. J Obstet Gynaecol Res. 2019; 35:609-22.
20. Kosus N, Kosus A, Yildirim M, Duran M, Turhan NO. Mean platelet volume as a marker of thrombosis in patients with missed abortion. Acta Haematol. 2011;125(4):208–9.
21. Aynıoglu O, Isık H, Sahbaz A, Harma MI, Isık M, Kokturk F. Can Plateletcrit be a Marker for Recurrent Pregnancy Loss? Clin Appl Thromb Hemost. 2016;22(5):447–52.
22. Christoforaki V,, Zafeiriou Z, Daskalakis G, Katasos T, Siristatidis C. First trimester neutrophil to lymphocyte ratio (NLR) and pregnancy outcome. J Obstet Gynaecol. 2020;40(1):59–64.
23. Nording HM, Seizer P, Langer HF. Platelets in inflammation and atherogenesis. Front Immunol. 2015;98(6):1-11.
24. Zhou X, Du Y, Huang Z, Xu J, Qiu T, Wanget J et al. Prognostic value of PLR in various cancers: a meta-analysis. PLoS One. 2014;9(6):101-19.
25. Sargın MA, Yassa M, Taymur BD, Celik A, Ergun E, Tug N. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios: are they useful for predicting gestational diabetes mellitus during pregnancy? Ther Clin Risk Manag. 2016;12:657–65.
26. Ekin A, Gezer C, Taner CE, Ozeren M, Uyar I, Gulhanet I. Risk factors and perinatal outcomes associated with latency in preterm premature rupture of membranes between 24 and 34 weeks of gestation. Arch Gynecol Obstet. 2014;290(3):449–55.
27. Tola EN. The association between in vitro fertilization outcome and the inflammatory markers of complete blood count among nonobese unexplained infertile couples. Taiwan J Obstet Gynecol. 2018;57(2):289–94.
28. Sahoo D, Gosaib H, Harsodaa JM, Palana BM. A Comparative Hematological Profile Study Among Young Individuals. Canadian Journal of Basic and Applied Sciences. 2015;3:178-81.
29. Tembe N, Joaquim O, Alfai E, Sitoe N, Viegas E, Macovela E,et al. Reference Values for Clinical Laboratory Parameters in Young Adults in Maputo, Mozambique. PLoS ONE. 2014;9:973-91.
30. Chandra S, Tripathi AK, Mishra S, Amzarul M, Vaish AK. Physiological Changes in Hematological Parameters During Pregnancy. Indian J Hematol Blood Transfus. 2014;28:144-6.
31. Elmas B, Kıncı MF, Gök İE, Alkan A, Toğrul C, Sarıkaya S. Is higher IgE levels in preeclamptic pregnancies suggest autoimmune pathophysiology? Cukurova Med J. 2019;44(1):547-54.
32. Keski-Nisula L, Heinonen S, Remes S, Pekkanen J Pre-eclampsia, placental abruption and increased risk of atopic sensitization in male adolescent offspring. Am J Reprod Immunol. 2009;62:293-300.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1124-1127.
DOI: 10.28982/josam.750145

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Determinants of amputation and mortality following thromboembolectomy in native acute lower limb arterial occlusions, the influence of early intervention: A retrospective cohort study

Akut alt ekstremite nativ arteriyel tıkanıklarında tromboembolektomi sonrası amputasyon ve mortalitenin belirleyicileri; erken müdahalenin etkisi: Retrospektif kohort çalışma

Selim Durmaz [1]

[1] **Aydın Adnan Menderes University, Faculty of Medicine, Department of Cardiovascular Surgery, Aydın, Turkey**

ORCID ID of the author(s)

SD: 0000-0001-5618-3270

Corresponding author/Sorumlu yazar:
Selim Durmaz
Address/Adres: Aydın Adnan Menderes Üniversitesi, Tıp Fakültesi, Kalp ve Damar Cerrahisi Anabilim Dalı, 09100, Aydın, Türkiye
E-mail: sdurmaz@adu.edu.tr

Ethics Committee Approval: The study was approved by Aydın Adnan Menderes University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (approval number: 53043469-050.04.04 / 05.07.2018). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma Aydın Adnan Menderes Üniversitesi Tıp Fakültesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu tarafından onaylandı (onay numarası: 53043469-050.04.04 / 05.07.2018). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: In acute arterial occlusion, there is a sudden blockage of blood flow to the extremity, threatening its viability. Early/emergency intervention is required to eliminate the risk of amputation, but some of these cases receive a delayed diagnosis. The aim of this study is to evaluate the influence of surgical timing on the incidence of amputation and other factors affecting the risk of extremity loss.

Methods: A total of 154 patients who underwent thromboembolectomy were analyzed. The patients were categorized into three groups, as follows: Group 1 included patients with symptoms present for less than 12 hours, Group 2 comprised those with symptoms present for more than 12 hours but less than one week, and Group 3 included patients with symptoms present for more than one week. The groups were evaluated in terms of amputation and mortality.

Results: The incidence of amputation was significantly lower in Group 1 compared to the other two groups ($P<0.05$), and similar between Groups 2 and 3. In-hospital mortality did not significantly differ between the groups. When categorical and continuous variables were evaluated, a significant relationship was found between the risk of amputation and increasing age, female gender, diabetes, and iliac occlusion ($P<0.05$). The risk of in-hospital mortality was higher in females and in cases with cardiac arrhythmia ($P<0.05$).

Conclusion: Early surgical embolectomy is more successful in limb salvage. The risk of amputation is increased in diabetics, females, the elderly, and in proximal arterial occlusion.

Keywords: Amputation, Balloon embolectomy, Acute arterial occlusion

Öz

Amaç: Akut arter tıkanıklığı, ekstremite canlılığını tehdit eden ani bir ekstremite kan akımının tıkanması durumudur. Akut arter tıkanıklığında, ampütasyon riskini ortadan kaldırmak için erken / acil müdahale gerekir, ancak bu vakalardan bazılarında tanı gecikmiştir. Bu çalışmanın amacı, cerrahi zamanlamanın amputasyon insidansına etkisini ve ekstremite kaybı riskini etkileyen diğer faktörleri değerlendirmektir.

Yöntemler: Tromboembolektomi uygulanan 154 hasta incelendi. Hastalar üç gruba ayrıldı: Grup 1: semptomlar 12 saatten daha kısa süreli, Grup 2: semptomlar 12 saatten fazla ancak bir haftadan kısa süreli, Grup 3: semptomlar bir haftadan daha uzun süreli. Gruplar ve kohort ampütasyon ve mortaliteye göre değerlendirildi.

Bulgular: Grup 1'de amputasyon insidansı diğer iki gruba göre anlamlı olarak daha düşüktü ($P<0.05$). Ancak; Grup 2 ve Grup 3 arasında amputasyon insidansı farklı bulunmadı. Hastane içi mortalite insidansları da gruplar arasında istatistiksel olarak farklı değildi. Kategorik ve sürekli değişkenler değerlendirildiğinde, ampütasyon riski ile artan yaş, kadın cinsiyet, diyabet ve iliak oklüzyon arasında anlamlı ilişki bulundu ($P<0,05$). Kadınlarda ve kardiyak aritmi bulunan olgularda hastane içi mortalite riski daha yüksek bulundu ($P<0,05$).

Sonuç: Erken cerrahi embolektomi, uzuv kurtarmada daha başarılıdır. Diyabetiklerde, kadınlarda, yaşlılarda ve proksimal arter tıkanıklığında amputasyon riski artmaktadır.

Anahtar kelimeler: Amputasyon, Balon embolektomi, Akut arter tıkanıklığı

How to cite/Atıf için: Durmaz S. Determinants of amputation and mortality following thromboembolectomy in native acute lower limb arterial occlusions, the influence of early intervention: A retrospective cohort study. J Surg Med. 2020;4(12):1124-1127.

Introduction

Acute arterial occlusion (AAO), one of the most serious conditions threatening the limb and the life of the patient, occurs due to a sudden decrease in blood supply to the extremity [1]. The diagnosis and evaluation of AAO, a major emergency vascular pathology faced by vascular surgeons, is based on clinical examination, and errors in diagnosis can lead to the loss of the limb or even the death of the patient. Amputation and mortality rates are 8-15%, 15-40%, respectively, despite early diagnosis and treatment [2]. Acute occlusion can occur with some pathologies in which blood flow is completely ceased. In most of these cases, embolism and thrombus constitute the etiology; however, peripheral vascular dissection, thrombophilic conditions, graft thrombosis, and trauma may also lead to this pathology. Clinically, it manifests by pain, pallor, pulselessness, poikilothermia, paresthesia and paralysis ('6 Ps' finding) [3]. In early stages, the extremity is cold and pale due to the rapid decrease of blood flow. If arterial flow cannot be achieved, neuromuscular ischemia-mediated paresthesia and paralysis develop. Early diagnosis and treatment are critical after ischemia for preserving the viability of the extremity [4]. Although there are newer endovascular techniques such as pharmacologic thrombolysis, percutaneous aspiration thrombectomy (PAT), and percutaneous mechanical thrombectomy (PMT) for the reconstruction of the arterial flow, catheter embolectomy is still a good option, especially in proximal lesions [5]. Today, it is still used by many vascular surgeons as a prompt treatment option. The critical period for surgical correction is twelve hours after the onset of ischemia. However, complaints up to 14 days from the onset of symptoms are considered acute [4,6].

It is unclear whether thromboembolectomy operations performed in delayed cases in acute arterial occlusion are effective in preventing limb loss. In this study, we evaluated the effect of surgical timing on amputation risk with regards to the onset of symptoms in patients who underwent thromboembolectomy.

Materials and methods

Patients, procedure, and study design

This retrospective clinical study design and protocol were approved by Aydın Adnan Menderes University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (approval number: 53043469-050.04.04 / 05.07.2018) and performed in Aydın Adnan Menderes University Faculty of Medicine, Cardiovascular Surgery, Turkey. All procedures in this study were carried out in accordance with the Helsinki Declaration. Patients who underwent surgical thromboembolectomy for symptomatic arterial occlusion between January 2010 and December 2018 were reviewed. Patients' demographic and clinical characteristics, diagnosis and treatment methods were collected retrospectively from hospital records. The diagnosis of acute arterial occlusion was based on physical examination and arterial imaging (Doppler ultrasonography, computed tomography, or magnetic resonance) at the time of admission. Patients with trauma, previous bypass graft or stent thrombosis, those treated with endovascular techniques, those who had symptoms for more than 14 days and underwent further revascularization after thromboembolectomy were excluded from the study. Clinical evaluation of the selected patients was made according to the Rutherford classification and class 3 patients who were not eligible for revascularization were also excluded from the study (Table 1) [7].

Table 1: The Rutherford classification of acute limb ischemia

Category	Description	Capillary return	Muscle paralysis	Sensory loss	Doppler signals	
					Arterial	Venous
1. Viable	Not immediately threatened	Intact	None	None	Audible	Audible
2a. Threatened	Salvageable if promptly treated	Intact/slow	None	Partial	Inaudible	Audible
2b. Threatened	Salvageable if immediately treated	Slow/absent	Partial	Partial / complete	Inaudible	Audible
3. Irreversible	Primary amputation	Absent staining	Complete tense compartment		Inaudible	Inaudible

A total of 154 patients were included in the study and categorized into three groups according to the time from the onset symptoms until surgery as follows: Group 1 included patients who had symptoms for less than 12 hours, Group 2 comprised those with symptoms present for more than 12 hours but less than one week, and in Group 3 were patients whose symptoms were present for more than one week. Preoperative data such as age, gender, presence of hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, peripheral artery disease, atrial fibrillation, and malignancy, along with smoking habits, were evaluated. Whether it was a proximal (iliac artery or superficial femoral artery) or a distal embolism (popliteal artery or trifurcation arteries) was noted. The primary endpoints of the study were the amputation of the limb or mortality within 30 days of embolectomy. Postoperative revision and neurological complications were considered secondary endpoints.

Surgical procedure

After the diagnosis of acute limb ischemia, patients were transferred to the operating room, and the operation began under local anesthesia. The main femoral artery and its branches were reached through an oblique incision made in the inguinal region. The arterial tree of the patients was carefully examined, and a transverse arteriotomy was performed from the non-calcified location of the main femoral artery. The procedure continued until the thromboembolic material was removed using Fogarty catheters of various lengths. Arteriotomy was closed using 5/0-7/0 polypropylene suture material in accordance with vessel diameter and quality. All patients were anticoagulated with heparin during the operation and afterwards and followed up with activated coagulation time (180-300). Amputations were noted regardless of whether they were major or minor and performed by the orthopedist.

Statistical analysis

Statistical analysis was performed using SPSS 18.0 (SPSS Inc. Chicago, IL, USA) package program. The normality of distribution was evaluated with Shapiro Wilk and Levene's Tests. Continuous variables were presented as mean and standard deviation and evaluated by t-test in independent groups. Categorical variables were evaluated with Fisher's Exact Test and Chi-Square test. Post hoc chi-square analysis was performed to determine from which groups the difference originated. In case the conditions were not met, "Bonferroni correction" was applied. A *P*-value of <0.05 was considered significant.

Results

The demographic characteristics of the groups are shown as percentages. A total of 154 patients, 97 men, and 57 women were included in the study (Table 2). The patients who underwent amputation and those who did not were significantly different in terms of age, gender, diabetes, symptoms, and level of obstruction (P<0.05) (Table 3).

Table 2: Demographic variables of groups

	Group 1 (n: 64, %41.6)	Group 2 (n: 52, %33.8)	Group 3 (n: 38, %24.7)
Age, mean (SD)	67.1 (13.9)	72.4 (11.2)	79.6 (8.7)
Gender (Male, %)	44/68.8	28/53.8	25/65.8
Hypertension (n, %)	8/12.5	13/25.0	6/15.8
DMT2 (n, %)	16/25.0	16/30.8	5/13.2
Dyslipidemia (n, %)	10/15.6	37/71.1	28/73.6
Coronary artery disease (n, %)	16/25.0	15/29.4	15/39.5
COPD (n, %)	9/14.1	7/13.5	10/16.9
Smoking (n, %)	34/53.1	21/40.4	19/50.0
Atrial fibrillation (n, %)	8/12.5	6/11.5	10/26.3
Peripheral artery disease (n, %)	14/21.9	10/19.2	6/15.8
CKD (n, %)	5/7.8	4/7.7	4/10.5
Malignancy (n, %)	2/3.1	8/15.4	4/10.5

DMT2: Diabetes Mellitus type 2, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease

Table 3: Evaluation of categorical variables according to the presence of amputation

		Non-Amputation n (%)[x]	Amputation n (%)[x]	P-value
Age, mean (SD)		70.69 (12.55)	72.33 (13.02)	0.011[μ]**
Gender	Female	41 (33.1)	16 (53.3)	0.039†
	Male	83 (66.9)	14 (46.7)	
Diabetes	N	103 (83.1)	15 (50.0)	0.000123†**
	Y	21 (16.9)	15 (50.0)	
Arrhythmia	N	105 (84.7)	25 (83.3)	0.786‡
	Y	19 (15.3)	5 (16.7)	
CAD	N	86 (69.4)	22 (73.3)	0.669†
	Y	38 (30.6)	8 (26.7)	
Smoking	N	66 (53.2)	24 (80.0)	0.080†
	v	58 (46.8)	6 (20.0)	
COPD	N	104 (83.9)	24 (80.0)	0.612†
	Y	20 (16.1)	6 (20.0)	
CKD	N	116 (93.5)	25 (83.3)	0.134‡
	Y	8 (6.5)	5 (16.7)	
Symptom	N	99 (79.8)	17 (56.7)	0.008†**
	Y	25 (20.2)	13 (43.3)	
Hematoma	N	115 (92.7)	27 (90.0)	0.703‡
	Y	9 (7.3)	3 (10.0)	
Revision	N	116 (93.5)	28 (93.3)	1‡
	Y	8 (6.5)	2 (6.7)	
Hyperlipidemia	N	96 (77.4)	26 (86.7)	0.263†
	Y	28 (22.6)	4 (13.3)	
Malignity	N	115 (92.7)	25 (83.3)	0.150‡
	Y	9 (7.3)	5 (16.7)	
Death	N	117 (94.4)	27 (90.0)	0.410‡
	Y	7 (5.6)	3 (10.0)	
Nerve injury	N	113 (91.1)	23 (76.7)	0.051
	Y	11 (8.9)	7 (23.3)	
Obstruction level	Iliac	74 (59.7	12 (40.0)	0.002†**
	Popliteal	43 (34.7)	10 (33.3)	
	Infra popliteal	7 (5.6)	8 (26.7)	
Total		124 (100)	30 (100)	

CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, μ Independent groups T test, x Column percentages are calculated, † Pearson Chi-Square Test, ‡ Fisher Exact Chi-Square Test, ** P<0.05

Gender and arrhythmia were significantly different between survivors and non-survivors (P<0.05) (Table 4). The three groups were different regarding amputation (P=0.05), and a significant difference was found between Groups 1 and 2, and Groups 1 and 3, while Groups 2 and 3 were similar (P<0.05) (Table 5). All three groups were similar in terms of mortality (P=0.134) (Table 5).

Table 4: Evaluation of categorical variables according to the presence of death

		Death no n (%)	Death yes n (%)	P-value
Gender	Female	50 (34.7)	7 (70.0)	0.039‡**
	Male	94 (65.3)	3 (30.0)	
Diabetes	N	110 (76.4)	8 (80.0)	1‡
	Y	34 (23.6)	2 (20.0)	
Arrhythmia	N	124 (86.1)	6 (60.0)	0.05‡**
	Y	20 (13.9)	4 (40.0)	
CAD	N	104 (72.2)	4 (40.0)	0.066‡
	Y	40 (27.8)	6 (60.0)	
Smoking	N	81 (56.3)	9 (90.0)	0.046‡
	Y	63 (43.8)	1 (10.0)	
COPD	N	121 (84.0)	7 (70.0)	0.374‡
	Y	23 (16.0)	3 (30.0)	
CKD	N	132 (91.7)	9 (90.0)	0.598‡
	Y	12 (8.3)	1 (10.0)	
Symptom	N	109 (75.7)	7 (70.0)	0.709‡
	Y	35 (24.3)	3 (30.0)	
Hematoma	N	133 (92.4)	9 (90.0)	0.567‡
	Y	11 (7.6)	1 (10.0)	
Revision	N	136 (94.4)	8 (80.0)	0.129‡
	Y	8 (5.6)	2 (20.0)	
Hyperlipidemia	N	116 (80.6)	6 (60)	0.218‡
	Y	28 (19.4)	4 (40)	
Malignity	N	13 1(91.0)	9 (90.0)	1‡
	Y	13 (9.0)	1 (10.0)	
Amputation	N	117 (81.3)	7 (70.0)	0.411‡
	Y	27 (18.8)	3 (30.0)	
Nerve injury	N	129 (89.6)	7 (70.0)	0.095‡
	Y	15 (10.4)	3 (30.0)	
Obstruction level	Iliac	80 (55.6)	6 (60.0)	-
	Popliteal	49 (34.0)	4 (40.0)	
	Infra popliteal	15 (10.4)	0 (0.0)	
Total		124 (100)	30 (100)	

CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, ‡ Fisher Exact Chi-Square Test, ** P<0. 05

Table 5: Relationship between amputation, death and groups

	Amputation no n (%)x	Amputation yes n (%)x	P-value
Group 1	57 (89.1)	7 (10.9)	0.005*‡
Group 2	43 (41.9)	9 (10.1)	
Group 3	24 (63.2)	14 (36.8)	
	Death no n (%)	Death yes n (%)	
Group 1	62 (96.9)	2 (3.1)	0.134 ‡
Group 2	49 (94.2)	3 (5.8)	
Group 3	33 (86.8)	5 (13.2)	

Compared to Group 2 and Group 3, ‡ Fisher Exact Chi-Square Test, * P<0.05

Discussion

Despite the advances in surgical and endovascular invasive procedures, the risk of amputation and mortality remain high in patients with acute arterial obstruction [8]. Although amputation in these cases is mostly due to late admission, its relationship with time is controversial. The longer the duration of ischemia symptoms, the worse the extremity viability. As expected, we found that the amputation rate was significantly higher in patients who underwent delayed interventions. In our opinion, the main reasons of amputation were clinical and demographic features, such as age, gender, diabetes, symptoms, and obstruction level, as well as delayed admission.

Acute artery occlusion affects approximately 2 in 2000 people per year. These patients have a higher risk for major cardiovascular events than others [4]. From this point, it is a socioeconomic health problem which affects the patients and their relatives. The primary goal must be to the prevention of limb loss and survival of patients [9]. After an acute ischemic attack, most patients are treated with appropriate treatment after admission to the hospital. Delay in the time of admission may lead to a delay in diagnosis and treatment. In a study of 103 patients retrospectively analyzed by Gulmen [10], it was emphasized that the first twelve hours are important to save the extremity in patients with acute arterial occlusion. In this study, in terms of recovery of the limb, similar results were found among patients whose admission time did not exceed twelve

hours and our study groups, which we evaluated twelve hours and one week after onset of symptoms. However, no statistical difference was found in the evaluation between the two delayed groups. Thromboembolectomy surgery can provide limb viability even in patients who have passed the twelve hours threshold after symptom onset. However, this success rate is significantly reduced in delayed patients. Collateral circulation that starts minutes after ischemia protects the limb during acute artery occlusion. Diagnosis may be delayed in patients who do not feel pain due to this limited blood flow. However, if the vascular bed is not healthy enough to maintain adequate blood flow, despite collateral circulation, high amputation and mortality risk may be encountered. The high amputation rate in delayed cases suggests that collateral circulation increases pain resistance but leads to late diagnosis.

We observed that the amputation rate increased depending on gender, diabetes, and increasing age. This may be due to the association of increased diabetes incidence with increasing age. The amputation rate increased approximately 5 times among diabetic patients compared to the non-diabetic population. Carmona et al. [11] found a 10-fold amputation risk in patients with diabetes. In the review of Narres et al. [12] including 19 studies, the amputation rate was high in diabetic patients and male individuals. The lower incidence in this study may be due to increasing endovascular developments and surgical techniques in recent years and improvement in the treatment planning of diabetic patients.

The early mortality rate in acute lower limb obstruction is between 3.6-30% [13,14]. However, long-term mortality rates are mostly investigated. In our study, mortality was approximately 19 percent and is in line with the literature [15], but low compared to older studies [16]. The reason for this may be the improvement in surgical materials and techniques. When the factors affecting mortality are examined, female gender and arrhythmia come to the fore. Hussain et al. [17] found more risks in men in their population-based study, in which early mortality was not studied. This suggests that patient groups may be affected by their demographic characteristics. We obtained similar mortality results among our study groups. However, this result should be evaluated carefully since early mortality results do not reflect long-term mortality outcomes.

Limitations

This study has several limitations. First, this is a retrospective single-center cohort study therefore it is difficult to interpret results to advocate recommendations that could be applicable in routine clinical practice. The sample size in the current study is also too small for extrapolation of definite judgments regarding the factors affecting mortality. We think that further, multi-center, prospective trials may aid in enlightening the effect of surgical timing on limb salvage and mortality in acute arterial occlusions.

Conclusions

Surgical treatment can be performed in delayed cases with lower extremity arterial occlusion for limb viability. However, the risk of amputation increases as the time from the onset of initial symptoms –which is pain in most cases- until surgical thromboembolectomy increases. The risk of mortality is high in acute arterial occlusions and we did not observe any effects of an early thromboembolectomy on in-hospital mortality in this cohort. We observed that the risk of amputation is increased in diabetics, females, the elderly, and in proximal occlusions; however, we think that further prospective, multi-center studies with a higher number of patients are needed to determine the risk of amputation in acute arterial occlusion.

References

1. Obara H, Matsubara K, Kitagawa Y. Acute Limb Ischemia. Ann Vasc Dis. 2018;11:443–8.
2. Hage AN, McDevitt JL, Chick JFB, Vadlamudi V. Acute Limb Ischemia Therapies: When and How to Treat Endovascularly. Semin Intervent Radiol. 2018;35:453–60.
3. PRATT GH. Arterial varices; a syndrome. Am J Surg. 1949;77:456-60.
4. Olinic DM, Stanek A, Tătaru DA, Homorodean C, Olinic M. Acute Limb Ischemia: An Update on Diagnosis and Management. J Clin Med. 2019;8:1215.
5. Moon HG, Cho SC, Jeong SW, Lee GI, Jo YE, Youn B, et al. Early versus late thrombolysis in acute arterial occlusion of lower extremity. Int J Cardiol. 2017;228:86-9.
6. Acar RD, Sahin M, Kirma C. One of the most urgent vascular circumstances: Acute limb ischemia. SAGE Open Med. 2013;1:2050312113516110.
7. McNally MM, Univers J. Acute Limb Ischemia. Surg Clin North Am. 2018 ;98:1081-96.
8. Lind B, Morcos O, Ferral H, Chen A, Aquisto T, Lee S, Lee CJ. Endovascular Strategies in the Management of Acute Limb Ischemia. Vasc Specialist Int. 2019 Mar;35:4-9.
9. Farber A, Eberhardt RT. The Current State of Critical Limb Ischemia: A Systematic Review. JAMA Surg. 2016;151:1070-7.
10. Gülmen Ş. Akut arter tıkanıklarınnda mortaliteye eşlik eden faktörler. SDÜ Tıp Fakültesi Dergisi. 2009;15:12-6.
11. Carmona GA, Hoffmeyer P, Herrmann FR, Vaucher J, Tschopp O, Lacraz A, et al. Major lower limb amputations in the elderly observed over ten years: the role of diabetes and peripheral arterial disease. Diabetes Metab. 2005;31:449-54.
12. Narres M, Kvitkina T, Claessen H, Droste S, Schuster B, Morbach S, Rümenapf G, Van Acker K, Icks A. Incidence of lower extremity amputations in the diabetic compared with the non-diabetic population: A systematic review. PLoS One. 2017;12:e0182081.
13. Clason AE, Stonebridge PA, Duncan AJ, Nolan B, Jenkins AM, Ruckley CV. Morbidity and mortality in acute lower limb ischaemia: a 5-year review. Eur J Vasc Surg. 1989;3:339-43.
14. Liang S, Zhou L, Ye K, Lu X. Limb Salvage after Percutaneous Mechanical Thrombectomy in Patients with Acute Lower Limb Ischemia: A Retrospective Analysis from Two Institutions Ann Vasc Surg. 2019;58:151-9.
15. Demir D, Kahraman N. Outcomes of intravenous thrombolytic and adjuvant surgery in acute limb ischemia: Review of 23 patients. J Surg Med. 2019;3(2):172-5.
16. Strom JA, Bernhard VM, Towne JB. Acute Limb Ischemia Following Aortic Reconstruction: A Preventable Cause of Increased Mortality. Arch Surg. 1984;119:470–3.
17. Hussain MA, Lindsay TF, Mamdani M, Wang X, Verma S, Al-Omran M. Sex Differences in the outcomes of peripheral arterial disease: a population-based cohort study. CMAJ Open. 2016;4:E124-31.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1128-1132.
DOI: 10.28982/josam.778883

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Evaluation of the relationship between non-alcoholic fatty liver disease and serum c-peptide, c-peptide to glucose and c-peptide to HbA1C ratio in obese children

Obez çocuklarda alkolsüz yağlı karaciğer hastalığı ile serum c-peptit, c-peptit-glikoz ve c-peptit-HbA1C oranı arasındaki ilişkinin değerlendirilmesi

Fatma Demirbaş [1], Gönül Çaltepe [1], Atakan Comba [1], Hasan Abbasguliyev [2], Ayhan Gazi Kalaycı [1]

[1] Ondokuz Mayıs University, Faculty of Medicine, Department of Pediatric Gastroenterology, Hepatology and Nutrition, Samsun, Turkey
[2] Ondokuz Mayıs University, Faculty of Medicine, Samsun, Turkey

ORCID ID of the author(s)

FD: 0000-0003-1788-2559
GÇ: 0000-0001-8525-6352
AC: 0000-0002-8576-9550
HA: 0000-0002-1055-0925
AGK: 0000-0003-2104-6801

Corresponding author/Sorumlu yazar:
Fatma Demirbaş
Address/Adres: Ondokuz Mayıs Üniversitesi Tıp Fakültesi, Çocuk Gastroenteroloji ve Hepatoloji ve Beslenme Anabilim Dalı, Kurupelit, Samsun, 55200, Türkiye
E-mail: fatmademirbas81@hotmail.com

Ethics Committee Approval: The study was approved by the Ethics Committee of Ondokuz Mayis University on 01.03.2019 (Clinical research ethics committee decision number: 2019/192). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma 01.03.2019 tarihinde Ondokuz Mayıs Üniversitesi Etik Kurulu tarafından onaylandı (Klinik araştırma etik kurul karar no: 2019/192). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: Obesity-related complications such as metabolic syndrome, insulin resistance and non-alcoholic fatty liver disease (NAFLD) have increased in childhood. The aim of this study is to investigate the fasting c-peptide, c-peptide to glucose and c-peptide to HbA1C ratios in obese children with NAFLD.

Methods: This case-control study was conducted from August through November 2018. A total of 60 obese children, 40 with and 20 without NAFLD, were included in the study. Patients with BMI > 2 z-score were considered obese. The ultrasonographic characteristics of NAFLD were identified with liver contrast and brightness in echogenicity. Serum fasting c-peptide levels of patients were compared.

Results: Of the 60 patients included in the study, 37 (61.7%) were male and the mean age was 11.9 (2.9) years. The mean ALT, weight BMI, waist circumference, waist to height ratio, serum c-peptide, fasting c-peptide to glucose ratio, fasting c-peptide to HbA1C ratio and insulin levels were considerably higher in patients with NAFLD (P<0.05 for each). When the c-peptide levels of all the patients was evaluated by ROC analysis, the area under the curve in patients with NAFLD was 0.70 (95% CL: 0.725-0.955) and the c-peptide cut off value was 2.62 ng/ml (sensitivity 60%, specificity 75%, P=0.011). Logistic regression analysis results showed that the risk of NAFLD was significantly higher in obese children with c-peptide levels greater than 2.62 ng/ml (OR: 4.52 95% CI: 1.65-3.25) (P<0.001).

Conclusion: In our study, a significant relationship was found between NAFLD and serum c-peptide level, c-peptide to glucose and c-peptide to HbA1C ratios. Even though BMI, waist circumference, waist to height ratio, HbA1c and insulin are better parameters in determining insulin resistance in NAFLD patients, c-peptide can be used as an inexpensive method for screening.

Keywords: Childhood, C-peptide, C-peptide to glucose ratio, C-peptide to HbA1C ratio, Non-alcoholic fatty liver disease, Obesity

Öz

Amaç: Obeziteye bağlı görülen metabolik sendrom, insulin direnci ve non-alkolik yağlı karaciğer hastalığı (NAYKH)gibi komplikasyonlar çocukluk çağında da sıklığı giderek artmaktadır. Bu çalışmanın amacı, NAYKH ile ilişkili obez çocuklarda açlık c-peptit, c-peptit-glukoz ve c-peptit-HbA1C oranlarını araştırmaktır.

Yöntemler: Bu vaka-kontrol çalışması Ağustos-Kasım 2018 arasında gerçekleştirildi. Çalışmaya 40'ı NAYKH ile ilişkili ve 20'si NAYKH olmayan toplam 60 obez çocuk alındı. VKİ> 2 z-skoru olan hastalar obez olarak kabul edildi. NAYKH'nin ultrasonografik özellikleri, karaciğer kontrastı ve ekojenitede parlaklık olarak tanımlandı. Hastaların serum açlık c-peptit düzeyleri karşılaştırıldı.

Bulgular: Çalışmaya dahil edilen 60 hastanın 37'si (%61,7) erkekti ve ortalama yaş 11,9 (2,9) yıldı. NAYKH'li hastalarda ortalama ALT, ağırlık, BMI, bel çevresi, bel çevresi-boy oranı, serum c-peptit, açlık c-peptit-glikoz oranı, açlık c-peptit-HbA1C oranı ve insülin seviyeleri, NAYKH olmayan obez çocuklara göre anlamlı olarak daha yüksekti. (her biri için P<0,05).

Bütün hastalar içinde ROC analizi ile değerlendirildiğinde, NAYKH'li hastalar için eğri altındaki alan 0,70 (%95 CI: 0,725-0,955) ve c peptit kesme değeri 2,62 ng / ml (duyarlılık %60, özgüllük %75, P=0,011) idi. Lojistik regresyon analizi ile, c-peptit seviyesi 2.62 ng / ml'den yüksek olan obez çocuklarda NAYKH riski anlamlı derecede daha yüksekti (OR: 4,52 %95 CI: 1,65-3,25) (P<0,001).

Sonuç: Bu çalışmada, NAYKH ile serum c-peptit düzeyi, c-peptit-glukoz ve c-peptit-HbA1C oranları arasında anlamlı bir ilişki bulunmuştur. NAYKH hastalarında insülin direncini belirlemede BMI, bel çevresi, bel-boy oranı, HbA1c ve insülin daha iyi standart parametreler olsa da, c-peptit tarama için pahalı olmayan bir yöntem olarak kullanılabilir.

Anahtar kelimeler: Çocukluk çağı, C-peptit, C-peptit-glikoz oranı, C-peptit-HbA1C oranı non-alkolik yağlı karaciğer hastalığı, Obezite

How to cite/Atıf için: Demirbaş F, Çaltepe G, Comba A, Abbasguliyev H, Kalaycı AG. Evaluation of the relationship between non-alcoholic fatty liver disease and serum c-peptide, c-peptide to glucose and c-peptide to HbA1C ratio in obese children. J Surg Med. 2020;4(12):1128-1132.

Introduction

Obesity is a common public health problem among non-communicable diseases worldwide. Comorbidities such as glucose intolerance, hypertension, dyslipidemia, non-alcoholic fatty liver disease (NAFLD) and ischemic heart disease are associated with obesity [1]. Obesity-related NAFLD is the most common cause of chronic liver disease in children in developed countries. NAFLD is characterized by excessive fat accumulation in hepatocytes and covers a wide spectrum of diseases ranging from simple non-alcoholic fatty liver (NAFL) disease to non-alcoholic steatohepatitis (NASH), cirrhosis and end stage liver disease [2].

The prevalence of NAFLD in childhood is about 7% and may reach 34% among obese children [3]. Recently, a meta-analysis showed that the global prevalence of NAFLD is 25.24% with the highest prevalence in the Middle East and South America and the lowest in Africa for the year of 2016 [4].

Obesity and insulin resistance are the leading causes of NAFLD in childhood. In the diagnosis, evaluation and staging of obesity, waist circumference (WC), and waist to height ratio, and body mass index (BMI) are utilized [5]. The role of insulin resistance, hemoglobin A1c (HbA1c), insulin level, and fasting glucose level have been demonstrated in the development of NAFLD.

The level of c-peptide in blood is a good indicator of beta cell activity and endogenous insulin secretion. Once the polypeptide structure – a preprohormone, produced in pancreatic beta cells, is released into the blood, the c-peptide part is separated, and the remainder is the insulin hormone [6]. Serum c-peptide level is positively correlated with fat distribution in nondiabetic subjects and increased levels of c-peptide is an indicator of insulin hypersecretion and resistance in healthy and diabetic subjects [7]. In addition, the serum c-peptide level is a risk factor for cardiovascular disease, metabolic syndrome and NAFLD in adult studies. [8-9].

According to the literature, the serum c-peptide levels and fasting c-peptide to glucose ratio, as well as c-peptide to HbA1C ratio in children with NAFLD have not been evaluated previously. The aim of this study was to determine the relationship between serum fasting c-peptide levels and NAFLD in children with obesity.

Materials and methods

Patients

This study was conducted between August 2018 and November 2018 in the Department of Pediatric Gastroenterology Hepatology and Nutrition. Sociodemographic characteristics of the patients together with physical (BMI, WC, waist to height ratio) and laboratory findings (venous, 8 h-fasting glucose level, lipid panel, aspartate aminotransferase [AST normal values: Females: 8–46 U/L, males: 8–40 U/L], alanine aminotransferase [ALT normal values: Females: 0–35 U/L, males: 0–40 U/L], insulin, 8h-fasting c-peptide level, HbA1C, HOMA index), as well as follow-up periods were recorded. In our study, NAFLD is defined as: (1) Moderate to severe hepatic steatosis on ultrasound (hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring), (2) no history of chronic liver diseases, (3) not infected with hepatitis B or hepatitis C. Other leading causes of NAFLD such as infectious, autoimmune, metabolic, and endocrine reasons were excluded by hepatitis A, B, C and autoimmune markers, serum α-1-antitrypsin and ceruloplasmin level tests.

The calculation of percentiles and z-scores of weight, height, and body mass index (BMI) were performed using WHO Anthroplus v 1.0.4 software [10]. Patients with BMI > 2 z-score were considered obese.

C-peptide measurement

Serum fasting c-peptide (IMMULITE 2000® DPC, USA) is a solid phase, competitive chemiluminescent enzyme immunoassay. Incubation Cycles: 1 × 30 minutes. Storage: Assay within 2-3 hours or store frozen at –20°C for 1 week.

The calculation of ratios of c-peptide to glucose and c-peptide to HbA1C was performed by dividing fasting c-peptide (ng/ml) to fasting plasma glucose (mg/dl) x100 and fasting plasma HbA1C, respectively. The formula of fasting insulin (μU/ml) x fasting plasma glucose (mg/dl) / 405 was used for the estimation of homeostatic model assessment of insulin resistance (HOMA-IR).

The study was approved by the Ethics Committee of Ondokuz Mayis University on 01.03.2019 (Clinical research ethics committee decision number: 2019/192). Written informed consent were obtained from the parents and/or legal guardians of all patients included in the study.

Statistical analysis

Statistical analyses were performed using SPSS v. 22.0 software (Statistical Package for Social Sciences, Inc.). Power analysis revealed that at least 20 patients were required for each group. Normally distributed data were stated as mean (standard deviation) and non-normally distributed data were stated as median (range) values. Comparisons of independent binary groups with normal distribution were made with the t test, and ANOVA variance analysis was applied to hypervariable groups. The Mann-Whitney U test was used to compare over-variant groups, and two groups of non-normally distributed data. For the comparison of percentages of qualitative data, the Paired chi-square test and z-test were applied. When interpreting the association based on Pearson correlation coefficients, reference ranges were adopted as follows: $0.00 < r < 0.25$-very weak; $0.26 < r < 0.49$-weak; $0.50 < r < 0.69$-moderate; $0.70 < r < 0.8$-high; and $0.90 < r < 1.00$-very high. A value of $P<0.05$ was considered statistically significant. Performance of different models was assessed by the area under the receiver operating characteristic (ROC) curve.

Results

This study comprised 37 males (61.7%), and 23 females (%38.3), with a mean age of 11.9 (2.9) years, and NAFLD was present in 40 (66.7%) out of 60 patients.

The mean weight z-score, BMI z-score and waist circumference were 2.6 (0.4), 2.58 (0.21), and 94.3 (17.4) cm, respectively.

Of the 40 obese children with NAFLD, 23 (57.5%) were male and the mean age was 12.9 (2.5) years. Their mean fasting c-peptide level, fasting c-peptide to fasting glucose ratio, fasting c-peptide to HbA1C ratio, and insulin levels were 4.05 (0.49)

ng/ml, 4.866 (0.62), 0.81 (0.10) (range: 0.06-1.1), and 22.8 (3.2) µU/ml, respectively. Of the patients with NAFLD, 23 (57.5%) had high ALT levels and a mean fasting c-peptide level of 4.29 (0.23) ng/ml.

Among 20 obese children without NAFLD, 14 (70%) were male and the mean age was 9.9 (2.5) years. The mean serum c-peptide level, fasting c-peptide to fasting glucose ratio, fasting c-peptide to HbA1C ratio, and insulin levels were 2.4 (0.32) ng/ml, 2.771 (0.33), 0.42 (0.02), and 18.6 (3.5) µU/ml, respectively. Demographic and laboratory parameters of the patients are shown in Table 1.

Table 1: Comparison of demographic findings of children with obesity

Total (n = 60)	Hepatosteatosis (n = 40)	Non-hepatosteatosis (n = 20)	*P*-value
Age (years)	12.9 (2.5)	9.9 (2.5)	0.530
Gender (Female/Male)	17/23	6/14	0.257
Height z-score	0.57 (0.17)	0.77 (0.19)	0.320
Weight (kg)	69.6 (5.02)	51.2 (3.4)	*0.039*
Weight z-core	2.7 (0.6)	2.3(0.13)	0.146
BMI (kg/m^2)	32.3 (1.4)	26.9(0.96)	< 0.001
BMI z Score	2.6 (0.21)	2.1(0.19)	0.145
Waist circumference (cm)	99.03 (18.2)	84.8 (10.3)	*0.001*
Waist-to-height ratio	0.67 (0.23)	0.59(0.05)	*0.015*
Fasting C-peptide(ng/ml)	4.05(0.49)	2.4(0.32)	*0.011*
C-peptide-to- glucose ratio	4.866 (0.62)	2.771(0.33)	*0.005*
C-peptide-to-HbA1C ratio	0.81(0.10)	0.42(0.02)	*0.003*
AST U/L	34.2 (14)	22.7(5.9)	0.252
ALT U/L	54.04(9.3)	20.4(9.7)	*0.016*
Fasting glucose (mg/dl)	83.9(10.1)	85.0(8.9)	0.210
Insulin	22.8(3.2)	18.6(3.5)	*0.031*
HOMA-IR	4.8(0.68)	4.55(0.55)	0.113
HbA1c	5.2(0.35)	5.3(0.33)	0.691
Triglyceride (mg/dl)	127.7(11.09)	124.4(7.5)	0.426
Total cholesterol (mg/dl)	158.2(34.8)	159.5(22.6)	0.877
HDL (mg/dl)	42.2(9.8)	44.7(7.8)	0.145
LDL (mg/dl)	92.1(20.2)	90.5(19.4)	0.961

F: female, M: male, AST: Aspartate aminotransferase ALT: Alanine aminotransferase, HDL: High density lipoprotein, LDL: Low density lipoprotein, BMI: Body mass index, HOMA-IR: homeostatic model assessment of insulin resistance (Normal values; AST, 8–46 U/L (female), 8–40 U/L (male); ALT, 0–35 U/L (female), 0–40 U/L (male); triglyceride, 0-200 mg/dl; total cholesterol,0-200 mg/dl; HDL, 35-75 mg/dl; LDL, 0-165 mg/dl; fasting glucose, 70-110 mg/dL; insulin, 3-30; HbA1c, 4-6; fasting c-peptide, (0.0-7.1) ng/ml)

The BMI, weight, waist circumference, waist to height ratio, ALT, c-peptide (Figure 1) fasting c-peptide to fasting glucose ratio, fasting c-peptide to HbA1C ratio and insulin levels of NAFLD patients were significantly higher than those without NAFLD (*P*<0.001, *P*=0.039, *P*=0.001, *P*=0.015, *P*=0.016, *P*=0.011, *P*=0.005, *P*=0.003 and *P*=0.031, respectively).

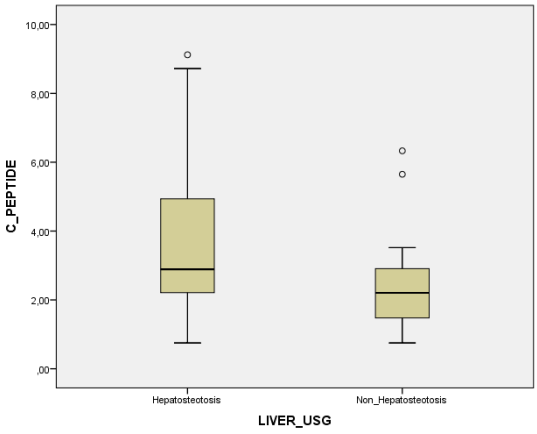


Figure 1: Comparison of C-peptide levels between the groups

A positive correlation was found between fasting c-peptide level and waist circumference (r = 0.333, *P*=0.009), BMI (r = 0.378, *P*=0.003) insulin (r = 0.845, *P*<0.001) and HOMA-IR (r = 0.785, *P*<0.001). When the c-peptide levels of all the patients were evaluated by ROC analysis, the area under the curve in patients with NAFLD was 0.70 (95% CL: 0.725-0.955) and the c-peptide cut off value was 2.62 ng/ml (sensitivity 60%, specificity 75%, *P*=0.011) (Figure 2). When evaluated by logistic regression analysis (OR: 4.52 95% CI: 1.65-3.25), the risk of fatty liver was significantly higher in obese children with c-peptide levels greater than 2.62 ng/ml (*P*<0.001).

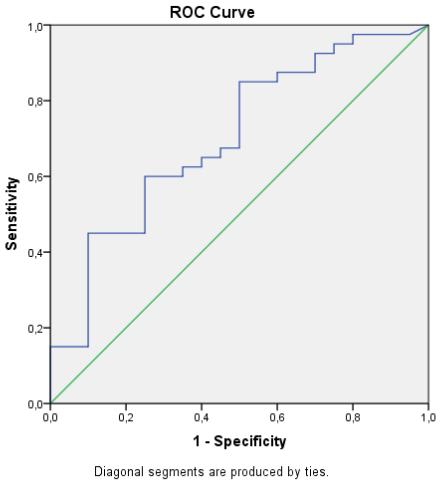


Figure 2: Cut-off C-peptide = 2.62 ng / mL level for NAFLD diagnosis with 60% sensitivity and 75% specificity

Discussion

Non-alcoholic fatty liver disease is one of the most common liver disorders. It is characterized by fat accumulation in liver (steatosis) and includes chronic liver diseases ranging from simple fatty infiltration to inflammation and fibrosis [2]. It is well known that pediatric NAFLD is associated with increased insulin resistance, dyslipidemia, cardiovascular disease, and most importantly, visceral adiposity [11-12]. The relationship between NAFLD and c-peptide has been described in adult studies [13-14].

Insulin resistance is the most common metabolic abnormality associated with NAFLD and it is related with disease severity and progression [15]. In clinical practice, while insulin resistance is routinely diagnosed with fasting plasma glucose, HbA1c and insulin levels, c-peptide is not commonly used [16]. In this study, the fasting c-peptide level of children with NAFLD was significantly higher than the non-NAFLD group. The risk of NAFLD was 4.52 times (95% CI: 1.65-3.25) higher in children with increased c-peptide levels. C-peptide is a widely used method for evaluating pancreatic beta cell function [17]. The pancreatic beta cells secrete proinsulin which cleaves into c-peptide and insulin prior to secretion. Even though the quantity of c-peptide is equal to the produced insulin level, the half-life of c-peptide (20-30 min) is higher when compared to insulin (3-5 min). That characteristic renders c-peptide a reliable method to test the functionality of beta cells [18].

In this study, c-peptide to HbA1C and c-peptide to fasting glucose ratios of NAFLD patients were considerably higher when compared to non-NAFLD patients. El-Koofy et al. [19] demonstrated that serum fasting insulin and c-peptide of obese patients were significantly higher than those of the control group. While the ratio of serum c-peptide to glucose was used in adult studies to determine the efficacy of treatment, no studies have investigated the relationship between peptide to fasting glucose, c-peptide to HbA1C ratio and hepatic steatosis [20]. In this study, the association between NAFLD and c-peptide to

fasting glucose and c-peptide to HbA1C ratios showed that the loss of β cell mass in obese children with fatty liver might be due to increased free fatty acids, oxidative stress, and inflammation.

In adult studies, the elevation of serum c-peptide in patients with obesity- and diabetes-associated NAFLD has been demonstrated [21]. The study of 542 patients by Francque et al. [22] reported a direct relationship between NAFLD patients and c-peptide levels. In a recent study, c-peptide was an independent risk factor for NAFLD and utilized to assess the insulin resistance in these patients [13]. Tricò et al. [21] found that in patients without NAFLD, high fasting glucose and c-peptide levels were risk factors for NAFLD development in follow-up periods.

In our study, the values of waist circumference, waist to height ratio and BMI of NAFLD patients were substantially higher than non-NAFLD patients. Manco et al. [23] reported that 92% of patients with NAFLD had a higher BMI and 84% had a wider waist circumference. It has been shown that every 5 cm increment in the waist circumference of obese children or adolescents increases the probability of ultrasound to detect fatty liver by 1.4 times [15]. In addition, a cross-sectional study involving 145 pediatric patients reported a significant relationship between the incidence of NAFLD and waist circumference, total fat mass, and intraabdominal adipose tissue [24]. For this reason, waist circumference can be utilized as a credible screening modality in pediatric NAFLD patients. In our study, waist circumference and waist to height ratio were significantly elevated in NAFLD patients, which indicate that patients with NAFLD accumulate more visceral adipose tissue than non-NAFLD ones. NAFLD patients are more insulin resistant than non-NAFLD patients. Both BMI and waist circumference are considered important parameters in predicting NAFLD severity and steatosis [24].

Increased ALT levels are frequently seen in pediatric patients with NAFLD [25]. Generally, slight elevation of aminotransferases (1.5-2 times the upper limit of normal) is observed [2]. In this study, the ALT levels of obese children with NAFLD were significantly higher than patients without NAFLD. The study by Arslan et al. [26] presented that BMI, AST, ALT, GGT and triglyceride values were remarkably high in obese children with NAFLD compared to non-NAFLD ones. Based on the serum ALT > 30 U/L threshold, the National Health and Nutrition Examination Survey in the United States estimated a prevalence of 8% NAFLD in a study of adolescents [27]. Central obesity has also been shown to reliably predict the evidence of ultrasonographic characteristics and elevated aminotransferase levels in NAFLD in more than 11,000 children with obesity aged 6-18 years [28].

Limitations

Only ultrasound was utilized for diagnosis in our study, however, liver biopsy is the most important method in diagnosing NAFLD. Another limitation is the lack of usage of elastography, which has increased diagnostic efficiency for it can determine tissue stiffness. Additionally, the sparse number of patients and absence of genetic examination for obesity are amongst constraints. Although the fasting c-peptide and c-peptide to glucose ratio of the patients were evaluated, they were not compared with postprandial values.

Conclusions

Obesity has become an increasingly common public health problem in childhood. The most common etiology is obesity-related insulin resistance. In this study, fasting c-peptide level besides ALT, BMI, waist circumference and weight to height ratio were main factors associated with NAFLD. In patients with NAFLD, serum fasting c-peptide level measurement was considered as significant as fasting insulin level. Even though BMI, waist circumference, waist to height ratio, HbA1c and insulin levels are better standard parameters in determining insulin resistance in NAFLD patients, c-peptide can also be used for screening as a non-invasive and inexpensive method.

References

1. GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med. 2017;377(1):13.
2. Goyal NP, Schwimmer JB. The progression and natural history of pediatric nonalcoholic fatty liver disease. Clin Liver Dis. 2016;20(2):325-38.
3. Anderson EL, Howe LD, Jones HE, Higgins JP, Lawlor DA, Fraser A. The Prevalence of Non-Alcoholic Fatty Liver Disease in Children and Adolescents: A Systematic Review and Meta-Analysis. PLoS One. 2015;10(10):0140908. doi: 10.1371/journal.pone.0140908
4. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73–84. doi: 10.1002/hep.28431
5. Bozorgmanesh M, Hadaegh F, Khalili D, Prof AF. Prognostic Significance of the Complex "Visceral Adiposity Index" vs. Simple Anthropometric Measures. Cardiovasc Diabetol. 2012;11(20):1-10. doi: 10.1186/1475-2840-11-20
6. Steiner DF, Cunningham D, Spigelman L, Aten B. Insulin Biosynthesis: Evidence for a Precursor. Science. 1967;157(3789):697–700. doi: 10.1126/science.157.3789.697.
7. Li Y, Meng L, Li Y, Sato Y. Associations of Serum C Peptide Level with Body Fat Distribution and Ever Stroke in Nondiabetic Subjects. J Stroke Cerebrovasc Dis. 2013;23:63-9. doi: 10.1016/j.jstrokecerebrovasdis.2013.09.013
8. Wang L, Lin P, Ma A, Zheng H, Wang K, Li W, et al. C-Peptide Is Independently Associated with an Increased Risk of Coronary Artery Disease in T2DM Subjects: A Cross-Sectional Study. PLoS One. 2015;10(6):0127112. doi: 10.1371/journal.pone.0127112
9. Gonzalez-Mejia ME, Porchia LM, Torres-Rasgado E, Ruiz-Vivanco G, Pulido-Pérez P, Báez-Duarte BG, et al. C-Peptide Is a Sensitive Indicator for the Diagnosis of Metabolic Syndrome in Subjects from Central Mexico. Metab Syndr Relat Disord. 2016;14(4):210–6. doi: 10.1089/met.2015.0067
10. WHO software World Health Organization (WHO) WHO anthroplus for personal computers manual software for assesing growth of the world's children and adolescents.2009 http://.who.int/growthref/tools/who_anthroplus_manual.pdf (accessed May 2019).
11. Berardis S, Sokal E. Pediatric non-alcoholic fatty liver disease: An increasing public health issue. Eur J Pediatr. 2014;173(2):131–9. doi: 10.1007/s00431-013-2157-6
12. Yalaki S, Pülat H. Does chronic hepatitis B infection have an impact on fasting blood glucose levels and fatty liver development? J Surg Med. 2020;4(5):406-9. doi: 10.28982/josam.739568
13. Atsawarungruangkit A, Chenbhanich J, Dickstein G. C-peptide as a key risk factor for non-alcoholic fatty liver disease in the United States population. World J Gastroenterol. 2018;24(32):3663–70. doi: 10.3748/wjg.v24.i32.3663
14. Chen M, Li T, Zhang R, Li L, Lu J, Bao Y, et al. Clinical features of non-alcoholic fatty liver disease and its relationship with serum C-peptide levels in patients with latent autoimmune diabetes in adults. Zhonghua Yi Xue Za Zhi. 2015;95:3575–8.
15. Chalasani N, Younossi Z, Lavine J.E, Li L, Lu J, Bao Y, et al. The diagnosis and management of non-alcoholic fatty liver disease: Practice guideline by the American association for the study of liver diseases, American college of gastroenterology, and the American gastroenterological association. Am. J. Gastroenterol. 2012;55(6):2005-23.
16. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;37(1):81–90. doi:10.2337/dc14-S081
17. Kulkarni CM, Patil S. Urinary C-peptide and urine C-peptide/creatinine ratio (UCPCR) are possible predictors of endogenous insulin secretion in T2DM subjects—a randomized study. Int J Pharma Bio Sci. 2016;7(4):443–6. doi: 10.22376/ijpbs.2016.7.4.b443-446
18. Leighton E, Sainsbury CA, Jones GC. A Practical Review of C-Peptide Testing in Diabetes. Diabetes Ther. 2017;8(3):475–87. doi: 10.1007/s13300-017-0265-4
19. El-Koofy NM, El-Karaksy HM, Mandour IM, Anwar GM, El-Raziky MS, El-Hennawy AM. Genetic polymorphisms in non-alcoholic fatty liver disease in obese Egyptian children. Saudi J Gastroenterol. 2011;17(4):265-7. doi: 10.4103/1319-3767.82582
20. Saisho Y, Kou K, Tanaka K, Abe T, Kurosawa H, Shimada A, et al. Postprandial serum C-peptide to plasma glucose ratio as a predictor of subsequent insulin treatment in patients with type 2 diabetes. Endocr J. 2011;58(4):315–22. doi: 10.1507/endocrj.K10E-399
21. Tricò D, Caprio S, Umano GR, Pierpont B, Nouws J, Galderisi A, et al. Santoro N. Metabolic Features of Nonalcoholic Fatty Liver (NAFL) in Obese Adolescents: Findings from a Multi-ethnic Cohort. Hepatology. 2018;68(4):1376-90. doi: 10.1002/hep.30035
22. Francque SM, Verrijken A, Hubens G, Marck EV, Pelckmans P, et al. Noninvasive assessment of nonalcoholic fatty liver disease in obese or overweight patients. Clin Gastroenterol Hepatol. 2012;10(10):1162-8. doi: 10.1016/j.cgh.2012.06.019
23. Manco M, Bedogni G, Marcellini M, Devito R, Ciampalini P, Sartorelli MR, et al. Waist circumference correlates with liver fibrosis in children with non-alcoholic steatohepatitis. Gut. 2008;57(9):1283–7. doi: 10.1136/gut.2007.142919.
24. Monteiro PA, Antunes Bde M, Silveira LS, Christofaro DG, Fernandes RA, Freitas Junior IF. Body composition variables as predictors of NAFLD by ultrasound in obese children and adolescents. BMC Pediatr. 2014;14: 947. doi: 10.1186/1471-2431-14-25.
25. Patel DA, Srinivasan SR, Chen W, Berenson G S. Serum alanine aminotransferase and its association with metabolic syndrome in children: the bogalusa heart study. Metab Syndr Relat Disord. 2001;9(3):211–6. doi: 10.1089/met.2010.0086.
26. Arslan N, Büyükebiz B, Öztürk Y, Cakmak H. Fatty liver in obese children: prevalence and correlation with anthropometric measurements and hyperlipidemia. The Turkish Journal of Pediatrics. 2005;47:23-7.

27. Fraser A, Longnecker MP, Lawlor DA. Prevalence of elevated alanine aminotransferase among US adolescents and associated factors: NHANES 1999–2004. Gastroenterology. 2007;133(6):1814–20. doi: 10.1053/j.gastro.2007.08.077
28. Manco M, Alisi A, Nobili V. Risk of severe liver disease in NAFLD with normal ALT levels: a pediatric report. Hepatology. 2008;48(6):2087–8. doi: 10.1002/hep.22631.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1133-1136.
DOI: 10.28982/josam.819626

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Effect of classical surgical treatment under spinal anesthesia on venous thromboembolism in varicose veins patients

Klasik cerrahi tedavinin spinal anestezi altında varisli hastalarda venöz tromboembolizme etkisi

Mevlüt Doğukan [1], Esma Kaplan Çalışkan [1]

[1] Department of Anesthesiology and Reanimation, Faculty of Medicine, Adıyaman University, Adıyaman, Turkey

ORCID ID of the author(s)

MD: 0000-0002-4890-758X
EKÇ: 0000-0002-2399-8534

Corresponding author/Sorumlu yazar:
Mevlüt Doğukan
Address/Adres: Adıyaman Üniversitesi Tıp Fakültesi Anesteziyoloji ve Reanimasyon Anabilim Dalı, Adıyaman, Türkiye
E-mail: drmevlud@hotmail.com

Ethics Committee Approval: The study was approved by the Adıyaman University Ethics Committee for Non-Invasive Research (2018/5-40). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma Adıyaman Üniversitesi İnvaziv Olmayan Araştırmalar Etik Kurulu (2018 / 5-40) tarafından onaylandı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: Although minimally invasive methods have developed rapidly in the treatment of varicose veins in recent years, high ligation + stripping (S/L), which is the classical surgical treatment, is still considered gold standard. Some thromboembolic events may occur due to varicose disease. Our aim is to determine the changes in mean platelet parameters after the procedure in patients who underwent S/L with spinal anesthesia and investigate the effect of this procedure on thromboembolic events.

Methods: Patients who visited the Anesthesia Reanimation outpatient clinic of Adiyaman University Faculty of Medicine and underwent S/L with spinal anesthesia were evaluated in this retrospective cohort study. Data was collected electronically with file scanning. Patients whose hemograms were obtained before and 1 day after the operation were included. Among the laboratory tests, MPV, PLT, platelet distribution width (PDW) and plateletcrit (PCT) were noted.

Results: Postoperative MPV (P<0,001) and PLT (P=0.01) values showed a significant decrease compared to the preoperative period, while PDW (P=0.194) and PCT (P=0.863) values remained similar.

Conclusion: If it is assumed that varicose veins and MPV are associated with thromboembolic events, a significant decrease in postoperative MPV value in patients who underwent S / L with spinal anesthesia will reduce thromboembolic events.

Keywords: Mean platelet volume, Thromboembolism, Stripping and ligation, Spinal anesthesia

Öz

Amaç: Varis tedavisinde minimal invaziv yöntemler özellikle son yıllarda hızla gelişme göstermesine rağmen klasik cerrahi tedavi olan yüksek ligasyon+stripping (S/L) halen altın standart kabul edilir. Varis hastalığına bağlı bazı tromboembolik olaylar meydana gelebilmektedir. Amacımız, spinal anestezi ve S/L uygulaması olan hastalarda işlem sonrası ortalama trombosit parametrelerindeki değişiklikleri belirlemek ve bu işlemin tromboembolik olaylara etkisini araştırmaktır.

Yöntemler: Bu çalışma retrospektif kohort çalışması olarak tasarlandı. Çalışmaya dahil edilen hastalar Adıyaman Üniversitesi Tıp Fakültesi Anestezi Reanimasyon polikliniğine başvuran ve spinal anestezi ile S/L yapılan hastalardan seçildi. Veriler elektronik ortamda dosya taraması şeklinde toplandı. Dosya taramasından operasyon öncesi ve 1 gün sonrası hemogram alınan hastalar çalışmaya dahil edildi. Laboratuvar tetkiklerinden MPV, PLT, trombosit dağılım genişliği (PDW) ve plateletcrit (PCT) tespit edilerek kaydedildi. İstatistiksel analizler SPSS 22,0 kullanılarak yapıldı.

Bulgular: Postoperatif MPV (P<0,001) ve PLT (P=0,01) değeri preoperatif döneme göre anlamlı düşüş gösterdi. PDW (P=0,194) ve PCT (P=0,863) değerlerinde postoperatif 1. gün, preoperatif döneme göre anlamlı bir değişim olmadığı görüldü.

Sonuç: Spinal anestezi altında S/L uygulanan hastalarda postoperatif MPV değerinde anlamlı bir düşüş gözlenmesi, varis hastalığının ve MPV ün tromboembolik olaylarla ilişkili olduğu varsayılırsa uygulanan cerrahi tromboembolik olayları azaltır.

Anahtar kelimeler: Mean platelet volüm, Tromboembolizm, Stripping ve ligasyon, Spinal anestezi

How to cite/Atıf için: Doğukan M, Çalışkan EK. Effect of classical surgical treatment under spinal anesthesia on venous thromboembolism in varicose veins patients. J Surg Med. 2020;4(12):1133-1136.

Introduction

Varicose veins and chronic venous insufficiency is a disease with high prevalence: It affects about half of the population [1,2]. Advanced age, sedentary lifestyle, positive family history, smoking, trauma, obesity, and previous thromboembolism play a role in the etiology [3]. Although minimally invasive methods such as thermal or non-thermal endovascular ablation have developed rapidly in recent years, the classical surgical method is still considered the gold standard treatment [2,4]. It is known that the tendency to thromboembolic events increases in patients with advanced varicose veins [5].

Stasis, slowing in blood flow and turbulence in varicose veins can activate coagulation mechanisms. Phlebothrombosis progresses to thrombophlebitis, which is a particularly painful condition. Delay in intervention may dislodge clots in the venous system and cause a severe and mortal complication, such as pulmonary embolism. This clinical progression can be prevented with timely treatments [5].

Many studies have shown that platelets play a role in cardiovascular events. Increased MPV levels are associated with an increased risk of thromboembolism [6,7]. Platelets, heterogeneous in activity and size, contain mitogenic and chemotactic factors that cause neointimal proliferation.

The most commonly used measure of platelet size is MPV. It is inexpensive and can be easily detected from the hemogram obtained from almost all patients undergoing surgery. Increased MPV is associated with increased platelet activity [8].

Our aim is to examine the changes in MPV and thrombocytes following the surgery, and the effect of varicose treatment on thrombogenicity in patients undergoing varicose vein surgery under spinal anesthesia, in light of the literature.

Materials and methods

The patients were selected from those who applied to Adıyaman University Faculty of Medicine Anesthesia Reanimation outpatient clinic between June 2018-December 2020 and underwent varicose vein surgery under spinal anesthesia. Adıyaman University Ethics Committee for Non-Invasive Research approved this retrospective cohort study with the reference number 2018/5-40. Patient data were obtained digitally with file scanning. Among 97 patients operated for varicose veins, 49 patients who had pre- and postoperative hemograms were included (Confidence interval: 95% (P<0.05), power: 80%). Patients with acute or chronic deep vein thrombosis, using anticoagulants for any other reason, those with peripheral artery disease, diabetes and those not receiving spinal anesthesia were not included in the study.

Blood samples for MPV and other platelet parameters were collected in tubes containing Ethylene Diamine Tetra Acetic Acid (EDTA) after an overnight fast and analyzed in the Cell DynRuby blood counter within half an hour. Coefficient of variation (inter assay) was <5 % in all measurements.

Statistical analysis

Analyses were performed with SPSS 22.0. The distribution of variables was evaluated with the Kolmogorov-Smirnov test. Descriptive statistics were presented as mean, standard deviation, median, lowest, highest, frequency and ratio values. A *P*-value of <0.05 was considered significant.

Results

A total of 49 patients (27 males, 22 females) who underwent S / L under spinal anesthesia with preoperative and postoperative hemogram values were included in the study. The mean age and body mass index values were 41.57 (11.3) years and 27.16 (3.26) kg/m^2, respectively (Table 1). The patients' white blood cell (WBC) (*P*<0.001), hemoglobin (HBG) (*P*=0.08) and hematocrit (HCT) (*P*<0.001) values showed a significant change on postoperative day 1 compared to the preoperative period (Table 2).

Table 1: Demographic data

		Min-Max	Median	Mean (SD)
Age		20-67	41.57	41.57(11.85)
BMI		19.40-35.40	27.50	27.16 (3.2)
		n (%)		
Gender	Male	27(55.1)		
	Female	22(44.89)		

Min: Minimum, Max: Maximum, SD: Standard deviation

Table 2: Preoperative and postoperative 1st day WBC, HBG and HCT values

	Min-max	Median	Mean (SD)	*P*-value
WBC				
Preoperative	4.50-17.50	7.80	8.48(2.73)	<0.001
Postoperative	5.40-14.50	10.30	10.13(2.37)	
HG				
Preoperative	9.90-17.30.	14.4	14.10(1.7)	0.008
Postoperative	9.20-17.10	13.6	13.67(1.8)	
HCT				
Preoperative	34.7-52.0	43.7	40.50 (4.0)	<0.001
Postoperative	31.4-50.0	41.0	840.50(4.8)	

WBC: White Blood Cell, HGB: Hemoglobin, HCT: Hematocrit, SD: Standard Deviation

On the 1st postoperative day, MPV (*P*<0.001) and PLT (*P*=0.001) values decreased significantly compared to the preoperative values, while platelet distribution width (*P*=0.194) and plateletcrit *(P*=0.863) values remained similar (Table 3). No thromboembolic event was noted in any of the patients in the study series.

Table 3: Preoperative and postoperative 1st day platelet parameters

	Min-max	Median	Mean (SD)	*P*-value
PLT				
Preoperative	80-349	227	229.28 (7.78)	0.001
Postoperative	72-343	206	212.26 (7.76)	
MPW				
Preoperative	5.6-15.7	7.4	8.1 (2.1)	0.000
Postoperative	4.9-16	6.8	7.3 (2.0)	
RDV				
Preoperative	11.30-22.1	18.6	17.6 (2.8)	0.194
Postoperative	10.8-22.8	18.9	17.9 (3.0)	
PCT				
Preoperative	0.08-0.65	0.17	0.18 (0.08)	0.863
Postoperative	0.08-09	0.15	018 (0.15)	

PLT: Platelet, PCT: Plateletcrit, MPV: Average platelet volume, PDW: Platelet distribution width, SD: Standard deviation

Discussion

Traditional anesthesia methods used in surgical treatments of varicose veins are general and spinal anesthesia [9]. Complications such as respiratory problems, nausea, vomiting and deep vein thrombosis are known to occur less frequently in spinal anesthesia compared to general anesthesia [10]. Neuraxial blocks reduce peripheral vasodilation and vascular resistance by creating efferent autonomic block and sympathetic block in nerve roots at the spinal level. [11]. After sympathetic block, tissue perfusion index increases, and tissue oxygenation improves. In a study performed on 355 patients who underwent classical varicose veins surgery, 10 patients (2.8%) received general anesthesia, 80 patients (22.5%), peripheral border block, and 265 patients (74.6%), spinal anesthesia [12].

In our study, the effects of classical varicose vein surgical treatment, performed under spinal anesthesia, on thromboembolic events was investigated. We showed that the postoperative value of MPV, which is predictive of venous thromboembolic events, significantly decreased compared to the preoperative period. This was an important result in terms of showing the protective effect of varicose surgery performed under spinal anesthesia against thromboembolic events.

Due to chronic venous insufficiency, venous hypertension and slow flow in varicose veins, intravascular coagulation mechanisms are activated. The event begins as superficial thrombophlebitis characterized by edema, pain, and hyperemia. If left untreated, this process may extend into the deep veins, causing deep vein thrombosis and even pulmonary embolism with high mortality. Varicose veins were detected in 32-100% of patients with superficial venous thrombophlebitis. Pulmonary embolism and deep vein thrombosis can develop in patients with varicose veins. Therefore, treatment of varicose veins is important [13,14]. Virchow's triad, consisting of endothelial damage, hypercoagulability, and stasis, plays a significant role in the etiopathogenesis of venous thromboembolism. Venous stasis is expected in patients with varicose veins, especially in those with dense pacts, which predisposes to thromboembolic events [15].

Inflammation and thrombogenic events cause changes in PLT size, which is determined by MPV and routine analyzers. MPV is affected by PLT aging and varies with turnover balance. Platelets, nucleated cells synthesized from megakaryocytes, play a role in vasoconstriction, hemostasis, vascular endothelial repair, and host defense. Recent studies have shown that atherogenesis formation is also effective in the development of many hematological diseases, tumor growth factor release and metastasis [16,17].

MPV is an inexpensive and easily measurable marker of platelet functions and activity. It is used in many routine clinical and preoperative applications. According to many reviews, increased MPV is associated with increased mortality in acute coronary syndromes, acute ischemic cerebrovascular events, and venous thromboembolic events [18–21].

In their study conducted with a total of 1094 patients, Chang et al. [17] showed that higher MPV in patients with acute coronary syndrome was associated with higher cardiovascular risk factors and higher cardiovascular events. Adam et al. [19] demonstrated that MPV, RDW and WBC are independent predictors of short-term mortality, and they are used in conjunction with coagulation profiles in the diagnosis of acute coronary syndrome in patients presenting with chest pain. Mayda-Domaç et al. [22] showed that MPV may be an early and important predictor for ischemic stroke, but the number of PLT plays a role in the outcome in hemorrhagic stroke. Again, in a different study of 327 patients, Farah et al. [21] concluded that MPV and the neutrophil-to-lymphocyte ratio may be useful for early detection of acute venous thromboembolism.

In thromboembolism, laboratory values are mostly used in differential diagnosis. Thrombocyte and platelet indices (such as MPV, platelet distribution width (PDW), plateletcrit (PCT)) increase in thromboembolic events. Normally, there is an inverse proportion between Platelets and MPV. Large MPV indicates low platelet count. Large platelets have been shown to contain more granules, are more adhesive, more metabolically and enzymatically active, more tightly bound to collagen, and therefore have increased thrombogenic properties [23].

Factors involved in the formation of varicose veins cause the remodeling of the vascular wall, the destruction and failure of the venous valves. With the inclusion of leukocyte-mediated inflammation, it may cause endothelial dysfunction, edema, ulcers and, in advanced stages, deep vein thrombosis [15]. All these events cause an increase in thrombocyte volume, a.k.a. MPV, in patients with varicose veins.

MPV can be studied on all hematology devices. Although the normal reference range varies depending on the device used, it is 7.2-11.7 fL. This value is affected by many factors, such as the device used, the tubes from which the blood samples are obtained, operating time, seasonal changes and even altitude [24].

In our study, blood samples were collected in tubes containing EDTA and studied within half an hour. There was no infectious disease, diabetes or other hematological diseases in patients that would affect MPV value. In addition, control blood samples were taken on the first postoperative day, preventing the result from being affected by intervening diseases. To the best of our knowledge, there has been no previous study in the literature investigating thromboembolic events with MPV value after surgical treatment under spinal anesthesia in varicose veins patients. None of the patients developed thromboembolic events postoperatively.

Limitations

The small number of patients, the retrospective nature of the study and the lack of a control group were the main limitations of our study. We believe that more effective results can be obtained with further prospective, controlled study conducted on larger patient populations.

Conclusions

Considering that MPV is involved in thromboembolic events, treatment of varicose veins may prevent related complications. We showed that a decrease in MPV can be achieved by treatment of varicose veins with the classical surgical method under spinal anesthesia.

Acknowledgements

I would like to thank a member of our faculty, a cardiovascular surgeon who I am happy to work with, Dr. Cengiz Güven, for sharing valuable information.

References

1. Callam MJ. Epidemiology of varicose veins. Br J Surg. 1994 Feb;81(2):167-73. doi: 10.1002/bjs.1800810204. PMID: 8156326.
2. Güven C, Haydar AB. Comparison of stripping/ligation and embolization with cyanoacrylate in venous insufficiency treatment. J Surg Med. 2020;4(5):400-5.
3. Youn YJ, Lee J. Chronic venous insufficiency and varicose veins of the lower extremities. Korean J Intern Med. 2019 Mar;34(2):269-83. doi: 10.3904/kjim.2018.230. Epub 2018 Oct 26. PMID: 30360023; PMCID: PMC6406103.
4. Güven C. Use of Cyanoacrylate in Venous Insufficiency and Varise Treatement and its Results. FÜ Sağ Bil Tıp Derg. 2020;34 (1):07-11.
5. Cosmi B. Management of superficial vein thrombosis. J Thromb Haemost. 2015 Jul;13(7):1175-83. doi: 10.1111/jth.12986. Epub 2015 May 25. PMID: 25903684.
6. Davi G, Patrono C. Platelet activation and atherothrombosis. N Engl J Med. 2007 Dec 13;357(24):2482-94. doi: 10.1056/NEJMra071014. PMID: 18077812.7.
7. Koza K, Grzelązka P, Trofimiuk A, Suppan K, Wasielewski M, Wiśniewska J, et al. Clinical risk factors for loss of stent primary patency in patients with chronic legs ischemia. Adv Clin Exp Med. 2017 Mar-Apr;26(2):311-8. doi: 10.17219/acem/58997. PMID: 28791851.
8. Rao AK, Goldberg RE, Walsh PN. Platelet coagulant activities in diabetes mellitus. Evidence for relationship between platelet coagulant hyperactivity and platelet volume. J Lab Clin Med. 1984 Jan;103(1):82-92. PMID: 6690642.9.

9. Memetoglu ME, Kurtcan S, Kalkan A, Özel D. Combination technique of tumescent anesthesia during endovenous laser therapy of saphenous vein insufficiency. Interact Cardiovasc Thorac Surg. 2010 Dec;11(6):774-7. doi: 10.1510/icvts.2010.240762. Epub 2010 Sep 16. PMID: 20847066.
10. Bar-Or D, Lau E, Winkler JV. A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia-a preliminary report. J Emerg Med. 2000 Nov;19(4):311-5. doi: 10.1016/s0736-4679(00)00255-9. PMID: 11074321.
11. Demirel CB, Kalayci M, Ozkocak I, Altunkaya H, Ozer Y, Acikgoz B. A prospective randomized study comparing perioperative outcome variables after epidural or general anesthesia for lumbar disc surgery. J Neurosurg Anesthesiol. 2003 Jul;15(3):185-92. doi: 10.1097/00008506-200307000-00005. PMID: 12826965.
12. Özyaprak B, Anarat K, Erkan G, Kahraman N, Retrospective evaluation of anesthesia methods applied in varicose surgery in our clinic. 6th Rize Thematic Anesthesia Symposium E-booklet. 2019:22-27.
13. Demirel CB, Kalayci M, Ozkocak I, Altunkaya H, Ozer Y, Acikgoz B. A prospective randomized study comparing perioperative outcome variables after epidural or general anesthesia for lumbar disc surgery. J Neurosurg Anesthesiol. 2003 Jul;15(3):185-92. doi: 10.1097/00008506-200307000-00005. PMID: 12826965.
14. Lee SH, Kim WH. Superficial Vein Thrombosis and Severe Varicose Veins Complicating Venous Thromboembolism. J Cardiovasc Imaging. 2019 Apr;27(2):154-5. doi: 10.4250/jcvi.2019.27.e14. PMID: 30993952; PMCID: PMC6470065..
15. Wu NC, Chen ZC, Feng IJ, Ho CH, Chiang CY, Wang et al.,Severe varicose veins and the risk of mortality: a nationwide population-based cohort study. BMJ Open. 2020 Jun 21;10(6):e034245. doi: 10.1136/bmjopen-2019-034245. PMID: 32565451; PMCID: PMC7311034.
16. Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: a link between thrombosis and inflammation? Curr Pharm Des. 2011;17(1):47-58. doi: 10.2174/138161211795049804. PMID: 21247392.
17. Altunisik N, Turkmen D, Sener S. Investigation of the relationship between inflammatory blood parameters and rosacea and demodex infestation. J Cosmet Dermatol. 2020 Aug;19(8):2105-8. doi: 10.1111/jocd.13254. Epub 2019 Dec 16. PMID: 31840349.
18. Chang HY, Hsu LW, Lee CH, Lin CC, Huang CW, Chen PW, et al. Impact of Platelet Volume on the Clinical Outcomes of Patients with Acute Coronary Syndrome. Acta Cardiol Sin. 2019 Nov;35(6):563-70. doi: 10.6515/ACS.201911_35(6).20190423B. PMID: 31879507; PMCID: PMC6859097.
19. Adam AM, Ali MA, Shah AA, Rizvi AH, Rehan A, Godil A, et al. Efficacy of Hematological and Coagulation Parameters in the Diagnosis and Prognosis of Patients with Acute Coronary Syndrome. J Tehran Heart Cent. 2018 Jul;13(3):115-25. PMID: 30745924; PMCID: PMC6368913.
20. Sadeghi F, Kovács S, Zsóri KS, Csiki Z, Bereczky Z, Shemirani AH. Platelet count and mean volume in acute stroke: a systematic review and meta-analysis. Platelets. 2020 Aug 17;31(6):731-9. doi: 10.1080/09537104.2019.1680826. Epub 2019 Oct 26. PMID: 31657263.
21. Farah R, Nseir W, Kagansky D, Khamisy-Farah R. The role of neutrophil-lymphocyte ratio, and mean platelet volume in detecting patients with acute venous thromboembolism. J Clin Lab Anal. 2020 Jan;34(1):e23010. doi: 10.1002/jcla.23010. Epub 2019 Sep 11. PMID: 31508844; PMCID: PMC6977138.
22. Mayda-Domaç F, Misirli H, Yilmaz M. Prognostic role of mean platelet volume and platelet count in ischemic and hemorrhagic stroke. J Stroke Cerebrovasc Dis. 2010 Jan;19(1):66-72. doi: 10.1016/j.jstrokecerebrovasdis.2009.03.003. PMID: 20123229.
23. Machin SJ, Briggs C. Mean platelet volume: a quick, easy determinant of thrombotic risk? J Thromb Haemost. 2010 Jan;8(1):146-7. doi: 10.1111/j.1538-7836.2009.03673.x. Epub 2009 Oct 30. PMID: 19874471.
24. Beyan C, Beyan E. Were the measurements standardized sufficiently in published studies about mean platelet volume? Blood Coagul Fibrinolysis. 2017 Apr;28(3):234-6. doi: 10.1097/MBC.0000000000000586. PMID: 27388283.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1137-1142.
DOI: 10.28982/josam.804767

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Evaluation of omentin levels in patients with unstable angina pectoris, non-ST elevated myocardial infarction (NSTEMI) and STEMI

Kararsız angina pektoris, ST elevasyonlu miyokard enfarktüsü (STEMI) ve Non-STEMI olan hastalarda omentin düzeylerinin değerlendirilmesi

Tayyar Akbulut [1], Ramazan Asoğlu [2], Mahmut Özdemir [3], Nesim Aladağ [1], İrem Karaüzüm [4], Abdulcebbar Şipal [1], Kurtuluş Karaüzüm [4]

[1] Van Training and Research Hospital, Cardiology Department, Van, Turkey
[2] Adıyaman University Training and Research Hospital, Cardiology Department, Adıyaman, Turkey
[3] İstanbul Aydın University, Cardiology Department, İstanbul, Turkey
[4] Department of Cardiology, Medicine Faculty of Kocaeli University, Kocaeli, Turkey

ORCID ID of the author(s)

TA: 0000-0002-5890-8420
RA: 0000-0002-4777-1166
MÖ: 0000-0002-0021-3415
NA: 0000-0003-2346-1152
İK: 0000-0002-8015-6253
AŞ: 0000-0002-6379-8342
KK: 0000-0002-7088-1590

Corresponding author/Sorumlu yazar:
Mahmut Özdemir
Address/Adres: İstanbul Aydın Üniversitesi, Kardiyoloji Bölümü, İstanbul, Türkiye
E-mail: dr.mahmutozdemr56@yahoo.com

Ethics Committee Approval: This study was approved by the Ethics Committee of the Kocaeli University Hospital (Ethic no: 053, Date: 18/05/2012). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma Kocaeli Üniversite Hastanesi Etik Kurulu tarafından onaylanmıştır (Etik no: 053, Tarih: 18/05/2012). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: Acute coronary syndrome (ACS) is an ischemic cardiac disease that could result in myocardial necrosis with prolonged ischemia. Omentin (intelectin-1) is a new biomarker that is released from adipose tissue. It is associated with coronary artery disease (CAD) and has an acute ischemic injury-reducing effect. This study aimed to assess the omentin levels in patients with unstable angina pectoris (USAP), Non-ST segment elevation myocardial infarction (NSTEMI), and ST-segment elevated myocardial infarction (STEMI).

Methods: This case-control prospective study included 59 patients with ACS and 22 healthy subjects. MB fraction of creatine kinase (CKMB), troponin, myoglobin, and omentin levels were measured from venous blood obtained from each patient within six hours after the onset of symptoms. Plasma omentin levels were determined with an omentin enzyme-linked immunosorbent assay kit.

Results: The patient group was older than the control group (P<0.05) but there was no difference between the groups in terms of gender (P>0.05). The rate of smoking was higher in the patient group, and the patient group was heavier than the control group (P>0.05). Omentin levels were similar in ACS patients and control subjects (6.0 (1.7) vs. 6.3 (1.3), P=0.40). There was no significant correlation among CKMB, troponin, myoglobin, and omentin levels. Moreover, omentin levels were similar in ACS subgroups (P=0.58). There was no significant correlation between body mass index and omentin levels (r =-0.186, P=0.09).

Conclusion: This study revealed that there was no significant relationship between omentin and myoglobin levels in ACS patients. The potential usefulness of blood concentrations of omentin levels in understanding the relationship with ACS warrants further studies.
Keywords: Omentin, Acute coronary syndrome, CKMB, Troponin, Myoglobin

Öz

Amaç: Çalışma vaka-kontrol şeklinde dizayn edildi. Akut koroner sendrom (AKS), uzun süreli iskemi sonrası miyokard nekrozu ile sonuçlanabilen iskemik bir kalp hastalığıdır. Omentin (intelectin-1), yağ dokusundan salınan yeni bir biyobelirteçtir. Omentin koroner arter hastalığı (CAD) ile ilişkilidir ve akut iskemik hasarı azaltıcı etkiye sahiptir. Bu çalışma, kararsız anjina pektoris (USAP), ST elevasyonsuz miyokard enfarktüsü (NSTEMI) ve ST elevasyonlu miyokard enfarktüsü (STEMI) olan hastalarda omentin düzeylerini değerlendirmeyi amaçlamıştır.

Yöntemler: Bu çalışmaya prospektif olarak 59 AKS hastası ve 22 sağlıklı birey dahil edildi. Semptomların başlamasından sonraki altı saat içinde her hastadan alınan venöz kandan kreatin kinaz MB formu (CKMB), troponin, miyoglobin ve omentin düzeyleri ölçüldü. Plazma omentin seviyeleri, bir omentin enzimine bağlı immünosorban test kiti ile belirlenmiştir.

Bulgular: Hasta grubu kontrol grubundan daha yaşlıydı (P<0,05) ancak cinsiyet açısından gruplar arasında fark yoktu (P>0,05). Hasta grubunda sigara içme oranı daha fazlaydı ve hasta grubu kontrol grubuna göre daha ağırdı (P>0,05). AKS hastalarında ve kontrol grubunda omentin düzeyleri benzerdi (6,0 (1,7) ve 6,3 (1,3); P=0,40). CKMB, troponin, miyoglobin ve omentin düzeyleri arasında anlamlı bir ilişki yoktu. CKMB, troponin, miyoglobin ve omentin düzeyleri arasında anlamlı bir korelasyon yoktu, ayrıca AKS alt gruplarında omentin düzeyleri benzerdi (P=0,58). Vücut kitle indeksi ile omentin düzeyleri arasında anlamlı bir ilişki yoktu (r = -0,186, P=0,09).

Sonuç: Bu çalışma AKS hastalarında omentin ve miyoglobin düzeyleri arasında anlamlı bir ilişki olmadığını ortaya koymuştur. Omentin düzeylerinin kan konsantrasyonlarının AKS ile ilişkisinin anlaşılmasındaki potansiyel faydası daha fazla çalışmaya ihtiyaç duyar.
Anahtar kelimeler: Omentin, Akut koroner sendrom, CKMB, Troponin, Miyoglobin

How to cite/Atıf için: Akbulut T, Asoğlu R, Özdemir M, Aladag N, Karaüzüm İ, Şipal A, Karaüzüm K. Evaluation of omentin levels in patients with unstable angina pectoris, non-ST elevated myocardial infarction (NSTEMI) and STEMI. J Surg Med. 2020;4(12):1137-1142.

Introduction

Ischemic heart disease is the main instigator of mortality worldwide [1]. Acute Coronary Syndrome or ACS is described as a conglomeration of various signs and symptoms that results due to an imbalance between myocardial oxygen supply and demand [2]. ACS can also be identified as an ischemic cardiac situation that can lead to both myocardial damage and necrosis in correlation with a protracted duration of ischemia. ACS represents the most damaging clinical expression of coronary artery disease (CAD), in which the pathophysiological mechanism is initiated by plaque rupture. ACS can be categorized into three types: ST elevated myocardial infarction (STEMI), unstable angina, and non-ST elevated myocardial infarction (NSTEMI). The most frequently used biomarkers in the diagnosis of ACS are CKMB, troponin, and myoglobin [3].

Many adipokines such as leptin, adiponectin, and visfatin are released from adipocytes in adipose tissue and function as an endocrine organ. These adipokines play physiological and pathophysiological roles in many systems in the body, including the cardiovascular system [4]. Omentin (intelectin-1) is a hydrophilic protein that is released from the adipose tissue, consists of 313 amino acids, has a molecular weight of 35kDa, and it is also a new biomarker in the good adipokine category. It is released from vascular stromal cells in adipose tissue, as well as from epicardial adipose tissue and endothelial cells [5]. Its anti-inflammatory effects have been reported in the literature [6]. These effects of omentin occur with different cellular signal pathways such as cyclooxygenase-2 (COX-2), endothelial nitric oxide synthase (eNOS), and nitric oxide (NO) [7]. Omentin levels significantly decrease in obesity, insulin resistance, and diabetes mellitus [8].

It is known that omentin plays a protective role against arterial calcification, and that low omentin levels are related to the development of atherosclerosis [9, 10]. In a previous study, it has been reported that omentin is strictly related to coronary artery disease (CAD), and it is a new biomarker which determines the presence of CAD [11]. In their study, Zhong et al. [12] showed that their patients in their study group, who were diagnosed with stable angina pectoris (SAP) and acute coronary syndrome (ACS), had lower serum omentin levels compared to the control group. Omentin levels during admission are observed to correlate with the severity of CAD in patients who have metabolic syndrome presenting with AMI [13]. Moreover, in a study, it has been demonstrated that omentin reduces acute ischemic damage in myocardial tissue by preventing myocyte apoptosis [14].

In the current study, our aim was to analyze and assess the omentin levels in patients diagnosed with unstable angina pectoris (USAP), Non-ST segment elevation myocardial infarction (NSTEMI), and ST-segment elevation. Our second objective was to analyze the correlation between omentin levels and myoglobin levels in patients with ACS. By a comprehensive literature review, we surmise that this is the first time that the relationship between omentin levels and myoglobin in ACS patients has been investigated in a study.

Materials and methods

The current case-control and prospective study included 59 patients who were admitted to Kocaeli University, Medical Faculty, Emergency Services with angina and diagnosed with ACS between December 2018 and December 2019. Twenty-two healthy individuals were selected to serve as a control group for this study. A cardiologist examined all of the subjects, and information on medical histories was obtained via a questionnaire. All of the enrolled patients had to undergo electrocardiography (ECG) within one hour of their admission. The exclusion criteria included patients with valvular heart disease, coronary artery bypass graft surgery, hematological disorders, malignant disease, acute or chronic infection, chronic heart failure (class III and IV), pharmacological immunosuppressive or glucocorticoid therapy, and decreased systolic function (ejection fraction <45%).

ACS patients were categorized into three distinct groups: STEMI, NSTEMI, and UAP. Twenty-nine patients were diagnosed with STEMI based on their clinical symptoms, including electrocardiogram evidence (ST elevation in two or more leads), coronary angiography findings (occlusion of a main coronary artery branch), significantly increased serum troponin-I levels (more than twice the upper limit of normal), and CKMB. Eighteen patients were diagnosed with STEMI based on their clinical symptoms including ST-segment depression, or marked T wave inversion on ECG, and with biomarkers of myocardial necrosis above the normal levels. Twelve patients were diagnosed with UAP based on having ischemic chest pain at rest within the preceding 48 hours or within the past month, with transient ST-T segment depression, or T wave inversion, and normal serum levels of CKMB and troponin.

Before conducting a primary percutaneous coronary intervention (PCI), STEMI patients were treated with clopidogrel 600 mg, aspirin 300 mg, and intravenous heparin (70 – 100 U/kg). Beta-blockers and statins were administered to the STEMI patients after PCI. NSTEMI patients were treated with aspirin (300 mg), low-molecular-weight heparin, statins, clopidogrel (initially 300 mg and subsequently 75 mg), and beta-blockers at the time of admission. Coronary angiography was performed with the Judkins technique within three hours from the initial chest pain symptoms in patients with STEMI by experienced cardiologists, according to the guidelines for coronary angiography and percutaneous coronary intervention of the American Heart Association. Angiography was performed within three days in NSTEMI patients. UAP patients were followed up medically, and angiography was evaluated according to the exercise test or myocardial scintigraphy results. All angiography was conducted utilizing a Philips (Integris BH 5000, Philips, Netherlands) coronary angiography equipment. Selective coronary angiograms, conducted with the femoral approach by utilizing 6-French (F) and 7-F Judkins catheters, were evaluated by quantitative analysis (AET-met S.P.A. Italy QCA). Luminal stenosis, which was more than 50% in any of the coronary vessels, was considered CAD.

Hypertension (HT) was defined as having systolic blood pressure greater than or equal to 140 mmHg, and diastolic blood pressure greater than or equal to 90 mmHg, or a condition requiring the use of any antihypertensive medications. The

diagnosis of Type 2 Diabetes Mellitus (DM) was made according to the criteria set by the American Diabetes Association. Smoking was defined as an active or prior use of tobacco for greater than 10 pack/years. Body mass index (BMI) was calculated by dividing the body weight in kilograms by the square of the height value. Before the initiation of the study, all of the patients signed their informed consent forms. This study was conducted according to the principles of the Declaration of Helsinki and approved by the local Ethics Committee of the Kocaeli University Hospital (Ethic no: 053, Date: 18/05/2012).

The levels of troponin I, MB fraction of creatine kinase (CKMB), myoglobin, creatinine, low-density lipoprotein-cholesterol (LDL), high-density lipoprotein-cholesterol (HDL), total cholesterol (TC), triglyceride, C-reactive protein (CRP), sedimentation rate, and whole blood count were measured using the venous blood samples that were obtained from each patient within 6 hours after the onset of the first symptoms. The cubital vein was used for obtaining the peripheral venous blood samples and the samples were collected into heparinized tubes, and subsequently, for the separation of the plasma, the cells were centrifuged at a rate of 3000 rpm for a duration of 10 minutes and then stored at a temperature of −80°C until the day of biochemical analysis. CK-MB and cardiac TnI levels were measured in the serum by Simens ADVIA Centaur Cp analyzers in the emergency laboratory. The measurement of the Myoglobin levels was conducted with a sandwich ELISA immunoassay using an anti-myoglobin monoclonal antibody and an anti-myoglobin polyclonal antibody. The determination of the plasma omentin levels was achieved with the use of an omentin enzyme-linked immunosorbent assay (ELISA) kit (Bio Vendor, NC, USA). The intra-assay and inter-assay coefficients of variation of this kit were 4.1% and 4.8%, respectively.

Statistical analysis

Data were analyzed with SPSS software version 25.0 for Windows (SPSS Inc, Chicago, Illinois). Kolmogorov-Smirnov test was used to verify that continuous variables were normally distributed. Normally distributed variables were expressed as mean (standard deviation (SD)), while non-normally distributed variables were expressed as median with interquartile range (IQR). The categorical variables were presented as percentages. The differences between the two groups were evaluated with Student's unpaired t-test for parameters with a normal distribution. In multiple comparisons, one-way analysis of variance (ANOVA) test followed by the Tukey post hoc test was used for the normally distributed continuous data, while the nonparametric Kruskal-Wallis test was used to analyze continuous, non-normally distributed data. The frequencies of nominal variables were compared using Fisher's exact test or chi-square test. Pearson and Spearman's tests were used to examine correlations between continuous variables. Statistical significance was defined as $P<0.05$.

Results

The study population's demographic and clinical data are provided in Table 1. In the study, there were 22 healthy individuals (14 males, 8 females) who constituted the control group, and 59 ACS patients who constituted the patient group (41 males, 18 females). Patients were older than the control group, but the two groups were similar in terms of gender distribution. The rate of smoking was higher in the patient group, and the patient group was heavier in weight compared to the control group. While TC, LDL, triglyceride levels were higher in the patient group, HDL level was higher in the control group. CRP levels and sedimentation rates, both of which are markers of inflammation, were higher in the patient group. While hemoglobin was higher in the control group, WBC was higher in the patient group. However, no significant difference was observed in platelet values between the groups. Omentin levels were similar in the control and patient groups (6.3 (1.3) vs. 6.0 (1.7); $P=0.40$). Figure 1 shows the values of omentin between groups. Troponin, CKMB, and myoglobin parameters are provided in Table 1.

Table 1: Demographic and clinical data of the study population

	Control (n=22)	Patients (n=59)	*P*-value
Age (years)	31.2(13.1)	59.9(12.2)	<0.001
Male/Female, n	14/8	41/18	0.60
BMI (kg/m^2)	24.2(2.2)	27.7(3.4)	<0.001
Smoking n(%)	3(13%)	26(44%)	0.001
Hypertension n(%)	-	46(77%)	-
Diabetes mellitus n(%)	-	21(35%)	-
Total cholesterol (mg/dl)	135.9(25.2)	183.8(36.6)	<0.001
Low density lipoprotein (mg/dl)	76.3(16.7)	118.6(33.3)	<0.001
High density lipoprotein (mg/dl	42.9(5.9)	37.5(8.7)	0.009
Triglyceride (mg/dl)	111.6(21.1)	137.6(58.3)	0.04
C-reactive protein (mg/L)	1.2(0.7)	2.3(0.7-5.4)	0.02
Creatinine (mg/dl)	0.7(0.2)	1.0(0.7-1.2)	0.001
Sedimentation rate (mm/hr)	10.0(5.5)	23.4(16.6)	<0.001
White blood cell count (10^3/mm^3)	5.7(1.4)	9.1(2.6)	<0.001
Platelet count (10^3/mm^3)	239.3(42.4)	265.5(72.8)	0.11
Hemoglobin (g/dL)	13.9(0.9)	12.8(1.7)	0.007
Omentin (ng/ml)	6.3(1.3)	6.0(1.7)	0.40
Troponin (ng/ml)	-	5.7(8.0)	-
CKMB (ng/ml)	-	83.0(9.0-234.0)	-
Myoglobin (ng/mL)	-	268.0(91-656)	-

BMI: Body mass index, CKMB: Creatine kinase-MB

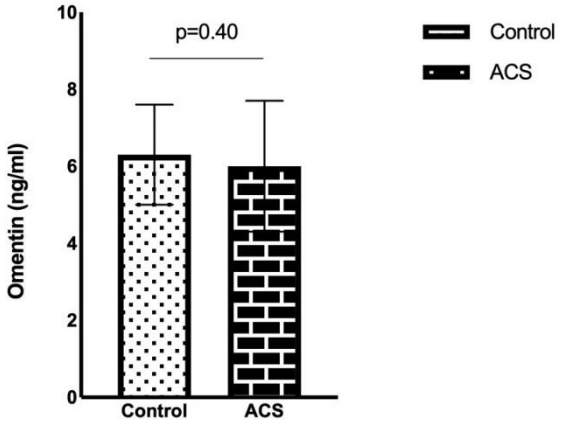


Figure 1: Omentin levels between study groups

A comparison of ACS subgroups and the control group are shown in Table 2. No statistically significant difference was observed in age, gender, BMI, HT, DM, and smoking rates within the ACS subgroups. Smoking rates were significantly higher in the STEMI group compared to the control group. While TC and LDL levels were similar in ACS subgroups, they were higher compared to the control group. The lowest HDL levels were observed in the NSTEMI group, and it was significantly different from the control group. Triglyceride levels were similar among ACS subgroups and the control group. While the sedimentation rate was higher in ACS subgroups, CRP levels were similar among the study groups. WBC, hemoglobin, and platelet counts were similar in the ACS subgroups.

The levels of omentin were similar in the USAP, NSTEMI, STEMI, and control groups ($P=0.58$). Figure 2 shows the levels of omentin in the ACS subgroups and the control

group. Troponin, CKMB, and myoglobin levels were highest in the STEMI group and lowest in the USAP group. In correlation analysis, no significant relationship was observed among omentin, troponin, CKMB, and myoglobin levels (Table 3).

Furthermore, no statistically significant correlation was found between Omentin levels and BMI. The correlation between omentin and myoglobin was shown in Figure 3 (r=-0.017 *P*=0.881).

Table 2: Clinical and demographic data of the control and acute coronary syndrome subgroups

	Control (n=22)	USAP (n=12)	NSTEMI (n=18)	STEMI (n=29)	*P*-value
Age (years)	31.2(13.1)	62.3(10.1)[a]	61.7(12.6)[a]	57.8(12.7)[a]	<0.001
Male/Female, n	14/8	8/4	12/6	21/8	0.92
BMI (kg/m^2)	24.2(2.2)	28.0(3.7)[a]	27.9(3.9)[a]	27.4(3.2)[a]	0.001
Smoking n(%)	3(13%)	4(33%)	5(28%)	17(56%)[a]	0.007
Hypertension n(%)	-	10(83%)	16(89%)	20(69%)	0.24
Diabetes mellitus n(%)	-	5(41%)	8(44%)	8(27%)	0.44
Total cholesterol (mg/dl)	135.9(25.2)	172.9(31.7)[a]	176.9(37.6)[a]	192.5(37.0)[a]	<0.001
Low density lipoprotein (mg/dl)	76.3(16.7)	116.8(32.4)[a]	111.8(35.1)[a]	123.6(33.0)[a]	<0.001
High density lipoprotein (mg/dl	42.9(5.9)	39.4(11.)2	34.9(8.4)[a]	38.3(7.7)	0.02
Triglyceride (mg/dl)	111.6(21.1)	131.1(55.9)	147.6(67.9)	134.1(54.1)	0.17
C-reactive protein (mg/L)	1.2(0.7)	1.6(0.4-5.3)	3.4(3.6)	2.7(1.1-4.9)	0.07
Creatinine (mg/dl)	0.7(0.2)	1.2(0.5)[a]	1.2(0.8-1.4)[a]	0.9(0.3)[b,c]	0.001
Sedimentation rate (mm/hr)	10.0(5.5)	17.5(10.0-27.5)[a]	17.0(12.3-30.0)[a]	23.0(10.5-36.5)[a]	0.001
White blood cell count (10^3/mm^3)	5.7(1.4)	8.5(1.9)[a]	8.5(2.9)[a]	9.7(2.7)[a]	<0.001
Platelet count (10^3/mm^3)	239.3(42.4)	291.6(87.2)	274.6(62.0)	249.0(71.0)	0.09
Hemoglobin (g/dL)	13.9(0.9)	12.8(2.0)	12.4(1.4)[a]	13.1(1.8)	0.02
Omentin (ng/ml)	6.3(1.3)	5.7(0.8)	5.8(1.1)	6.2(2.2)	0.58
Troponin (ng/ml)	-	0.10(0.10-0.19)	0.80(0.2-3.2)[b]	6.9(2.4-17.5)[b,c]	<0.001
CKMB (ng/ml)	-	2.3(1.1)	33.0(14.8-129.5)[b]	169.0(97.0-408.5)[b,c]	<0.001
Myoglobin (ng/mL)	-	28.0(13.0-54.5)	278.0(136.8-403.8)[b]	543.0(216.5-900.0)[b,c]	<0.001

USAP: Unstable angina pectoris, NSTEMI: Non-ST segment elevation myocardial infarction, STEMI: ST segment elevation myocardial infarction, BMI: Body mass index, CKMB: Creatine kinase-MB, [a] Control vs Other groups, [b] USAP vs. NSTEMI/STEMI, [c] NSTEMI vs. STEMI

Table 3: Correlation analyses between Omentin and CKMB, Troponin and Myoglobin

	Omentin	
	r	*P*-value
CKMB	-0.083	0.463
Troponin	-0.095	0.397
Myoglobin	-0.017	0.881
BMI	-0.186	0.09

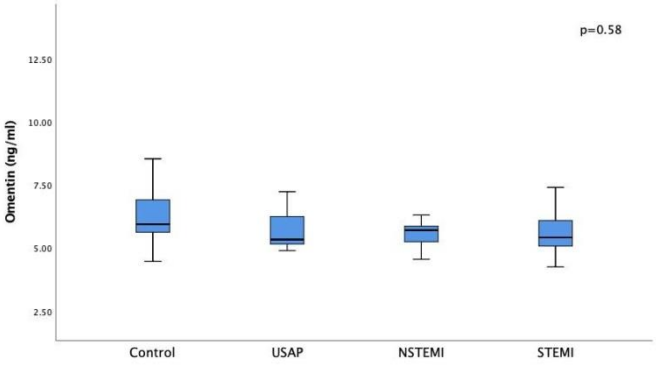


Figure 2: Omentin levels between acute coronary syndrome subgroups and control group

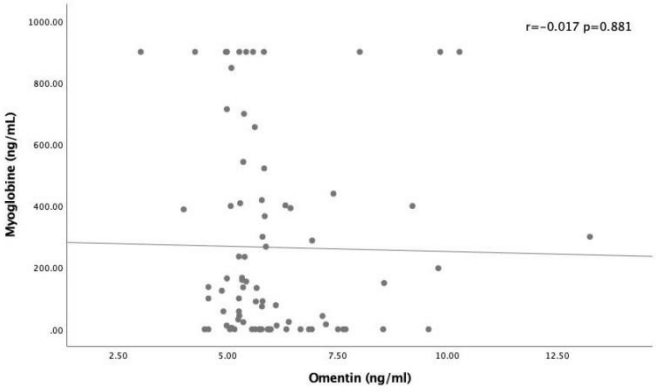


Figure 3: The correlation relationship between omentin and myoglobin levels

Discussion

In the current study, omentin levels were similar among ACS patients and healthy subjects. There was no significant correlation between the omentin and ischemic biomarkers such as CKMB and troponin. As far as we know, this is the first study in the literature to investigate the relationship between omentin levels and myoglobin in ACS patients. Moreover, we presented that no association exists between omentin and myoglobin levels in patients with ACS.

Recent studies have determined that there is an association between omentin levels and inflammatory responses. Turkcu et al. [15] reported that while serum omentin levels decrease, the TNF-α/omentin ratio and TNF-α levels increase in patients with Behcet's disease. The low levels of serum omentin values can predict adverse cardiac events in patients with heart failure (HF). It has also been suggested that omentin is a new prognostic marker in the risk classification of patients with HF. Serum omentin levels have been shown to decrease in cases of oxidative stress and chronic inflammation in HF patients [16]. Moreover, low serum omentin levels are associated with many metabolic risk factors such as high blood pressure, glucose tolerance, dyslipidemia, and increased navel environment [17]. The inflammation-reducing effects of omentin occur through signaling pathways such as Cyclooxygenase-2 (COX-2), endothelial nitric oxide synthase (eNOS), nitric oxide (NO), and nuclear factor kappa B (NF-κB) [18]. Omentin activates the AMP-activated protein kinase (AMPK), which reduces endothelial inflammation through E-selectin inhibition [7]. AMPK also activates eNOS, which has a vasodilating effect. Activated eNOS blocks the c-Jun N-terminal protein kinases (JNK) activation, which plays a role in the activation of inflammation through TNF-α-mediated COX2 induction in the cell [18]. Omentin has an antiangiogenic effect by inhibiting Akt and NF-κB signaling pathways. So, AMPK- and Akt-dependent mechanisms show acute ischemic damage reducing effects in the myocardial tissue [7]. A recent study demonstrated that omentin activated the Akt – eNOS signaling pathway in order to improve the revascularization and endothelial cell function in response to ischemia [19].

The production of pro- and anti-inflammatory adipocytokines from epicardial adipose tissue (EAT) could change in certain pathological situations [20]. Adiponectin expression decreases, and proinflammatory adipocytokine expressions such as IL-6 and TNF-alpha increases in patients with CAD [21]. So, it is accepted that these adipocytokines released from the EAT via vasocrine and paracrine routes regulate the atherosclerotic process [22]. Endothelial dysfunction is associated with subclinical atherosclerosis. Omentin shows anti-atherogenic effects through increasing endothelial NO and by reducing inflammation and oxidative stress. In a study by Yamawaki et al. [23], it was reported that omentin can inhibit vasoconstriction by endothelium-dependent mechanisms in mice aorta. Moreno-Navarrete et al. [24] suggested that the levels of plasma omentin are a marker indicating endothelial function due to their relationship with endothelial vasodilation. Omentin is inversely associated with CAD, and it was reported that omentin can be utilized as a biomarker to diagnose CAD [10, 11].

Previous studies reported that low omentin levels existed in coronary endothelium, epicardial adipose tissue, and serum in patients with CAD [25, 26]. Omentin levels positively correlated with BMI, serum interleukin-6, systolic blood pressure, hemoglobin-A1c (glycosylated hemoglobin), and total cholesterol levels, and negatively correlated with HDL and adiponectin levels [12, 27]. It has been determined that omentin levels predict adverse cardiac events regardless of the severity of angiographic lesions [17].

Previous studies presented that omentin levels were significantly lower in DM patients with ischemic heart disease. Another study also suggests that ACS patients have lower omentin levels [12]. Omentin has a reducing effect on myocyte apoptosis in ischemic tissue by suppressing AMPK- and Akt-dependent mechanisms [14]. Omentin also decreases the vascular smooth muscle cell proliferation and neointimal formation after arterial injury [28]. Moreover, it improves myocardial damage and myocardial functions in patients with STEMI [14]. Time-dependent kinetic changes in omentin levels have been associated with early improvement of ejection fraction and negative remodeling in patients with anterior STEMI. Because omentin ameliorates the myocardial damage, it was considered a cardioprotective acute phase reactant in ACS patients. High omentin levels and low CKMB levels were observed in ACS patients at the time of admission [29]. Du et al. [25] demonstrated that omentin levels were lower in CAD, and the amount of omentin expression was lower in adipose tissue around the stenotic coronary artery than the adipose tissue surrounding the non-stenotic coronary artery. However, there was no difference in the expression of adiponectin levels in the adipose tissue around the stenotic and non-stenotic coronary arteries. Omentin level was significantly lower, and IL-6 level was significantly higher in ACS patients compared to stable angina pectoris (SAP) group and the control group. Furthermore, omentin was a CAD predictor, and it also negatively correlated with IL-6 [12].

In the present study, omentin levels were similar between ACS patients and healthy subjects.

Several reports indicated that omentin levels were lower in ACS patients. These reports suggest that the principal reason for low omentin levels was the reduced release of omentin into plasma [25]. Harada et al. [30] presented that a low omentin level was associated with EAT volume in CAD patients, but this relationship was not significant. In this study, we thought that omentin levels were similar in study groups due to the similar EAT thickness, volume, or mRNA expression of omentin in EAT. However, we did not evaluate EAT thickness, volume, and mRNA expression of omentin. It has previously been shown in patients with ACS that there was an inverse correlation between omentin levels and BMI [31]. In our study, no significant correlation was observed between omentin levels and BMI, and it could explain the similar omentin levels between the study groups. Furthermore, no statistically significant relationship was observed among omentin, CKMB, troponin, and myoglobin levels. These non-significant correlations could be explained by the timing of the blood analyses, which were conducted within six hours after the observation of the initial symptoms. If serial measurements were made, a significant correlation could be observed. So, further studies need to be conducted to verify these findings.

Limitations

One of the significant limitations of our study was that the study group was limited to patients who were diagnosed with ACS. Hence, the findings of this study cannot be generalized to all patients with atypical symptoms, stable angina pectoris, and CAD. The relatively limited number of patients could limit the strength of results and conclusions obtained from this study. Although we measured the CKMB, troponin, myoglobin, and omentin levels within 6 hours of admission, we did not perform serial measurements of these parameters. Future investigations with more number of patients are needed to evaluate the CKMB, troponin, myoglobin, and omentin measurement levels for patients presenting with ACS. The other limitation of the study was that the ischemic modified albumin, which is an ischemia biomarker, was not measured and compared with omentin levels. Moreover, the effect of omentin on prognosis in ACS patients was not evaluated in this study. Despite these limitations, our study is still essential as it provides significant results for further studies about CKMB, troponin, myoglobin, and omentin levels in patients with ACS.

Conclusion

In conclusion, our data reveal that levels of omentin were similar in patients with ACS and healthy subjects. In the study, no statistically significant correlation was found between Omentin, CKMB, and Troponin levels. This is thought to be the first study in the literature to investigate the relationship between omentin levels and myoglobin in ACS patients and hence it may shed light on for future ACS diagnosis options. For ACS patients, no significant relationship was observed between omentin and myoglobin levels. Hence, the potential usefulness of blood concentrations of omentin levels in understanding the relationship with ACS needs to be examined with further studies.

References

1. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation. 2011;123(4):e18–209.
2. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. Journal of the American College of Cardiology. 2007;50(22):2173–95.
3. Anwaruddin S, Januzzi Jr JL, Baggish AL, Lewandrowski EL, Lewandrowski KB. Ischemia-modified albumin improves the usefulness of standard cardiac biomarkers for the diagnosis of myocardial ischemia in the emergency department setting. American journal of clinical pathology. 2005;123(1):140–5.
4. Koleva DI, Orbetzova MM, Atanassova PK. Adipose Tissue Hormones and Appetite and Body Weight Regulators an Insulin Resistance/ Folia medica. 2013;55(1):25–32.
5. Schäffler A, Neumeier M, Herfarth H, Fürst A, Schölmerich J, Büchler C. Genomic structure of human omentin, a new adipocytokine expressed in omental adipose tissue. Biochimica et Biophysica Acta (BBA)-Gene Structure and Expression. 2005;1732(1–3):96–102.
6. Sengul E, Duygulu G, Dindar S, Bunul F. Serum omentin-1, inflammation and carotid atherosclerosis in patients with non-diabetic chronic kidney disease. Renal failure. 2013;35(8):1089–93.
7. Tan Y-L, Zheng X-L, Tang C-K. The protective functions of omentin in cardiovascular diseases. Clinica Chimica Acta. 2015;448:98–106.
8. Jaikanth C, Gurumurthy P, Cherian K, Indhumathi T. Emergence of omentin as a pleiotropic adipocytokine. Experimental and Clinical Endocrinology & Diabetes. 2013;121(07):377–83.
9. Duan X-Y, Xie P-L, Ma Y-L, Tang S-Y. Omentin inhibits osteoblastic differentiation of calcifying vascular smooth muscle cells through the PI3K/Akt pathway. Amino acids. 2011;41(5):1223–31.
10. Van de Voorde J, Pauwels B, Boydens C, Decaluwé K. Adipocytokines in relation to cardiovascular disease. Metabolism. 2013;62(11):1513–21.
11. Shang F-J, Wang J-P, Liu X-T, Zheng Q-S, Xue Y-S, Wang B, et al. Serum omentin-1 levels are inversely associated with the presence and severity of coronary artery disease in patients with metabolic syndrome. Biomarkers. 2011;16(8):657–62.
12. Zhong X, Zhang H, Tan H, Zhou Y, Liu F, Chen F, et al. Association of serum omentin-1 levels with coronary artery disease. Acta Pharmacologica Sinica. 2011;32(7):873–8.
13. Kadoglou NP, Tahmatzidis DK, Giannakoulas C, Kapelouzou A, Gkontopoulos A, Parissis J, et al. Serum levels of novel adipokines, omentin-1 and chemerin, in patients with acute myocardial infarction: KOZANI STUDY. Journal of Cardiovascular Medicine. 2015;16(5):341–6.
14. Kataoka Y, Shibata R, Ohashi K, Kambara T, Enomoto T, Uemura Y, et al. Omentin prevents myocardial ischemic injury through AMP-activated protein kinase-and Akt-dependent mechanisms. Journal of the American College of Cardiology. 2014;63(24):2722–33.

15. Türkcü FM, Şahin A, Cingü AK, Kaya S, Yüksel H, Cinar Y, et al. Serum omentin, resistin and tumour necrosis factor-α levels in Behcet patients with and without ocular involvement. Graefe's Archive for Clinical and Experimental Ophthalmology. 2015;253(9):1565–8.
16. Narumi T, Watanabe T, Kadowaki S, Kinoshita D, Yokoyama M, Honda Y, et al. Impact of serum omentin-1 levels on cardiac prognosis in patients with heart failure. Cardiovascular diabetology. 2014;13(1):84.
17. Shibata R, Ouchi N, Takahashi R, Terakura Y, Ohashi K, Ikeda N, et al. Omentin as a novel biomarker of metabolic risk factors. Diabetology & metabolic syndrome. 2012;4(1):37.
18. Yamawaki H, Kuramoto J, Kameshima S, Usui T, Okada M, Hara Y. Omentin, a novel adipocytokine inhibits TNF-induced vascular inflammation in human endothelial cells. Biochemical and biophysical research communications. 2011;408(2):339–43.
19. Maruyama S, Shibata R, Kikuchi R, Izumiya Y, Rokutanda T, Araki S, et al. Fat-derived factor omentin stimulates endothelial cell function and ischemia-induced revascularization via endothelial nitric oxide synthase-dependent mechanism. Journal of Biological Chemistry. 2012;287(1):408–17.
20. De Jager SC, Pasterkamp G. Atheroprotective properties of human Omentin-1 in experimental atherosclerosis. 2016;???:???.
21. Gao X, Mi S, Zhang F, Gong F, Lai Y, Gao F, et al. Association of chemerin mRNA expression in human epicardial adipose tissue with coronary atherosclerosis. Cardiovascular diabetology. 2011;10(1):87.
22. Iacobellis G. Local and systemic effects of the multifaceted epicardial adipose tissue depot. Nature Reviews Endocrinology. 2015;11(6):363.
23. Yamawaki H, Tsubaki N, Mukohda M, Okada M, Hara Y. Omentin, a novel adipokine, induces vasodilation in rat isolated blood vessels. Biochemical and biophysical research communications. 2010;393(4):668–72.
24. Moreno-Navarrete JM, Ortega F, Castro A, Sabater M, Ricart W, Fernández-Real JM. Circulating omentin as a novel biomarker of endothelial dysfunction. Obesity. 2011;19(8):1552–9.
25. Du Y, Ji Q, Cai L, Huang F, Lai Y, Liu Y, et al. Association between omentin-1 expression in human epicardial adipose tissue and coronary atherosclerosis. Cardiovascular diabetology. 2016;15(1):90.
26. Watanabe K, Watanabe R, Konii H, Shirai R, Sato K, Matsuyama T, et al. Counteractive effects of omentin-1 against atherogenesis. Cardiovascular research. 2016;110(1):118–28.
27. Shibata R, Ouchi N, Kikuchi R, Takahashi R, Takeshita K, Kataoka Y, et al. Circulating omentin is associated with coronary artery disease in men. Atherosclerosis. 2011;219(2):811–4.
28. Uemura Y, Shibata R, Kanemura N, Ohashi K, Kambara T, Hiramatsu-Ito M, et al. Adipose-derived protein omentin prevents neointimal formation after arterial injury. The FASEB Journal. 2015;29(1):141–51.
29. Zhu Y, Hu C, Du Y, Zhang J, Liu J, Cheng G, et al. Time-Dependent Change in Omentin-1 Level Correlated with Early Improvement of Myocardial Function in Patients with First Anterior ST-Segment Elevation Myocardial Infarction After Primary Percutaneous Coronary Intervention. Journal of atherosclerosis and thrombosis. 2019;26(10):856–67.
30. Harada K, Shibata R, Ouchi N, Tokuda Y, Funakubo H, Suzuki M, et al. Increased expression of the adipocytokine omentin in the epicardial adipose tissue of coronary artery disease patients. Atherosclerosis. 2016;251:299–304.
31. Wu S-S, Liang Q-H, Liu Y, Cui R-R, Yuan L-Q, Liao E-Y. Omentin-1 stimulates human osteoblast proliferation through PI3K/Akt signal pathway. International journal of endocrinology. 2013;2013.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1143-1146.
DOI: 10.28982/josam.743746

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Relationship between cardiovascular risk factors and coronary artery disease severity assessed by coronary angiography in Turkish patients

Koroner anjiyografi ile değerlendirilmiş Türk hastalarda kardiyovasküler risk faktörleri ve koroner arter hastalığı ciddiyeti arasındaki ilişki

Şeyda Günay [1], Seçkin Dereli [2], Osman Akın Serdar [1], Güven Özkaya [3], Serhat Çalışkan [4]

[1] Bursa Uludağ University, Faculty of Medicine, Department of Cardiology, Bursa, Turkey
[2] Ordu University Education and Research Hospital Department of Cardiology, Ordu, Turkey
[3] Bursa Uludağ University, Faculty of Medicine, Department of Biostatistics, Bursa, Turkey
[4] Istanbul Bahcelievler State Hospital, Istanbul, Turkey

ORCID ID of the author(s)
ŞG: 0000-0003-0012-345X
ŞD: 0000-0003-0090-3835
OAS: 0000-0003-3529-5649
GÖ: 0000-0003-0297-846X
SÇ: 0000-0002-0260-5463

Corresponding author/Sorumlu yazar:
Şeyda Günay
Address/Adres: Bursa Uludağ Üniversitesi Tıp Fakültesi Kardiyoloji Anabilim Dalı, Görükle, 16059, Bursa, Türkiye
E-mail: seydagunaymedical@yahoo.com

Ethics Committee Approval: Ethics approval was obtained from the local ethics committee of Bursa Uludag University, Faculty of Medicine (Approval number: 2012-26/4). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Etik onayı Bursa Uludağ Üniversitesi Tıp Fakültesi yerel etik kurulundan alınmıştır (Onay no: 2012-26/4). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: Established coronary risk factors are good predictors of the occurrence of coronary artery disease (CAD), but their correlation with angiographic seriousness of the disease is argumentative and may vary among ethnic groups. In this study, we examined which of these factors are associated with the angiographic seriousness in Turkish patients with attested CAD.

Methods: A total of 2433 patients who underwent coronary angiography and were diagnosed with critical lesions in at least one coronary artery were included in the study. Coronary risk factors were determined by retrospectively scanning the patient records and the relationship with the angiographic severity of coronary artery disease was investigated.

Results*:* Most patients (36.4%) were between 60-69 years of age and approximately two thirds of patients (76.8%) were men. Hypertension, diabetes mellitus and hyperlipidemia were common cardiovascular risk factors (CRFs), present in 54.8%, 43.2% and 50.3% of patients, respectively. Multiple logistic regression analysis showed that diabetes mellitus, male sex and age since 6th decade significantly raised the risk of multivessel CAD (Odds ratios: 1.29 (1.08-1.54; *P*=0.004), 1.35 (1.1-1.66; *P*=0.004), 3.53 (1.85-6.75; *P*<0.001), respectively). Hypertension and hyperlipidemia were not correlated with CAD angiographic severity.

Conclusion: Diabetes mellitus appeared as the modifiable coronary risk factor forecasting multivessel coronary artery disease in Turkish patients.

Keywords: Turkish, Ethnic, Angiography, Risk, Multi vessel

Öz

Amaç: Koroner arter hastalığı risk faktörleri, koroner arter hastalığının (KAH) ortaya çıkışının iyi öngördürücülerdir, ancak bunların hastalığın anjiyografik ciddiyeti ile korelasyonları tartışmalıdır ve etnik gruplar arasında farklılık gösterebilir. Bu çalışmada, kanıtlanmış KAH olan Türk hastalarda kardiyovasküler risk faktörlerinin hastalığın anjiyografik ciddiyeti ile ilişkisi araştırıldı.

Yöntemler: Koroner anjiyografi ile değerlendirilerek en az bir koroner arterde kritik lezyon saptanan 2433 hasta çalışmaya dahil edildi. Hasta kayıtları retrospektif taranarak hastaların koroner risk faktörleri tespit edildi ve koroner arter hastalığının anjiyografik ciddiyeti ile ilişkisi araştırıldı.

Bulgular: Çalışma popülasyonunda hastaların çoğu (%36,4) 60-69 yaşları arasındaydı ve hastaların yaklaşık üçte ikisi (%76,8) erkekti. Hipertansiyon, diyabetes mellitus ve hiperlipidemi hastaların sırasıyla% 54,8,%43,2 ve %50,3'ünde mevcuttu. Çoklu lojistik regresyon analizinde, diabetes mellitus, erkek cinsiyet ve 6. dekattan itibaren yaşın, çok damarlı KAH riskini önemli ölçüde artırdığı saptandı (odds oranları sırasıyla 1,29 (1,08-1,54; *P*=0,004), 1,35 (1,1-1,66; *P*=0,004), 3,53 (1,85-6,75; *P*<0,001). Hipertansiyon ve hiperlipidemi, KAH'ın anjiyografik ciddiyeti ile ilişkili değildi.

Sonuç: Türk hastalarda çok-damar koroner arter hastalığını ön gördüren düzeltilebilir koroner arter hastalığı risk faktörü diyabetes mellitustur.

Anahtar kelimeler: Türk, Etnik, Anjiyografi, Risk, Çoklu damar

How to cite/Atıf için: Günay Ş, Dereli S, Serdar OA, Özkaya G, Çalışkan S. Relationship between cardiovascular risk factors and coronary artery disease severity assessed by coronary angiography in Turkish patients. J Surg Med. 2020;4(12):1143-1146.

Introduction

One of the leading causes of morbidity and death is coronary artery disease. Male sex, advancing age, hypertension, dyslipidemia, obesity, abnormal glucose metabolism, family history of ischemic heart disease and smoking are well known risk factors of coronary artery atherosclerosis [1].

The correlation between these cardiovascular risk factors (CRFs) and the occurrence of CAD and clinical outcomes is consistent [2,3]. Nonetheless, the association between these risk factors and the coronary angiography findings is less coherent with research showing contradictory findings [4-10]. Previous studies have also indicated that effects of these risk factors may vary across different ethnic groups [11,12].

Few data about the effects of CRFs on disease severity in angiographically assessed Turkish patients is available [13,14]. The purpose of our research was therefore to investigate which CRFs are correlated with the severity of atherosclerosis, assessed by coronary angiography, in Turkish patients.

Materials and methods

Study population

Hospital records of consecutive patients who underwent coronary angiography at Bursa Uludag University Faculty of Medicine between 2002 and 2012 were examined. Ethics approval was obtained from the local ethics committee of Bursa Uludag University, Faculty of Medicine (Approval number: 2012-26/4). Information about the presence of CRFs (diabetes mellitus, hypertension and hyperlipidemia) could be gained from the hospital registry system only for 4368 patients. Among these patients, according to the coronary angiography results, we excluded 1100 patients with normal coronary angiograms and 790 patients with non-critical coronary lesions. Data regarding CRFs of 45 patients were not complete and they were also excluded. Finally, a total of 2433 patients were included. According to drug information records, patients taking antihypertensive drugs, oral antidiabetics and/or insulin, statins or fenofibrate were grouped as hypertensive. diabetic and hyperlipidemic, respectively.

Coronary angiography

Selective coronary angiography views of the study population were analyzed by two interventional cardiologists independently. In all epicardial vessels we described a critical coronary lesion and significant CAD as atherosclerotic luminal involvement of more than 50% in a major coronary artery or its major branches. The diameter and degree of lumen narrowing of the vessels were measured into a guiding catheter's lumen (6 French). Patients were grouped into one vessel CAD group and multivessel CAD group (patients with ≥2 vessel disease).

Statistical analysis

For comparisons, we categorized the patients into two groups in conformity with the presence of one or multiple (≥2) vessel disease. Normality tests were performed for the distributions of the data to select parametric or non-parametric tests. Logistic regression analysis was used to investigate the relationship between CRFs and the angiographic severity of CAD as the dependent variable. Odds ratios (ORs) and 95% confidence intervals were calculated. The risk factors studied were diabetes mellitus, age, gender, hypertension, and hyperlipidemia. SPSS Statistics software, version 19 was used and a *P*-value <0.05 was assumed to be statistically significant. All tests were two-sided.

Results

A total of 2433 patients were included in the study. Most of the patients were males (76.9 %). The most frequently involved vessel was the left anterior descending artery (55.8%) in patients with one-vessel disease (Figure 1).

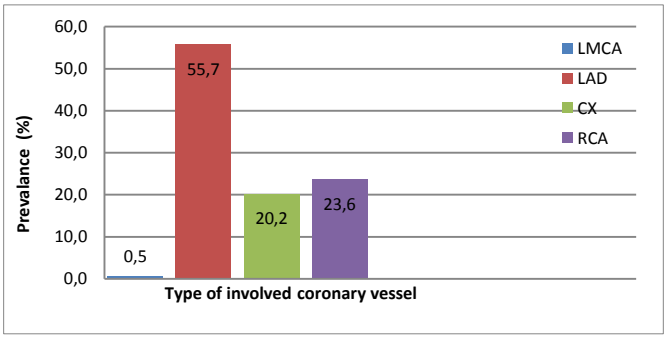


Figure 1: Distribution of involved coronary artery in one vessel coronary artery disease patients (LMCA: left main coronary artery, LAD: Left anterior descending coronary artery, Cx: Circumflex coronary artery, RCA: Right coronary artery)

The CRFs and angiographic severity of CAD were shown in Table-1. Diabetes mellitus was more prevalent in multivessel CAD patients than in one vessel CAD patients (45.2% versus 39.2%, respectively, *P*=0.005). A logistic regression analysis involving gender, age, diabetes mellitus, hypertension and hyperlipidemia as independent variables displayed that male gender, diabetes mellitus and increasing age since 6th decade significantly raised the risk of multivessel involvement by 1.35 (1.1-1.66, *P*=0.004), 1.29 (1.08-1.54, *P*=0.004), 3.53 (1.85-6.75, *P*<0.001), 4.52 (2.37-8.63, *P*<0.001), 6.01 (3.08-11.73, *P*<0.001), and 9.33 (3.83-22.73, *P*<0.001), respectively (Table 1).

After subdivision of the population according to type of involved coronary vessels, we also investigated the relationship between coronary risk factors and involved coronary artery type in patients with one vessel disease (Table 2). We noted that involvement of all types of coronary arteries are associated with male sex and existence of diabetes mellitus. Although left main coronary artery (LMCA) involvement was increasing since the 8th decade, involvement of left anterior descending (LAD) artery, circumflex (Cx) artery and right coronary artery (RCA) were associated with an earlier age, which is since the 5th decade.

Table 1: Characteristics of patients and logistic regression analysis for multivessel coronary artery disease

	All (n=2433)	Two or three vessel disease			Multivariable logistic regression		
		Yes (n=1636)	No (n=797)	*P*-value	Odds ratio	95% CI	*P*-value
Male sex	1870 (76.8)	1274 (77.8)	596 (74.7)	0.09	1.35	(1.1-1.66)	0.004
Diabetes mellitus	1053 (43.2)	740 (45.2)	313 (39.2)	0.005	1.29	(1.08-1.54)	0.004
Hypertension	1334 (54.8)	897 (54.8)	437 (54.8)	0.99	-	-	-
Hyperlipidemia	1226 (50.3)	823 (50.3)	403 (50.5)	0.9	-	-	-
4.decade	44 (1.8)	15 (0.9)	29 (3.6)	-	-	-	-
5.decade	267 (10.9)	136 (8.3)	131 (16.4)	-	-	-	-
Age 6.decade	744 (30.5)	485 (29.5)	259 (32.4)	<0.001	3.53	1.85-6.75	<0.001
7.decade	888 (36.4)	625 (38.2)	263 (32.9)		4.52	2.37-8.63	
8.decade	422 (17.3)	319 (19.4)	103 (12.9)		6.01	3.08-11.73	
9.decade	68 (2.7)	56 (3.4)	12 (1.5)		9.33	3.83-22.73	

Data: number (%), CI: confidence interval

Table 2: Relationship between type of involved coronary vessel and coronary risk factors

		Logistic regression		
		OR	95 % CI	*P*-value
LMCA involvement	Male sex	4.25	2.46-7.37	<0.001
	Diabetes mellitus	2	1.37-2.91	<0.001
	5.decade	-	-	-
	6.decade	-	-	-
	7.decade	-	-	-
	8.decade	8.24	1.11-61.13	0.039
	9.decade	15.01	1.79-125.36	0.012
LAD involvement	Male sex	2.48	2.17-2.84	<0.001
	Diabetes	1.26	1.11-1.44	<0.001
	5.decade	1.85	1.25-2.73	0.002
	6.decade	3.81	2.62-5.54	<0.001
	7.decade	5.27	3.63-7.66	<0.001
	8.decade	8.58	5.76-12.78	<0.001
	9.decade	12.33	6.68-22.76	<0.001
CX involvement	Male sex	2.94	2.56-3.39	<0.001
	Diabetes	1.21	1.07-1.38	0.003
	5.decade	1.69	1.07-2.66	0.024
	6.decade	3.64	2.36-5.61	<0.001
	7.decade	4.61	2.99-7.1	<0.001
	8.decade	6.53	4.17-10.24	< 0.001
	9.decade	17.54	9.34-32.93	<0.001
RCA involvement	Male sex	2.6	2.27-2.99	<0.001
	Diabetes	1.28	1.12-1.45	<0.001
	5.decade	1.95	1.22-3.11	0.005
	6.decade	4	2.56-6.25	<0.001
	7.decade	5.18	3.33-8	<0.001
	8.decade	6.94	4.38-11	<0.001
	9.decade	13.87	7.46-25.81	<0.001

OR: odds ratio, CI: Confidence interval, LMCA: Left main coronary artery, LAD: Left anterior descending artery, CX: Circumflex coronary artery, RCA: Right coronary artery

Below are our findings.

LMCA involvement

Male patients had more common LMCA involvement by 4.25 (2.46-7.37, *P*<0.001). Also, diabetes mellitus and advanced age since 8th decade increased the prevalence of LMCA involvement. Odds ratios were 2 (1.37-2.91, *P*<0.001), 8.24 (1.11-61.13, *P*=0.039), 15.01 (1.79-125.36, *P*=0.012) for diabetes mellitus, 8th and 9th decades, respectively.

LAD involvement

Male patients had more common LAD involvement by 2.48 (2.17-2.84, *P*<0.001). Also, diabetes mellitus and advanced age since 5th decade increased the prevalence of LAD involvement: Odds ratios were 1.26 (1.11-1.44, *P*<0.001), 1.85 (1.25-2.73 *P*=0.002), 3.81 (2.62-5.54 *P*<0.001), 5.27 (3.63-7.66 *P*<0.001), 8.58 (5.76-12.78 *P*<0.001), 12.33 (6.68-22.76, *P*<0.001) respectively, for diabetes mellitus, 5th-9thdecades.

Cx involvement

Male patients had more common Cx involvement by 2.94 (2.56-3.39, *P*<0.001). Diabetes mellitus and advanced age since 5th decade increased the prevalence of Cx involvement. Odds ratios were 1.21 (1.07-1.38, *P*=0.003), 1.69 (1.07-2.66 *P=0.024*), 3.64 (2.36-5.61, *P*<0.001), 4.61 (2.99-7.1 *P*<0.001), 6.53 (4.17-10.24, *P*<0.001), 17.54 (9.34-32.93, *P*<0.001) respectively, for diabetes mellitus, 5th-9th decades.

RCA involvement

Male patients had more common RCA involvement by 2.6 (2.27-2.99, *P*<0.001). Also, diabetes mellitus and advanced age since 5th decade increased the prevalence of RCA involvement. Odds ratios were 1.28 (1.12-1.45, *P*<0.001), 1.95 (1.22-3.11 *P*=0.005), 4 (2.56-6.25, *P*<0.001), 5.18 (3.33-8 *P*<0.001), 6.94 (4.38-11, *P*<0.001), 13.87 (7.46-25.81, *P*<0.001) respectively, for diabetes mellitus, 5-9th decades.

Discussion

The most common cause of death is coronary artery disease (CAD). Established cardiovascular risk factors (CRFs) like gender, obesity, smoking, age, diabetes mellitus, hypertension, hyperlipidemia and family history are well known [3,15,16]. Nonetheless, the angiographically assessed association between CRFs and atherosclerotic burden is not as well known, with studies resulting varying and inconsequent findings [5,6,8,10,17-20].

In this study, we mainly searched for the correlation between multivessel CAD and CRFs in Turkish patients who underwent conventional coronary angiography electively. Our study displayed that diabetes mellitus, male gender and advanced age were significantly associated with multi vessel coronary artery disease, while hypertension, and hyperlipidemia were not.

The results of a former study by Veeranna et al, which stated that diabetes mellitus was the unique forecaster of the CAD burden in a cohort of 631 elderly patients (mean age 73 years) are consistent with our study [21]. The significance of diabetes mellitus as a risk factor for angiographic CAD progression has been noted in previous studies [22]. Metabolic disorders seen in diabetics may contribute to high CAD severity [23]. Impaired glucose tolerance and an impaired fasting glucose status are also independently correlated with the extent of CAD [24].

Our results support the idea that established cardiovascular risk factors may not have the same treasure in foretelling the severeness of angiographic findings. While most of the well-known cardiovascular risk factors are thought to be strong predictors of the severity of CAD assessed angiographically [7], some studies revealed that only few of these factors are effective forecasters of CAD severity [8]. Different ethnic characteristics and designs of studies may define these conflicting results.

Several studies reported the impact of ethnic differences on the relationship between CRFs and CAD severity [25]. Presentation of CAD can also vary among ethnic groups [11,26]. We need further angiographic data of other ethnic groups to compare.

These findings state that the comparative effect of established risk factors on the angiographically assessed severity of CAD may differ depending on the selected population.

Limitations

Our analysis was firstly limited with its retrospective design. However, selective coronary angiography technique also has limitations. It gives us information about the arterial lumen only, not the vessel wall and plaque volume, like intravascular ultrasound.

The study was conducted to determine the relationship between established CRFs and multivessel CAD, but it did not give information about clinical outcomes including cardiovascular morbidity and mortality.

Finally, while our study is a single center study, our conclusions cannot be extrapolated to entire population.

Conclusions

Diabetes is an independent modifiable risk factor related to multivessel coronary artery disease in Turkish patients. The underlying mechanisms need further studies, which may give way to preventing and managing CAD risk factors in different ethnic groups.

References

1. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008 Feb 12;117(6):743-53. doi: 10.1161/CIRCULATIONAHA.107.699579. Epub 2008 Jan 22. PMID: 18212285.
2. Murray CJ, Lopez AD. Evidence-based health policy--lessons from the Global Burden of Disease Study. Science. 1996 Nov 1;274(5288):740-3. doi: 10.1126/science.274.5288.740. PMID: 8966556.
3. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004 Sep 11-17;364(9438):937-52. doi: 10.1016/S0140-6736(04)17018-9. PMID: 15364185.
4. Banerjee A, Lim CC, Silver LE, Heneghan C, Welch SJ, Mehta Z,et al. Family history does notpredict angiographic localization or severity of coronary arterydisease. Atherosclerosis. 2012;221:451-7.
5. Guo YH, Zhang WJ, Zhou YJ, Zhao D, Zhou ZM, Zhang H. Study of the relationship between cardiovascular risk factors and severity of coronary artery disease in patients underwent coronary angiography.Zhonghua Xin Xue Guan Bing Za Zhi. 2005;33:415-8.
6. Hasin Y, Eisenberg S, Friedlander J, Lewis BS, Gotsman MS. Relationship between extent of coronary artery disease and correlative risk factors. Am Heart J. 1979 Nov;98(5):555-61. doi: 10.1016/0002-8703(79)90279-5. PMID: 227261.
7. Koliaki C, Sanidas E, Dalianis N, Panagiotakos D, Papadopoulos D, Votteas V, et al. Relationship between established cardiovascular risk factors and specific coronary angiographic findings in a large cohort of Greek catheterized patients. Angiology. 2011 Jan;62(1):74-80. doi: 10.1177/0003319710370960. Epub 2010 May 24. PMID: 20498145.
8. Krishnaswami S, Jose VJ, Joseph G. Lack of correlation between coronary risk factors and CAD severity. Int J Cardiol. 1994 Nov;47(1):37-43. doi: 10.1016/0167-5273(94)90131-7. PMID: 7868283.
9. Tacoy G, Balcioglu AS, Akinci S, Erdem G, Kocaman SA, Timurkaynak T, et al. Traditional risk factors are predictive on segmental localization of coronary artery disease. Angiology. 2008 Aug-Sep;59(4):402-7. doi: 10.1177/0003319708318379. Epub 2008 May 27. PMID: 18505741.
10. Wang XL, Tam C, McCredie RM, Wilcken DE. Determinants of severity of coronary artery disease in Australian men and women. Circulation. 1994 May;89(5):1974-81. doi: 10.1161/01.cir.89.5.1974. PMID: 8181120.
11. Chaturvedi N. Ethnic differences in cardiovascular disease. Heart. 2003 Jun;89(6):681-6. doi: 10.1136/heart.89.6.681. PMID: 12748237; PMCID: PMC1767706.
12. Harding S, Rosato M, Teyhan A. Trends for coronary heart disease and stroke mortality among migrants in England and Wales, 1979-2003: slow declines notable for some groups. Heart. 2008 Apr;94(4):463-70. doi: 10.1136/hrt.2007.122044. Epub 2007 Aug 9. PMID: 17690159; PMCID: PMC2565582.
13. Onat A. Risk factors and cardiovascular disease in Turkey. Atherosclerosis. 2001 May;156(1):1-10. doi: 10.1016/s0021-9150(01)00500-7. PMID: 11368991.
14. Kutlu R., Memetoğlu ME, Evaluation of cardiovascular risk factors among university students in Turkey: a cross-sectional survey. Russian Open Medical Journal. 2013;2:3-7.
15. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2008 Jan 29;117(4):e25-146. doi: 10.1161/CIRCULATIONAHA.107.187998. Epub 2007 Dec 17. Erratum in: Circulation. 2010 Jul 6;122(1):e10. Kissela, Bret [corrected to Kissela, Brett]. PMID: 18086926.
16. Greenland P, Knoll MD, Stamler J, Neaton JD, Dyer AR, Garside DB, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. JAMA. 2003 Aug 20;290(7):891-7. doi: 10.1001/jama.290.7.891. PMID: 12928465.
17. Phillips GB, Pinkernell BH, Jing TY. Are major risk factors for myocardial infarction the major predictors of degree of coronary artery disease in men? Metabolism. 2004 Mar;53(3):324-9. doi: 10.1016/j.metabol.2003.11.008. PMID: 15015144.
18. Vlietstra RE, Kronmal RA, Frye RL, Seth AK, Tristani FE, Killip T 3rd. Factors affecting the extent and severity of coronary artery disease in patients enrolled in the coronary artery surgery study. Arteriosclerosis. 1982 May-Jun;2(3):208-15. doi: 10.1161/01.atv.2.3.208. PMID: 6979996.
19. Anderson AJ, Barboriak JJ, Rimm AA. Risk factors and angiographically determined coronary occlusion. Am J Epidemiol. 1978 Jan;107(1):8-14. doi: 10.1093/oxfordjournals.aje.a112511. PMID: 623092.
20. Opherk D, Scola R, Morgenstern W, Stockmann G, Nüssel E, Kübler W. Beziehungen von "Risikofaktoren" der Arterioskelrose zum Schweregrad der angiographisch nachweisbaren Koronarsklerose [Coronary risk factors and extent of angiographically proven coronary artery stenoses (author's transl)]. Z Kardiol. 1979 Jun;68(6):369-74. German. PMID: 463194.
21. Veeranna V, Pradhan J, Niraj A, Fakhry H, Afonso L. Traditional cardiovascular risk factors and severity of angiographic coronary artery disease in the elderly. Prev Cardiol. 2010 Summer;13(3):135-40. doi: 10.1111/j.1751-7141.2009.00062.x. PMID: 20626669.
22. Alderman EL, Corley SD, Fisher LD, Chaitman BR, Faxon DP, Foster ED et al. Five-year angiographic follow-up of factors associated with progression of coronary artery disease in the Coronary Artery Surgery Study (CASS). CASS Participating Investigators and Staff. J Am Coll Cardiol. 1993 Oct;22(4):1141-54. doi: 10.1016/0735-1097(93)90429-5. PMID: 8409054.
23. Kirpichnikov D, Sowers JR. Diabetes mellitus and diabetes-associated vascular disease. Trends Endocrinol Metab. 2001 Jul;12(5):225-30. doi: 10.1016/s1043-2760(01)00391-5. PMID: 11397648.
24. Nurkalem Z, Hasdemir H, Ergelen M, Aksu H, Sahin I, Erer B, et al. The relationship between glucose tolerance and severity of coronary artery disease using the Gensini score. Angiology. 2010 Nov;61(8):751-5. doi: 10.1177/0003319710373747. Epub 2010 Jun 21. PMID: 20566575.
25. LaRosa JC, Brown CD. Cardiovascular risk factors in minorities. Am J Med. 2005 Dec;118(12):1314-22. doi: 10.1016/j.amjmed.2005.04.041. PMID: 16378771.
26. Hasan RK, Ginwala NT, Shah RY, Kumbhani DJ, Wilensky RL, Mehta NN. Quantitative angiography in South Asians reveals differences in vessel size and coronary artery disease severity compared to Caucasians. Am J Cardiovasc Dis. 2011;1(1):31-7. Epub 2011 Apr 20. PMID: 22254183; PMCID: PMC3253512.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1147-1151.
DOI: 10.28982/josam.751196

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

An epidemiological and clinical analysis of cutaneous drug eruption: A cohort of 164 patients

Kutanöz ilaç erüpsiyonunun epidemiyolojik ve klinik analizi: 164 hastadan oluşan kohort çalışması

Dua Cebeci [1], Şirin Yaşar [1], Sema Aytekin [1], Fatih Göktay [1], Pembegül Güneş [2]

[1] Haydarpaşa Numune Training and Research Hospital, Dermatology and Venereology Department, Istanbul, Turkey
[2] Haydarpaşa Numune Training And Research Hospital, Department of Pathology, Istanbul, Turkey

ORCID ID of the author(s)

DC: 0000-0001-5746-9326
ŞY: 0000-0002-4110-1874
FG: 0000-0002-2380-7697
SA: 0000-0003-1376-1573
PG: 0000-0002-4982-5156

Corresponding author/Sorumlu yazar:
Dua Cebeci
Address/Adres: Famagusta Stat Hospital, Famagusta, Cyprus
E-mail: perolidua@gmail.com

Ethics Committee Approval: The approval for this study was obtained from Haydarpaşa Numune Training and Research Hospital Ethics Committee of Clinical Studies (decision number: 2017/07). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma için onay Haydarpaşa Numune Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu'ndan alınmıştır (karar numarası: 2017/07). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: Drug reactions are important and frequent complications of medical treatments. In this study we aimed to investigate the patients hospitalized with a diagnosis of cutaneous drug eruptions, implicated drugs, and related skin manifestations considering the literature.

Methods: This retrospective cohort study was performed in Haydarpaşa Numune Training and Research Hospital, Dermatology and Venereology Department. The study comprised 164 patients that were diagnosed with cutaneous drug eruption between January 2010 and December 2016. Some parameters, such as demographic characteristics, type of the reaction, culprit drug groups, multiple drug usage, time between the onset of the drug intake and beginning of the eruption were recorded. Age, gender, symptoms, laboratory tests, diagnosis and treatment information were obtained through patient files. Causal relationship was assessed by Naranjo algorithm. Adverse drug reactions were categorized as definite, probable, possible, and absent. All values were expressed in percentages. The severity of the reaction caused by the drug was assessed with Hartwig's Severity Assessment Scale.

Results: Among 164 patients, there were 104 females and 60 males with a mean age of 46.3 (18.8) years. The most commonly encountered type of drug reactions were urticaria and angioedema (42.1%), followed by morbilliform drug eruption (31.7%). More cutaneous reactions were noted with NSAIDs (18.9%), antibiotics (15.2%) and the combination of NSAIDs and antimicrobial agents (9.8%). Time between the onset of eruption and the intake of the drug varied by hours to months. Some of these patients also described similar reactions related to drugs in the past.

Conclusion: Knowledge of these drug eruptions, the causative drugs and the prognostic factors is important for clinicians. It is recommended to advise patients to carry a list in their wallets indicating their drug allergies and/or intolerances, especially if they had a severe reaction before. We conclude that a careful follow-up should be performed with NSAIDs, antibiotics and anti-epileptics. The combination of drugs, including NSAIDs and antibiotics should be avoided as much as possible.

Keywords: Cutaneous drug eruptions, Reaction patterns, Epidemiological and clinical features, Scales

Öz

Amaç: İlaç reaksiyonları medikal tedavinin önemli ve sık bir komplikasyonudur. Bu çalışmada ki amacımız, kutanöz ilaç reaksiyonu tanısı ile kliniğimizde yatırılan olgularda, sorumlu ilaçlar ve bu ilaçların neden olduğu klinik tablolar literatür bilgileri eşliğinde incelemektir.

Yöntemler: Çalışmaya Ocak 2010-Aralık 2016 tarihleri arasında kutanöz ilaç erüpsiyonu tanısı ile Haydarpaşa Numune Eğitim Araştırma Hastanesi Deri Ve Zührevi Hastalıkları Kliniğinde yatırılarak tedavi edilen 164 olgu alınmıştır. Hastaların yaşı, cinsiyeti, semptomları, laboratuar tetkikleri, tanı ve tedavi bilgileri hasta epikrizlerden incelenerek elde edildi. Demografik özellikler, reaksiyonun tipi, reaksiyona yol açtığı düşünülen ilaç grupları, multipl ilaç kullanımının varlığı, ilaç alımından döküntünün başlangıcına kadar geçen süre gibi parametreler kayıt edildi. Nedensellik ilişkisi Naranjo algoritması ile değerlendirildi. KİE'ler,
kesin, muhtemel, olası ve yok olarak gruplandırıldı. Bütün değerler yüzdelik olarak ifade edilmiştir. İlacın yol açtığı reaksiyonun şiddeti Hartwig's Ciddiyet Değerlendirme Skalası ile değerlendirildi.

Bulgular: Çalışmaya alınan 164 hastanın 104'ü kadın (%63,4) ve 60'ı erkek (%36,6) idi. Hastalarımızın yaşları 4 ile 97 arasında değişmekle birlikte yaş ortalaması 46,3 (18,8) idi. En sık reaksiyon tipi %42,1 oranında saptadığımız ürtiker ve anjiyoödemdi. Bunu sırasıyla, %31.7 olarak saptanan makülopapüler ilaç erüpsiyonu izlemekteydi.kutanöz reaksiyonlara en sık yol açan NSAİİ'ler (%18,9), antibiyotikler (%15,2) ve bunları izleyen NSAII ve antbiyotiklerin kombinasyonu idi (%9,8). İlacın ilk alınmasından döküntünün başlangıcına kadar geçen süre saatler ile aylar arasında değişmekteydi. Bu olguların bir kısmı da öyküde geçmişte ilaçlarla ilişikli benzer reaksiyonlar tanımlamaktadır.

Sonuç: Kutanöz ilaç Erüpsiyonu ve ona neden olan ilaçların ve prognostik faktörlerin bilinmesi klinisyenler için büyük önem arz etmektedir. Bu durumda hasta bilinçlendirilmeli ve uyarıcı olarak yanında daha önce hangi ilaçların reaksiyonlara sebep olduğunu gösteren alerji kartı ya taşınması sağlanmalıdır. NSAİİ'ler, antibiyotikler ve bunları içeren kombine ilaç kullanımından mümkün olduğunca kaçınılması, antibiyotikler ve antiepileptikler konusunda dikkatli bir izlem yapılması, uzun süreden beri kullanılan ilaçların da irdelenmesi gerektiği sonucuna varıldı.

Anahtar kelimeler: Kutanöz ilaç erüpsiyonları, Reaksiyon paternleri, Epidemiyolojik ve klinik özellikler, Ölçekler

How to cite/Atıf için: Cebeci D, Yaşar Ş, Aytekin S, Göktay F, Güneş P. An epidemiological and clinical analysis of cutaneous drug eruption: A cohort of 164 patients. J Surg Med. 2020;4(12):1147-1151.

Introduction

Cutaneous drug eruptions (CDE) or cutaneous drug reactions (CDR) are defined as undesirable toxic reactions when drugs are administered at standard doses for the diagnosis, treatment, or prophylaxis of a particular disease [1,2]. The clinical manifestation of CDE varies widely, from a simple asymptomatic skin rash to life-threatening emergencies [3]. Drug reactions are frequently encountered by dermatologists in clinical practice. Most frequent cause of cutaneous drug eruptions are antibiotics, especially penicillins, cephalosporins and nonsteroidal anti-inflammatory drugs (NSAIDs). CDEs are seen in 1-8% of the population and 0.1-16.8 % of the hospitalized patients [4-5].

Materials and methods

This retrospective study was conducted in Haydarpaşa Numune Training and Research Hospital Dermatology and Venereology (DVL) Department located in Istanbul, between January 2010 and December 2016. A total of 2757 inpatient diagnoses were analyzed retrospectively, and 164 patients with definite diagnoses of adverse drug reactions were evaluated. In 73 cases, histopathological examination of the skin was performed. Laboratory findings that may be helpful in the diagnosis such as liver and renal function disorders and presence of eosinophilia were evaluated. Infectious diseases, which are often similar to drug reactions, and other etiological factors had been ruled out in all patients with appropriate laboratory investigation. Patients were categorized according to their age as children and adolescents (0-19 years), adults (20-64 years) and elderly (age 65 and over). The time between the suspected drug intake and adverse cutaneous drug reaction was categorized into three groups, as follows: 0-3 weeks, 3 weeks-3 months and 3 months-1 year. Causative drugs were grouped as antibiotics, NSAIDs, anticonvulsants, antihypertensives, antiepileptics, vitamins, common cold medications, chemotherapeutics, spasmolytics and combined drugs. In patients with combined drug usage, cutaneous drug eruptions were assessed for causality with Naranjo's algorithm.

Naranjo Algorithm is a questionnaire designed by Naranjo et al. [6] for determining the likelihood of whether a cutaneous drug eruption is due to the suspected drug rather than the result of other factors, and probability is divided into four categories: Definite, probable, possible, or unlikely.

The severity and preventability of the reported reactions were assessed with modified Hartwig categorization as mild, moderate, and severe with seven levels of severity [7].

Ethics committee approval

The approval for this study was obtained from the Haydarpaşa Numune Traininig and Research Hospital Ethics Committee of Clinical Studies (decision number: 2017/07). All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committees and 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statistical analysis

The SPSS / Windows (version 21.0) was used to perform descriptive analysis (mean, standard deviation, minimum, median, maximum). For quantitative variables, one sample Kolmogorov-Smirnov test was used to detect normality of distribution. Mann-Whitney *U* test was later used based on the results. Binary outcomes were compared between groups using the Chi-square test for assessing significance. *P*-value <0.05 was considered significant. The analyses were performed using MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013).

Results

Of the 164 patients included in the study, 104 were female (63.4%) and 60 were male (36.6%). The age range of the patients was 4–97 years with a mean age of 46.3 (18.8) years. The most common age peak was the 6th decade, and the data were presented in Figure 1.

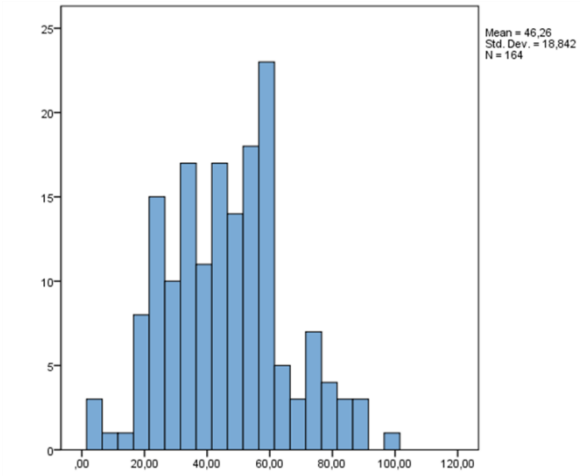


Figure 1: Mean age of inpatients with cutaneous drug eruption

Among all, 87.2% of the patients had drug reactions for the first time, while 12.8% reported a history of a previous adverse drug reaction. A systemic illness was present in 64% of the patients. In terms of patient characteristics, 13 patients (7.9%) had a history of atopy. The most common drug group causing cutaneous drug reactions was NSAIDs (18.9%), followed by antimicrobial drugs (15.2%). Antibiotic+ NSAID combined drug use was the third most common cause for cutaneous drug reactions (9.8%) (Table 1). Cutaneous drug eruption was mostly caused by flurbiprofen (34.5%) and metamizole (20%) from the NSAID group, by cephalosporins (32.8%) and penicillins (29.5%) among antimicrobial agents, and by phenytoin (50%), lamotrigine, and carbamazepine from the anticonvulsant group. Antihypertensive drugs caused CDE in 6 patients. The most common were beta blockers (75%), followed by ACE inhibitors (25%).

The most frequent cause of the use of drugs causing CDE was an upper respiratory tract infection (34.1%). Epilepsy was another common cause (4.3%). The time from drug intake to the development of the reaction was between 1 day and 1 year. More than half (87.4%, n=144) of the cutaneous drug eruptions occurred within hours to days of drug ingestion, 19 (11.6%) occurred between 3 weeks and 3 months, 1 occurred between 3 months-1 year. There was no significant relationship between the duration of drug use and the reaction pattern (Fisher Exact test *P*=0.752).

Table 1: Causative agents for the three most common types of cutaneous drug reactions

Drugs	n	%
NSAIDs	31	18.9
Antibiotics	25	15.2
Antiepileptics	7	4.3
Antispasmolytics	7	4,3
Antihypertensives	6	3.7
Anticonvulsants	6	3.7
Antifungals	6	3.7
Common cold medications	5	3.0
Unknown	5	3.0
Antineoplastics	4	2.4
Antipyretics	4	2.4
Common cold drug+ NSAID	3	1.8
Antibiotic + antipyretic	3	1.8
Antiepileptic + NSAID	3	1.8
Antigout (allopurinol)	3	1.8
Antibiotic + common cold drug	2	1.2
Antibiotics+spasmolytics	2	1.2
Antibiotic + contrast agent	2	1.2
Antidepressants	2	1.2
Antidiabetics	2	1.2
Antimalarials	2	1.2
Antivertigo drug	1	0.6
Antianemic	1	0.6
Antibiotic + antipsychotic	1	0.6
Antibiotic + NSAID + expectorant	1	0.6
Antibiotic+antianemic	1	0.6
Antidepressant	1	0.6
Antipyretic+antidiabetic+antibiotic	1	0.6
Antiepiletic + antipsychotic	1	0.6
Anticonvulsant + antiepileptic	1	0.6
Antihyperlipidemic	1	0.6
Antimycotic + allopurinol	1	0.6
Spasmolytic + antifungal	1	0.6
Spasmolytic+antianemic	1	0.6
NSAID + paracetamol	1	0.6
NSAID + antispasmodic	1	0.6
Paracetamol	1	0.6
Vitamins	1	0.6
Agricultural medicine	1	0.6
Total	164	100.0

One of the commonest manifestations of CDE, urticaria, was found in 69 (42%) patients, morbilliform rash was observed in 46 patients (31.7%), followed by eosinophilia and systemic symptoms (DRESS) in 10 (6.1%) and acute generalized exanthematous pustulosis (AGEP) in 7 (4.3%) (Figures 2, 3) (Table 2).

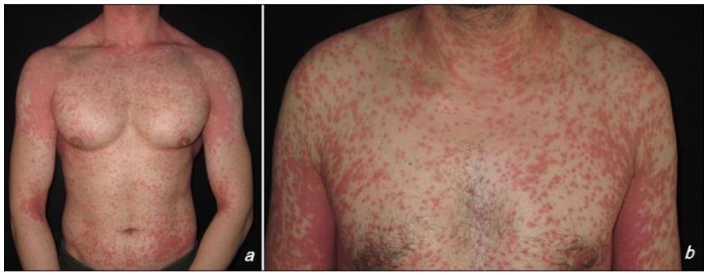


Figure 2: Morbilliform or Maculopapular drug reaction

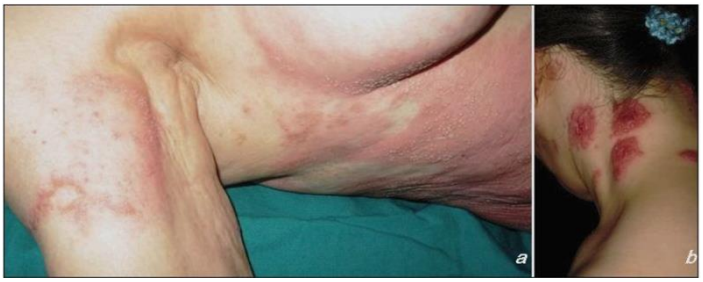


Figure 3: A: Acute Generalized Exanthematous Pustulosis (AGEP) Caused by Oral Retinoids, B: Sweet syndrome

In addition to clinical findings, 73 patients (44.5%) underwent histopathological examination, which revealed superficial perivascular dermatitis in 47 patients (64.4%), degeneration in dermoepidermal junction in 31 patients (42.5%), and dermal eosinophilic infiltration in 30 patients (41.1%). Small vessel vasculitis is found in 12 patients (16.44%) and keratinocyte necrosis was present in 7 patients (9.59%). The first treatment step consisted of cessation of the suspected drugs.

Table 2: Cutaneous manifestation of CDE

Clinical feature	n	%
Urticaria	69	42
Morbilliform rash	52	31.7
DRESS	10	6.1
Fixed drug eruption	7	3
Stevens Johnson Syndrome	5	3
Other patterns	5	3
Sweet Syndrome	4	2.4
Toxic epidermal necrolysis	4	2.4
Erythroderma	1	0.6
Total	164	100

In 90.9% (n=149) of the cases, the disease was controlled with both topical and systemic medical treatments, 7.3% (n=12) were treated with topical agents and 1.8% (n=3) received systemic medical therapy only.

The most used causality assessment modality is Hartwig's Severity Assessment Scale. The severity of cutaneous drug eruption is divided into 7 levels (Levels 1-2: Light, levels 3-4: Medium, levels 5-6-7: Severe). Among all, 78% of the patients were level 4, 15.9% were level 3 and 4.9% were level 5.

According to the Naranjo Algorithm, the drug reactions of 61.6% of patients were possibly related, that of 30.5% were probably related, that of 4.3% were unlikely to be related, and that of 3.7% were definitely related to the suspected drugs.

Discussion

Considering drugs are an essential component of medical therapy, drug-related adverse reactions are important and frequent complications of medical treatment. Cutaneous drug eruptions are seen more commonly in females compared to males [8-10]. In their study of 300 patients with CDE, Jelvehgari et al. [11] reported that the number of female patients were more than that of the male patients (♀ = 152, ♂ = 148). In our study, we also found that the proportion of female patients were greater than men. This may be because women are more likely to use drugs than men. Cutaneous drug reactions can occur at any age. While infants and children are at lower risk, adults and geriatric age groups are at higher risk for adverse drug reactions [12-13]. In our study, the mean age of the inpatients was 46.3 + 18.8 years, and the majority of the patients were 50 years and older. Our findings showed comparable results to other studies on cutaneous drug reactions. Using multiple drugs, especially due to systemic and chronic diseases, cross-reactivity among them, and diseases that lead to an inability to detoxify the toxic drug metabolites can all increase the chance of CDE development [12]. In our study, 64% (n=106) of the patients had at least one systemic disease and multiple drug use. In a 2-year retrospective study, Farshchian et al. [14] found that 20 of the 308 patients (6.5%) had a history of drug reaction which means that careful history taking can prevent recurrence of CDE in these patients. Among our patients, recurrence rate of CDE was 12.8%. These results show that patients do not adequately avoid the previously allergenic or cross-reacting drugs. In this case, the patient should be informed and should carry an allergy card or wristband to warn health care workers about which drugs can cause reactions.

In many studies, most drug reactions are caused by penicillins, cephalosporins, antibiotics, NSAIDs and anticonvulsants [3-15,16]. However, this rank varies according to demographic features like ethnicity and geographical region. For

example, in the study by Akpınar et al. [17] evaluating 106 cases in Turkey, the most frequent causative agents for CDE were antibiotics (40.5%), NSAIDs (31.1%) and antiepileptics. In an epidemiological study that examined 117 cases in a dermatology clinic in Brazil, severe drug reactions developed mostly against anticonvulsants (23.9%), antibiotics (22.1%) and with combination drugs [18].

When we compared the reports of previous studies to our study, NSAIDs (18.9%), antibiotics (15.2%), combined drug use (9.8%), and antiepileptics (4.3%) were the most common culprits of CDEs. This may be since NSAIDs can be obtained from pharmacies easily without prescription.

Cutaneous drug eruptions can present with all kinds of skin manifestations, but the most common types include morbilliform rash, urticaria and/or angioedema, erythroderma, and erythema multiforme [19-20]. However, the frequency of these patterns varies according to the geographical location, ethnic differences and the drugs used. Botelho et al. [16] examined 117 cases of CDE and reported the most common clinical forms as morbilliform rash (37.6%), DRESS (14.5%) and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) (12.8%). In India, Sasidharanpillai et al. [21] have noted SJS-TEN (5 SJS, 12 TEN) in 43 patients as the most common type of adverse drug reaction followed by morbilliform rash, DRESS, and fixed drug eruption. In these two studies, anticonvulsants were the predominant drugs causing CDE in different patterns. The most common forms of drug eruption in our study were urticaria-angioedema, morbilliform rash and DRESS, which were parallel to other researches from our country. In our study, the most common causes of urticaria were antibiotics and NSAIDs. This result was like the study of Naldi et al. [10] who observed the same reaction patterns in 2224 patients. In this study, which evaluated hospitalized patients only, urticaria was more common than morbilliform rash. This can be explained by the fact that morbilliform drug eruptions are relatively benign and mild forms do not require hospitalization. The interval between the offending drug intake and the eruption ranges from a few minutes to several hours for urticaria, and from a few hours to one week for morbilliform rash, DRESS, SJS and TEN. Akpınar et al. [17] studied the time between drug intake and the initial eruption and found that 84.6% of the cases occurred within the first two weeks and 7.5% of the cases occurred in between 1 to 3 months. In our study, akin to other results in the literature, the time between drug intake and CDE ranged from 0-3 weeks in 87.8% of patients and between 3 weeks-3 months in 11.6% of patients. This result suggests that the medications used in the last three weeks in patients with CDE need to be investigated more thoroughly. In our hospital, the patients included in the study were treated with combined topical and systemic therapy without consideration of the reaction pattern. Systemic treatments administrated most frequently were antihistamines and systemic steroids. In patients with DRESS, 40 patients received systemic corticosteroids, 1 patient received both systemic corticosteroids and IVIG, and 7 patients were treated conservatively.

In our study, we evaluated the causality of CDE in patients with Naranjo criteria, however, due to the inability of rechallenge test in our hospital and retrospective nature of this study, it led us to modify the Naranjo criteria. Similar to the other studies, causality relation was “probable” in 61.6%, “more likely” in 30.5% and “definite” in only a few.

According to Hartwig's scale, 78% of patients had “moderate” (level 4), 15.9% had “mild” (level 3) and 4.9% had “severe” (level 5) CDE.

Limitations

The most notable limitations of this study were its retrospective nature, and that the evaluation of some cases were limited to standard parameters. Incomplete documentation in patient files also resulted in loss of valuable data.

Conclusion

A detailed drug history and chronology of events should be investigated in detail for the patient presenting with CDE. Patients with a history of drug allergy should be informed, and the use of combined medication should be avoided as much as possible in the elderly population. All drugs should be considered potentially hazardous and the risk of drug reactions should be assessed in terms of the expected therapeutic benefit for each patient.

NSAIDs, antibiotics and antiepileptics, the most frequently accused agents, should draw special attention during history taking. Drug allergy history must always be taken from the patient or the patient’s relatives before prescribing. Using criteria that can be modified according to the conditions of our country, such as Naranjo criteria, will be guiding in determining the causality of drugs. Consequently, both the patient and the physician will be more cautious of riskier medications.

References

1. Temple ME, Robinson RF, Miller JC, Hayes JR, Nahata MC. Frequency and preventability of adverse drug reactions in paediatric patients. Drug Saf. 2004;27(11):819-29. doi: 10.2165/00002018-200427110-00005. PMID: 15350153.
2. Kessler DA. Introducing MEDWatch. A new approach to reporting medication and device adverse effects and product problems. J Am Podiatr Med Assoc. 1994 Jan;84(1):35-8. doi: 10.7547/87507315-84-1-35. PMID: 8295131
3. Zaraa I, Jones M, Trojjet S, Cheikh Rouhou R, El Euch D, Mokni M, Ben Osman A. Severe adverse cutaneous drug eruptions: epidemiological and clinical features. Int J Dermatol. 2011 Jul;50(7):877-80. doi: 10.1111/j.1365-4632.2010.04785.x. PMID: 21699528.
4. Knowles SR, Shear NH. Recognition and management of severe cutaneous drug reactions. Dermatol Clin. 2007 Apr;25(2):245-53. viii. doi: 10.1016/j.det.2007.01.011. PMID: 17430761.
5. Adışen E, Karaca F, Gürer MA. Dermatolojide İlaç Reaksiyonları. Turk J Dermatol 2008;2:1-5.
6. Busto U, Naranjo CA, Sellers EM. Comparison of two recently published algorithms for assessing the probability of adverse drug reactions. Br J Clin Pharmacol. 1982;13(2):223-7. doi:10.1111/j.1365-2125.1982.tb01361.
7. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm. 1992 Sep;49(9):2229-32. PMID: 1524068.
8. Mokhtari F, Nikyar Z, Naeini BA, Esfahani AA, Rahmani S. Adverse cutaneous drug reactions: Eight year assessment in hospitalized patients. J Res Med Sci. 2014 Aug;19(8):720-5. PMID: 25422656; PMCID: PMC4235091.
9. East-Innis AD, Thompson DS. Cutaneous drug reactions in patients admitted to the dermatology unit at the University Hospital of the West Indies, Kingston, Jamaica. West Indian Med J. 2009 Jun;58(3):227-30. PMID: 20043529.
10. Naldi L, Conforti A, Venegoni M, Troncon MG, Caputi A, Ghiotto E, Cocci A, Moretti U, Velo G, Leone R. Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions. Br J Clin Pharmacol. 1999 Dec;48(6):839-46. doi: 10.1046/j.1365-2125.1999.00096.x. PMID: 10594488; PMCID: PMC2014315.
11. Jelvehgari M, Azimi H, Montazam H. Prevalence of cutaneous drug eruption in hospitalized patients: a report from sina hospital of Tabriz. Iranian Journal of Dermatology. 2009;12(1):16-9.
12. Valeyrie-Allanore L, Sassolas B, Roujeau JC. Drug-induced skin, nail and hair disorders. Drug Saf. 2007;30(11):1011-30. doi: 10.2165/00002018-200730110-00003. PMID: 17973540.
13. Ahmed AM, Pritchard S, Reichenberg J. A review of cutaneous drug eruptions. Clin Geriatr Med. 2013 May;29(2):527-45. doi: 10.1016/j.cger.2013.01.008. PMID: 23571043.
14. Farshchian M, Ansar A, Zamanian A, Rahmatpour-Rokni G, Kimyai-Asadi A, Farshchian M. Drug-induced skin reactions: a 2-year study. Clin Cosmet Investig Dermatol. 2015 Feb 9;8:53-6. doi: 10.2147/CCID.S75849. PMID: 25709487; PMCID: PMC4330003.
15. Bigby M. Rates of cutaneous reactions to drugs. Arch Dermatol. 2001 Jun;137(6):765-70. PMID: 11405768.
16. Carneiro SC, Azevedo-e-Silva MC, Ramos-e-Silva M. Drug eruptions in the elderly. Clin Dermatol. 2011 Jan-Feb;29(1):43-8. doi: 10.1016/j.clindermatol.2010.07.006. PMID: 21146731.
17. Akpinar F, Dervis E. Drug Eruptions: An 8-year Study Including 106 Inpatients at a Dermatology Clinic in Turkey. Indian J Dermatol. 2012 May;57(3):194-8. doi: 10.4103/0019-5154.96191. PMID: 22707770; PMCID: PMC3371522.
18. Botelho LF, Porro AM, Enokihara MM, Tomimori J. Adverse cutaneous drug reactions in a single quaternary referral hospital. Int J Dermatol. 2016 Apr;55(4):e198-203. doi: 10.1111/ijd.13126. Epub 2015 Dec 29. PMID: 26710962.

19. Marzano AV, Borghi A, Cugno M. Adverse drug reactions and organ damage: The skin. Eur J Intern Med. 2016 Mar;28:17-24. doi: 10.1016/j.ejim.2015.11.017. Epub 2015 Dec 7. PMID: 26674736.
20. Yawalkar N. Drug-induced exanthems. Toxicology. 2005 Apr 15;209(2):131-4. doi: 10.1016/j.tox.2004.12.023. PMID: 15767025
21. Sasidharanpillai S, Riyaz N, Khader A, Rajan U, Binitha MP, Sureshan DN. Severe cutaneous adverse drug reactions: a clinicoepidemiological study. Indian J Dermatol. 2015 Jan-Feb;60(1):102. doi: 10.4103/0019-5154.147834. PMID: 25657416; PMCID: PMC4318022.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1152-1156.
DOI: 10.28982/josam.823448

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Do hysterectomy techniques affect sexual functions and lower urinary system complaints?

Histerektomi tekniklerinin cinsel fonksiyonlara, alt üriner sistem semptomları ve yaşam kalitesi üzerine etkisi var mıdır?

Demet Aydoğan Kırmızı [1], Emre Başer [1]

[1] Department of Obstetrics and Gynecology, Yozgat Bozok University, Faculty of Medicine, Yozgat, Turkey

ORCID ID of the author(s)

DAK: 0000-0001-7849-8214
EB: 0000-0003-3828-9631

Corresponding author/Sorumlu yazar:
Demet Aydoğan Kırmızı
Address/Adres: Yozgat Bozok Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı, Yozgat, Türkiye
E-mail: demet.aydogan.kirmizi@gmail.com

Ethics Committee Approval: Approval was obtained from the Yozgat Bozok University Clinical Research Ethics Committee (2017-KAEK-189_2019.12.25_12). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Yozgat Bozok Üniversitesi Klinik Araştırmalar Etik Kurulu'ndan (2017-KAEK-189_2019.12.25_12) onay alındı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: Hysterectomy is the most common gynecological surgical procedure. Therefore, detailed consultation about the postoperative effects of hysterectomy is an integral part of the operation. However, available data on these issues are limited and conflicting. The aim of this study is to evaluate the effects of hysterectomy types on lower urinary tract symptoms (LUTS), sexual function and quality of life.

Methods: Patients between 38-60 years of age who underwent total laparoscopic hysterectomy (TLH), vaginal hysterectomy (VH), and, in addition to standard total abdominal hysterectomy (TAH), uterosacral ligament-cuff suturing operation between June 2017 and 2019 were included in this cross-sectional study. Urgency, urge incontinence, frequency, abnormal emptying, hesitancy, nocturia, overflow, and interrupted stream are considered LUTS symptoms. Sexual functions were evaluated by Index of Female Sexual Function Index (FSFI) and the quality of life was evaluated by the EQ-5D (European Quality of Life Five- Dimension Scale) during the post-operative period.

Results: There was a significant decrease in urgency, urge incontinence, frequency, abnormal emptying, nocturia and interrupted stream symptoms (P<0.05) in the VH group (n=30), and urge and urge incontinence symptoms in TAH group (n=213) (P<0.05) postoperatively. In terms of the FSFI total score, the highest sexual dysfunction was in the TAH group whereas the lowest was in the TLH (n=60) group.

Conclusions: Hysterectomy does not worsen LUTS. The best post-operative sexual functions were found in the TLH group. The post-operative quality of life was better in patients operated vaginally and laparoscopically.

Keywords: Vaginal hysterectomy, Abdominal hysterectomy, Laparoscopic hysterectomy, Sexual dysfunction, Lower urinary tract symptoms, Quality of life

Öz

Amaç: Histerektomi, en yaygın jinekolojik cerrahi prosedürdür. Bu nedenle, histerektominin postoperatif etkileri hakkında ayrıntılı konsültasyon operasyonun ayrılmaz bir parçasıdır. Ancak, bu konularla ilgili mevcut veriler sınırlıdır ve çelişkilidir. Bu çalışmanın amacı, histerektomi tiplerinin alt üriner sistem semptomları (LUTS), cinsel fonksiyon ve yaşam kalitesi üzerine etkilerini değerlendirmektir.

Yöntemler: Haziran 2017-2019 tarihleri arasında benign nedenlerle total laparoskopik (TLH), vajinal (VH) ve standart total abdominal histerektomi (TAH) operasyonuna ek olarak sakrouterin ligamanent-cuff sütürizasyonu yapılmış olan 38-60 yaş arasındaki hastalar bu kesitsel çalışmaya dahil edildi. Urge, urge inkontinansı, frequency, anormal boşalma, zor idrar yapma, noktüri, taşma, kesik kesik idrar yapma AÜSS semptomları olarak değerlendirildi. Sexüel fonksiyon Index of Female Sexual Function Indexi (FSFI) ve yaşam kalitesi European Quality of Life Five-Dimension Scale (EQ-5D) ölçeği ile postoperatif dönemde değerlendirildi.

Bulgular: Preoperatif döneme göre postoperatif dönemde, VH (n=30) grubunda urgency, urge incontinence, frequency, anormal boşalma, noktüri ve kesik kesik idrar yapma semptomlarında (P<0,05), TAH (n=213) hastalarında ise urge ve urge inkontinans semptomlarında anlamlı olarak azalma olduğu saptandı (P<0,05). FSFI total skoruna göre sexual disfonksiyonun en fazla TAH ve en az TLH (n=60) grubunda görüldü. En iyi genel yaşam kalitesi skorunun VH ve ardından TLH grubunda saptandı.

Sonuç: Histerektomi AÜSS'nı kötüleştirmemektedir. Vajinal yaklaşım pelvik taban onarımı imkanıyla en belirgin düzelmeyi sağlamaktadır. Post-operatif en iyi sexual fonksiyonlar TLH grubunda saptanmıştır. Vajinal ve laparoskopik olarak opere edilen hastalarda postoperatif yaşam kalitesinin daha iyi olduğu görülmektedir.

Anahtar kelimeler: Vajinal histerektomi, Abdominal histerektomi, Laparoskopik histerektomi, Cinsel işlev bozukluğu, Alt üriner sistem semptomları, Yaşam kalitesi

How to cite/Atıf için: Kırmızı DA, Başer E. Do hysterectomy techniques affect sexual functions and lower urinary system complaints? J Surg Med. 2020;4(12):1152-1156.

Introduction

Hysterectomy is the most common major procedure in gynecological practices and is often performed for benign reasons [1]. The choice of hysterectomy technique varies depending on the patient, surgeon, and indication. Between 2000 and 2015, of the 157.589 hysterectomies performed in the United States for benign reasons, 52.8% was minimal invasive, 28.6% was abdominal and 18.6% was vaginal hysterectomy (VH) [2]. American College of Obstetrician and Gynecologist (ACOG) states that laparoscopic hysterectomy should be the standard approach in patients in which VH cannot be performed [3]. Although total laparoscopic hysterectomy (TLH) has the advantages of minimally invasive surgery such as shorter hospital stay, lower intraoperative blood loss, less postoperative pain, faster recovery, and lower infection rate compared to total abdominal hysterectomy (TAH), abdominal hysterectomy is performed more frequently [4]. Regardless of the technique, 85% of women who underwent hysterectomy are sexually active [5]. Therefore, along with the technique, the effects of the operation on urinary and genital systems, and hence on the pelvic floor, should be well known. Although it was thought for many years that hysterectomy damages the pelvic floor, recent studies have indicated that it improves existing sexual functions and some urinary complaints.

The effects of hysterectomy types, especially laparoscopic procedures, which have been applied more frequently in recent years, on the continence mechanisms and pelvic floor are important research subjects. It is still unclear whether this surgery targeting minimal tissue damage is superior to vaginal and abdominal procedures which have been performed for many years. Evaluating the effects of hysterectomy types on the pelvic floor can clarify problems and help find suitable solutions. The present study aimed to evaluate the quality of life, lower urinary tract symptoms, and sexual functions of women after vaginal, abdominal, and laparoscopic hysterectomy.

Materials and methods

This present cross-sectional research included women who underwent benign hysterectomy between June 2017 and June 2019 at the Gynecology Clinic of Yozgat Bozok University Hospital, Yozgat, Turkey. Approval was granted by Yozgat Bozok University Clinical Research Ethics Committee (2017-KAEK-189_2019.12.25_12) and written consent forms were obtained from the patients.

Women aged 38-60 years, who underwent pre-operative basic laboratory tests, transvaginal ultrasound and TAH, TLH, VH for benign reasons were included in the study. Lower urinary tract symptoms (LUTS), sexual functions, and quality of life levels of the patients who completed at least one year postoperatively were questioned. Preoperative pelvic organ prolapse - Q (POP-Q) examination and LUTS were obtained from the file records. Patients with stress urinary incontinence, morbid obesity, hysterectomy due to malignancy, and Stage 3 and 4 pelvic organ prolapse, and those who underwent TAH operation without sacrouterine ligament-cuff suturing were excluded from the study.

LUTS

Urgency, urge incontinence, frequency, abnormal emptying, hesitancy, nocturia, overflow, interrupted stream and are considered LUTS symptoms [6].

FSFI

FSFI features six domains including, 1. Desire (q1 and q2), 2. Arousal (q3, q4, q5, and q6), 3. Lubrication (q7, q8, q9, and q10), 4. Orgasm (q11, q12, and q13), 5. Satisfaction (q14, q15, and q16), 6. Pain (q17, q18, and q19). The total score ranges from 2, indicating severe sexual dysfunction, to 36, indicating full sexual function [7].

EQ-5D

It is a self-report scale developed by the EuroQoL group, the Western European quality of life research community. It has five basic parameters: Mobility, self-care, usual daily activities, pain/ discomfort, anxiety/depression. These five parameters are calculated with an index score ranging from -0.59 to 1 [8].

Surgical procedure

The type of hysterectomy to be applied to the patients is determined by the surgical team. VH is usually offered and administered as an option to patients with grade I and II urogenital prolapses. Anterior and posterior colporrhaphy are also performed to patients with anterior and posterior compartment defects. TLH is performed to patients with no large myomas and previous operative complications due to severe adhesion. TAH is performed as a standard for other cases. In our clinic, in addition to the standard TAH operation, where applicable, cuff fixation of uterosacral ligaments has been performed since 2017. This procedure is illustrated in Figure 1.

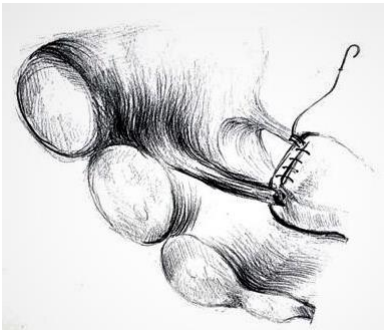


Figure 1: The illustration of the uterosacral ligament-cuff suturing applied in total abdominal hysterectomy

Statistical analysis

The statistical package software SPSS version 20 (IBM Co., Armonk, NY) was used for statistical evaluations. The obtained results were presented as mean (standard deviation) and in percentages. Continuous variables were analyzed by the Kolmogorov-Smirnov and Shapiro-Wilk's tests to evaluate whether the distribution was normal. For non-parametric and parametric data, Kruskal Wallis and One-way ANOVA tests were performed, respectively. Bonferroni correction was used for post-hoc tests. Since the continuous variables were non-normally distributed in pre-postoperative comparisons, Wilcoxon's signed-rank tests were used. Relationships between categorical variables were evaluated by the Chi-square test. $P<0.05$ were considered statistically significant.

Results

A total of 375 women underwent hysterectomy for benign reasons in the gynecology clinic of our hospital between the indicated periods; 303 of these cases met the inclusion criteria and underwent TAH (n=213), TLH (n=60) and VH (n=30) (Figure 2).

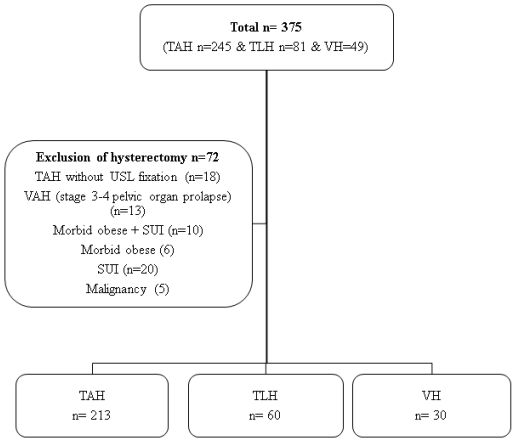


Figure 2: Details of sample size distribution (Flowchart)

There were no significant differences between the groups in terms of age, body mass index (BMI), smoking, and menopausal status (P>0.05). However, gravidity and the number of vaginal deliveries were significantly higher in the VH group than those in the other groups (P<0.05). Operation indications and demographic characteristics of the patients are given in Table 1.

A statistically significant improvement was detected in Aa, Ba, C, Ap, Bp, and D values and shortening in total vaginal length (TVL) in patients who underwent VH (P<0.05). In patients with TAH, statistically significant improvements were determined in C, Ap, Bp, and D values and TVL shortened (P<0.05). In patients who underwent TLH, there were no significant changes in any of the post-operative values compared to the pre-operative period (P>0.05) (Table 2).

Table 1: Demographic characteristics of patients

	TAH n=213	TLH n=60	VAH n=30	*P*-value
Age (years)	51.2 (4.9)	49.4 (5.8)	50.9 (4.1)	0.055
BMI (kg/m^2)	26.9 (14.2)	26.2 (2.2)	25.4 (3.6)	0.111
Gravidity	2.7 (1)	2.7 (1)	3.9 (1.8)	0.001
Parity	2.6 (1)	2.5 (0.9)	3.5 (1.5)	0.002
Smoking status, n (%)	27 (12.7)	13 (21.7)	7 (23.3)	0.109
Menopausal condition, n (%)				0.526
Premenopausal	125 (58.7)	39 (65.0)	16 (53.3)	
Postmenopausal	88 (41.3)	21 (35.0)	14 (46.7)	
Indications, n (%)				0.010
Meno/metrorrhagia	62 (29.1)	17 (28.3)	11 (36.7)	
Leiomyoma	102 (47.9)	20 (33.3)	9 (30.0)	
Adnexal mass	40 (18.8)	13 (21.7)	5 (16.7)	
Endometriosis / pelvic pain	9 (4.2)	10 (16.7)	5 (16.7)	

Unless otherwise specified, results are presented as mean (SD), BMI: body mass index, TVL: total vaginal length, TAH: total abdominal hysterectomy, TLH: total laparoscopic hysterectomy, VH: vaginal hysterectomy

Table 2: Mean distribution of Aa, Ba, C, D, Ap and Bp points/Gh, TVL and Pb changes of POP-Q of cases between pre and postoperative periods

	TAH n=213			TLH n=60			VAH n=30		
	Preop	Postop	*P*	Preop	Postop	*P*	Preop	Postop	*P*
Aa	-2.5 (0.7)	-2.6 (0.6)	0.059	-2.5 (0.6)	-2.6 (0.5)	0.066	-0.3 (0.8)	-1.9 (0.7)	<0.001
Ba	-2.9 (0.8)	-3 (0.7)	0.059	-3 (0.7)	-3 (0.6)	0.317	-0.5 (1.1)	-2.3 (0.7)	<0.001
Ap	-2.4 (0.8)	-2.6 (0.6)	<0.001	-2.5 (0.6)	-2.6 (0.5)	0.317	-0.3 (0.8)	-1.4 (0.6)	<0.001
Bp	-2.9 (0.9)	-3 (0.7)	0.003	-3 (0.7)	-3.1 (0.6)	0.180	-0.6 (1.1)	-2.4 (1)	<0.001
C	-4.9 (3)	-5.1 (2.6)	0.001	-5.2 (2.4)	-5.3 (2.4)	0.083	-0.1 (0.9)	-2.1 (1.3)	<0.001
D	-6 (3.2)	-6.3 (2.8)	0.002	-6.3 (2.6)	-6.4 (2.6)	0.102	0.1 (0.7)	-2.5 (2)	<0.001
TVL	9.5 (1.1)	8.9 (1.3)	<0.001	9.6 (0.7)	9.5 (0.7)	0.059	9.6 (1.1)	8.8 (1.1)	0.001
GH	4.5 (1.1)	4.5 (1.1)	0.568	4.5 (1.2)	4.6 (1)	0.705	4.2 (1.1)	4.3 (1)	0.157
PB	2.6 (0.9)	2.7 (0.8)	0.274	2.6 (1)	2.6 (0.9)	0.782	2.7 (0.9)	2.6 (0.8)	0.480

Data presented as mean (SD), Gh: genital hiatus, Pb: perineal body, TVL: total vaginal length, TAH: total abdominal hysterectomy, TLH: total laparoscopic hysterectomy, VH: vaginal hysterectomy

The changes in LUTS are given in Table 3. Accordingly, it was found that there were significant improvements in the complaints of post-operative urge and urge incontinence in patients with TAH (P<0.05) whereas no significant changes were found in other symptoms (P>0.05). There were no significant changes in the symptoms in the TLH group (P>0.05). In the VH group, there was a statistically significant improvement in symptoms other than hesitancy and overflow (P<0.05).

The FSFI scores of the groups are given in Table 4. The patients in the TLH group were significantly higher than those in TAH and VH in terms of lubrication, satisfaction, pain, orgasm, and total score (P<0.05). There were no significant differences between the groups in desire and arousal scores (P=0.461, P=0.840, respectively).

Table 3: Pre and postoperative LUTS of cases

	AH			TLH			VAH		
	Preop	Postop	*P*	Preop	Postop	*P*	Preop	Postop	*P*
Urgency	50 (23.5)	32 (15.0)	<0.001	8 (13.3)	10 (16.7)	0.500	12 (40.0)	3 (10.0)	0.004
Urge incontinence	31 (14.6)	15 (7.0)	<0.001	3 (5.0)	6 (10.0)	0.250	10 (33.3)	3 (10.0)	0.016
Frequency	24 (11.3)	30 (14.1)	0.109	7 (11.7)	10 (16.7)	0.250	14 (46.7)	6 (20.0)	0.021
Nocturia	25 (11.7)	28 (13.1)	0.250	9 (15)	7 (11.7)	0.500	10 (33.3)	3 (10)	0.016
Overflow	13 (6.1)	11 (5.2)	0.625	3 (5.0)	1 (1.7)	0.500	6 (20.0)	2 (6.7)	0.125
Hesitancy	15 (7.0)	13 (6.1)	0.625	5 (8.3)	3 (5.0)	0.500	7 (23.3)	3 (10.0)	0.125
Interrupted stream	31 (14.6)	34 (16.0)	0.375	8 (13.3)	4 (6.7)	0.125	12 (40.0)	3 (10.0)	0.004
Abnormal emptying	16 (7.5)	12 (5.6)	0.125	5 (8.3)	3 (5.0)	0.500	7 (23.3)	1 (3.3)	0.031

Data presented as n (%), TAH: total abdominal hysterectomy, TLH: total laparoscopic hysterectomy, VH: vaginal hysterectomy, LUTS: lower urinary tract symptoms

Table 4: Postoperative FSFI scores of cases

FSFI Domain	TAH n=213	TLH n=60	VAH n=30	*P*-value
Desire	4.0 (0.8)	3.9 (0.7)	3.8 (0.7)	0.461
Arousal	4.0 (1.1)	4.0 (1.2)	4.0 (1.3)	0.840
Lubrication	3.9 (1)	4.4 (1.1)[a,c]	4.0 (0.7)	<0.001
Orgasm	3.9 (0.9)	4.1 (0.8)[a]	4.0 (0.8)	0.008
Satısfactıon	3.9 (0.9)	4.4 (0.9)[a,c]	4.3 (0.9)	<0.001
Pain	4 (1)	4.6 (0.9)[a,c]	3.7 (1.6)	<0.001
Total	23.7 (4)	25.5 (4.3)[a,c]	23.8 (2.8)	<0.001

Results are presented as mean (SD), FSFI: female sexual function index, TAH: total abdominal hysterectomy, TLH: total laparoscopic hysterectomy, VH: vaginal hysterectomy

The mean values of EQ-5D scores in the TAH, TLH, and VH groups were 0.83 (0.56), 0.89 (0.47), and 0.95 (0.39), respectively. The EQ-5D score was statistically higher in the VH group compared to those of the other groups (P<0.001) (Figure 3).

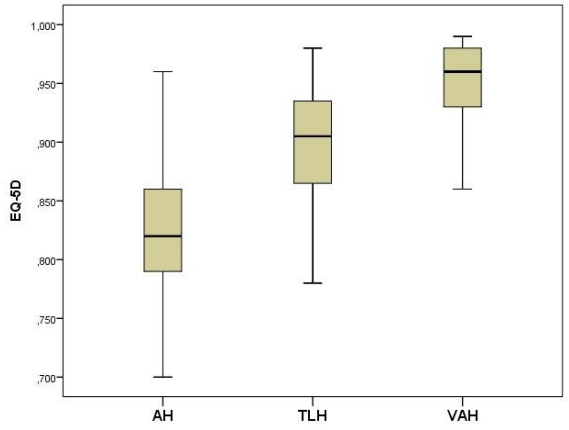


Figure 3: EQ-5D scores according to the groups

Discussion

Usually, hysterectomy does not adversely affect pelvic floor functions. The most significant improvement in LUTS is seen in the vaginal hysterectomy group. In patients undergoing abdominal hysterectomy, cuff suturing of USLs can yield improvement in urge and urge incontinence. It was seen that

sexual functions were better in patients who underwent laparoscopic surgery.

The most valid theory that fully explains the female urinary functions is the Integral Theory [9], according to which, even a minimal change in one of the parts can lead to disruption of harmony. Some studies have indicated that hysterectomy may also be a risk factor for genital prolapse and urinary incontinence by disrupting the pelvic floor [10-12]. In these studies, it has been reported that there was an increase in postoperative urinary incontinence and this result was based on temporary changes in bladder capacity, increased intravesical pressure, and impaired sensory innervation of the bladder during the operation [13]. On the contrary, many randomized controlled prospective studies have reported an improvement in lower urinary tract complaints of hysterectomy [14, 15]. However, which of the hysterectomy types has a stronger effect on LUTS is controversial [16]. In their studies evaluating the effects of TAH and VH on the lower urinary system, Altman et al. have reported that frequencies decreased and urgency and dysuria did not change in both groups [17]. In another study, de novo urinary incontinence and its affecting factors after hysterectomy were evaluated, and a higher decrease was observed in the rate of urinary incontinence remission after VH compared to TAH [18]. The current study group consisted of patients without pre-operative stress urinary incontinence and apparent pelvic organ prolapse. Evaluating the data, it was seen that lower urinary tract symptoms improved significantly in the VH group. While there was a significant improvement in urge incontinence in patients who underwent TAH, no significant improvement was observed among TLH cases. This result was associated with the significant improvement in lower urinary tract symptoms in accordance with the integral theory of pelvic floor repair in patients undergoing VH. Improvement in TAH cases, especially in urge, may be related to the involvement of uterosacral ligaments in these patients and subsequent attachment to the cuff. This procedure preserves the supportive function of the anterior vagina wall and ensures that the apical vagina is raised to support the bladder base and bladder neck. Providing upper anterior vaginal wall tension may inhibit the early stimulation of receptors in the bladder floor, preventing the formation of urge [19]. Uterosacral ligaments (USL) are the major attachment structures in the small pelvis. Proper anatomic fixation of USL with polyvinylidene fluoride bands of the same length and shape, elevating the anterior vaginal wall to support the bladder base and bladder neck may improve the mix and urge incontinence. It has been reported that vaginosacropexy (VASA) operation, which is performed in addition to hysterectomy, provides a higher reduction in urge and urge incontinence compared to drug treatments [20]. Another continence mechanism in TAH can be associated with the disappearance of vesical hyperactivity caused by these structures due to the intake of fibroids, large uterus, or adnexal masses [21]. In our clinic, TLH is often applied to patients with a relatively small uterus. This may explain the absence of a significant improvement in patients' post-operative period LUTS.

Female sexuality is a complex issue that can be affected by many factors. Various anatomical factors such as the presence/absence of the uterus and cervix, cuff suturing, the length of the vagina, the presence of ovaries, and patients' beliefs and attitudes affect sexual functions. In 1966, Master and Jonhsan reported that the uterus did not affect the orgasm, whereas Fox claimed that uterine contractions played an active role in the orgasm in the following years [22,23]. The results of the study evaluating the effect of hysterectomy on sexual functions show variations. In the studies evaluating the effect of hysterectomy on libido and genital sexual sensitivity at the end of 1900s, it was reported that there was no change in these parameters regardless of the type of operation, while the studies in the following years showed that there was a significant improvement in sexual functions, especially in the late period [24,25]. The improvement of hysterectomy in sexual functions is related to the decrease of dyspareunia, the absence of fear of pregnancy, and the relief caused by the disappearance of the pathology with the operation indication [26,27]. However, each of the hysterectomy modalities can affect sexual functions, causing different injuries in the pelvic floor, including vessels, innervations, and support structures [28-30].

Evaluating the hysterectomy techniques in the present study, it was seen that the highest post-operative FSFI scores were in the TLH group. It was found that there were no significant changes in desire and arousal scores. Pain in VH patients was higher than those in other groups. All other scores were found to be significantly higher in TLH patients. It was thought that good sexual functions in TLH may be related to the technique. Pelvic autonomic nerves innervate the vaginal wall for lubrication. The risk of injury to these nerves is higher in laparotomy cases and even higher in radical surgeries. This leads to decreased lubrication and vaginal vasocongestion during sexual arousal [31]. The risk of injury was much lower in minimally invasive procedures. Therefore, it was thought that the lubrication and satisfaction scores were higher in TLH cases. A higher postoperative comfort compared to TAH in these patients and good psychological effects due to better cosmetic results also affect the improvement in sexual functions [32]. Another factor we deem important was that the length of the vagina was longer in TLH compared to those in other groups. The shortening of the vagina was considered as a factor that negatively affects sexual function by some researchers [33].

In the present study in which the quality of life was evaluated according to EQ-5D, it was seen that VH patients had a significantly better quality of life score compared to other types of operations. This result can also be associated with the appropriate surgical method chosen for patients. As also stated by Radosa et al. [26], it was thought that the improvement in LUTS obtained by hysterectomy in patients with early-stage uterine prolapse has a greater effect on the quality of life. LUTS are a multifactorial group of heterogeneous symptoms that can change in severity over time, and these symptoms can negatively affect the quality of life. The surgical method that provided the second-best quality of life was laparoscopic hysterectomy due to being a minimal invasive surgery.

Limitations

It is difficult to fully evaluate the dysfunctions of the pelvic floor. The most important limitation of the present study was the lack of pre-operative evaluation of the quality of life and sexual functions. However, presenting the effects of three

hysterectomy techniques on quality of life and urinary symptoms together provided a strong analysis opportunity.

Conclusion

Comparing the effects of these alternative treatment modalities on the quality of life and female sexuality appears to be an important aspect for further research to improve the treatment of benign uterine disorders. At this point, it should be considered that the decisions regarding the surgical approach in hysterectomy should be made by the patient based on discussions that will be made with the surgeon about the relative benefits and harms of the operations.

Acknowledgments

We thank Çiğdem Aydoğan for preparing the illustration in Figure 1.

References

1. Clarke-Pearson DL, Geller EJ. Complications of hysterectomy. Obstet Gynecol. 2013;121(3):654-73.
2. Agrawal S, Chen L, Tergas AI, Hou JY, Clair CMS, Ananth CV, et al. Characteristics associated with prolonged length of stay after hysterectomy for benign gynecologic conditions. Am J Obstet Gynecol. 2018;219(1):89. e81-9.
3. Obstetricians ACo, Gynecologists. Choosing the route of hysterectomy for benign disease. Acog committee opinion no. 444. Obstet Gynecol. 2009;114:1156-58.
4. Wright JD, Herzog TJ, Tsui J, Ananth CV, Lewin SN, Lu Y-S, et al. Nationwide trends in the performance of inpatient hysterectomy in the united states. Obstet Gynecol. 2013;122:233-41.
5. Lethaby A, Mukhopadhyay A, Naik R. Total versus subtotal hysterectomy for benign gynaecological conditions. Cochrane database of systematic reviews. 2012
6. Turgal M, Sivaslioglu A, Yildiz A, Dolen I. Anatomical and functional assessment of anterior colporrhaphy versus polypropylene mesh surgery in cystocele treatment. Eur J Obstet Gynecol Reprod Biol. 2013;170(2):555-8.
7. Rosen CB, Heiman J, Leiblum S, Meston C, Shabsigh R, Ferguson D, D'Agostino R. The female sexual function index (fsfi): A multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000;26(2):191-208.
8. Group TE. Euroqol-a new facility for the measurement of health-related quality of life. Health policy. 1990;16(3):199-208.
9. Petros P. A ligamentous explanation for overactive bladder symptoms as defined by international continence society in the female. Central European journal of urology. 2018;71(1):105-7.
10. Milsom I, Ekelund P, Molander U, Arvidsson L, Areskoug B. The influence of age, parity, oral contraception, hysterectomy and menopause on the prevalence of urinary incontinence in women. J Urol. 1993;149(6):1459-62.
11. Parys B, Woolfenden K, Parsons K. Bladder dysfunction after simple hysterectomy: Urodynamic and neurological evaluation. Eur Urol. 1990;17(2):129-33.
12. Van der Vaart C, Van der Bom J, De Leeuw J, Roovers J, Heintz A. The contribution of hysterectomy to the occurrence of urge and stress urinary incontinence symptoms. BJOG. 2002;109(2):149-54.
13. Smith P, Ballantyne B. The neuroanatomical basis for denervation of the urinary bladder following major pelvic surgery. Br J Surg. 1968;55(12):929-33.
14. Thakar R, Ayers S, Clarkson P, Stanton S, Manyonda I. Outcomes after total versus subtotal abdominal hysterectomy. N Engl J Med. 2002;347(17):1318-25.
15. Gimbel H, Zobbe V, Andersen BM, Filtenborg T, Gluud C, Tabor A, et al. Randomised controlled trial of total compared with subtotal hysterectomy with one-year follow up results. BJOG. 2003;110(12):1088-98.
16. Virtanen H, Mäkinen J, Tenho T, Kiilholma P, Pitkänen Y, Hirvonen T. Effects of abdominal hysterectomy on urinary and sexual symptoms. B J Urol. 1993;72:868-72.
17. Altman D, Lopez A, Falconer C, Zetterström J. The impact of hysterectomy on lower urinary tract symptoms. Int Urogynecol. J 2003;14(6):418-23.
18. Bohlin KS, Ankardal M, Lindkvist H, Milsom I. Factors influencing the incidence and remission of urinary incontinence after hysterectomy. Am J Obstet Gynecol. 2017;216(1):53.e1-53.e9.
19. Petros PE, Ulmsten U. Bladder instability in women: A premature activation of the micturition reflex. Neurourol Urodyn. 1993;12(3):235-9.
20. Ludwig S, Becker I, Mallmann P, Jager W. Comparison of solifenacin and bilateral apical fixation in the treatment of mixed and urgency urinary incontinence in women: Urge 1 study, a randomized clinical trial. In vivo (Athens, Greece). 2019;33(6):1949-57.
21. Andrada AO, De Vicente JMG, Cidre MÁJ. Pelvic plexus compression due to a uterine leiomyoma in a woman with acute urinary retention: A new hypothesis. Int Urogynecol J. 2014;25(3):429-31.
22. Masters W, Johnson V. Human sexual response, boston (little, brown and company) 1966.
23. Fox C, Fox B. A comparative study of coital physiology, with special reference to the sexual climax. Reprod. 1971;24(3):319-36.
24. Wierrani F, Huber M, Grin W, Henry M, Grünberger W. Postoperative libido and genital sexual sensitivity following various forms of hysterectomy. J Gynecol Surg. 1995;11(3):127-32.
25. Galyer KT, Conaglen HM, Hare A, Conaglen JV. The effect of gynecological surgery on sexual desire. J Sex Marital Ther. 1999;25(2):81-8.
26. Radosa JC, Meyberg-Solomayer G, Kastl C, Radosa CG, Mavrova R, Gräber S, et al. Influences of different hysterectomy techniques on patients' postoperative sexual function and quality of life. J Sex Med. 2014;11(9):2342-50.
27. He H, Yang Z, Zeng D, Fan J, Hu X, Ye Y, et al. Comparison of the short-term and long-term outcomes of laparoscopic hysterectomies and of abdominal hysterectomies: A case study of 4,895 patients in the guangxi zhuang autonomous region, china. Chinese J Cancer Res. 2016;28(2):187-96.
28. Kilkku P. Supra vaginal uterine amputation vs. Hysterectomy: Effects on coital frequency and dyspareunia. Acta Obstet Gynecol Scand. 1983;62(2):141-5.
29. Roovers J-PW, van der Bom JG, van der Vaart CH, Heintz APM. Hysterectomy and sexual wellbeing: Prospective observational study of vaginal hysterectomy, subtotal abdominal hysterectomy, and total abdominal hysterectomy. BMJ. 2003;327(7418):774-8.
30. Tunuguntla HS, Gousse AE. Female sexual dysfunction following vaginal surgery: A review. J Urol. 2006;175(2):439-46.
31. Maas CP, Weijenborg PTM, Ter Kuile MM. The effect of hysterectomy on sexual functioning. Annu Rev Sex Res 2003;14:83-113.
32. Ayoubi J, Fanchin R, Monrozies X, Imbert P, Reme J, Pons J. Respective consequences of abdominal, vaginal, and laparoscopic hysterectomies on women's sexuality. Eur J Obstet Gynecol Reprod Biol. 2003;111(2):179-82.
33. Ercan Ö, Özer A, Köstü B, Bakacak M, Kıran G, Avcı F. Comparison of postoperative vaginal length and sexual function after abdominal, vaginal, and laparoscopic hysterectomy. Int J Gynaecol Obstet. 2016;132(1):39-41.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1157-1160.
DOI: 10.28982/josam.826917

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Can we predict poor prognosis in Fournier gangrene?

Fournier gangreninde kötü prognozu ön görebilirmiyiz?

Yusuf Özlülerden [1], Aykut Başer [2], Sinan Çelen [1], Okan Alkış [3]

[1] Pamukkale University, Faculty of Medicine, Department of Urology, Denizli, Turkey
[2] Hitit University, Faculty of Medicine, Department of Urology, Corum, Turkey
[3] Kütahya SBÜ, Faculty of Medicine, Department of Urology, Kutahya, Turkey

ORCID ID of the author(s)
YÖ: 0000-0002-6467-0930
AB: 0000-0003-0457-512X
SÇ: 0000-0003-4309-2323
OA: 0000-0001-6116-9588

Corresponding author/Sorumlu yazar:
Okan Alkış
Address/Adres: Kütahya SBÜ Tıp Fakültesi, Üroloji Anabilim Dalı, Kütahya, Türkiye
E-mail: okanalks@hotmail.com

Ethics Committee Approval: The study was approved by Pamukkale University Ethics Committee on 12/10/2019 with the decision number 21. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma Pamukkale Üniversitesi Etik Kurulu tarafından 10.12.2019 tarihinde 21 karar numarası ile onaylandı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: Fournier's gangrene (FG) is a rapidly progressing and highly mortal necrotizing fasciitis that develops due to polymicrobial infection of the genital, perineal and perianal regions. Advanced age, comorbidities, width of the infected area, leukocyte-lymphocyte ratio, number of debridement performed, and Fournier's gangrene severity index (FGSI) score are reported as prognostic factors for FG. In our study, we aimed to present the clinical and laboratory findings that can be used to predict poor prognosis in Fournier gangrene.

Methods: In this retrospective cohort study, the files of 83 patients treated for FG were retrospectively analyzed. Demographic data, laboratory findings, treatments, age adjusted Charlson comorbidity index (ACCI), FGSI score, LRINEC score, complications and mortality were noted. Risk factors affecting mortality were determined.

Results: Male/female ratio was 7.3. The mean age of the patients were 55.4 years. The mortality rate was 21.7%. The mean ACCI scores (Mortality group: 6.00 (2.72), survivors' group: 2.66 (2.39)) and FGSI scores (Mortality group; 11.22 (3.2), survivors' group; 3.25 (2.08)) of non-surviving patients were higher than those of survivors (P<0.001, P<0.001, respectively). Also, the mean neutrophil-lymphocyte ratio (Mortality group: 21.05 (15.67), survivors' group: 11.62 (10.50), (P=0.013), and the mean LRINEC score (Mortality group: 7.17 (2.03), survivors' group: 3.18 (2.59)) (P=0.001) were higher among non-survivors. Cut off values for FGSI score, LRINEC, ACCI, and neutrophil / lymphocyte ratio were 7.5 (94.4% sensitivity and 95.4% specificity), 4.5 (94.4% sensitivity and 67.7% specificity), 3.5 (77.8% sensitivity and 73.8% specificity), and 8.70 (72.2% sensitivity and 52.3% specificity), respectively, in predicting mortality. Mortality was higher in female patients compared to males (P=0.02), and among the diabetics (P=0.05).

Conclusion: We think that risk factors such as advanced age, diabetes, female gender, high ACCI score, high FGSI scores, high LRINEC scores and high neutrophil lymphocyte ratio are predictive of poor prognosis in FG.

Keywords: Fournier's gangrene, Mortality, Risk factors

Öz

Amaç: Fournier gangreni (FG), genital, perineal ve perianal bölgelerin polimikrobiyal enfeksiyonuna bağlı olarak gelişen, hızla ilerleyen ve oldukça ölümcül bir nekrotizan fasiittir. İleri yaş, komorbiditeler, enfekte bölgenin genişliği, lökosit-lenfosit oranı, debridman sayısı, Fournier'in kangren şiddet indeksi (FGSI) skoru FG için prognostik faktörler olarak gösterilmiştir. Çalışmamızda fournier gangreninde kötü prognozu tahmin etmede kullanılabilecek klinik ve laboratuvar bulgularını sunmayı amaçladık.

Yöntemler: Bu retrospektif kohort çalışmada FG tedavisi gören 83 hastanın dosyası incelendi. Demografik veriler, laboratuvar bulguları, tedaviler, yaşa göre düzenlenmiş Charlson komorbidite indeksi (ACCI), FGSI skoru, LRINEC skoru, komplikasyonlar ve mortalite dosyalardan kaydedildi. Mortaliteyi etkileyen risk faktörleri belirlendi.

Bulgular: Erkek / kadın oranı 7,3 idi. Ortalama yaş 55,4 idi. Ölüm oranı % 21,7 olarak saptandı. Mortalitesi olan hastaların ortalama ACCI skorları (mortalite grubu; 6,00 (2,72) - sağ kalanlar grubu; 2,66 (2,39)) ve FGSI skorları (mortalite grubu; 11,22 (3,2) - sağ kalanlar grubu; 3,25 (2.08)), sağ kalanlardan daha yüksekti (sırasıyla, P<0,001, P<0,001). Ayrıca ortalama nötrofil-lenfosit oranı (mortalite grubu; 21,05 (15,67) - hayatta kalanlar grubu; 11,62 (10,50)) (P=0,013) ve ortalama LRINEC skoru (mortalite grubu; 7,17 (2,03) - hayatta kalanlar grubu; 3,18 (2,59)). FGSI skoru için kesme değeri 7,5 (%94,4 duyarlılık ve %95,4 özgüllük), LRINEC için 4,5 (%94,4 duyarlılık ve %67,7 özgüllük), ACCI 3,5 için (%77,8 duyarlılık ve %73,8 özgüllük), nötrofil / lenfosit oranı için mortaliteyi öngörmede 8,70 (%72,2 duyarlılık ve %52,3 özgüllük) olarak saptandı. Kadın hastalarda mortalite erkeklere göre daha yüksekti (P=0,02) ve diyabetli hastalarda mortalite daha yüksekti (P=0,05).

Sonuç: İleri yaş, diyabet, kadın cinsiyet, yüksek ACCI skoru, yüksek FGSI skoru, yüksek LRINEC skoru ve yüksek nötrofil lenfosit oranı gibi risk faktörlerinin FG'de kötü prognozu öngörmede kullanılabileceğini düşünmekteyiz.

Anahtar kelimeler: Fournier gangreni, Mortalite, Risk faktörleri

How to cite/Atıf için: Özlülerden Y, Başer A, Çelen S, Alkış O. Can we predict poor prognosis in Fournier gangrene? J Surg Med. 2020;4(12):1157-1160.

Introduction

Fournier's gangrene (FG) is an idiopathic polymicrobial necrotizing fasciitis observed in the scrotal, perineal and perianal areas. FG can be observed in both genders and at all ages [1]. Local trauma, anorectal and scrotal infections are important factors in etiology [2]. Emergency debridement and antibiotherapy are used in the treatment [3]. Repeated debridement can be performed in the follow-up of patients. After the complete regression of the infection, the exposed area is closed with skin flaps.

It is still a disease with a high mortality (16-40%) despite emergency debridement and adequate antibiotherapy [4,5]. In the literature, the factors affecting mortality are reported as age, coexisting comorbidities, the width of the infection area, intensive care requirement, the number of debridement performed, the leukocyte-lymphocyte ratio, and the lymphocyte-platelet ratio [6-8]. Laor et al. published the Fournier Gangrene Severity Index (FGSI) score for predicting mortality [7], which includes temperature, heart rate, respiratory rate, white blood cell count, hematocrit, serum creatinine, sodium, bicarbonate, and potassium. After FGSI, alternative scoring systems were determined for predicting mortality in FG [9-12], including simplified Fournier gangrene severity index (SFGSI), Uludag FGSI (UFGSI), sAPGAR, Age-Adjusted Charlson Comorbidity Index (ACCI), Laboratory Risk Indicator for Necrotizing Fasciitis score (LRINEC), and APACHE II. LRINEC score is calculated by measuring leukocyte count, hemoglobin, serum creatinine sodium, C-reactive protein, and glucose levels. In our study, we aimed to reveal the treatment outcomes of the patients who were followed up and treated for FG and investigate the factors that may affect the prognosis.

Materials and methods

Study population

Patients who underwent surgery with the diagnosis of Fournier's gangrene in the urology departments of our tertiary hospital, where approximately 80000 patients were admitted annually, were included in this study. Informed consent forms were obtained from all patients for surgical intervention.

Subject selection

In this retrospective cohort study, the data of 83 patients who were treated for Fournier's gangrene in our hospital between 2015 and 2019 were analyzed. Patients who underwent surgical intervention in the urology department were included in the study. Per-operative consultation was requested from the department of general surgery when needed. The postoperative follow-up of the patients was performed by the urology department (except when intensive care was required).

Data collection and outcome measures

The study was approved by Pamukkale University Ethics Committee on 10.12.19 with the decision number 21. All information of the patients was obtained from the hospital information management system retrospectively. The patients with skin infection who were found to have necrosis in the genital and perianal areas in clinical examination and underwent debridement with the diagnosis of FG were included in the study. Patients underwent debridement immediately after the diagnosis. Broad-spectrum parenteral antibiotic treatment was initiated. Repeated debridement was performed in patients who had infection findings in the follow-up. In patients with open wound sites, when the infection regressed and granulation tissue formed after antibiotherapy, wound sites were closed with skin flaps. All patients' demographic information, systemic diseases, etiological factors for FG, initial lesion sites, laboratory findings, number of debridement performed, skin flap counts used, duration of hospital stay, whether cystostomy and/or colostomy was performed, and mortality data were determined. Charlson comorbidity index scores, defined by Charlson ME, who revealed the morbidity and mortality risks of cases with systemic diseases, were calculated [13]. The presence of diabetes, cardiovascular, pulmonary, neurological, gastrointestinal, urinary, hematological disease and malignancy were noted, ACCI scores were calculated based on the severity of these comorbidities. Respiratory rate, heart rate, white blood cell count, hematocrit level, serum sodium, potassium, creatinine, and bicarbonate levels were recorded for calculating FGSI score.

Statistical analysis

The tests to compare data were decided in line with the central limit theory. To evaluate the findings obtained in this study, IBM SPSS Statistics 22 for statistical analysis (SPSS IBM, Turkey) program was used. Normal distribution of the data was tested by visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov / Shapiro-Wilks tests). Number, percentage, median and interquartile range values were used for descriptive statistics. The Mann–Whitney U test and Student-t test were used for nonnormally and normally distributed parameters, respectively. Categorical variables were evaluated with the Chi square test or Fisher exact test (when Chi ‑square test assumptions do not hold due to low expected cell counts). Correlation analyses were performed using the Pearson test, and the Spearman correlation test when the Pearson test was not suitable. The cut-off points were chosen based on the ROC (receiver operating characteristics) curve analysis. When a significant cut-off value was observed, the sensitivity and specificity were presented. While evaluating the area under the curve (AUC), a 5% type-1 error level was used to accept the statistically significant predictive value of the test variables. The significance value for the results was set as $P<0.05$.

Results

In our study, 73 (87.9%) of the patients were male and 10 (12.1%) were female (Table 1). The overall mean age of the patients was 55.4 (17.65) years. Gangrene developed in the scrotal region in 55 patients, in the perianal region in 20 patients and in the penile region in 8 patients. FG occurred due to colorectal cancer in 3 patients, due to perianal abscess in 20 patients, due to penile cancer in 1 patient, and after penile prosthesis implantation in 1 patient. Gangrene developed idiopathically in 58 patients. The predisposing factors for the formation of FG were diabetes in 43 patients, malignancy in 5 patients and paraplegia in 7 patients (Table 1). The mean ACCI scores evaluating the coexisting diseases of the patients was 3.06 (2.6). The mean blood leukocyte count and neutrophil-lymphocyte ratio of all patients were 16444 (2200-51000) mcL and 13.66 (12.6), respectively (Table 1).

Table 1: Patients' demographics, comorbidities and mortality

			Total patients (n=83)
Age (years) mean (SD)			55.4 (17.65)
Sex	-	Female n(%)	10 (12.1)
	-	Male n(%)	73 (87.9)
Diabetes n(%)			43 (51.8)
Malignancy n(%)			5 (6.02)
Paraplegia n(%)			7 (8.43)
Mortality n(%)			18 (21.7)
Etiology	-	İdiopathic n(%)	58(69.87)
	-	Perianal abscess n(%)	20(24.09)
	-	Colorectal cancer n(%)	3(3.61)
	-	Penile cancer n(%)	1(1.20)
	-	Penile prosthesis n(%)	1(1.20)
First lesion region	-	Scrotal n(%)	55(66.26)
	-	Perianal n(%)	20(24.09)
	-	Penile n(%)	8(9.63)
Laboratory findings	-	Blood leukocyte count n(%)	16444 (9579)
	-	Neutrophil/lymphocyte ratio n(%)	13.66 (12.6)
Diversion	-	Cystostomy n(%)	4 (3.1)
	-	Colostomy n(%)	15 (11.5)
Number of debridement mean (SD)			1.69 (0.79)
Number of flaps mean (SD)			1.05 (0.76)
Mean hospital stay (days) mean (SD)			24.92 (18.96)

All patients underwent debridement immediately after the diagnosis. Cystostomy was performed in 4 patients (3.1%), and colostomy was required in 15 patients (11.5%) in order to prevent wound site contamination during debridement. Debridement was repated in patients who had infection findings during follow-up. The mean number of debridement performed was 1.69 (0.79). After the wound infection of the patients regressed and granulation tissue formed, the wound sites were closed by turning flaps. In patients with reinfected or opened wound sites, the wound sites were closed by turning flaps again after the treatment. The mean number of flaps used was 1.05 (0.76), and the mean duration of hospitalization was 24.92 (18.96) days (Table 1).

Mortality was observed in 18 patients (21.7%). The mean ACCI score (6.00 (2.72)) of the non-surviving patients was statistically significantly higher compared to those who survived (2.66 (2.39)) (P<0.001). The mean FGSI, LRINEC scores, and neutrophil-lymphocyte ratios of non-survivors (P<0.001, P<0.001, and P=0.013, respectively) were significantly higher compared to patients who were discharged. The mean age of non-survivors (68.28 years) was higher compared to surviving patients (50.02 years) (P<0.001). Mortality was observed significantly more frequently in female patients compared to male patients (P=0.02), and among diabetics (P=0.05). No statistically significant relationship was found between the number of debridement, requiring cystostomy or colostomy and mortality (Table 2). ROC curve analysis showed that FGSI score, LRINEC score, ACCI score and Neutrophil/lymphocyte ratios can be used as markers for predicting mortality in FG. When the cut-off value is 7.5 for FGSI score, it predicts mortality with 94.4% sensitivity and 95.4% specificity [AUC=0.988, P<0.001, 95% CI (0.000-1.000]. A cut-off value of 4.5 for LRINEC score predicts mortality with 94.4% sensitivity and 67.7% specificity [AUC=0.868, P<0.001, 95% CI (0.791-0.944], and a cut-off value of 3.5 for ACCI score predicts mortality with 77.8% sensitivity and 73.8% specificity [AUC=0.832, P<0.001, 95% CI (0.723-0.941]. Values above 8.70 for neutrophil/lymphocyte ratio predict mortality with 72.2% sensitivity and 52.3% specificity [AUC=0.692, P=0.013, 95% CI (0.539-0.846] (Figure 1).

A significant correlation was found between mortality and gender, age, LRINEC score, FGSI score, ACCI score and neutrophil-lymphocyte ratio (Table 3).

Table 2: Factors affecting mortality

	Non-surviving Patients (n=18) mean (SD)	Discharged Patients (n=65) mean (SD)	*P*-value
Age (year)	68.28 (14.58)	50.02 (16.40)	<0.001
Female gender n(%)	5 (27.7)	5 (7.6)	0.002
Diabetes n(%)	13 (72.2)	30 (46.1)	0.005
Cystostomy n(%)	2 (11.1)	2 (3.0)	0,159
Colostomy n(%)	5 (27.7)	13 (20.0)	0,227
Number of debridement	1.50 (0.85)	1.74 (0.77)	0.142
Neutrophile/lymphocyte ratio	21.05 (15.67)	11.62 (10.50)	0.013
Charlson Comorbidity score	6.00 (2.72)	2.66 (2.39)	<0.001
FGSI score	11.22 (3.2)	3.25 (2.08)	<0.001
LRINEC score	7.17 (2.03)	3.18 (2.59)	<0.001

Table 3: Correlation analysis between mortality and gender, age, LRINEC, FGSI, ACCI score and neutrophil-lymphocyte ratio

	Gender	Age	LRINEC score	FGSI score	ACCI score	Neutrophil-lymphocyte ratio
rho	-0.254	0.433	0.529	0.700	0.480	0.275
P-value	0.020	<0.001	<0.001	<0.001	<0.001	0.012

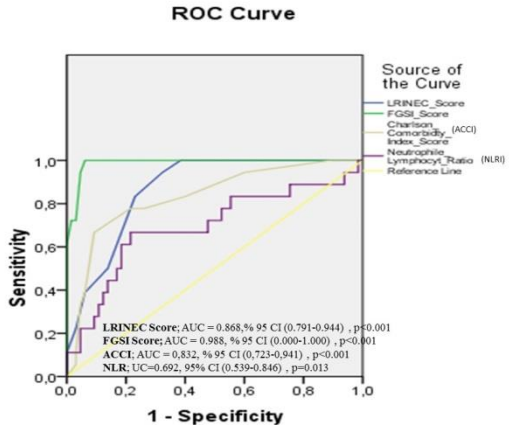


Figure 1: ROC curve analysis for determining mortality

Discussion

FG is a rare serious disease, with an incidence of 1.6 in 100,000 [5]. It is approximately 10 times more common in men [14]. In our study, the male-female ratio was 7.3. It is usually observed between the ages of 50-70 years [15]. The mean age of the patients in our study (55.4 years) was in accordance with the literature.

FG is most common in the genital and perianal regions [16]. We also found it mostly in the scrotal region, then in the perianal region. It begins as a local skin infection, and after abscess formation, necrosis begins on the skin. There are predisposing factors such as diabetes, malignancy, alcoholism, liver and kidney failure that usually facilitate the formation and progression of infection [17]. Diabetes facilitates FG by disrupting the function of phagocytes and cellular immunity [3]. Alcoholism, malignancy, liver and kidney failure also facilitate FG by causing immunosuppression. However, some cases are idiopathic and there are no predisposing factors. In our study, in most of the patients, FG developed due to idiopathic genital or perianal region infections. The most common predisposing factor was diabetes, followed by paraplegia and malignancies.

Although the diagnosis of FG is easily made by physical examination, the prognosis is not always favorable. It is of vital importance to perform emergency debridement immediately after the diagnosis [18]. In our study, emergency debridement was performed after all patients were diagnosed. In the studies

conducted, 16-40% mortality was found despite early interventions [4,5,14,19]. In our study, 21.7% mortality was observed in accordance with the literature. The time between the onset of infection and the admission to the hospital is as important as emergency debridement for the prognosis. Other prognostic factors were the width of the lesion, age, female gender, accompanying malignancy and diabetes [20]. Many studies, regarding factors affecting prognosis, were carried out to predict mortality. Laor et al. [7] revealed a scoring system called Fournier gangrene severity score (FGSS), which included vital signs and laboratory results. This scoring system indicated that 75% mortality was observed in patients with 9 points and higher. Wong et al. described the LRINEC scoring system, like FGSS, to predict the prognosis [9]. Hsiao et al. [21] and Gönüllü et al. [22] have also revealed that the LRINEC score can be used to predict mortality. Based on the above-mentioned research, we used ACCI, FGSI and LRINEC score to predict mortality, and found that the mean ACCI, FGSI and LRINEC scores were significantly higher in non-survivors.

Advanced age has been shown as one of the factors affecting mortality in FG [5,14], which was also a finding of our study. This is associated with an increase in comorbidities and a decrease in immune system function in older age.

In parallel to our study, female gender was reported to increase mortality [23]. This may be because the female genital anatomy makes it easier and faster for the infection to spread to the retroperitoneum.

It is controversial that the number of debridement may be a risk factor for mortality. Laor et al. [7] did not find a relationship between the number of debridement performed and mortality, while Chawla et al. found that the number of debridement was significantly higher among non-survivors [24]. We think that in cases with high number of debridement, the area of infection is larger, and therefore the prognosis is worse. However, in our study, we could not find a significant relationship between debridement number and mortality.

Yim et al. [25] determined that neutrophil-lymphocyte ratio is more effective than FGSI for predicting mortality in FG. We determined that non-surviving patients had higher neutrophil-lymphocyte ratios than survivors.

Furthermore, we found that factors such as FGSI score, ACCI score, advanced age, female gender, presence of diabetes, neutrophil-lymphocyte ratio increased mortality, in accordance with the literature.

Limitations

The fact that our study was a retrospective study conducted with a limited group may have limited the generalizability of the findings. Prospective randomized controlled studies are required for further deductions.

Conclusion

It is of vital importance to perform emergency debridement and initiate antibiotherapy after the diagnosis in FG, which is a disease with high mortality and morbidity. However, mortality is observed in some cases despite all efforts. We found that advanced age, high Charlson score, female gender, high neutrophil-lymphocyte ratio and the presence of diabetes were the factors affecting mortality.

References

1. Smith GL, Bunker CB, Dinneen MD. Fournier's gangrene. Br J Urol. 1998;81:347-55.
2. Korkut M, Içöz G, Dayangaç M, Akgün E, Yeniay L, Erdoğan O, et al. Outcome analysis in patients with Fournier's gangrene: report of 45 cases. Dis Colon Rectum. 2003;46:649-52.
3. Aşgın N, Satılmış Ş. Which antibiotics should we prefer empirical treatment of urinary tract infections in elderly patients? J Surg Med. 2019;3(12):856-60.
4. Thwaini A, Khan A, Malik A, Cherian J, Barua J, Shergill I, et al. Fournier's gangrene and its emergency management. Postgrad Med J. 2006;82:516-9.
5. Sorensen MD, Krieger JN, Rivara FP, Klein MB, Wessells H. Fournier's gangrene: management and mortality predictors in a population based study. J Urol. 2009;182:2742-7.
6. Kahramanca Ş, Kaya, O, Özgehan, G, Irem B, Dural I, Küçükpınar T, et al. Are neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as effective as Fournier's gangrene severity index for predicting the number of debridements in Fourner's gangrene? Ulus Travma Acil Cerr Derg. 2014;Mar;20(2):107-12.
7. Laor E, Palmer LS, Tolia BM, Reid RE, Winter HI. Outcome prediction in patients with Fournier's gangrene. J Urol. 1995;154:89-92.
8. Sallami S, Maalla R, Gammoudi A, Ben Jdidia G, Tarhouni L, Horchani A. Fournier's gangrene: what are the prognostic factors? Our experience with 40 patients. Tunis Med. 2012;Oct;90(10):708-14.
9. Wong CH, Khin LW, Heng KS, Tan KC, Low CO. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med. 2004;32(7):1535–41.
10. Yilmazlar T, Ozturk E, Ozguc H, Ercan I, Vuruskan H, Oktay B. Fournier's gangrene: an analysis of 80 patients and a novel scoring system. Tech Coloproctol. 2010;14:217-23.
11. Lin TY, Ou CH, Tzai TS, Tong YC, Chang CC, Cheng HL, et al. Validation and simplification of Fournier's gangrene severity index. Int J Urol. 2014;Jul;21(7):696-701.
12. Selvi I, Aykac A, Baran O, Burlukkara S, Ozok U, Sunay MM. A different perspective for morbidity related to Fournier's gangrene: which scoring system is more reliable to predict requirement of skin graft and flaps in survivors of Fournier's gangrene? Int Urol Nephrol. 2019;Aug;51(8):1303-11.
13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis. 1987;40:373.
14. Eke N. Fournier's gangrene: a review of 1726 cases. Br J Surg. 2000;87:718-28.
15. Yücel M, Özpek A, Başak F, Kılıç A, Ünal E, Yüksekdağ S, et al. Fournier's gangrene: A retrospective analysis of 25 patients. Ulus Travma Acil Cerrahi Derg. 2017;23:400-4.
16. Montrief T, Long B, Koyfman A, Auerbach J. Fournier Gangrene: A Review for Emergency Clinicians. J Emerg Med. 2019 Oct;57(4):488-500.
17. Göktaş C, Yıldırım M, Horuz R, Faydacı G, Akça O, Cetinel CA. Factors affecting the number of debridements in Fournier's gangrene: our results in 36 cases. Ulus Travma Acil Cerrahi Derg. 2012 Jan;18(1):43-8.
18. Mallikarjuna MN, Vijayakumar A, Patil VS, Shivswamy BS. Fournier's gangrene: Current Practices. ISRN Surg. 2012;2012:937–42.
19. Yanar H, Taviloglu K, Ertekin C, Guloglu R, Zorba U, Cabioglu N, et al. Fournier's gangrene: risk factors and strategies for management. World J Surg. 2006;30:1750-4.
20. Barupal SR, Soni ML, Barupal R. Factors Affecting Mortality Following Necrotizing Soft-Tissue Infections: Randomized Prospective Study. J Emerg Trauma Shock. 2019;12:108-16.
21. Hsiao CT, Chang CP, Huang TY, Chen YC, Fann WC. Prospective Validation of the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) Score for Necrotizing Fasciitis of the Extremities. PLoS One. 2020;Jan 24;15(1):e0227748.
22. Gönüllü D, Ilgun AS, Demiray O, Sayar S, Er AM, Kır G, et al. The Potential Prognostic Significance of the Laboratory Risk Indicator for the Necrotizing Fasciitis (LRINEC) Score in Necrotizing Fasciitis. Chirurgia. 2019;May-Jun;114(3):376-83.
23. Czymek R, Frank P, Limmer S, Schmidt A, Jungbluth T, Roblick U, et al. Fournier's gangrene: is the female gender a risk factor? Langenbecks Arch Surg. 2010;395:173-80.
24. Chawla SN, Gallop C, Mydlo JH. Fournier's gangrene: an analysis of repeated surgical debridement. Eur Urol. 2003;43:572-5.
25. Yim SU, Kim SW, Ahn JH, Cho YH, Chung H, Hwang EC, et al. Neutrophil to Lymphocyte and Platelet to Lymphocyte Ratios Are More Effective than the Fournier's Gangrene Severity Index for Predicting Poor Prognosis in Fournier's Gangrene. Surg Infect (Larchmt). 2016;Apr;17(2):217-23.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1161-1164.
DOI: 10.28982/josam.826766

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Detecting isolated superior mesenteric artery dissection with computed tomography

İzole süperior mezenterik arter diseksiyonunun bilgisayarlı tomografi ile tespit edilmesi

Esra Özgül [1]

[1] **Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Radiology Afyonkarahisar, Turkey**

ORCID ID of the author(s)
EÖ: 0000-0002-6005-134X

Abstract

Aim: Isolated superior mesenteric artery (SMA) dissection without associated aortic dissection is a rare entity. The aim of the study is to evaluate its incidence, and multidetector computed tomography (MDCT) and computed tomography angiography (CTA) findings, as well as show the clinical importance of this condition, which should be diagnosed and treated urgently.

Methods: Images of all patients who underwent contrast enhanced CTA or MDCT scan from July 2017 to July 2020 at our radiology department were examined retrospectively. A total of 600 CTA and 14000 contrast enhanced MDCT scans (14600 CT) were evaluated. Only the cases with isolated SMA dissections without aortic involvement, who had arterial phases on contrast enhanced MDCT images, were included. Aortic dissection cases with SMA involvement, and non-contrast MDCT images were excluded. Age, gender, symptoms, presence of thrombosis or bowel ischemia were noted. Average extension of dissection and distance from origin were measured.

Results: Ten patients (7 M, 3 F), aged between 48-66 years (mean: 57 years), had isolated SMA dissection. The mean distance of dissection from origin and mean extension were 1.9 cm and 3.4 cm, respectively. Patients were treated with conservative anticoagulation therapy. Follow-up CTA or MDCT showed normal SMA without evidence of dissection in 5 patients, decreased extension and length of dissection in 3 patients and no significant difference in 2 patients.

Conclusion: Isolated SMA dissection is a rare but important cause of abdominal pain. Early diagnosis allows correct treatment. CT is a useful noninvasive method for diagnosis and anticoagulation therapy is successful.

Keywords: Superior mesenteric artery, Dissection, Computed tomography, Mesenteric ischemia, İsolated

Öz

Amaç: Aort diseksiyonu olmaksızın görülen izole süperior mezenterik arter (SMA) diseksiyonu nadir bir durumdur. Çalışmanın amacı, insidansı ve çok dedektörlü bilgisayarlı tomografi (ÇKBT) ve bilgisayarlı tomografi anjiyografi (BTA) bulgularını değerlendirmek ve acilen teşhis ve tedavi edilmesi gereken bu durumun klinik önemini ortaya koymaktır.

Yöntemler: Temmuz 2017'den Temmuz 2020'ye kadar radyoloji bölümümüzde kontrastlı BTA veya ÇKBT taraması yapılan tüm hastaların görüntüleri geriye dönük olarak incelendi. 600 BTA ve 14000 kontrastlı ÇKBT taraması değerlendirildi. Sadece, aort tutulumu olmayan izole SMA diseksiyonları dahil edildi. SMA tutulumu olan aort diseksiyonları dahil edilmedi. Arteriyel faza sahip kontrastlı ÇKBT görüntüleri dahil edildi. Yaş, cinsiyet, semptomlar, tromboz veya bağırsak iskemisi varlığı kaydedildi. Ortalama diseksiyon uzunluğu ve orijinden uzaklık ölçüldü.

Bulgular: 10 hastada (7 E, 3 K) izole SMA diseksiyonu vardı. Hastaların yaş aralığı 48 ile 66 (ortalama 57) arasındaydı. Diseksiyonun orijinden ortalama uzaklığı 1,9 cm ve ortalama uzunluğu 3,4 cm idi. Hastalar konservatif olarak antikoagülan ile tedavi edildi. Takip BTA veya ÇKBT'de 5 hastada diseksiyonda kaybolma, 3 hastada diseksiyon uzunluğunda azalma izlenirken 2 hastada anlamlı bir fark saptanmadı.

Sonuç: İzole SMA diseksiyonu nadir görülen önemli karın ağrısı nedenlerindendir. Erken teşhis doğru ve zamanında tedaviye izin verir. BT tanı için yararlı noninvaziv bir yöntemdir ve antikoagülan tedavi başarılıdır.

Anahtar kelimeler: Superior mezenterik arter, Diseksiyon, Bilgisayarlı tomografi, Mezenterik iskemi, İzole

Corresponding author/Sorumlu yazar:
Esra Özgül
Address/Adres: Afyonkarahisar Sağlık Bilimleri Üniversitesi, Tıp Fakültesi, Radyoloji Anabilim Dalı, Zafer Sağlık Külliyesi A Blok Dörtyol Mah. 2078 Sok. No: 3, Afyonkarahisar, Türkiye
E-mail: dresrayam@gmail.com

Ethics Committee Approval: This study was approved by the Ethics Committee of Afyonkarahisar Health Sciences University, Faculty of Medicine (2020/308). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma Afyonkarahisar Sağlık Bilimleri Üniversitesi Tıp Fakültesi Etik Kurulu (2020/308) tarafından onaylanmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

How to cite/Atıf için: Özgül E. Detecting isolated superior mesenteric artery dissection with computed tomography. J Surg Med. 2020;4(12):1161-1164.

Introduction

Bauersfeld first described the dissection of superior mesenteric artery (SMA) in 1947, as accompanying a dissecting aneurysm of the aorta [1]. Isolated dissection without aortic involvement is a rare entity. To best of our knowledge, there have been only 147 reported cases in the literature from 1975 to 2020. With the improvement in the computed tomography (CT) techniques, isolated SMA dissections are diagnosed more commonly and much earlier. This explains the increased number of cases reported recently.

Dissection involves the SMA more frequently, when compared with other gastrointestinal arteries. Due to its rarity, clinical presentation, use of imaging studies, management, and outcomes of isolated SMA dissection have not been investigated in detail [2].

Acute mesenteric ischemia causes acute abdominal pain and isolated dissection of SMA rarely causes this condition [3,4]. SMA dissection can be classified into three types: Type I: A patent true lumen exists alongside a patent false lumen with re-entry, Type II: A patent true lumen exists alongside an either patent (Type IIa) or thrombosed (Type IIb) false lumen without re-entry, and Type III: Both lumens are thrombosed [5,6].

The goal of this study is to evaluate the incidence and CT Angiography (CTA) and contrast enhanced multidetector CT (MDCT) findings of this rare and important condition.

Materials and methods

The abdomen CTA and contrast enhanced MDCT images of all patients, obtained from July 2017 to July 2020 at our radiology department were evaluated retrospectively. A total of 600 CTA and 14000 contrast enhanced MDCT scans were examined. Only the cases with isolated SMA dissections without aortic involvement, who had arterial phases on contrast enhanced MDCT images, were included, while aortic dissection cases with SMA involvement, and non-contrast MDCT images were excluded.

Intravenous contrast enhanced CTA or MDCT (Toshiba Aquilion (80x2), Otawara, Japan) was performed. The patients were administered iodinated nonionic contrast agent (Omnipaque, Daiichi Pharmaceutical Co., Tokyo, Japan) with an iodine concentration of 300 mg/mL with mechanical injection at a flow rate of 3 mL. Postcontrast axial CTA images with 0.75 mm slice thickness were obtained, and coronal and sagittal maximum intensity projection (MIP) reconstructions were performed for CTA images. Contrast enhanced arterial phase MDCT images had the following parameters: Slice thickness: 2 mm, reconstruction index: 1 mm, tube voltage: 120 kVp, pitch: 0,75. Slices were extended from the diaphragmatic dome to the end of the pelvis. Optimal MIP reconstructions could not be performed from contrast enhanced MDCT images due to slice thickness and retrospective design of study.

Age, gender, symptoms of patients, presence of thrombosis or bowel ischemia were noted. Extensions of dissections, distance of dissection from origin, and SMA diameters were measured. Presence of follow-up CTA was determined, and their findings were evaluated.

Results

Ten (0.06%) patients (7 M, 3 F) aged between 48 to 66 years (mean age: 57 years), had isolated SMA dissection, three of which underwent CTA and 7 had contrast enhanced MDCT. All patients were admitted to the hospital with sudden onset abdominal or epigastric pain, which increased after meals in 5 patients. None of the patients had a history of trauma, while 2 had a history of hypertension. On physical examination, abdominal bruit was present in three patients and all patients had abdominal tenderness. Laboratory examinations were unremarkable.

The mean distance of dissection from SMA origin and the mean extension length were 1.9 cm (1.5-2.5) and 3.4 (2.6-4.3) cm, respectively. Only 3 patients had axial, coronal, and sagittal MIP images in thin slices, obtained via CTA. Seven patients were diagnosed with contrast enhanced arterial phase MDCT images with 2 mm slice thickness, and their MIP reconstructions could not be performed optimally. Dissection types were determined in only three patients with CTAs, among which 2 had Type IIa (Figures 1 and 2) and 1 had Type IIb SMA dissection (Figure 3). The other 7 patients had isolated SMA dissections but had no MIP images (Figure 4). None of the patients had any signs of bowel ischemia.

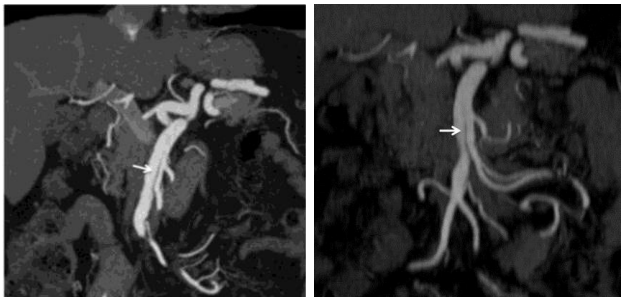


Figure 1: A 64-year-old man was admitted to the hospital with abdominal pain. On coronal maximum intensity projection (MIP) reconstruction CTA scan (a), an isolated SMA (Type IIa) dissection is observed (arrow). Follow up CTA (b) was performed 8 months later, which showed no progression in dissection (arrow).

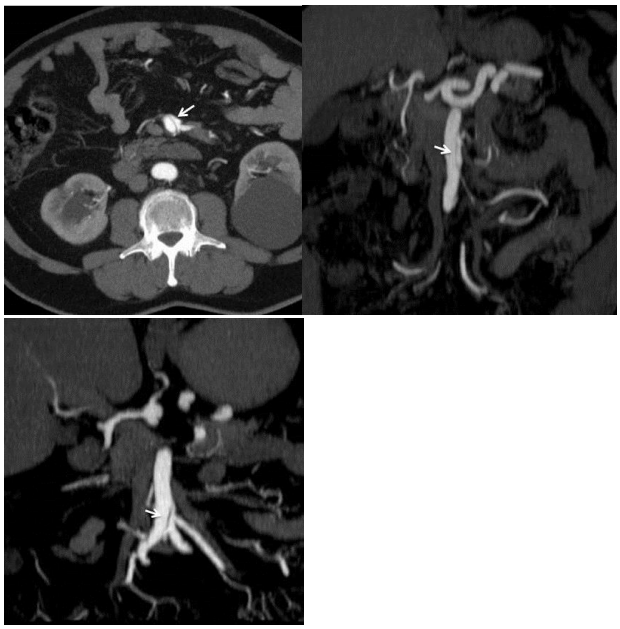


Figure 2: A 55-year-old woman with sudden onset abdominal pain. On axial (a) and coronal (b) MIP reconstruction CTA scans, a type IIa isolated SMA dissection is observed (arrow). After 10 months follow up, CTA (c) was performed, which showed decreased in extension of dissection (arrow).

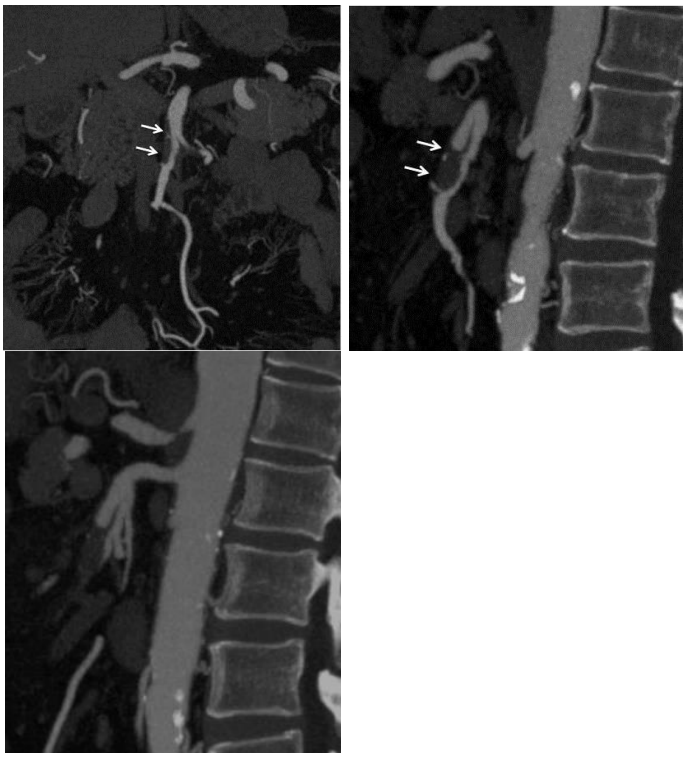


Figure 3: A 52-year-old man with abdominal pain. On coronal (a) and sagittal (b) MIP reconstruction CTA images, an isolated SMA dissection and thrombosis of false lumen (Type IIb) are observed (arrows). After 10 months, follow up CTA (C) was performed, which showed no significant difference in dissection (arrows).

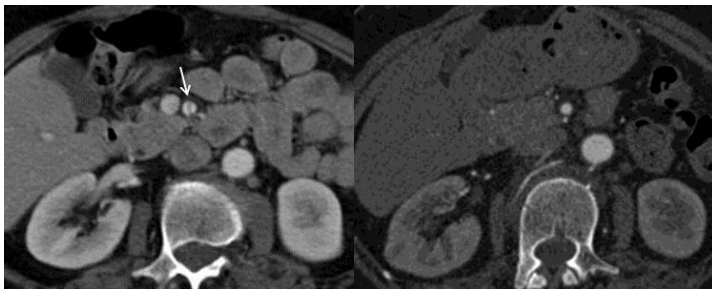


Figure 4: A 66-year-old woman was admitted with epigastric pain. The dissection is observed on axial (a) contrast enhanced MDCT images (arrow). After 9 months, follow up MDCT (b) was performed, which showed no evidence of dissection (arrow).

Two of the patients were started on an antihypertensive medical therapy for persistently elevated blood pressure. After hospitalization, patients were treated with unfractionated heparin (12,000 units/day) for 7-10 days. All patients were treated with Coumadin anticoagulation therapy for 9-12 months. Their symptoms resolved within 2-4 days of treatment. No surgical or endovascular intervention was deemed necessary because no bowel ischemia signs were present, and all patients responded well to medical treatment.

Follow-up CTA was performed after 8-10 (average: 9) months of medical therapy. Follow-up CTA or MDCT showed normal SMA without evidence of dissection in 5 patients, decreased extension and length of dissection in 3 patients and no significant difference in dissection in 2 patients.

Discussion

Visceral ischemia is divided into two subgroups, as occlusive and nonocclusive. Occlusive is further categorized into acute and chronic types and is caused by obstruction of major visceral arteries. Rarely, mesenteric ischemia occurs due to vasculitis, vasoconstriction and aortic or mesenteric dissection [3].

Isolated SMA dissection occurs predominantly in males (87%) at a mean age of 55 years. Its etiology is unclear because of the scarcity of reported cases. Probable etiologic factors include fibromuscular dysplasia, arteriosclerosis, trauma, cystic medial necrosis, and hypertension [7-14]. Solis et al. [9] hypothesized that stress on the arterial wall at the inferior edge of pancreas cause SMA dissection.

Patients often present with acute epigastric pain [8, 14] and findings of intestinal obstruction or intestinal angina are caused by ischemia [13]. Abdominal or epigastric pain sometimes increases after meals [7]. Shock may occur after rupture of the dissection [8, 11], and epigastric bruit may be heard on physical examination [7, 8, 11].

Before 1972, the prognosis of SMA dissection was extremely poor, and all 10 reported patients died [1, 8, 10, 15]. Diagnosis was made at autopsy. Four of them died of unrelated causes, such as renal infarction, myocardial infarction, subarachnoid hemorrhage, and uremic coma. The other six patients died of SMA infarction or rupture of the SMA [15]. To the best of our knowledge, since 1975, only one of the reported isolated SMA dissection cases died [16]. Drop in mortality rates is probably due to early diagnosis with improvement of imaging methods.

Early diagnosis improves the prognosis. Abdominal Doppler ultrasound, CTA, or selective digital subtraction angiography (DSA) may be performed for diagnosis. CTA reveals the type of dissection, intimal flap, thrombosis of false lumen and enlarged SMA diameter. Selective DSA is gold standard and has a double benefit, as it gives better information about dissection and offers endovascular treatment [12].

Isolated dissection of SMA begins around 1.5-3 cm from the origin [11], just as in our study. The mean distance of dissection from SMA origin was 1.9 cm (range: 1.5-2.5 cm), which indicated the fixed, retropancreatic portion of SMA. More distally, the SMA is relatively mobile, and it may transmit a shear force to the fixed retropancreatic portion [9,11].

Isolated SMA dissection may be treated with conservative or invasive (surgical or endovascular intervention) techniques. There is no consensus in the literature concerning which treatment is superior to other, however, the disease extent, bowel ischemia, clinical status of the patient and the response to the medical treatment are all factors effecting the choice of treatment. For a patient who initially begins anticoagulant therapy, surgery should be performed at a later stage, when the clinical status (bowel ischemia, sepsis, etc.) worsens. There is no standard treatment regimen for isolated SMA dissection, each case should be evaluated separately.

Indications for surgery include increasing size of aneurysmal dilatation of SMA, total thrombosis of the SMA lumen, and persisting symptoms despite anticoagulation [15]. Several surgical methods have been reported in the literature including reimplantation of SMA on the aorta [9], resection of affected arterial segment with graft interposition [17, 18], simple arteriotomy with thrombectomy [19], intimectomy [20], right gastroepiploic artery bypass [21], obtaining revascularization using arterial conduits [22], endoaneurysmorrhaphy [23], and superficial femoral artery transposition repair [24]. According to literature, there are 43 reported cases who underwent endovascular repair, out of which 38 were treated with percutaneous stent placement [2].

Another approach for treatment is the conservative therapy (i.e., bowel rest, anticoagulants, antihypertensives, antiplatelets, anticholesterol agents). In the literature, sixty-one reported cases were treated conservatively [2, 25]. Anticoagulation may prevent clot formation or emboli in the true lumen [7]. Hemodynamically stable patients with no clinical or imaging evidence of ruptured SMA dissection may be treated conservatively. Reported cases in literature treated with anticoagulation therapy had successful resolution of symptoms during their follow with no mortality [2]. Patients treated with anticoagulation therapy require close follow-up and it may not always prevent progression of disease [15]. There is no consensus on the optimal anticoagulant and the duration of treatment against SMA dissection [7]. All our cases were treated with anticoagulation therapy and their symptoms resolved within 2-4 days. Follow-up CTA revealed normalization of SMA in most patients.

Limitations

Repeat CT scans should be performed on follow up in all patients to evaluate the resolution or progression of dissection in cases of conservatively treated patients. Due to the retrospective design of the study, regular CTA or contrast enhanced MDCT follow-up was not performed, and the type of dissection could not be determined in all patients due to the lack of MIP images of some. Patients could not be followed up for more than 1 year and course of the SMA dissection after 1 year is incomplete in this study.

Conclusion

Isolated SMA dissection is a rare condition. It may remain unrecognized if the examining physician does not suspect this entity, which makes it essential to highlight it as an important cause of acute or chronic abdominal pain. Timely and accurate diagnosis allows correct treatment. Abdominal CTA is a useful noninvasive method revealing isolated SMA dissection findings clearly, and anticoagulation therapy is usually successful.

References

1. Bauersfeld SR. Dissecting aneurysm of the aorta: a presentation of fifteen cases and a review of the recent literature. Ann Intern Med. 1947;26:873-89. doi: 10.7326/0003-4819-26-6-873.
2. Ullah W, Mukhtar M, Abdullah HM, Ur Rashid M, Ahmad A, Hurairah, A et al. Diagnosis and management of isolated Superior Mesenteric Artery dissection: A systemic review and meta-analysis. Korean Circ J. 2019;49(5):400-18. doi: 10.4070/kcj.2018.0429
3. Leung DA, Schneider E, Kubik-Huch R, Marincek B, Pfammatter T. Acute mesenteric ischemia caused by spontaneous isolated dissection of the superior mesenteric artery: treatment by percutaneous stent placement. Eur Radiol. 2000;10:1916-9. doi: 10.1007/s003300000520
4. Lamprecht G, Trabold T, Gregor M, Lamberts R. Spontaneous, self-limited, non-atherosclerotic dissection of the superior mesenteric artery. Eur J Gastroenterol Hepatol. 2003;15:437-9. doi: 10.1097/00042737-200304000-00018
5. Elshiekh A, Matharu NM. Type 3 intestinal failure after bypass grafting for isolated acute superior mesenteric artery dissection: A case report. Turkish Journal of Vascular Surgery. 2020;29(10):1-4.
6. Garrett HE Jr. Options for treatment of spontaneous mesenteric artery dissection. J Vasc Surg. 2014;59(5):1433-9.e92. doi: 10.1016/j.jvs.2014.01.040.
7. Nagai T, Torishima R, Uchida A, Nakashima H, Takahashi K, Okawara H, et al. Spontaneous dissection of the superior mesenteric artery in four cases treated with anticoagulation therapy. Internal Medicine. 2004;43:437-78. doi: 10.2169/internalmedicine.43.473
8. Suzuki S, Furui S, Kohtake H, Sakamoto T, Yamasaki M, Furukawa A, et al. Isolated dissection of the superior mesenteric artery: CT findings in six cases. Abdom Imaging. 2004;29:153-7. doi: 10.1007/s00261-003-0110-2
9. Solis MM, Ranval TJ, McFarland DR, Eidt JF. Surgical treatment of superior mesenteric artery dissecting aneurysm and simultaneous celiac artery compression. Ann Vasc Surg. 1993; 7:457-62. doi: 10.1007/BF02002130
10. Hirai S, Hamanaka Y, Mitsui N, Isaka M, Kobayashi T. Spontaneous dissection of the main trunk of the superior mesenteric artery. Ann Thorac Cardiovasc Surg. 2002;8:236-40.
11. Sheldon PJ, Esther JB, Sheldon EL, Sparks SR, Brophy DP, Oglevie SB. Spontaneous dissection of the superior mesenteric artery. Cardiovasc Intervent Radiol. 2001;24:329-31. doi: 10.1007/s00270-001-2565-0.
12. Miyomato N, Sakurai Y, Hirokami M, Takahashi K, Nishimori H, Tsuji K, et al. Endovascular stent placement for isolated spontaneous dissection of the superior mesenteric artery: report of a case. Radiat Med. 2005;23(7):520-4.
13. Sagiuchi T, Asano Y, Yanaihara H, Aoki Y, Woodhams R, Hayakawa K. Three-dimensional CT in isolated dissecting aneurysm of the superior mesenteric artery: a case report. Radiat Med. 2001;19:271-3. PMID:11724259
14. Gouëffic Y, Costargent A, Dupas B, Heymann MF, Chaillou P, et al. Superior mesenteric artery dissection: case report. J Vasc Surg. 2002;35:1003-5. doi: 10.1067/mva.2002.122152
15. Sparks SR, Vasquez JC, Bergan JJ, Owens EL. Failure of nonoperative management of isolated superior mesenteric artery dissection. Ann Vasc Surg. 2000;14:105-9. doi: 10.1007/s100169910019
16. Akuzawa N, Seki H, Oku Y, Totsuka M, Hatori T, Imai K. Three cases of spontaneous isolated dissection of the superior mesenteric artery. J Emerg Med. 2015;48:e111-6. doi: 10.1016/j.jemermed.2014.12.017
17. Cormier F, Ferry J, Artru B, Wechsler B, Cormier JM. Dissecting aneurysms of the main trunk of the superior mesenteric artery. J Vasc Surg. 1992;15:424-30.
18. Takehara Y, Takahashi M, Fukaya T, Kaneko M, Koyano K, Sakaguchi S. Computed tomography of isolated dissecting aneurysm of the superior mesenteric artery. J Comput Assist Tomogr. 1988;12:678-80. doi: 10.1097/00004728-198807000-00036
19. Corbetti F, Vigo M, Bulzacchi A, Angelini F, Burigo E, Thiene G. CT diagnosis of spontaneous dissection of the superior mesenteric artery. J Comput Assist Tomogr. 1989;13(6):965-7. doi: 10.1097/00004728-198911000-00006
20. Krupski WC, Effenecy DJ, Ehrenfeld WK. Spontaneous dissection of the superior mesenteric artery. J Vasc Surg. 1985;22:731-4. doi: 10.1016/0741-5214(85)90046-1
21. Vignati PV, Welch JP, Ellison L, Cohen JL. Acute mesenteric ischemia caused by isolated superior mesenteric artery dissection. J Vasc Surg. 1992;16:109-12.
22. Kochi K, Orihashi K, Murakami Y, Sueda T. Revascularization using arterial conduits for abdominal angina due to isolated and spontaneous dissection of the superior mesenteric artery. Ann Vasc Surg. 2005;19:1-3. doi: 10.1007/s10016-005-0018-0
23. Tsuji Y, Hino Y, Sugimoto K, Matsuda H, Okita Y. Surgical intervention for isolated dissecting aneurysm of the superior mesenteric artery: a case report. Vasc Endovascular Surg. 2004;38(5):469-72. doi: 10.1177/153857440403800513.
24. Picquet J, Abilez O, Penard J, Jousset Y, Rousselet MC, Enon B. Superficial femoral artery transposition repair for isolated superior mesenteric artery dissection. J Vasc Surg. 2005;42(4):788-91. doi: 10.1016/j.jvs.2005.05.048.
25. Asif S, Qureini A, Bennett J. A Rare Case of Spontaneous Isolated Dissection of the Superior Mesenteric Artery. Cureus 2019.11(5):e4725. doi: 10.7759/cureus.4725.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1165-1168.
DOI: 10.28982/josam.829084

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Prognostic value of the Selvester QRS score for re-hospitalization in patients with ischemic heart failure

İskemik kalp yetmezliği olan hastalarda tekrar hastaneye yatış için Selvester QRS skorunun prognostik değeri

Alper Karakuş [1], Berat Uğuz [2]

[1] Department of Cardiology, Besni State Hospital, Adıyaman, Turkey
[2] Department of Cardiology, Bursa City Hospital, Bursa, Turkey

ORCID ID of the author(s)

AK: 0000-0002-9632-395X
BU: 0000-0002-4834-5572

Abstract

Aim: The Selvester QRS score (SSc) on surface electrocardiogram (ECG) has prognostic value in various cardiac events related to myocardial scarring. Furthermore, the SSc system has been validated by post-mortem studies. In this cohort, we assessed the utility of the SSc system for prediction of re-hospitalization in patients with ischemic heart failure (HF).

Methods: In this retrospective cohort study, the data of fifty-four consecutive patients with ischemic HF were analyzed. ECGs were collected at first day of admission and SScs were calculated. The primary endpoint was re-hospitalization within the first 3 months.

Results: At baseline, the mean age was 62.1 years, LVEF was 29(6) %, NT-proBNP level was 2830 pg/mL. Twenty-one re-hospitalizations were observed due to HF. Patients who were re-hospitalized had significantly higher SScs than those who were not (5.6 vs.3.3 *P*=0.01). Cox regression analysis demonstrated that the SSc was an independent predictor of re-hospitalization rate (HR, 1.12; 95% CI, 0.95–1.34; *P*=0.04). Roc curve analysis showed that SSc was predictive for rehospitalization with a cut-off value 4.3, with a sensitivity of 65% and a specificity of 49% (AUC 0.618, *P*=0.02). Our analysis indicated a positive correlation between SSc with NT-proBNP and a negative correlation between SSc and LVEF (respectively r=0.33, *P*=0.03 and r =-0.67, *P*=0.04).

Conclusion: Our results suggest that baseline SSc can be used as a predictor of re-hospitalization due to ischemic HF.

Keywords: Heart failure, Re-hospitalization, Selvester QRS score

Öz

Amaç: 12 derivasyonlu elektrokardiyogramda Selvester QRS skorunun miyokardiyal skarla ilgili çeşitli kardiyak olaylardaki prognostik etkileri bilinmektedir. Ayrıca, Selvester QRS skor sisteminin otopsi ile ölçülen miyokardiyal skar boyutu ile de yüksek derecede korelasyona sahip gösterilmiştir. Bu çalışmada, Selvester QRS skorunun iskemik kalp yetmezliğine bağlı yeniden hastaneye yatışı öngörmedeki rolünü değerlendirmeyi amaçladık.

Yöntemler: İskemik kalp yetmezliği olan elli dört hastanın verileri geriye dönük olarak incelendi. Hastaneye başvuru sırasındaki EKG'ler temel alınarak Selvester QRS skorları hesaplandı. Birincil son nokta, ilk 3 ay içindeki yeniden hastaneye yatış kabul edildi.

Bulgular: Çalışma popülasyonunda, ortalama yaşın 62,1 yıl, sol ventrikül ejeksiyon fraksiyonun (LVEF) %29(6), plazma beyin natriüretik peptit seviyesin (NT-proBNP) 2830 pg / mL olduğu görüldü. Çalışma boyunca 21 hastaneye yeniden yatış gözlendi. Yeniden hastaneye yatırılan hasta grubunda Selvester skoru, diğer gruba göre anlamlı olarak daha yüksekti (5,6'ya karşı 3,3 *P*=0,01). Cox orantısal risk regresyon analizi, Selvester QRS skorunun yeniden hastaneye yatış için bağımsız bir belirleyici olduğunu ortaya koydu (HR, 1.12; %95 güven aralığı, 0,95-1,34; *P*=0,04). En iyi cut-off değeri %65 duyarlılık ve %49 özgüllük ile 4,3 puan olarak belirlendi (eğri altındaki alan, 0,618, *P*=0,02). Ayrıca Selvester QRS skoru ile NT-proBNP arasında anlamlı pozitif korelasyon (r=0,33, *P*=0,03) ve Selvester QRS skoru ile LVEF arasında negatif korelasyon saptandı (r=-0,67, *P*=0,04).

Sonuç: Bulgularımız, başvuru anındaki Selvester QRS skorunun iskemik kalp yetmezliğine bağlı yeniden hastaneye yatışın bir öngörücü olarak kullanılabileceğini düşündürmektedir.

Anahtar kelimeler: Kalp yetersizliği, Yeniden hastaneye yatış, Selvester QRS skoru

Corresponding author/Sorumlu yazar:
Alper Karakuş
Address/Adres: Besni Devlet Hastanesi Kardiyoloji Bölümü, 02300, Adıyaman, Türkiye
E-mail: alpkarakus06@gmail.com

Ethics Committee Approval: The study protocol was approved with registration number of 2020 – 7/8 by the Bursa City Hospital Ethics committee. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma protokolü Bursa Şehir Hastanesi etik kurulu tarafından 2020 - 7/8 kayıt numarası ile onaylandı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

How to cite/Atıf için: Karakuş A, Uğuz B. Prognostic value of the Selvester QRS score for re-hospitalization in patients with ischemic heart failure. J Surg Med. 2020;4(12):1165-1168.

Introduction

Heart failure (HF) most often develops due to ischemic scar tissue caused by myocardial infarction [1]. Today, HF is considered a global health problem. It remains a prominent cause of recurrent hospitalizations despite optimal treatment [2].

Myocardial scar assessed on cardiovascular magnetic resonance (CMR) is associated with poor outcome in HF [3]. However, CMR is not in widespread clinical use. The electrocardiography (ECG) is an inexpensive, easily accessible, reproducible, and non-invasive diagnostic tool which provides risk stratification regarding myocardial scars [4]. The Selvester QRS score (SSc), first described in 1972, provides data on myocardial scar location and size using changes in cardiac electrical activity on surface ECG and its validation has been shown in autopsy series [5,6]. This primary version of the SSc could only be applied in the absence of confounders. So, the SSc QRS system criteria were presented with a new version in 2009 to expand their utility in patients with bundle branch blocks, fascicular blocks or ventricular hypertrophy. The simplified version of SSc consists of 37 criteria and 29 points [7].

Previous studies have documented the capability of SSc as prognostic markers for cardiac events in different clinical entities (including ST elevation myocardial infarction, aortic stenosis, nonischemic dilated cardiomyopathy), by reflecting the amount of myocardial fibrosis [7,9].

In this current study, we hypothesized that SSc, which reflects the amount of scar, has a prognostic significance in HF with ischemic origin and can be used for hospitalization. So, the current study was built to determine the utility of the SSc system for prediction of recurrent hospitalization due to ischemic HF (prior myocardial infarction (MI)).

Materials and methods

Study design and patients

This study was conducted at Besni State Hospital (Adıyaman, Turkey) and completed in collaboration with Bursa City Hospital (Bursa, Turkey). The study protocol was approved with registration number of 2020 – 7/8 by the Bursa City Hospital Ethics committee.

Assuming an alpha of 0.05, a power of 0.80, and with 30% estimated re-hospitalization rate in line with the previous reports, the estimated sample size was at least 46 patients in total.

The study inclusion criteria were as follows:

- Patients with HFrEF
- Prior MI (over > 3 months)

The study exclusion criteria were as below:

- Patients with newly arisen, de novo, non-ischemic HF or cardiomyopathy
- Patients with ICD or pacemaker
- Acute coronary syndrome within 3 months of the study
- Atrial fibrillation at admission
- Any more than mild valvulopathy
- Patients with preexcitation syndrome
- Patients who do not receive optimal treatment
- Patients with electrolyte imbalances

Consecutive fifty-seven patients with ischemic HF (with Reduced Ejection Fraction, HFrEF) who met the inclusion criteria were enrolled in this cross-sectional study. HFrEF was diagnosed and treated based on the criteria of ESC 2016 Guidelines for the diagnosis and treatment of acute and chronic HF [10].

Patient data including demographic, electrocardiographic and echocardiographic measurements, laboratory data and medical treatments were obtained. Follow-up information was collected for each patient regarding hospitalization, MI, and death at 3 months. For avoiding any selection bias against hospitalization, the patients with possible pathologies that could affect The SSc before or during follow-up were excluded and hospitalization indications for all patients were determined in terms of the need for intravenous treatment, in accordance with current guidelines. Patients were divided into two groups based on rehospitalization (due to HF) within 3 months.

Electrocardiographic analysis

The ECG measurements were made using a Cardiofax M ECG-1350K (Nihon Kohden, Tokyo, Japan, paper speed of 25 mm/sec, signal size of 1 mV/cm) at the time of admission. The electrocardiographic reader was blinded to study groups. The simplified version of SSc (37-criteria/29-point) was retrospectively calculated for each patient according to an algorithm, as previously reported [7].

Briefly; First, ECGs were classified according to primary ventricular conduction or hypertrophy type. Second, the SSc system was used for the primary conduction/hypertrophy type, which includes measurements of Q-, R-, and S-wave notches, amplitudes and its ratios and durations.

Statistical analysis

Normality was analyzed by The Kolmogorov-Smirnov test. According to the normality pattern, Student's T test and Mann-Whitney U test were used. Analysis results were presented as mean (standard deviation). For categorical variables, the Chi-square test was used, and the results were presented as percentages. To assess the association between SSc and HFrEF, two categories were defined on basis of re-hospitalization. The effects of different variables on re-hospitalization were determined with multivariate analysis. *P*-value<0.05 was considered statistically significant. SPSS 26.0 Statistical Package Software was used to perform all data analyses.

Results

Fifty-seven patients were evaluated for the study. Three patients were excluded from the cohort (one patient died, and 2 had MI during follow-up). The data of the remaining 54 patients were analyzed. The study group was divided into two based on rehospitalization at the end of the 3-month follow up. Of the 54 patients, twenty-one re-hospitalizations due to HF were observed. The median age of 54 patients was 62.1(12.7) years, Left Ventricular Ejection Fraction (LVEF) was 29(6) %, N Terminal prohormone brain natriuretic peptide (NT-proBNP) level was 2830 pg/mL.

Baseline clinical and demographic characteristics

Table 1 shows the detailed baseline characteristics (demographic/clinical) of study populations. On admission, there was no significant difference between the two groups regarding age, hypertension, diabetes mellitus, coronary artery disease, median Left Ventricular Ejection Fraction (LVEF), median estimated Glomerular Filtration Rate (GFR), and median NT-

proBNP. The comparison of the study patients regarding HF features is presented in Table 2.

Table 1: Baseline characteristics and laboratory findings of the study patients

Variables	Patients with re-hospitalization (Group 1, N=21, 38.8%)	Patients without re-hospitalization (Group 2, N=33, 61.1%)	*P*-value
Age (years)	61.5(17.4)	62.4(13.5)	0.69
Sex (n, %) females	10 (47.6%)	16 (48.4%)	0.77
Hypertension, (n, %)	7 (33.3%)	12 (36.3%)	0.81
DM, (n, %)	3 (14.2%)	4 (12.1%)	0.51
Creatinine (mg/dl)	1.26 (0.44)	1.31 (0.51)	0.33
HsCRP (nmol/L)	2.7 (0.8)	2.5 (0.5)	0.76
NT-proBNP (pg/mL),	2796 (1254)	3105 (1388)	0.21
TSH (µIU/mL)	2.34 (1.1)	2.19 (1.5)	0.34
Na (mmol/L)	137 (6.5)	138 (9.3)	0.22
K (mmol/L)	4.5 (1.2)	4.4 (0.9)	0.44
Leukocyte (10^9/L)	9.9 (5.2)	9.6 (3.4)	0.29
Hemoglobin (g/dl)	12.5 (3.4)	12.9 (3.1)	0.63
Platelet (10^9/L)	232 (69)	251 (79)	0.17

DM: Diabetes mellitus, HsCRP: High sensitive C reactive protein, NT-proBNP: N Terminal prohormone brain natriuretic peptide, TSH: Thyroid-stimulating hormone, Na: Sodium, K: Potassium

Table 2: Comparison of the study patients regarding heart failure features

Variables	Patients with re-hospitalization (Group 1, N=21, 38.8%)	Patients without re-hospitalization (Group 2, N=33, 61.1%)	*P*-value
Ejection fraction, (%)	28.2 (6.5)	29.4 (5.9)	0.61
Heart rate, median, beats/min	72 (23)	75 (31)	0.13
QRS duration, median, ms	111 (21)	114 (19)	0.17
NYHA heart failure			
▪ Class 3	42%	41%	0.73
▪ Class 4	58%	59%	0.88
Drug treatment (n)			
• ACEi/ARBs/ARNI	21	33	0.14
• Beta Blockers	21	33	0.14
• MRAs	21	33	0.14
• Ivabradine	6	9	0.09
• Diuretics	21	33	0.14

NYHA: New York Heart Association, ACEi: Angiotensin converting enzyme inhibitor, ARBs: Angiotensin receptor blockers, ARNI: Angiotensin receptor neprilysin inhibitor, MRA: Mineralocorticoid receptor antagonists

The Selvester QRS score and re-hospitalization

Patients who were re-hospitalized had significantly higher SSc values than those who were not (5.6 vs.3.3 P= 0.01). The models of regression were assessed for rehospitalization regarding gender, age, creatinine, NTproBNP, LVEF, and SSc. Cox regression analysis revealed that SSc was an independent determinant of re-hospitalization (HR, 1.12; 95% CI, 0.95–1.34; P=0.04). Roc curve analysis showed that SSc was predictive for rehospitalization with a cut-off value 4.3, with a sensitivity and a specificity of 65% and 49%, respectively (AUC 0.618, P=0.02).

Correlations were constructed for age, NTproBNP, LVEF and SSc. There was a significant positive correlation between SSc with NT-proBNP and a negative correlation between SSc and LVEF (r=0.33, P=0.03 and r =-0.67, P=0.04, respectively). No significant correlation was found in terms of other parameters (P>0.05).

Discussion

Our findings suggest that SSC can be an independent determinant of re-hospitalization in patients with ischemic HFrEF. The odds of rehospitalization increase with SSc values. Our findings suggest that the predictive cut-off value for rehospitalization was 4.3 points with 65% sensitivity and 49% specificity.

ECG findings such as pathological Q waves and QS complexes, widened QRS, left branch bundle block (LBBB), prolonged PR interval and increased heart rate are all associated with poor outcomes in HF [11]. Despite their prognostic value, their utility for clinical risk stratification is limited when used alone. Beyond traditional ECG diagnostic assessment, Selvester et al. developed a system using a series of abnormal findings on ECG, which considered each QRS-point as representing an infarct the equivalent of 3% of the LV. In this scoring system, higher scores correlate with larger scar sizes [12]. So, we believed that detection of myocardial scar by SSc, which is an inexpensive and easily available method, in HF patients may be more appropriate instead of the other cardiac imaging modalities.

In this cohort, 46.3% of the patients presented with ECG confounders. There were 12 patients with LBBB (22.2%), 2 with right branch bundle block (RBBB) (3.7%), 3 with left anterior fascicular block (LAFB) (5.5%), 3 with RBBB and LAFB (5.5%), 5 with left ventricular hypertrophy (9.2%). One of most important points of the present study is the timing of the ECG capture. ECGs were collected at first day of admission to avoid subtle ECG changes which may occur during treatment. The patients in our study had HF symptoms and were classified as NYHA functional class 3 or 4. Our results show that there was a higher SSc trend in re-hospitalized patients. Previous studies, which yielded comparable results to ours, evaluated the diagnostic performance of the QRS scores in various events among HF subjects. The mean QRS score in nonischemic dilated cardiomyopathy patients was reported as 4.2 points by Hiraiwa et al. [13]. Wieslander et al. [14] showed that SSc was a strong predictor of LV remodeling (echocardiographic) than clinical outcomes in HF patients. Additionally, Strauss et al. [15] demonstrated that subjects with no myocardial scar based on SSc have less ventricular arrhythmia events. We found a positive relationship between SSc and NTproBNP, which is an indicator of decompensation. It was not surprising that we found a negative correlation between SSc and LV EF. Although there was no difference regarding LVEF between the groups, there was a difference in QRS scores. It may be partially explained by the fact that a dissociation in conduction pathway can occur after MI, which may explain the relatively low sensitivity and specificity of SSc in our study. Nevertheless, our data suggest that SSc is a potential candidate for clinical risk stratification to predict myocardial scar and cardiac events in HFrEF.

Limitations

This study has some limitations worth noting, beginning with limited sample size, and its single center design. Also, a subgroup analysis for each ECG confounder could not be performed. There is a need for larger and multi-center studies investigating long term clinical outcomes. Our results are only applicable to patients with HFrEF due to ischemia. Beyond these limitations, we believe that higher value of SSc can be used for the risk stratification of patients with ischemic HFrEF. Therefore, we expect this study to be helpful for upcoming research.

Conclusions

Mortality, morbidity, quality of life and long-term survival in patients with HF are directly related to the grade of ventricular dysfunction. Our analysis showed that ECG quantification of myocardial scar with SSc can be used as a predictor of re-hospitalization due to ischemic HF. Patients with higher myocardial scar scores have an increased risk of decompensation and re-hospitalization.

Acknowledgements

We would like to thank our valuable colleagues, Şifa Kaya and Gökhan Kafa, for their support.

References

1. Castelvecchio S, Pappalardo OA, Menicanti L. Myocardial reconstruction in ischaemic cardiomyopathy. Eur J Cardiothorac Surg. 2019 Jun 1;55(Suppl 1):i49-i56. doi: 10.1093/ejcts/ezy367. PMID: 31106339; PMCID: PMC6526097.
2. Rossignol P, Hernandez AF, Solomon SD, Zannad F. Heart failure drug treatment. Lancet. 2019 Mar 9;393(10175):1034-44. doi: 10.1016/S0140-6736(18)31808-7. PMID: 30860029.
3. Matusik PS, Bryll A, Matusik PT, Popiela TJ. Ischemic and non-ischemic patterns of late gadolinium enhancement in heart failure with reduced ejection fraction. Cardiol J. 2020 Feb 10. doi: 10.5603/CJ.a2020.0009. Epub ahead of print. PMID: 32037500.
4. Markendorf S, Benz DC, Messerli M, Grossmann M, Giannopoulos AA, Patriki D, et al. Value of 12-lead electrocardiogram to predict myocardial scar on FDG PET in heart failure patients. J Nucl Cardiol. 2019 Aug 9. doi: 10.1007/s12350-019-01841-6. Epub ahead of print. PMID: 31399902.
5. Selvester RH, Wagner GS, Hindman NB. The Selvester QRS scoring system for estimating myocardial infarct size: the development and application of the system. Archives of Internal Medicine. 1985;145(10):1877-81.
6. Wagner GS, Freye CJ, Palmeri ST, Roark SF, Stack NC, Ideker RE, et al. Evaluation of a QRS scoring system for estimating myocardial infarct size. I. Specificity and observer agreement. Circulation. 1982;65(2):342-7.
7. Tiller C, Reindl M, Reinstadler SJ, Holzknecht M, Schreinlechner M, Peherstorfer A, et al. Complete versus simplified Selvester QRS score for infarct severity assessment in ST-elevation myocardial infarction. BMC Cardiovascular Disorders. 2019;19(1):1-7.
8. Bignoto TC, Le Bihan D, de Mattos Barretto RB, de Oliveira Ramos AI, Moreira DAR, Simonato M, et al. Predictive role of Selvester QRS score in patients undergoing transcatheter aortic valve replacement. Catheter Cardiovasc Interv. 2020 Apr 16. doi: 10.1002/ccd.28905.
9. Hiraiwa H, Okumura T, Sawamura A, Sugiura Y, Kondo T, Watanabe N, et al. The Selvester QRS score as a predictor of cardiac events in nonischemic dilated cardiomyopathy. Journal of Cardiology. 2018;71(3):284-90.
10. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats A, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European heart journal. 2016;37(27):2129-200.
11. Gouda P, Brown P, Rowe BH, McAlister FA, Ezekowitz JA. Insights into the importance of the electrocardiogram in patients with acute heart failure. European Journal of Heart Failure. 2016;18(8):1032-40.
12. Strauss DG, Selvester RH, Lima JA, Arheden H, Miller JM, Gerstenblith G, et al. ECG quantification of myocardial scar in cardiomyopathy patients with or without conduction defects: correlation with cardiac magnetic resonance and arrhythmogenesis. Circulation: Arrhythmia and Electrophysiology. 2008;1(5):327-36.
13. Hiraiwa H, Okumura T, Sawamura A, Sugiura Y, Kondo T, Watanabe N, et al. The Selvester QRS score as a predictor of cardiac events in nonischemic dilated cardiomyopathy. Journal of Cardiology. 2018;71(3):284-90.
14. Wieslander B, Loring Z, Zareba W, McNitt S, Wagner GS, Daubert JP, et al. Scar burden assessed by Selvester QRS score predicts prognosis, not CRT clinical benefit in preventing heart failure event and death: A MADIT-CRT sub-study. Journal of Electrocardiology. 2016;49(4):603-9.
15. Strauss DG, Poole JE, Wagner GS, Selvester RH, Miller JM, Anderson J, et al. An ECG index of myocardial scar enhances prediction of defibrillator shocks: an analysis of the Sudden Cardiac Death in Heart Failure Trial. Heart Rhythm. 2011;8(1):38-45.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1169-1172.
DOI: 10.28982/josam.829499

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Evaluation of cerebroplacental ratio as a new tool to predict adverse perinatal outcomes in patients with isolated oligohydramnios

Serebroplasental oranın izole oligohidroamniyoslu hastalarda kötü perinatal sonuçların öngörülmesindeki yeri

Emre Destegül [1], Hatica Akkaya [2], Barış Büke [3], Güliz Gürer [4]

[1] Nigde Omer Halisdemir University Medical Faculty Training and Research Hospital Department of Obstetrics and Gynecology, Nigde, Turkey
[2] Ankara City Hospital Training and Research Hospital, Department of Obstetrics and Gynecology, Ankara, Turkey
[3] Private BB, Obstetric & Gyneocology Clinic, İzmir, Turkey
[4] Nigde Omer Halisdemir University Medical Faculty Training and Research Hospital Department of Pediatrics, Nigde, Turkey

ORCID ID of the author(s)
ED: 0000-0001-5726-0223
HA: 0000-0002-9613-1712
BB: 0000-0001-8761-2023
GG: 0000-0003-2922-430X

Corresponding author/Sorumlu yazar:
Emre Destegül
Address/Adres: Niğde Ömer Halisdemir Üniversitesi Rektörlüğü, Merkez Kampüs, Bor Caddesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Niğde, 51240, Türkiye
E-mail: destegulemre@hotmail.com

Ethics Committee Approval: This study was approved by Kayseri University Ethical Committee (03.10.2018 / 2018-455). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma Kayseri Üniversitesi Etik Kurulu (03.10.2018 / 2018-455) tarafından onaylanmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: There is conflicting information in the literature regarding perinatal outcomes and management of isolated oligohydramniotic (IO) pregnancies. Recent studies show that IO is associated with poor perinatal outcomes. However, there is still no definitive method for deciding the optimal delivery timing for these patients. In this study, we aimed to assess the relationship between Doppler parameters, especially cerebro-placental ratio, and perinatal outcomes in isolated oligohydramnios (IO) patients.

Methods: This prospective case control study was conducted between October-November 2018. A total of 98 patients were recruited and divided into two groups, as pregnant women with normal amounts of amniotic volume and the isolated oligohydramnios group. Oligohydramnios diagnosis was made by amniotic fluid index measurement (AFI<5 cm). Pregnancies with hypertension, fetal growth restriction, thrombophilia, preeclampsia, diabetes mellitus, preterm births and chromosomal/structural abnormalities were excluded. Cerebro placental ratios of groups were compared in terms of composite adverse outcomes, low APGAR score in 1st and 5th minutes, C/S operation due to non-reassuring fetal heart rate patterns, admission to neonatal intensive care unit and still births.

Results: In the isolated oligohydramnios group (n=45) cerebro-placental ratio (CPR) was lower compared to control group (P<0.001). IO was associated with lower (APGAR score<7) 1st (55.6% vs. 7.5%, P<0.001) and 5th (13.3% vs. 1.9% P=0.028) minute APGAR scores and higher rates of NICU admission (26.7% vs. 3.8% P=0.001). Number of fetal distress cases was higher in patients with low CPR in the IO group (9 vs. 6 P=0.023).

Conclusion: Measurement of CPR among IO patients seems useful for detection of fetuses with higher risk for poor neonatal outcomes.

Keywords: Cerebroplacental ratio, CPR, Isolated oligohydramnios, Perinatal outcome, Fetal Doppler

Öz

Amaç: İzole oligohidramniotik (IO) gebeliklerin perinatal sonuçları ve yönetimi ile ilgili literatürde hala çelişkili bilgiler mevcuttur. Son çalışmalarda ise IO'nun kötü perinatal sonuçlar ile ilişkili olduğu yönündedir. Yine de bu hastaların optimal doğum zamanlamasına karar vermek için elimizde hala kesin bir yöntem bulunamamaktadır. Biz de çalışmamızda IO hastalarında Doppler parametreleri, özellikle serebro-plasental oran ve perinatal sonuçlar arasındaki ilişkiyi değerlendirmektir.

Yöntemler: Bu prospektif vaka kontrol çalışması Ekim-Kasım 2018 arasında gerçekleştirildi. Çalışmaya 98 hasta dahil edilmiştir. İzole oligohidroamnios ve normal amnion miktarı olan gebeler grubu olmak üzere iki gruba ayrıldı. Oligohidramnios tanısı amniyotik sıvı indeksi ölçümü ile konuldu (AFI <5 cm). Hipertansiyon, intrauterin büyüme kısıtlılığı, trombofili, preeklampsi, diyabet ve kromozomal / yapısal anormallikleri olan gebelikler çalışma dışı bırakıldı. Gruplar cerebroplasental oran (CPR) ölçümleri göz önüne alınarak; kompozit advers sonuçlar, 1. ve 5. dakikalarda düşük APGAR skoru, güven verici olmayan fetal kalp hızı paternlerine bağlı sezaryen (C/S) operasyonu, yenidoğan yoğun bakım ünitesine yatışı ve ölü doğumlar bakımından karşılaştırıldı.

Bulgular: CPR <1,08 olan hastalarda fetal distress görülme oranı daha yüksekti (9'a karşı 6 P=0,023). İzole oligohidramnios grubunda (n=45) CPR kontrol grubuna göre daha düşük saptandı. Ayrıca IO, daha düşük (APGAR <7) 1. (%55,6 ve %7,5, P<0.001) ve 5. (%13,3 ve %1,9, P=0,028) dakika APGAR skorları ve daha yüksek YYBÜ kabul oranları ile (%26,7 ve %3,8, P=0,001) ilişkili idi.

Sonuç: CPR ölçümü, IO hastalarında kötü neonatal sonuçlar açısından daha yüksek risk taşıyan fetüslerin saptanmasında yararlı görünmektedir.

Anahtar kelimeler: Serebroplasental oran, CPR, İzole oligohidramnios, Perinatal sonuç, Fetal Doppler

How to cite/Atıf için: Destegül E, Akkaya H, Büke B, Gürer G. Evaluation of cerebroplacental ratio as a new tool to predict adverse perinatal outcomes in patients with isolated oligohydramnios. J Surg Med. 2020;4(12):1169-1172.

Introduction

The amniotic fluid volume being less than expected for gestational age is defined as oligohydramnios. Its incidence at term pregnancies ranges between 0.5-5% depending on measurement methods, patient population, and gestational age (GA) [1,2]. Definition of oligohydramnios is mostly performed by amniotic fluid index (AFI) <5cm and single deepest pocket (SDP) <2 cm. Adequate amniotic fluid is important for normal fetal growth, fetal lung development, and for protecting the fetus and umbilical cord from trauma.

Various conditions such as premature rupture of membranes, placental dysfunction, chromosomal and congenital abnormalities, and medications can cause oligohydramnios, or it may be isolated. It is well known that oligohydramnios, regardless of its etiology (except isolated oligohydramnios), is related to increased adverse perinatal outcomes, such as low APGAR scores, neonatal intensive care unit admission (NICU), meconium presence in amniotic fluid, meconium aspiration syndrome (MAS), and increased cesarean section ratings due to fetal distress [3-12].

Although data about the importance of isolated oligohydramnios (IO) in the literature is controversial, last reviews showed an increase in adverse perinatal adverse outcomes such as increased cesarean delivery rates, low APGAR scores, and a higher rate of NICU admission [13-25].

Routine Antenatal Imaging with Ultrasound (RADIUS) trial reported that in IO patients, fetal growth did not deteriorate, but placental insufficiency could be present, even with growth percentiles higher than 10% [26]. Furthermore, Locatelli and colleagues reported an underlying fetal growth retardation in 13.2% of pregnancies with IO, which could not be detected before delivery [14].

On the other hand, The American College of Obstetricians and Gynecologists (ACOG) pointed out in 1999 that insufficient data was present for labor induction in IO. Therefore, ACOG did not declare a definitive statement regarding the optimal timing of delivery [27]. Despite this information, when an IO diagnosis is made in term pregnancies (beyond 37 weeks of GA) clinicians almost always lean towards induction of labor [28].

Evaluation of fetal vascular structures, maternal uterine artery circulation and amniotic fluid is widely used in the assessment of fetal well-being in contemporary obstetric practice. Umbilical artery (UA), middle cerebral artery (MCA), ductus venosus doppler have been used so far for assessment of fetal status. The cerebro placental ratio (CPR), which was reported first in 1987 [29], represents the alteration of the blood flow towards the brain due to cerebrovascular dilatation. Also, an increase in placental bed resistance and decreased diastolic flow in the umbilical artery contribute to CPR. CPR can be calculated as MCA resistance index (RI) divided by UA resistance index or MCA pulsatility index (PI) divided by UA pulsatility index. We know that CPR measurement is more valuable than UA and MCA Doppler in pregnancies with fetal growth restriction (FGR) [30]. Also, near-term, detection of potential FGR can be difficult because of the imprecise evaluation of the fetal weight due to intra and inter-observer variability [31]. Detection of acute hypoxia with CPR is the most useful parameter [32].

In this study, we aimed to assess the CPR changes in IO patients, because research seems lacking in this area.

Materials and methods

This prospective case-control study was held in a University hospital between October - November in 2018. After approval of study by the local ethics committee (Kayseri Erciyes University Medical Faculty Ethics Committee, approval ID no: 2018/455), each participant was informed, and consent was obtained. The study population was recruited from 37-40 gestational weeks singleton, isolated oligohydramniotic pregnant women (IO group) based on the last menstrual period and gestational age, gravida, parity, body mass index-matched pregnant women with normal amounts of amniotic fluid volume according to her gestational age (control group). All recruited patients were examined before active labor (cervical dilatation ≤4cm). Patients who gave birth in three days after the fetal Doppler measurement were included in the study. Fetuses with chromosomal/structural abnormalities and fetal growth restriction, pregnancies with ruptured membranes, multiple gestations, fetal placental, and umbilical cord abnormalities, Rh isoimmunization, patients with maternal systemic disease, pregnancy-induced hypertension, pregestational or gestational diabetes, prior cesarean section, preterm and post-term pregnancies were excluded.

All the participants underwent an ultrasound examination performed by an experienced clinician (E.D.). Obstetric and general health data of each patient were also recorded.

Doppler ultrasound examinations were performed using a Mindray DC-7 ultrasound machine (Shenzhen Mindray Bio-Medical Electronics Co., China), equipped with a 3,5-MHz convex array sector transducer, taking into consideration fetal movements, and breathing periods. After fetal ultrasound examination of fetal middle cerebral artery (MCA), and umbilical artery (UA), pulsatility index, systolic-to-diastolic ratio (S/D), peak systolic velocity (PSV) of MCA were measured and recorded. Amniotic volume was measured with a four-quadrant amniotic fluid index technique and AFI ≤5 cm was considered oligohydramnios. IO group and control group were compared in terms of fetal CPR and adverse perinatal outcomes.

Statistical analysis

The SPSS for Windows 21.0 (SPSS Inc.IL, USA) software was used for statistical analyses. *P*-value <0.05 was considered statistically significant. The Shapiro-Wilk test was used to assess the normality of distribution of variables. Normally distributed variables were expressed as mean (SD). Comparisons of variables between the groups were performed by independent samples t-test, Mann– Whitney U test, and Chi-square test.

Results

A total of 98 women who met the inclusion criteria were recruited for the study. Comparison of both groups' demographic and fetal Doppler parameters was shown in Tables 1 and 2. The demographic features of both groups were similar, but perinatal

adverse outcomes were significantly higher in the IO group. The mean maternal age of the whole study population was 27.3 (5.9) years. Twenty-seven of 98 pregnant women (27.6%) were on their first pregnancy, while 71 (72.4%) women were on their second or more pregnancy. The average gestational age of inclusion in the study was 38.3 (1.05) weeks according to the last menstrual period (LMP) (Table 1).

Comparison of all Doppler indices showed a statistical difference between the groups (UA PI P=0.014, UA S/D P=0.01, MCAPI P=0.004, MCA PSV P=0.037 and CPR P<0.001) (Table 2). Patients with low fetal biophysical profiles (BPP≤4) and impaired CPR (CPR <1.08) showed a significant correlation among themselves (r=0.23 positive correlation P=0.02, Spearman Rho test). The coexistence of low BPP scores and low CPR levels in the IO group resulted in a significant increase in C/S rates due to fetal distress (Table 3). Also, there was a significant correlation between low CPR and fetal distress among the groups (r= 0.035, P<0.001). In patients with low BPP in the IO group, the CPR levels of 7 patients were higher than 1.08, while 8 patients' CPR was <1.08 (P=0.078). Statistical results showed significant differences between the groups in terms of 1st and 5th minute APGAR scores and admission to NICU. In both groups, patients with low BPP scores were associated with lower 1st and 5th minute APGAR scores (r=0.40 p <0.001, r=0.32 P=0.001 respectively), higher fetal distress (r=0.34 P=0.001) and C/S rates (r=0.25 P=0.013) (P=0.023). No stillbirth or neonatal deaths were observed in any of the groups.

Table 1: Maternal demographic and obstetric features of the whole study population

Characteristics	Oligohydramnios group n=45	Control group n=53	*P*-value
Maternal age(year)*	26.4(5.48)	28.1(6.23)	0.15
Gestational age(week)**	37.2(1.9)	37.5(1.8)	0.2
Gravida**	1.98(0.9)	2.24(0.97)	0.15
Parity**	0.82(0.8)	0.87(0.83)	0.81
BMI (kg/m^2)*	27.01(4.7)	27.18(4.4)	0.85
Gender male†	28(62.2%)	25(47.2%)	0.13
Induction and/or augmentation of labor (oxytocin) †	12(26.7%)	17(32.1%)	0.55
Mode of delivery C/S†	20(44.4%)	16(30.2%)	0.14
Fetal distress (emergency C/S)	15(33.3%)	5(9.4%)	0.003
NICU admission rate	12(26.7%)	2(3.8%)	0.001
1-min Apgar score ≤7†	25(55.6%)	4(7.5%)	<0.001
5-min Apgar score ≤7†	6(13.3%)	1(1.9%)	0.028
Birth weight (g)*	3132(307)	3222(373)	0.21
Birth length (cm)	49.2(1.4)	48.9(2.04)	0.4

* Independent Sample t Test, ** Mann-Whitney u test, † Chi -Square test

Table 2: Fetal Doppler indices of the whole study population

Characteristics	Oligohydramnios group n=45	Control group n=53	*P*-value
Umbilical artery S/D*	2.64(0.61)	2.38(0.37)	0.01
Umbilical artery PI**	0.84(0.17)	0.76(0.13)	0.014
MCA PI*	1.50 (0.39)	1.74(0.44)	0.004
MCA PSV(cm/s)*	69.2(14.2)	63.1(14.6)	0.037
Cerebro Placental Ratio**	1.99(1.6)	2.34(0.70)	<0.001
Amniotic Fluid Index*	36.8(7.17)	101.3(41.2)	<0.001
Biophysical profile ≤4 (n, %)	15(33.3%)	7(13.2%)	0.017

S/D: Systole/ Diastole PI: Pulsatility index PSV: Peak systolic velocity CPR: Cerebro-Placental Ratio

Table 3: Relationship between CPR and BPP in oligohydramnios group

Oligohydramnios group	CPR ≤1.08	CPR >1.08	*P*-value
*BPP≤4	8	7	0.078
BPP>4	8	22	
Apgar1st Min. ≤7	9	16	0.94
Apgar1st Min. >7	7	13	
Fetal distress (+)	9	6	0.023
Fetal distress (-)	7	23	

* Biophysical profile

Discussion

In this prospective case-control study, we found that patients with low CPR levels were more likely to have a cesarean section (C/S) for non-reassuring fetal heart rates (NRFHR) in the IO group, and poor perinatal outcomes, such as low 1st and 5th minutes APGAR scores and a higher number of admissions to NICU.

In the literature review, perinatal outcomes of fetuses with IO have conflicting results. A meta-analysis made by Rossi and Prefumo in 2013 showed no significant differences concerning perinatal outcomes, except a rise in C/S rates due to NRFHR [19], which did not lead to an increased low incidence of APGAR scores, low umbilical artery pH, NICU admissions, or mortality compared to pregnancies with normal amniotic fluid. Also, they did not find any increase in meconium-stained amniotic fluid, which is another conflicting issue in oligohydramnios. The other two studies revealed similar results. In one of them, Karahanoglu et al. [33] investigated the optimal timing of delivery for IO patients. They stratified the patients as early term, full-term, and late-term, and analyzed the perinatal outcomes to find no differences in terms of NICU admission, low APGAR score, and low cord pH. However, this study had two limitations, one being its retrospective nature and the other, the lack of a control group. In the second study, which was also retrospectively designed, Naveiro-Fuentes et al. [34] stated that IO was not associated with poor perinatal outcomes, except for fetuses with SGA.

On the other hand, the recent two meta-analyses reported a relationship between IO and poor perinatal outcomes. In 2016, Shrem et al. [25] showed higher C/S rates due to NRFHR, lower 1st, and 5th minute APGAR scores, and more admission to NICU in the IO group compared to pregnancies with normal amniotic fluid, similar to our study. Another meta-analysis was performed by Rabie et al. [24] in 2017, which also reported results parallel to ours: Low APGAR score in 5th minute and higher C/S rates due to NRFHR. They also found an increase in meconium aspiration syndrome which we did not assess. In another study, Casey et al. [8] reported higher stillbirth rates in the IO group. We did not observe any stillbirth, but this may have resulted from a relatively small sample size of the cohort.

In 2017, Khalil et al. [35] demonstrated that low CPR is significantly associated with impaired fetal growth and poor neonatal outcomes, even in appropriate for gestational age (AGA) fetuses. They stated that low CPR is a biometric marker of failure to reach growth potential even in AGA fetuses (≥ the 10th percentile). Also, several studies have been reported a relationship between low CPR and adverse outcomes in low risk and/or AGA pregnancies [36-44]. In 2018, Kalafat and Khalil published a review about the utility of CPR in SGA and AGA fetuses, and they underlined the importance of close intrapartum surveillance of AGA fetuses due to the risk of fetal intrapartum compromise and operative delivery [45].

In the present study, further evaluation of fetal well-being status was also performed with a biophysical profile (BPP). Fetuses with low BPP (BPP≤4) had more C/S rates due to NRFHR and lower 1st and 5th minute APGAR scores. These results were consistent with the literature [46,47]. Moreover, CPR levels were positively correlated with BPP scores. We think that these results may be related to an unrecognized subtle placental insufficiency in IO.

Limitations

Although our study is the first on this subject, several limitations remain. The main limitation of our study is the relatively small size of the cohort. Secondly, we did not assess umbilical cord pH alterations and the existence of meconium-stained amniotic fluid among the groups to evaluate the poor neonatal outcome.

Conclusion

As mentioned above, the perinatal outcomes of IO are controversial in the literature. Our present study showed an increase in C/S rates due to non-reassuring fetal heart rate patterns, lower 1st, and 5th minute APGAR scores, and higher NICU admission rates in IO patients with low CPR. Since our study is the first to investigate the relationship between IO and CPR, we recommend clinicians to closely follow up IO patients with low CPR levels and BPP scores due to risk of fetal distress and poor neonatal outcomes.

References

1. Hill LM, Breckle R, Wolfgram KR, O'Brien PC. Oligohydramnios: ultrasonically detected incidence and subsequent fetal outcome. Am J Obstet Gynecol. 1983;147:407–10.
2. Mercer LJ, Brown LG, Petres RE, Messer RH. A survey of pregnancies complicated by decreased amniotic fluid. Am J Obstet Gynecol. 1984;149:355–61.
3. Youssef AA, Abdulla SA, Sayed EH, Salem HT, Abdelalim AM, Devoe LD. Superiority of amniotic fluid index over amniotic fluid pocket measurement for predicting bad fetal outcome. South Med J. 1993;86:426–9.
4. Magann EF, Kinsella MJ, Chauhan SP, McNamara MF, Gehring BW, Morrison JC. Does an amniotic fluid index of ≤5 cm necessitate delivery in high-risk pregnancies? A case–control study. Am J Obstet Gynecol. 1999;180:1354–9.
5. Driggers RW, Holcroft CJ, Blakemore KJ, Graham EM. An amniotic fluid index < or =5 cm within 7 days of delivery in the third trimester is not associated with decreasing umbilical arterial pH and base excess. J Perinatol. 2004;24:72–6.
6. Rutherford SE, Phelan JP, Smith CV, Jacobs N. The four-quadrant assessment of amniotic fluid volume: an adjunct to antepartum fetal heart rate testing. Obstet Gynecol. 1987;70:353–6.
7. Magann EF, Chauhan SP, Martin JN Jr. Is amniotic fluid volume status predictive of fetal acidosis at delivery? Aust N Z J Obstet Gynaecol. 2003;43:129–33.
8. Casey BM, McIntire DD, Bloom SL, Lucas MJ, Santos R, Twickler DM et al. Pregnancy outcomes after antepartum diagnosis of oligohydramnios at or beyond 34 weeks' gestation. Am J Obstet Gynecol. 2000;182:909–12.
9. Alchalabi HA, Obeidat BR, Jallad MF, Khader YS. Induction of labor and perinatal outcome: the impact of the amniotic fluid index. Eur J Obstet Gynecol Reprod Biol. 2006;129:124–7.
10. Sultana S, Akbar Khan MN, Khanum Akhtar KA, Aslam M. Low amniotic fluid index in high-risk pregnancy and poor apgar score at birth. J Coll Physicians Surg Pak. 2008;18:630–4.
11. Venturini P, Contu G, Mazza V, Facchinetti F. Induction of labor in women with oligohydramnios. J Matern Fetal Neonatal Med. 2005;17:129–32.
12. Chauhan SP, Sanderson M, Hendrix NW, Magann EF, Devoe LD. Perinatal outcome and amniotic fluid index in the antepartum and intrapartum periods: a meta-analysis. Am J Obstet Gynecol. 1999;181:147.
13. Melamed N, Pardo J, Milstein R, Chen R, Hod M, Yogev Y. Perinatal outcome in pregnancies complicated by isolated oligohydramnios diagnosed before 37 weeks of gestation. Am J Obstet Gynecol. 2011;205:241.e241–241.e246
14. Locatelli A, Vergani P, Toso L, Verderio M, Pezzullo JC, Ghidini A. Perinatal outcome associated with oligohydramnios in uncomplicated term pregnancies. Arch Gynecol Obstet. 2004;269:130–3.
15. Rainford M, Adair R, Scialli AR, Ghidini A, Spong CY. Amniotic fluid index in the uncomplicated term pregnancy. Prediction of outcome. J Reprod Med. 2001;46:589–92.
16. Conway DL, Adkins WB, Schroeder B, Langer O. Isolated oligohydramnios in the term pregnancy: is it a clinical entity? J Matern Fetal Med. 1998;7:197–200.
17. Ashwal E, Hiersch L, Melamed N, Aviram A, Wiznitzer A, Yogev Y. The association between isolated oligohydramnios at term and pregnancy outcome. Arch Gynecol Obstet. 2014;290:875–81.
18. Bachhav AA, Waikar M. Low amniotic fluid index at term as a predictor of adverse perinatal outcome. J Obstet Gynaecol India. 2014;64:120–3.
19. Rossi Ac, Prefumo F. Perinatal outcomes of isolated oli- gohydramnios at term and post-term pregnancy: a systematic review of literature with meta-analysis. eur J Obstet Gynecol reprod Biol. 2013;169(2):149–54.
20. Zhang J, Troendle J, Meikle S, Klebenoff MA, Rayburn WF. Isolated oligohydramnios is not associated with adverse perinatal outcomes. BJOC. 2004;111:220–5.
21. Magann EF, Chauhan SP, Dohorty DA, Barrileaux PS, Martin JR. JN. Predictability of intrapartum and neonatal outcomes with the amniotic fluid volume distribution: a reassessment using amniotic fluid index, single deepest pocket, and a dye-determined amniotic fluid volume. Am J Obstet Gynecol. 2003;188(6):1523–7.
22. Chauhan SP, Cowan BD, Magann EF, Roberts WE, Morrison JC, Martin JR. JN. Intrapartum amniotic fluid index. A poor diagnostic test for adverse perinatal outcome. J reprod Med. 1996;41(11):860–6.
23. Chauhan SP, Hendrix NW, Morrison JC, Magann EF, Devore LD. Intrapartum oligohydramnios does not predict adverse peripartum outcome among high risk parturients. Am J Obstet Gynecol. 1997;176(6):1130–6.
24. Rabie N, Mgann E, Steelman Sand S, Ounpraseuth S. Oligohydramnios in complicated and uncomplicated pregnancy: a systematic review and meta-analysis Ultrasound Obstet Gynecol. 2017;49:442–9.
25. Shrem G, Nagawkar SS, Hallak M, Walfisch A. Isolated oligohydramnios at term as an indication for labor induction: a systematic review and meta-analysis. Fetal diagnosis and therapy. 2016;40(3):161-73.
26. Ewigman BG, Crane JP, Frigoletto FD, LeFevre ML, Bain RP, McNellis D et al. Effect of prenatal ultrasound screening on perinatal outcome. New England journal of medicine. 1993;329(12):821-7.
27. American College of Obstetricians and Gynecologists. ACOG practice bulletin. Antepartum fetal surveillance. Number 9, October 1999. Clinical management guidelines for obstetrician-gynecologists. Int J Gynaecol Obstet. 2000;68:175-85.
28. Scwartz N, Sweeting R, Young BK. Practice patterns in the management of isolated oligo-hydramnios: a survey of perinatologists. J Matern Fetal Neonatal Med. 2009;22:357–36.
29. Arbeille P, Roncin A, Berson M, Patat F, Pourcelot L. Exploration of the fetal cerebral blood flow by duplex Doppler—linear array system in normal and pathological pregnancies. Ultrasound Med Biol. 1987;13:329–37.
30. Cruz-Martinez R, Figueras F, Hernandez-Andrade E, Oros D, Gratacos E. Fetal brain Doppler to predict cesarean delivery for non-reassuring fetal status in term 20 small-for- gestational-age fetuses. Obstet Gynecol 2011;117:618-26.
31. Chang TC, Robson SC, Spencer JAD, Gallivan S. Ultrasonic fetal weight estimation: Analysis of inter- and intra-observer variability. J Clin Ultrasound 1993; 21:515–9.
32. Arbeille P, Maulik D, Fignon A, Stale H, Berson M, Bodard S, et al. Assessment of the fetal PO2 changes by cerebral and umbilical Doppler on lamb fetuses during acute hypoxia. Ultrasound Med Biol. 1995;21:861–70.
33. Karahanoglu E, Akpinar F, Demirdag E, Yerebasmaz N, Ensari T, Akyol A, et al. Obstetric outcomes of isolated oligohydramnios during early-term, full-term and late-term periods and determination of optimal timing of delivery. Journal of Obstetrics and Gynaecology Research. 2016;42(9):1119-24.
34. Naveiro-Fuentes M, Prieto AP, Ruiz RS, Badillo MPC, Ventoso FM, Vellejo JLG. Perinatal outcomes with isolated oligohydramnios at term pregnancy. Journal of perinatal medicine. 2016;44(7):793-8.
35. Khalil A, Morales-Rosello J, Khan N, Nath M, Agarwal P, Bhide, A, et al. Is cerebroplacental ratio a marker of impaired fetal growth velocity and adverse pregnancy outcome? American journal of obstetrics and gynecology. 2017;216(6):606-e1.
36. Chainarong N, Petpichetchian C. The relationship between intrapartum cerebroplacental ratio and adverse perinatal outcomes in term fetuses. Eur J Obstet Gynecol Reprod Biol. 2018;228:82–6.
37. Dall'Asta A, Ghi T, Rizzo G, Morganelli G, Galli L, Roletti E, et al. Early labor cerebroplacental ratio assessment in uncomplicated term pregnancies and prediction of adverse perinatal outcomes: a prospective, multicentre study. Ultrasound Obstet Gynecol. 2019;53(4):481-7.
38. Flatley C, Kumar S. Is the fetal cerebroplacental ratio better that the estimated fetal weight in predicting adverse perinatal outcomes in a low risk cohort? J Matern Fetal Neonatal Med. 2019;32(14):2380-6.
39. Fratelli N, Mazzoni G, Maggi C, Gerosa V, Lojacono A, Prefumo F. Cerebroplacental ratio before induction of labour in normally grown fetuses at term and intrapartum fetal compromise. Eur J Obstet Gynecol Reprod Biol 2018;227:78–80.
40. Morales-Roselló J, Khalil A, Fornés-Ferrer V, Perales-Marín A. Accuracy of the fetal cerebroplacental ratio for the detection of intrapartum compromise in nonsmall fetuses. The Journal of Maternal-Fetal & Neonatal Medicine. 2019;32(17):2842-52.
41. Atabay I, Kose S, Cagliyan E, Baysal B, Yücesoy E, Altınyurt S. A prospective cohort study on the prediction of fetal distress and neonatal status with arterial and venous Doppler measurements in appropriately grown term fetuses. Arch Gynecol Obstet. 2017;296:721–30.
42. Bligh LN, Alsolai AA, Greer RM, Kumar S. Cerebroplacental ratio thresholds measured within 2 weeks before birth and risk of Cesarean section for intrapartum fetal compromise and adverse neonatal outcome. Ultrasound Obstet Gynecol. 2018;52(3):340-6.
43. Bligh LN, Alsolai AA, Greer RM, Kumar S. Prelabor screening for intrapartum fetal compromise in low-risk pregnancies at term: cerebroplacental ratio and placental growth factor. Ultrasound in Obstetrics & Gynecology. 2018;52(6):750-6.
44. Migda M, Gieryn K, Migda B, Migda MS, Maleńczyk M. Utility of Doppler parameters at 36–42 weeks' gestation in the prediction of adverse perinatal outcomes in appropriate-for-gestational-age fetuses. J Ultrason. 2018;18:22–8.
45. Kalafat E, Khalıl A. Clinical significance of cerebroplacental ratio. Current Opinion in Obstetrics and Gynecology, 2018;30(6):344-54.
46. Ribbert LS, Snijders RJ, Nicolaides KH, Visser GHA. Relationship of fetal biophysical profile and blood gas values at cordocentesis in severely growth-retarded fetuses. Am J Obstet Gynecol. 1990;163:569–71.
47. Vintzileos AM, Fleming AD, Scorza WE, Wolf EJ, Balducci J, Campbell WA, et al. Relationship between fetal biophysical activities and umbilical cord blood gas values. Am J Obstet Gynecol. 1991;165:707–13.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1173-1176.
DOI: 10.28982/josam.823298

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

An evaluation of functional outcome in elderly patients with proximal humeral fractures treated conservatively

Konservatif takip edilen ileri yaş proksimal humerus kırıklı hastaların fonksiyonel sonuçlarının değerlendirilmesi

Emre Çalışal [1]

[1] **Amasya University, School of Medicine, Department of Orthopedics and Traumatology, Amasya, Turkey**

ORCID ID of the author(s)

EÇ: 0000-0002-2824-669X

Corresponding author/Sorumlu yazar:
Emre Çalışal
Address/Adres: Amasya Üniversitesi, Tıp Fakültesi, Ortopedi ve Travmatoloji Anabilim Dalı, Amasya, Türkiye
E-mail: calisall@yahoo.com

Ethics Committee Approval: This study was approved by the Amasya University Non-Invasive Clinical Research Ethics Committee on 05/15/2020 with the project number 15386878-044. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma Amasya Üniversitesi Non-İnvaziv Klinik Araştırmalar Etik Kurulu tarafından 05/15/2020 tarihinde 15386878-044 proje numarası ile onaylanmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: The relationship between radiological data and the clinical outcomes in elderly patients with incomplete proximal humeral fractures treated conservatively is limited and controversial in the literature. We aimed to report the short-to-mid-term results of the radiological data and functional outcome in these patients.

Methods: A total of 114 patients over 65 years of age, diagnosed with unilateral isolated incomplete proximal displaced humerus fractures, and treated conservatively, were recruited in the study. Demographic characteristics, radiological data and clinical scores of all patients were recorded. Fractures were classified according to the Neer classification. Functional evaluation of patients was performed via Quick-Disabilities of Arm, Shoulder, and Hand (Quick-DASH) and Visual Analog Scale (VAS).

Results: Mean VAS and Quick-DASH scores of the patients were 3.6 (1.4) and 34.5(13.7), respectively, both of which changed significantly as the number of the parts of fracture increased (P=0.02 and P=0.04, respectively). The VAS and the Quick-DASH scores were significantly higher in females (P=0.02 and P=0.03, respectively), similar among the smokers (P=0.58 and P=0.41, respectively), and significantly higher in diabetic and osteoporotic patients (P<0.001 and P=0.39, respectively).

Conclusion: Functional outcomes after conservative follow-up in patients over 65 years of age with incomplete proximal humerus fractures are good in most patients. Therefore, conservative treatment can be an option regardless of the fracture type in elderly patients with incomplete proximal humeral fractures.

Keywords: Proximal humerus fractures, Conservative treatment, Elderly patients

Öz

Amaç: Literatürde radyolojik veriler ile klinik sonuçlar arasındaki bilgiler sınırlı ve tartışmalıdır. Konservatif tedavi edilen inkomplet proksimal humerus kırığı olan ileri yaş hastalarda radyolojik veriler ile fonksiyonel sonuçlarının kısa-orta dönem sonuçlarını incelemeyi amaçladık.

Yöntem: Çalışmamıza, konservatif olarak tedavi edilen, tek taraflı izole, inkomplet proksimal humerus kırığı tanısı almış 65 yaş üstü 114 hasta dahil edildi. Tüm hastaların demografik özellikleri, radyolojik verileri ve klinik skorları kaydedildi. Kırıklar Neer sınıflamasına göre sınıflandırıldı. Fonksiyonel sonuçların değerlendirmesi Quick-Disabilities of Arm, Shoulder, and Hand (Quick-DASH) ve Visual Analog Scale (VAS) ile yapıldı.

Bulgular: Hastaların VAS skorları ortalama 3,6 (1,4) ve Quick-DASH skorları ise 34,5 (13,7) idi. VAS ve Quick-DASH skorlarındaki fark sırasıyla kırığın parça sayısı arttıkça istatistiksel olarak anlamlıydı (P=0,02, P=0,04). VAS ve Quick-DASH skorları, kadınlarda sırasıyla istatistiksel olarak anlamlı daha yüksekti (P=0,02, P=0,03). Sigara içen grupta VAS ve Quick-DASH skorları sırasıyla istatistiksel olarak anlamlı değildi (P=0,58, P=0,41). VAS ve Quick-DASH skorları, diyabet ve osteoporozlu hasta grubu lehine sırasıyla istatistiksel olarak anlamlıydı (P<0,001, P=0,39).

Sonuç: Tam deplasmanı olmayan 65 yaş üstü humerus proksimal kırıklı hastaların konservatif takip sonrası ağrı ve fonksiyonel sonuçlar çoğu hastada iyidir. Bu nedenle ileri yaş proksimal humerus kırıklı hastalarda konservatif tedavi kırık tipinden bağımsız olarak bir seçenek olabilir.

Anahtar kelimeler: Proksimal humerus kırıkları, Konservatif tedavi, İleri yaş hastalar

How to cite/Atıf için: Çalışal E. An evaluation of functional outcome in elderly patients with proximal humeral fractures treated conservatively. J Surg Med. 2020;4(12):1173-1176.

Introduction

Humerus fractures account for 4-5% of all fractures, and are the third most common after hip and Colles' fractures in elderly osteoporotic patients after a fall [1,2]. They are observed in approximately 260 of every 100 000 people a year, especially between the ages of 80 and 89 years. Around 80% of the cases are women and 87% are osteoporotic patients of older age who received low energy trauma [3]. Minimal displacement and/or angulation is observed in 85% of incomplete proximal humerus fractures and these patients are treated conservatively [4]. Functional outcomes after conservative treatment are often sufficient, but some patients are likely to feel residual pain [5]. The displacement of the diaphysis diameter by more than 50% and varus or valgus malposition of more than 20 degrees of the head-shaft angle are acknowledged as surgical treatment indications. There is not compelling evidence regarding whether conservative or surgical treatment is superior, especially in osteoporotic elderly patients [4, 6]. Surgical treatment may not always provide satisfactory results, even in elderly patients with incomplete proximal humerus fractures who absolutely required it. Due to the comorbid conditions of the patients, surgery can be risky, and surgical complications such as implant failure, nonunion, and infections may occur [7]. In the literature, conservative treatment is recommended instead of surgical treatment in elderly patients with incomplete proximal humerus fractures with angulation and/or displacement within acceptable limits [8-10].

Based on the limited literature, it wouldn't be wrong to argue that the relationship between the radiological data (displacement percentage, malposition of the fracture, and the number of parts of the fracture) and the clinical outcomes is controversial. Therefore, more studies examining the effect of radiological data and functional outcomes in elderly patients with incomplete proximal humerus fractures over 65 years of age are needed. Patients with surgical indications are excluded in the most studies. In the present study, however, we also included patients with incomplete proximal humeral fractures who did not accept surgical treatment or who could not be treated surgically due to high risk. In this study, we intended to examine the short-to-mid-term results of the radiological data and clinical results of elderly patients with incomplete proximal humeral fractures who had conservative treatment indications and could not be surgically treated.

Materials and methods

We recruited patients over 65 years of age, who were followed conservatively with a diagnosis of incomplete proximal humerus fracture between January 2015 and April 2019 in our outpatient clinic of Amasya University Sabuncuoğlu Şerefeddin Training and Research Hospital and whose fracture union was completed at the end of radiological examinations. Exclusion criteria included patients under 65 years of age, those with severe cognitive dysfunction who could not answer given questionnaires, those who died during the study period, patients with completely displaced fractures, and additional injury to the fractured extremity. Three patients were excluded from the study due to weakness in the fractured side because of cerebrovascular disease, two patients, due to a history of wrist fracture in the same extremity, and three patients, due to inadequate cooperation. Finally, a total of 114 patients whose fracture union was completed in radiographic evaluation at the time of last follow up, who were scheduled for surgery but could not be operated due to high risk (ASA 4) and/or the patient's disapproval were included. Demographic (age, gender, dominant extremity, smoking, diabetes, and osteoporosis diagnosis), radiological data, functional, and pain scores of all patients were recorded. Fractures were evaluated via direct anteroposterior (AP) radiography and 3D computed tomography (CT) at the time of admission and classified into one, two, three, and four parts according to the Neer classification [11]. All patients were followed up using the Velpeau bandage. The bandage was left in place between 4-6 weeks, depending on the patient's age and fracture type. We started passive pendulum exercises at intervals after the first week. At the end of the second week, active-assisted exercises were usually initiated as part of the home rehabilitation process. Depending on the patient's age and fracture healing, the Velpeau bandage was removed in 4-6 weeks, and active shoulder rum exercises were initiated.

Clinical evaluation of patients with a follow-up period of at least 1 year, along with Quick-Disabilities of Arm, Shoulder, and Hand (Quick-DASH) and Visual Analog Scale (VAS) scoring were assessed without measuring the radiological data of the fracture during evaluation [12]. According to the Quick DASH scale, the results were interpreted as mild if <25, moderate if 25-50, severe if 50-75, and most severe if > 75 [13]. According to the VAS scale, the results were assessed as painless (0), mild (1-3), moderate (4-6), and severe (7-10) [14].

Statistical analysis

SSPS version 22.0 statistical package program (SPSS Inc., Chicago, IL, United States of America) was used for statistical analysis of all data obtained. Whether Quick-DASH and VAS scores showed normal distribution was evaluated by the Kolmogorov Smirnov test. Independent sample t-test and Mann Whitney U tests were used for normally and non-normally distributed parameters, respectively. $P<0.05$ was considered statistically significant.

Results

A total of 114 patients with a mean age of 78 (7.7) years were included in our study. Among them, there were 75 (65.8%) females and 39 (34.2%) males. The right extremity was affected in 58 (50.9%) patients, and the left extremity was affected in 56 (49.1%) patients. Sixty-three (55.3%) patients had fractures in the dominant extremity. While less than 50% fracture displacement was observed in 80 (70.2%) patients, more than 50% fracture displacement was observed in 34 (29.8%) patients. According to the Neer classification, 75 (65.8%), 28 (24.6%), and 11 (9.6%) of the fractures were 2, 3 and 4-part fractures, respectively. The mean follow-up period of the patients was 29 (13) months. Fifteen patients (13.2%) were smokers, nine (7.9%) were diabetic, and forty-three (37.7%) were osteoporotic (Table 1).

The mean VAS and Quick-DASH scores were 3.6 (1.4) and 34.5 (13.7), respectively, both of which changed significantly as the number of the parts of fracture increased

(*P*=0.02 and *P*=0.04, respectively). The VAS and the Quick-DASH scores were significantly higher in females (*P*=0.02 and *P*=0.03, respectively), similar among the smokers (*P*=0.58 and *P*=0.41, respectively), and significantly higher in diabetic and osteoporotic patients (*P*<0.001 and *P*=0.39, respectively). Both scores were insignificantly higher in fractures in the dominant extremity (*P*>0.05) (Table 2).

Table 1: Demographic characteristics of patients

	n = 114	
Age*	78	(7.0)
Gender**		
Male	39	(34.20)
Female	75	(65.80)
Injury side**		
Right	58	(50.90)
Left	56	(49.10)
Displacement **		
>%50	34	(29.80)
<%50	80	(70.20)
Dominant Arm (Injury side) **	63	(55.30)
Parts of fracture **		
2 – part	75	(65.80)
3 – part	28	(24.60)
4 - part	11	(9.60)
Duration (months)***	29.3	(13.7)
Smoking**	15	(13.20)
Diabetes mellitus **	9	(7.90)
Osteoporosis **	43	(37.70)

n: Total cohort, * mean (standard deviation) age at the time of the survey, ** Number of patients (%), *** mean time (standard deviation) since fracture

Table 2: Relationship between patients' demographic characteristics and clinical scores

	n	Quick-DASH score		*P*-value	VAS score		*P*-value
		Mean	SD		Mean	SD	
Total	114	34.50	(13.73)		3.68	(1.45)	
Gender							
Male	39	30.65	(13.83)	0.033*	3.28	(1.35)	0.028*
Female	75	36.50	(13,33)		3.89	1.46	
Dominant Arm							
Yes	63	35.55	(12.61)	0.290	3.77	(1.36)	0.435
No	51	33,19	(15.03)		3.56	(1.56)	
Parts of fracture							
2 - Part	75	29.29	(11.81)	0.020*	3.14	(1.21)	0.040*
3 - Part	28	41.01	(11.05)		4.35	(1.16)	
4 - Part	11	53.45	(7.23)		5.63	(1.28)	
Smoking							
Yes	15	32.23	(14.97)	0.413	3.46	(1.45)	0.586
No	99	34.84	(13.58)		3.71	(1.45)	
Diabetes mellitus							
Yes	9	58.12	(2.97)	<0.001*	6.33	(0.70)	<0.00*
No	105	32.47	(12.32)		3.45	(1.26)	
Osteoporosis							
Yes	43	38.20	(13.80)	0.039*	4.09	(1.46)	0.039*
No	71	32.26	(13.29)		3.43	(1.40)	

n: Total cohort, **P*<0.05 values were considered statistically significant

Discussion

In the present study, pain and functional results of patients with unilateral isolated incomplete proximal humerus fractures over 65 years of age were evaluated. Patients had an adequate level of functional satisfaction in VAS scores (mean: 3.6 (1.4)), and moderate functional satisfaction in Quick-DASH scores (mean: 34.5 (13.7)). The reason why these results were acceptable in the elderly patients in our study may be related to the fact that elderly patients do not require a full glenohumeral motion, and normal shoulder joint function is not expected for daily activities, as stated previously in the literature [15].

The management of elderly patients with proximal humerus fractures is yet to be fully revealed, and it is challenging for orthopedic surgeons. If the fracture is minimally comminuted and/or displaced, it is treated conservatively [16,17], but the management of complex fractures is controversial. Although surgical treatment is generally recommended for patients with complex fractures, there is evidence to suggest that conservative treatment results are published [10,11,18-20]. In these studies, some authors reported that conservative treatment in complex fractures is a valid option for elderly patients, although the treatment does not ensure complete functional recovery [8,9,21,22]. Also, in different studies conducted by Zyto et al. [10,23], it is argued that conservative treatment is an alternate option despite lower functional scores and non-anatomic reduction of fractures in the last follow-up of patients.

The literature postulates that the effects of the number of parts of the fracture and the patient's age on the functional results of the patient are controversial. Hanson et al. reported that the number of parts of the fractures affects functional results [8]. Additionally, Court-Brown et al. [15] stated that patient age is another important factor affecting the functional scores of the patient. In another study, it has been shown that functional results are related to fracture type, but not age and follow-up period [17]. Yuksel et al. [21] reported that the number of fragment of fractures did not affect the functional status of the patient, but the results were better in patients under 65 years of age. In our study, although there was a statistically significant relationship between the number of parts of the fracture, pain and functional results of the patient, pain and functional results were satisfactory in all patients. The hemiarthroplasty option recommended in 4-part humerus fractures in the literature is also controversial. Although Neer recommends hemiarthroplasty in 4-part proximal humerus fractures, some authors did not find adequate shoulder movement and functional results after arthroplasty [24,25].

There has been no consensus on the rehabilitation program of patients with proximal humeral fractures who were conservatively treated [8,9,21,22]. The hanging cast, shoulder sling, or Velpeau bandage can be used in conservative follow-up. Although the hanging cast was considered to provide distraction in the fracture line, the results were not as expected. The superiority of the results of the studies on this subject has not been proven [11,26]. Therefore, we followed our patients with Velpeau bandage and recommended an exercise program.

Limitations

In the current study, we have two important limitations. The first one was that we could not compare the patients who required surgical treatment but were followed up conservatively to those who underwent surgery for the same fracture type. The second one was that our study results include short-medium term results, but long term results are not reported. Further research is required to investigate this topic.

Conclusion

Functional outcomes after conservative follow-up in patients over 65 years of age with incomplete proximal humerus fracture are good in most patients. Therefore, conservative treatment can be an option regardless of the fracture type in elderly patients with incomplete proximal humeral fractures.

References

1. Fink HA, Ensrud KE, Nelson DB, Kerani R, Schreiner PJ, Zhao Y, et al. Disability after clinical fracture in postmenopausal women with low bone density: the fracture intervention trial (FIT). Osteoporos Int. 2003;14(1):69-76.
2. Palvanen M, Kannus P, Niemi S, Parkkari J. Update in the epidemiology of proximal humeral fractures. Clin Orthop. (1976-2007) 2006;442:87-92.
3. Bell J-E, Leung BC, Spratt KF, Koval KJ, Weinstein JD, Goodman DC, et al. Trends and variation in incidence, surgical treatment, and repeat surgery of proximal humeral fractures in the elderly. J Bone Joint Surg Am. 2011;93(2):121.
4. Murray I, Amin A, White T, Robinson C. Proximal humeral fractures: current concepts in classification, treatment and outcomes. J Bone Joint Surg Br. 2011;93(1):1-11.
5. Vrancken PM-JT, Kastelein GW, Breslau PJ. Proximal humerus fractures a prospective study of the functional outcome after conservative treatment. Eur J Trauma. 2001;27(3):133-6.

6. Court-Brown C, Cattermole H, McQueen M. Impacted valgus fractures (B1. 1) of the proximal humerus: the results of non-operative treatment. J Bone Joint Surg Br. 2002;84(4):504-8.
7. Smith AM, Mardones RM, Sperling JW, Cofield RH. Early complications of operatively treated proximal humeral fractures. J Shoulder Elbow Surg. 2007;16(1):14-24.
8. Hanson B, Neidenbach P, de Boer P, Stengel D. Functional outcomes after nonoperative management of fractures of the proximal humerus. J Shoulder Elbow Surg. 2009;18(4):612-21.
9. Court-Brown C, McQueen M. The impacted varus (A2. 2) proximal humeral fracture Prediction of outcome and results of nonoperative treatment in 99 patients. Acta Orthop Scand. 2004;75(6):736-40.
10. Zyto K. Non-operative treatment of comminuted fractures of the proximal humerus in elderly patients. Injury 1998;29(5):349-52.
11. Charles S Neer I. Displaced proximal humeral fractures: Part II. Treatment of three-part and four-part displacement. JBJS. 1970;52(6):1090-103.
12. Kennedy CA, Beaton DE, Smith P, Van Eerd D, Tang K, Inrig T, et al. Measurement properties of the QuickDASH (disabilities of the arm, shoulder and hand) outcome measure and cross-cultural adaptations of the QuickDASH: a systematic review. Qual Life Res. 2013;22(9):2509-47.
13. Angst F, Schwyzer HK, Aeschlimann A, Simmen BR, Goldhahn J. Measures of adult shoulder function: Disabilities of the Arm, Shoulder, and Hand Questionnaire (DASH) and its short version (QuickDASH), Shoulder Pain and Disability Index (SPADI), American Shoulder and Elbow Surgeons (ASES) Society standardized shoulder assessment form, Constant (Murley) Score (CS), Simple Shoulder Test (SST), Oxford Shoulder Score (OSS), Shoulder Disability Questionnaire (SDQ), and Western Ontario Shoulder Instability Index (WOSI). Arthritis Care Res. (Hoboken) 2011;63(S11):S174-S88.
14. Aun C, Lam Y, Collett B. Evaluation of the use of visual analogue scale in Chinese patients. Pain. 1986;25(2):215-21.
15. Court-Brown C, Garg A, McQueen M. The translated two-part fracture of the proximal humerus: epidemiology and outcome in the older patient. J Bone Joint Surg Br. 2001;83(6):799-804.
16. Vallier HA. Treatment of proximal humerus fractures. J Orthop Trauma. 2007;21(7):469-76.
17. Rasmussen S, Hvass I, Dalsgaard J, Christensen B, Holstad E. Displaced proximal humeral fractures: results of conservative treatment. Injury. 1992;23(1):41-3.
18. van den Broek CM, van den Besselaar M, Coenen JM, Vegt PA. Displaced proximal humeral fractures: intramedullary nailing versus conservative treatment. Arch Orthop Trauma Surg. 2007;127(6):459-63.
19. Fjalestad T, Strømsøe K, Blücher J, Tennøe B. Fractures in the proximal humerus: functional outcome and evaluation of 70 patients treated in hospital. Arch Orthop Trauma Surg. 2005;125(5):310-6.
20. Stableforth P. Four-part fractures of the neck of the humerus. J Bone Joint Surg Br. volume 1984;66(1):104-8.
21. Yüksel HY, Yimaz S, Aksahin E, Çelebi L, Muratli HH, Biçimoglu A. The results of nonoperative treatment for three-and four-part fractures of the proximal humerus in low-demand patients. J Orthop Trauma. 2011;25(10):588-95.
22. Schai P, Imhoff A, Preiss S. Comminuted humeral head fractures: a multicenter analysis. J Shoulder Elbow Surg. 1995;4(5):319-30.
23. Zyto K, Ahrengart L, Sperber A, Törnkvist H. Treatment of displaced proximal humeral fractures in elderly patients. J Bone Joint Surg Br. 1997;79(3):412-7.
24. Goldman RT, Koval KJ, Cuomo F, Gallagher MA, Zuckerman JD. Functional outcome after humeral head replacement for acute three-and four-part proximal humeral fractures. J Shoulder Elbow Surg. 1995;4(2):81-6.
25. Kontakis G, Koutras C, Tosounidis T, Giannoudis P. Early management of proximal humeral fractures with hemiarthroplasty: a systematic review. J Bone Joint Surg Br. 2008;90(11):1407-13.
26. Rees J, Hicks J, Ribbans W. Assessment and management of three-and four-part proximal humeral fractures. Clin Orthop Relat Res. (1976-2007) 1998;353:18-29.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1177-1181.
DOI: 10.28982/josam.803699

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

A pediatric nephrologist's experience on real-time ultrasound-guided kidney biopsy

Bir çocuk nefroloğunun eş-zamanlı ultrasonografi eşliğinde böbrek biyopsisi deneyimi

Behçet Şimşek [1]

[1] **Haydarpasa Numune Research Hospital, Paediatrics Clinic, Paediatric Nephrology Unit Uskudar, Istanbul, Turkey**

ORCID ID of the author(s)

BŞ: 0000-0002-3917-2374

Abstract

Aim: Kidney biopsy is crucial in management of renal diseases. Biopsies in children have added difficulties. The aim of this study is to investigate our 5-year experience of real-time ultrasound (USG)-guided percutaneous renal biopsy (PRB).

Methods: Institutional database of children who underwent PRB in a tertiary hospital between January 2015 and March 2020 were evaluated retrospectively. A single pediatric nephrologist performed all the biopsies using an automated spring-loaded biopsy gun under real-time USG guidance.

Results: Thirty-two biopsies were performed in 17 males (53.1%) and 15 females (46.9%), and the median age of the children was 14.5 years. The most common indication for biopsy was nephrotic syndrome in 13 /32 children (40.6%). Median number of glomeruli obtained from biopsy specimens was 18 (min-max=7-54 glomeruli). A diagnosis was achieved in all cases (100%) by a histopathologist. The only complication observed in a 16-year-old boy was a self-limited gross hematuria (3.1%) episode with subcapsular hematoma.

Conclusion: Real-time USG-guided PRB with an automated biopsy gun is an effective and safe technique, providing superior yield when performed by a pediatric nephrologist. Performing kidney biopsy is an essential tool in a nephrologist's workshop.

Keywords: Kidney biopsy, Children, Simultaneous ultrasonography, Biopsy gun

Öz

Amaç: Böbrek biyopsisinin böbrek hastalıklarının yönetiminde oldukça önemli bir yeri vardır. Özellikle çocuklarda yapılan biyopsiler ek zorluklar gösterir. Bu çalışmanın amacı, çocuklarda uygulamış olduğumuz beş yıllık ultrasonografi eşliğinde perkutan böbrek biyopsisi (PRB) deneyimimizi değerlendirmektir.

Yöntemler: Ocak 2015- Mart 2020 arasında bir üçüncü basamak hastanesinde PRB uygulanan çocukların hastane kayıtları geriye dönük olarak irdelenmiştir. Tüm biyopsiler, eş zamanlı USG altında tek bir çocuk nefroloğu tarafından otomatik biyopsi tabancası kullanılarak uygulanmıştır.

Bulgular: Medyan yaşı 14,5 yaş olmak üzere; 17 erkek (%53,1) ve 15 kız çocuğuna (%46,9) 32 böbrek biyopsisi uygulandı. En sık biyopsi endikasyonu, çocukların 13/32'sinde (%40,6) nefrotik sendrom idi. Biyopsi örneklerinden alınan medyan glomerül sayısı 18 (min-max=7-54 glomerül) idi. Histopatolog tarafından tüm olgularda (%100) tanı konulabildi. Gözlenen tek komplikasyon, 16 yaşındaki bir erkek çocuğunda subkapsüler hematomla birlikte kendiliğinden düzelen gross hematüri süreci idi (%3,1).

Sonuç: Çocuklarda; PRB Bir çocuk nefroloğu tarafından otomatik biyopsi tabancası kullanılarak, eş-zamanlı USG altında yapıldığında, yeterince fazla örneğin alınmasını sağlayan, etkili ve güvenli bir tekniktir. Böbrek biyopsisi, bir nefroloğun çalışma sorumluluğunda yapması gereken önemli bir uygulamadır.

Anahtar kelimeler: Böbrek biyopsisi, Çocuklar, Eş-zamanlı ultrasonografi, Biyopsi tabancası

Corresponding author/Sorumlu yazar:
Behçet Şimşek
Address/Adres: Haydarpaşa Numune Araştırma Hastanesi, Çocuk Kliniği, Çocuk Nefroloji Birimi Üsküdar, İstanbul, Türkiye
E-mail: behcetmd@gmail.com

Ethics Committee Approval: The study was approved by the institutional review board. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma, kurumsal inceleme kurulu tarafından onaylandı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

How to cite/Atıf için: Şimşek B. A pediatric nephrologist's experience on real-time ultrasound-guided kidney biopsy. J Surg Med. 2020;4(12):1177-1181.

Introduction

Kidney biopsy is the gold standard in the diagnosis, prognosis and management of many renal diseases [1]. However, there is a downward trend in number of biopsy-performing nephrologists over last years, provoking a novel debate over a nephrologist's job description.

Since Iversen and Brun introduced percutaneous renal biopsy (PRB) in 1951, advances have emerged in biopsy technique from indirect visualization to real-time ultrasound (USG) guidance [2]. Biopsy devices also have been evolved from the introduction of Vim-Silverman needle to spring-loaded automated biopsy gun [2,3]. Today, automated spring loaded biopsy device is being used with real-time USG guidance by many kidney biopsy performers [1]. Despite the advances in safety, handiness, and remarkably improved diagnostic power, with the use of "automated spring-loaded biopsy gun," this invasive procedure is not risk-free, depending partly on the skill of the operator or the clarity of imaging of the needle-tip's path in the USG screen [4,5]. Complications of PRB range from minor perirenal hematomas to major bleedings requiring blood transfusions and rarely up to the loss of kidney [6].

Furthermore, biopsies in children have added difficulties due to smaller kidney size and decreased ability of the patient to co-operate [3]. Additionally, there has been a diversity of implementations in performing kidney biopsy among nephrology clinics. Thus, British Association of Pediatric Nephrology (BAPN) had emphasized the need of a protocol for standardization for renal biopsies in 2003 and revised thereafter in 2010 and 2015, amid optimized protocols for USG-guidance in kidney biopsy in children and guidelines for percutaneous needle biopsy for radiologists were also been proposed [6-9]. However, more has been required to determine optimized global standards for kidney biopsies in children [6].

Although "The Accreditation Council on Graduate Medical Education" requires nephrologists' competence in performing native and allograft PRBs, 15-20% of young nephrologists admitted that they did not feel competent in performing PRBs in a survey between 2004 and 2008 [1,4]. Moreover, many nephrology related skills have been taken over by non-nephrologists in a variety of institutions in recent years, scaling the appeal down of nephrology as a sub-specialty for young doctors.

The aim of this study is to retrospectively investigate the 5-year experience of a pediatric nephrologist on real-time USG-guided PRB using an automated biopsy gun, compare complication rates and diagnostic power of biopsies with the literature, and evaluate the varieties of complications, sample adequacy, biopsy indications and diagnoses made in children.

Materials and methods

Institutional database of 32 children who underwent PRB in a tertiary hospital between January 2015 and March 2020 were evaluated retrospectively. The study was approved by the institutional review board. There was no conflict of interest associated with this study. Signed informed consents from a parent had been obtained before the procedures.

To the best of our knowledge, currently, our 5-year-old unit stands out in performing PRB under real-time USG-guidance with a spring-loaded automated biopsy gun by a pediatric nephrologist, among many pediatric nephrology clinics that perform blind biopsies after USG localization or referring to radiologists for biopsies in Turkey.

Specifically, demographic data (age, gender), clinical symptoms and signs, accompanying clinical diagnoses, laboratory findings including estimated GFR (eGFR) at presentation, indications, and complications of the biopsy with histological diagnoses of children were gathered [1,10-12]. Clinical diagnosis of hypertension was evaluated according to "American Academy of Pediatrics Clinical Practice Guideline" [13].

A pediatric nephrologist confirmed indications and evaluated the contraindications prior to biopsies [1]. "The British Association of Paediatric Nephrology" (BAPN) standards were followed as a standard preparation procedure [7,8]. Vital signs and oxygen saturations of the patients were monitored throughout the procedure [8]. Biopsies were performed in the treatment room on the ward to ease the patient transport to bed. Patients were placed in the prone position with a sandbag set under the abdomen for native kidney biopsies whereas transplanted patients laid supine. Kidneys were scanned with an USG machine (Toshiba Aplio 80 SSA-770A) using a 3.75 MHz transducer by the nephrologist to determine the optimal biopsy site. Lower pole of the left kidney in native or upper pole in the transplant kidney were regarded as the preferred biopsy sites. The area was set; then a small incision was made in the skin following prilocaine administration. Local sterility standards were adhered throughout the procedures. If needed, the child was sedated consciously with midazolam (0.05-0.6 mg/kg body weight) or additionally Ketamine (0.5–2 mg/kg body weight) only after the initial sedation. Biopsy was performed under general anesthesia in patients considered inappropriate for conscious sedation.

A single pediatric nephrologist performed all the biopsies using an automated spring-loaded biopsy gun (Bard Magnum US Patent 5.546.947) loaded with a 16 Gauge needle (16 G tru-cut Gallini BM Italy) under real-time USG guidance. Following infiltration of the anesthetic agent, the biopsy needle was advanced through the incision site with an approximately $30\text{-}40^0$ angle into the skin until the tip was seen pushing on the kidney at USG; subsequently the gun was fired and removed to check for tissue specimen. Two cores are obtained in native kidney biopsies and one core for the renal transplant patient [7,8,14]. The cores were immediately transferred in normal saline in Petri plates to a histopathologist who determined with a dissecting microscope whether enough glomeruli were present to enable a diagnosis to be made and allow proper division for light, immunofluorescence and electron microscopic studies.

An USG imaging was performed to assess post-procedure complications immediately after biopsy and repeated before discharge. Desmopressin acetate was administered in none of the cases. Following the procedure, the child was kept on 6-hour strict bed rest and monitored every 30 min (pulse and blood pressure) for 2 h and then hourly for a further 4 h and 2 hourly till discharge. A complete blood count was checked at 1^{st},

4th, 8th hours following the biopsy. Patients were allowed home after 24 h if they were fully conscious, free of pain, and were able to drink and pass urine without gross hematuria.

Sample size and location

In this study, an adequate biopsy was defined as one in which the pathologist could achieve a confident diagnosis, and generally included >10 glomeruli for native biopsy sampling [4,7,8,15,16]. However, an "adequate" specimen was defined as a biopsy with 10 or more glomeruli and at least two arteries, complying to Banff 97 criteria in a transplant biopsy [14].

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (IBM SPSS version 21.0). Descriptive statistics such as percentages and median were calculated. $P<0.05$ was considered of statistical significance.

Results

Throughout the study period, 32 biopsies were performed in 17 boys (53.1%) and 15 girls (46.9%); male to female ratio was 1.3:1. Median age of children included in the study was 14.5 years (min-max ages: 3-17 years). Among these, 5 children (15.6%) were aged ≤10 years, and 27 (84.4%) were aged between 11 and 17 years old. Median of body mass index (BMI) was 22.4 kg/m^2 (min-max=16.4-34.1). Median of hemoglobin (Hgb) was 10.8 gr/dl (min-max=9.3-13.9 gr/dl); median eGFR was 94.7 ml/min/1.73m^2 (min-max=11.1-131.1 ml/min/1.73m^2). Estimated GFR was <60 ml/min/1.73m^2 in 7/32 (21.9%) patients (30). Median s-albumin was 3.5 gr/dl (min-max= 1.6-4.8 gr/dl). Hypertension was diagnosed in 5 children on admission; 1 girl, 4 boys, and all were >10 years old (15.6%) (3/5 children: Stage 1 hypertension; 2/5 children: Stage 2 hypertension).

The clinical characteristics considered as a biopsy indication at the time of the biopsy are illustrated in Table 1. The most common indication for biopsy was nephrotic syndrome (NS) in 13 /32 children (40.6%). Only one female patient with FSGS who turned 10 (1/13 (7.6%)) among 13 children was steroid resistant at the time the decision for biopsy was made.

Table 1: Clinical characteristics at the time of renal biopsy

Clinical Characteristics	Cases total / percentage n=32/(%)
Proteinuria (UP/Cre ≥0.5g/g)[1]	7/(21.9%)
Hematuria[2]	6/(18.8%)
Nephrotic Syndrome[3]	13/(40.6%)
Acute Renal Failure	5/(15.6%)
Rapidly Progressive Glomerulonephritis	1/(3.1%)

[1] UP/Cre ≥0.5g/g or clinician marked proteinuria or nephritic syndrome [10], [2]u-Dipstick≥1 or clinician marked hematuria or nephritic syndrome, [3]UP/Cre>2mg/mg, 1g/m^2/d and s-albumin<35g/L or clinician marked nephrotic syndrome [11]

Local anesthesia, conscious sedation with local anesthesia and general anesthesia were performed in 31/32 (96.9%), 3/32(9.4%), and 1/32 (3.1%) patients respectively.

Median glomeruli number obtained from biopsy specimens was 18 (min-max=7-54 glomeruli). A diagnosis was achieved in all of 32 cases (100%) by a histopathologist, despite 2/32 (6.2%) cases from whom 7 glomeruli were obtained individually.

The distribution of histopathological diagnoses is illustrated in Table 2. Glomerulopathies were identified in most cases 25/32 (78.1%), tubulointerstitial nephritis and normal histology constituted the remaining 7/32 (21.9%) of tissue specimen examinations. The most common diagnoses were focal segmental glomerulosclerosis (FSGS), IgA nephropathy (IgAN) and membranous glomerulonephritis (MG), with 5/32 (15.6%) of cases individually.

Table 2: Histopathological Diagnosis following Renal Biopsy

	Histopathology	n (%)
Glomerulopathy	Minimal Change disease	3 (9.4%)
	Membranous GN	5(15.6%)
	FSGS	5(15.6%)
	Membranoproliferative GN	1(3.1%)
	IgM Nephropathy	1(3.1%)
	IgA Nephropathy	5(15.6%)
	Alport syndrome	2(6.4%)
	Acute T cell rejection	1(3.1%)
	Crescentic GN	1(3.1%)
	Postinfectious GN	1(3.1%)
Miscellaneous	TIN	3 (9.4%)
	Normal histology	3(9.4%)
	Juvenile Nephronophthisis	1(3.1%)
	Total	32 (100%)

During the follow-up on the ward, median Hgb levels obtained from patients at the 1st, 4th and 8th hours were 10.8, 10.4, 10.8 gr/dl respectively, neither a statistically significant Hgb descent nor a major complication requiring blood transfusion was seen ($P>0.05$). The only complication due to the procedure was observed in a 16-year-old boy with an eGFR of 28.6 ml/min/1.73m^2 and Stage 1 hypertension had lost his cooperation at the time the biopsy gun had fired. He suffered from gross hematuria (3.1%) in only one urination episode without Hgb descent. Additionally, a 10 mm subcapsular hematoma was observed on ultrasound scene just after the biopsy resolved spontaneously in a week. All patients were discharged after 24 hours, without readmissions due to complications.

Discussion

Herein, an experience of real-time ultrasound-guided PRB with an automated spring-loaded biopsy gun in children by a pediatric nephrologist is presented with the data regarding indications, safety, and efficiency of kidney biopsy, as well as histopathologic diagnoses achieved. Our unit was established in January 2015, hence the patients included in this study were mostly among new admissions and the figures of kidney biopsies were limited compared to populations reported from some prior clinics [1,6].

A quick glance at the demography of the study sample reveals a slight male predominance (1.3:1) that was comparable to sex-specific differences in prevalence reported previously [17,18]. Lee et al. [17] and Printza et al. [18] stated that around half of children who underwent kidney biopsy in their series were under 11 years of age; however, minority of our cases (15.6%) were under 11. The limited study population or abundance of first admissions might contribute to such a discrepancy.

The major indication for kidney biopsy was NS (40.6%) among the study population, in accordance with the previous reports [1,5,17,18]. Printza et al. reported NS as the main indication (34.5%), whereas Tondel et al. not only pointed out the higher frequency of NS (40.1%), but also represented proteinuria (79.3%) as the primary reason for biopsy in Norwegian children [1,18]. However, hematuria was claimed as a leading indication in some reports [5,17]. Hematuria was the third frequent indication following proteinuria in our study.

There is paucity of data regarding the efficiency of biopsy guns and PRB outcomes in children [3,7,16]. Automated

biopsy gun offers an easier, single-step and faster and effective technique to obtain kidney tissue in children. Because of the speed of cutting and the more tightly packed glomeruli nature of child kidney, a rapid–firing biopsy gun allows superior yield with less tissue damage with even smaller-bore needles [3,7,16]. With real-time USG guidance, the ability to obtain adequate renal tissue for a diagnosis rose >95% of renal biopsies performed by a biopsy gun [4,5]. Whittier et al. reported a perfect diagnostic yield, constituting 92% of 767 native and 885 of 938 renal transplant biopsies including 10 glomeruli or more, with sufficient tissue for making a diagnosis in over 99% of cases [19]. Pongsittisak et al. [20] recently reported superior yield with real-time USG-guided PRB compared to blind PRB. A diagnosis was achieved in all children (100%) included in our study, with a perfect diagnostic yield in 93.8% and a sufficient tissue obtained in 6.2% of biopsies, indicating a higher diagnostic efficiency of the technique.

Kidney biopsy is crucial in the research of renal diseases, changing the initial clinical diagnosis in more than 50% and therapy in 30% of cases [4,5,21]. Glomerulopathies were the major diagnosis (78.1%), enabling proper treatments and managements in our study, compatible with figures of Printza et al. (80%). The frequencies of histopathologic diagnoses in this study were comparable with the literature reporting IgAN as the most prevalent form of GN worldwide [17].

Besides its superior diagnostic competence and safety, PRB guided by real-time USG is not complication free. Among several complications after renal biopsy, macroscopic hematuria and perirenal hematoma are the most common [19,22,23]. However, Tondel et al. reported percentage of gross hematuria in children as 1.7% and stated that frequency of hematoma was higher in children (8.1%) than adults (3.5%, $P<0.001$), becoming more evident with a rate of 18.9%, during the latest years of the study [1]. Significant bleeding and major complication rates were reported as 4-7% on average, up to 25% and 5.9% of biopsies respectively [4,19,24,25]. There have been conflicting reports indicating bleeding complications were observed more often with 14 and 18 gauge needles [1,5,26]. There are also anomalous essays on effects of biopsy technique over complications, giving hassle to interpret among studies [20]. In this study 16-gauge needles were preferred due to smaller sample size with less diagnostic success of 18-G with a spring–loaded automatic gun under real-time USG in all biopsies [26]. Gross hematuria rate (3.1%) in the study population was slightly lower than the average rate of bleeding complications reported [2]. Similarly, our hematoma ratio was 3.1%, far lower than the figures reported [1]. It might be inaccurate to interpret our data confidently due to the limited sample size.

Advancements in biopsy technique might not stave off risk factors provoking adverse outcomes. Lower Hgb levels in patients with acute kidney injury (AKI), eGFR <60ml/min per 1.73 m^2, systolic hypertension, acute renal failure and smaller clinical size (<30 biopsies/yr) were represented among risk factors for major complications of kidney biopsy. It was reported that the more eGFR declined below 60ml/min per 1.73 m^2, the more tendency for a complication rose; even up to 16 fold when compared with cases with an eGFR>60 ml/ min per 1.73m^2 [2,4,22]. However, although median of Hgb was 10.8 gr/dl, and almost one-fifth of the study population had an eGFR<60 ml min per 1.73m^2 and about 15% were hypertensive, no major complication was seen [1]. Only a self-limited minor complication of macroscopic hematuria episode with subcapsular hematoma was observed in a 16-year-old boy with Stage1 hypertension and an eGFR<30 ml min per 1.73m^2 among the study sample, which was comparable with the reported risk factors [4]. However, a transplant kidney biopsy performed in a 16-year-old boy with an eGFR=11.1ml/min per 1.73m^2 was free from complications. Performing a single needle pass might have accounted for, if any correlation had been reported between the number of passes and complications [1,23,27].

In addition, performing the biopsy on ward was convenient as it eased patient transport. Secondly, real-time USG guidance ensured the confidence achieved with continuous visualization of the needle position in the renal parenchyma and finally, automated biopsy gun shortened biopsy time, providing superior tissue specimen. Since over a third of complications might be detected beyond 8h in patients undergoing native biopsy we observed our patients on ward for 24 h [27].

There has been an ongoing debate over whom the biopsy should be performed by: A nephrologist or a radiologist? Korbet considered the development of the PRB among major technical advancements leading to nephrology becoming a sub-specialty. Although a renal biopsy is regarded among essential skills of pediatric nephrology, there has been an alarming decrease in the number of biopsies done by nephrologists lately [1,2]. Tondel et al. [1] stated that only one third of biopsies were was performed by a nephrologist. Performing PRB has been neglected in fellow curriculum in some centers, subjecting young colleagues to quiz their position as a sub-specialist and dissatisfaction with their career choice. However, a nephrologist is principally responsible from the histopathologic diagnoses provided by the biopsy, directly affecting the care provided for patients.

Conclusion

To sum up, this study claims that real-time USG-guided PRB with an automated biopsy gun is a safe, easy, and quick technique, providing superior yield in kidney biopsies in children. In our study population, its efficacy to reach a diagnosis was high and complication rate was lower than previously reported [1,4]. Acknowledging its limited population size, this study is sort of a challenge, aspiring to call attention to the importance of performing nephrology related skills by nephrologists. Nephrologists should consider kidney biopsy among the principal tools in their workshop, deserving to be embraced tightly.

References

1. Tondel C, Vikse BE, Bostad L, Svarstad E. Safety and complications of percutaneous kidney biopsies in 715 children and 8573 adults in Norway 1988-2010. Clin J Am Soc Nephrol. 2012;7:1591-7.
2. Korbet SM. Nephrology and the Percutaneous Renal Biopsy: A Procedure in Jeopardy of Being Lost Along the Way. Clin J Am Soc Nephrol. 2012;7:1545–7.
3. Poster RB, Jones DB, Spirt BA. Percutaneous Pediatric Renal Biopsy: Use of the Biopsy Gun. Radiology. 1990;176:725-7.
4. Hogan JJ, Mocanu M, Berns JS. The native kidney biopsy: Update and evidence of best practice Clin J Am Soc Nephrol. 2016;11:354-62.
5. Golay V, Roychowdhury A. The percutaneous native kidney biopsy: a nephrologist's perspective. OA Nephrology. 2013;May 27;1:8.
6. Franke M, Kramarczyk A, Taylan C, Maintz D, Hoppe B, Koerber F. Ultrasound- Guided Percutaneous Renal Biopsy in 295 Children and Adolescents: Role of Ultrasound and Analysis of Complications. PLoS ONE. 2014;9(12):e114737. doi:10.1371/journal.pone.0114737.

7. Hussain F, Mallik M, Marks SD, Watson AR, British Association of Paediatric Nephrology. On behalf of the British Association of Paediatric Nephrology. Renal biopsies in children: current practice and audit of outcomes. Nephrol Dial Transplant. 2010;25:485–9.
8. Hussain F, Watson A, Hayes J, Evans J. Standards for renal biopsies; comparison of inpatient and day care procedures. Pediatr Nephrol. 2003;18:53-6.
9. Gupta S, Wallace MJ, Cardella JF, Kundu S, Miller DL, Rose SC. Quality improvement guidelines for percutaneous needle biopsy. J Vasc Interv Radiol. 2003;14(Suppl):S227-S30.
10. Hama T, Nakanishi K , Shima Y, Mukaiyama H, Togawa H, Tanaka R, et al. Renal biopsy criterion in children with asymptomatic constant isolated proteinuria . Nephrol Dial Transplant. 2012;27:3186–90.
11. Gattineni J. Highlights for the Management of a Child with Proteinuria and Hematuria. International Journal of Pediatrics. 2012;768142:1-7.
12. Schwartz GJ and Work DF. Measurement and estimation of GFR in children and adolescents. J Am Soc Nephrol. 2009;4:1832-43.
13. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR et al. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics. 2017;140(3):e20171904.
14. Racusen LC, Solez K, Colvin RB, Bonsib SM, Castro MC, Cavallo T, et al. The Banff 97 working classification of renal allograft pathology. Kidney International. 1999;55:713-23.
15. Fogo AB. Approach to renal biopsy. AJKD. 2003;Vol 42: No4 (October).
16. Esposito V, Mazzon G, Baiardi P, Toreggiani M, Semeraro L, Catucci D et al. Safety and adequacy of percutaneous kidney biopsy performed by nephrology trainees. BMC Nephrology. 2018;19:14.
17. Lee SA, Kim MS, Kim SC, Lee DY. Clinical and Pathological Findings of Renal Biopsy in Children: Outcomes from a Single Center Over 27 Years Child Kidney Dis. 2017;21:8-14.
18. Printza N, Bosdou J, Pantzaki A, Badouraki M, Kollios K, Ghogha Ch, et al. Percutaneous ultrasound-guided renal biopsy in children: a single centre experience. Hippokratia. 2011;15;258-61.
19. Whittier WL, Gashti C, Saltzberg S, Korbet S. Comparison of native and transplant kidney biopsies: diagnostic yield and complications. Clin Kidney J. 2018;11:616–22.
20. Pongsittisak W, Wutilertcharoenwong N, Ngamvichchukorn T, Kurathong S, Chavanisakun C, Teepprasan T, et al. The efficacy of blind versus real-time ultrasound-guided percutaneous renal biopsy in developing country. SAGE Open Medicine. 2019;7:1-7.
21. Turner MW, Hutchinson TA, Barre PE, Jothy S. A prospective study on the impact of renal biopsy in clinical management. Clin Nephrol. 1986;26:217-21.
22. Korbet SM, Gashti CN, Evans JK, Whittier WL. Risk of percutaneous renal biopsy of native kidneys in the evaluation of acute kidney injury. Clinical Kidney Journal. 2018;11;610–5.
23. Sethi I, Brier M, Dwyer A. Predicting post renal biopsy complications Semin Dial. 2013;26:633-5.
24. Korbet SM. Percutaneous renal biopsy. Semin Nephrol. 2002;22:254-67.
25. Lees JS, McQuarrie EP, Mackinnon B. Renal biopsy: it is time for pragmatism and consensus. Clinical kidney Journal. 2018;11:605-9.
26. Nicholson ML, Wheatley TJ, Doughman TM, White SA, Morgan JD, Veitch PS, et al. A prospective randomized trial of three different needle for renal transplant biopsy. Kidney Int. 2000;58:390-5.
27. Gupta A, Smith JC, Hayes W, Deal JE, Gilbert RD, Inward C, et al. Positive trends in paediatric renal biopsy service provision in the UK: a national survey and re-audit of paediatric renal biopsy practice. Pediatr Nephrol. 2016;31:613-21.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1182-1185.
DOI: 10.28982/josam.755934

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

An evaluation of treatment options for lateral epicondylitis

Lateral epikondilitte tedavi seçeneklerinin değerlendirilmesi

Burç Özcanyüz [1], Hasan Ulaş Oğur [1], Fırat Seyfettinoğlu [1], Mehmet Baydar [2], Fırat Ozan [3], Salih Müjde [4]

[1] Clinic of Orthopedic Surgery, Adana City Training and Research Hospital, Adana, Turkey
[2] Clinic of Orthopedic Surgery, Baltalimani Metin Sabanci Bone and Joint Diseases Education and Research Hospital, İstanbul, Turkey
[3] Clinic of Orthopedic Surgery, Kayseri City Training and Research Hospital. Kayseri, Turkey
[4] Department of Orthopedic Surgery, İzmir Tınaztepe University, İzmir, Turkey

ORCID ID of the author(s)
BÖ: 0000-0002-9938-0749
HUO: 0000-0002-0534-7068
FS: 0000-0002-5218-1072
MB: 0000-0002-1020-1207
FO: 0000-0002-2417-8343
SM: 0000-0003-1903-2857

Corresponding author/Sorumlu yazar:
Burç Özcanyüz
Address/Adres: Clinic of Orthopedic Surgery, Adana City Training and Research Hospital, Yüreğir, 01230 Adana, Turkey
E-mail: burcozcanyuz@gmail.com

Ethics Committee Approval: Ethics committee of Adana City Research and Educational Hospital, decision no: 413, date: 27/03/2019. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Adana Şehir Eğitim ve Araştırma Hastanesi Etik Kurulu, karar no: 413, tarih: 27/03/2019. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: Lateral pain in the elbow is a widespread problem in orthopedics and physiotherapy. There are different conservative treatment options available, but there is no consensus on their superiority to each other. The aim of this study was to evaluate the efficacy of three different treatment methods applied to patients followed up with a diagnosis of lateral epicondylitis.

Methods: The study included a total of 105 patients who were diagnosed with lateral epicondylitis between 2010 and 2016 and treated conservatively. The patients were separated into three groups according to the treatment administered. In Group 1 (n:28), 1 ml betamethasone dipropionate (Diprospan®, Schering-Plough Corp., Kenilworth, NJ, ABD) was applied with the peppering method. In Group 2 (n:28), the same peppering method was used to apply 1 ml local anesthetic (prilocaine hydrochloride, Citanest®, AstraZeneca plc., London, UK). In Group 3 (n:49), extracorporeal shockwave therapy (ESWT) treatment was performed. Data were evaluated before and at one, three, and six months after treatment. Clinical scores were evaluated according to the Quick Dash (Q-DASH, Quick disabilities of arm, shoulder, and hand) scoring system and VAS (visual analog scale) scores during the daily activities of the patients. Quality of life and patient satisfaction levels were evaluated based on Quick Dash scores.

Results: A significant improvement was observed in all three methods in the VAS and quality of life of the patients at one, three, and six months after treatment compared to pre-treatment values (P<0.001). A higher level of patient satisfaction was determined in Groups one and two compared to the ESWT group (P<0.001).

Conclusion: Significant rates of satisfaction were determined in all three methods, and the corticosteroid treatment administered with the peppering method was not superior over local anesthetic applied with the same method. Although ESWT was beneficial, it was less effective than the other methods and cost higher.

Keywords: Lateral elbow pain, peppering, ESWT

Öz

Amaç: Dirsek yan ağrısı, ortopedi ve fizik tedavi pratiğinde sık karşılaşılan bir problemdir. Farklı konservatif tedavi seçenekleri mevcut olup, birbirlerine üstünlükleri konusunda fikir birliği yoktur. Bu çalışmada lateral epikondilit tanısıyla takip edilen hastalarda üç farklı tedavi yönteminin etkinliğini değerlendirilmek amaçlanmıştır.

Yöntemler: 2010-2016 yılları arasında lateral epikondilit tanısıyla takip edilen ve konservatif olarak tedavi edilen 105 hasta çalışmaya dahil edildi. Hastalar yapılan tedavi metoduna göre 3 gruba ayrıldı. Birinci gruptaki 28 hastaya 1 ml betametazon dipropiyonat (Diprospan®, Schering-Plough Corp., Kenilworth, NJ, ABD), ikinci gruptaki 28 hastaya sadece 1 ml lokal anestezik prilokain hidroklorür (Citanest®, AstraZeneca plc., Londra, Birleşik Krallık), aynı yöntemle 30-40 kez iğne ucu ciltten çıkarılmadan aynı bölgeye batırılıp çıkarılarak (peppering yöntemiyle) uygulandı. Üçüncü gruptaki 49 hastaya Ekstrakorporeal şok dalga terapisi (ESWT) tedavisi uygulandı. Tedavi öncesi ve 1. 3. ve 6. aydaki veriler değerlendirildi. Klinik skorlar Quick Dash (Q-DASH, Quick disabilities of arm, shoulder and hand) skorlama sistemine göre değerlendirilerek, hastaların günlük yaşam aktiviteleri sırasındaki VAS (Visual Analog Scale) skorlarına bakıldı. Yaşam kalitesi ve hasta memnuniyeti düzeyleri Quick Dash skorlarına göre değerlendirildi.

Bulgular: Her üç yöntemde tedavi sonrası birinci ay, üçüncü ay ve altıncı aydaki VAS skorunda ve hastanın yaşam kalitesinde tedavi öncesine göre anlamlı olarak iyileşme gözlendi (P<0,001). İlk iki grupta ESWT grubuna göre daha yüksek hasta memnuniyet oranı tespit edildi (P<0,001).

Sonuç: Her üç yöntem içinde anlamlı memnuniyet oranları ile karşılaşılmış olup, peppering yöntemiyle uygulanan kortikosteroid (KS) tedavisinin aynı yöntemle uygulanan lokal anesteziklere üstünlüğü olmadığı görülmüştür. Üçüncü yöntemin (ESWT) faydalı olduğu görülse de diğerlerine göre daha az etkili olduğu ve daha maliyetli olduğu sonucuna varıldı.

Anahtar kelimeler: Lateral dirsek ağrısı, Peppering, ESWT

How to cite/Atıf için: Özcanyüz B, Oğur HU, Seyfettinoğlu F, Baydar M, Ozan F, Müjde S. An evaluation of treatment options for lateral epicondylitis. J Surg Med. 2020;4(12):1182-1185.

Introduction

Lateral epicondylitis (LE) is the most diagnosed cause of elbow pain, which progresses with degeneration following repeated trauma or overuse of the forearm extensors attached over the lateral epicondyle in the elbow [1]. Although the incidence of LE is equal in males and females, it is observed more in the working age group and most often between the 3rd and 5th decades [2,3]. Despite the common name "tennis elbow," tennis players only constitute 10% of patients in clinical practice [4]. Degeneration develops at the tendon adhesion site associated with repeated microtrauma, and this is defined as tendinosis [5]. Treatment of this frequently encountered problem is firstly conservative [6,7]. In current LE treatment, several treatment forms are recommended starting with simple local injections and extending as far as complex surgical techniques. However, as LE can be self-limiting, the majority of studies has been conducted with short follow-up periods and because of the presence of several factors that can affect the results and insufficient physiological data, enough evidence does not exist to demonstrate which treatment method is better than the others [8].

The aim of this study was to retrospectively evaluate the efficacy of the 3 different techniques, namely, local corticosteroid injection and local anesthetic injection with the peppering technique, along with extracorporeal shockwave therapy in patients with LE.

Materials and methods

The study included a total of 105 patients diagnosed with lateral epicondylitis (LE) between 2010 and 2016. The patients were randomly separated into treatment groups and the data were examined retrospectively, after approval was obtained from the Ethics committee of Adana City Research and Educational Hospital (decision no.: 413 date: 27/03/2019). Consent forms were obtained from all patients, which consisted of 52 males and 53 females with a mean age of 44.6 years (range: 20-72 years). Inclusion criteria were defined as sensitivity with palpation over the lateral epicondyle of the elbow, positive wrist extension test with the elbow in extension, and that the patient had received anti-inflammatory treatment various times for at least 3 months. Patients were excluded from the study if they had a history of elbow trauma or cervical discopathy, medial epicondylitis, radial tunnel syndrome, rheumatoid arthritis, systemic diseases such as diabetes mellitus, had undergone surgery for LE, or received an injection within the previous 6 months. One patient in the corticosteroid group received physical therapy for 3 weeks and 1 patient received epicondylitis bandage treatment. Two and five patients had received physical therapy in the local anesthetic and ESWT groups, respectively.

Data were evaluated before treatment and at one, three, and six months after treatment. Clinical scores were evaluated according to the Quick Dash (Q-DASH, Quick disabilities of arm, shoulder and hand) scoring system and VAS (visual analog scale) scores during the daily activities of the patients.

Group 1 included 28 patients (15 male, 13 female) who were administered 1 ml betamethasone dipropionate (Diprospan®, Schering-Plough Corp., Kenilworth, NJ, USA), and Group 2 included 28 patients (18 male, 10 female) who received 1 ml prilocaine hydrochloride (Citanest®, AstraZeneca plc., London, UK). The mean follow-up period was 8.4 months (range, 6-12 months).

Technique

In Groups 1 and 2, the most sensitive point over the LE was identified, and the injection was made over and around the epicondyle by injecting, withdrawing, redirecting, and reinserting the needle 30-40 times without completely removing it from the skin.

In Group 3 (n:49, 19 males, 30 females), ESWT treatment was performed 3 times at weekly intervals (2000 impulse, 1.8 bar, 15 Hz frequency).

The demographic data of the 3 groups are shown in Table 1.

LE was determined in the right elbow in 25 cases and the left elbow in 3 in Group 1, in the right elbow in 21 and the left elbow in 7 in Group 2, and in the right elbow in 35 and the left elbow in 14 in Group 3.

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS v21 software. Conformity of the data to normal distribution was assessed with the Shapiro Wilk test. In the comparison of age, VAS and DASH scores between the ESWT, corticosteroid and local anesthetic groups, One-Way Analysis of Variance (ANOVA) and post-hoc Tukey tests were used. Chi-square test was applied when examining the distribution of gender and affected side. $P<0.05$ was considered statistically significant.

The study consisted of three groups with four measurements for each group. Taking the time-group interaction into account, we planned to include at least 101 patients in the study with a partial eta-square of 0.02, 5% type 1 error, 80% power and a correlation of at least 0.40 between the measurements. The computations were carried out with G*power.

Results

According to the Quick-DASH (Q-DASH) scoring system, the mean scores in Group 1 were 56.3 pre-treatment and 15.7 at 6 months post-treatment, in Group 2, 56.5 pre-treatment and 14.6 at 6 months post-treatment, and in Group 3, 60.8 pre-treatment and 29.1 at 6 months post-treatment. The treatments were effective in all 3 groups. The changes in Q-DASH and VAS scores at 1, 3, and 6 months after treatment are shown in Table 2. Statistically significant results were obtained in all 3 methods. The change showing treatment efficacy was lower in Group 3 (EWST) than in Groups 1 and 2. Statistically significant differences were determined between the groups with regards to 6-month VAS values ($P<0.001$), more specifically, between EWST and corticosteroid group ($P=0.001$) and between the EWST and local anesthetic group ($P=0.002$). A statistically significant difference was determined between the groups with respect to the Q-DASH scores at 6 months after treatment ($P<0.001$) between the EWST and corticosteroid group ($P<0.001$) and between the EWST and local anesthetic group ($P<0.001$). No statistically significant difference was determined between the corticosteroid and local anesthetic groups with

respect to the VAS and Q-DASH scores (P=0.997). The Q-DASH scores of the patients are shown in Figure 1.

Table 1: Demographic data of the patients according to gender and affected side

		Groups			
Gender	Steroid	Local anesthetic	ESWT	Total	*P*-value
Female	13 (48.1%)	10 (35.7%)	30 (61.2%)	53 (50.5%)	0.087
Male	15 (53.6%)	18 (64.3%)	19 (38.8%)	52 (49.5%)	
Total	28 (100.0%)	28 (100.0%)	49 (100.0%)	105 (100.0%)	
		Groups			
Side	Steroid	Local anesthetic	ESWT	Total	*P*-value
Right	25 (89.3%)	21 (75.0%)	35 (71.4%)	81 (77.1%)	0.190
Left	3 (10.7%)	7 (25.0%)	14 (28.6%)	24 (22.9%)	
Total	28 (100.0%)	28 (100.0%)	49 (100.0%)	105 (100.0%)	

Table 2: The change in clinical scores according to the treatment results

Q-DASH scores	Steroid	Local anesthetic	ESWT	*P*-value
	Mean (SD)	Mean (SD)	Mean (SD)	
Pre-treatment	56.34 (8.56)	56.52 (10.28)	60.84 (11.42)	0.102
1st month	26.69 (16.02)	26.46 (17.95)	37.16 (16.54)	0.007
3rd month	16.10 (10.55)	16.37 (11.39)	33.18 (16.39)	<0.001
6th month	15.78 (10.30)	14.62 (11.36)	29.19 (17.23)	<0.001
P-value	<0.001	<0.001	<0.001	
General *P*-value	0.008			
VAS values	Steroid	Local anesthetic	ESWT	*P*-value
	Mean (SD)	Mean (SD)	Mean (SD)	
Pre-treatment	6.50 (1.11)	6.54 (1.20)	7.18 (1.70)	0.065
1st month	2.93 (2.02)	2.79 (2.35)	4.27 (2.15)	0.005
3rd month	1.79 (1.34)	1.82 (1.56)	3.88 (2.06)	<0.001
6th month	1.72 (1.46)	1.76 (1.32)	3.35 (2.12)	<0.001
P-value	<0.001	<0.001	<0.001	
General *P*-value	0.048			

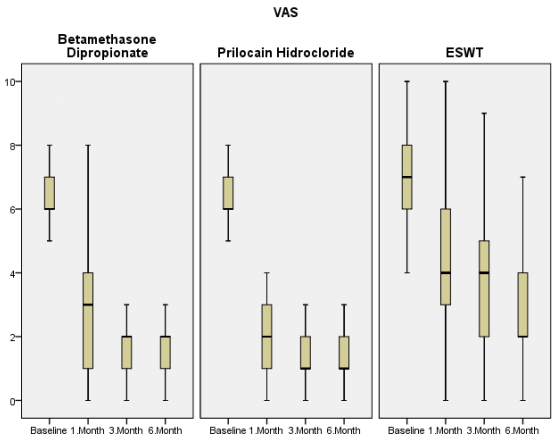


Figure 1: Schematic form of the Q-DASH scores of the 3 patient groups according to time

Discussion

Lateral epicondylitis (tennis elbow) which presents with pain and function loss, is associated with degenerative changes that develop secondary to mechanical pain and loading at the adhesion site of the extensor muscles, particularly of the carpi radialis brevis to the bone [3-10]. In biopsies taken from this region, acute inflammatory cells, no inflammation, vascular hyperplasia, disorganized collagen bundles and intense fibroblast clusters are observed, all of which is known as angiofibroblastic degeneration (tendinosis) [5,11,12].

Many different methods have been described in LE treatment [3,8,12]. Starting with corticosteroid injection, several methods such as platelet-rich plasma (PRP) and autologous blood transfusion, physical therapy, and shockwaves (ESWT) have been recommended in literature [3,8,9,12,13].

To the best of our knowledge, there has been no previous study which has compared the ESWT method with local anesthetic only, and steroid therapy without local anesthetic, applied with the peppering method.

Several studies have reported that the application of corticosteroid (triamcinolone) is the most preferred method in the treatment of tennis elbow and the best option in the short term [3,8,12-14].

In a randomized, controlled study of 146 patients by Hay et al. [15], steroid was more effective than placebo or naproxen in the first 4 weeks, but in the 12th month, no difference was found between the 3 groups. Smidt et al. [16] compared the 3 separate methods of corticosteroid, physical therapy, and a watch-and-wait policy, and while the best result was obtained in the steroid group in a 6-week period, this was the group with the most recurrences in the long term. In the current study, the best results were obtained in Groups 1 and 2 (corticosteroid and local anesthetic) in the early period (first month). In a study by Bisset et al. [12] and a review of 17 studies by Combes et al [17], corticosteroid treatment was more effective than other methods in the reduction of pain in the short term, but this effect was reversed in the long term.

Yi et al. [18] also reported that corticosteroid was as effective as deep friction massage in the short term (4 weeks), but in the long term (6 months), deep friction massage was the best method. In a meta-analysis of 6 high-quality, randomized, controlled studies, Orchard et al. stated that after 3 months, corticosteroid was harmful compared to a placebo injection or conservative treatment. The authors stated that there was no high-quality review showing the opposite, and therefore recommended that it not be used considering the mid-term harm rather than the short-term benefit [19].

In the current study, corticosteroid and local anesthetic treatment were administered with different methods of the peppering technique, in which the needle is injected, withdrawn and re-inserted 30-40 times with the aim of increasing blood flow. The effective results seen in the early period (4 weeks) was observed to persist at 6 months with this technique. The peppering technique increases the surrounding bleeding, which potentially increases the healing process. In the studies of Kraushaar et al. [5] and Regan et al. [20], the peppering technique was used, and the bleeding in the degenerative myxoid tissue of patients with epicondylitis triggered the healing process by creating new channels.

Injection treatment can be applied in the form of a single injection to the epicondyle region or by inserting and withdrawing the needle 30-40 times to the origin of the extensor muscles in the lateral epicondyle region [21-24]. In the current study, peppering technique was applied to Groups 1 and 2, and effective results were obtained within a 6-month period.

In a study by Okcu et al. [22], corticosteroid and local anesthetic combined were applied with the peppering technique and as a single injection, and it was shown that in the long-term, the same combination of drugs administered with a peppering technique was relatively more effective. In another study by Dogramaci et al [23], local corticosteroid injection administered with the peppering technique was reported to provide more successful results than corticosteroids administered with the classic technique or a single local anesthetic administered with the peppering technique. Altay et al. [24] applied local anesthetic only and a combination of local anesthetic and corticosteroid (lidocaine+triamcinolone) with the peppering technique and reported a high success rate with both methods at the end of the first year.

In contrast to the results of those studies, no difference was determined in the results of the present study between the application of local anesthetic only and steroid treatment only, both applied with the peppering technique. Compared to ESWT, the results were better. The improvements in VAS and Q-DASH scores at 1 and 3 months (early term) were more advanced than those of ESWT at 6 months, which can be considered mid-term.

There are many studies that have reported that ESWT is effective in the treatment of lateral epicondylitis [25-31]. In a study that compared ESWT with corticosteroid treatment, it was emphasized that although ESWT was beneficial, it was less effective than steroid treatment and more costly [32]. Some studies have reported that it has the same effect as a placebo [33-36]. Aydin et al. [37] compared ESWT and wrist extensor splints and reported that successful results were obtained with both methods.

Although effective results were obtained with ESWT treatment in the current study, the success rate was more limited than that of the other two methods. When the ESWT treatment group was evaluated over the study period, a statistically significant improvement was seen in the clinical scores, and improvement became more pronounced as time progressed. The efficacy at 3 months was greater than at the first month, and a greater improvement was seen in the clinical scores at 6 months.

Limitations

There were numerous limitations to our study. First, the patients were randomly divided into groups. The number of patients participating in the study was sparse. Radiological criteria were not included in the study and follow-up period was not long enough.

Conclusion

For the optimal treatment of lateral epicondylitis, it is important to interpret the scientific evidence. By combining this with experience and the facilities available, an evidence-based, appropriate choice should be made for the patients. The results of this study demonstrated that in the application of an injection, the outcome was attributed more to the technique of peppering rather than the drug. Patient preference should also be taken into consideration when selecting the treatment method. Nevertheless, there is a need for further, well-planned, high-quality, randomized, controlled studies which follow the natural course of the disease to be able to determine the most effective treatment.

References

1. Vicenzino B, Wright A. Lateral epicondylalgia I: epidemiology, pathophysiology, aetiology and natural history, Physical Therapy Reviews. 1996;1(1):23-34. doi: 10.1179/ptr.1996.1.1.23
2. Allander E. Prevalence, incidence, and remission rates of some common rheumatic diseases or syndromes. Scand J Rheumatol. 1974;3(3):145-53. doi: 10.3109/03009747409097141. PMID: 4428194.
3. Gündüz R, Malas FÜ, Borman P, Kocaoğlu S, Özçakar L. Physical therapy, corticosteroid injection, and extracorporeal shock wave treatment in lateral epicondylitis. Clinical and ultrasonographical comparison. Clin Rheumatol. 2012 May;31(5):807-12. doi: 10.1007/s10067-012-1939-y. Epub 2012 Jan 27. PMID: 22278162.
4. Kane SF, Lynch JH, Taylor JC. Evaluation of elbow pain in adults. Am Fam Physician. 2014 Apr 15;89(8):649-57. PMID: 24784124.
5. Kraushaar BS, Nirschl RP. Tendinosis of the elbow (tennis elbow). Clinical features and findings of histological, immunohistochemical, and electron microscopy studies. J Bone Joint Surg Am. 1999 Feb;81(2):259-78. PMID: 10073590.
6. Hong QN, Durand MJ, Loisel P. Treatment of lateral epicondylitis: where is the evidence? Joint Bone Spine. 2004 Sep;71(5):369-73. doi: 10.1016/j.jbspin.2003.05.002. PMID: 15474386.
7. Barrington J, Hage W. Lateral epicondylitis (tennis elbow): nonoperative, open, or arthroscopic treatment?. Current Opinion in Orthopaedics. 2003;14:291–5. doi: 10.1097/00001433-200308000-00013.
8. Labelle H, Guibert R, Joncas J, Newman N, Fallaha M, Rivard CH. Lack of scientific evidence for the treatment of lateral epicondylitis of the elbow. An attempted meta-analysis. J Bone Joint Surg Br. 1992 Sep;74(5):646-51. doi: 10.1302/0301-620X.74B5.1388172. PMID: 1388172.
9. Buchbinder R, Green SE, Struijs P. Tennis elbow. BMJ Clin Evid. 2008 May 28;2008:1117. PMID: 19450309; PMCID: PMC2907994.
10. Shergill R, Choudur HN. Ultrasound-Guided Interventions in Lateral Epicondylitis. J Clin Rheumatol. 2019 Apr;25(3):e27-e34. doi: 10.1097/RHU.0000000000000879. PMID: 30074911.
11. Khan KM, Cook JL, Taunton JE, Bonar F. Overuse tendinosis, not tendinitis part 1: a new paradigm for a difficult clinical problem. Phys Sportsmed. 2000 May;28(5):38-48. doi: 10.3810/psm.2000.05.890. PMID: 20086639.
12. Bisset L, Beller E, Jull G, Brooks P, Darnell R, Vicenzino B. Mobilisation with movement and exercise, corticosteroid injection, or wait and see for tennis elbow: randomised trial. BMJ. 2006 Nov 4;333(7575):939. doi: 10.1136/bmj.38961.584653.AE. Epub 2006 Sep 29. PMID: 17012266; PMCID: PMC1633771.
13. Price R, Sinclair H, Heinrich I, Gibson T. Local injection treatment of tennis elbow--hydrocortisone, triamcinolone and lignocaine compared. Br J Rheumatol. 1991 Feb;30(1):39-44. doi: 10.1093/rheumatology/30.1.39. PMID: 1991216.
14. Sölveborn SA, Buch F, Mallmin H, Adalberth G. Cortisone injection with anesthetic additives for radial epicondylalgia (tennis elbow). Clin Orthop Relat Res. 1995 Jul;(316):99-105. PMID: 7634730.
15. Hay EM, Paterson SM, Lewis M, Hosie G, Croft P. Pragmatic randomised controlled trial of local corticosteroid injection and naproxen for treatment of lateral epicondylitis of elbow in primary care. BMJ. 1999 Oct 9;319(7215):964-8. doi: 10.1136/bmj.319.7215.964. PMID: 10514160; PMCID: PMC28251.
16. Smidt N, van der Windt DA, Assendelft WJ, Devillé WL, Korthals-de Bos IB, Bouter LM. Corticosteroid injections, physiotherapy, or a wait-and-see policy for lateral epicondylitis: a randomised controlled trial. Lancet. 2002 Feb 23;359(9307):657-62. doi: 10.1016/S0140-6736(02)07811-X. PMID: 11879861.
17. Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: a systematic review of randomised controlled trials. Lancet. 2010 Nov 20;376(9754):1751-67. doi: 10.1016/S0140-6736(10)61160-9. Epub 2010 Oct 21. PMID: 20970844.
18. Yi R, Bratchenko WW, Tan V. Deep Friction Massage Versus Steroid Injection in the Treatment of Lateral Epicondylitis. Hand (N Y). 2018 Jan;13(1):56-59. doi: 10.1177/1558944717692088. Epub 2017 Feb 1. PMID: 28719982; PMCID: PMC5755866.
19. Orchard JW, Vicenzino B. Cortisone injections for tennis elbow should be an "avoid", rather than a recommended procedure. Med J Aust. 2017 Nov 20;207(10):453. doi: 10.5694/mja17.00445. PMID: 29129178.
20. Regan W, Wold LE, Coonrad R, Morrey BF. Microscopic histopathology of chronic refractory lateral epicondylitis. Am J Sports Med. 1992 Nov-Dec;20(6):746-9. doi: 10.1177/036354659202000618. PMID: 1280910.
21. Okcu, G. & Yercan, H.S. & Öziç, U.. (2002). The comparison of single dose versus multi-dose local corticosteroid injections for tennis elbow. J Arthroplasty Arthroscopic Surg. 13. 158-163.
22. Okçu G, Erkan S, Sentürk M, Ozalp RT, Yercan HS. Evaluation of injection techniques in the treatment of lateral epicondylitis: a prospective randomized clinical trial. Acta Orthop Traumatol Turc. 2012;46(1):26-9. doi: 10.3944/aott.2012.2577. PMID: 22441448.
23. Dogramaci Y, Kalaci A, Savaş N, Duman IG, Yanat AN. Treatment of lateral epicondilitis using three different local injection modalities: a randomized prospective clinical trial. Arch Orthop Trauma Surg. 2009 Oct;129(10):1409-14. doi: 10.1007/s00402-009-0832-x. Epub 2009 Feb 14. PMID: 19219442.
24. Altay T, Günal I, Oztürk H. Local injection treatment for lateral epicondylitis. Clin Orthop Relat Res. 2002 May;(398):127-30. PMID: 11964641.
25. Stasinopoulos D, Johnson MI. Effectiveness of extracorporeal shock wave therapy for tennis elbow (lateral epicondylitis). Br J Sports Med. 2005 Mar;39(3):132-6. doi: 10.1136/bjsm.2004.015545. PMID: 15728688; PMCID: PMC1725150.
26. Trentini R, Mangano T, Repetto I, Cerruti P, Kuqi E, Trompetto C, Franchin F. Short- to mid-term follow-up effectiveness of US-guided focal extracorporeal shock wave therapy in the treatment of elbow lateral epicondylitis. Musculoskelet Surg. 2015 Sep;99 Suppl 1:S91-7. doi: 10.1007/s12306-015-0361-4. Epub 2015 May 10. PMID: 25957547.
27. Haake M, König IR, Decker T, Riedel C, Buch M, Müller HH; Extracorporeal Shock Wave Therapy Clinical Trial Group. Extracorporeal shock wave therapy in the treatment of lateral epicondylitis: a randomized multicenter trial. J Bone Joint Surg Am. 2002 Nov;84(11):1982-91. doi: 10.2106/00004623-200211000-00012. PMID: 12429759.
28. Yalvaç B, Mesci N, Geler Külcü D, Yurdakul OV. Comparison of ultrasound and extracorporeal shock wave therapy in lateral epicondylosis. Acta Orthop Traumatol Turc. 2018 Sep;52(5):357-362. doi: 10.1016/j.aott.2018.06.004. Epub 2018 Jun 28. PMID: 30497658; PMCID: PMC6204478.
29. Stasinopoulos D. Can extracorporeal shock-wave therapy be used for the management of lateral elbow tendinopathy? World J Methodol. 2018 Nov 29;8(3):37-39. doi: 10.5662/wjm.v8.i3.37. PMID: 30519537; PMCID: PMC6275556.
30. Spacca G, Necozione S, Cacchio A. Radial shock wave therapy for lateral epicondylitis: a prospective randomised controlled single-blind study. Eura Medicophys. 2005 Mar;41(1):17-25. PMID: 16175767.
31. Ozkut AT, Kilinçoğlu V, Ozkan NK, Eren A, Ertaş M. Lateral epikondilitli olgularda ekstrakorporeal şok dalga tedavisi [Extracorporeal shock wave therapy in patients with lateral epicondylitis]. Acta Orthop Traumatol Turc. 2007;41(3):207-10. Turkish. PMID: 17876120.
32. Crowther MA, Bannister GC, Huma H, Rooker GD. A prospective, randomised study to compare extracorporeal shock-wave therapy and injection of steroid for the treatment of tennis elbow. J Bone Joint Surg Br. 2002 Jul;84(5):678-9. doi: 10.1302/0301-620x.84b5.12741. PMID: 12188483.
33. Buchbinder R, Green SE, Youd JM, Assendelft WJ, Barnsley L, Smidt N. Shock wave therapy for lateral elbow pain. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD003524. doi: 10.1002/14651858.CD003524.pub2. PMID: 16235324.
34. Capan N, Esmaeilzadeh S, Oral A, Basoglu C, Karan A, Sindel D. Radial Extracorporeal Shock Wave Therapy Is Not More Effective Than Placebo in the Management of Lateral Epicondylitis: A Double-Blind, Randomized, Placebo-Controlled Trial. Am J Phys Med Rehabil. 2016 Jul;95(7):495-506. doi: 10.1097/PHM.0000000000000407. PMID: 26544854.
35. Chung B, Wiley JP. Effectiveness of extracorporeal shock wave therapy in the treatment of previously untreated lateral epicondylitis: a randomized controlled trial. Am J Sports Med. 2004 Oct-Nov;32(7):1660-7. doi: 10.1177/0363546503262806. PMID: 15494330.
36. Beyazal MS, Devrimsel G. Comparison of the effectiveness of local corticosteroid injection and extracorporeal shock wave therapy in patients with lateral epicondylitis. J Phys Ther Sci. 2015 Dec;27(12):3755-8. doi: 10.1589/jpts.27.3755. Epub 2015 Dec 28. PMID: 26834345; PMCID: PMC4713784.
37. Aydın A, Atiç R. Comparison of extracorporeal shock-wave therapy and wrist-extensor splint application in the treatment of lateral epicondylitis: a prospective randomized controlled study. J Pain Res. 2018 Aug 2;11:1459-67. doi: 10.2147/JPR.S166679. PMID: 30122976; PMCID: PMC6080668.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1186-1189.
DOI: 10.28982/josam.840971

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Is quantitative DCE-MRI useful in differentiation of indolent and significant prostate cancers?

Sessiz ve anlamlı prostat kanseri ayrımında kantitatif DCE-MRG faydalı mıdır?

Mehmet Coşkun [1], Merve Horoz Dönmez [2]

[1] Department of Radiology, Health Science University Dr. Behçet Uz Child Disease and Surgery Training and Research Hospital, İzmir, Turkey
[2] Department of Radiology, İzmir Kâtip Çelebi University Atatürk Training and Research Hospital, İzmir, Turkey

ORCID ID of the author(s)

MC: 0000-0003-4339-898X
MHD: 0000-0002-5564-2196

Corresponding author/Sorumlu yazar:
Mehmet Coşkun
Address/Adres: Dr. Behçet Uz Child Hospital, İsmet Kaptan Mh. Sezer Doğan Sk. No:11 Konak, İzmir, Turkey
E-mail: dr.mehmetcoskun@hotmail.com

Ethics Committee Approval: All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: Direct visual assessment is recommended in prostate magnetic resonance imaging (MRI) for dynamic contrast enhancement (DCE), however, being a qualitative approach, it may cause inter-reader variability. The purpose of this study was to compare quantitative DCE parameters in the differentiation of clinically significant prostate cancer from indolent cancer using whole-mount histopathology.

Methods: Seventy-six patients who underwent multiparametric MRI with suspicion of prostate cancer and subsequent radical prostatectomy were included. Index tumor location was determined with pathology reports. MRI findings of this location were evaluated by a different radiologist using prostate imaging-reporting and data system version 2.1 (PI-RADSv2.1) guideline. Gleason 3+3 tumors were considered indolent, and Gleason ≥ 3+4 tumors were considered significant cancers. Region-of-interests (ROI) were placed in the lesion and the normal peripheral zone. Lesion values and lesion/normal ratios of Ktrans, Kep, Ve, area under curve (iAUC) were calculated. T test was used in statistical analysis.

Results: The numbers of cases with PI-RADSv2.1 scores of 2, 3, 4 and 5 were 5, 4, 24, and 43, respectively. There were 13 indolent cases and 63 patients with significant prostate cancer. Lesion/normal ratios of Ktrans, Kep, Ve, iAUC were 1.6, 1.59, 12, 2.1, respectively, in indolent cancers, and 3.1, 4.04, 1.39, 2.8, respectively, in significant cancers. Lesion/normal ratio of Ktrans was higher in significant cancers while lesion/normal ratio of Ve was higher in indolent cancers. Kep and iAUC were similar (P>0.05 for each).

Conclusion: Quantitative DCE assessment may demonstrate more reproducible results. Lesion/normal tissue ratios of Ktrans and Ve were helpful in differentiation between indolent and significant prostate cancers.

Keywords: Dynamic MRI, Gleason, Multiparametric prostate MRI, Perfusion MRI, Prostate cancer

Öz

Amaç: Prostat manyetik rezonans görüntülemede (MRG) dinamik kontrastlı inceleme (DKİ) için direk görsel değerlendirme önerilir. Kalitatif bir yaklaşım olarak bu okuyucular arası uyumsuzluğa neden olur. Bu çalışmada, tüm-spesimen histopatolojisini referans kabul ederek sessiz ve anlamlı prostat kanserlerinde kantitatif DKİ parametrelerinin karşılaştırılması amaçlanmıştır.

Yöntemler: Multiparametrik MRG ve ardından radikal prostatektomi yapılan 76 olgu çalışmaya dahil edildi. İndeks tümörün yeri patoloji raporu kullanılarak tespit edildi. Bu bölgenin MRG bulguları başka bir radyolog tarafından prostat görüntüleme-raporlama ve bilgi sistemi versiyon 2.1 (PI-RADSv2.1) kullanılarak incelendi. Gleason 3+3 tümörler sessiz, Gleason ≥ 3+4 tümörler anlamlı kanser kabul edildi. İlgi alanı (ROI), lezyona ve normal periferal zona yerleştirildi. Ktrans, Kep, Ve, başlangıç eğrisinin altındaki alan (EAA) için lezyon değeri ve lezyon/normal oranı hesaplandı. Bu parametreler T testi kullanılarak sessiz ve anlamlı kanserlerde karşılaştırıldı.

Bulgular: Olguların PI-RADSv2.1 skoru 2'den 5'e olgu sayısı sırasıyla 5, 4, 24 ve 43'tü. Sessiz kanserli olgu sayısı 13, anlamlı kanserli olgu sayısı 63 idi. Ktrans, Kep, Ve, EAA lezyon/normal oranları sessiz kanserler için sırasıyla 1.6, 1.59, 12, 2.1 iken, anlamlı kanserler için 3.1, 4.04, 1.39, 2.8 idi. Ktrans lezyon/normal oranı anlamlı kanserlerde yüksek iken, Ve lezyon/normal oranı sessiz kanserlerde yüksekti. Kep ve EAA için sessiz ve anlamlı kanserlerde anlamlı fark yoktu (P>0,05).

Sonuç: Kantitatif değerlendirme, dinamik MRG'de daha objektif-kopyalanabilir sonuçlar sunar. Ktrans ve Ve lezyon/normal doku oranları, sessiz ve anlamlı kanserin ayrımında yardımcıdır.

Anahtar kelimeler: Dinamik MRG, Gleason, Multiparametrik prostat MRG, Perfüzyon MRG, Prostat kanseri

How to cite/Atıf için: Coşkun M, Dönmez MH. Is quantitative DCE-MRI useful in differentiation of indolent and significant prostate cancers? J Surg Med. 2020;4(12):1186-1189.

Introduction

Prostate cancer (PCa) has become an important health problem, especially in developed countries, with the increase in average life expectancy. The American cancer society estimates that prostate cancer will rank 5th in cancer-related deaths in 2020 [1]. PCa is screened with prostate-specific antigen (PSA), digital rectal examination (DRM) and systematic biopsy [2]. Magnetic resonance imaging (MRI), with high diagnostic performance, is utilized for cancer detection and risk stratification of PCa, as well [3].

Prostate MRI is evaluated with multiparametric (mp) approach including T2 weight imaging (WI), diffusion weighted imaging (DWI), and dynamic contrast enhancement (DCE) in prostate imaging-reporting and data system version 2.1 (PI-RADSv2.1). Category 3 peripheral zone (PZ) lesions were upgraded to category 4 when DCE was positive. DCE has a limited role in scoring, which revives biparametric (bp) approach without DCE-MRI [4]. BpMRI had comparable results in meta-analysis [5,6]. However, PI-RADS steering committee was concerned that frequency of missed significant cancer may increase with bpMRI. DCE is a "back-up" sequence and remains essential in assessment of prostate MRI [4].

PI-RADSv2.1 proposed direct visual assessment in DCE-MRI, and the criteria on DCE did not change: "Focal, and earlier than or contemporaneously with enhancement of adjacent normal prostatic tissues is positive for DCE-MRI" [4]. This qualitative definition has resulted in inter-reader variability [7]. The inter-reader agreement of DCE-MRI was lower than DWI-MRI [8]. Quantitative DCE assessment has a potential to overcome those limitations.

In this study, we aimed to compare quantitative DCE parameters in the differentiation of clinically significant prostate cancer from indolent cancer using whole-mount histopathology as the reference test.

Materials and methods

Study population

The principles of the Declaration of Helsinki were conformed with. Written informed consent was obtained from all participants. The patients who underwent mpMRI with suspicion of prostate cancer and subsequently, radical prostatectomy (RP), were included in this retrospective study between January 2019 and March 2020. The patients who underwent bpMRI due to contraindications for contrast media administration, those who had more than 6 months between mpMRI and RP, had severe artifacts or received hormonotherapy or radiotherapy before mpMRI were excluded.

Radiological evaluation

All MR scans were obtained on a 1.5T scanner (Aera, Siemens Healthineers, Erlangen, Germany) using a pelvic-surface coil with 18 channels. All technical parameters complied with PI-RADSv2.1 [4]. All three basic sequences including axial T2WI, DWI, and DCE were performed with a slice thickness of 3 mm without any gap. Slice locations of 3 sequences were the same. DCE was performed using ultra-fast gradient echo (GRE) in axial plane (repetition time, 2.48 msec; echo time, 1.52 msec; the field of view, 260×215 mm; acquisition matrix, 160×108). Temporal resolution was high, 7 seconds. T1 mapping was added to protocol in 2019 to make quantitative analysis. Gadobutrol (0.1ml/kg) was injected with automatic pump via antecubital vein using an injection rate of 3 ml/sec followed by a 15 ml saline flush.

One radiologist determined the location of the tumor with highest Gleason score using whole mount histopathology report. Other radiologist blinded to the pathology result evaluated only this part of mpMRI and assigned a PI-RADSv2.1 score. Gleason 3+3 tumors were considered indolent, and Gleason ≥ 3+4 tumors were considered significant cancers.

Quantitative evaluation was performed in the workstation (Syngo.via, Siemens Healthineers, Erlangen, Germany) with tissue 4D analysis (Tofts model) [9]. Free handed region-of-interests (ROI) were placed to the lesion, and normal PZ, and Ktrans, Kep, Ve, initial under the curve (iAUC) were calculated (Ktrans: Transfer constant, Kep: Efflux rate constant, Ve: Extracellular-extravascular volume fraction).

Prostate volume was calculated from axial and sagittal T2WI using ellipsoid formula. Patients' age and serum PSA level before mpMRI were recorded. PSA density (PSAd) was calculated using the formula of serum PSA/prostate volume.

Statistical analysis

Statistical analyses were conducted using SPSS version 20 (IBM®, Armonk, NY, USA). Perfusion parameters including lesion k-trans, Kep, Ve, iAUC and lesion/normal ratios of k-trans, Kep, Ve, iAUC were compared between indolent and significant cancer using student's T test. A *P*-value < 0.05 was considered statistically significant.

Results

Median age of 76 patients included in this study was 69 (6.6) years. Mean serum PSA and PSAd values were 12.03 (12.13) ng/ml, and 0.306 (0.371) ng/ml/cm^3, respectively. Mean lesion diameter was 17.6 (8.6) mm with a range of 5-51 mm (Table 1).

There was no case with PI-RADSv2.1 score 1. The numbers of cases with PI-RADSv2.1 scores of 2, 3, 4 and 5 were 5, 4, 24, and 43, respectively. Pathology results were as follows: 13 patients had Gleason 3+3, 29 patients, Gleason 3+4, 22 patients, Gleason 4+3, 8 patients, Gleason 4+4, 3 patients, Gleason 4+5 and 1 patient had Gleason 5+4. Finally, there were 13 indolent and 63 significant prostate cancers (Table 2).

Table 1: Demographic results of this cohort

Parameters	Mean (SD)	Minimum	Maximum
Age (years)	67.31 (6.6)	47	80
PSA (n/ml)	12.03 (12.13)	3.16	75.66
PSAd (ng/ml/cm3)	0.306 (0.371)	0.060	2.680
Dimension (mm)	17.6 (8.6)	5	51

SD: standard deviation

Table 2: PI-RADSv2.1 score vs Gleason grade

PI-RADSv2.1	Gleason grade						
	3+3	3+4	4+3	4+4	4+5	5+4	Total
Score 2	3	2	0	0	0	0	5
Score 3	2	2	0	0	0	0	4
Score 4	5	13	4	2	0	0	24
Score 5	3	12	18	6	3	1	43
Total	13	29	22	8	3	1	76

Lesion values of Ktrans, Kep, Ve, iAUC were 0.11, 0.57, 0.24, 0.12 in indolent cancers, and 0.13, 0.94, 0.21, 0.13 in significant cancers, respectively. Lesion/normal ratios of Ktrans, Kep, Ve, iAUC were 1.6, 1.59, 12, 2.1 in indolent cancers, 3.1, 4.04, 1.39, 2.8 in significant cancers, respectively (Figure 1).

Lesion/normal ratio of Ktrans was higher in significant cancers (p = 0.04) while lesion/normal ratio of Ve was higher in indolent cancers (*P*<0.001). Other parameters were similar between indolent and significant cancer groups (Table 3).

Table 3: Comparison of quantitative DCE parameters in indolent and significant cancer groups

Quantitative DCE Parameters		Indolent cancer with Gleason 3+3 Mean (SD)	Significant cancer with Gleason ≥ 3+4 Mean (SD)	*P*-value
Lesion	Ktrans	0.11 (0.65)	0.13 (0.11)	0.398
	Kep	0.57 (0.29)	0.94 (2)	0.357
	Ve	0.24 (0.2)	0.21 (0.14)	0.504
	iAUC	0.12 (0.075)	0.13 (0.085)	0.682
Lesion / Normal tissue	Ktrans	1.6 (0.72)	3.1 (2.6)	0.04
	Kep	1.59 (0.95)	4.04 (7.7)	0.094
	Ve	12 (39)	1.39 (1.2)	< 0.001
	iAUC	2.1 (1.3)	2.8 (2.4)	0.255

DCE: dynamic contrast enhancement, SD: standard deviation, iAUC: area under curve

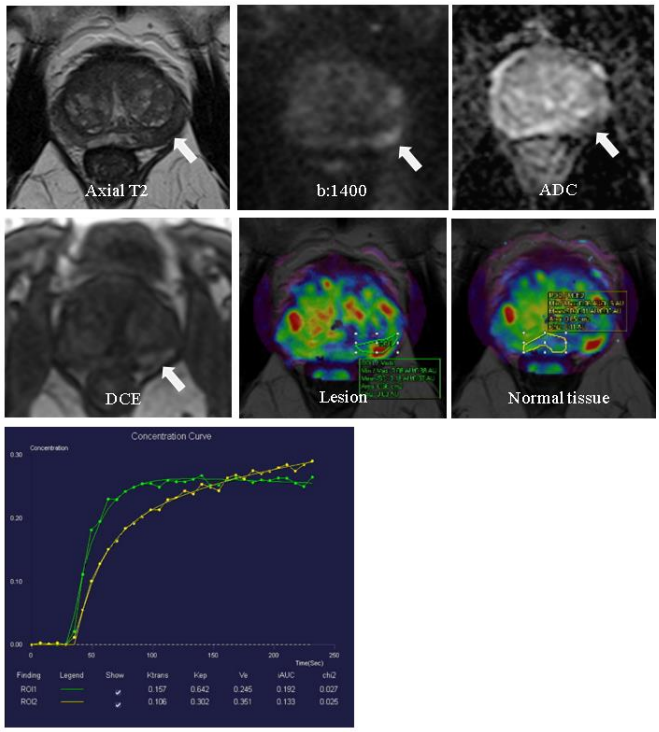


Figure 1: Multiparametric MRI and quantitative DCE-MRI results of a 73-year-old male with a PSA of 4.77 ng/ml and PSAd of 0.08 ng/ml/cm3. Arrows are showing a PI-RADS category 5 lesion placed on left mid-peripheral zone. Green curve is representing the lesion whereas yellow curve is showing normal prostate. Lesion Ktrans, Kep, Ve, and iAUC values are 0.157, 0.642, 0.245 and 0.192, respectively. Lesion/normal ratios of Ktrans, Kep, Ve, and iAUC are 1.49, 2.13, 0.70 and 1.44, respectively. The lesion was Gleason 4+3 tumor in whole-mount report.

Discussion

Qualitative and visual evaluation was suggested for DCE-MRI in PI-RADSv2.1. DCE-MRI had a limited role in scoring and was used only when positive to elevate a finding in the PZ with score 3 [4]. In this study, we evaluated quantitative DCE parameters and found that lesion/normal ratio of Ktrans was significantly higher in clinically significant prostate cancer. Conversely, lesion/normal ratio of Ve was negatively correlated with increasing tumor grade from Gleason 3+3 to Gleason ≥ 3+4.

Cancer tissue includes increased number of vessels. These vessels are also more permeable, disorganized, and chaotic than normal vessels. More aggressive tumors have more ability of angiogenesis using factors such as vascular endothelial growth factor [10]. DCE-MRI contains information about tissue perfusion and vascular permeability. A contrast agent mimics the blood and T1 signal changes of the tissue recorded repeatedly, dynamically [11]. Pharmacokinetic model of Tofts, one of the most popular quantitative modeling methods in practice, is based on determination of contrast exchange rate between intravascular (plasma) and extravascular space using transfer rate constant, such as Ktrans, Kep, Ve, iAUC. Ktrans is forward volume transfer constant and closely related with vascular permeability. It demonstrates flux from intravascular to extravascular space. Kep is reverse reflux rate constant between extravascular space and plasma and demonstrates efflux of contrast from extracellular space back to plasma. Ve is the extracellular extravascular volume fraction and can be calculated with the formula of Kep = Ktrans/Ve [9,11,12]. iAUC represents area under the concentration curve in time [13]. High values of Ktrans, Kep, and iAUC were positively correlated with poor prognosis in some other cancers such as invasive ductal carcinoma, and glioblastoma [13-16].

Ktrans and Kep were elevated in prostate cancer [17-19]. Vos et al. [20] reported that there was a significant correlation between tumor aggressiveness and Ktrans and Kep. Wei et al. [21] found significant Ktrans and Kep differences between benign and Gleason 3+3 tumor. Ktrans was significantly different between Gleason 3+3 and Gleason ≥ 3+4, as well. The sensitivity of MRI increased from 56.6% to 92.1% with addition of Ktrans assessment. On the other hand, there were some challenging factors in quantitative method. The measurements can be affected by changing cardiac output, and the T1 time of the tissue [11]. In our study, no lesion perfusion parameters reached a significant level. However, lesion/normal ratio of Ktrans was positively correlated with increasing tumor grade from Gleason 3+3 to Gleason ≥ 3+4. Lesion/normal ratio of Ve was significantly lower in patients with Gleason ≥ 3+4 tumors. We believe that lesion/normal ratio is more appropriate than measurement from the lesion alone. The proportion may not be affected from challenging factors and may yield more reliable and reproducible results.

One of the most critical factors affecting the diagnostic performance of quantitative MRI is shorter acquisition time. PI-RADSv2 proposed a temporal resolution of ≤ 10 sec (<7 sec is preferred) [22]. This criterion was softened in PI-RADSv2.1 as ≤ 15 sec not to compromise image quality [4]. Benign-malign differentiation was better with higher temporal resolution. Ultra-fast T1 weighted gradient echo is performed for rapid imaging. The advantage of GRE sequence is fast acquisition [23]. However, it is sensitive to metal implants, such as hip prosthesis. Considering that prostate cancer risk increases with aging, adequate imaging may be challenging. In our study, DCE-MRI was performed with a high temporal resolution of 7 sec. Rapid imaging provided more detailed information on tissue perfusion. We excluded the cases (n=4) with hip prostheses not to contaminate the results of quantitative DCE-MRI.

Limitations

This study had several limitations. First, this was a retrospective study had a potential of selection bias. Second, it was conducted in a single center with a small sample size. The results should be supported with prospective, large, and multicenter studies. Third, considering complexity of post-processing, the result should be replicated with different software and workstations. Fourth, we used radical prostatectomy specimens as the reference test. There might be some selection bias because the patients with low risk, and those with aggressive

tumors with pelvic or rectal invasion could not undergo RP. Fifth, the locations of the tumors were marked by one radiologist using pathology reports. Then, another radiologist assigned a PI-RADSv2.1 score to this marked lesion. Score assignment was performed while blinded to pathological outcome. This method provided a perfect overlap between mpMRI and pathological results with a bias risk for assignment of higher PI-RADSv2.1 score. The reader of MRIs was blinded to pathological outcomes to minimize the bias risk. Interreader agreement may be tested with multireader and multicenter studies in future.

Conclusion

Quantitative DCE-MRI may demonstrate more objective and reproducible results. Lesion/normal ratios of Ktrans and Ve were helpful in differentiation between indolent and significant prostate cancers.

References

1. American Cancer Society. Key Statistics for Prostate Cancer, 2020. [Internet]. https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html. Accessed on 01 Nov 2020.
2. Roobol MJ, Kranse R, Bangma CH, van Leenders AG, Blijenberg BG, van Schaik RH, et al. Screening for prostate cancer: results of the Rotterdam section of the European randomized study of screening for prostate cancer. Eur Urol. 2013;64(4):530-9. Epub 2013/06/14. doi: 10.1016/j.eururo.2013.05.030. PubMed PMID: 23759326.
3. Oberlin DT, Casalino DD, Miller FH, Meeks JJ. Dramatic increase in the utilization of multiparametric magnetic resonance imaging for detection and management of prostate cancer. Abdom Radiol (NY). 2017;42(4):1255-8. Epub 2016/11/20. doi: 10.1007/s00261-016-0975-5. PubMed PMID: 27858090.
4. Turkbey B, Rosenkrantz AB, Haider MA, Padhani AR, Villeirs G, Macura KJ, et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. Eur Urol. 2019;76(3):340-51. Epub 2019/03/23. doi: 10.1016/j.eururo.2019.02.033. PubMed PMID: 30898406.
5. Woo S, Suh CH, Kim SY, Cho JY, Kim SH, Moon MH. Head-to-Head Comparison Between Biparametric and Multiparametric MRI for the Diagnosis of Prostate Cancer: A Systematic Review and Meta-Analysis. AJR Am J Roentgenol. 2018;211(5):W226-w41. Epub 2018/09/22. doi: 10.2214/ajr.18.19880. PubMed PMID: 30240296.
6. Alabousi M, Salameh JP, Gusenbauer K, Samoilov L, Jafri A, Yu H, et al. Biparametric vs multiparametric prostate magnetic resonance imaging for the detection of prostate cancer in treatment-naïve patients: a diagnostic test accuracy systematic review and meta-analysis. BJU Int. 2019;124(2):209-20. Epub 2019/04/01. doi: 10.1111/bju.14759. PubMed PMID: 30929292.
7. Smith CP, Harmon SA, Barrett T, Bittencourt LK, Law YM, Shebel H, et al. Intra- and interreader reproducibility of PI-RADSv2: A multireader study. J Magn Reson Imaging. 2019;49(6):1694-703. Epub 2018/12/24. doi: 10.1002/jmri.26555. PubMed PMID: 30575184; PubMed Central PMCID: PMCPMC6504619.
8. Rosenkrantz AB, Babb JS, Taneja SS, Ream JM. Proposed Adjustments to PI-RADS Version 2 Decision Rules: Impact on Prostate Cancer Detection. Radiology. 2017;283(1):119-29. Epub 2016/10/27. doi: 10.1148/radiol.2016161124. PubMed PMID: 27783538.
9. Tofts PS, Brix G, Buckley DL, Evelhoch JL, Henderson E, Knopp MV, et al. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. J Magn Reson Imaging. 1999;10(3):223-32. Epub 1999/10/03. doi: 10.1002/(sici)1522-2586(199909)10:3<223::aid-jmri2>3.0.co;2-s. PubMed PMID: 10508281.
10. Nicholson B, Schaefer G, Theodorescu D. Angiogenesis in prostate cancer: biology and therapeutic opportunities. Cancer Metastasis Rev. 2001;20(3-4):297-319. Epub 2002/06/28. doi: 10.1023/a:1015543713485. PubMed PMID: 12085968.
11. Verma S, Turkbey B, Muradyan N, Rajesh A, Cornud F, Haider MA, et al. Overview of dynamic contrast-enhanced MRI in prostate cancer diagnosis and management. AJR Am J Roentgenol. 2012;198(6):1277-88. Epub 2012/05/25. doi: 10.2214/ajr.12.8510. PubMed PMID: 22623539; PubMed Central PMCID: PMCPMC6309691.
12. Tofts PS, Wicks DA, Barker GJ. The MRI measurement of NMR and physiological parameters in tissue to study disease process. Prog Clin Biol Res. 1991;363:313-25. Epub 1991/01/01. PubMed PMID: 1988983.
13. Lee HS, Kim SH, Kang BJ, Baek JE, Song BJ. Perfusion Parameters in Dynamic Contrast-enhanced MRI and Apparent Diffusion Coefficient Value in Diffusion-weighted MRI:: Association with Prognostic Factors in Breast Cancer. Acad Radiol. 2016;23(4):446-56. Epub 2016/02/08. doi: 10.1016/j.acra.2015.12.011. PubMed PMID: 26852247.
14. Awasthi R, Pandey CM, Sahoo P, Behari S, Kumar V, Kumar S, et al. Dynamic contrast-enhanced magnetic resonance imaging-derived kep as a potential biomarker of matrix metalloproteinase 9 expression in patients with glioblastoma multiforme: a pilot study. J Comput Assist Tomogr. 2012;36(1):125-30. Epub 2012/01/21. doi: 10.1097/RCT.0b013e31823f6c59. PubMed PMID: 22261782.
15. Nguyen TB, Cron GO, Mercier JF, Foottit C, Torres CH, Chakraborty S, et al. Preoperative prognostic value of dynamic contrast-enhanced MRI-derived contrast transfer coefficient and plasma volume in patients with cerebral gliomas. AJNR Am J Neuroradiol. 2015;36(1):63-9. Epub 2014/06/21. doi: 10.3174/ajnr.A4006. PubMed PMID: 24948500.
16. Choi YS, Kim DW, Lee SK, Chang JH, Kang SG, Kim EH, et al. The Added Prognostic Value of Preoperative Dynamic Contrast-Enhanced MRI Histogram Analysis in Patients with Glioblastoma: Analysis of Overall and Progression-Free Survival. AJNR Am J Neuroradiol. 2015;36(12):2235-41. Epub 2015/09/05. doi: 10.3174/ajnr.A4449. PubMed PMID: 26338911.
17. Turkbey B, Pinto PA, Mani H, Bernardo M, Pang Y, McKinney YL, et al. Prostate cancer: value of multiparametric MR imaging at 3 T for detection--histopathologic correlation. Radiology. 2010;255(1):89-99. Epub 2010/03/24. doi: 10.1148/radiol.09090475. PubMed PMID: 20308447; PubMed Central PMCID: PMCPMC2843833.
18. Fütterer JJ, Heijmink SW, Scheenen TW, Veltman J, Huisman HJ, Vos P, et al. Prostate cancer localization with dynamic contrast-enhanced MR imaging and proton MR spectroscopic imaging. Radiology. 2006;241(2):449-58. Epub 2006/09/13. doi: 10.1148/radiol.2412051866. PubMed PMID: 16966484.
19. Moradi M, Salcudean SE, Chang SD, Jones EC, Buchan N, Casey RG, et al. Multiparametric MRI maps for detection and grading of dominant prostate tumors. J Magn Reson Imaging. 2012;35(6):1403-13. Epub 2012/01/24. doi: 10.1002/jmri.23540. PubMed PMID: 22267089; PubMed Central PMCID: PMCPMC5478377.
20. Vos EK, Litjens GJ, Kobus T, Hambrock T, Hulsbergen-van de Kaa CA, Barentsz JO, et al. Assessment of prostate cancer aggressiveness using dynamic contrast-enhanced magnetic resonance imaging at 3 T. Eur Urol. 2013;64(3):448-55. Epub 2013/06/12. doi: 10.1016/j.eururo.2013.05.045. PubMed PMID: 23751135.
21. Wei C, Jin B, Szewczyk-Bieda M, Gandy S, Lang S, Zhang Y, et al. Quantitative parameters in dynamic contrast-enhanced magnetic resonance imaging for the detection and characterization of prostate cancer. Oncotarget. 2018;9(22):15997-6007. Epub 2018/04/18. doi: 10.18632/oncotarget.24652. PubMed PMID: 29662622; PubMed Central PMCID: PMCPMC5882313.
22. Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, Macura KJ, et al. PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. Eur Urol. 2016;69(1):16-40. Epub 2015/10/03. doi: 10.1016/j.eururo.2015.08.052. PubMed PMID: 26427566; PubMed Central PMCID: PMCPMC6467207.
23. Rosenkrantz AB, Geppert C, Grimm R, Block TK, Glielmi C, Feng L, et al. Dynamic contrast-enhanced MRI of the prostate with high spatiotemporal resolution using compressed sensing, parallel imaging, and continuous golden-angle radial sampling: preliminary experience. J Magn Reson Imaging. 2015;41(5):1365-73. Epub 2014/05/17. doi: 10.1002/jmri.24661. PubMed PMID: 24833417; PubMed Central PMCID: PMCPMC4233205.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1190-1194.
DOI: 10.28982/josam.832595

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Effects of creation of bladder flap during cesarean section on long-term residual urine volume and postoperative urinary retention

Sezaryen sırasında mesane flebi oluşumunun uzun süreli rezidüel idrar hacmi ve postoperatif idrar retansiyonu üzerindeki etkileri

Derya Kanza Gül [1], Ayça Solt Kırca [2]

[1] Medipol University, School of Medicine Health, Department of Gynecology and Obstetrics, Istanbul, Turkey
[2] Kirklareli University, School of Health, Midwifery Depertmant, Kirklareli, Turkey

ORCID ID of the author(s)

DKG: 0000-0001-8879-9299
ASK: 0000-0001-6733-5348

Corresponding author/Sorumlu yazar:
Derya Kanza Gül
Address/Adres: Medipol University, School of Medicine Health, Department of Gynecology and Obstetrics, Istanbul, Turkey
E-mail: deryakanza@yahoo.com

Ethics Committee Approval: Medipol University Clinical Research Ethics Committee approved the study. (R.N: 108400098-604.01.01-E.53606). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Medipol Üniversitesi Klinik Araştırmalar Etik Komitesi çalışmayı onayladı. (R.N: 108400098-604.01.01-E.53606). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: Postpartum urinary retention (PUR) is an important clinical condition that is frequently detected after both vaginal and cesarean delivery. The aim of this study was to evaluate PUR in women who did and did not have bladder flaps created during cesarean section and the effect of Kegel exercises on long-term bladder muscle function in those with high postnatal residual urine volume.

Methods: This prospective randomized study was conducted with 100 primiparous pregnant women who were to undergo elective cesarean section between April and December 2019. Patients were divided into two groups: The experimental group (bladder flap group, n=50) and the control group (non-bladder flap group, n=50). The study data were collected with the Maternal Information Form and UDI-6. Kegel exercise results, post-void residual volume and urinary system symptoms were assessed on the 2nd and 5th postoperative day and 6 weeks after birth.

Results: There were no significant differences between the groups in terms of socio-demographic characteristics, postoperative 5th day and 6th week residual urine volume, postoperative urinary retention volume, urinary system symptoms (UDI-6 scores) and bladder injury. There were significant differences between the groups in terms of residual urine volume, duration of surgery, and pain values assessed on the second day (P=0.045, P<0.001, P<0.001, respectively). Intra group comparisons demonstrated a decrease in residual urine volume in the participants with high residual urine volume after Kegel exercises, and their postoperative 2nd day and 6th week residual urine volumes and UDI-6 scores were significantly different (P<0.001, P<0.001).

Conclusion: The present study determined that bladder flaps created during cesarean section increases postoperative urinary retention. In patients with high residual urine volume, Kegel exercises reduce residual urine volumes and urinary symptoms in the long term.

Keywords: Bladder flap, Omission of a bladder flap, Urinary retention, Cesarean section

Öz

Amaç: Postpartum idrar retansiyonu hem vajinal hem de sezaryen doğumdan sonra sıklıkla saptanan önemli bir klinik durumdur. Bu çalışma ile sezaryen sırasında mesane flebi olan ve olmayan kadınlarda idrar retansiyonunu ve ayrıca doğum sonrası rezidüel idrar hacmi yüksek olanlarda Kegel egzersizlerinin uzun süreli mesane kas fonksiyonu üzerindeki etkisini değerlendirmek amaçlanmıştır.

Yöntemler: Bu ileriye dönük randomize çalışma, Nisan-Aralık 2019 tarihleri arasında elektif sezaryen operasyonu geçiren 100 primipar gebe kadınla gerçekleştirildi. Deney grubu (mesane flebi grubu, n=50) ve kontrol grup (mesane dışı flep grubu, n=50). Çalışma verileri Anne Bilgi Formu ve UDI-6 ile toplandı. Doğumdan sonraki 2. gün, 5. gün ve 6. haftalarda Kegel egzersiz sonuçları, işeme sonrası rezidüel hacim ve üriner sistem semptomları değerlendirildi.

Bulgular: Gruplar arasında sosyo-demografik özellikler, postoperatif 5. gün ve 6. hafta rezidüel idrar hacmi, postoperatif idrar retansiyon hacmi, üriner sistem semptomları (UDI-6 skorları) ve mesane yaralanması açısından anlamlı farklılık yoktu. İkinci gün değerlendirilen rezidüel idrar hacmi, ameliyat süresi ve ağrı değerleri açısından gruplar arasında anlamlı farklılık vardı (sırasıyla P=0,045, P<0,001 ve P<0,001). Grup içi karşılaştırmalar, Kegel egzersizlerinden sonra rezidüel idrar hacmi yüksek olan katılımcılarda rezidüel idrar hacminde azalma olduğunu gösterdi ve postoperatif 2. gün ve 6. hafta rezidüel idrar hacimleri ve UDI-6 skorları istatistiksel olarak anlamlı farklıydı (P<0,001, P<0,001).

Sonuç: Bu çalışmada sezaryen sırasında yapılan mesane flebin ameliyat sonrası üriner retansiyonu artırdığını belirlemiştir. Yüksek rezidüel idrar hacmine sahip hastalarda yapılan Kegel egzersizinin uzun vadede rezidüel idrar hacimini ve idrar semptomlarını azalttığı bulunmuştur.

Anahtar kelimeler: Mesane flebi, Mesane flebi açılmaması, İdrar retansiyonu, Sezaryen

How to cite/Atıf için: Gül DK, Kırca AS. Effects of creation of bladder flap during cesarean section on the long-term residual urine volume and postoperative urinary retention. J Surg Med. 2020;4(12):1190-1194.

Introduction

The number of Cesarean sections performed has significantly increased in the last two decades, especially in developed and developing countries [1,2]. A usual technique used in Cesarean section is the creation of a bladder flap following the abdominal incision, then making the uterine incision. Among the aims of formation of bladder flap during Cesarean section are to prevent the spread of infection to the intrauterine cavity, to minimize of the possibility of bladder injury caused by the surgeon and to allow the surgeon to access the lower uterine segment [3,4]. Although several studies have revealed that bladder flap creation is not beneficial during Caesarean section, many obstetricians routinely perform this procedure [4-6].

Postpartum urinary retention (PUR) is observed at a rate of 3.2% to 24.2% after vaginal cesarean delivery [7-9]. Because the effects of surgical techniques and anesthetic agents used in the postpartum period on the bladder are not clear yet, it is difficult to determine the role of Caesarean section in PUR [7]. In the literature, PUR indicates a post-void residual bladder volume (PVRBV) [10] ≥ 150 ml [11]. Ultrasound scanning or intermittent catheterization method is used in the assessment of the residual bladder volume [12]. Most obstetricians and gynecologists prefer to use ultrasound scan in the detection of postoperative urinary retention rather than intermittent catheters, since the former is a non-invasive, fast, painless, comfortable, and safe method compared to the latter [7].

This study was designed to assess PUR in women with and without bladder flaps created during Caesarean section, and the effect of Kegel exercises on long-term bladder muscle function in those with high postpartum residual urine volume.

Materials and methods

Medipol University Clinical Research Ethics Committee approved the study (R.N: 108400098-604.01.01-E.53606). Written consent was obtained from Nisa Hospital administration and the patients prior to the study, which was conducted in accordance with the guides on human participants in research, taking into account the 1964 Helsinki Declaration and ethical rules.

Between April 2019 and December 2019, 120 of the women who had cesarean section under general anesthesia were primiparas. The presence of urinary retention in women who did and did not have bladder flaps created, and the regression in urinary retention and urinary system symptoms with Kegel exercises were evaluated with UDI-6 score and ultrasonography. With a type 1 error of 0.05, and a power of 0.90 ($\alpha = 0.05$, $1-\beta = 0.90$), the minimum sample size was 92 (n=46 for each group). Fifty participants were included in each group (G*Power version 3.1).

In the present study, changes in the urinary symptoms evaluated by UDI-6 scores were considered the primary outcome. According to the mean UDI-6 scores between the groups at the first and sixth weeks, while the effect size of the study was $\alpha = 0.91$ for the intervention group and $\alpha = 1.08$ for the control group, the post hoc power of the study was 1.00 (100%) for both groups. The sample size of the study was considered sufficient.

Before surgery, patients with even protocol numbers were included in the bladder flap intervention group, and those with odd protocol numbers were included in the non-bladder-flap group. Randomization was achieved with a computer-based random number generator (Figure 1).

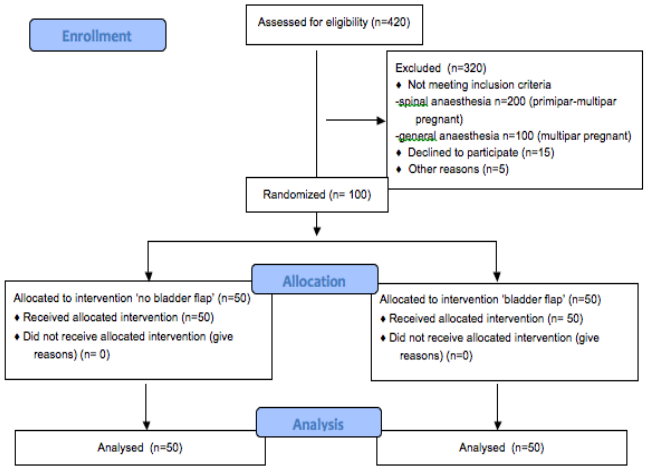


Figure 1: Diagram showing the recruitment and progression the trial of postpartum women

All participants were operated by the same doctor (D.K.G) and a different midwife. Another researcher (A.Ş.K) gave training on Kegel exercises to those who had high residual urine volume during discharge from the hospital, but did not know which group they were in. Both the patients and the doctor did not know which group the patients belonged to.

Being between 20-40 years of age, at the 37^{th}-42^{nd} weeks of gestation, being primipara, and having a cesarean section were the inclusion criteria, while having a chronic disease that requires medication (diabetes, hypertension, etc.), previous urinary tract infection, previous laparotomy, emergency cesarean section (abruptio placenta, fetal distress, etc.) constituted the exclusion criteria.

Maternal Information Form contained 30 items that questioned the socio-demographic characteristics of the participants, ultrasonographic measurements of the remaining urine volume, the presence of urinary infection, hematuria levels, and hemoglobin levels.

Urogenital Distress Inventory (UDI-6) was developed by Vassalo et al [13]. Çam et al. conducted a Turkish adaptation study of the UDI scale [14]. 1^{st} and 2^{nd} items evaluate irritant symptoms, 3^{rd} and 4^{th} items evaluate stress symptoms and 5^{th} and 6^{th} items evaluate the uncomfortable urination symptoms. The higher the score, the higher the urinary retention.

Visual Analogue Scale (VAS)

Developed by Bond and Pilowsky, VAS is a 10 cm long ruler, with 0-10 points, where 0 indicates no pain, and 10 indicates the most severe pain ever felt by the patient [15].

Cesarean section was performed under general anesthesia. Pfannenstiel skin incision was made in all patients. Subcutaneous tissues, fascia, parietal peritoneum were opened and the abdominal cavity was entered.

1. Flap steps for the study group: A small transverse midline incision was made with a scalpel at the vesicouterine peritoneum and the bladder peritoneum was bluntly separated from the uterus using both index fingers.

2. Steps for the control group: A bladder flap was not created; a transverse incision was made 1 cm above the peritoneal vesicouterine layer.

The uterine cavity was entered bluntly in all patients. The placenta was separated after the fetus was delivered. The uterus was closed with a continuous suture. The parietal peritoneum, the fascia and skin were closed. 20 units of oxytocin was administered in 1000 mL saline to prevent uterine atony after birth.

Four hours after surgery, each participant was administered 20 IU oxytocin in 1000 mL 5% dextrose saline and 40 drops/min. In the postoperative period, nonsteroidal anti-inflammatory 75 mg Diclofenac Sodium was administered intramuscularly (IM) and 500 mg paracetamol were administered orally twice daily to the participants. Bladder catheters were removed 6 hours after surgery in both groups. When the patient urinated, urine samples were collected, and residual urine volumes were assessed with the 3D portable ultrasound device. Among them, those who had ≥150 ml of residual urine and high UDI-6 scores were given training on Kegel exercises by the researcher (A.Ş.K.) on the postoperative 2nd day using illustrated brochures.

Kegel Exercise

The patients were instructed to tighten the vagina and anus for 10 seconds, rest for 3 seconds and repeat this exercise 10 times. Kegel exercises were performed for 20 minutes every day. Then, the efficacy of Kegel exercises and urinary symptoms were assessed by the UDI-6 score on the postoperative 5th day and 6th week. In addition, residual urine volume was assessed through ultrasonography.

Statistical analysis

Data analyses were performed with SPSS for Windows, version 22.0. The distribution of variables was examined with skewness and kurtosis coefficients (16) and it was determined that the data was normally distributed according to Skewness (between -.62 and 1.30) and Kurtosis (between -2.00 and -1.96) values. The Pearson chi-square test, Fisher's exact test, the independent samples t-test and Cochran's Q test were used where appropriate. Values of *P* <0.05 were considered statistically significant.

Results

There were no significant differences between the two groups in terms of education level, perceived income levels, mean age and BMI (*P*>0.05 for all, Table 1), and given these characteristics, the groups were homogeneous. The mean duration of surgery was higher in the bladder flap group compared to the control group (32.46 (4.79) vs. 26.16 (3.39) minutes) (*P*=0.045, Table 1). The mean VAS score was higher in the bladder flap group than the control group (4.42 (1.54) vs. 2.82 (1.47)) (*P*<0.001, Table 1). There was no significant difference in the neonates' birthweight and head circumference between the groups (*P*=0.681, *P*=0.843, respectively) (Table 1).

Urinary culture positivity was detected in 8% and 4% of the participants in the bladder flap and control groups, respectively (*P*=0.678, Table 2). The incidence of hematuria and bladder injury was 30% and 6%, respectively in the bladder flap group and 6% and 0%, respectively in the control group, with no significant differences between the groups (*P*=0.499, *P*=0.242 respectively) (Table 2). The pre- and post-cesarean section mean hemoglobin and hematocrit values were also similar between the groups (*P*>0.05 for all, Table 3).

Table 1: Descriptive characteristics of the puerpera in the bladder flap and control groups

	Bladder Flap Group (n=50)		Non-Bladder Flap Group (n=50)		Test	
	n	%	n	%	χ^2	*P*-value
Educational status						
≤ Primary school	10	20.0	16	32.0	2.051	0.359
High school	30	60.0	24	48.0		
University	10	20.0	10	20.0		
Income status						
Lom	2	4.0	7	14.0	3.053	0.217
Middle	39	78.0	35	70.0		
High	9	18.0	8	16.0		
	min.-max	$\bar{x}$ (SD)	min.-max	$\bar{x}$ (SD)	T	*P*-value
Age	23-41	32.32(5.30)	23-41	31.68(5.44)	0.596	0.553
BMI	23.53-41.02	29.48(3.46)	23.53(41.02)	29.23(3.63)	0.357	0.722
Operation time (min)	22-40	32.46(4.79)	20-35	26.16(3.39)	7.587	<0.001
Post-op Pain (VAS)	2-7	4.42(1.54)	1-6	2.82(1.47)	5.321	<0.001
Baby's characteristics						
Weight (gr)	2750-4500	3403.200 (331.327)	2750-4500	3376.000 (327.682)	0.413	0.681
Size (cm)	48-53	49.56(1.20)	48-53	49.40(1.16)	0.678	0.499
Head circumference (cm)	34-35	34.50(51)	34-35	34.48(50)	0.198	0.843

χ^2: Pearson Chi-square analysis, SD: 2, t: Independent samples t-test, SD: 98

Table 2: Comparison of the incidence of urinary tract infection, hematuria and bladder injury in the participants in the intervention and control groups

	Bladder Flap (n=50)		Omission of a Bladder Flap (n=50)		Test	*P*-value
	n	%	n	%		
Urine culture						
Positive	4	8.0	2	4.0		0.678 [F]
Negative	46	92.0	48	96.0		
Hematuria						
Yes	15	30.0	12	24.0	χ^2:0.457	0.499
No	35	70.0	38	76.0		
Bladder injury						
Yes	3	6.0	-	-		0.242 [F]
No	47	94.0	50	100.0		

χ^2: Pearson Chi-square analysis, SD: 2 t: Independent samples t-test, SD: 98

Table 3: Comparison of the mean hemogram values of the participants by group and time

Hemogram Values	Bladder Flap (n=50)	Omission of a Bladder Flap (n=50)	Difference between groups	
	$\bar{x}$ (SD) (min-max)	$\bar{x}$ (SD) (Min-max)	t*	*P*-value
Preoperative hemogram (g/dl)	11.82(1.14) (9.2-14)	11.83(1.11) (9.2-13.8)	0.044	0.965
Postoperative hemogram (g/dl)	11.09(1.10) (8.8-13.3)	11.16(1.04) (8.8-13.4)	0.318	0.751
Intra-group differences test: t**	5.984	9.948		
P-value	<0.001	<0.001		
Preoperative hematocrit (%)	34.99(2.84) (29-41)	35.20(2.85) (29-41.6)	0.365	0.716
Postoperative hematocrit (%)	32.97(2.76) (27.3-38.3)	33.02(2.86) (27-37.8)	0.093	0.926
Intra-group differences test: t**	6.001	9.852		
P-value	<0.001	<0.001		

t *: independent samples t-test, SD: 98 t **: dependent samples t-test, SD: 49

The residual urine volume on the 2nd postoperative day was significantly different between the two groups (*P*=0,045, Table 4), while it was similar on the 5th postoperative day and 6th postoperative week (*P*=1.000, Table 4). However, the incidence of residual volume determined during the three measurements significantly differed between the groups (*P*<0.001, Table 4). According to the results of further analysis, the incidence of residual urine detection on the 2nd postoperative day was significantly higher than that which was detected on the 5th

postoperative day and 6th postoperative week, both in the bladder flap and the control groups (P<0.001, P<0.001, respectively, Table 4), while postoperative 5th day and 6th week measurements were similar (P>0.05 for all, Table 4). When the participants in the groups presented to have their controls at the 6th week, there was no significant difference between the groups in terms residual urine volumes (P=1.000, Table 4).

Mean post-cesarean section UDI-6 scores determined on the postoperative second day and the eighth week were similar (P=1.000, Table 5). However, when the intragroup differences in terms of the post-cesarean section mean UDI-6 scores were analyzed, it was determined that the scores obtained at the postoperative sixth week both in the bladder flap and control groups (11.67 (7.21) and 11.11 (6.92), respectively) were lower than were those obtained on the second postoperative day (29.33 (21.91) and 29.33 (19.28), respectively) (P=0.695, Table 5).

Table 4: Comparison of the residual urine volumes of the participants by group and time

	Bladder Flap (n=50)		Omission of a Bladder Flap (n=50)		Difference between groups	
	n	%	n	%	Test	*P*-value
2nd day residual urine volume >150ml						
Yes	14	28.0	6	12.0	χ^2: 4.000	0.045
No	36	72.0	44	88.0		
5th day residual urine volume >150ml						
Yes	3	6.0	3	6.0		1.000F
No	47	94.0	47	94.0		
6th week residual urine volume >150ml						
Yes	-	-	-	-		
No	50	100.0	50	100.0		AY
Intra-group differences test C-Q / P	23.286 /0 .000		19.500 /0 .000			
Difference	2nd day > 5th day and 6th week		2nd day > 5th day and 6th week			

χ2: Pearson chi-square test, SD: 1, F: Fisher's Exact test) AY: Analysis could not be performed because there was not enough sample size. C-Q: Cochran's Q test, SD: 2, Post hoc analysis: McNemar test with a Bonferroni correction

Table 5: Comparison of the mean UDI-6 scores obtained by the participants by group and time

Measurement time	Bladder Flap (n=50) $\bar{x}$ (SD) (Min-max)	Omission of a Bladder Flap (n=50) $\bar{x}$ (SD) (Min-max)	Difference between groups t*	*P*-value
2nd day UDI-6 total score	29.33(21.91) (11.11 - 72.22)	29.33(19.289 (11.11 - 72.22)	<0.001	1.000
6th week UDI-6 total score	11.67(7.21) (0 - 33.33)	11.11(6.92) (0 - 33.33)	0.393	0.695
Intra-group differences test t**	5.382	8.328		
P-value	<0.001	<0.001		
d / post hoc power	0.91 / 1.00	1.08 / 1.00		

t *: independent samples t-test, SD: 98 t **: dependent samples t-test, SD: 49

Discussion

In most of the Cesarean sections, the bladder flap technique is widely used depending on the preference of the obstetrician. Since antibiotic use was not widespread in the past years, surgeons performed bladder flaps to prevent the spread of infection to the peritoneal cavity and to reach the lowest uterine segment with minimal damage to the bladder. Nowadays, although the bladder flap application has become standard in Cesarean sections, there is not enough evidence indicating its effectiveness [3,17]. Therefore, many factors such as bladder flap application and the effects of analgesic agents increase the incidence of PUR after cesarean section [7].

The homogeneity of the groups in this study terms of age, BMI, income status, and the neonates' birthweights and head circumference measurements is important. The present study results are consistent with those of other studies conducted on the issue [7,18].

Comparison of the groups in terms of surgery time and postpartum VAS scores revealed a significant difference between the two groups. Both the duration of the surgery and postoperative pain values were significantly higher in the bladder flap group compared to the control group. In Hohlagschwandtner et al.'s study [19], the duration of the surgery was longer and need for analgesics were higher in the group who had bladder flaps created than in the group who did not. Similarly, according to meta-analysis of O'Neill et al. [20], the duration of the surgery was longer in groups undergoing bladder flap procedure. In Aklaghi et al.'s study [21] conducted with 201 primiparous women having undergone cesarean section, the duration of the surgery was longer and the need for analgesia was higher in the bladder flap group than in the non-bladder flap group. However, in other studies to investigate urinary symptoms after Cesarean section, the duration of the surgery was insignificantly shorter in the group with bladder flaps than in those without [1]. On the other hand, in a study conducted by Çetin et al. [18], there was no significant difference between the groups in terms of surgery time. In a randomized controlled study conducted by Tuuli et al. [5], the comparison of the VAS scores of the groups determined on the first postoperative day demonstrated that there was no significant difference between the groups. The duration of the surgery in the present study was different from that in other studies, which was probably due to the fact that conditions in the operating rooms were different and that the surgeon performing the operation did not use the flap technique routinely. In addition, every different application performed during cesarean surgery may have increased the level of pain felt by the person in the postoperative period, and VAS scores may have been significantly different due to the clinical and cultural differences regarding analgesic drugs administered postoperatively.

There was a statistically significant difference between the bladder flap and non-bladder flap groups in terms of the residual urine volume on the postoperative second day, which were similar on the 5th postoperative day and the 6th postoperative week. Hemoglobin and hematocrit values and the incidence of hematuria, urinary system infection, and injury of bladder were similar between the two groups. The results of the study conducted by Tuuli et al. [5] on 258 women indicated that there were no significant differences between the groups in terms of hemoglobin and hematocrit values, and the incidence of bladder injury, urinary tract infection and hematuria. Similarly, according to O'Neill et al.'s [20] meta-analysis conducted to investigate whether the omission of bladder flap would decrease postpartum morbidity during post-Cesarean section, there were no differences between bladder flap and non-bladder flap applications in terms of developing postoperative complications. The results of another study revealed that while there were no significant differences between the groups in terms of hemoglobin and hematocrit values, the residual urine volume was significantly higher in the flap group than in the non-flap

group [18]. The results of the present study were consistent with those of the other study results.

Postpartum PUR is a significant risk factor for maternal morbidity [22,23]. In this study conducted to determine the effect of bladder flap and omission of the bladder flap application during cesarean section performed under general anesthesia on the long-term urinary retention, there was no significant difference between the groups when urinary symptoms were evaluated with the UDI-6 scale at postpartum 2nd day and 6th week, which was similar to the results of the study of Boyle et al., which investigated the same parameters among patients in which bladder flaps were and were not created [1].

The results of this study demonstrated a decrease in residual urine volume in the participants with high residual urine volume after Kegel exercises, and their postoperative 2nd day and 6th week residual urine volumes and UDI-6 scores were significantly different. In their studies evaluating the effectiveness of Kegel exercises in preventing urine retention and edema formation in perineal sutures, Sumiasih et al. [24] found that Kegel exercise not only prevented postpartum urinary retention and edema in the perineal suture, but also helped mothers to return to their pre-pregnancy states.

The strengths of our study include the training of patients with high residual urine volume and urinary symptoms on Kegel exercises during discharge. The ultrasonographic evaluations performed on the 5th postoperative day and 6th week indicated that Kegel exercises decreased residual urine volume in both groups. In addition, in both groups, urinary symptom-related UDI-6 scores measured on the postoperative 6th week were statistically significantly lower than were those measured on the postoperative 2nd day.

Limitations

The present study has some limitations. First, it is a single-center study with a small sample size and second, the results obtained from this study are applicable only to the primiparous pregnant women who participated in the study, and thus cannot be generalized to other women. Similar future studies with multi-center design may promote the reliability of results for the general pregnant population.

Conclusion

In the current study, residual urine volume on the 2nd postoperative day was higher, the duration of the surgery was longer, and the postoperative pain was higher in the bladder flap group compared to the non-bladder flap group. There were no differences between the groups in terms of residual urine volume, UDI-6 scores and bladder injury on the postoperative 5th day and 6th week. In addition, Kegel exercises taught to the participants during discharge by healthcare workers played a significant role in reducing the residual urine volume and urinary symptom complaints.

References

1. Boyle AL, Mulla BM, Lamb SV, Greer JA, Shippey SH, Rollene NL. Urinary symptoms after bladder flap at the time of primary cesarean delivery: a randomized controlled trial (RTC). International urogynecology journal. 2017;29(2):223-8.
2. Betrán AP, Ye J, Moller AB, Zhang J, Gülmezoglu AM, Torloni MR. The increasing trend in caesarean section rates: global, regional and national estimates: 1990-2014. PloS one. 2016;11(2):e0148343.
3. Malvasi A, Tinelli A, Gustapane S, Mazzone E, Cavallotti C, Stark M et al. Surgical technique to avoid bladder flap formation during cesarean section. G Chir. 2011;32(11-12):498-503.
4. Berghella V, Baxter JK, Chauhan SP. Evidence-based surgery for cesarean delivery. Am J Obstet Gynecol. 2005;193:1607–17.
5. Tuuli MG, Odibo AO, Fogerty P, Roehl K, Stamilio D, Macones GA. Utility of the bladder flap at cesarean delivery: a randomized controlled trial. Obstet Gynecol. 2012;119:815–21.
6. Dahlke JD, Mendez-Figueroa HM, Rouse DJ, Berghella V, Baxter JK, Chauhan SP. Evidence-based surgery for cesarean delivery: an updated systematic review. Am J Obstet Gynecol. 2013;209(4):294–306.
7. Liang CC, Chang SD, Chang YL, Chen SH, Chueh HY, Cheng PJ. Postpartum urinary retention after cesarean delivery. International Journal of Gynecology & Obstetrics. 2007;99(3):229-32.
8. Chai AT, Wong T, Mak HLJ, Cheon C, Yip SK, Wong ASM. Prevalence and associated risk factors of retention of urine after cesarean section. Int Urogynecol J. 2008;19:537–42.
9. Mulder FEM. Postpartum urinary retention: Risk factors, clinical impact and management. University of Amsterdam, Faculteit der Geneeskunde; 2017.
10. Bates CP, Bradley WE, Glen ES, Griffiths D, Melchior H, RowanD. Third Report on the Standardization of Terminology of Lower Urinary Tract Function Procedures related to the evaluation of micturition: pressure-flow relationships. Residual urine. Produced by the International Continence Society, February 1977. Br J Urol. 1980;52:348–50.
11. Yip SK, Sahota D, Pang MW, Chang A. Post- partum urinary retention. Acta Obstet Gynecol Scand. 2004;83:881–91.
12. Thanagumtorn K. Accuracy of Post-Void Residual Urine Volume Measurement Using an Ultrasound Bladder Scanner among Postoperative Radical Hysterectomy Patients. J Med Assoc Thai. 2016;99(10):1061-6.
13. Vassalo BJ, Kleeman SD, Segal LJ, et al. Tension free vaginal tape: A QOL assessment. Obstet Gynecol. 2002;100:518-24.
14. Cam C, Sakalli M, Ay P, Cam M, Karateke A. Validation of the short forms of the incontinence impact questionnaire (IIQ-7) and the urogenital distress inventory (UDI-6) in a Turkish population. Neurourology and Urodynamics. Official Journal of the International Continence Society. 2007;26(1):129-33.
15. Aslan FE Öntürk KZ. Ağrı ölçümü ve değerlendirilmesi. Aslan Eti, F. (Ed). Ağrı Doğası ve Kontrolü. Ankara. Akademisyen Tıp kitapevleri. 2014: 67-100.
16. George D, Mallery M. SPSS for Windows Step by Step: A Simple Guide and Reference, 17.0 update (10a ed.) Boston: Pearson (2010).
17. Mahajan NN: Justifying formation of bladder flap at Cesarean section? Arch Gynecol Obstet. 2009;279:853–5.
18. Cetin BA, Mathyk BA, Barut S, Zindar Y, Seckin KD, Kadirogullari P. Omission of a Bladder Flap during Cesarean Birth in Primiparous Women. Gynecologic and obstetric investigation. 2018;83(6):564-8.
19. Hohlagschwandtner M, Ruecklinger E, Husslein P, Joura EA. Is the formation of a bladder flap at cesarean necessary? A randomized trial. Obstetrics & Gynecology. 2001;98(6):1089-92.
20. O'Neill HA, Egan G, Walsh CA, Cotter AM, Walsh SR. Omission of the bladder flap at caesarean section reduces delivery time without increased morbidity: a meta-analysis of randomised controlled trials. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2014;174:20-6.
21. Farideh Akhlaghi MD, Azadeh Khazaie MD, Fateme Jafaripour MS. Comparing Formation or Non-Formation of Bladder Flap at Cesarean Section on Perioperative and Postoperative Complications: Double-Blind Clinical Trial. J Family Reprod Health. 2017;11(3):152–8.
22. Kermans G, Wyndaele JJ, Thiery M, De Sy W: Puerperal urinary retention. Acta Urologica Belgica. 1986;54:376–85.
23. Yip SK, Sahota D, Pang MW, Chang A: Post- partum urinary retention. Acta Obstet Gynecol Scand. 2004;83:881–91.
24. Sumiasih NN, Sri Erawati NLP, Dwi Purnamayanti NM. The Effectivity of kegel Exercise to prevent the occurence of urınary retention and edema on the sutures of the perineum. The Journal of Health. 2012;9:167-72.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1195-1200.
DOI: 10.28982/josam.824815

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

An experimental study on the long-term and short-term effects of PRP treatment on the endometrium and ovaries

PRP tedavisinin endometriyum ve yumurtalıklar üzerindeki uzun vadeli ve kısa vadeli etkileri üzerine deneysel bir çalışma

Özcan Budak [1], Veysel Toprak [2], Can Türkler [3]

[1] Sakarya University Faculty of Medicine, Department of Histology and Embryology, Sakarya, Turkey
[2] Tatvan Can Hospital, Department of Gynecology and Obstetrics, Bitlis, Turkey
[3] Erzincan Binali Yıldırım University Faculty of Medicine, Department of Gynecology and Obstetrics, Erzincan, Turkey

ORCID ID of the author(s)
ÖB: 0000- 0002-2617-3175
VT: 0000-0002-3280-851X
CT: 0000- 0003-2716-0322

Corresponding author/Sorumlu yazar:
Özcan Budak
Address/Adres: Sakarya Üniversitesi Tıp Fakültesi Histoloji-Embriyoloji A.D., Sakarya, Türkiye
E-mail: ozcanbudak@sakarya.edu.tr

Ethics Committee Approval: Sakarya University Medical Experimental Application and Research Center (SUDETAM), Ethics Committee (Number: 05.02.2020/14) approved the study.
Etik Kurul Onayı: Sakarya Üniversitesi Tıbbi Deneysel Uygulama ve Araştırma Merkez (tarihi ve numarası: 05.02.2020/14) çalışmayı onayladı.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: It has been reported that ovaries have stem cells, and they can be used in the treatment of patients with low ovarian reserves by maturing them through some growth factors. PRP, a new therapy, has many bioactive compounds including growth factors. This study aimed to investigate the long and short-term biochemical and histopathological effects of platelet-rich plasma (PRP) treatments on the lining of the uterus and the ovaries in rats.

Methods: Female rats (n = 21) were randomly divided into 3 groups: A sham group, a short-term PRP group and a long-term PRP group. At the end of the study, anti-Mullerian hormone (AMH) and follicle-stimulating hormone (FSH) levels were examined in blood samples obtained from the intracardiac area, and the ovaries and uterus of the rats were examined to determine the histopathological and immunohistochemical findings.

Results: The results of this study demonstrated that, in the blood samples of the rats, the AMH levels increased and FSH levels decreased in the short-term PRP group ($P<0.05$). When the uteri and ovaries of the rats were examined histopathologically, positive and beneficial effects of the PRP therapy were found in the short-term PRP group. However, considering the long-term results, the positive effects of PRP decrease as time goes on.

Conclusion: This study showed that PRP application delivers beneficial effects to the uterus and ovaries in female rats in the short term.
Keywords: Anti-Mullerian hormone, Follicle-stimulating hormone, Ovary, Platelet-rich plasma, Rat, Endometrium

Öz

Amaç: Yumurtalıkların kök hücrelere sahip olduğu ve yumurtalık rezervi düşük olan hastaların bazı büyüme faktörleri ile olgunlaştırılarak tedavisinde kullanılabileceği bildirilmiştir. Yeni bir tedavi olan PRP, büyüme faktörleri dahil olmak üzere birçok biyoaktif bileşiğe sahiptir. Bu çalışma, sıçanlarda trombositten zengin plazma (PRP) tedavilerinin uterus ve yumurtalıkların iç yüzeyine uzun ve kısa vadeli biyokimyasal ve histopatolojik etkilerini araştırmayı amaçladı.

Yöntemler: Dişi sıçanlar (n=21) rastgele 3 gruba ayrıldı: Sham grup, kısa süreli bir PRP grubu ve bir uzun süreli PRP grubu. Çalışma sonunda intrakardiyak alandan alınan kan örneklerinde anti-Mullerian hormonu (AMH) ve folikül stimüle edici hormon (FSH) seviyeleri incelendi ve ratların yumurtalık ve uterusu incelendiğinde histopatolojik ve immünohistokimyasal bulgular.

Bulgular: Sıçanların kan örneklerinde kısa süreli PRP grubunda AMH düzeylerinin arttığını ve FSH düzeylerinin düştüğünü göstermiştir ($P<0.05$). Sıçanların rahim ve yumurtalıkları histopatolojik olarak incelendiğinde, kısa süreli PRP grubunda PRP tedavisinin olumlu ve faydalı etkileri tespit edildi. Ancak uzun vadeli sonuçlar dikkate alındığında PRP'nin olumlu etkileri zaman geçtikçe azalmaktadır.

Sonuç: PRP uygulamasının kısa vadede dişi sıçanlarda rahim ve yumurtalıklara faydalı etkiler sağladığını göstermiştir.
Anahtar kelimeler: Anti-Mullerian hormone, Follicle-stimulating hormone, Over, Platelet-Rich plasma, Rat, Endometriyum

How to cite/Atıf için: Budak Ö, Toprak V, Turkler C. An experimental study on the long-term and short-term effects of PRP treatment on the endometrium and ovaries. J Surg Med. 2020;4(12):1195-1200.

Introduction

It is thought that the number of female reproductive cells is fixed at birth and exhausted over time due to increasing age, natural periods, and external factors such as toxins [1]. In some studies, it has been reported that ovaries have stem cells and that they can be used in the treatment of patients with low ovarian reserves by maturing them with some growth factors [2].

Platelet-rich plasma (PRP), a new therapy, is used in many health fields (surgery, dermatology, orthopedics, and dentistry) [3, 4]. PRP is defined as the autologous concentration of platelets: 3 to 5 times more than the physiological concentration of platelets in normal blood [5]. PRP has a therapeutic effect due to the presence of various factors, such as transforming growth factor β (TGF-β), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1), platelet-derived growth factor (PDGF), connective tissue growth factor (CTGF), zinc (Zn) and superoxide dismutase (SOD). The beneficial effects of PRP arise mainly from these many bioactive compounds [6].

In experimental studies in rats, PRP has also been shown to protect the ovaries in ovarian ischemia-reperfusion injury [7]. It has been observed that the growth of the primordial germ cell line is due to the growth factors contained in PRP, which induce their proliferation in in vitro culture mediums [8]. It has been reported that in many studies involving menopausal patients, the ovarian reserves are insufficient, follicle-stimulating hormone (FSH] levels decrease, and that the application of intraovarian PRP can increase oocyte production [2,9,10]. There is no conclusion about how long the positive effect of PRP continues in these studies.

Also, the long- and short-term effects of PRP on the uterus and ovaries have not been reported in published literature yet. The aim of this study was to investigate the long- and short-term biochemical and histopathological effects of PRP therapy applied to rat uteri and ovaries.

Materials and methods

Animals

Experimental animals were obtained from the Sakarya University Medical Experimental Application and Research Center (SUDETAM). A total of twenty-one Sprague-Dawley female rats weighing 235 ± 20 grams were randomly selected for use in the experiments. The rats were all 3 months old, sexually active and had a menstrual cycle. Animals were housed and fed at normal room temperature (22 to 24°C) prior to the experiment. The study was conducted at the Sakarya University Experimental Studies and Research Center. The experimental procedure was approved by the Sakarya University Committee for Animal Research. The recommendations of the 'The European Commission Directive 86/609/ECC guidelines' were taken into consideration. (Ethics Committee Number: (05.02.2020/14).

PRP preparation method

The blood samples were taken from the tail veins of the rats to prepare for PRP therapy. These blood samples from rats were placed into vacuum tubes containing 0.1 M of citrate buffer. PRP was prepared using the two-stage centrifuge method. The final concentration of the PRPs obtained was confirmed to be 6.2 × 106 platelets/ml and was made ready for application [11].

Experimental groups and procedures

Rats were randomly divided into three groups before the experiment as follows: The short-term PRP group, the long-term PRP group and a control group scheduled for a sham operation. The Sprague-Dawley female rats had a menstrual cycle 6 times in one month and all rats completed the study without any fatalities.

Sham group (SG; n = 7): A single dose of 0.9% saline (1 ml/kg) was administered to the uterus and ovaries of the rats in this group; the rats were sacrificed by decapitation after 3 menstrual cycles.

Short-term PRP group (ST-PRP; n = 7): A single dose of PRP (1 ml/kg) was administered to the uterus and ovaries of the rats; the rats were sacrificed by decapitation after 3 menstrual cycles.

Long-term PRP group (LT-PRP; n = 7): The rats with a single dose of PRP (1 ml/kg) to the uterus and ovaries were kept for 3 months. At the age of 6 months (after 18 menstrual cycles), the rats were sacrificed by decapitation to examine the long-term effects of PRP on the ovaries and endometrium [12, 13].

All surgical procedures were carried out under sterile conditions in proper laboratory settings. All rats were intraperitoneally administered 200/10 mg/kg (i.p.) of ketamine/xylazine for anesthesia and then the uterus and ovaries were observed through a 2 to 2.5 cm incision in the lower abdomen. PRP was injected into the uterus and ovaries of the rats in the ST-PRP and LT-PRP groups. At the same time, the same volume of 0.9% saline was injected into the SG group. The abdomens of all groups were sutured after the procedure. The rats in the SG and ST-PRP groups were sacrificed by decapitation after 3 menstrual cycles. The rats in the LT-PRP groups were sacrificed by decapitation after 18 menstrual cycles.

When the groups were sacrificed, blood was taken intracardially under anesthesia for anti-Mullerian hormone (AMH) and FSH measurement. Their uterine and ovarian tissues were removed, and tissue samples were evaluated histopathologically. The biochemical, immunohistochemical (IHC) and histopathological results were compared between the three groups.

Biochemical analysis of AMH and FSH

Under anesthesia, intracardiac blood samples were taken from rats with the help of an injector and transferred into glass tubes. These samples were centrifuged at 3000 rpm for 10 minutes and their serum was separated. FSH and AMH levels in the serum samples were measured by the Roche Modular Analytics system E170 electrochemiluminescence immunoassay method. Serum hormone levels were measured with an autoanalyzer (Beckman Coulter DXI-600). The results were expressed as nanograms/milliliter (ng/ml).

Histopathological analysis

A histological examination was performed at the histology department in the medical faculty of Sakarya University. After removal of the uterus and ovaries, samples were fixed in 10% formaldehyde. The tissues were passed through a 50%, 60%, 70%, 80%, 90%, 96% and 100%

concentrated ethanol series, respectively. The tissues were firstly embedded in paraffin and then cut into 4 µm-thick sections, which were deparaffinized with xylene and rehydrated with alcohol and water. Sections were stained with hematoxylin-eosin (HE) and Masson-Trichrome (MT) (According to the BioOptica application procedure, Milan, ITALY). Tissue sections examined under a microscope (Nikon Eclipse Ni-inverted microscope, Nikon Corp., Japan) with a digital camera system (NIS Elements Imaging Software, Nikon Corp., Japan) by a histologist under blind conditions.

The histological findings in the uterine tissue, including fibrosis, vascular proliferation and inflammation (neutrophil infiltration), were evaluated. Semi-quantitatively, a scoring scale from 0 to 3 was used. The amount of fibrosis was scored as follows:

0 = no fibrosis

1 = minimal fibrosis

2 = moderate fibrosis, and

3 = dense fibrosis.

Inflammation was scored as follows:

0 = no inflammation

1 = occasional lymphocytes and plasma cells

2 = presence of plasma cells, eosinophils and neutrophils

3 = presence of many inflammatory cells.

Vascular proliferation was scored as follows:

0 = no vascular proliferation

1 = mild vascular proliferation

2 = moderate vascular proliferation, and

3 = intense vascular proliferation [14].

2.6 Immunohistochemical examination

Ki-67 (GeneTex; Cat. No: GTX16667; USA) and VEGF (GeneTex; Cat. No: GTX102643; USA) were used to demonstrate tissue stimulation and proliferation in the endometrium and ovaries. Sections of 5 µm were taken from the tissue samples. The prepared slides were incubated

values were used for the descriptive statistical analysis. The differences between with VEGF (1: 400) and Ki-67 (1: 400) for 1 hour at room temperature in a humid environment. At the end of the incubation period, the slides were washed with Phosphate Buffered Saline (PBS). The slides were then stained with diaminobenzidine (DAB) and HE for 10 minutes.

For the Ki-67 and VEFG immunoreactivity assessment in uterine tissue, a light microscope was used at 200× magnification. Ki-67 was analyzed semi-quantitatively in the immuno-staining assessment by selecting ten random areas on the stained slide. One hundred cells were selected and displayed from each area. Ki-67 indices were expressed as the percentage of cells stained positively compared to all cells [15,16]. To assess VEGF expression, the number of capillaries and proliferation cells were counted, and counting was done by selecting at least 3 random areas [17].

For the Ki-67 and VEFG immunoreactivity assessment in ovarian tissue, a light microscope was used at 200× magnification. For Ki-67, positive cells were randomly counted in five different areas. The VEGF was randomly counted in 10 areas and the scoring system used was 1 = weak, 2 = medium and 3 = strong [18].

Statistical analysis

SPSS software version 22.0 was used to conduct the statistical analysis (SPSS Inc., Chicago, IL). Mean and standard deviation the groups were assessed by One-Way ANOVA (Tukey analysis). A *P*-value of less than 0.05 was considered statistically significant.

Results

The blood hormone results of this study are summarized in Table 1. The AMH level in the blood was 1 (0.14) ng/ml in the SG and 1.5 (0.33) ng/ml in the ST-PRP. When compared with SG, the increase in AMH level in ST-PRP was significant ($P<0.05$). However, sufficient AMH elevation was not detected in the LT-PRP group.

Short-term PRP application significantly decreased the FSH level in the blood of rats compared to SG ($P<0.05$). Long-term PRP application, by comparison with the SG, significantly decreased the FSH level (1 (0.07) ng/ml) in the LT-PRP ($P<0.05$).

The immunohistochemical results for ovarian and uterine tissues in this study are summarized in Table 2. When the uterus and ovaries were examined in terms of the presence of Ki-67 and VEGF, a statistically significant increase was observed in the ST-PRP and LT-PRP groups ($P<0.05$).

The histopathological scoring results of uterine tissues were compared between the 3 groups and are summarized in Table 3. After PRP application, while the amounts of fibrosis and inflammation decrease in the uterine tissue, vascular proliferation increases. Compared to the SG group, this effect was statistically significant in the ST-PRP group ($P<0.05$), but not statistically significant in the LT-PRP group ($P>0.05$).

Table 1: The blood hormone results of rats for the three groups

	SG (n:7)	ST-PRP (n:7)	LT-PRP (n:7)	P1	P2	P3
FSH	1.4(0.31)	0.85(0.11)	1(0.07)	0.001	0.005	0.335
AMH	1(0.14)	1.5(0.33)	1(0.11)	0.002	0.889	0.005

P1: Comparison of SG and ST-PRP, P2: Comparison of SG and LT-PRP, P3: Comparison of ST-PRP and LT-PRP

Table 2: The immunohistochemical results of ovarian and uterine tissues for three groups

	SG (n:7)	ST-PRP (n:7)	LT-PRP (n:7)	P1	P2	P3
Ki-67 (ovary)	22(1.9)	37.5(2.5)	28.4(2)	<0.001	<0.001	<0.001
VEGF (ovary)	24.7(2.4)	38.8(2.9)	31.5(2.3)	<0.001	<0.001	<0.001
Ki-67 (uterus)	15.8(1)	31.2(1.6)	25.2(3.7)	<0.001	<0.001	<0.001
VEGF (uterus)	25(1.6)	36.7(1.3)	31.1(1.3)	<0.001	<0.001	<0.001

P1: Comparison of SG and ST-PRP, P2: Comparison of SG and LT-PRP, P3: Comparison of ST-PRP and LT-PRP

Table 3: The histopathological scoring results of uterine tissues for the three groups

Uterus	SG (n:7)	ST-PRP (n:7)	LT-PRP (n:7)	P1	P2	P3
Fibrosis	1.29(0.48)	0.57(0.53)	0.71(0.48)	0.041	0.114	0.858
Inflammation	1.29(0.48)	0.57(0.53)	0.86(0.69)	0.041	0.367	0.631
Vascular proliferation	1.00(0.00)	1.57(0.53)	1.29(0.48)	0.049	0.424	0.424

P1: Comparison of SG and ST-PRP, P2: Comparison of SG and LT-PRP, P3: Comparison of ST-PRP and LT-PRP

The uterine sections of the study groups stained with HE are shown in Figure 1, and the MT-stained sections are shown in Figure 2. The Ki-67 and VEGF stained sections of the uterine and ovarian tissues of the study groups are shown in figures 3, 4, 5 and 6.

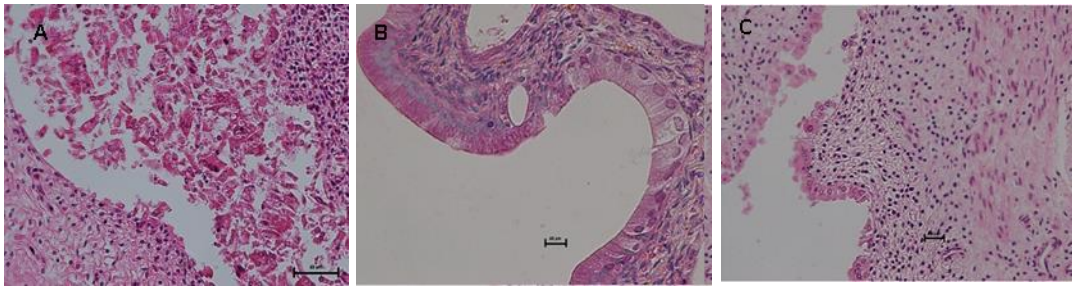


Figure 1: Hematoxylin-eosin (HE) sections from a single rat uterus of each group (×200). (A (SG): The epithelial layer is irregular, the endometrium epithelium has been shed in most areas. B (ST-PRP): The epithelial layer appears smooth and it is noteworthy that it is more regular than both the LT-PRP group and the SG group. C (LT-PRP): Although the epithelial layer is irregular in some areas, the endometrial epithelial cells in the area facing the lumen show a more regular structure compared to the SG group.)

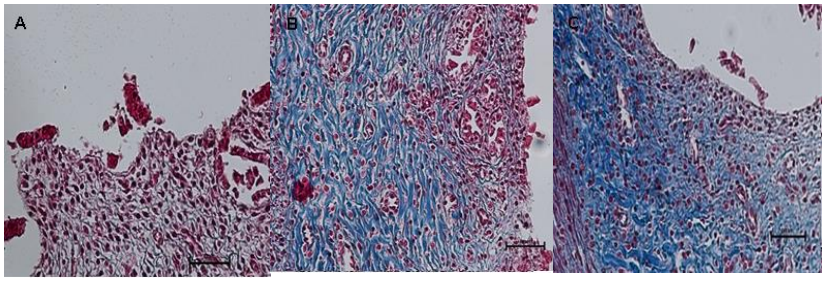


Figure 2: Masson-Trichrome (MT) sections from a single rat uterus of each group (×200). (A (SG): The epithelial layer is irregular, but the fibrosis and collagen fiber areas are observed to be more regular. B (ST-PRP): It seems that the epithelial layer is regular in some areas, and the fibrosis and collagen fiber areas are more regular and dense than the SG and LT-PRP groups. C (LT-PRP): Although the epithelial layer is only a small amount, the fibrosis and collagen fiber areas were extensively evaluated.)

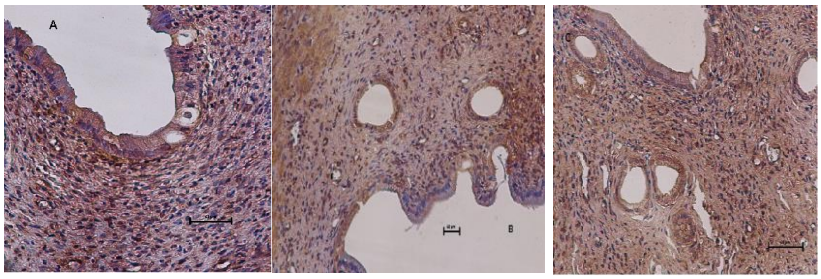


Figure 3: Indication of the activity of Ki-67 expression on the uterus using the IHC staining method for each group (×200). (A (SG), B (ST-PRP), C (LT-PRP): The SG group is less intensely stained than the PRP-treated groups. The expression density of Ki-67 in the ST-PRP group is higher than in the LT-PRP group.)

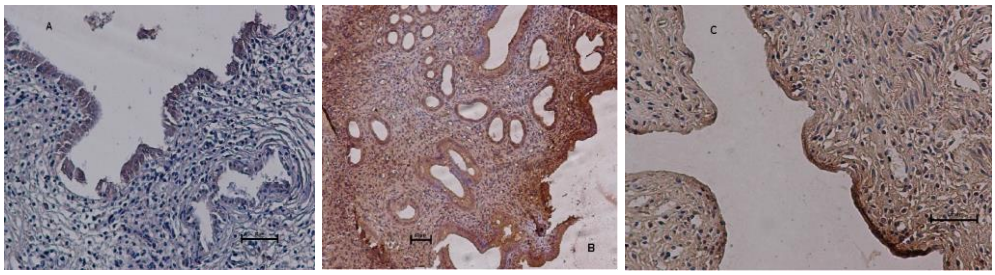


Figure 4: Indication of the activity of VEGF expression on the uterus using the IHC staining method for each group (×200). (A (SG), B (ST-PRP), C (LT-PRP): The SG group is less intensely stained than the PRP-treated groups. VEGF expression intensity in the ST-PRP group is higher than in the LT-PRP group.)

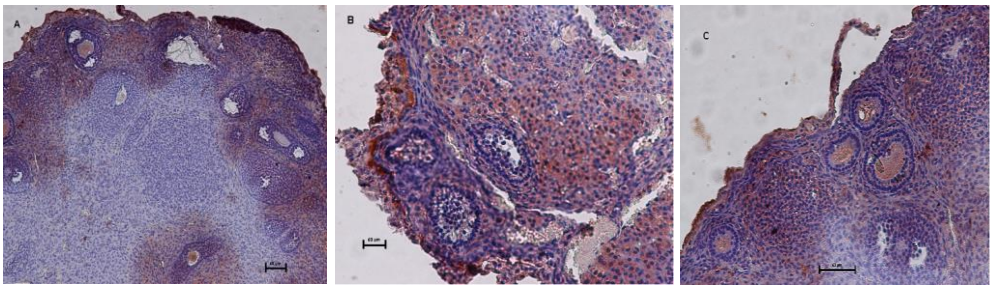


Figure 5: Indication of the activity of Ki-67 expression on the ovaries using the IHC staining method for each group (×200). (A (SG), B (ST-PRP), C (LT-PRP): Compared to the PRP-treated groups, regions close to the germinal epithelium were stained in the SG group. In the ST-PRP and LT-PRP groups, Ki-67 expression was intensely observed over the entire ovarian tissue.)

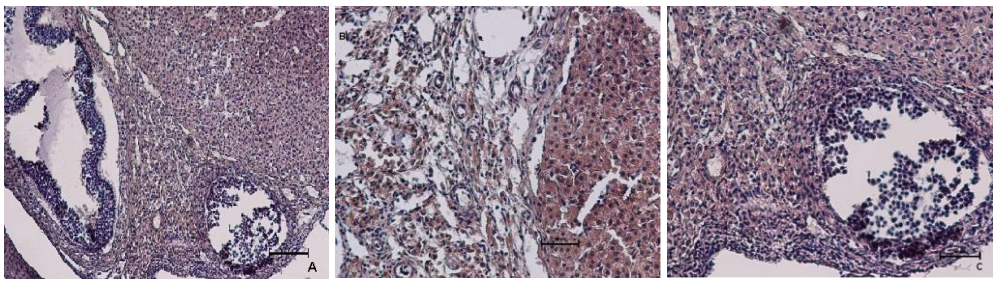


Figure 6: Indication of the activity of VEGF expression on the ovaries using the IHC staining method for each group (×200). (A (SG), B (ST-PRP), C (LT-PRP): The SG group was less intensely stained than the PRP-treated groups. In the ST-PRP and LT-PRP groups, VEGF expression was observed to be intense over the entire ovarian tissue.)

Discussion

PRP is an autologous serum that contains various growth factors and cytokines such as FGF, PDGF, VEGF, TGF-β, IGF-1, IGF-2, CTGF and IL-8 [19]. These molecules are involved in tissue proliferation and regeneration. Some researchers have shown that PRP application has a positive effect on the growth and development of follicles in the ovaries [8]. When the literature was examined, it was seen that PRP applied before intrauterine insemination has a positive effect on the increase of endometrial thickness [20].

When the studies in the field of gynecology were examined, it was seen that PRP application is performed alongside infertility treatments and for a brief time. There is an uncertainty about the long-term effects of this application, which is considered effective and beneficial in the short term in infertility treatments [10,20]. Because of these reasons, this study planned to show – for the first time – the short-term and long-term effects of PRP treatment on uterine and ovarian tissue. The intention was also to try and clarify what caused changes to the parameters like AMH and FSH, which provide information about the reproductive capacity of women.

Sfakianoudis et al. [10] showed that the FSH value decreased, the AMH value increased, and even pregnancy could be achieved in patients with premature menopause following PRP treatment. In this current study, when the SG group and ST-PRP group were compared, it was found that FSH decreased and AMH increased. In addition, when the SG group and LT-PRP group were compared, the decrease observed in FSH was statistically significant. However, there was no difference between the AMH amounts between the two groups. AMH is a marker that provides information about the reproductive capacity in women, regardless of the menstrual cycle. Therefore, by looking at the blood results of the study groups, it can be said that the positive effect of PRP gradually decreased in the long term.

VEGF is the main molecule that plays a role in angiogenesis and vasculogenesis [21]. Ki-67 is known as the main proliferation marker [22]. When Table 2 is examined, it is seen that Ki-67 and VEGF staining increased in both uterine and ovarian tissue in the PRP-treated groups. As a result of the growth factors that PRP contains, tissue proliferation and angiogenesis increased. When the results of the LT-PRP group were examined, the changes in VEGF and Ki-67 expression at the tissue level continued for a long time, contrary to the blood results.

When the histopathological results of the SG group and ST-PRP group were compared for the uterus, it was seen that the amount of inflammation and fibrosis decreased, but vascular proliferation increased. This positive effect of PRP at a tissue level was not seen in the LT-PRP group.

PRP applications are mostly used to increase the success of assisted reproductive techniques in the field of infertility. In order to increase endometrial thickness and pregnancy rates, PRP is applied in the same cycle in which the assisted reproductive technique is applied. The results of this current study support the literature showing that the positive effects of PRP decrease as time goes on [19,23,24].

When Figure 2 is examined, the amount of collagen fiber and fibrosis increased in the stroma of the uterus for PRP-treated groups. It is noteworthy that especially in the LT-PRP group, the amount of collagen fiber increased and became more concentrated. It is thought that this is related to the CTGF which is contained in the PRP. Uncontrolled increases in the amount of connective tissue in the organs can disrupt the microenvironment of the tissues. Uncontrolled increases in connective tissue can lead to decreased flexibility of organs and thus to decreased function of the organs [25]. The increase in the amount of connective tissue in the organs due to CTGF may be the limiting factor in repeated PRP applications.

In the literature, intra-abdominal PRP application is reported to decrease adhesion formation and accelerate wound healing [4]. Spartalis et al. [26] reported that intra-abdominal PRP application would be inconvenient in patient groups undergoing operations for malignancies. It is estimated that growth factors in PRP can increase malignant cell formation and occult metastases.

Limitations

This current study featured some limitations. Firstly, prior to this study, there has been no data about the long-term effects of PRP treatments for uterine and ovarian tissue. Secondly, as the aim of the study was to investigate if PRP had beneficial effects on the uterus and ovaries, only a single and average dose of 1 ml/kg was examined. It would be better to compare different doses of PRP to find the mean effective dose. Thirdly, the study did not examine the follicle counts via histopathology in the ovaries. Counting primordial, developing and atretic follicles could enable us to show the effects of PRP on ovarian tissue in more detail. Fourthly, the results of experimental studies on animals should not be extrapolated to humans. We think that more accurate information will be possible in the future should more studies on this subject be carried out.

Conclusion

As a result of our study, positive effects of PRP application on the ovaries and endometrium are observed on histological and hormonal levels. Since we applied a single dose of PRP in our study, we observed that the positive effects of PRP were more effective in a short time after the application and that the effects of PRP application decreased in the long term. If PRP application is to be preferred as a treatment, we think that applying a cure at regular intervals instead of a single dose application may have longer and permanent effects in terms of treatment efficiency. This idea should be supported by further research.

References

1. Garcia-Velasco JA, Acevedo B, Alvarez C, Monica A, Jose B, Juan F, et al. Strategies to Manage Refractory Endometrium: State of the Art in 2016. Reprod Biomed Online. 2016;32(5):474-89.
2. Sills ES, Wood SH. Autologous Activated Platelet-Rich Plasma Injection Into Adult Human Ovary Tissue: Molecular Mechanism, Analysis, and Discussion of Reproductive Response. Biosci Rep. 2019;39(6):BSR20190805.
3. Lubkowska A, Dolegowska B, Banfi G. Growth Factor Content in PRP and Their Applicability in Medicine. J Biol Regul Homeost Agents. 2012;26(2 Suppl 1):3S-22S.
4. Kaya F, Kismet K, Ozer H, Soylu VG, Duymus ME, Akgun YA, et al. Can Platelet-Rich Plasma Be Used Safely in Intra-Abdominal Operations? Bratisl Lek Listy. 2016;117(9):525-29.
5. Knezevic NN, Candido KD, Desai R, Kaye AD. Is Platelet-Rich Plasma a Future Therapy in Pain Management? Med Clin North Am. 2016;100(1):199-217.
6. Magalon J, Bausset O, Serratrice N, Laurent G, Houssein A, Julie V, et al. Characterization and Comparison of 5 Platelet-Rich Plasma Preparations in a Single-Donor Model. Arthroscopy. 2014;30(5):629-38.

7. Bakacak M, Bostanci MS, İnanc F, Yaylali A, Serin S, Attar R, et al. Protective Effect of Platelet Rich Plasma on Experimental Ischemia/Reperfusion Injury in Rat Ovary. Gynecol Obstet Invest. 2016;81(3):225-31.
8. Hosseini L, Shirazi A, Naderi MM, Shams-Esfandabadi N, Borjian Boroujeni S, Sarvari A, et al. Platelet-rich Plasma Promotes the Development of Isolated Human Primordial and Primary Follicles to the Preantral Stage. Reprod Biomed Online. 2017;35(4):343-50.
9. Sfakianoudis K, Simopoulou M, Nitsos N, Rapani A, Pantou A, Vaxevanoglou T, et al. A Case Series on Platelet-Rich Plasma Revolutionary Management of Poor Responder Patients. Gynecol Obstet Invest. 2019;84(1):99-106.
10. Sfakianoudis K, Simopoulou M, Nitsos N, Rapani A, Pappas A, Pantou A, et al. Autologous Platelet-Rich Plasma Treatment Enables Pregnancy for a Woman in Premature Menopause. J Clin Med. 2018;8(1):1.
11. Nagata MJ, Messora MR, Furlaneto FA, Fucinia SE, Boscoa AF, Garciaa VG, et al. Effectiveness of Two Methods for Preparation of Autologous Platelet-Rich Plasma: An Experimental Study in Rabbits. Eur J Dent. 2010;4(4):395-402.
12. Jang HY, Myoung SM, Choe JM, Kim T, Cheon YP, Kim YM, et al. Effects of Autologous Platelet-Rich Plasma on Regeneration of Damaged Endometrium in Female Rats. Yonsei Med J. 2017;58(6):1195-203.
13. Zhang S, Li P, Yuan Z, Tan J. Platelet-rich Plasma Improves Therapeutic Effects of Menstrual Blood-Derived Stromal Cells in Rat Model of Intrauterine Adhesion. Stem Cell Res Ther. 2019;10(1):61.
14. Irkorucu O, Ferahköşe Z, Memiş L, Ekinci O, Akin M. Reduction of Postsurgical Adhesions in a Rat Model: A Comparative Study. Clinics (Sao Paulo). 2009;64(2):143-8.
15. Yokoyama Y, Takahashi Y, Morishita S, Hashimoto M, Niwa K, Tamaya T. Telomerase Activity in the Human Endometrium Throughout the Menstrual Cycle. Mol Hum Reprod. 1998;4(2):173-7.
16. McCampbell AS, Walker CL, Broaddus RR, Cook JD, Davies PJ. Developmental Reprogramming of IGF Signaling and Susceptibility to Endometrial Hyperplasia in the Rat. Lab Invest. 2008;88(6):615-26.
17. Li X, Sun H, Lin N, Hou X, Wang J, Zhou B, et al. Regeneration of Uterine Horns in Rats by Collagen Scaffolds Loaded With Collagen-Binding Human Basic Fibroblast Growth Factor. Biomaterials. 2011;32(32):8172-81.
18. Ribeiro AA, Martin I, Derussi AA, Ferioli RB, Laufer-Amorim R, Lopes MD. Histological Characterization and Immunohistochemical Localization of ki-67 and VEGF Factors in Bitches' Corpus Luteum at Cyclic and Early and Late Gestational Diestrous. Reprod Domest Anim. 2012;47 Suppl 6:61-5.
19. Nazari L, Salehpour S, Hoseini S, Zadehmodarres S, Ajori L. Effects of autologous platelet-rich plasma on implantation and pregnancy in repeated implantation failure: A pilot study. Int J Reprod Biomed (Yazd). 2016;14(10):625-8.
20. Sipahi M. Effects of Autologous Platelet-Rich Plasma on Endometrium Thickness and Pregnancy Rates During Intrauterine Insemination. Middle Black Sea Journal of Health Science. 2019; 5(2):63-6.
21. Apte RS, Chen DS, Ferrara N. VEGF in Signaling and Disease: Beyond Discovery and Development. Cell. 2019;176(6):1248-64.
22. Sun X, Kaufman PD. Ki-67: more than a proliferation marker. Chromosoma. 2018;127(2):175-186.
23. Chang Y, Li J, Chen Y, Wei L, Yang X, Shi Y, et al. Autologous platelet-rich plasma promotes endometrial growth and improves pregnancy outcome during in vitro fertilization. Int J Clin Exp Med. 2015;8(1):1286-90.
24. Sfakianoudis K, Simopoulou M, Nitsos N, Lazaros L, Rapani A, Pantou A, et al. Successful Implantation and Live Birth Following Autologous Platelet-rich Plasma Treatment for a Patient with Recurrent Implantation Failure and Chronic Endometritis. In Vivo. 2019;33(2):515-21.
25. Wu CK, Wang YC, Lee JK, Chang SN, Su MY, Yeh HM, et al. Connective tissue growth factor and cardiac diastolic dysfunction: human data from the Taiwan diastolic heart failure registry and molecular basis by cellular and animal models. Eur J Heart Fail. 2014;16(2):163-72.
26. Spartalis E, Damaskos C, Athanasiou A. Safety of platelet-rich plasma application in abdominal operations. Bratisl Lek Listy. 2017;118(7):437.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1201-1204.
DOI: 10.28982/josam.822731

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Effect of air pollution, air pressure and air temperature on new onset pulmonary thromboembolism: A case-control study

Hava kirliliği, hava basıncı ve hava sıcaklığı değişikliklerinin yeni başlangıçlı pulmoner tromboembolizm üzerine etkisi: Olgu kontrol çalışması

Engin Akgül [1], Gündüz Yümün [2]

[1] Health Sciences University, Evliya Çelebi Training and Research Hospital, Department of Cardiovascular Surgery Kütahya, Turkey
[2] Corlu State Hospital, Department of Cardiovascular Surgery, Corlu, Turkey

ORCID ID of the author(s)

EA: 0000-0001-7361-0430
GY: 0000-0002-1503-329X

Corresponding author/Sorumlu yazar:
Engin Akgül
Address/Adres: Sağlık Bilimleri Üniversitesi, Evliya Çelebi Eğitim ve Araştırma Hastanesi, Kalp Damar Cerrahisi Anabilim Dalı Kütahya, Türkiye
E-mail: engin_akgul@hotmail.com

Ethics Committee Approval: The study was approved by the institutional Ethical Committee of Evliya Celebi Training and Research Hospital (2017-KAEK-86/05-37). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma, Evliya Çelebi Eğitim ve Araştırma Hastanesi Kurumsal Etik Kurulu (2017-KAEK-86/05-37) tarafından onaylandı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: Air pollution affects many people globally and there are allegations and studies that it leads to serious health problems, such as pulmonary thromboembolism. In this study, we investigated the possible relationship between air conditions and pulmonary thromboembolism.

Methods: This study was carried out by archive scanning. Patients with acute dyspnea who were shown to have PE by contrast-enhanced CT were included in the analysis. Patients with a history of trauma, malignancy, recent surgical intervention, or immobility were excluded from the study. On the day of complaints, Particulate matter 10 (PM10), sulfur dioxide (SO_2), air temperature and air pressure values were obtained online from the relevant institution of Environment and Urban Ministry. These 215 patients' data were then evaluated statistically.

Results: Results suggest that the incidence of pulmonary embolism was higher on days when PM10 (P<0.001) and air pressure levels were high (P<0.001). However, SO_2 and temperature were not directly associated with the frequency of pulmonary embolism (P=0.422, P=0.778).

Conclusion: In light of this study, it can be said that air quality may have different consequences on human health. Elevated PM10 and air pressure levels can affect the circulatory system negatively and aggravate thromboembolism.

Keywords: Particulate matter, PM10, SO_2, Air pressure, Pulmonary thromboembolism, Air pollution

Öz

Amaç: Hava kirliliği, dünyada pek çok kişiyi etkiliyor ve pulmoner tromboembolizm gibi ciddi sağlık sorunlarına yol açtığına dair iddialar ve araştırmalar var. Bu çalışmada, hava koşulları ile pulmoner tromboembolizm arasındaki olası ilişkiyi araştırdık.

Yöntemler: Bu çalışma arşiv taramasıyla gerçekleştirildi. Kontrastlı BT ile PE olduğu gösterilen akut nefes darlığı olan hastalar analize dahil edildi. Travma, malignite, yakın zamanda cerrahi müdahale veya hareketsizlik öyküsü olan hastalar çalışma dışı bırakıldı. Şikayet günü Çevre ve Şehircilik Bakanlığı'nın ilgili kurumundan Partikül madde 10 (PM10), kükürt dioksit (SO2), hava sıcaklığı ve hava basıncı değerleri online olarak alındı. Bu 215 hastanın verileri daha sonra istatistiksel olarak değerlendirildi.

Bulgular: Bulgular, pulmoner emboli insidansının PM10 (P<0,001) ve hava basıncı düzeylerinin yüksek (P<0,001) olduğu günlerde daha yüksek olduğunu göstermektedir. Ancak, SO2 ve sıcaklık, pulmoner emboli sıklığı ile doğrudan ilişkili değildi (P=0,422, P=0,778).

Sonuç: Bu çalışmanın ışığında hava kalitesinin insan sağlığı üzerinde farklı sonuçları olabileceği söylenebilir. Yüksek PM10 ve hava basıncı seviyeleri dolaşım sistemini olumsuz etkileyebilir ve tromboembolizme neden olabilir.

Anahtar kelimeler: Partikül madde, PM10, SO_2, Hava basıncı, Pulmoner tromboembolizm, Hava kirliliği

How to cite/Atıf için: Akgül E, Yümün G. Effect of air pollution, air pressure and air temperature on new onset pulmonary thromboembolism: A case-control study. J Surg Med. 2020;4(12):1201-1204.

Introduction

Air pollution, a global problem that is common in developing countries, can cause serious health problems. According to the World Health Organization data, air pollution causes 700000 premature births in the world every year [1]. It is also reported as a risk factor for mortality and morbidity from cardiovascular and cerebrovascular events [2]. One of the possible mechanic pathways is enhanced thrombosis, hypercoagulability, and vascular endothelial damage. In addition, trauma, immobilization, and malignancy are among the risk factors. Hypercoagulation is a hallmark of thromboembolism, which can manifest as deep venous thrombosis (DVT) or pulmonary embolism (PE). PE is one of the major sudden death causes.

The idea that PM and DVT/PE may be related has recently emerged and studies have shown that there is indeed an interaction. Although studies are limited and some findings are conflicting, there is growing evidence that air pollution is a risk factor for cardiovascular and cerebrovascular events. Studies have been conducted on the effects of meteorological and air pollution parameters on the cardiovascular system and it is stated that the risk of cardiovascular disease may vary depending on the seasons [3]. It has also been reported that the incidence of PE increases when weather conditions are poor or rainy [4], but there is no consensus on this finding [5]. In this study, we investigated whether air pollution, pressure, temperature, and PE are related.

Materials and methods

Patients

After approval of local institutional of Evliya Celebi Training and Research Hospital Ethical Committee (2017-KAEK-86/05-37), the study was conducted by scanning the files of 215 patients, including 97 females and 118 males. The patients were selected among those admitted to the emergency department or chest diseases clinic with sudden onset dyspnea and diagnosed with acute PE by contrast-enhanced computed tomography (C-CT) between January 2012 and March 2019. The control group consisted of patients without PE, who applied with the same complaints. Demographic characteristics of the patients included in the study are listed in Table 1. Patients with a history of PE, malignancy, immobility, hematologic disorders, and recent trauma were excluded from the study. The history of the patients' complaints were recorded from the anamnesis.

Air quality parameters

PM10 and SO_2 values for the period of study were available at www.havaizleme.gov.tr (National air quality monitoring network). The air pressure and air temperature of those days were obtained from www.mgm.gov.tr (General Directorate of Meteorology). Air quality measurement takes different parameters such as PM2.5, O3, NO2 and CO into account. However, since only PM10 and SO_2 measurements were performed regularly in the city where the study was conducted, the study was carried out by considering these two parameters only.

Statistical analysis

We used Statistical Package for the Social Sciences (IBM SPSS Statistic Inc. version 21.0, Chicago, IL, USA) for statistical analysis. Continuous and ordinal variables were expressed as mean (standard deviation) and nominal variables were expressed as frequency and percentage. Kolmogorov-Smirnov test and Shapiro-Wilk tests of normality were used to identify distribution of variables. Chi Square test was used to compare two groups for nominal variables. Mann-Whitney U test was used to compare two groups of non-normally distributed continuous variables, while Student's t test was used to compare two groups of normally distributed continuous variables. The relationship between the air pollutants and PE was evaluated by binary logistic regression analysis. For all tests, a *P*-value of <0.05 was considered statistically significant. Receiver-operating characteristic (ROC) curve was applied for the prediction of PE and the area under the curve was calculated for PM10 and air pressure levels.

Results

Demographic characteristics of the patients are presented in Table 1. A total of 215 patients in the PE (+) group (54.8% male, mean age: 59.7 (6.3) years), and 150 patients in PE (-) group (59.3 male, mean age: 60.2 (5.4) years) were evaluated. Most patients in PE (+) group (66.8%) had concomitant deep vein thrombosis (DVT) (*P*<0.001), and they were either active or previous smokers (65.8%), which was a predisposing factor for PE (*P*=0.014). The other parameters such as gender (*P*=0.189), age (*P*=0.354), BMI (*P*=0.453), HT (*P*=0.181) and coronary heart disease (*P*=0.190) were not related with PE.

Air quality had a remarkable effect on PE development. PM10 levels were higher in the PE (+) group (*P*<0.001), and air pressure levels were significantly different between the two groups (*P*<0.001), while SO_2 and air temperature levels were similar (*P*=0.422, *P*=0.778 respectively) (Table 2).

Table 1: Demographic features of the patients

	PE (+) (n=215)	PE (-) (n=150)	*P*-value
Male (%)	54,8	59,3	0.189*
Age	59.7 (6.3)	60.2 (5.4)	0.354#
BMI (kg/m^2) mean (SD)	25.6 (7.4)	26.4 (4.6)	0.453a
Hypertension (%)	36.7	29.5	0.181*
Coronary Heart Disease (%)	23.8	17.6	0.190*
Deep Venous Thrombosis (%)	66.8	10.2	<0.001*
Smoking (%)			
Current or in the past	65.8	52.5	0.014*

* Pearson Chi- Square, # Student's *t* test, a Mann-Whitney U test

Table 2: Air quality and the other parameters for study groups

	PE (-) group n=150	PE (+) group n=215	*P*-value*
PM 10	78.36 (2.82	100.64 (2.65	<0.001*
SO2	9.79 (0.74	11.43 (0.78	0.422
Air Pressure	902.55 (0.45	905.15 (0.34	<0.001*
Air Temperature	17.038 (0.93	17.27 (0.79	0.778

PM10: Particulate matter 10, SO2: Sulphur dioxide, * Mann Whitney U test

Logistic regression analysis performed for air pollutants showed that the incidence of PE was correlated with PM10 (*P*<0.001, OR [Odds Ratio]: 1.022, 95% CI [Confidence interval]: 1.012-1.032) and air pressure (*P*=0.009, OR:1.147, CI: 1.032-1.272), and was not correlated with SO_2 (*P*=0.908, OR:1.002, CI: 0.971-1.034) and air temperature (*P*=0.629, OR:992, CI: 0.961-1.025) (Table 3).

Table 3: Binary Logistic regression analysis to identify predictors of PE

Variables	*P*-value	Exp(B) Odds Ratio	95% CI Lower Upper
PM10	<0.001	1.022	1.012 – 1.032
SO2	0.908	1.002	0.971 – 1.034
Air Pressure	0.009	1.147	1.035 – 1.272
Air Temperature	0.629	.992	0.961 – 1.025

ROC curve analysis determined a cut-off level of 84.5 for PM10 (Area under the curve (AUC): 0.668, 95% CI: 0.613-723, Long rank $P<0.001$, 64.2% sensitivity and 61.3% specificity) (Figure 1) and 903.5 for air pressure (AUC: 0.670, 95% CI: 0.614-725, Long rank $P<0.001$, 64.2% sensitivity and 63.3% specificity) (Figure 2) for predicting PE.

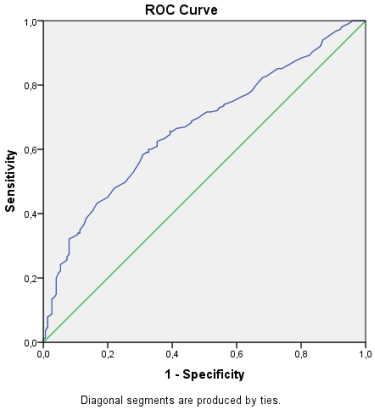


Figure 1: ROC Curve for PM10 and Pulmonary embolism

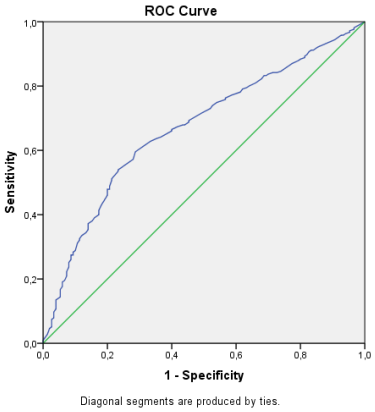


Figure 2: ROC Curve for Air Pressure and Pulmonary embolism

Discussion

The National Morbidity, Mortality and Air Pollution study, which examines the impact of air pollution on health, showed that air pollution above 20-µg / m^3 increases the risk of cardiovascular disease [6]. In another study involving 691 patients, air pollution increased myocardial infarction risk [7]. Myocardial infarction is the secondary systemic effect of pollutants. After pollutant inhalation, pulmonary inflammation occurs first. After translocation of the polluting agent from the lung to blood, secondary systemic effects, such as myocardial infarction, are observed.

Only PM10 and SO2 values could be measured by the National Air Monitoring Center in Kütahya. According to our study, the short-term exposure to an elevated level of air pollutants is a risk factor for PE. Therefore, our study involved these two pollutants. However, carbon monoxide, nitrogen dioxide and sulfur dioxide are also reported to cause air pollution and cardiovascular events [8,9]. This is the major lack of this study.

The air pressure is 1013 mbar at sea level, and values greater than 1013 mbar indicate high pressure. The source of the air pressure is atmospheric gas density, and it decreases with altitude increase. Changes in air temperature and climate affect gas density, causing changes in average air pressure. In the literature, fatal PE cases have also been reported in air pressure changes [10,11]. Kütahya air pressure values for the days included in the study ranged from 894 to 918 mbar (904 (0.25)). In our study, the mean air pressure was significantly higher in the PE (+) group, There are studies indicating that PE frequency increases in cold weather [11,12]. This may be due to exposure to higher concentrations of N_2O and O_3 in cold weather because of decreased gas expansion [12]. However, there are also arguments suggesting that cardiovascular diseases are more common in hot weather [13]. This is a result of dehydration and increased blood viscosity [1]. In our study, the mean air temperature was 17.1°C (0.6) with no significant differences between the groups. The air is also more polluted due to the fuel used for heating in winter. Although higher incidences of PE were reported during winter, there is no consensus in the literature regarding the relationship between air temperature and PE. We also could not detect any relationship between temperature and PE.

Although SO_2 is one of the basic air pollutants [14,15], there are limited series showing the association between SO_2 and PE. A few studies reported that SO_2 was positively correlated with serious cardiovascular disease [16,17,18]. The values measured on the days included in the study were normal. The fact this study was not conducted in an industrial city and the lack of thermal power plants have enabled SO_2 values to remain at normal levels. Consequently, there was no significant relationship between PE and SO_2.

Ambient PM is named according to particle size. Particles between 2.5µg-10µg are called PM10. In various studies, it is stated that especially <2.5µg PMs are more toxic, cause increased inflammatory response and platelet activation and are therefore more dangerous [19,20]. In addition, PM's sympathetic system activation, inflammatory and vasoconstrictive effects begin within the first 12 hours, which later increase coagulation [21]. In our study, PM2.5 was not measured, and our analysis was limited to PM10, which is also one of the main pollutants used in air quality measurement. Diseases caused by high levels of PM10 have been extensively studied in the literature, especially its negative impact on the cardiovascular system [22-24]. In our research, we found that PM10 values significantly correlated with the number of PE cases. Thus, we can easily state that air pollution causes PE.

Limitation

This study was conducted by examining the data of an uncrowded city. Larger studies involving different cities may yield clearer results.

Conclusion

Our study identified that elevated air pollutants are risk factors for PE. Elevated PM10 levels and high air pressure are correlated with acute PE cases. It will be useful to be aware of this relationship and take measures, especially in industrial cities.

References

1. Schinder A, Panagiotakos D, Picciotto S, Katsouyannı K, Lövel H. Air temperature and inflammatory responses in myocardial infarction survivors Epidemiology. 2008 May;19(3):391-400.
2. Franchini M, Mannucci PM. Particulate air pollution and cardiovascular risk: short-term and long-term effects Semin Thromb Hemost. 2009 Oct;35(7):665-70.
3. Stein PD, Kayalı F, Olson RE. Analysis of occurrence of venous thromboembolic disease in the four seasons Am J Cardiol. 2004 Feb 15;93(4):511-3.
4. Clauss R, Mayes J, Hilton P, Lawrenson R. The influence of weather and environment on pulmonary embolism: pollutants and fossil fuels Med Hypotheses. 2005;64(6):1198-201.
5. Anar C, Inal T, Erol S, Polat G, Unsal I, Ediboglu Ö, et al. Are Meteorological Parameters a Risk Factor for Pulmonary Embolism? A Retrospective Analysis of 530 Patients Balkan Med J. 2015 Jul;32(3):279-84.
6. Dominici F, McDermott A, Daniels M, Zeger SL, Samet JM. Revised analyses of the National Morbidity, Mortality, and Air Pollution Study: mortality among residents of 90 cities J Toxicol Environ Health A. 2005 Jul 9-23;68(13-14):1071-92.
7. Peters A, Von Klot S, Heier M, Trentinaglia I, Hormann A. Exposure to traffic and the onset of myocardial infarction N Engl J Med. 2004 Oct 21;351(17):1721-30.
8. Chuang GC, Yang Z, Westbrook DG, Pompilius M, Ballinger CA. Pulmonary ozone exposure induces vascular dysfunction, mitochondrial damage, and atherogenesis Am J Physiol Lung Cell Mol Physiol. 2009 Aug;297(2):L209-16.
9. Wang XB, Jin HF, Tang CS, Du JB. The biological effect of endogenous sulfur dioxide in the cardiovascular system Eur J Pharmacol. 2011 Nov 16;670(1):1-6.
10. Oztuna F, Ozsu S, Topbas M, Bulbul Y, Kosucu P, Ozlu T. Meteorological parameters and seasonal variations in pulmonary thromboembolism Am J Emerg Med. 2008 Nov;26(9):1035-41.
11. Törö K, Pongracz R, Bartholy J, Varadi TA, Marcsa B, Szilagyi B, et al. Evaluation of meteorological and epidemiological characteristics of fatal pulmonary embolism.Int J Biometeorol. 2016 Mar;60(3):351-9.
12. DE Miguel-diez J, Jimenza R, Lopez de Andreas A. Analysis of environmental risk factors for pulmonary embolism: A case-crossover study (2001-2013). Eur J Intern Med. 2016 Jun;31:55-61.
13. Bhaskaran K, Hajat S, Haines A, Herrett E, Wilkinson P, Smeeth L. Effects of ambient temperature on the incidence of myocardial infarction Heart. 2009 Nov;95(21):1760-9.
14. Lelieved J, Evans JS, Fnais M, Giannadaki D, Pozzer A. The contribution of outdoor air pollution sources to premature mortality on a global scale Nature. 2015 Sep 17;525(7569):367-71.
15. Pope CA, Dockery DW. Health effects of fine particulate air pollution: lines that connectJ Air Waste Manag Assoc. 2006 Jun;56(6):709-42.
16. Atkinson RW, Carey IM, Kent AJ, van Staa TP, Anderson HR, Cook DG. Long-term exposure to outdoor air pollution and incidence of cardiovascular diseases. Epidemiology 2013;24:44-53.
17. Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, et al. Longterm exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med 2007;356:447-58.
18. Rosenlund M, Berglind N, Pershagen G, Hallqvist J, Jonson T, Bellander T. Long-term exposure to urban air pollution and myocardial infarction. Epidemiology 2006;17:383-90.
19. Meng X, Ma Y, Chen R, Zhou Z, Chen B, Kan H. Size-fractionated particle number concentrations and daily mortality in a Chinese city Environ Health Perspect. 2013 Oct;121(10):1174-8.
20. Zhao A, Chen R, Wang C, Zhao Z, Yang C. Associations between size-fractionated particulate air pollution and blood pressure in a panel of type II diabetes mellitus patients Environ Int. 2015 Jul;80:19-25.
21. Wang C, Chen R, Zhao Z, Cai J, Lu J. Particulate air pollution and circulating biomarkers among type 2 diabetic mellitus patients: the roles of particle size and time windows of exposure Environ Res. 2015 Jul;140:112-8.
22. Colais P, Serienelli M, Faustini A, Stafoggia M, Randi G. Air pollution and urgent hospital admissions in nine Italian cities. Results of the Epi Air Project Epidemiol Prev. 2009 Nov-Dec;33(6 Suppl 1):77-9.
23. Sen T, Astarcioglu MA, Asarcikli LD, Kilit C, Kafes H. The effects of air pollution and weather conditions on the incidence of acute myocardial infarction Am J Emerg Med. 2016 Mar;34(3):449-54.
24. Franchini M, Mannucci PM. Short-therm effects of air pollution on cardiovascular disease outcomes and mechanism. J Thromb Haemost. 2007;5:2169-74.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1205-1208.
DOI: 10.28982/josam.829330

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Radiological comparison of parallel fixation and divergent fixation using K-wire in pediatric lateral condyle fractures

Pediatrik humerus lateral kondil kırıklarında K-teli kullanılarak yapılan paralel tespit ile divergan tespitin radyolojik karşılaştırması

Necip Güven [1], Sezai Özkan [1], Can Özcan [1], Tülin Türközü [1], Abbas Tokyay [1], Ruhat Tanlı [2]

[1] Van Yüzüncü Yıl University, Faculty of Medicine, Department of Orthopedics and Traumatology, Van, Turkey
[2] Istanbul Beylikdüzü State Hospital, Department of Orthopedics and Traumatology, Istanbul, Turkey

ORCID ID of the author(s)

NG: 0000-0002-0363-1524
SÖ: 0000-0003-4444-6939
CÖ: 0000-0001-5929-1103
TT: 0000-0002-0966-9080
AT: 0000-0002-3914-1906
RT: 0000-0001-9377-1792

Corresponding author/Sorumlu yazar:
Sezai Özkan
Address/Adres: Van Yüzüncü Yıl Üniversitesi Tıp Fakültesi Ortopedi ve Travmatoloji Bölümü, 65080 Tuşba, Van, Türkiye
E-mail: doktorsezai@hotmail.com

Ethics Committee Approval: The approval was obtained from the Ethics Committee of Van Yüzüncü Yıl University Dursun Odabaş Medical Center dated 18/09/2020 and numbered 2020/06-02. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Van Yüzüncü Yıl Üniversitesi Dursun Odabaş Tıp Merkezi etik kurulunun onayı 18/09/2020 tarih ve 2020/06-02 sayılı kurul kararı ile alınmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: Lateral condyle fractures (LCF) of the humerus are the second most common (10-20%) after supracondylar fractures in childhood. Many methods have been described in the literature for their treatment, but a gold standard method has not been proposed. In this study, we aimed to compare the radiological results and complications of 2 different fixation methods (parallel or divergent) with K-wire in treatment.

Methods: Patients under 18 years of age who were operated in our hospital due to humeral LCF between January 2014 and January 2020 were included in this retrospective cohort study. They were divided into Group 1 (fixed with parallel K-wire) and Group 2 (fixed with divergent K-wire). The age, and gender of the patients were noted, and side, type of fracture, type of treatment, radiological union times, nonunion or delayed union, fishtail deformity, excessive growth of the lateral condyle (spur) and avascular necrosis were evaluated using plain radiographs.

Results: The mean age of 41 patients included in the study were 4.69 years, there were 28 males and 13 females. The most common type of fracture was Weiss type 2 (n=23). The most common complication was lateral overgrowth (spur) (n=7). There was no significant difference between the radiological union times and the number of complications in both groups (P=0.079, P=0.56 respectively).

Conclusion: Both methods used in LCF fractures yielded satisfactory results. Avascular necrosis rates are high in the treatment of type 3 fractures, in which strict follow-up is important.

Keywords: Lateral condyle, Fracture, Humerus, Lateral spur, Child

Öz

Amaç: Çocukluk çağında humerusun lateral kondil kırıkları (LKK), suprakondiler kırıklardan sonra en sık (%10-20) ikinci sıradadır. Literatürde bu kırıkların tedavisi için birçok yöntem tanımlanmıştır, ancak altın standart bir yöntem önerilmemiştir. Bu çalışmada, tedavide K-teli ile 2 farklı fiksasyon yönteminin (parallel veya diverjan) radyolojik sonuçlarını ve komplikasyonlarını karşılaştırmayı amaçladık

Yöntemler: Ocak 2014-Ocak 2020 tarihleri arasında hastanemize humerus LKK nedeniyle başvuran ve 18 yaş altı olan çocuk hastalar bu retrospektif kohort çalışmaya dahil edildi. Çalışmaya dahil edilen hastalarımızın tamamı LKK nedeniyle ameliyat edilen 18 yaş altı çocuklardan oluştu. Hastalar Grup 1; paralel K-teli ile sabitlenmiş ve Grup 2; diverjan K-teli ile sabitlendi. Her iki grupta yaş, cinsiyet, taraf, kırık tipi, tedavi tipi, radyolojik kaynama süreleri, kaynamama veya gecikmiş kaynama, fishtail deformitesi, lateral kondilde aşırı büyüme ve avasküler nekroz olan hastalar direk radyografiler kullanılarak değerlendirildi.

Bulgular: Çalışmaya dahil edilen 41 hastanın yaş ortalaması 4,69 yıl, 28'i erkek, 13'ü kadındı. En sık görülen kırık tipi Weiss tip 2 idi (23 hasta). En sık görülen komplikasyon 7 hastada lateral aşırı büyümeydi. Her iki grupta da radyolojik kaynama süreleri ile komplikasyon sayısı arasında istatistiksel olarak anlamlı bir fark yoktu (sırasıyla P=0,079, P=0,56).

Sonuç: LKK kırıklarında uygulanan 2 farklı yöntemin her ikisi de tatmin edicidir. Tip 3 kırıkların tedavisinde avasküler nekroz oranları yüksektir ve bu kırıklar da sıkı takip önemlidir.

Anahtar kelimeler: Lateral kondil, Kırık, Humerus, Lateral spur, Çocuk

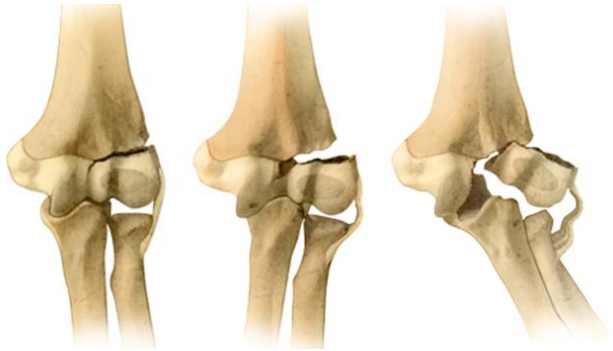
How to cite/Atıf için: Güven N, Özkan S, Özcan C, Türközü T, Tokyay A, Tanlı R. Radiological comparison of parallel fixation results with divergent fixation using k-wire in pediatric lateral condyle fractures. J Surg Med. 2020;4(12):1205-1208.

Introduction

Pediatric humerus LCFs are rare, and account for approximately 10-20% of all childhood elbow fractures. They usually occur because of forcing the extended arm to varus due to falling from height [1,2]. Displaced fractures require open reduction and internal fixation for anatomic reduction of the intra-articular component. While internal fixation is usually achieved with K-wires in young children, compression screws can be used in older children [3,4]. Although different treatment methods have been defined depending on the degree of fracture [5], the treatment of nondisplaced or minimally displaced fractures is still controversial [6,7]. The most widely used classification system for LCF is the Milch classification system. However, it has been reported that this classification does not predict the treatment results [8,9]. Weiss et al. described a new classification system for these fractures in 2009, in which, considering the displacement of the fracture, the complication rates of the treatment are specified in more detail [8]. In our study, the radiological union times, and complications of 2 different surgical methods (fixation with 2 parallel K-wires and divergent 2 K-wires) were compared using the Weiss classification.

Materials and methods

The pediatric LCF patients, who applied to our clinic between January 2014 and January 2020, were included in the study. The study started after obtaining the approval of the local ethics committee of our university on 18/09/2020 with the number 2020 / 06-02. The data was collected from the automation recording system of our hospital. Pediatric patients under 18 years of age who were operated for lateral condyle fractures and whose latest data were available were included in the study. Patients with distal humerus fractures and open fractures were excluded. After the implementation of these criteria, 41 patients whose information were available and met the inclusion criteria were evaluated. Standard antero-posterior (AP), lateral and oblique radiographs of all patients were examined. All preoperative fractures were classified according to the Weiss classification (Figure 1).



Type 1 Type 2 Type 3

Figure 1: Weiss classification

The Weiss classification, used for lateral humeral condyle fractures, is based on the degree of displacement measured from the elbow:

- Type 1: <2 mm displacement
- Type 2: 2-4 mm displacement
- Type 3: >4 mm displacement

All patients were administered general anesthesia, and a tourniquet was placed above the elbow. The plane between the brachioradialis and the triceps was determined laterally. The extensor communis muscle was partially released to view the joint surface. After the joint surface was anatomically restored, it was fixed with parallel K-wires (Figure 2) and divergent K-wires (Figure 3). In both groups, K-wires were left exposed from the skin and the long arm was splinted. Patients were called for clinical and radiological controls once a week. K-wires were removed 4-6 weeks later in patients with radiographic union. Age, gender, side, type of fracture, treatment modality, duration of radiological union and complications of both groups were evaluated. Nonunion or delayed union, fishtail deformity, and excessive growth of the lateral condyle (spur) were evaluated as complications using direct radiographs. Patients whose treatment was completed with conservative methods and patients who were followed up were excluded from the study.

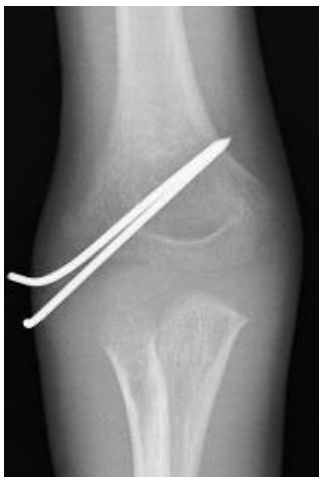


Figure 2: Postoperative radiographic image of a patient who underwent the parallel K-wire method

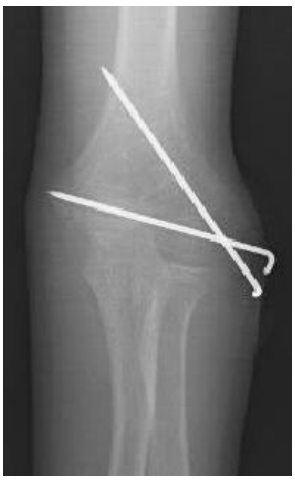


Figure 3: Postoperative radiographic image of a patient who underwent the divergent K-wire method

Statistical analysis

SPSS 21 (IBM Corp., Armonk, NY, USA) package program was used to analyze the data obtained in the study. Differences and normal values between both groups were measured using Student's t-test. Numerical data were expressed as mean (SD) and categorical data were expressed as percentages. Chi-square test or Fisher's exact test was used in the analysis of categorical data. Values of $P<0.05$ were considered statistically significant.

Results

Among 41 patients included in the study (Group 1, n=23 and Group 2, n=18), 28 were males and 13 were females. Their mean age was 4.69 years, 19 had right elbow fractures, and 22 patients had left elbow fractures. Detailed demographic data of our patients are presented in Table 1.

Lateral condyle fractures of the humerus were more common in males and more fractures occurred in the left extremity. Union occurred insignificantly earlier in the group who underwent parallel K-wire (*P=0.79*). Radiologically, Weiss fracture classification was performed for all LCF patients, and the type of intervention for fractures is presented in Table 2.

Type 2 fractures are the most common (n=23, 56%), and the least common was type 1 fractures. The radiological complications of our study are given in Table 3.

Table 1: Demographic data of our patient

	Group 1 Fixation with parallel 2 K-wire	Group 2 Fixation with divergent 2 K-wire	*P*-value
Gender			
Male(%)	15 (53.6)	13 (46.4)	0.066
Female(%)	3 (23.1)	10 (76.9)	
Side			
Right (%)	7 (36.8)	12 (63.2)	0.298
Left(%)	11(50)	11(50)	
Complication developed (%)	5 (41.7)	7 (58.3)	0.566
Average Age (SD)	4.21 (1.9)	5.17 (1.8)	0.004
Radiological union time (weeks) (SD)	5.05 (1.5)	5.34 (0.9)	0.079

SD: Standard deviation

Table 2: Distribution of patients according to the Weiss classification

Weiss Type	Group 1 Fixation with parallel 2 K-wire	Group 2 Fixation with divergent 2 K-wire	Total
Type1	1	3	4
Type 2	10	13	23
Type 3	7	7	14

Table 3: Radiological complication

	Group 1 Fixation with parallel 2 K-wire	Group 2 Fixation with divergent 2 K-wire	Total
Lateral overgrowth (Spur)	3 (16.6%)	4 (17.3%)	7 (17.07%)
Non-union	1(5.5%)	1 (4.3%)	1 (2.4%)
Avascular necrosis	1(5.5%)	1 (4.3%)	2 (4.8%)
Fishtail deformity	0	1 (4.3%)	1 (2.4%)

Three (16.6%) of 18 patients in group 1 had lateral spur, 1 (5.5%) had nonunion and 1 (5.5%) patient had avascular necrosis. In group 2, 4 (17.3%) of 23 patients had lateral spur, 1 (4.3%) had nonunion, 1 (4.3%) developed fishtail deformity and 1 (4.3%) patient had avascular necrosis.

Discussion

Although conservative treatment is recommended in pediatric humerus LCFs, the course of nondisplaced or minimally displaced fractures cannot be predicted. Later displacement of non-displaced fractures occurs in as many as 11-42%. Determining the fracture fragment by mobilizing the soft tissues in subsequent surgical procedures has been reported to cause necrosis. These are some researchers suggesting closed reduction with percutaneous nailing for minimally displaced fractures [10-12]. In the treatment of these fractures, surgical treatment is preferred in patients with a displacement of more than 2 mm to prevent significant complications such as malunion and nonunion [13]. In our clinic, surgical treatment is performed in all Type 2 and Type 3 fractures based on Weiss classification in pediatric LCFs, while Type 1 fractures are followed up closely for the reasons mentioned above. Weekly radiographic controls are performed, and the parents are informed that fracture displacement may occur. In our study, four patients with nondisplaced fractures (Weiss type 1) who were followed up with a long arm cast were provided surgical treatment in the early period and healed without complications. Three of these patients were fixed with divergent K-wires and 1 was fixed with parallel K-wires. In a study conducted by Pirker et al., displacement developed in the fracture line in 9.8% of the cases treated conservatively with plaster in minimally displaced condyle fractures [14].

After pediatric humerus LCF, complications such as lateral spur formation, nonunion, avascular necrosis of the capitellum, cessation of physis growth or excessive stimulation of physis can be observed [15]. Considering the complications that occurred at the end of our study, the most common was lateral spur in 7 cases. Lateral spur developed in 3 cases in group 1 and in 4 cases in group 2. The etiology of lateral spur formation after humerus lateral condyle fractures in children has not been fully elucidated. However, it has been stated that reasons such as insufficient reduction, physical stimulation of the lateral condyle and periosteal flap caused by the fracture fragment may play a role in the formation of lateral spur after these fractures [16,17].

In their study, Pribaz et al. [18] found that the initial fracture displacement degree was related to the degree of the spur, which did not affect the range of motion of the elbow joint. As a result of the study, we did not perform any additional surgical interventions in our 7 cases of lateral spur in both groups. One of the major complications of lateral humeral condyle fractures in children is avascular necrosis. It has been reported that the protection of the soft tissue in the lateral condyle fragment is important in reducing the possibility of avascular necrosis [19]. Both AVN cases we encountered in our study underwent traditional bonesetter intervention and presented 3 weeks after the fracture. Roye et al. [20] reported that they treated 4 LCF cases without AVN, who presented 8 weeks later. Gaur et al. [21] reported that in a study of 15 patients in which they performed open reduction and internal fixation, a more appropriate reduction was achieved with the Z-plasty they performed in the origin of the extensor communis muscle, and that these patients had almost complete union without AVN. In a study conducted by Shimada et al. [22] on 16 children with LCF, they reported AVN in only one child who had been operated twice before. In our study, the soft tissues of the posterior capitellum were preserved using a lateral approach, and thus the possibility of AVN development was reduced.

In a large-scale review in the literature, it was reported that nonunion is a rare complication in pediatric humeral LCFs and this rate is 1.4%. The absence of callus in the fracture fragment for 8 weeks can be considered nonunion. It has been reported that the most important risk factor for nonunion is type 3 fractures, and this complication has been overcome by fixing the fracture fragment with a threaded screw [23]. Nonunions were detected in 2 of 41 patients included in our study. There were cases of nonunion in 2 patients (4.8%), one in each group of 41 patients in both groups.

There are only a few studies in the literature about the superiority of parallel K-wire and divergent K-wire to one another. Although the clinical significance of joint surface reduction is well known, the ideal pinning technique has not been covered in the literature. Two or three K-wires placed parallelly or divergently were compared in terms of union and functional results in 2 previous studies on this subject [24, 25]. Bloom et al. proposed that 2 K-wires sent divergently at an angle of 60 degrees constitute the most effective method of fixation. In addition, in this biomechanical study, they reported loss of reduction in the fracture line because of the valgus test in fractures treated with 2 parallel K-wires [26]. Blasier [27] defined the potential for reduction loss in the fracture line of parallel 2 K-wire application.

Limitations

The main limitations of our study include its retrospective nature and that the elbow joint range of motion was not measured. However, since our study was based on

radiological results, functional results were not considered. Failure to evaluate varus and valgus angulations in the elbow joint after LCF can be considered a limitation.

Conclusion

In our study, no reduction loss was experienced in either method. In this study in which radiological results and complications in the treatment of pediatric LCF with 2 different methods were performed in a tertiary health center, one method was not superior to the other, and satisfactory results were obtained in both. In our clinic, it can be said that there is a tendency towards performing divergent two K-wires, at about 60 degrees to each other. Regardless of the treatment method, it is important to define the fracture well, to ensure fixation with percutaneous methods surgically, and to protect the posterior structures in incisions to be made. Avascular necrosis rates are high in the treatment of type 3 fractures, and strict follow-up, as well as informing the parents about these fractures are extremely important.

References

1. Jakob R, Fowles JV, Rang M, Kassab MT. Observations concerning fractures of the lateral humeral condyle in children. J Bone Joint Surg Br. 1975 Nov;57(4):430-6. PMID: 1104630.
2. Marcheix PS, Vacquerie V, Longis B, Peyrou P, Fourcade L, Moulies D. Distal humerus lateral condyle fracture in children: when is the conservative treatment a valid option? Orthop Traumatol Surg Res. 2011 May;97(3):304-7. doi: 10.1016/j.otsr.2010.10.007. Epub 2011 Apr 7. PMID: 21478066.
3. Loke WP, Shukur MH, Yeap JK. Screw osteosynthesis of displaced lateral humeral condyle fractures in children: a mid-term review. Med J Malaysia. 2006 Feb;61Suppl A:40-4. PMID: 17042228.
4. Li WC, Xu RJ. Comparison of Kirschner wires and AO cannulated screw internal fixation for displaced lateral humeral condyle fracture in children. Int Orthop. 2012 Jun;36(6):1261-6. doi: 10.1007/s00264-011-1452-y. Epub 2011 Dec 17. PMID: 22179811; PMCID: PMC3353087.
5. Mirsky EC, Karas EH, Weiner LS. Lateral condyle fractures in children: evaluation of classification and treatment. J Orthop Trauma. 1997 Feb-Mar;11(2):117-20. doi: 10.1097/00005131-199702000-00009. PMID: 9057147.
6. Bhandari M, Tornetta P, Swiontkowksi MF; Evidence-Based Orthopaedic Trauma Working Group. Displaced lateral condyle fractures of the distal humerus. J Orthop Trauma. 2003 Apr;17(4):306-8. doi: 10.1097/00005131-200304000-00012. PMID: 12679694.
7. Song KS, Kang CH, Min BW, Bae KC, Cho CH, Lee JH. Closed reduction and internal fixation of displaced unstable lateral condylar fractures of the humerus in children. J Bone Joint Surg Am. 2008 Dec;90(12):2673-81. doi: 10.2106/JBJS.G.01227. PMID: 19047713.
8. Weiss JM, Graves S, Yang S, Mendelsohn E, Kay RM, Skaggs DL. A new classification system predictive of complications in surgically treated pediatric humeral lateral condyle fractures. J Pediatr Orthop. 2009 Sep;29(6):602-5. doi: 10.1097/BPO.0b013e3181b2842c. PMID: 19700990.
9. Thomas DP, Howard AW, Cole WG, Hedden DM. Three weeks of Kirschner wire fixation for displaced lateral condylar fractures of the humerus in children. J Pediatr Orthop. 2001 Sep-Oct;21(5):565-9. PMID: 11521019.
10. Wattenbarger JM, Gerardi J, Johnston CE. Late open reduction internal fixation of lateral condyle fractures. J Pediatr Orthop. 2002 May-Jun;22(3):394-8. PMID: 11961463.
11. Bast SC, Hoffer MM, Aval S. Nonoperative treatment for minimally and nondisplaced lateral humeral condyle fractures in children. J Pediatr Orthop. 1998 Jul-Aug;18(4):448-50. PMID: 9661850.
12. Kamegaya M, Shinohara Y, Kurokawa M, Ogata S. Assessment of stability in children's minimally displaced lateral humeral condyle fracture by magnetic resonance imaging. J Pediatr Orthop. 1999 Sep-Oct;19(5):570-2. PMID: 10488852.
13. Abzug JM, Dua K, Kozin SH, Herman MJ. Current Concepts in the Treatment of Lateral Condyle Fractures in Children. J Am Acad Orthop Surg. 2020 Jan 1;28(1):e9-e19. doi: 10.5435/JAAOS-D-17-00815. PMID: 31268870
14. Pirker ME, Weinberg AM, Höllwarth ME, Haberlik A. Subsequent displacement of initially nondisplaced and minimally displaced fractures of the lateral humeral condyle in children. J Trauma. 2005 Jun;58(6):1202-7. doi: 10.1097/01.ta.0000169869.08723.c8. PMID: 15995471.
15. Canale ST. Fractures and Dislocations in Children. In: Canale ST, Beaty JH editors. Campell's operative orthopeadics, Mosby Elsevier, 2008: 1531-1725.
16. Beaty JH, Kasser JR. The elbow: Physeal fractures, apophyseal injuries of the distal humerus, osteonecrosis of the trochlea and condylar fractures. In: Beaty JH, Kasser JR, eds. Rockwood and Wilkin's Fractures in Children. Philadelphia: Lippincott Williams &Wilkins; 2006:591–660.
17. Koh KH, Seo SW, Kim KM, Shim JS. Clinical and radiographic results of lateral condylar fracture of distal humerus in children. J Pediatr Orthop. 2010 Jul-Aug;30(5):425-9. doi: 10.1097/BPO.0b013e3181df1578. PMID: 20574257.
18. Pribaz JR, Bernthal NM, Wong TC, Silva M. Lateral spurring (overgrowth) after pediatric lateral condyle fractures. J Pediatr Orthop. 2012 Jul-Aug;32(5):456-60. doi: 10.1097/BPO.0b013e318259ff63. PMID: 22706459.
19. Shaerf DA, Vanhegan IS, Dattani R. Diagnosis, management and complications of distal humerus lateral condyle fractures in children. Shoulder Elbow. 2018 Apr;10(2):114-120. doi: 10.1177/1758573217701107. Epub 2017 Apr 11. PMID: 29560037; PMCID: PMC5851120.
20. Roye DP Jr, Bini SA, Infosino A. Late surgical treatment of lateral condylar fractures in children. J Pediatr Orthop. 1991 Mar-Apr;11(2):195-9. doi: 10.1097/01241398-199103000-00011. PMID: 2010520.
21. Gaur SC, Varma AN, Swarup A. A new surgical technique for old ununited lateral condyle fractures of the humerus in children. J Trauma. 1993 Jan;34(1):68-9. doi: 10.1097/00005373-199301000-00012. PMID: 8437198.
22. Shimada K, Masada K, Tada K, Yamamoto T. Osteosynthesis for the treatment of non-union of the lateral humeral condyle in children. J Bone Joint Surg Am. 1997 Feb;79(2):234-40. doi: 10.2106/00004623-199702000-00011. PMID: 9052545.
23. Pace JL, Arkader A, Sousa T, Broom AM, Shabtai L. Incidence, Risk Factors, and Definition for Nonunion in Pediatric Lateral Condyle Fractures. J Pediatr Orthop. 2018 May/Jun;38(5):e257-e261. doi: 10.1097/BPO.0000000000001153. PMID: 29635260.
24. Shrader MW. Pediatric supracondylar fractures and pediatric physeal elbow fractures. Orthop Clin North Am. 2008 Apr;39(2):163-71, v. doi: 10.1016/j.ocl.2007.12.005. PMID: 18374807.
25. van Vugt AB, Severijnen RV, Festen C. Fractures of the lateral humeral condyle in children: late results. Arch Orthop Trauma Surg. 1988;107(4):206-9. doi: 10.1007/BF00449669. PMID: 3408313.
26. Bloom T, Chen LY, Sabharwal S. Biomechanical analysis of lateral humeral condyle fracture pinning. J Pediatr Orthop. 2011 Mar;31(2):130-7. doi: 10.1097/BPO.0b013e3182074c5b. PMID: 21307705.
27. Blasier RD. Operative treatment of lateral condyle fractures. In: Tolo VT, Skaggs DL, eds. Master Techniques in Orthopaedic Surgery Pediatrics. Philadelphia, PA: Lippincott Williams & Wilkens; 2008:2.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1209-1214.
DOI: 10.28982/josam.814941

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Retrospective evaluation of ultrafiltration during cardiac surgery with cardiopulmonary bypass in adult patients with increased neutrophil to lymphocyte ratio

Erişkin hastalarda kardiyopulmoner baypas ile uygulanan konvansiyonel ultrafiltrasyonun nötrofil / lenfosit oranı ile retrospektif olarak değerlendirilmesi

Şahin Şahinalp [1], Kadir Çeviker [2], Mehmet Fazıl Tolga Soyal [3], Ali Kemal Gür [1]

[1] Van Yuzuncu Yil University, Department of Cardiovascular Surgery, Van, Turkey e-mail:
[2] Izmir Western Anatolia Central Hospital, Department of Cardiovascular Surgery, Izmir, Turkey
[3] Atilim University, Department of Cardiovascular Surgery, Ankara, Turkey

ORCID ID of the author(s)

ŞŞ: 0000-0003-2202-7063
KÇ: 0000-0002-6860-7058
MFTS: 0000-0001-6276-3140
AKG: 0000-0002-6460-4941

Corresponding author/Sorumlu yazar:
Şahin Şahinalp
Address/Adres: Van Yüzüncü Yıl Üniversitesi, Kalp Damar Cerrahisi Anabilim Dalı, Tuşba, Van, Türkiye
E-mail: ssahinalp@gmail.com

Ethics Committee Approval: Ethics Committee approval was received from Van Yuzuncu Yil University Medical Faculty, Ethical committee (reference number: 2020/03-31;22/05/2020). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Van Yüzüncü Yıl Üniversitesi Tıp Fakültesi, Etik kurul onayı (referans numarası: 2020/03-31;22/05/2020) alındı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: The aim of this study was to investigate the efficacy of the ultrafiltration (UF) in adult patients undergoing open-heart surgery with cardiopulmonary bypass (CPB) by evaluating the neutrophil to lymphocyte ratio (NLR).

Methods: A retrospective case-control study was conducted on 288 adult patients who underwent CPB in a University hospital from January 2016 to December 2018. The study groups were composed of a control group (n=116) of patients who underwent surgery without UF and the study group (n=172) of patients who underwent surgery with UF. All perioperative clinical data, including neutrophil, lymphocyte and platelet count, BUN, creatinine, and C-reactive protein (CRP) values were collected. The efficacy of UF and its association with NLR, neutrophil, lymphocyte and platelet count, postoperative bleeding, extubation time, duration of intensive care unit (ICU) stay and in-hospital stay were analyzed.

Results: Neutrophil count, NLR and CRP significantly increased post-operatively compared to pre-operative values (P<0.05). The increased post-operative levels of NLR and decreased platelet counts were significantly associated with UF (P<0.05). Multivariate linear regression analysis revealed that elevated NLR was significantly and independently associated with UF.

Conclusion: UF followed by CPB in adult patients undergoing cardiac surgery was associated with increased post-operative NLR and low platelet counts, which nonetheless, were not associated with postoperative complications. UF should be chosen only for selective patients with low hematocrit and should not be chosen to attenuate whole body inflammatory response after CPB in adult cardiac surgery patients.

Keywords: Adult patients, Cardiopulmonary bypass, Ultrafiltration, Neutrophil lymphocyte ratio, Platelet, Inflammation

Öz

Amaç: Bu çalışmanın amacı, nötrofil / lenfosit oranını (NLO) değerlendirerek, kardiyopulmoner baypas (CPB) ile açık kalp cerrahisi geçiren yetişkin hastalarda ultrafiltrasyonun (UF) etkinliğini araştırmaktır.

Yöntemler: Ocak 2016'dan Aralık 2018'e kadar bir Üniversite hastanesinde CPB uygulanan 288 yetişkin hasta üzerinde retrospektif bir kohort çalışması yapılmıştır. Nötrofil, lenfosit ve trombosit sayısı, BUN, kreatinin ve C-reaktif protein (CRP) dahil olmak üzere tüm perioperatif klinik veriler geriye dönük olarak toplandı. UF'nin etkinliği ve NLO, nötrofil, lenfosit ve trombosit sayısı, postoperatif kanama, ekstübasyon süresi, yoğun bakım ünitesinde (YBÜ) kalış süresi ve hastanede kalış süresi ile ilişkisi analiz edildi.

Bulgular: Nötrofil sayısı, NLO ve CRP ameliyat öncesi değerlere göre ameliyat sonrası anlamlı olarak arttı (P<0,05). Ameliyat sonrası artan NLO seviyeleri ve azalmış trombosit sayıları UF ile anlamlı olarak ilişkili idi (P<0,05). Çok değişkenli doğrusal regresyon analizi, yükselmiş NLR'nin UF ile anlamlı ve bağımsız olarak ilişkili olduğunu ortaya çıkarmıştır.

Sonuç: Açık kalp cerrahisi uygulanan yetişkin hastalarda UF uygulamaları, artmış postoperatif NLO ve düşük trombosit sayıları ile ilişkiliydi, ancak yine de postoperatif komplikasyonlarla ilişkili değildi. UF, yalnızca düşük hematokriti olan seçici hastalar için seçilmeli ve yetişkin kalp cerrahisi hastalarında CPB'den sonra tüm vücut enflamatuar yanıtını hafifletmek için seçilmemelidir.

Anahtar kelimeler: Erişkin hasta, Kardiyo-pulmoner baypas, Ultrafiltrasyon, Nötrofil lenfosit oranı, Trombosit, Enflamasyon

How to cite/Atıf için: Şahinalp Ş, Çeviker K, Soyal MFT, Gür AK. Retrospective evaluation of ultrafiltration during cardiac surgery with cardiopulmonary bypass in adult patients with increased neutrophil to lymphocyte ratio. J Surg Med. 2020;4(12):1209-1214.

Introduction

Previous studies have demonstrated that material dependent factors, such as exposure of blood to artificial surfaces, and condition, patient, and prevalent disease-dependent factors, such as surgical trauma, ischemia-reperfusion to the organs, changes in body temperature, and release of endotoxins inevitably affect the outcomes of cardiopulmonary bypass (CPB). The activation of a complex inflammatory response, including complement activation, release of cytokines, leukocyte activation along with the expression of adhesion molecules, and the production of oxygen-free radicals, arachidonic acid metabolites, platelet-activating factor, nitric oxide, and endothelin have been well demonstrated [1-3]. These inflammatory reactions, which are invoked at the beginning of the surgery, may contribute to the development of postoperative complications including respiratory failure, renal dysfunction, bleeding disorders, neurological dysfunction, altered liver function and ultimately, multiple organ failure [2,4].

Several studies have demonstrated a relationship between over-production of inflammatory mediators, fluid accumulation to the third space of the body and/or vital organs and postoperative complications in adult patients after on-pump cardiac surgery [1-4].

The theory of ultrafiltration (UF) involves the retention of solutes of high molecular weight when the excess fluid and low molecular weight solutes such as inflammatory mediators in the blood stream are forced under hydraulic pressure through a membrane of a very fine pore size, typically between 0.001 and 0.1 μm [5-6]. Although several studies have indicated a high rate of favorable outcomes when UF was performed during CPB in cardiac surgery, some studies suggested that the long duration needed to carry out UF and UF related technical and material causes may augment the adverse effects of CPB [1-4].

Systemic inflammation during CPB is triggered by neutrophil activation, which can be monitored by a novel biomarker, the neutrophil to lymphocyte ratio (NLR) [7]. A high NLR has been associated with poor prognosis in many cardiovascular diseases [8]. Besides, recent studies suggest that increased perioperative NLR is related to poor outcomes in adult cardiac surgery patients [9]. However, NLR has not been studied well exclusively in adult patients undergoing on-pump cardiac surgery along with UF. Therefore, the objective of the present study was to examine the association of NLR levels with clinical outcomes in adult patients undergoing on-pump cardiac surgery with UF.

Materials and methods

Study design, population, and patients

288 adult patients undergoing cardiac surgery requiring CPB from January 2016 to December 2018 were included in this retrospective study (Van Yuzuncu Yil University Medical Faculty, Ethical committee approval reference number: 2020/03-31, 22/05/2020). The inclusion criteria of this study were as follows: Being between 18 and 72 years of age and undergoing cardiac surgery requiring CPB. Exclusion criteria of this study included pediatric cardiac surgery, age greater than 80 years, emergency surgery, previously diagnosed chronic renal or hepatic insufficiency, malignancy, systemic inflammatory disease, a history of cardiac surgery and failure to obtain patient data necessary for the study. The study groups were composed of a control group (n=116) of patients who underwent surgery without UF and the study group (n=172) of patients who underwent surgery with UF.

Anesthesia and management of CPB

Anesthesia and management of CPB were performed using standard techniques. Briefly, anesthesia and endotracheal intubation was performed after an intravenous injection of fentanyl (5 μg/kg), cisatracurium (0.15 mg/kg), propofol (3 mg/kg), and midazolam (0.05 mg/kg). For continuation of anesthesia, propofol (8 mg/kg/h), cisatracurium (2 μg/kg/min), and sevoflurane (1–3%) were used. Methylprednisolone (1 mg/kg) and cefazolin sodium (1000 mg) were used before skin incision as a routine surgery technique. None of the patients received intraoperative steroids.

The extracorporeal circuit included a membrane oxygenator (Affinity Fusion® oxygenator, Medtronic Inc., Minneapolis MN) and a roller pump system (Sorin C5, Sorin Group, München, Germany) equipped with a heat exchanger (Stockert®, Sorin Group, München, Germany). The circuit was primed with 500 ml of crystalloid solution (Laktatlı Ringer Solüsyonu®, Polifarma Ilac San.ve Tic. A.Ş. Ankara, Turkey), 500 ml of colloid solution (Voluven®, Fresenius Medical Care AG, Bad Homburg, Germany) and 250 ml of 20% mannitol (20% Mannitol®, Polifarma Ilac San.ve Tic. A.Ş. Ankara, Turkey) according to institutional standards. Heparin (Nevparin®, Mustafa Nevzat Ilac Sanayii A.S. Gayrettepe, Istanbul, Turkey) was administered repetitively to maintain an activated clotting time (ACT) of greater than 400 s. During CPB, non–pulsatile flow was maintained at 2.6-3 l/min/m² and the mean arterial blood pressure was maintained at 50–70 mmHg by the addition of norepinephrine (Arterenol®, Sanofi-Aventis GmbH, Hoechst, Germany). Myocardial protection was achieved with cold blood cardioplegia (4-8°C).

The prime used in the CPB circuit consisted of Ringer's acetate solution, 20% mannitol, 5% sodium bicarbonate and heparin. Blood HCT was diluted to 24–28% during CPB. The body was cooled to a target esophageal temperature of 18 to 37°C, considered moderate / mild / deep hypothermia. Once the surgery was completed, the patients were warmed and weaned from CPB. To reverse the anticoagulant effects of heparin, protamine sulfate (Promin, VEM Ilac San.ve Tic. A.Ş. Cankaya, Ankara, Turkey) was administered, guided by the ACT.

Indicators for UF were hypervolemia, hyperpotassemia, dilution of hematocrit levels and lowering the inflammatory mediators after a long duration of CPB. UF (Adult Hemofiltration Package, Sasan Ilac San.ve Tic. A.Ş. Ankara, Turkey) was initiated while the patient was being warmed using a filtration pressure of 150 - 250 mmHg at a filtration rate of 10 to 15 mL/min. The filtration membrane pressure was increased to 350 - 450 mm Hg by the end of CPB and during residual blood UF with a filtration rate of 40 to 75 mL/min. The duration of UF was maintained for at least 20- 30 minutes, unless mean blood pressure decreased to 50-60 mm Hg.

Data collection

The hospital patient database system was used to obtain pre-operative and post-operative levels of neutrophils, lymphocytes and platelet counts, urea, creatinine and CRP. NLR was calculated based on the data collated. Clinical observation data were obtained from medical and nursing records of the patient.

Statistical analysis

Categorical and numerical data are expressed as n (%) and mean (SD), respectively. Post-operative neutrophil and lymphocytes counts, NLR and CRP were compared with the pre-operative counts using the repeated measures test and between group analysis were compared with ANOVA. Spearman rank correlation coefficients were used to assess the association between neutrophil counts, NLR, CRP and continuous clinical outcomes. Multivariate linear regression was used to further examine the relationship between post-operative neutrophil counts, NLR and CRP and clinical outcome variables, including extubation time, postoperative bleeding, the duration of the ICU stay, and length of hospital stay. The significance level was defined as a $P<0.05$. All statistical analyses were performed with SPSS 21.0 (SPSS Inc., Chicago, IL).

Results

During the study period (January 2016 to December 2018), 288 patients who underwent CPB (Ultrafiltration n= 172, 44.8% female, control n= 116, 36.2% female) were included in the final analysis. The procedures that 288 study participants underwent comprised of coronary artery bypass surgery (CABG, UF =41.9%, control= 73.3%), mitral valve replacement (MVR, UF =25.6%, control= 13.8%), aortic valve replacement (AVR, UF =7.6%, control= 1.7%), atrial septal defect (ASD, UF =2.9%, control= 5.2%), ventricular septal defect (VSD, UF =0.6%, control= 0.9%), aorta aneurism (UF =3.5%, control= 0.9%), aorta dissection (UF =8.7%, control= 0.9%), multiple valve replacement (UF =4.7%, control= 2.6%), and CABG with valve replacement (UF =4.8%, control= 0.9%) (Table 1).

The median age and body mass index of the UF and control groups were 57 (15) vs 57 (13) years (P=0.926) and 27.1 (2.94) vs 27.53 (3.85) kg/m^2 (P=0.483), respectively. The mean duration of cross clamp and CPB in UF vs control groups were 72.67 (33.48) vs 57.54 (25.71) (P< 0.001) and 112.37 (45.48) vs 90.72 (31.55) (P<0.001) minutes, respectively. The mean filtrate volume was 880 (800) ml (ranging from 50 to 2800 ml). The study demographics, preoperative characteristics and operative features of the entire study are presented in Table 1.

The data showed that post-operative neutrophil counts and NLR were significantly higher compared to their respective pre-operative levels in the UF group (Table 2, P<0.001 and P<0.001, respectively) and also were significantly higher compared to the control group (Figure 1A and 1C, P<0.001). Inversely, post-operative lymphocyte and platelet counts were significantly lower compared to their respective pre-operative levels in the UF group (Table 2, P<0.001 for all comparisons) and also were significantly lower compared to the control group (Figure 1B, 2D, P<0.001 for all comparisons). The post-operative platelet counts remained low after the 5th postoperative day in the UF group, while the same was raised to preoperative levels in the control group at postoperative 5th day (Table 2).

Table 1: Demographic and preoperative features of patients with UF (n=172) and controls (n=116) participating in the study

		Ultrafiltration (n=172)	Controls (n=116)	*P*-value
Age (year) (SD)		57 (15)	57 (13)	0.926
Gender, Woman (%)		44.8	36.2	0.180
Body mass index (kg/m^2) (SD)		27.1 (2.94)	27.53 (3.85)	0.483
Procedure (%)	CABG	41.9	73.3	none
	MVR	25.6	13.8	
	AVR	7.6	1.7	
	VSD Closure	0.6	0.9	
	ASD Closure	2.9	5.2	
	Aorta aneurism	3.5	0.9	
	Aorta dissection	8.7	0.9	
	Multiple valve surgery	4.7	2.6	
	Valve and bypass surgery	4.8	0.9	
Operation temperature classification (C°)	Deep	8.7	0.9	<0.001
	Cold	34.3	16.4	
	Moderate	57.0	82.8	
	Warm	0	0	
Cross clamp duration (minutes) (SD)		72.67 (33.48)	57.54 (25.71)	<0.001
CPB duration (minutes) (SD)		112.37 (45.48)	90.72 (31.55)	<0.001
Ringer lactate volume in prime (ml) (SD)		485 (60)	484 (54)	0.872
Mannitol volume in prime (ml) (SD)		103 (25)	102 (10)	0.765
Colloidal fluid volume in prime (ml) (SD)		433 (109)	426 (99)	0.625
FFP suspension usage in prime (%)		11	0	<0.001
Erythrocyte suspension usage in prime (%)		49.4	24.1	<0.001
Total filtrate volume (ml) (SD)		880 (800)	0	none
Rest of the prime after operation (ml) (SD)		111 (112)	70 (95)	0.002
Postoperative drainage volume (ml) (SD)		716 (386)	725 (438)	0.854

Data are expressed as mean [Standard Deviation (SD)] or %. The Wilcoxon rank-sum test was used for continuous variables, and the Fisher exact test was used for categorical variables in univariate analysis. P<0.05 was considered as significant. ASD: Atrial Septal Defect, AVR: Aorta Valve Replacement, CABG: Coronary Artery Bypass Grafting, FFP: Fresh Frozen Plasma, MVR: Mitral Valve Replacement, VSD: Ventricular Septal Defect

Table 2: Within group analysis of the study groups [UF (n=172) and controls (n=116)]

		Preoperative (T1)	Postoperative 24th Hours (T2)	Postoperative 5th Days (T3)	*P*-value
Neutrophil count (10^9/l)	Ultrafiltration	6.29 (3.419	10.75 (4.21)*	7.97 (4.31)	<0.001
	Control	5.73 (2.81)	9.26 (2.78)*	5.91 (2.13)	<0.001
Lymphocyte count (10^9/l)	Ultrafiltration	1.96 (0.89)	1.04 (0.97)*	1.39 (0.74)**	<0.001
	Control	2.08 (0.93)	1.01 (1.33)*	1.70 (0.71)	<0.001
Neutrophile / lymphocyte ratio	Ultrafiltration	3.99 (3.43)	15.27 (10.47)*	7.6 (5.96)**	<0.001
	Control	3.41 (2.4)	13.85 (7.84)*	4.20 (3.26)	<0.001
Urea (mg/dl)	Ultrafiltration	42.95 (20.42)	44.56 (20.24)	45.38 (23.23)	0.597
	Control	42.98 (20.01)	46.08 (20.71)	42.91 (18.53)	0.004
Creatinine (mg/dl)	Ultrafiltration	0.97 (0.64)	1.02 (0.79)	0.98 (0.72)	0.008
	Control	1.06 (0.88)	1.15 (0.99)	0.98 (0.96)	<0.001
C-reactive protein (mg/dl)	Ultrafiltration	3.96 (1.21)	-	41.27 (26.73)**	<0.001
	Control	3.96 (1.22)	-	41.11 (24.84)**	<0.001
Platelet Count (10^9/L)	Ultrafiltration	231.54 (71.84)	183.67 (68.68)*	193.29 (82.49)**	<0.001
	Control	248.67 (79.42)	191.20 (59.12)*	253.42 (88.89)	<0.001

Data are expressed as mean [Standard Deviation (SD)]. The Repeated Measures Friedman test was used for within group analysis and test results indicated as *P*-value which <0.05 was considered as significant.

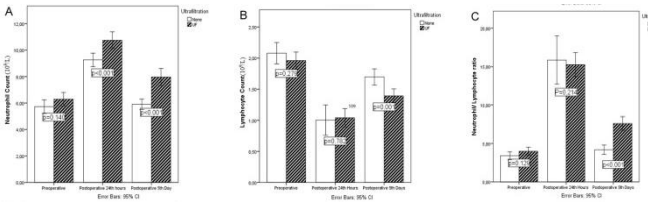


Figure 1: Graph representing the mean level of preoperative, postoperative 24th hours and postoperative 5th days of the neutrophil counts (A), lymphocyte counts (B), and neutrophil / lymphocyte ratio (NLR) (C) of the patients undergoing ultrafiltration during cardiopulmonary bypass in cardiac surgery. Post-operative neutrophil, lymphocytes counts and NLR were analyzed by using the ANOVA. *P*-value of <0.05 was considered to be statistically significant.

The data showed that post-operative urea, creatinine and CRP levels were similar in the UF and control groups (Figure 2A-C) but were significantly higher compared to their respective pre-operative levels in both groups. The exception was the urea level, which was similar to the pre-operative level in the UF group (Table 3, P<0.001).

The statistically significant changes in serum lymphocyte, neutrophil and platelet counts, and neutrophil / lymphocyte ratio may be biased due to the prolonged duration of CPB. Therefore, to account for this factor, we also analyzed a subgroup of patients in whom the CPB lasted longer than 120 minutes (Figure 3). The results showed that serum lymphocyte, neutrophil and platelet counts, and neutrophil / lymphocyte ratio were similar when CPB lasted longer than 120 minutes in both UF and control groups (Figure 3).

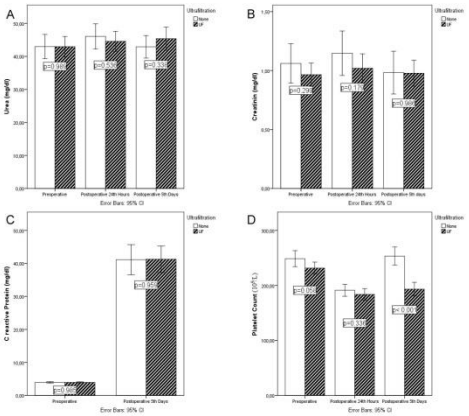


Figure 2: Graph representing the mean level of preoperative, postoperative 24th hours and postoperative 5th days of the urea (A), creatinine (B), C reactive protein (C) and platelet counts (D) of the patients undergoing ultrafiltration during cardiopulmonary bypass in cardiac surgery. Variables were analyzed by using the ANOVA. *P*-value of <0.05 was considered to be statistically significant.

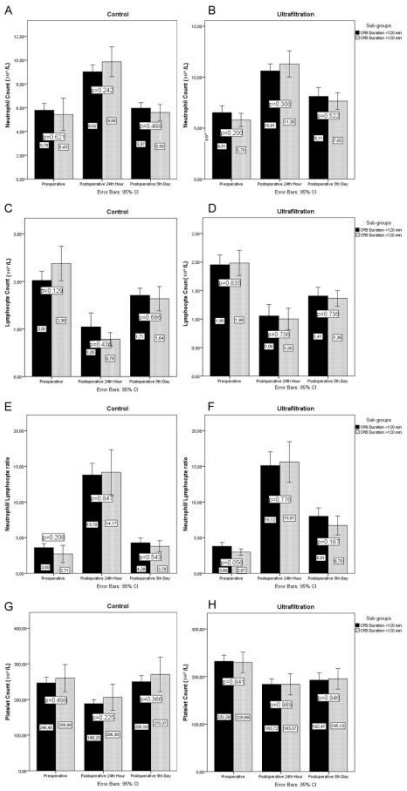


Figure 3: Graphs representing the mean levels of neutrophil counts (A and B), lymphocyte counts (C and D), neutrophil / lymphocyte ratio (NLR) (E and F), and platelet counts (G and H) of UF patients and control groups divided into subgroups according the cardiopulmonary bypass duration (< 120 minutes and > 120 minutes). Variables were analyzed by using the ANOVA. A *P*-value of <0.05 was considered to be statistically significant.

Using a univariate analysis of clinical outcomes (Table 4), we observed that on the 5th postoperative day, the NLR and platelet counts were significantly associated with UF ($P<0.05$). However, pre-operative NLR was significantly associated with the duration of cross clamping and cardiopulmonary bypass time ($P<0.05$). An additional regression analysis to determine the association between post-operative 5th day NLR and platelet counts (Table 5) indicated a significant association with UF.

Table 3: Postoperative complications of patients with UF and controls participating in the study

	Ultrafiltration (n=172)	Controls (n=116)	*P*-value
Pneumothorax (%)	0.6	0.9	0.469
Delirium (%)	4.7	2.6	
Atrial fibrillation (%)	5.2	6	
Temporary ventricular arrythmia (%)	1.2	6	
Long duration of intubation (%)	4.7	5.2	
Acute renal insufficiency (%)	3.5	2.6	
Exitus (%)	3.1	3.4	

Table 4: Spearman rank correlation coefficients of neutrophil / lymphocyte ratio (NLR) after operation with clinical outcome

Variables	NLR preoperative		NLR postoperative 24th hours		NLR postoperative 5th Days		Platelet count postopreative 5th days	
	r	*P*-value	r	*P*-value	r	*P*-value	r	*P*-value
Duration of Cross Clamping	-0.141	0.071	0.056	0.342	0.083	0.159	-0.068	0.252
Duration of Cardiopulmonary bypass	-0.127	0.322	0.051	0.392	0.094	0.113	-0.071	0.228
Total Filtrate volume	0.025	0.742	0.011	0.888	-0.133	0.081	0.103	0.178
Length of Intubation	-0.094	0.112	-0.043	0.467	0.026	0.655	0.025	0.674
Length of Intensive Care Unite Stay	-0.059	0.321	0.043	0.467	-0.004	0.940	0.059	0.321
Postoperative drainage volume	-0.086	0.145	0.032	0.591	-0.042	0.477	-0.029	0.624
In-hospital Stay	-0.053	0.369	0.071	0.229	0.089	0.133	-0.062	0.292
Ultrafiltration	0.017	0.778	0.073	0.214	0.315	<0.001	-0.334	<0.001

r: Spearman Correlation Coefficient

Table 5: Relationship between the ultrafiltration and postoperative neutrophil / lymphocyte ratio (NLR) and platelet count variables. (Multiple linear regression analysis)

Variables at postoperative 5th Days	B	Standard Error	β	*P*-value
NLR	0.020	0.006	0.218	<0.001
Platelet Count	-0.001	0.0003	-0.241	<0.001
	Adjusted R Square = 0.142			
	F(2,285)= 24.683			
	n=288			
	P<0.001			

Discussion

The main findings of this study were that neutrophil count and NLR were significantly increased, and platelet and lymphocyte counts were significantly decreased post-operatively compared to their pre-operative levels in adult patients undergoing UF during CPB. In addition, the post-operative increase of NLR and decrease of platelet count were significantly correlated with UF. However, none of the other perioperative or post-operative patient features was associated with the studied variables. Our data suggest that UF may be implicated in post-operative inflammation, especially in adult patients who have undergone CPB.

Recently, several studies have demonstrated that extracorporeal circulation during CPB triggered a systemic inflammatory response, which was a major cause of postoperative complications after cardiac surgery [1,2,4,10]. Neutrophils, which are central in the mediation of systemic inflammatory responses to CPB and are activated by the complement system and kallikrein, arrive rapidly at sites of acute inflammation where they are responsible for phagocytosis and killing of invading pathogens by releasing proteolytic and cytotoxic enzymes (including elastase, myeloperoxidase and lactoferrin), chemokines, cytokines and arachidonate metabolites [7]. Over-activation of neutrophils, on one hand, is involved in the collateral destruction of tissues and cell together with injury from oxygen free radicals. On the other hand, activation of inflammatory cascades by the 'non-self' foreign surfaces of the CPB circuit result in cellular damage, endothelial cell and

leukocyte activation, histamine release, increased vascular permeability and generalized inflammatory responses [11].

Miniaturizing the CPB and related extracorporeal circulation (ECC) units [12], improving the inner surface of the ECC that has direct contact with blood [13] or working on the beating heart without CPB [14] may attenuate the negative outcomes of CPB by diminishing the inflammatory response during cardiac surgery. New generation CPB devices are manufactured with simple and miniaturized ECC units [15]. Similarly, reducing the duration of CPB during surgery was suggested as a method to attenuate the inflammatory response of CPB [16]. Mongero et al. [10] have demonstrated a positive correlation between postoperative complications with the duration of CPB in a review of 73,506 cardiac procedures from a national registry (SCOPE). In the current study, subgroup analysis of extended CPB duration (longer than 120 minutes) did not reveal any association with postoperative complications.

UF during CPB (just before the cessation of CPB) is also a favored technique to attenuate inflammation attributed to prolonged CPB by filtering the circulating mediators and to hemoconcentrate the blood in low HCT patients by removing excess water that may accumulate by priming CPB and intravenously administered fluids [10]. Hemoconcentration of the blood during UF is an imperfect technique resulting in confusing and opposing data on the evaluation of UF and the generation of inflammatory mediators [17,18]. Torina et al. [17] reported an increased inflammatory response despite the use of modified UF in adults undergoing coronary bypass grafting. Soliman et al. [18] reported an increase in serum lactate levels after UF during CPB. NLR can be easily calculated using complete blood count and is a simple and cost-effective test to provide valuable data about systemic inflammatory responses [19]. In the current study, NLR was used to evaluate the inflammatory status of adult patients who underwent UF during CPB. We have shown for the first time that NLR was increased at the 5^{th} postoperative day in adult patients with CPB undergoing UF compared to CPB patients who did not undergo UF.

Giakoumidakis et al. reported an association between increased NLR and increased mortality and morbidity in patients undergoing cardiac surgery [20]. However, in that study, postoperative complications were not associated with increased NLR whereas in the current study, the use of UF during CPB was significantly associated with high NLR. In a study that evaluated adult patients undergoing CABG with MUF after CPB, it was observed that UF patients had higher SVR, cardiac output and PVR at the end of the surgery, which were decreased to baseline levels after 48 hours [21]. We hypothesize that an increased systemic inflammatory response resulted in a rollback in cardiovascular improvement 48 hours after cardiac surgery in the UF group. Future investigations are needed to establish this hypothesis.

In addition, to account for any bias in data interpretation due to the long duration of CPB in patients undergoing UF, a subgroup analysis was carried out with patients classified according to the duration (<120 minutes and > 120 minutes) of the CPB. The increase in the NLR was similar between the groups, which suggests that UF led to the increase in NLR, and not the duration of CPB (Figure 3). In addition, there was a significant and positive correlation between the UF and serum NLR in adult patients after cardiac surgery with UF during CPB. These findings suggest that monitoring of the NLR has the potential to make simple predictions about the status of inflammation in adult patients undergoing cardiac surgery with CPB.

Data from the current study demonstrated that UF was associated with a significant decrease in platelet levels even though postoperative blood loss was not significantly different between the groups. In a review article, Weerasinghe et al. [22] reported that upon exposure to CPB and artificial surfaces, platelet counts are decreased but platelet cell functions are increased due to structural changes such as expression of a range of surface molecules that mediate their hemostatic and inflammatory functions and biochemical changes such as secretion of the α-granules that contains a trimeric glycoprotein named thrombospondin [22]. In subgroup analyses in the current study, CPB lasting for two hours showed significantly decreased platelet counts; moreover, CPB accompanied by UF decreased the platelet counts even more (please see Table 5 for the regression analysis). Of note, the postoperative blood loss in both groups was similar suggesting that the activation of platelets may compensate for impaired platelet counts and lead to lower postoperative risk of bleeding and/or need for transfusion. Kiziltepe et al. [23] reported that UF resulted in low platelet levels but also less bleeding related complications. The current study supports this observation. An analysis of previously published data and results of the current study demonstrates the need for careful platelet focused management of unavoidable bleeding during surgery in patients with complaints such as complicated aneurism or dissection repair.

Limitations

The first limitation of the present study was the low number of patients in one hospital. Therefore, a multicenter study with a large number of patients needs to be carried out in order to further confirm our findings. Secondly, although it has been carefully studied, collected prospectively and analyzed independently, the retrospective design of our study may potentially be susceptible to systematic error and bias. The third limitation was lacking the measurement of inflammation specific parameters or acute phase reactants to support the study results. Finally, the patient groups belonging to different preoperative diagnoses were not balanced because of ethical rules while conducting and the inclusion of the patients in the study. Again, for the same reason, patients had different volumes of ultrafiltration. Future studies are needed to further develop and confirm these initial findings by classifying the procedures for each type of heart disease.

Conclusion

The use of UF during CPB was associated with increased post-operative NLR and decreased platelet count in adult patients after CPB surgery. Although this association was statistically significant, none of the other postoperative complications were significantly associated with the use of UF. In the light of the study results, it is recommended that the UF procedure is chosen solely for those patients with low hematocrit because of volume overload. It should not be chosen for reducing

circulating mediators for the attenuation of whole body inflammatory response by after CPB in adult cardiac surgery patients.

References

1. Laffey JG, Boylan JF, Cheng DC. The systemic inflammatory response to cardiac surgery: implications for the anesthesiologist. Anesthesiology. 2002 Jul;97(1):215-52. doi: 10.1097/00000542-200207000-00030.
2. Wan S, LeClerc JL, Vincent JL. Inflammatory response to cardiopulmonary bypass: mechanisms involved and possible therapeutic strategies. Chest. 1997 Sep;112(3):676-92. doi: 10.1378/chest.112.3.676.
3. Allan CK, Newburger JW, McGrath E, Elder J, Psoinos C, Laussen PC, et al. The relationship between inflammatory activation and clinical outcome after infant cardiopulmonary bypass. Anesth Analg. 2010 Nov;111(5):1244-51. doi: 10.1213/ANE.0b013e3181f333aa.
4. Sarkar M, Prabhu V. Basics of cardiopulmonary bypass. Indian J Anaesth. 2017 Sep;61(9):760-767. doi: 10.4103/ija.IJA_379_17.
5. Chew MS. Does modified ultrafiltration reduce the systemic inflammatory response to cardiac surgery with cardiopulmonary bypass? Perfusion. 2004;19 Suppl 1:S57-60. doi: 10.1191/0267659104pf719oa.
6. Gaynor JW. Use of ultrafiltration during and after cardiopulmonary bypass in children. J Thorac Cardiovasc Surg. 2001 Aug;122(2):209-11. doi: 10.1067/mtc.2001.115925.
7. Mongero LB, Tesdahl EA, Stammers A, Weinstein S. The influence of ultrafiltration on red blood cell transfusion during cardiopulmonary bypass. Perfusion. 2019 May;34(4):303-309. doi: 10.1177/0267659118821026.
8. Song J, Zheng Q, Ma X, Zhang Q, Xu Z, Zou C, et al. Predictive Roles of Neutrophil-to-Lymphocyte Ratio and C-Reactive Protein in Patients with Calcific Aortic Valve Disease. Int Heart J. 2019 Mar 20;60(2):345-351. doi: 10.1536/ihj.18-196.
9. Özer A, Mardin B, Kılıç Y, Oktar L, İriz E, Arslan M, et al. The effect of neutrophil-lymphocyte ratio on the postoperative course of coronary artery bypass graft surgery. Turk J Med Sci. 2018 Oct 31;48(5):1036-1040. doi: 10.3906/sag-1804-94.
10. Mongero L, Stammers A, Tesdahl E, Stasko A, Weinstein S. The effect of ultrafiltration on end-cardiopulmonary bypass hematocrit during cardiac surgery. Perfusion. 2018 Jul;33(5):367-374. doi: 10.1177/0267659117747046.
11. Aldemir M, Baki ED, Adali F, Çarşanba G, Tecer E, Taş HU. Comparison of neutrophil:lymphocyte ratios following coronary artery bypass surgery with or without cardiopulmonary bypass. Cardiovasc J Afr. 2015 Jul-Aug;26(4):159-64. doi: 10.5830/CVJA-2015-015.
12. Rex S, Brose S, Metzelder S, de Rossi L, Schroth S, Autschbach R, et al. Normothermic beating heart surgery with assistance of miniaturized bypass systems: the effects on intraoperative hemodynamics and inflammatory response. Anesth Analg. 2006 Feb;102(2):352-62. doi: 10.1213/01.ane.0000194294.67624.1a.
13. Hatemi AC, Çeviker K, Tongut A, Özgöl İ, Mert M, Kaya A. Oxidant Status following Cardiac Surgery with Phosphorylcholine-Coated Extracorporeal Circulation Systems. Oxid Med Cell Longev. 2016;2016:3932092. doi: 10.1155/2016/3932092.
14. Al-Ruzzeh S, Ambler G, Asimakopoulos G, Omar RZ, Hasan R, Fabri B, et al. United Kingdom Multi-Center Comparative Analysis of Early Clinical Outcome. Off-Pump Coronary Artery Bypass (OPCAB) surgery reduces risk-stratified morbidity and mortality: a United Kingdom Multi-Center Comparative Analysis of Early Clinical Outcome. Circulation. 2003 Sep 9;108 Suppl 1:II1-8. doi: 10.1161/01.cir.0000087440.59920.a1.
15. Valtonen M, Vähäsilta T, Kaila-Keinänen T, Kuttila K. New mini-extracorporeal circulation system (ECC.O) is a safe technique in coronary surgery. Scand Cardiovasc J. 2007 Oct;41(5):345-50. doi: 10.1080/14017430701446933.
16. Elçi ME, Kahraman A, Mutlu E, İspir CS. Effects of Minimal Extracorporeal Circulation on the Systemic Inflammatory Response and the Need for Transfusion after Coronary Bypass Grafting Surgery. Cardiol Res Pract. 2019 Jun 4;2019:1726150. doi: 10.1155/2019/1726150.
17. Torina AG, Silveira-Filho LM, Vilarinho KA, Eghtesady P, Oliveira PP, Sposito AC, et al. Use of modified ultrafiltration in adults undergoing coronary artery bypass grafting is associated with inflammatory modulation and less postoperative blood loss: a randomized and controlled study. J Thorac Cardiovasc Surg. 2012 Sep;144(3):663-70. doi: 10.1016/j.jtcvs.2012.04.012.
18. Soliman R, Fouad E, Belghith M, Abdelmageed T. Conventional hemofiltration during cardiopulmonary bypass increases the serum lactate level in adult cardiac surgery. Ann Card Anaesth. 2016 Jan-Mar;19(1):45-51. doi: 10.4103/0971-9784.173019.
19. Xu H, Sun Y, Zhang S. The Relationship Between Neutrophil to Lymphocyte Ratio and Clinical Outcome in Pediatric Patients After Cardiopulmonary Bypass Surgery: A Retrospective Study. Front Pediatr. 2019 Jul 31;7:308. doi: 10.3389/fped.2019.00308.
20. Giakoumidakis K, Fotos NV, Patelarou A, Theologou S, Argiriou M, Chatziefstratiou AA, et al. Perioperative neutrophil to lymphocyte ratio as a predictor of poor cardiac surgery patient outcomes. Pragmat Obs Res. 2017 Feb 15;8:9-14. doi: 10.2147/POR.S130560.
21. Bogă M, Islamoğlu, Badak I, Cikirikçioğlu M, Bakalim T, Yağdi T, et al. The effects of modified hemofiltration on inflammatory mediators and cardiac performance in coronary artery bypass grafting. Perfusion. 2000 Mar;15(2):143-50. doi: 10.1177/026765910001500209.
22. Weerasinghe A, Taylor KM. The platelet in cardiopulmonary bypass. Ann Thorac Surg. 1998 Dec;66(6):2145-52. doi: 10.1016/s0003-4975(98)00749-8.
23. Kiziltepe U, Uysalel A, Corapcioglu T, Dalva K, Akan H, Akalin H. Effects of combined conventional and modified ultrafiltration in adult patients. Ann Thorac Surg. 2001 Feb;71(2):684-93. doi: 10.1016/s0003-4975(00)02518-2.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1215-1218.
DOI: 10.28982/josam.784139

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Can nasal septum deviation be one of the factors affecting diabetic retinopathy?

Nazal septum deviasyonu, diyabetik retinopatiyi etkileyen faktörlerden biri olabilir mi?

Erdoğan Yaşar [1], Serkan Kayabaşı [2]

[1] Aksaray University, Medicine Faculty, Department of Ophthalmology, Aksaray, Turkey
[2] Aksaray University, Medicine Faculty, Department of Otorhinolaryngology, Aksaray, Turkey

ORCID ID of the author(s)
EY: 0000-0001-5129-9397
SK: 0000-0002-5292-5940

Corresponding author/Sorumlu yazar:
Erdoğan Yaşar
Address/Adres: Aksaray Üniversitesi, Tıp Fakültesi, Göz Hastalıkları Anabilim Dalı, Aksaray, Türkiye
E-mail: dr.e.yasar@gmail.com

Ethics Committee Approval: Ethics Committee approval was received from the Aksaray University Ethics Committee with the number 2019/44. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Aksaray Üniversitesi Etik Kurulu'ndan 2019/44 numara ile etik kurul onayı alındı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: Information on the extraocular causes of diabetic retinopathy is limited. Therefore, when researching etiology in a patient with diabetic retinopathy, if glucose, blood pressure and cholesterol are normal, other reasons must be investigated. Our aim was to evaluate the effect of nasal septum deviation (NSD) on the presence and severity of diabetic retinopathy in patients with diabetes mellitus.

Methods: This prospective case-control study included 100 eyes of 50 patients with only diabetes mellitus (DM+ NSD-, control group) and 120 eyes of 60 patients with DM and nasal septum deviation (DM+NSD+, NSD group). After evaluation of NSD patients using a nasal obstruction symptom evaluation scale (NOSE scale), 22 patients were classified as mild, 21 as moderate, and 17 as severe. Anterior segment and dilated fundus examinations were performed in all patients. Diabetic retinopathy (DR) was classified as mild, moderate, and severe non-proliferative DR and proliferative DR (PDR).

Results: The mean age of patients in the NSD and control groups was 58.7 (15.2) years (range: 41–69) and 59.6 (8.1) years (range: 44–67), respectively. The prevalence of DR and PDR were 70% (n=14) and 30% (n=6), respectively, in the severe NSD group (P=0.045 and P=0.035, respectively). The relationship between PDR and other factors in patients with NSD were evaluated, and a correlation was detected with DM duration (P=0.024, OR=1.272), HbA1c (P=0.032, OR=3.085), and NOSE scale severity (P=0.040, OR=2.566).

Conclusion: The results of the present study show an increased risk of DR and PDR in patients with severe NSD. In addition to other risk factors in PDR etiology, NSD should also be considered.

Keywords: Diabetic retinopathy, Proliferative diabetic retinopathy, Nasal septum deviation, Hypoxia

Öz

Amaç: Diyabetes Mellituslu hastalarda nazal septum deviasyonunun diyabetik retinopatinin varlığı ve şiddeti üzerine etkisini değerlendirmek.

Yöntemler: Bu prospektif vaka kontrol çalışmasına Diabettes Mellitus (DM) olan 50 hastanın 100 gözü ve nazal septum deviasyonu (NSD) olan DM'li 60 hastanın 120 gözü (kontrol grubu) dahil edildi. NSD hastaları burun tıkanıklığı semptom değerlendirme ölçeği (NOSE ölçeği) ile değerlendirme sonrası hastalar; 22 hafif, 21 orta ve 17 ağır evre olarak sınıflandırıldı. Tüm hastalara ön segment ve dilate fundus muayenesi yapıldı. Diyabetik Retinopati(DR);hafif, orta, şiddetli non-proliferatif DR ve proliferatif DR olarak sınıflandırıldı.

Bulgular: NSD grubundaki hastaların yaş ortalaması 58,7 (15,2) (dağılım, 41-69) ve kontrol grubundaki hastaların yaş ortalaması 59,6 (8,1) (dağılım, 44-67) idi. DR prevalansı şiddetli evre NSD grubunda %70 (n=14), proliferatif DR prevalansı %30 (n=6) idi ve aradaki fark anlamlı bulundu (sırasıyla P=0,045, P=0,035). Proliferatif DR ile NSD hastalarındaki diğer faktörler arasındaki ilişki değerlendirildi ve DM süresi (P=0,024, OR=1,272), HbA1c (P=0,032, OR=3,085) ve NOSE skalası şiddeti (P=0,040, OR= 2,566) arasında pozitif ilişki saptandı.

Sonuç: Sonuçlarımız ağır tip NSD hastalarında artmış DR ve proliferatif DR riskini göstermektedir. Bu nedenle PDR etiyolojisinde diğer risk faktörlerine ek olarak NSD de düşünülmelidir.

Anahtar kelimeler: Diyabetik retinopati, Proliferatif diyabetik retinopati, Nazal septum sapması, Hipoksi

How to cite/Atıf için: Yaşar E, Kayabaşı S. Can nasal septum deviation be one of the factors affecting diabetic retinopathy? J Surg Med. 2020;4(12):1215-1218.

Introduction

Diabetic retinopathy (DR) is a progressive disease of retinal vessels due to chronic hyperglycemia (retinal vascular capillary occlusion, vascular hyperpermeability, and neovascularization) [1]. Diabetes mellitus (DM) is a serious microvascular complication that threatens visual acuity and is one of the leading causes of blindness [2]. The prevalence of DR is about 35% in individuals with DM, and it is diagnosed in about 60% individuals who have had diabetes for 20 years [3-5]. The duration of DM and the severity of hyperglycemia are the main risk factors associated with retinopathy [6-7]. DR can be classified as non-proliferative DR (NPDR) and proliferative DR (PDR) depending on the presence or absence of neovascularization (NV) because of development and progression of DR [8]. The main factor in the etiology of PDR is the development of hypoxia [9-10].

Nasal septum deviation (NSD) is the displacement of the nasal septum from the midline to the right or left. NSD is the most common anatomical cause of nasal congestion [11]. Chronic alveolar hypoxia, which occurs in patients with NSD, arises due to decreased airflow obstruction in the upper respiratory tract, increased pulmonary vascular resistance, and insufficiency to regulate movements of the thorax via reflexes [12-13]. Although the prevalence of NSD can reach up to 80%, only some individuals are affected by nasal congestion [14]. Therefore, NOSE survey, a specific and reliable tool for assessing nasal congestion in adults, is used [15-16].

To the best of our knowledge, the relationship between DR and NSD, which can cause hypoxia, has not been studied to date. Therefore, we aimed to investigate the relationship between the presence and severity of DR and NSD.

Materials and methods

This prospective study included 120 eyes of 60 DM patients with NSD (DM+NSD+, NSD group) who presented to the ENT outpatient clinic between March and September 2019 and 100 eyes of 50 DM patients without NSD (DM+ NSD-, control group) who were evaluated at the eye clinic. All study procedures were conducted in accordance with the Helsinki Declaration. Ethics Committee approval was granted by Aksaray University Ethics Committee with the number 2019/44, and informed consent forms were received from all patients prior to their participation.

The study group comprised 50 patients without NSD and 60 patients aged>18 years who were diagnosed with NSD by endoscopic and/or radiological imaging. Patients with NSD were classified into the following three groups as evaluated by the nasal obstruction symptom evaluation (NOSE) scale: Mild cases (n=22), moderate cases (n=21), and severe cases (n= 17). The NOSE scale mainly focuses on nasal congestion and provides an assessment before and after the treatment [15-16]. The NOSE scale consists of 0–4 points (0: Not a problem; 1: Very mild problem; 2: Moderate problem; 3: Fairly bad problem; and 4: Severe problem). NOSE [16] was used to assess the following symptoms: Swelling or fullness in the nose, nasal congestion, difficulty in breathing and sleeping, and not being able to comfortably breathe during exercise or exertion. Each question was scored using the 5-point Likert scale, and finally scored between 0 and 100 points in total. Higher NOSE survey scores correspond to more severe nasal congestion. Patients who had previously undergone nasal surgery, those with nasal polyps or chronic sinusitis, those scheduled to undergo rhinoplasty surgery, those with craniofacial anomalies, and those with active upper respiratory tract infection were excluded from the study.

The criteria for exclusion for both groups included known hypertension, hypercholesterolemia, coronary artery disease, heart failure, metabolic syndrome, obstructive sleep apnea syndrome, smoking and alcohol consumption, pregnancy, the presence of anterior segment pathologies (central corneal pathology, iris pathology, pupil disorders, intensive cataract, and uveitis) that prevent imaging of the retina as well as known or previous non-diabetes retinal vascular diseases.

Patients' data, such as gender, age, diabetes duration, glycosylated hemoglobin (HbA1c) level, and treatment type were recorded. After routine anterior segment examination with slit lamp biomicroscopy, the pupils of both eyes were dilated with a drop of mydriatic eye drops (0.1% tropicamide). Fundus examination was performed after 30 minutes of rest, by the same ophthalmologist using a 78D Volk lens.

DR was classified according to the International Clinical Diabetic Retinopathy (DR) Disease Severity Scale as mild NPDR (microaneurysm only), moderate NPDR (more than just microaneurysm, but less than severe NPDR), severe NPDR (severe intraretinal hemorrhages and microaneurysms in each of the four quadrants, precise venous beading in two or more quadrants, and moderate IRMA in one or more quadrants), and PDR (one or both of the following: Neovascularization, vitreous/preretinal hemorrhage). The degree of retinopathy was assessed for each eye and individual classification was made with regards to the worse eye. Fundus fluorescein angiography was performed when neovascularization was unclear.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) 23.0-Windows (SPSS Inc., Chicago, IL) was used for statistical analysis. The normality of distribution of quantitative data was evaluated using Shapiro–Wilk test. Independent sample t-test (for normal distribution) and Mann–Whitney's (for non-normal distribution) test were used to compare the means of quantitative variables. Chi-square test was performed to compare the means of categorical variables. Binomial logistic regression analysis was performed to calculate the odds ratios of the relationship between descriptive variables. Values of $P < 0.05$ were considered statistically significant.

Results

The mean age of patients in NSD group was 58.7 (15.2) (range: 41–69) years, and the group comprised 36 female and 34 males. The mean age of the patients in the control group was 59.6 (8.1) (range: 44–67) years, and the group comprised 27 women and 23 men. No significant difference was observed between the groups in terms of mean age and gender ratio ($P>0.05$).

Comparisons among the mild, moderate, and severe cases in the NSD group determined by the NOSE scale and the control group in terms of DR, NPDR, PDR, HbA1c, and DM

duration are shown in Table 1. No differences were observed between the mild and moderate groups and the control group in terms of DR, NPDR, PDR, HbA1c, and DM duration (P<0.05). The prevalence of DR was 70% (n=14) in the group with severe cases, and 40% (n=20) in the control group. The deference was higher in DR group (P=0.045). The prevalence of PDR was 30% (n=6) in the group with severe cases and 8% (n=4) in the control group, and the deference was higher in PDR group (P=0.035). No differences were observed between the two groups in terms of NPDR, HbA1c, and DM duration (P>0.05).

Table 1: The comparison of control group and nasal septum deviation stage groups in terms of diabetic retinopathy

Parameters	Control group Mean(SD)	Mild Group Mean(SD)	*P*-value	Moderate Group Mean(SD)	*P*-value	Severe Group Mean(SD)	*P*-value
HgA1C	8.9(1.3)	8.8(1.2)	0.781	9.1(1.2)	0.586	8.7(1.6)	0.543
DM duration	11.8(4.4)	12.1(3.9)	0.199	11.4 (3.9)	0.148	12.2(3.9)	0.169
DR %(n)	44(22)	40(8)	0.784	45(9)	0.923	70(14)	0.045
NPDR %(n)	36(18)	35(7)	0.912	40(8)	0791	40(8)	0.791
PDR%(n)	8(4)	5(1)	0.406	10(2)	0.838	30(6)	0.027

DM: Diabetes Mellitus, DR: Diabetic Retinopathy, NPDR: Non-proliferative Diabetic Retinopathy, PDR: Proliferative Diabetic Retinopathy, mean: mean, SD: Standard Deviation

Factors affecting the presence of PDR, NPDR, and DR in patients with NSD were evaluated by binominal logistic regression (Table 2). A positive relationship was observed between DM duration (P=0.024, OR=1.272), HbA1c (P=0.032, OR=3.085), and NOSE (P=0.040, OR=2.566) in the PDR group, and no relationship was found between PDR, age, gender, and nasal septum lateralization (right/left; P>0.05). In the NPDR group, there were a positive relationship between DM duration (P=0.005, OR=1.573) and HbA1c (P=0.007, OR=2.969), and no relationship between NPDR and NOSE scale severity, nasal septum lateralization (right/left), age, and gender (P>0.05). In the DR group, there was a positive relationship between DM duration (P=0.014, OR=1.152), HbA1c (P=0.001, OR=2.621), and NOSE scale severity (P=0.040, OR=2.586), and no relationship between DR and nasal septum lateralization (right/left), age, and gender (P>0.05).

Table 2: The factors affecting the severity of diabetic retinopathy in patients with nasal septum deviation

Parameter	PDR		NPDR+		DR	
	P-value	OR	p-value	OR	*P*-value	OR
Age	0.186	-	0.204	-	0.259	-
Gender	0.524	-	0.356	-	0.429	-
DM duration	0.024	1.272	0.005	1.573	0.014	1.152
HgA1C	0.032	3.085	0.007	2.969	0.001	2.621
NOSE severity	0.040	2.566	0.254	-	0.040	2.586
NSL	0.356	-	0.439	-	0.643	-

DM: Diabetes Mellitus, DR: Diabetic Retinopathy, NPDR: Non-proliferative Diabetic Retinopathy, PDR: Proliferative Diabetic Retinopathy, mean: mean, SD: Standard Deviation, NOSE: Nose Obstruction Symptom Evaluation, NSL: Nasal Septum Lateralization, OR: Odds Ratio

Discussion

Diabetic retinopathy, which is a complication of diabetes, is usually associated with hyperglycemia or hypoglycemia [1]. However, in some cases, although glucose is normal, diabetic retinopathy may occur due to secondary causes. Commonly known secondary causes are HT and hypercholesterolemia, and researches on other causes are still ongoing [6]. The main result of this study is that PDR and total DR rates were higher in patients with severe NSD than in controls.

DM duration and severity of hyperglycemia (HBA1c) are the main risk factors for DR in various studies [6-7]. In the present study, similar to the literature, HbA1c and DM duration correlated with PDR and NPDR. Other risk factors for DR include hypertension, hypercholesterolemia, coronary artery disease, heart failure, abdominal obesity, obstructive sleep apnea, smoking, alcohol use, ethnicity, and the age of onset [16-25]. In the present study, no comparison could be made as these associated diseases were determined as exclusion criteria so that diabetic retinopathy is not affected. To the best of our knowledge, there is no study investigating the relationship between NSD and DR in the literature.

Diabetic retinopathy can be classified as non-proliferative and proliferative. The earliest clinical signs of non-proliferative diabetic retinopathy are retinal hemorrhages and microaneurysms. The development of venous beading, cotton wool spots, and intraretinal microvascular abnormalities are hallmarks of progressive capillary perfusion. Neovascularization on the surface of the optic disc and retina indicates the presence of proliferative diabetic retinopathy with more retinal ischemia [26]. The key factor in the etiology of PDR is the development of hypoxia, which is considered important for the release of growth factors that increase the permeability of the retinal vessels and stimulate neovascularization [9-10].

Pathological ocular angiogenesis in diabetic retinopathy is regulated by vascular endothelial growth factor-A (VEGF-A). In the retina, VEGF-A is released by ganglion cells, Müller cells, and retinal pigment epithelial cells [27]. High affinity VEGF receptors have been shown in retinal endothelial cells and pericytes. Hypoxia is the main regulator of VEGF-induced ocular neovascularization via hypoxia-inducible factor-1 [28]. Secondary to induction of VEGF by hypoxia, angiogenesis can be controlled by angiogenic inducers and inhibitors. VEGF is an important growth factor, especially for angiogenesis due to hypoxia, and is associated with the formation of new pathological vessels [27-28]. This new vessel formation becomes pathological as they are fragile and permeable. New vessels rupture and grow along the surface of the retina and towards the posterior hyaloid face. However, these delicate vessels are easily disrupted by vitreous traction, resulting in bleeding into the vitreous space or preretinal space. Intravitreal hemorrhage and tractional retinal detachment may occur in these pathological new vessels [29]. In the present study, proliferative DR may have occurred because of hypoxia induced by a severe NSD with a similar mechanism.

Nasal septal deviations play a critical role in nasal obstruction and chronic alveolar hypoxia occurs in patients with NSD, especially in patients in severe stage, because of a decrease in airflow obstruction in the upper respiratory tract, an increase in pulmonary vascular resistance, and the inability of the chest to regulate movements through reflexes [11-13]. In our study, we think that in patients with severe stage nasal septum deviation, retinal hypoxia and ischemia may have occurred with a similar mechanism.

When PDR is detected, the causes that will cause retinal ischemia are considered first. Diabetes-related causes are always insufficient to explain the etiology. Other systemic diseases that can cause ischemia and hypoxia in the retina should also be considered. This study will contribute to the literature by showing that NSD should also be taken into account in addition to other risk factors in the etiology of PDR. We concluded that

patients with treatment-resistant PDR should be assessed by otolaryngologists in terms of severe NSD that may cause hypoxia after other secondary causes are excluded. Studies with a larger number of patients are needed to investigate to what extent NSD can affect the development and progression of PDR.

Limitations

Limitations of this study include the fact that oxygen saturation was not measured in patients with NSD, the study was conducted only according to the severity assessment of the NOSE Scale. The other limitation of study was the relatively low number of patients.

Conclusion

The present study has demonstrated that patients with NSD who are severely affected based on NOSE scale severity are at risk for diabetic eye complications (DR, PDR), but those with mild to moderate NSD are not at such risk. In view of NSD-related effects, it was found that PDR increased by about 2.5 times with NOSE scale severity. Ophthalmologists and otolaryngologists should be informed about this in patients with DM. Studies with a larger number of patients are needed to investigate to what extent NSD can affect the development and progression of PDR.

References

1. Rosenblatt BJ, Benson WE.Diabetic retinopathy. In: Yanoff M, Duker J, eds. Ophthalmology. 3rd ed. Philadelphia: Mosby. 2009;613e621.
2. Klein BE. Overview of epidemiologic studies of diabetic retinopathy. Ophthalmic Epidemiol. 2007;14:179-83.
3. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski J W, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes care. 2012;35(3):556-64.
4. Xie XW, Xu L, Jonas JB, Wang YX. Prevalence of diabetic retinopathy among subjects with known diabetes in China: the Beijing Eye Study. Eur J Ophthalmol. 2009;19:91-9.
5. Perumalsamy N, Prasad NM, Sathya S, Ramasamy K. Software for reading and grading diabetic retinopathy: Aravind Diabetic Retinopathy Screening 3.0. Diabetes Care 2007;30:2302–6.
6. Zhang L, Krzentowski G, Albert A, Lefebvre PJ. Risk of developing retinopathy in Diabetes Control and Complication Trial type 1 diabetic patients with good or poor metabolic control. Diabetes Care. 2001;24(7):1275–9.
7. Van Leiden HA. Risk factors for incident retinopathy in a diabetic and non-diabetic population: The Hoorn Study. Arch Ophthalmol. 2003;121:245–51.
8. Stitt AW, Curtis TM, Chen M, Medina RJ, McKay GJ, Jenkins A, et al. The progress in understanding and treatment of diabetic retinopathy. Progre Retin Eye Res. 2016;51:156-86.
9. Bandello F, Lattanzio R, Zucchiatti I, Del Turco C. Pathophysiology and treatment of diabetic retinopathy. Acta Diabetol. 2013;50:1–20.
10. Wang X, Wang G, Wang Y. Intravitreous vascular endothelial growth factor and hypoxia-inducible factor 1a in patients with proliferative diabetic retinopathy. Am J Ophthalmol. 2009;148:883-9.
11. Van Egmond MM, Rovers MM, Hendriks CT, van Heerbeek N. Effectiveness of septoplasty versus nonsurgical management for nasal obstruction due to a deviated nasal septum in adults: study protocol for a randomized controlled trial. Trials. 2015;16:500.
12. Ulu S, Ulu MS, Bucak A, Kahveci OK, Yucedag F, Aycicek A. Evaluating the relationship between nasal obstruction and mean platelet volume by using acoustic rhinometry in patients with septum deviation. Rhinology. 2013;51:249–52.
13. Blum RH, McGowan Jr, F. X. Chronic upper airway obstruction and cardiac dysfunction: anatomy, pathophysiology and anesthetic implications. Pediatric Anesthesia. 2004;14(1):75-83.
14. Roblin DG, Eccles R. What, if any, is the value of septal surgery? Clin Otolaryngol Allied Sci. 2002;27:77-80.
15. Onerci CO, Araz SE, Yigit O, Longur ES. Adaptation and validation of the Turkish version of the Nasal Obstruction Symptom Evaluation scale. Int Forum Allergy Rhinol. 2018;8:72-16.
16. Stewart MG, Witsell DL, Smith TL, Weaver EM, Yueh B, Hannley MT. Development and validation of the nasal obstruction symptom evaluation (NOSE) scale. Otolaryngol Head Neck Surg. 2004;130:157-63.
17. Leske C. Incidence of diabetic retinopathy in the Barbados Eye Studies. Ophthalmology. 2003;110:941–7.
18. Stratton IM, Kohner EM, Aldington SJ, Turner RC, Holman RR, Manley SE, et al.UKPDS 50: risk factors for incidence and progression of retinopathy in Type II diabetes over 6 years from diagnosis. Diabetologia. 2001;44(2):156–63.
19. Pradeepa R, Surendar J, Indulekha K, Chella S, Anjana RM, Mohan V. Relationship of diabetic retinopathy with coronary artery disease in Asian Indians with type 2 diabetes: the Chennai Urban Rural Epidemiology Study (CURES) Eye Study—3. Diabetes technology & therapeutics. 2015;17(2):112-8.
20. Aguilar D, Hallman DM, Piller LB, Klein BE, Klein R, Devereux RB, Hanis CL. Adverse association between diabetic retinopathy and cardiac structure and function. American heart journal. 2009;157(3):563-8.
21. Keen H. The appearance of retinopathy and progression to proliferative retinopathy: The WHO multinational study of vascular disease in diabetes. Diabetologia. 2001;44(Supplement 2):S22–30.
22. Liu L, Yue S, Wu J, Zhang J, Lian J, Teng W, Chen L. Prevalence and risk factors of retinopathy in patients with or without metabolic syndrome: a population-based study in Shenyang. BMJ open. 2015;5(12).
23. Chang AC, Fox TP, Wang S, Wu A Y. Relationship between obstructive sleep apnea and the presence and severity of diabetic retinopathy. Retina. 2018;38(11):2197-206.
24. Giuffre G, Lodato G, Dardanoni G. Prevalence and risk factors of diabetic retinopathy in adult and elderly subjects: The Castedaccia Eye Study. Graefes Arch Clin Exp Ophthalmol. 2004;242(7):535–40.
25. Krakoff J, Lindsay RS, Looker HC, Nelson RG, Hanson RL, Knowler WC. Incidence of retinopathy and nephropathy in youth-onset compared with adult-onset type 2 diabetes. Diabetes Care. 2003;26(1):76–81.
26. Arjamaa O, Nikinmaa M. Oxygen-dependent diseases in the retina: role of hypoxia-inducible factors. Exp Eye Res. 2006;83:473-83.
27. Hirota K, Semenza GL. Regulation of angiogenesis by hypoxia inducible factor 1. Crit Rev Oncol Hematol. 2006;59:15-26.
28. Aouiss A, Idrissi DA, Kabine M, Zaid Y. Update of inflammatory proliferative retinopathy: Ischemia, hypoxia and angiogenesis. Current research in translational medicine. 2019.
29. Salam A, Mathew R, Sivaprasad S. Treatment of proliferative diabetic retinopathy with anti-VEGF agents. Acta Ophthalmol. 2011;89(5):405-11.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1219-1222.
DOI: 10.28982/josam.820639

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Describing the heterotopic gastric mucosa (inlet patch) located in the esophagus with cases

Olgular eşliğinde özofagusta lokalize heterotopik gastrik mukozayı (inlet patch) tanıyalım

Selma Şengiz Erhan [1], Sevinç Hallaç Keser [2], Tuğba Ipin [1], Yasemin Gökden [3], Sibel Sensu [4]

[1] Prof. Dr. Cemil Tascioglu City Hospital, Department of Pathology, Istanbul, Turkey
[2] University of Health Sciences, Kartal Dr. Lutfi Kirdar City Hospital, Department of Pathology, Istanbul, Turkey
[3] Istanbul Prof. Dr. Cemil Tascioglu City Hospital, Department of Gastroenterology, Istanbul, Turkey
[4] University of Istinye, Medical Faculty, Department of Pathology, Istanbul, Turkey

ORCID ID of the author(s)
SSE: 0000-0001-8810-8806
SHK: 0000-0002-6987-0333
TI: 0000-0002-1715-6891
YG: 0000-0001-6767-3072
SS: 0000-0002-4607-780X

Corresponding author/Sorumlu yazar:
Selma Şengiz Erhan
Address/Adres: Istanbul Prof. Dr. Cemil Tascıioglu City Hospital, Department of Pathology, Kaptanpasa Mah. Darulaceze Cad. No: 27 Okmeydani, Sisli, Istanbul, Türkiye
E-mail: selmaserhan@hotmail.com

Ethics Committee Approval: This study was approved by University of Health Sciences, Okmeydani Education and Research Hospital Ethic Committee with the number 1054 on 19.11.2019. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma Sağlık Bilimleri Üniversitesi Okmeydanı Eğitim ve Araştırma Hastanesi Etik Kurulu tarafından 1054 numara ve 19.11.2019 tarihiyle onaylanmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: The inlet patch, also called as the heterotopic gastric mucosa, is often located in proximal esophagus and is generally asymptomatic. These lesions are rarely polypoid and mostly have a patchy pattern. In the literature, there are only few cases of inlet patches that show a malignant progression following a metaplasia- dysplasia- adenocarcinoma sequence. In our study, we aimed to present the endoscopic and morphological features of our case series.

Methods: The study, which was conducted in two clinics, included the inlet patch cases diagnosed in esophagus biopsy materials between 2016 and 2019. The slides and the demographic data of the cases were re-analyzed.

Results: Among 4190 cases whose esophageal biopsies were examined, 63 inlet patches (1.5%) were diagnosed. Thirty four cases were male and 29 were female. Age range was 16-82 years. The cases were mostly located in proximal esophagus and the size of the lesions ranged between 0.2-3.5 cm. One of the four cases with polypoid appearance was microscopically diagnosed as a hyperplastic polyp. The most common gastric type epithelium was the oxyntic type. Helicobacter pylori was observed in four cases, and intestinal metaplasia and low-grade dysplasia were observed in one. No malignancy was diagnosed in our series.

Conclusion: Although benign, the inlet patch is significant due to its risk of progression to malignancy. Thus, obtaining biopsies from each lesion endoscopically considered as inlet patch is recommended. This will help determine the precise incidence of the inlet patch and more importantly, identify neoplasia earlier.

Keywords: Inlet patch, Esophagus, Polyp, Dysplasia

Öz

Amaç: Heterotopik gastrik mukoza olarak da adlandırılan inlet patch sıklıkla proksimal özofagusta lokalizedir. Genellikle asemptomatiktir. Polipoid yapıda seyrek saptanan bu lezyonlar, sıklıkla endoskopik olarak yamasal tarzda izlenir. Literatürde metaplazi-displazi-adenokarsinom sekansını takiben malign progresyon gösterebilen az sayıda inlet patch olguları yer almaktadır. Çalışmamızda inlet patch tanılı olgu serimizi endoskopik ve morfolojik özellikleriyle sunmayı amaçladık.

Yöntemler: Çalışma iki klinik üzerinden yürütüldü. Her iki klinikte 2016-2019 yılları arasında özofagusa ait biyopsi materyalleri içinde inlet patch tanısı alan olgular dahil edildi. Olgulara ait preparatlar ve demografik bilgiler tekrar gözden geçirildi.

Bulgular: Özofagus biyopsisi incelenen 4190 olgu içinde 63 olgu (%1,5) inlet patch tanısı aldı. Olguların 34'ü erkek, 29'u kadındı. Olguların yaşları 16 ile 82 arasında değişmekteydi. En sık görüldüğü yaş aralığı 30-50 yaşdı. En sık proksimal özofagusta lokalizeydi (59 olgu). Lezyonların boyutları 0,2-3,5 cm arasında değişmekteydi. Polipoid görünümdeki dört olgudan biri histopatolojik olarak hiperplastik polip tanısı aldı. En sık gözlenen gastrik tip epitel oksintik tipti (29 olgu). Helikobakter pilori dört olguda izlendi. Olgulardan birinde intestinal metaplazi ve düşük dereceli displazi saptandı. Malignite tanısı olan olgumuz yoktu.

Sonuç: Benign bir lezyon olmasına rağmen maligniteye dönüşüm riski nedeniyle inlet patch olgularının önemsenmesi gerekmektedir. Bu nedenle endoskopik incelemede inlet patch olarak saptanan her lezyondan biyopsi alınması, özellikle büyük boyut, ülser gibi farklı klinik tablo sergileyen olguların da yakın klinik takiplerinin yapılması bizlere inlet patchin gerçekte görülme sıklığının ne olduğunu ve en önemlisi gelişen neoplazilerin erken dönemde saptanmasına olanak sağlayacaktır.

Anahtar kelimeler: İnlet patch, Özofagus, Polip, Displazi

How to cite/Atıf için: Erhan SŞ, Keser SH, Ipin T, Gökden Y, Sensu S. Describing the heterotopic gastric mucosa (inlet patch) located in the esophagus with cases. J Surg Med. 2020;4(12):1219-1222.

Introduction

Heterotopic gastric mucosa can be observed anywhere in the gastrointestinal tract, as well as the gallbladder, abdomen, and liver [1,2]. The most common location in the gastrointestinal tract is the proximal esophagus, where it is called the inlet patch [3,4]. The lesions located just below the upper esophageal sphincter can be missed during endoscopic examination [5]. They are either patchy or circular, and polyps are rarely seen [3,6]. Though mostly asymptomatic, the inlet patch can also manifest clinically with spasm, web, esophagitis, ulceration, bleeding or extraesophageal fistula due to acid secretion from the gastric mucosa [7,8]. It may occasionally exhibit malignant progression following the metaplasia-dysplasia-adenocarcinoma sequence as in other parts of the gastrointestinal tract [9,10]. In our study, we aimed to present a series of our cases of inlet patch along with their clinicopathological findings.

Materials and methods

Our retrospective study was conducted in two centers, and included the cases diagnosed with inlet patch between 2016 and 2019. In addition to the demographic characteristics (age and gender), the endoscopic findings and pathological data of the cases (hematoxylin & eosin (H&E), histochemistry and immunohistochemistry results) were reviewed. The location of the lesion in the esophagus (upper, middle, and lower), number (single or multiple), size, appearance (patchy or polypoid) of the lesion, type of gastric epithelium, as well as concomitant inflammation, Helicobacter pylori (HP) positivity, intestinal metaplasia and dysplasia were noted. The gastric type of epithelium detected in the inlet patch biopsies were classified into three main groups as oxyntic, antral, and mixed type. For the detection of HP, Giemsa and Warthin–Starry as well as H&E stained slides were reviewed. Sydney Classification was performed for the gastric biopsies taken simultaneously with esophageal biopsies.

This study was approved by University of Health Sciences, Okmeydani Education and Research Hospital Ethic Committee, by the number 1054 on 19.11.2019.

Statistical analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, Pearson Chi-Square test, Fisher Freeman Halton test and Fisher's Exact test were used to compare the descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) as well as the qualitative data. $P<0.05$ was considered significant.

Results

During the study, among 4190 esophageal biopsies, 63 (1.5%) were diagnosed with inlet patch, 34 (53.9%) of which were males. The ages of the patients ranged between 16 and 82 years, with mean of 42.83 (13.44) years. In the study, which also included the pediatric age group, the inlet patch was most common between 30-50 years of age (30-40 years old (n=18), 40-50 years old (n=16)). Of the lesions detected endoscopically, 59 (93.6%) were located in the proximal esophagus, three (4.7%) in the middle esophagus and one (1.5%) in the distal esophagus. The sizes of the lesions ranged between 0.2-3.5 cm. While 42 cases (66.7%) were 0.5 cm or less, 17 cases (27%) had a size of 1 cm or more. In 54 (85.7%) of the cases, there was a single focus, while 9 (14.3%) had multiple foci. In 7 of the cases with more than one focus, the size was 0.5 cm or below. In 59 cases (93.6%), the lesions were patchy, while in four, a polypoid structure was observed. The size of one of these cases was 1 cm (Figure 1).

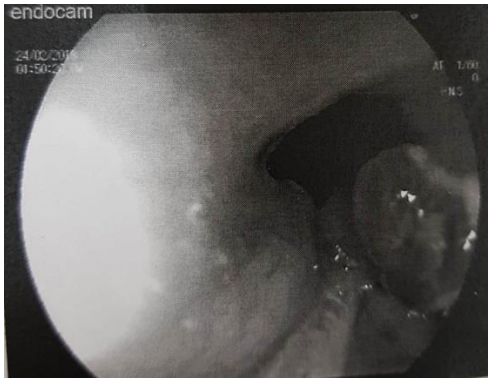


Figure 1: Endoscopic view of esophageal polyp which is located at tenth cm of esophagus

Histopathologically, oxyntic type of epithelium was observed in 29 cases (46.1%), the antral type, in 24 cases (38.1%) and the mixed type, in 10 cases (15.8%). Chronic inflammation was found in 32 cases (50.8%), while in 22 cases (34.9%) active inflammation was also present. Nine patients (14.3%) had no signs of inflammation. HP was detected in four cases (6.3%). While one of these cases had chronic inflammation, three had signs of chronic active inflammation. Histopathological examination of one of the lesions with a polypoid appearance was reported as a hyperplastic polyp (Figure 2). Other lesions had mucosal edema leading to polypoid appearance. Intestinal metaplasia and low-grade dysplasia were detected in one of the cases (Figure 3, 4) which was a single, 0.5 cm lesion found in an 82-year-old patient. This case is still under follow up.

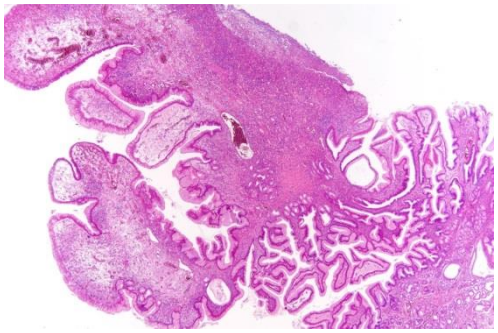


Figure 2: Hyperplastic polyp (H&E x20)

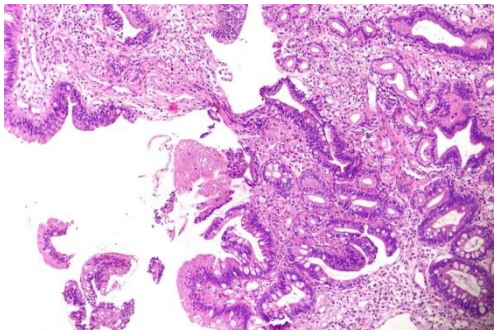


Figure 3: Intestinal metaplasia and low grade dysplasia in inlet patch focus (H&E x200)

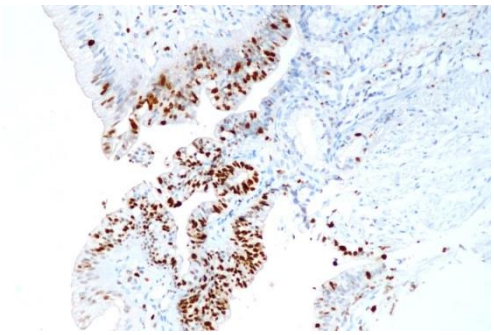


Figure 4: Dysplastic epithelium with Ki-67 proliferative activity (x200)

Chronic inflammation was found in 25 cases (39.6%), chronic active inflammation was detected in 24 cases (38.1%), intestinal metaplasia was found in 7 cases (11.1%), HP was found in 29 cases (46.1%) and 1 case (1.5%) had low grade dysplasia in gastric mucosa. HP was observed in the inlet patch foci as well as the stomach in four patients. With respect to gender, the age distribution of the cases, lesion sizes, gastric epithelium types, inlet patch gastric HP and inflammation were not significantly different (P=0.100, P=0.340, P=0.261, P=0.613, P=0.346).

No statistically significant relationship was found between the presence of HP, gastric epithelial types of the inlet patch foci and the size of lesions (P=0.463, P=0.062). Among cases where HP was and was not observed in the inlet patch foci, there was no significant difference regarding findings of chronic inflammation, chronic active inflammation, intestinal metaplasia, and dysplasia in stomach (P=0.239).

Demographic features and endoscopic findings are presented in Table 1 and histopathological findings, in Table 2.

Table 1: Demographic and endoscopic characteristics of the patients

	n (%)
Age (years)	42.83 (13.44) (min 16- max 82)
Gender	
Female	29 (46.1%)
Male	34 (53.9%)
Location	
Proximal esophagus	59 (93.6%)
Middle esophagus	3 (4.7%)
Lower esophagus	1 (1.5%)
Size	
≥5 mm	42 (66.7%)
6-9 mm	4 (6.3%)
≤10 mm	17 (27%)
Number of foci	
Single	54 (85.7%)
Multiple	9 (14.3%)
Appearance	
Patchy	59 (93.6%)
Polypoid	4 (6.3%)

Table 2: Histopathological findings in heterotopic gastric mucosa and accompanying gastric mucosa

Findings	n (%)
Cell type (heterotopic gastric mucosa)	
Oxyntic	29 (46.1%)
Antral	24 (38.1%)
Mixed	10 (15.8%)
Histopathological findings (heterotopic gastric mucosa)	
Chronic inflammation	32 (50.7%)
Chronic active inflammation	22 (34.9%)
Helicobacter pylori	4 (6.3%)
Intestinal metaplasia	1 (1.5%)
Dysplasia	1 (1.5%)
Histopathological findings (accompanying gastric mucosa)	
Chronic inflammation	25 (39.6%)
Chronic active inflammation	24 (38.1%)
Helicobacter pylori	29 (46.1%)
Intestinal metaplasia	7 (11.1%)
Dysplasia	1 (1.5%)

Discussion

Pathogenesis of the inlet patch is still not fully understood [8]. The most accepted hypothesis is that it is a congenital anomaly which results from the incomplete transformation of columnar epithelium into the squamous epithelium during embryonic development. Inlet patch is generally asymptomatic and detected incidentally during endoscopic examination [8]. Since most of the studies are retrospective, there is no exact data on its frequency. Rates ranging from 0.1% to 18% are reported in the literature [7,8,11]. The rate increases even more in autopsies [7]. It is often difficult to notice due to the contraction of the upper esophageal sphincter, and the attention of the endoscopist also affects its detection [3,5]. In our study, patients diagnosed with inlet patch were incidentally detected during endoscopic examination. Our study was retrospective, and the inlet patch rate was compatible with the literature.

Inlet patch can be detected at any age including the pediatric group. While the incidence in the pediatric group is between 0.1-6%, this rate varies between 0.1-18% in adults [8,11,12]. Our study included a wide age range, and one patient was in the pediatric group [1,8]. In studies, the incidence of males is slightly higher than that of females and our study was compatible with the literature in this regard. Inlet patch foci have a velvety, dark pink appearance endoscopically, and are usually found as single or multiple patchy foci [7,13,14]. In our study, while a single focus was observed in endoscopic examination in most of the cases, there were nine cases with two or more foci and our rates were similar to those reported in the literature.

Polyp development is rare in inlet patch cases [8,14]. The number of hyperplastic polyps diagnosed in cervical esophagus is very low in the literature [6,15]. In our study, we present a case located in the esophagus and diagnosed as a hyperplastic polyp (1 cm). The most common mucosa detected in the inlet patch foci is the oxyntic mucosa, which is followed by the antral type [13,14,16]. In our study, in accordance with the literature, the oxyntic type mucosa was seen more frequently.

Microscopic examination may be accompanied by mononuclear inflammatory cells (plasma cells and lymphocytes), polymorphonuclear leucocytes and HP in these foci at varying rates [8,14,17]. Studies report that 0-86% of cases with gastric HP may also have HP in the inlet patch foci [13,16]. Oral route and gastroesophageal reflux is reported among the causes of colonization of HP in the inlet patch foci [18]. In our study, HP was observed in the inlet patch foci in four cases.

Histopathologically, intestinal metaplasia may accompany the inlet patch, but dysplasia and adenocarcinoma are extremely rare [7,9,10,19]. According to some authors, lack of histopathological correlation of each inlet patch case is the reason for the low rate of neoplasia [3]. In our study, only one of our patients had a low-grade dysplasia, which was accompanied by intestinal metaplasia. We did not have a case diagnosed as adenocarcinoma. The inlet patch cases, generally known as benign lesions, remain stable during their follow up [14]. Since most of them are asymptomatic, there is no accepted standard treatment. Thus, some authors find endoscopic follow up sufficient for asymptomatic cases without taking a biopsy [16]. However, because of the possibility of neoplastic development,

some authors also recommend taking a biopsy to determine the presence or absence of preneoplastic or neoplastic lesions from endoscopically detected lesions [3,16]. Proton pump inhibitors can provide dramatic improvement for symptomatic patients [20]. In cases diagnosed with dysplasia and neoplasia, argon plasma coagulation, endoscopic mucosal resection, endoscopic submucosal dissection, and radiofrequency ablation can be performed [8].

Limitations

Our study has a few limitations. First, this study was planned retrospectively. Second, the number of cases was few, and one case was diagnosed with preneoplasia, which was excluded.

Conclusions

The incidence of our inlet patch cases was consistent with the literature in terms of the presence of the gastric type epithelium, HP, intestinal metaplasia, and dysplasia. Our case diagnosed with a hyperplastic polyp is of particular importance for the literature. Since the inlet patch, which is a benign lesion, has the potential to transform into malignancy, we need to obtain more information about these lesions and their significance. Therefore, taking biopsies from each lesion suspected of being an inlet patch in endoscopic examination, and performing a close clinical follow up, especially in patients with different clinical features such as large size and ulcers, will allow us to identify the precise frequency of the inlet patch and most importantly, detect early neoplasms. In our daily routine, we think that our study will increase awareness especially for endoscopists and pathologists and may be a guide for further studies that will be conducted among larger patient groups.

References

1. Terada T. Heterotopic gastric mucosa of the gastrointestinal tract: A histopathologic study of 158 cases. Pathol Res Pract. 2011;207(3):148-50. doi: 10.1016/j.prp.2010.12.004.
2. Orizio P, Villanacci V, Bassotti G, Falchetti D, Torri F, Ekema G. Heterotopic gastric mucosa in the cystic duct. Int J Surg Pathol. 2011;19(3):364-5. doi: 10.1177/1066896909337717.
3. Peitz U, Vieth M, Evert M, Arand J, Roessner A, Malfertheiner P. The prevalence of gastric heterotopia of the proximal esophagus is underestimated, but preneoplasia is rare - correlation with Barrett's esophagus. BMC Gastroenterol. 2017;17(1):87. doi: 10.1186/s12876-017-0644-3.
4. Lupu VV, Ignat A, Paduraru G, Mihaila D, Burlea M, Ciubara A. Heterotopic Gastric Mucosa in the Distal Part of Esophagus in a Teenager: Case Report. Medicine . 2015;94(42):e1722. doi: 10.1097/MD.0000000000001722.
5. Mete R, Oran M, Yüksek A, Gürdal SÖ, Coşkunkan U, Aydın U, et al. Yutma güçlüğü ile başvuran inlet patch olgusu. Int J Basic Clin Med. 2013;1(2):120-2. http://hdl.handle.net/20.500.11776/2223.
6. Alagozlu H, Ergun M, Cindoruk M, Unal S, Dumlu S, Poyraz A, et al. The rare presentations of a large polyp and an esophageal carcinoma in heterotopic gastric mucosa: a case series. J Med Case Rep. 2007;127:1-4. doi: 10.1186/1752-1947-1-127.
7. Chong VH. Clinical significance of heterotopic gastric mucosal patch of the proximal esophagus. World J Gastroenterol. 2013;19(3):331-8. doi: 10.3748/wjg.v19.i3.331.
8. Rusu R, Ishaq S, Wong T, Dunn JM. Cervical inlet patch: new insights into diagnosis and endoscopic therapy. Frontline Gastroenterol. 2018;9(3):214-20. doi: 10.1136/flgastro-2017-100855.
9. Riddiough GE, Hornby ST, Asadi K, Aly A. Gastric adenocarcinoma of the upper oesophagus: A literature review and case report. Int J Surg Case Report. 2017;30:205-14. doi: 10.1016/j.ijscr.2016.11.014.
10. Ajmal S, Young JS, Ng T. Adenocarcinoma arising from cervical esophageal gastric inlet patch. J Thorac Cardiovasc Surg. 2015;149(6):1664-5. doi: 0rg/10.1016/j.jtcvs.2015.03.050.
11. Vesper I, Schmiegel W, Brechmann T. Equal detection rate of cervical heterotopic gastric mucosa in standard white light, high definition and narrow band imaging endoscopy. Z Gastroenterol. 2015;53(11):1247-54. doi: 10.1055/s.0041-104226.
12. Georges A, Coopman S, Rebeuh J, Molitor G, Rebouissoux L, Dabadie A, et al. Inlet patch: clinical presentation and outcome in children. J Pediatr Gastroenterol Nutr. 2011;52(4):419-23. doi: 10.1097/MPG.0b013e3181f2a913.
13. Weickert U, Wolf A, Schröder C, Autschbach F, Vollmer H. Frequency, histopathological findings, and clinical significance of cervical heterotopic gastric mucosa (gastric inlet patch): a prospective study in 300 patients. Dis Esophagus. 2011;24(2):63-8. doi: 10.1111/j.1442-2050.2010.01091.x.
14. Fang Y, Chen L, Shen DF, Xu Y, Xia YJ, Li JW, et al. Prevalence, histologic and clinical characteristics of heterotopic gastric mucosa in Chinese patients. World J Gastroenterol. 2014;20(46):17588-94. doi: 10.3748/wjg.v20.i46i17588.
15. Oguma J, Ozawa S, Omori T, Kitagawa Y, Saikawa Y, Mikami S, et al. EMR of a hyperplastic polyp arising in ectopic gastric mucosa in the cervical esophagus: case report. Gastrointest Endosc. 2005;61(2):335-8. doi: 10.1016/S0016-5107(04)02469-1.
16. Ciocalteu A, Popa P, Ionescu M, Gheonea D. Issues and controversies in esophageal inlet patch. World J Gastroenterol. 2019;25(30):4061-73. doi: 10.3748/wjg.v25.i30.4061.
17. Alagozlu H, Simsek Z, Unal S, Cindoruk M, Dumlu S, Dursun A. Is there an association between Helicobacter pylori in the inlet patch and globus sensation? World J Gastroenterol. 2010;16(1):42-7. doi: 10.3748/wjg.v16.i1.42.
18. Gutierrez O, Akamatsu T, Cardona H, Graham DY, El-Zimaity HMT. Helicobacter pylori and hetertopic gastric mucosa in the upper esophagus (the inlet patch). Am J Gastroenterol. 2003;98(6):1266-70. doi: 10.1111/j.1572-0241.2003.07488.x.
19. Tanaka M, Ushiku T, Ikemura M, Shibahara J, Seto Y, Fukayama M. Esophageal adenocarcinoma arising in cervical inlet patch with synchronous Barrett's esophagus-related dysplasia. Pathol Int. 2014;64(8):397-401. doi: 10.1111/pin.12181.
20. Yamada T, Tsuji A, Onoue S, Kaneko M, Tanioka F, Osawa S, et al. Acid suppressive therapy improved symptoms due to circumferential cervical inlet patch with proton pumps (H+/K+-ATPase). World J Clin Cases. 2017;5(11):403-6. doi: 10.12998/wjcc.v5.i11.403.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1223-1226.
DOI: 10.28982/josam.823584

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Review of upper extremity bone metastasis: A retrospective cohort study of 61 patients

Üst ekstremite kemik metastazlarının gözden geçirilmesi: 61 hastadan oluşan retrospektif kohort çalışma

Koray Başdelioğlu [1]

[1] **Istanbul Oncology Hospital Department of Orthopedics and Traumatology, Istanbul, Turkey**

ORCID ID of the author(s)

KB: 0000-0003-0235-4497

Abstract

Aim: Although bone metastasis is the most common bone cancer in adults, its spread to the upper extremity is relatively low. Distribution characteristics of upper extremity bone metastases are not clearly defined. In this study, we aimed to investigate upper extremity metastases, reveal the distribution of upper extremity metastases compared to primary cancers, and evaluate their relationship with additional bone metastases and additional visceral organ metastases.

Methods: Sixty-one patients diagnosed with upper extremity metastasis between 2018-2020 were included in the study and analyzed retrospectively. Clinical data, pathology, PET-CT and MRI reports were evaluated. Demographic characteristics (age, gender), primary cancer type, metastasis location (scapula, clavicle, humerus (proximal, diaphysis, distal) and forearm (proximal, diaphysis and distal)), number of metastases (single / multiple foci), additional bone and visceral organ metastases were evaluated.

Results: Thirteen (52.00%) female and 22 (61.11%) male patients had multiple upper extremity metastases (P=0.657). The most common location of metastasis was proximal humerus for both genders. Proximal humerus was the most common metastasis location in breast (58.82%), lung (55.56%) and prostate (87.50%) cancers. Scapula was the most common metastasis location in gastrointestinal (87.50%) and urinary tract (83.33%) cancers. Scapula and proximal humerus were the most common metastasis locations in gynecologic (66.67%) cancers. The most common accompanying bone metastasis site was the vertebra for both genders. The most common visceral organ metastasis was the lung (20.00%) in females and liver (16.67%) in males.

Conclusion: The most common location of metastases in the upper extremity is the proximal humerus, followed by the scapula. The incidence of upper extremity metastasis decreases from proximal to distal. Solving this mechanism may be beneficial for treatment and survival.

Keywords: Upper extremity, Bone metastases, Primary cancer

Öz

Amaç: Kemik metastazı yetişkinlerde en sık görülen kemik kanseri olmasına rağmen, üst ekstremiteye yayılımı nispeten azdır. Üst ekstremite kemik metastazlarının dağılım özellikleri açıkça tanımlanmamıştır. Bu çalışmada üst ekstremite metastazlarının araştırılması, üst ekstremite metastazlarının primer kanserler açısından dağılımının ortaya çıkarılması, ek kemik metastazları ve ek visseral organ metastazları ile ilişkisinin değerlendirilmesi amaçlanmıştır.

Yöntemler: 2018-2020 yılları arasında üst ekstremite metastazı tanısı olan 61 hasta çalışmaya dahil edildi ve retrospektif olarak incelendi. Klinik veriler, patoloji, PET-CT ve MRI raporları değerlendirildi. Demografik özellikler (yaş, cinsiyet), primer kanser tipi, metastaz lokalizasyonu (skapula, klavikula, humerus (proksimal, diafiz, distal) ve ön kol (proksimal, diafiz ve distal)), metastaz sayısı (tek/multiple odak), ek kemik ve viseral organ metastazları açısından hastalar değerlendirildi.

Bulgular: 13 kadın hastada (%52,00) multiple üst ekstremite metastazı varken 22 erkek hastada (%61,11) multiple üst ekstremite metastazı vardı (P=0,657). Metastazın en yaygın yeri her iki cinsiyet için proksimal humerustu. Proksimal humerus meme (%58,82), akciğer (%55,56) ve prostat (%87,50) kanserlerinde en sık metastaz bölgesiydi. Skapula, gastrointestinal sistem (%87,50) ve idrar yolu (%83,33) kanserlerinde en sık metastaz yeriydi. Jinekolojik kanserlerde (%66,67) en sık metastaz yerleri skapula ve proksimal humerustu. Eşlik eden en yaygın ek kemik metastaz alanı her iki cinsiyet için de vertebraydı. Kadınlarda en sık görülen viseral organ metastazı akciğer (%20,00), erkeklerde ise karaciğerde (%16,67) görüldü.

Sonuç: Üst ekstremite metastazlarının en sık yerleşim yeri proksimal humerustur ve bunu skapula izlemektedir. Üst ekstremite metastazının görülme insidansı proksimalden distale doğru azalmaktadır. Bu mekanizmanın çözülmesi tedavi ve sağ kalım için faydalı olabilir.

Anahtar kelimeler: Üst ekstremite, Kemik metastazı, Primer kanser

Corresponding author/Sorumlu yazar:
Koray Başdelioğlu
Address/Adres: Istanbul Oncology Hospital Department of Orthopaedic and Traumatology, Istanbul, Turkey
E-mail: drkoraybasd@gmail.com

Ethics Committee Approval: The study protocol was approved Istinye University Ethics Committee (2/2020.K-078-10/5/2020). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma protokolü İstinye Üniversitesi Etik Kurulu tarafından onaylandı (2/2020.K-078-05.10.2020). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

How to cite/Atıf için: Başdelioğlu K. Review of upper extremity bone metastasis: A retrospective cohort study of 61 patients. J Surg Med. 2020;4(12):1223-1226.

Introduction

Bone metastasis is the most common bone cancer in adults [1,2]. After lung and liver metastases, the most common metastasis region is the bones. Primary cancers most frequently associated with bone metastasis are lung, breast, kidney, and prostate cancers [3]. Bone metastasis significantly affects the prognosis for patients and is a serious cause of morbidity [4,5]. Previous studies reported that important prognostic factors in bone metastasis are age, primary cancers, onset of bone symptoms, pathological fracture, metastasis to other organs, performance score, and preoperative hemoglobin level [6-8]. Severe bone pain, pathological fractures, spinal cord compression, and hypercalcemia are among the major complications of bone metastases, so bone metastasis is a major threat to the quality of life and even survival of patients [9,10].

Spine, femur, pelvis and humerus are the most common sites of bone metastasis [3,6]. Upper extremity metastases (24%) are much less common than lower extremity metastases (76%) [11]. According to the few studies investigating upper extremity metastases, bone metastasis is seen most frequently in the proximal humerus in the upper extremity, while this rate gradually decreases distally in the extremity [5,11].

There are very few studies in the literature investigating the distribution and characteristics of upper extremity bone metastases [5,11]. In this study, it was aimed to investigate upper extremity metastases and their distribution characteristics according to primary cancers, reveal the demographic characteristics of the patients and the features of additional bone metastases that may accompany upper extremity metastases.

Materials and methods

Patients who were followed up with a diagnosis of cancer in Istanbul Oncology Hospital between 2018 and 2020 were retrospectively analyzed. Outpatients clinic files of the patients, the results of 18F-fluoro-2-deoxyglucose (FDG) Positron Emission Tomography / Computerized Tomography (PET-CT), Magnetic Resonance Image (MRI) and pathology results of primary cancers were examined. While inclusion criteria consisted of being followed up with a diagnosis of cancer between 2018-2020, having upper extremity metastases and complete data, primary bone cancers and patients with a lack of data were excluded from the study. Sixty-one patients were included in the study in line with the determined inclusion and exclusion criteria.

The demographic characteristics (age, gender), pathology reports of primary cancers, PET-CT and MRI results of 61 patients included in the study were evaluated retrospectively. Primary cancers were divided into 6 groups as lung cancer, breast cancer, gastrointestinal tract cancers (gastric cancer, pancreatic cancer, colon cancer, gallbladder cancer, rectum cancer), urinary tract cancers (renal cancer, bladder cancer), prostate cancer, gynecological cancers (endometrial cancer, cervical cancer) and unknown origin (Table 1). The groups were evaluated in terms of age, gender, number of upper extremity metastases (single focus, multiple focus) and localization of upper extremity metastasis. Localization of upper extremity metastasis was categorized as scapula, clavicle, humerus and forearm. Humerus and forearm were examined in detail anatomically in 3 regions as proximal, diaphysis and distal. In addition, additional bone metastases accompanying upper extremity metastases were evaluated. Additional bone metastases were classified into six regions as spine (cervical spine, thoracic spine, lumbar spine), lower limb (femur, tibia, ankle, foot), thoracic bones (ribs, sternum) and pelvis (sacroiliac joint, sacrum, ilium, ischium, pubis, acetabulum).

The protocol of the study, which was and carried out in accordance with the principles of the Helsinki Declaration, was approved by Istinye University Ethics Committee (2/2020.K-078-10/5/2020).

Statistical analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test was used to determine whether variables are normally distributed. Data are given as mean (SD) for continuous variables and as frequency (percentage) for categorical variables. Normally distributed variables were analyzed with the independent samples t test or one-way analysis of variances (ANOVA) depending on the number of groups being compared. Pairwise comparisons were performed with the Tukey test. Categorical variables were analyzed with the Chi-square tests or Fisher's exact tests. Two-tailed *P*-values of less than 0.05 were considered statistically significant.

Results

We included 61 patients (25 females and 36 males) with a mean age of 61.82 (10.47) years (range 42 - 86) in this study. There were no significant differences between genders in terms of age (P=0.438). The most common primary cancer type was lung cancer (29.51%) among all patients. The most common primary cancer types were breast (68.00%), lung (16.00%) and gynecologic (12.00%) cancers in females and lung (38.89%), gastrointestinal tract (22.22%) and prostate (22.22%) cancers in males (P<0.001). The primary cancer type was unknown in one female patient.

Thirteen (52.00%) female patients and 22 (61.11%) male patients had multiple upper extremity metastases (P=0.657). The most common location of metastasis was proximal humerus for both genders. There were no significant differences between the genders in terms of metastases. Distribution of localizations of upper extremity metastases by gender was shown in Figure 1.

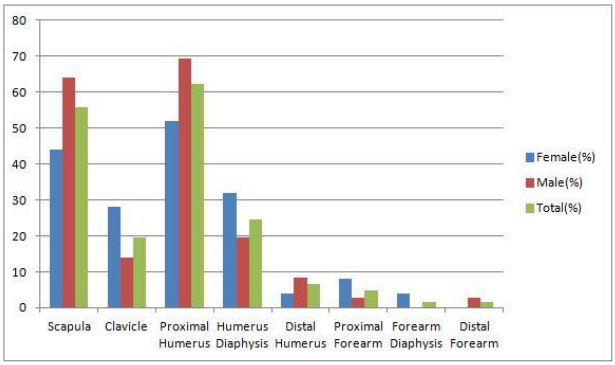


Figure 1: Distribution of upper extremity metastasis localizations according to gender

Nineteen (76.00%) female and 22 (61.11%) male patients had accompanying bone metastases. The most common metastasis site was the vertebra in both genders. Six (24.00%)

female patients and 11 (30.56%) male patients had accompanying visceral organ metastases. The most common visceral organ metastasis was the lung (20.00%) in females and liver (16.67%) in males. There were no significant differences between genders with regards to accompanying bone or visceral organ metastasis (Table 1).

Table 1: Summary of age and metastasis characteristics with regards to gender

	Female (n=25)	Male (n=36)	Total (n=61)	*P*-value
Age, mean (SD)	60.56 (9.39)	62.69 (11.20)	61.82 (10.47)	0.438
Primary tumor	n (%)	n (%)	n (%)	
Breast	17 (68.00)	0 (0.00)	17 (27.87)	<0.001
Lung	4 (16.00)	14 (38.89)	18 (29.51)	
Gastrointestinal Tract	0 (0.00)	8 (22.22)	8 (13.11)	
Gastric	0 (0.00)	2 (5.56)	2 (3.28)	
Pancreatic	0 (0.00)	1 (2.78)	1 (1.64)	
Gallbladder	0 (0.00)	1 (2.78)	1 (1.64)	
Colonic	0 (0.00)	2 (5.56)	2 (3.28)	
Rectal	0 (0.00)	2 (5.56)	2 (3.28)	
Urinary tract	0 (0.00)	6 (16.67)	6 (9.84)	
Renal	0 (0.00)	3 (8.33)	3 (4.92)	
Urinary Bladder	0 (0.00)	3 (8.33)	3 (4.92)	
Prostate	0 (0.00)	8 (22.22)	8 (13.11)	
Gynecologic	3 (12.00)	0 (0.00)	3 (4.92)	
Endometrial	1 (4.00)	0 (0.00)	1 (1.64)	
Cervical	2 (8.00)	0 (0.00)	2 (3.28)	
Unknown	1 (4.00)	0 (0.00)	1 (1.64)	
Number of metastasis	n (%)	n (%)	n (%)	
Single	12 (48.00)	14 (38.89)	26 (42.62)	0.657
Multiple	13 (52.00)	22 (61.11)	35 (57.38)	
Location	n (%)	n (%)	n (%)	
Scapula	11 (44.00)	23 (63.89)	34 (55.74)	0.202
Clavicle	7 (28.00)	5 (13.89)	12 (19.67)	0.203
Humerus	16 (64.00)	30 (83.33)	46 (75.41)	0.155
Proximal	13 (52.00)	25 (69.44)	38 (62.30)	0.265
Diaphysis	8 (32.00)	7 (19.44)	15 (24.59)	0.414
Distal	1 (4.00)	3 (8.33)	4 (6.56)	0.638
Forearm	2 (8.00)	2 (5.56)	4 (6.56)	1.000
Proximal	2 (8.00)	1 (2.78)	3 (4.92)	0.562
Diaphysis	1 (4.00)	0 (0.00)	1 (1.64)	0.410
Distal	0 (0.00)	1 (2.78)	1 (1.64)	1.000
Accompanying bone metastasis	19 (76.00)	22 (61.11)	41 (67.21)	0.347
Vertebra	15 (60.00)	20 (55.56)	35 (57.38)	0.935
Lower extremity	12 (48.00)	8 (22.22)	20 (32.79)	0.067
Thorax	9 (36.00)	10 (27.78)	19 (31.15)	0.688
Pelvis	13 (52.00)	13 (36.11)	26 (42.62)	0.332
Accompanying visceral organ metastasis	6 (24.00)	11 (30.56)	17 (27.87)	0.786
Lung	5 (20.00)	3 (8.33)	8 (13.11)	0.254
Liver	3 (12.00)	6 (16.67)	9 (14.75)	0.725
Peritoneum	1 (4.00)	3 (8.33)	4 (6.56)	0.638
Suprarenal gland	0 (0.00)	3 (8.33)	3 (4.92)	0.262
Urinary bladder	0 (0.00)	1 (2.78)	1 (1.64)	1.000

Patients with prostate cancer were significantly older than patients with breast and lung cancers (P=0.005). There were no significant differences between other cancer types in terms of age. The groups were similar in terms of multiple metastasis presence (P=0.941). Proximal humerus was the most common metastasis site in breast (58.82%), lung (55.56%) and prostate (87.50%) cancers. Scapula was the most common metastasis site in gastrointestinal (87.50%) and urinary tract (83.33%) cancers. Scapula and proximal humerus were the most common metastasis sites in gynecologic (66.67%) cancers. Distribution of upper extremity metastasis localizations according to primary cancers was shown in Figure 2 and Table 2.

The most common accompanying bone metastasis site was the vertebra in the breast (64.71%), lung (55.56%) and gastrointestinal tract (62.50%) cancers, and the vertebrae and pelvis in urinary tract (50.00%), prostate (50.00%) and gynecologic (66.67%) cancers. The most common accompanying visceral organ metastasis was lung in breast (23.53%) cancer, peritoneum, and suprarenal gland in lung (16.67%) cancer, lung and liver in gastrointestinal tract (25.00%) cancers, liver in prostate (25.00%) cancer, and lung and liver in gynecologic (33.33%) cancers. There was not any accompanying visceral organ metastasis in urinary tract cancers. We found no significant differences between primary cancer types regarding accompanying bone or visceral organ metastases (Table 2).

Table 2: Summary of age and metastasis characteristics with regard to primary cancer types

	Breast (n=17)	Lung (n=18)	GI Tract (n=8)	Urinary Tract (n=6)	Prostate (n=8)	Gynecologic (n=3)	*P*-value
Age	59.88 (10.08) [a]	57.00 (8.22) [a]	60.13 (9.67) [ab]	65.00 (8.67) [ab]	73.50 (11.51) [b]	65.00 (3.46) [ab]	0.005
Number of Metastasis	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Single	8 (47.06)	8 (44.44)	3 (37.50)	2 (33.33)	3 (37.50)	2 (66.67)	0.941
Multiple	9 (52.94)	10 (55.56)	5 (62.50)	4 (66.67)	5 (62.50)	1 (33.33)	
Location	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Scapula	6 (35.29)	8 (44.44)	7 (87.50)	5 (83.33)	5 (62.50)	2 (66.67)	0.102
Clavicle	4 (23.53)	4 (22.22)	2 (25.00)	1 (16.67)	0 (0.00)	1 (33.33)	0.748
Humerus	11 (64.71)	15 (83.33)	5 (62.50)	5 (83.33)	7 (87.50)	2 (66.67)	0.655
Proximal	10 (58.82)	10 (55.56)	5 (62.50)	4 (66.67)	7 (87.50)	2 (66.67)	0.750
Diaphysis	6 (35.29)	5 (27.78)	1 (12.50)	2 (33.33)	0 (0.00)	0 (0.00)	0.330
Distal	0 (0.00)	3 (16.67)	0 (0.00)	0 (0.00)	1 (12.50)	0 (0.00)	0.330
Forearm	2 (11.76)	1 (5.56)	0 (0.00)	0 (0.00)	1 (12.50)	0 (0.00)	0.792
Proximal	2 (11.76)	0 (0.00)	0 (0.00)	0 (0.00)	1 (12.50)	0 (0.00)	0.490
Diaphysis	1 (5.88)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0.766
Distal	0 (0.00)	1 (5.56)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0.796
Accompanying bone metastasis	13 (76.47)	12 (66.67)	6 (75.00)	3 (50.00)	5 (62.50)	2 (66.67)	0.880
Vertebra	11 (64.71)	10 (55.56)	5 (62.50)	3 (50.00)	4 (50.00)	2 (66.67)	0.971
Lower extremity	8 (47.06)	7 (38.89)	1 (12.50)	1 (16.67)	2 (25.00)	1 (33.33)	0.514
Thorax	7 (41.18)	7 (38.89)	2 (25.00)	1 (16.67)	2 (25.00)	0 (0.00)	0.625
Pelvis	9 (52.94)	6 (33.33)	2 (25.00)	3 (50.00)	4 (50.00)	2 (66.67)	0.641
Accompanying visceral organ metastasis	5 (29.41)	5 (27.78)	4 (50.00)	0 (0.00)	2 (25.00)	1 (33.33)	0.505
Lung	4 (23.53)	0 (0.00)	2 (25.00)	0 (0.00)	1 (12.50)	1 (33.33)	0.206
Liver	2 (11.76)	2 (11.11)	2 (25.00)	0 (0.00)	2 (25.00)	1 (33.33)	0.630
Peritoneum	1 (5.88)	3 (16.67)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0.454
Suprarenal gland	0 (0.00)	3 (16.67)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0.195
Urinary bladder	0 (0.00)	0 (0.00)	1 (12.50)	0 (0.00)	0 (0.00)	0 (0.00)	0.251

Same letters denote the lack of statistically significant difference between groups.

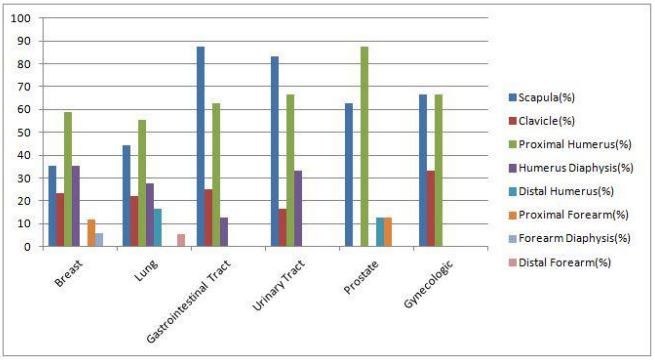


Figure 2: Distribution of upper extremity metastasis localizations according to primary cancers

Discussion

In the present study in which 61 patients with upper extremity metastases were included, demographic characteristics, pathology reports, PET-CT and MRI results of the patients were examined retrospectively. Upper extremity metastases were evaluated in terms of anatomical regions, as the scapula, clavicle, humerus, and forearm. Humerus and forearm were divided into 3 regions as proximal, diaphysis and distal. In addition to examining the distribution characteristics of upper extremity metastases of primary cancers, the number of metastases, additional bone and visceral organ metastases were also evaluated in this study.

There are very few studies in the literature evaluating the distribution characteristics of upper extremity metastases [5,11]. Upper extremity metastases were evaluated with case reports or comparative studies [12-16]. In the study of Wisanuyotin et al. [5], 102 patients with upper extremity metastases were examined. In this study, they reported that the most common upper extremity metastatic sites were humerus (64.7%), clavicle (13.7%) and scapula (12.7%). The most

common primary cancers with upper limb metastases were lung (31.4%), liver (14.7%), breast (12.7%), thyroid (7.8%), and renal (3.9%) cancers [5]. Similarly, the most common upper extremity metastatic sites in our study were the humerus, followed by the scapula (55.74%) and the clavicle (19.67%). Differences in the number of patients may have caused this discrepancy. In addition, in the present study, the humerus and forearm were anatomically divided into 3 regions, proximal diaphysis and distal. The most common primary cancers that metastasized to the upper extremity were lung (29.51%), breast (27.87%), prostate (13.11%) and gastrointestinal tract (13.11%) cancers. The study of Ratasvouri et al. [11], in which they evaluated all bone metastases, reported that the most common metastasis site in the upper extremity was the humerus (21.0%), among which 58.0% of humeral metastases were reported in the diaphysis and 29.0% were located proximally [11]. The results of this study also indicate that the most common upper extremity metastasis region is the humerus, but differently, the most common humerus metastasis localization is the proximal region.

Limitations

The major limitation of the study is its retrospective design. More than half of the patients in the study had breast and lung cancer. In this case, it may be considered as a limitation, but it should be taken into consideration that these cancers are the most common in the society [17,18]. Pathological fracture rates of the upper extremity, surgical treatment options and survival rates could be added to the study. The number of patients participating in the study could have been higher, but the relatively low incidence of upper extremity metastases should be considered in this regard. Nevertheless, studies with higher patient numbers may reveal more objective results.

Conclusion

Regardless of the primary cancer type, the most common localization of metastases in the upper extremity is the proximal humerus, followed by the scapula. The rate of metastasis in the upper extremity decreases from proximal to distal regions, and clarification of its mechanism may be beneficial for treatment and survival. Studies with higher number of patients may yield more objective and comprehensive results regarding the distribution of upper extremity metastases compared to primary cancers and their effects on survival.

References

1. Dijkstra S, Stapert J, Boxma H, Wiggers T. Treatment of pathological fractures of the humeral shaft due to bone metastases: a comparison of intramedullary locking nail and plate osteosynthesis with adjunctive bone cement. Eur J Surg Oncol. 1996;22:621-6.
2. Frassica FJ, Frassica DA. Evaluation and treatment of metastases to the humerus. Clin Orthop Relat Res. 2003:S212-8. doi:10.1097/01.blo.0000093052.96273.a7
3. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev. 2001 Jun;27(3):165-76. doi: 10.1053/ctrv.2000.0210.
4. Memon AG, Jaleel A, Aftab J. Patten of prostatic carcinoma metastases in bones detected by bone scans using Technitium 99m methyl dipohsphate (Tc99m MDP) imaging technique. Pak J Med Sci. 2006;22:180–3.
5. Wisanuyotin T, Sirichatipavee W, Sumnanoont C, Paholpak P, Laupattarakasem P, Sukhonthamarn K, et al.. Prognostic and risk factors in patients with metastatic bone disease of an upper extremity. J Bone Oncol. 2018 Sep 22;13:71-5. doi: 10.1016/j.jbo.2018.09.007.
6. Budczies J, Winterfeld MV, Klauschen F, Bockmayr M, Lennerz JK, Denkert J, et al. The landscape of metastatic progression patterns across major human cancers. Oncotarget. 2015 Jan 1;6(1):570-83. doi: 10.18632/oncotarget.2677.
7. Kirkinis MN, Lyne CJ, Wilson MD, Choong PFM. Metastatic bone disease: A review of survival, prognostic factors and outcomes following surgical treatment of the appendicular skeleton. Eur J Surg Oncol. 2016 Dec;42(12):1787-97. doi: 10.1016/j.ejso.2016.03.036
8. Kirkinis MN, Spelman T, May D, Choong PFM. Metastatic bone disease of the pelvis and extremities: rationalizing orthopaedic treatment. ANZ J Surg. 2017 Nov;87(11):940-4. doi: 10.1111/ans.13615
9. Zhu M, Liu X, Qu Y, Hu S, Zhang Y, Li W, et al. Bone metastasis pattern of cancer patients with bone metastasis but no visceral metastasis. J Bone Oncol. 2019 Apr;15:100219. doi: 10.1016/j.jbo.2019.100219
10. Rubens RD. Bone metastases – the clinical problem. Eur J Cancer. 1998;34:210–3. doi: 10.1016/s0959-8049(97)10128-9.
11. Ratasvuori M, Wedin R, Keller J, Nottrott M, Zaikova O, Bergh P, et al. Insight opinion to surgically treated metastatic bone disease: Scandinavian Sarcoma Group Skeletal Metastasis Registry report of 1195 operated skeletal metastasis. Surg Oncol. 2013 Jun;22(2):132-8. doi:10.1016/j.suronc.2013.02.008.
12. Cai L, Dong S, Chen H. Olecranon metastases from primary lung cancer: case report and review of the literature. J Int Med Res. 2019 Oct;47(10):5312–7.
13. Hasegawa S, Sakurai Y, Imazu H, Matsubara T, Ochiai M, Funabiki T, et al. Metastasis to the Forearm Skeletal Muscle from an Adenocarcinoma of the Colon: Report of a Case. Surg Today. 2000;30(12):1118-23.
14. Wedin R, Hansen BH, Laitinen M, Trovik C, Zaikova O, Bergh P, et al. Complications and survival after surgical treatment of 214 metastatic lesions of the humerus. J Shoulder Elbow Surg. 2012 Aug;21(8):1049-55.
15. Lahrach K, Chbani B, Amar F, Bennani A, Marzouki A, Boutayeb F. Humerus pathological fracture revealing biliary carcinoma. Orthop. Traumatol. Surg. Res. 2010;96(8):910-2.
16. Dijkstra S, Stapert J, Boxma H, Wiggers T. Treatment of pathological fractures of the humeral shaft due to bone metastases: a comparison of intramedullary locking nail and plate osteosynthesis with adjunctive bone cement. Eur J Surg Oncol. 1996 Dec;22(6):621-6.
17. Bıldırcın FD, Özdemir AZ, Karlı P, Çetinkaya MB. Breast cancer and ovulation induction. J Surg Med. 2019;3(8):612-8. doi: 10.28982/josam.605570
18. Özmen S, Ceylan O. Trends in lung cancer incidence within the last 10 years: An Eastern Anatolian single center experience. J Surg Med. 2020;4(2):112-5.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1227-1230.
DOI: 10.28982/josam.827520

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Association of routine hematological and inflammation parameters with surgical treatment results in patients with carpal tunnel syndrome

Karpal tünel sendromlu hastalarda rutin hematolojik ve inflamasyon parametrelerinin cerrahi tedavi sonuçları ile ilişkisi

Muzaffer Güneş [1]

[1] **Aksaray University School of Medicine, Department of Neurology, Aksaray, Turkey**

ORCID ID of the author(s)
MG: 0000-0002-9325-1292

Corresponding author/Sorumlu yazar:
Muzaffer Güneş
Address/Adres: Aksaray University School of Medicine, Department of Neurology, Aksaray, Turkey
E-mail: drmuzaffergunes@gmail.com

Ethics Committee Approval: The study was approved by the Aksaray University Human Research Ethics Committee (10/21/2020, 2020/09-15). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma Aksaray Üniversitesi İnsan Araştırmaları Etik Kurulu tarafından onaylandı (21.10.2020, 2020/09-15). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Previous presentation: This study was presented as an oral presentation at the 1st National Clinical Neurophysiology EEG-EMG Virtual Congress held on 20 - 22 November 2020.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: Neutrophil/lymphocyte ratio, neutrophil/eosinophil ratio (NER), and C-reactive protein-to-albumin ratio (CAR) reflect systemic inflammation. However, their relationship with the surgical treatment of carpal tunnel syndrome (CTS) has not been studied. In the present research, the association between systemic inflammation parameters and CTS surgical treatment results was investigated in patients with neurophysiologically moderate CTS.

Methods: The present study was conducted retrospectively on patients who underwent surgical treatment owing to moderate CTS. The postoperative results were evaluated by a nerve conduction study (NCS) performed approximately 6 months after the surgery. Patients were divided into three groups based on the postoperative NCS: Patients who did not have CTS according to NCS were defined as "the group fully benefiting" from surgical treatment, patients with mild CTS were included in "the group partially benefiting," from surgical treatment, and patients with moderate or severe CTS were included in "the group with no benefit."

Results: Forty-one patients with moderate CTS were included in the study. There was a significant difference between the groups in terms of median CAR, white blood cell, neutrophil, NER, and C-reactive protein (CRP) levels (P<0.001, P=0.012, P=0.014, P=0.005 and P=0.001, respectively). There was also a statistically significant and strong positive correlation among postoperative CTS severity, CAR (rho: 0.633, P<0.001) and CRP (rho: 0.603, P<0.001).

Conclusion: In the current study, it was found that CTS patients with higher CAR levels achieved less benefit from the surgical treatment.

Keywords: C-reactive protein/albumin ratio, Surgical treatment, Carpal tunnel syndrome, Neutrophil/eosinophil ratio, Systemic inflammation

Öz

Amaç: Nötrofil/lenfosit oranı (NLO), nötrofil/eozinofil oranı (NEO) ve C-reaktif protein/albumin oranı (CAO) sistemik inflamasyonu yansıtır. Ancak, bunların karpal tünel sendromu (KTS) cerrahi tedavisi ile ilişkisi çalışılmamıştır. Bu çalışmada, nörofizyolojik olarak orta KTS'li hastalarda sistemik inflamasyon parametreleri ile KTS cerrahi tedavi sonuçları arasındaki ilişki araştırıldı.

Yöntemler: Bu çalışma, orta KTS nedeniyle cerrahi tedavi yapılmış hastalar üzerinde retrospektif olarak yapıldı. Cerrahi sonrası sonuçlar, ameliyattan yaklaşık 6 ay sonra yapılmış bir sinir iletim çalışması (SİÇ) ile değerlendirildi. Cerrahi sonrası SİÇ'e göre hastalar üç gruba ayrıldı: SİÇ ile KTS saptanmayan hastalar cerrahi tedaviden "tam faydalanan grup", hafif KTS saptanan hastalar "kısmi faydalanan grup" ve orta veya şiddetli KTS saptanan hastalar ise cerrahi tedaviden "hiç faydalanmayan grup" olarak tanımlandı.

Bulgular: Çalışmaya, 41 orta KTS'li hasta alındı. Gruplar arasında medyan CAO, beyaz kan hücresi (WBC), nötrofil, NEO ve C-reaktif protein (CRP) düzeyleri açısından anlamlı fark gözlenmiştir (sırasıyla P<0,001; P=0,012; P=0,014; P=0,005 ve P=0,001). Ayrıca, cerrahi sonrası KTS şiddeti ile CAO (rho: 0,633; P<0,001) ve CRP (rho: 0,603; P<0,001) arasında istatistiksel olarak anlamlı ve güçlü pozitif korelasyon vardı.

Sonuç: Bu çalışmada, daha yüksek CAO düzeyine sahip KTS hastalarının cerrahi tedaviden daha az fayda sağladığı bulunmuştur.

Anahtar kelimeler: C-reaktif protein/albumin oranı, Cerrahi tedavi, Karpal tünel sendromu, Nötrofil/eozinofil oranı, Sistemik inflamasyon

How to cite/Atıf için: Güneş M. Association of routine hematological and inflammation parameters with surgical treatment results in patients with carpal tunnel syndrome. J Surg Med. 2020;4(12):1227-1230.

Introduction

Surgical treatment of moderate and advanced carpal tunnel syndrome (CTS) is known as the most effective method of treatment [1,2]. However, not all patients benefit from this approach [3]. It is emphasized that the underlying causes of surgical failure stem from the surgeon and the patient [4,5]. Patient-related causes of unsuccessful carpal tunnel surgery are identified as follows: Tenosynovitis of flexor tendons, necrosis of palmar fascia after surgery, development of fibrous proliferation in the carpal tunnel, infections developing in the surgical site, and compression of the palmar cutaneous branch of the median nerve. Surgeon-related causes include incomplete transection of the transverse carpal ligament and, in rare cases, iatrogenic median nerve incisions [4,5]. According to a recently published study, obesity and advanced age also have a role in surgical failure [6]. In many recent studies, C-reactive protein/albumin ratio (CAR) [7], neutrophil/eosinophil ratio (NER) [8], neutrophil/lymphocyte ratio (NLR) [9], and increased levels of neutrophils [10] have been established to reflect systemic inflammation and to play a role in the prognosis of many diseases [7-10]. To the best of our knowledge, the role of systemic inflammation in the success of CTS surgery has never been studied. Therefore, the present study investigates the relationship between surgical treatment results of CTS and CAR, NER, NLR, white blood cells (WBC), neutrophils, and C-reactive protein (CRP).

Materials and methods

This study was performed retrospectively on patients who underwent surgical treatment owing to moderate CTS between July 2014 and August 2019. First, patients with moderate CTS were identified through a nerve conduction study (NCS) in our neurophysiology laboratory. Among them, 852 had moderate CTS, 475 of whom had been already operated. Of the patients who had been operated, 41 had preoperative laboratory results and a report of NCS conducted nearly 6 months after the operation. The study was done with this group of 41 patients for whom complete data were available.

Those with missing data, those with moderate CTS patients who had not undergone surgical treatment, and patients less than 18 years of age were excluded from the study. None of the patients included herein were pregnant. Also, those who had cervical radiculopathy, brachial plexopathy, and generalized peripheral neuropathy were not included in the study.

In our clinic, the diagnosis of CTS is confirmed by a neurophysiologically-performed NCS along with the presence of clinical symptoms of CTS. During the neurophysiological examination, the hand temperature of the patients is kept above 32°C. During NCS, the median and ulnar nerves are bilaterally examined. The sensory conductions are performed antidromically using surface recording electrodes on the 2nd and 5th fingers, respectively, while the NCS of the median motor is performed with surface recording electrodes on the muscle of the abductor pollicis brevis. The motor and sensory conduction amplitudes, distal latencies (ms), and nerve conduction rates (m/s) of the bilateral median and ulnar nerves are measured. Accordingly, the patients diagnosed with moderate CTS were included in the study. The patients were classified as (neurophysiologically) mild, moderate, and severe CTS [9]. Two-channel electroneuromyography device (Micromed SpA-Via Giotto, 2-31021 Mogliano Veneto-Italy, 2014) was used for neurophysiological diagnosis.

The patients were divided into three groups based on postoperative NCS: Patients who did not have CTS according to NCS were defined as "the group fully benefiting" from the surgical treatment, patients with mild CTS as "the group partially benefiting" from surgical treatment and patients with moderate or severe CTS as "the group with no benefit."

The patients' blood sample analysis was performed using an autoanalyzer (Sysmex XN-1000 hematology analyzer, Kobe, Japan) installed in our hematology laboratory. CAR was calculated by dividing the amount of C-reactive protein by the albumin level, while NER was calculated by dividing the neutrophil count by the eosinophil count, and NLR by dividing the neutrophil count by the lymphocyte count.

This study was approved by Aksaray University Human Research Ethics Committee (October 21, 2020, Number: 2020/09-15), and the study was conducted in accordance with the Helsinki Declaration.

Statistical analysis

Results are presented as mean (SD) or median (min-max). The distribution pattern of the data was investigated using Kolmogorov-Smirnov normality test. Age, neutrophil, WBC, BMI, NLR, NER, CRP, and CAR were compared using Kruskal-Wallis test. Mann-Whitney U test was used for post-hoc comparisons. Correlations of postoperative CTS severity with the other parameters were checked using Spearman non-parametric correlation test because postoperative CTS severity was ordinal. The correlation results were interpreted according to the principles set by Cohen [11]. SPSS 23.0 (SPSS Inc., Chicago, IL) was used for all statistical analysis. A P-value <0.05 was considered statistically significant. Additionally, for non-parametric post-hoc comparisons, Bonferroni correction was applied and a P-value under 0.05/3=0.017 (triple combination) was considered statistically significant.

Results

Forty-one patients who had undergone surgery for CTS were eligible for this study. While no patients were present in the severe-CTS group, the moderate-CTS group (the group with no benefit) consisted of 15 patients [4 males and 11 females, mean age: 53.7 (11.2) years], the mild-CTS group (the group partially benefiting) consisted of 9 patients [9 females, mean age: 47.7 (6.7) years], and the non-CTS group (the group fully benefiting) consisted of 17 patients [7 males and 10 females, mean age: 47.1 (12.8) years]. The groups were age and gender-matched (P=0.240 and P=0.084, respectively).

The comparison of inflammatory parameters among the three groups is presented in Table 1. According to the Kruskal-Wallis test, the median NLR did not significantly differ among the three groups (P=0.069), but the median WBC, neutrophil, BMI, NER, CRP, and CAR did (P=0.012, P=0.014, P=0.001, P=0.005, P=0.001, and P<0.001, respectively). Post-hoc tests revealed that the median neutrophil and NER were not significantly different between the mild-CTS group and the non-

CTS group (*P*=0.133 and *P*=0.535, respectively), but the median BMI, WBC, CRP and CAR were significantly higher in the mild-CTS group than in the non-CTS group (*P*=0.004, *P*=0.045, *P*=0.015, and *P*=0.014, respectively). In addition, the median BMI, WBC, neutrophil, NER, CRP, and CAR were significantly higher in the moderate-CTS group than in the non-CTS group (*P*<0.001, *P*=0.006, and *P*=0.014, respectively). Median NER was significantly higher in the moderate-CTS group than in the mild-CTS group (*P*=0.002), however, median BMI, WBC, neutrophil, CRP, and CAR were similar between the moderate and mild-CTS groups (*P*=0.482, *P*=0.29, *P*=0.123, *P*=0.144, and *P*=0.074, respectively).

Table 1: The comparison of median inflammatory parameters among the groups defined according to post-surgical nerve conduction study results

	Non-CTS (the group fully benefiting) (n=17)	Mild-CTS (the group partially benefiting) (n=9)	Moderate-CTS (the group with no benefit) (n=15)	*P*-value[#]
Neutrophil, 10^9/L	3.23 (2.04-6.39)	4.3 (3.11-6.73)	5.65 (2.09-12.46)	0.014
WBC, 10^9/L	7.24 (4.53-9.2)	8.87 (6.34-10.28)	9.23 (4.26-14.06)	0.012
BMI, kg/m^2	29.3 (24.8-34)	36.3 (28.1-39)	37 (24.3-48.3)	0.001
NLR	1.45 (0.82-3.39)	1.51 (1.17-3.32)	2.41 (1.17-10.4)	0.069
NER	22.08 (7-169.2)	19.22 (12.53-40.4)	48.26 (19.13-778.75)	0.005
CRP, mg/dL	1.44 (0.11-6)	4.2 (1.02-8.59)	5.7 (1.4-30)	0.001
CAR	0.36 (0.03-1.31)	0.87 (0.24-1.86)	1.16 (0.29-7.14)	<0.001

[#] Kruskal Wallis test, CTS: Carpal tunnel syndrome, WBC: White blood cell, BMI: Body mass index, NLR: Neutrophil/lymphocyte ratio, NER: Neutrophil/eosinophil ratio, CRP: C- reactive protein, CAR: C- reactive protein/albumin ratio, NOTE: Since no patients with severe-CTS were detected after surgical treatment, the severe-CTS group was not included in the study.

Spearman correlation analysis revealed that the severity level of CTS (after surgery) was positively, strongly, and significantly correlated with CAR (rho: 0.633 and *P*<0.001; Figure 1), CRP (rho: 0.603 and *P*<0.001; Figure 2), and BMI (rho: 0.578 and *P*<0.001). In addition, the severity level of CTS (after surgery) was positively, moderately, and significantly correlated with NLR (rho: 0.351 and *P*=0.024), NER (rho: 0.389 and *P*=0.012), WBC (rho: 0.467 and *P*=0.002), and neutrophil count (rho: 0.461 and *P*=0.002).

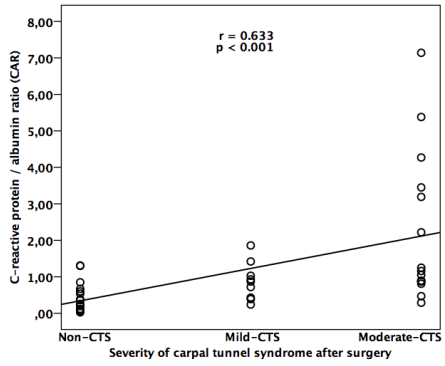


Figure 1: Graph showing the correlation between C-reactive protein/albumin ratio and the (neurophysiological) severity of carpal tunnel syndrome after the surgical treatment

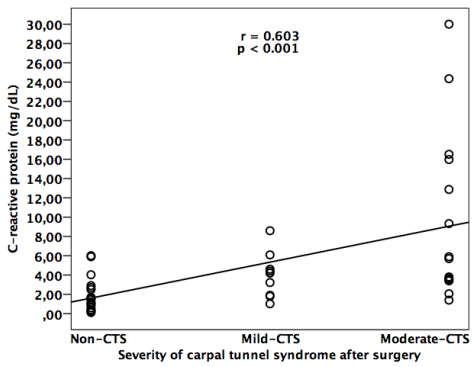


Figure 2: Graph showing the correlation between C-reactive protein and the (neurophysiological) severity of carpal tunnel syndrome after the surgical treatment

Discussion

This study concludes that patients with failed CTS surgery had higher WBC, BMI, NER, CRP, and CAR. There was also a positive correlation between the severity of CTS and these parameters after surgical treatment. To the best of our knowledge, the current study has been the first one to investigate the relationship between systemic inflammation parameters and surgical treatment results in CTS.

NER, CRP, WBC, NLR, and CAR are the blood parameters that reflect systemic inflammation [7-9,12,13]. In recent years, these parameters have been associated with the prognosis of various diseases such as ischemic stroke [8,12], hemorrhagic stroke [7,14], and CTS [9] or the severity of the disease.

Surgical treatment has a prominent place in the treatment of patients with moderate and advanced CTS [2]. However, it was emphasized that one out of four patients undergoing surgical treatment (25%) did not benefit from it [3]. The underlying reasons for the failure of surgical treatment might be attributed to the patient or the surgeon [5]. However, systemic inflammation in unsuccessful CTS surgery has not been studied at all. A recent study [9] emphasized that there is a positive correlation between NLR and severity of CTS. It is not exactly known why CTS is more severe in patients with a higher level of systemic inflammation. Therefore, systemic inflammation may be associated with the severity of CTS as well as with the surgical treatment outcomes in CTS. It has been determined in this study that patients with higher WBC, NER, CRP, and CAR achieve less benefit from the surgical treatment or no benefit at all, which supports the presence of this correlation. The underlying pathophysiological mechanisms are not yet fully known. Further studies are needed to clarify them.

NLR is a hematological parameter that reflects systemic inflammation [9,13,14]. NLR has been associated with diabetic polyneuropathy [15] and Guillain-Barré Syndrome [16-18] in several studies conducted in recent years. In the present study, patients who did not benefit from CTS surgery had higher NLR compared to those who benefited from it. However, there was no statistically significant difference between the groups. It is believed that this may be due to the small number of patients in the groups.

A recent study found that advanced age and high BMI had adverse effects on surgical treatment success in CTS [6]. Similar to this study, it was found that patients with higher BMI derived less benefit out of the surgical treatment. Thus, the determination of the presence of a positive correlation between BMI and severity of CTS was consistent with the study [6] in literature. Losing weight before the surgical treatment might increase the chances of success in patients with high BMI [6].

Limitations

Although this study is considered to contribute novel information to the literature, it has some limitations. First, this study is a monocentric retrospective study. Secondly, the present study was conducted with a small number of patients. Thirdly, owing to its retrospective nature, patients with moderate CTS who had elevated levels of inflammation were not administered anti-inflammatory treatments to lower the levels of inflammation

in combination with surgical treatment; therefore, they were not included in a particular follow-up process.

Conclusion

The presence of an elevated level of systemic inflammation in patients with CTS can adversely affect its surgical treatment. Long-term use of systemic anti-inflammatory treatments in combination with surgical treatment in such patients can offer additional benefit. The role of systemic inflammation in the success of surgical treatment of CTS can be clarified by further prospective studies.

Acknowledgments

The authors would like to thank Associate Professor Dr. P. Güneş for their assistance with the statistical analysis.

References

1. Bland JD. Carpal tunnel syndrome. BMJ. 2007;335(7615):343-6. doi: 10.1136/bmj. 39282.623553.AD
2. Shi Q, MacDermid JC. Is surgical intervention more effective than non-surgical treatment for carpal tunnel syndrome? A systematic review. J Orthop Surg Res. 2011;6:17. doi: 10.1186/1749-799X-6-17.
3. Bland JD. Treatment of carpal tunnel syndrome. Muscle Nerve. 2007;36(2):167-71. doi: 10.1002/mus.20802
4. Campagna R, Pessis E, Feydy A, et al. MRI assessment of recurrent carpal tunnel syndrome after open surgical release of the median nerve. AJR Am J Roentgenol. 2009;193(3):644-50. doi: 10.2214/AJR.08.1433.
5. Mosier BA, Hughes TB. Recurrent carpal tunnel syndrome. Hand Clin. 2013;29(3):427-34. doi: 10.1016/j.hcl.2013.04.011.
6. Güneş M, Özeren E. Effect of age and body mass index on surgical treatment outcomes in patients with carpal tunnel syndrome. Turk Neurosurg. Published Online Oct 28, 2020. doi: 10.5137/1019-5149.JTN.29704-20.2
7. Bender M, Haferkorn K , Friedrich M, Uhl E, Stein M. Impact of Early C-Reactive Protein/Albumin Ratio on Intra-Hospital Mortality Among Patients With Spontaneous Intracerebral Hemorrhage. J Clin Med. 2020;9(4):1236. doi: 10.3390/jcm9041236.
8. Güneş M. Is neutrophil/eosinophil ratio at admission a prognostic marker for in-hospital mortality of acute ischemic stroke? J Stroke Cerebrovasc Dis. 2020 Aug;29(8):104999. doi: 10.1016/j.jstrokecerebrovasdis.2020.104999
9. Güneş M, Büyükgöl H. Correlation of neutrophil/lymphocyte and platelet/lymphocyte ratios with the severity of idiopathic carpal tunnel syndrome. Muscle Nerve. 2020;61:369–74. doi: 10.1002/mus.26791.
10. Özeren E, Güneş M. Do early neutrophil to eosinophil ratio and the levels of neutrophil and white blood cells predict intra-hospital mortality in patients with spontaneous intracerebral hemorrhages? J Surg Med. 2020;4(9):812-16.
11. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Abington, UK: Routledge; 1988.
12. Emerging Risk Factors Collaboration; Kaptoge S, Di Angelantonio E, Lowe G, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010;375:132–40. doi: 10.1016/S0140-6736(09)61717-7.
13. Fest J, Ruiter R, Ikram MA, Voortman T, van Eijck CHJ, Stricker BH. Reference values for white blood-cell-based inflammatory markers in the Rotterdam Study: a population-based prospective cohort study. Sci Rep. 2018;8(1):10566. doi: 10.1038/s41598-018-28646-w.
14. Liu S, Liu X, Chen S, Xiao Y, Zhuang W. Neutrophil-lymphocyte Ratio Predicts the Outcome of Intracerebral Hemorrhage: A meta-analysis. Medicine (Baltimore). 2019;98(26):e16211. doi: 10.1097/MD.000000016211.
15. Demirdal T, Sen P. The significance of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and lymphocyte-monocyte ratio in predicting peripheral arterial disease, peripheral neuropathy, osteomyelitis and amputation in diabetic foot infection. Diabetes Res Clin Pract. 2018;144:118-25. doi: 10.1016/j.diabres.2018.08.009.
16. Tunç A. Early predictors of functional disability in Guillain-Barré Syndrome. Acta Neurol Belg. 2019;119(4):555-9. doi: 10.1007/s13760-019-01133-3.
17. Ozdemir HH. Analysis of the albumin level, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio in Guillain-Barre syndrome. Arq Neuropsiquiatr. 2016;74(9):718-22. doi: 10.1590/0004-282X20160132.
18. Huang Y, Ying Z, Quan W, et al. The clinical significance of neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio in Guillain-Barre syndrome. Int J Neurosci. 2018;128(8):729-35. doi: 10.1080/00207454.2017.1418342.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1231-1235.
DOI: 10.28982/josam.830293

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Effects of contraception methods on female sexual function and quality of life

Kontrasepsiyon yöntemlerinin kadın cinsel fonksiyonu ve yaşam kalitesi üzerindeki etkisi

Tuğba Gürbüz [1], Nur Dokuzeylül Güngör [2], Nefise Tanrıdan Okçu [3], Arzu Yurci [4]

[1] Medistate Hospital, Department of Obstetrics & Gynecology, IVF Clinic, Istanbul, Turkey
[2] Medicalpark Göztepe Hospital, Department of Obstetrics & Gynecology, IVF Clinic, Istanbul, Turkey
[3] Adana City Training & Research Hospital, Department of Obstetrics & Gynecology, Adana, Turkey
[4] Memorial Kayseri Hospital, Department of Obstetrics & Gynecology, IVF Center, Kayseri, Turkey

ORCID ID of the author(s)

TG: 0000-0003-3555-3767
NDG: 0000-0002-7234-3876
NTO: 0000-0003-2307-7628
AY: 0000-0003-4808-9019

Corresponding author/Sorumlu yazar:
Arzu Yurci
Address/Adres: Memorial Kayseri Hospital IVF Center, Gevher Nesibe Mahallesi Çiçek Sokak No: 10, Kayseri, Turkey
E-mail: arzuyurci@yahoo.com

Ethics Committee Approval: Permission for this study was granted by Research Ethics Committee of Adana City Research Hospital (CAAE number: 12.08.2020, Decision no: 1039). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışmaya Adana Şehir Araştırma Hastanesi Araştırma Etik Kurulu tarafından izin verildi (İzin verildi / CAAE numarası: 12.08.2020, Karar no: 1039). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: Many women of reproductive age who use contraceptive methods have sexual dysfunction and reduced quality of life. This study aimed to evaluate the effects of various contraceptive methods on female sexual function index (FSFI) and quality of life scale (SF-12).

Methods: This prospective observational study was conducted on the patients admitted to the Gynecology and Obstetrics outpatient clinic between August and October 2020. FSFI total score and FSFI sub-domains (desire, arousal, lubrication, orgasm, satisfaction, and pain) and SF- 12 were used to compare the differences between the groups using various contraceptive methods (Mirena, Copper RIA, tubal ligation, condom, and oral contraceptive pill). The demographic characteristics of the patients, the FSFI, and SF-12 data were collected by the researchers face to face.

Results: A total of 228 subjects with a mean age of 30.32 years participated in the study. FSFI scores of the patients using and not using contraceptive methods were significantly different (P<0.001), while PCS-12 (P=0.122) and MCS-12 (P=0.122) scores were similar. The mean total FSFI score was 23.36.

Conclusion: The study concluded that women using contraceptive methods had lower total FSFI scores than those who did not, and statistically significant differences were found between the two groups in terms of lubrication, desire, and pain subdomains. We found that contraception methods significantly affected the sexual function of women, but not their quality of life.

Keywords: Female sexual dysfunction, Quality of life, Contraception, Female sexual function index

Öz

Amaç: Bu çalışmamızda, kontrasepsiyon yöntemlerinin kadın cinsel fonksiyonuna ve yaşam kalitesine etkisinin, Kadın Cinsel Fonksiyon Ölçeği (KCFÖ) ve Yaşam Kalitesi Ölçeği (SF-12) doğrultusunda ölçülmesi amaçlandı.

Yöntemler: Bu prospektif gözlemsel araştırmaya, Ağustos-Ekim 2020 tarihleri arasında Kadın hastalıkları ve doğum polikliniğimize başvuran hastalar dahil edildi. KCFÖ ve alt grupları skorları (arzu, uyarılma, lubrikasyon, orgasm, memnuniyet ve ağrı) ile SF-12 skorları korunma yöntemleri (Mirena, Bakır RIA, tüp ligasyonu, kondom, ve oral kontraseptif hap) kullananlar ile kullanmayanların cinsel işlevleri ve yaşam kaliteleri açısından farklılık olup olmadığını araştırmak amacıyla kullanıldı. Hastaların demografik özellikleri, KCFÖ ve SF-12 skorları araştırmacılar tarafından yüz yüze toplandı.

Bulgular: Çalışmaya 228 kişi dahil edildi, çalışmaya katılan kadınların ortalama yaşı 30,32 saptandı. Toplam KCFÖ skoru bakımından, gruplar arasında istatistiksel olarak anlamlı bir fark söz konusudur (P<0,001). Ortalama toplam KCFÖ skoru 23.36 olarak ölçüldü. PCS-12 (P=0,122) ve MCS-12 (P=0,122) arasında istatistiksel olarak anlamlı bir fark tespit edilmedi.

Sonuç: Kontrasepsiyon yöntemi kullanan kadınların, kontrasepsiyon yöntemi kullanmayan kadınlara göre daha düşük toplam KCFÖ skorlarına sahip olduğu ve her iki grubun da arzu, lubrikasyon ve ağrı alt gruplarında istatistiksel olarak anlamlı bir fark bulunduğu gösterildi. Kontrasepsiyon yöntemleri kadın cinsel fonksiyon bozukluğu üzerinde önemli bir etkiye sahipken, kadınların yaşam kalitesi kontrasepsiyon yöntemlerinden etkilenmemektedir.

Anahtar kelimeler: Kadın cinsel fonksiyon bozukluğu, Yaşam kalitesi, Doğum kontrolü, Kadın cinsel fonksiyon ölçeği

How to cite/Atıf için: Gürbüz T, Güngör ND, Okçu ND, Yurci A. Effects of contraception methods on female sexual function and quality of life. J Surg Med. 2020;4(12):1231-1235.

Introduction

One of the major components of quality of life and health is satisfactory sexual life [1], and factors affecting the individual's health may also negatively affect their sexual life [2]. Several health problems, which include hormonal, biological, and psychological factors, cause sexual dysfunction among women [3]. FSD describes various sexual problems such as difficulty or inability to achieve orgasm, reduced desire, low arousal, and dyspareunia [4]. Female sexual dysfunction is a progressive, age-related, and widespread problem from which 30-50% of women suffer [5-7].

World Health Organization (WHO) declared sexual health to be an essential human right for women. In the recent reports, sexual disorders have been shown to cause morbidity and reduced QOL [8].

FSD is divided into subcategories such as reduced sexual feelings of interest, thoughts, and fantasies, the difficulty of arousal, lubrication, or orgasm despite being adequately aroused, or feeling of pain resulting from intercourse [9].

One of the main factors affecting sexual life is family planning. There are several contraceptive methods including implants, intrauterine devices (IUD), oral contraceptive pills (OCPs), tubal ligation (TL), contraceptive injections, and female sterilization [10], but some studies have reported undesirable effects of TL on women's QOL and sexual life [11-13]. Today, one of the important components of quality of life and health is satisfactory sexual habits, but unfortunately, sexual problems are reported in a minimum of 43% of women [14].

In our study, the Female Sexual Function Index (FSFI) was used as a valid survey method for evaluating the effects of contraception methods (Mirena, Copper RIA, tubal ligation, condom, and oral contraceptive pill) on female sexual life and QOL.

The FSFI as a valid and reliable questionnaire with six domains including desire, satisfaction, subjective arousal, orgasm, pain, and lubrication and 19 questions for measuring female sexual function [15]. A maximum and minimum score is assigned to each domain and all domains are measured to determine sexual function total score. A score ≤ 26.5 is regarded as FSD [16] meaning that the higher individual domain score or total score, the better sexual functioning. The reliable and valid version for the Turkish population is the Turkish version of the FSFI [17]. The SF-12 is a subset of the SF-36 with 12 items containing two summary measures, including scores of Mental (MCS-12) and Physical (PCS-12) Component Summary [18]. Higher scores show better health.

The aim of the current study was to evaluate whether contraceptive methods affect female sexual functions and their quality of life and compare it with the normal population.

Materials and methods

This prospective cross-sectional observational study was performed in Adana City Research Hospital, Gynecology and Obstetrics outpatient clinic. Permission was obtained from Research Ethics Committee of Adana City Research Hospital (Permission granted /CAAE number: 12.08.2020, Decision no: 1039). All procedures in studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. A total of 228 patients who were admitted to Gynecology & Obstetrics outpatient clinic between August 2020 and October 2020 were included in this study. Patients were classified based on the contraceptive methods they were using, namely, Mirena, Copper RIA, Tubal ligation, Condom, Oral contraceptive, and no contraception groups. Informed consents were obtained from all participants before enrolling in this study. Patients aged 18 - 40 years who were in a heterosexual relationship for the last year were included in this study. Pregnant women, those with systemic and gynecological diseases, patients undergoing hormone therapy, using vitamins or oral contraceptives, those who had gynecological surgery, mental disorders, and premenstrual syndrome or endometriosis were excluded from the study.

FSFI total score, FSFI sub-domains (desire, lubrication, arousal, satisfaction, orgasm, and pain) and QOL scale (SF- 12) were used to compare the groups in terms of female sexual function and quality of life. The researchers collected the demographic characteristics of the patients, the FSFI, and SF-12 data face to face.

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 26.0 (SPSS Inc., Chicago, IL, USA) was used to conduct statistical analyses. The normal distribution of data was evaluated by the Kolmogorov-Smirnov test. Chi-square test was used to analyze the categorical data. Kruskal-Wallis and one-way ANOVA tests were used for evaluating the differences between groups for non-normally and normally distributed data, respectively. *P*-value <0.05 was considered statistically significant.

Results

A total of 228 subjects with a mean age of 30.32 years were included in the study. A significant difference was found between patients using and not using contraceptive methods in terms of age ($P<0.001$). The mean BMI of the subjects was 26.02 kg/m^2, which were similar between the two groups ($P=0.716$). The number of births ($P<0.001$), method of birth ($P<0.001$), and education levels ($P<0.001$) of the groups were significantly different. Among all, 33.3% of the subjects had given one birth, 49.1%, two births and 8.3%, three births. Around 62.5% of Copper RIA users and, 89.18% of women who underwent TL had given two births, and 12.6% of those who used Mirena had given three births. Of patients who used no contraceptive methods, 47.72% had given one birth, 45.45% had given two births, and 6.83% had three given births. The rates of birth by caesarian section, normal birth and no births were 59.6%, 31.1%, and 9.2%, respectively. Around 65.2% of condom users had never given birth, 91.89% of those who underwent Tubal ligation had given birth by Cesarean section, 50% of patients with copper RIAs had undergone normal vaginal delivery, and among those who did not use any contraceptive methods, 50% gave birth via caesarian section while the other 50% delivered vaginally. The rates of those who received primary, secondary, and tertiary levels of education were 8.8%,

61.5%, and 29.8%, respectively. Among oral contraceptive users, 57.15% had received tertiary education, while that rate was 15.91% for those who used no contraceptive methods. The number of marriages were significantly different between the groups (P<0.001), 92.5% of the subjects had one marriage. The mean duration of marriage was 5.63 years.

The groups showed statistically significant differences in duration of marriage (P<0.001) while they were similar in terms of working status (P=0.73). Table 1 shows the patients' clinical and demographic variables.

Table 1: Demographic and clinical variables of the patients

		Mirena (n=48)	Copper RIA (n=32)	Tubal ligation (n=37)	Condom (n=32)	Oral contraceptive (n=35)	No contraception (n=44)	*P*-value
Age (Women)		32 (3)	28.50 (8)	31 (3)	26 (4)	31 (6)	29 (7)	<0.001**
BMI (Kg/m2)		25.60 (3)	25.25 (3.6)	26.10 (1.8)	25.30 (3.7)	26 (5.2)	25.95 (3.2)	0.716**
Number of births n (%)	No birth	-	-	-	21 (65.62)	-	-	<0.001*
	One	20 (41.6)	20 (62.5)	-	11 (34.38)	4 (11.42)	21 (47.72)	
	Two	22 (45.8)	10 (31.25)	33 (89.18)	-	27 (77.16)	20 (45.45)	
	Three	6 (12.6)	2 (6.25)	4 (10.82)	-	4 (11.42)	3 (6.83)	
Method of birth n (%)	No birth	-	-	-	21 (65.62)	-	-	<0.001*
	Cesarean	28 (58.33)	16 (50)	34 (91.89)	10 (31.25)	26 (74.28)	22 (50)	
	Normal	20 (41.67)	16 (50)	3 (8.11)	1 (3.13)	9 (25.72)	22 (50)	
Education level n (%)	Elementary school	9 (18.75)	2 (6.25)	-	-	-	9 (20.45)	<0.001*
	High school	23 (47.91)	23 (71.87)	25 (67.56)	26 (81.25)	15 (42.85)	28 (63.64)	
	University	16 (33.34)	7 (21.88)	12 (32.44)	6 (18.75)	20 (57.15)	7 (15.91)	
Number of marriages n (%)	One	39 (81.25)	26 (81.25)	37 (100)	32 (100)	35 (100)	42 (95.45)	<0.001*
	Two	9 (18.75)	6 (18.75)	-	-	-	2 (4.55)	
Marriage period (Year)		6 (2)	6 (4)	6 (2)	2 (2)	6 (2)	6 (3)	<0.001**
Working status n (%)	Working	27 (56.25)	18 (56.25)	24 (64.86)	25 (78.12)	26 (74.28)	35 (79.54)	0.73*
	Not working	21 (43.75)	14 (43.75)	13 (35.14)	7 (21.88)	9 (25.72)	9 (20.46)	

As shown by Table 2, there is a statistically significant difference among the groups in terms of desire (P=0.001), lubrication (P<0.001), and pain (P=0.011) while arousal (P=0.051), orgasm (P=0.108), and satisfaction (0.826) were similar.

The groups were significantly different in terms of total FSFI score (P<0.001), and similar in terms of PCS-12 and MCS-12 scores (P=0.122 for both). The mean FSFI score was 23.36.

Table 2: Questionnaire parameters

Parameters	Mirena (n=48)	Copper RIA (n=32)	Tubal ligation (n=37)	Condom (n=32)	Oral contraceptive (n=35)	No contraception (n=44)	*P*-value
FSFI desire score	4.2 (1.2)	4.2 (1.2)	4.2 (1.5)	5.4 (1.8)	4.2 (0.6)	4.2 (0.6)	0.001*
FSFI arousal score	4.2 (0.9)	4.5 (1.7)	3.9 (0.9)	4.5 (1.8)	4.2 (2.1)	4.5 (1.8)	0.051*
FSFI lubrication score	3.6 (1.1)	4.2 (2.1)	3.3 (2.2)	4.65 (2.4)	2.7 (1.2)	4.2 (2.1)	<0.001*
FSFI orgasm score	3.4 (1.6)	3.2 (1.2)	3.2 (0.8)	3.6 (1.9)	3.6 (1.2)	3.6 (1.6)	0.108*
FSFI satisfaction score	3.6 (2)	3.6 (1.5)	3.6 (1.4)	3.6 (2.3)	3.2 (2)	3.6 (2.2)	0.826*
FSFI pain score	4.4 (1.9)	4.4 (2)	3.6 (2.2)	4.8 (2.1)	4.4 (2.6)	4.8 (1.8)	0.011*
Total FSFI score	23.10 (2.66)	23.40 (2.20)	21.66 (2.93)	25.66 (2.85)	21.89 (3.27)	24.53 (2.38)	<0.001**
PCS-12	46.15 (7.3)	47.45 (7.8)	47.1 (5)	45.5 (6.8)	46.9 (6.8)	44.3 (7.8)	0.122*
MCS-12	45.13 (4.56)	46.22 (4.03)	45.41 (4.22)	46.60 (5.51)	45.82 (4.51)	45.93 (4.43s)	0.762**

* Kruskal-Wallis test, **One-way ANOVA test, Normally distributed data are expressed as mean (SD) and non-normal distributed data are expressed as median (interquartile range). FSFI indicates female sexual function index; PCS-12, physical component summary-12, MCS-12, mental component summary-12.

Discussion

In the present research, the effect of contraceptive methods on women's sexual function and quality of life were evaluated with FSFI and SF-12. The subjects were divided into Mirena, Copper RIA, tubal ligation, condom, and oral contraceptive pill and no contraception groups. The results showed no statistically significant differences between the groups in terms of BMI and working status, while the number of births, method of birth and education level, number of marriages, marriage duration significantly differed. We also determined that the education levels of women using contraceptive methods were higher than those who did not use them. Our study found a statistically significant difference between the groups in terms of FSFI desire score, FSFI lubrication score, FSFI pain score and Total FSFI score, while the groups were similar in FSFI arousal score, FSFI orgasm score, and FSFI satisfaction score.

PCS-12 and MCS-12 scores did not significantly differ between the groups, meaning that contraceptive use did not significantly affect the quality of life of the studied groups.

Desire, lubrication, and pain scores were the highest in women who used condoms. Total FSFI score was the highest (25.66) among subjects using condoms, meaning that they had the highest sexual function. The findings show that the method of contraception affect the sexual functions of individuals.

FSD is associated with physiological, psychological, social, interpersonal, medical, and cultural factors [3]. The epidemiological studies show at least one sexual dysfunction in 40% of women [14].

The results of the research by Safarinejad [19] and Koseoglu et al. [20] found no significant differences between women who did and did not use contraceptive methods in terms of sexual function, which contradict our findings.

In their study on QOL, Sadatmahalleh [11] revealed that FSD was prevalent in women who underwent TL compared to those who did not (44% vs. 20%), which was consistent with the studies of Bolourian and Ganjloo [21], and Gulum et al. [22], who found that the female sexual desire and satisfaction were significantly reduced, and dyspareunia was caused by surgery to female sexual organs, such as TL, among the Iranian women. The study result of Oksuz et al. [23], which found that contraceptive methods did not significantly affect the quality of lives of the studied women, contradicted our study.

A study conducted at a family planning center in Italy found improved quality of life, reduced coital pain and improved sexual desire with contraceptive use, based on the data obtained from the Female Sexual Function Index questionnaires and EuroQuality of Life-5D [24], which were not comparable to our results.

A research by Skrzypulec et al. [13] on the sexual functions of women using contraceptive methods, determined the effect of levonorgestrel with intrauterine devices and found statistically significant differences between the groups in arousal, orgasm, sexual desire, dyspareunia, and satisfaction, showing that women with Mirena had higher sexual functions. In our study, the Total FSFI score in the subjects using Mirena was lower than those who did not use contraceptive methods.

In their study, Sakinci et al. (2016) found an increase in sexual pain among the women using Cu-IUD compared to those

who used no contraception, possibly reducing sexual arousal, lubrication, and orgasm among these women [25], while our study did not find any significant differences between the groups in terms of arousal. However, desire, lubrication and pain were significantly different among the groups.

In a study conducted on women using LNG IUD or oral contraceptives, Suhonen et al. [26] found that LNG IUD positively affected the quality of life and observed no differences in women's sexual functions between the two groups. Gomez and Clark [27] also found that IUD users stated that the contraceptive method does not interfere with sexual pleasure, which does not support our study findings. Some studies found significant differences between the contraceptive methods and sexual life [28,29] while others [30-32] did not find any significant differences.

Bahri et al. [33] found that women who underwent tubal ligation had worse 'physical functions' and their quality of life was affected by the contraception methods which they used, while in our study, patients who underwent tubal ligation were found to have lower sexual function than those who did not use contraception, but their quality of life was not affected significantly.

Williams et al. [34] found better mental quality of life in those who used contraceptives than those who did not and observed better mental and physical quality of life among the women who received injections, compared to those using combined hormonal methods. Our study finding is not consistent with those of Zhao et al. [31] and Leon et al. [35], which stated that women had significantly increased quality of life after using contraceptive methods.

Oksuz et al. [36] found that FSD was highly prevalent in women with TL, and that TL had a significant effect on QOL, which contradicted with our findings.

In their research on groups of women using progestogen injections, IUDs, and oral contraceptives, Li et al. [10] found that their quality of life and sexual function did not significantly change, and no significant difference was found in each of the three subscale scores of Derogatis Sexual Functioning Inventory in the IUD groups.

In their study on the effect of contraceptive methods among women, Umran et al. [37] did not find any differences between various contraceptive methods. They concluded that sexual life among the studied women is partly negatively affected by some modern contraceptive methods, and women who used the modern contraceptive methods had higher education levels than those who did not use them, all of which were consistent with our study results.

Ertekin et al. [38] stated that the contraception methods used did not affect their quality of life, which was comparable to our results, except for the part where they stated that the contraception method did not affect sexual life.

Bastianelli et al. [24] found the positive and negative effect of contraceptives on women's sexuality extending beyond sexual functioning alone. Most women who reported positive sexual changes reported the highest control over pregnancy which is consistent with our study finding.

Limitations

The small sample size was the primary limitation of this study. Also, contraceptive counseling could help women avoid impairment of sexuality and QoL, unintended pregnancies in future and risk of abortion.

Conclusion

In the present study, women using and not using contraception were significantly different in terms of age, number of births, method of birth, education level, number of marriages, marriage period, and turban status. Women using all contraceptives (Mirena, Copper RIA, tubal ligation, and oral contraceptive pill), but condoms, had lower total FSFI score than those who did not use any contraceptives. The groups were significantly different in desire, lubrication, and pain subdomains. The contraception methods used by the women in our research significantly affected sexual life but did not affect their quality of life.

References

1. Sakinci M, Ercan CM, Olgan S, Coksuer H, Karasahin KE, Kuru O. Comparative analysis of copper intrauterine device impact on female sexual dysfunction subtypes. Taiwan J Obstet Gynecol. 2016;55(03):460-1.
2. Kütmeç C. Kadınlarda cinsel fonksiyon bozukluğu ve hemşirelik bakımı. Fırat Sağlık Hizmetleri Dergisi. 2009;4(12):111-36.
3. Kingsberg S, Woodard T. Female sexual dysfunction: focus on low desire. Obstet Gynecol. 2015;125(2):477-86.
4. Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB. Sexual problems and distress in United States women:prevalence and correlates. Obstet Gynecol. 2008;112(5):970-8.
5. Kohn IJ, Kaplan SA. Female sexual dysfunction: What is known and what remains to be determined. Contemporary Urology 1999;9:54-72.
6. Rosen RC, Taylor JF, Leiblum SR, Bachmann GA. Prevalence of sexual dysfunction in women:results of a survey study of 329 women in an outpatient gynecological clinic. J Sex Marital Ther. 1993;19(3):171-88.
7. Aygin D, Aslan FE. Turkish adaptation of the Female Sexual Function Index. Türkiye Klinikleri. J Med Sci.2005;25(3):393-99.
8. Biddle AK, West SL, D'Aloisio AA, Wheeler SB, Borisov NN, Thorp J. Hypoactive sexual desire disorder in postmenopausal women:quality of life and health burden. Value Health. 2009;12(5):763-72.
9. Lewis RW, Fugl-Meyer KS, Bosch R, Fugl-Meyer AR, Laumann EO, Lizza E, et al. Epidemiology/risk factors of sexual dysfunction. J Sex Med 2004;1(1):35-9.
10. Li RH, Lo SS, Teh DK, Tong NC, Tsui MH, Cheung KB, et al. Impact of common contraceptive methods on quality of life and sexual function in Hong Kong Chinese women. Contraception. 2004;70(60):474-82.
11. Sadatmahalleh SJ, Ziaei S, Kazemnejad A, Mohamadi E. Evaluation of sexual function and quality of life in Iranian women with tubal ligation: a historical cohort study. Int J Impot Res. 2015;27(5):173–7.
12. Smith A, Lyons A, Ferris J, Richters J, Pitts M, Shelley J. Are sexual problems more common in women who have had a tubal ligation? A population-based study of Australian women. BJOG. 2010;117(4):463–8.
13. Skrzypulec V, Drosdzol A. Evaluation of quality of life and sexual functioning of women using levonorgestrel-releasing intrauterine contraceptive system Mirena. Coll Antropol. 2008;32(4):1059-68.
14. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA. 1999;281(6):537-44.
15. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, et al. The Female Sexual Function Index (FSFI):a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000;26(2):191-208.
16. Yaylali GF, Tekekoglu S, Akin F. Sexual dysfunction in obese and overweight women. Int J Impot Res. 2010;22(4):220-6.
17. Oksuz E, Malhan S. The reliability and validity of Turkish version of female sexual function index. Sendrom. 2005;17(7):54-60.
18. Ware JE, Kosinski M, Turner-Bowker DM, Gandek B:How to Score Version 2 of the SF-12 Health Survey (With a Supplement Documenting Version 1). Lincoln, RI:QualityMetric Incorporated; 2002.
19. Safarinejad MR. Female sexual dysfunction in a population-based study in Iran:prevalence and associated risk factors. Int J Impot Res. 2006;18(4):382-95.
20. Koseoglu SB, Deveer R, Akin MN, Gurbuz AS, Kasap B, Guvey H. Is there any impact of copper intrauterine device on female sexual functioning? J Clin Diagn Res. 2016;10(10):QC21.
21. Bolourian Z, Ganjloo J. Evaluating sexual dysfunction and some related factors in women attending Sabzevar Health Care Centers. J Reprod Infertil. 2007;8(2):163-70.
22. Gulum M, Yeni E, Sahin MA, Savas M, Ciftci H. Sexual functions and quality of life in women with tubal sterilization. Int J Impot Res. 2010;22(4):267–71.
23. Oksuz E, Malhan S. Prevalence and risk factors for female sexual dysfunction in Turkish women. J Urol. 2006;175(2):654–58.
24. Bastianelli, C, Farris, M, Benagiano G. Use of the levonorgestrel-releasing intrauterine system, quality of life and sexuality. Experience in an Italian family planning center. Contraception. 2011;84(4):402–8.
25. Sakinci M, Ercan CM, Olgan S, Coksuer H, Karasahin KE, Kuru O. Comparative analysis of copper intrauterine device impact on female sexual dysfunction subtypes. Taiwan J Obstet Gynaecol. 2016;55(1):30-4.
26. Suhonen S, Haukkamaa M, Jakobsson T, Rauramo I. Clinical performance of a levonorgestrel-releasing intrauterine system and oral contraceptives in young nulliparous women:a comparative study. Contraception. 2004;69(5):407–12.
27. Gomez AM, Clark JB. The relationship between contraceptive features preferred by young women and interest in IUDs:an exploratory analysis. Perspect Sex Reprod Health. 2014;46(3):157–63.
28. Casey PM, MacLaughlin KL, Faubion SS. Impact of contraception on female sexual function. Journal of Women's Health. 2017 Mar 1;26(3):207-13.

29.Ferreira JM, Carreiro AV, Fernandes A, Bahamondes L. Sexual function and quality of life in a cohort of Brazilian users of two kind of intrauterine contraceptives. Revista Brasileira de Ginecologia e Obstetrícia. 2019 Apr;41(4):236-41
30.Toorzani ZM, Zahraei RH, Ehsanpour S, Nasiri M, Shahidi S, Soleimani B. A study on the relationship of sexual satisfaction and common contraceptive methods employed by the couples. Iran J Nurs Midwifery Res. 2010;15(3):115-9.
31.Wallwiener M, Wallwiener LM, Seeger H, Mueck AO, Zipfel S, Bitzer J, et al. Effects of sex hormones in oral contraceptives on the female sexual function score:a study in German female medical students. Contraception. 2010;82(2):155-9.
32.Hamadiyan H, Asadpour Ghasem Oladi M, Rahbar P, Azad M. Prevalence of sexual dysfunction among women using contraceptive methods. International Journal of Medical Research & Health Sciences. 2016;5(12):163-7.
33.Bahri N, Tohidinik HR, Bilandi RR, Larki M, Hooshangi F, Soltanian M. The relation between contraception methods and quality of life. Epidemiol Biostat Public Health. 2016;13(4):11986.
34.Williams SL, Parisi SM, Hess R, Schwarz EB. Associations between recent contraceptive use and quality of life among women. Contraception. 2012;85(3):282–7.
35.Leon-Larios F, Vazquez-Valeo CG, Sanchez-Sanchez A, Gomez-Baya D, Macías-Seda J, Cabezas-Palacios MN. Health-related quality of life in undergraduate women using any contraceptive. Health Qual Life Outcomes. 2019;17(1):90.
36.Oksuz E, Malhan S. Prevalence and risk factors for female sexual dysfunction in Turkish women. J Urol. 2006;175(2):654–58.
37.Umran O, Melike RD. Effect of the contraceptive methods on female sexual function. Int J Caring Sci. 2016;10(3):1-366.
38.Ertekin Pinar S, Demirel G, Yildirim G, Daglar G. Sexual experiences and quality of life in Turkish women using methods of contraception. J Obstet Gynaecol. 2019;39(6):782-7.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1236-1239.
DOI: 10.28982/josam.842133

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Effects of vitamin D on doxorubicin-induced lung injury and TRPM2 immunoreactivity in rats

D vitamininin sıçanlarda doksorubisin kaynaklı akciğer hasarı ve TRPM2 immünoreaktivitesi üzerindeki etkileri

Alper Yalçın [1], Ahmet Türk [2], Hasan Aydın [3], Erkan Yılmaz [4], İbrahim Seyfettin Çelik [5], Fatih Üçkardeş [6]

[1] Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Histology and Embryology, Kahramanmaras, Turkey
[2] Adiyaman University, Faculty of Medicine, Department of Histology and Embryology, Adiyaman, Turkey
[3] Adiyaman University, Faculty of Pharmacy, Department of Pharmaceutical Toxicology, Adiyaman, Turkey
[4] Adiyaman University, Faculty of Pharmacy, Department of Pharmacognosy, Adiyaman, Turkey
[5] Kahramanmaras Sütcü Imam University Institute of Science, Department of Bioengineering and Sciences, Kahramanmaras, Turkey
[6] Adiyaman University, Faculty of Medicine, Department of Biostatistics and Medical Informatics, Adiyaman, Turkey

ORCID ID of the author(s)
AY: 0000-0002-8975-1008
AT: 0000-0003-0903-3522
HA: 0000-0002-1955-6178
EY: 0000-0002-0947-3096
İSÇ: 0000-0001-6946-4477
FÜ: 0000-0003-0677-7606

Corresponding author/Sorumlu yazar:
Alper Yalçın
Address/Adres: Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Histology and Embryology, Kahramanamaras, Turkey
E-mail: alperyalcin0171@hotmail.com

Ethics Committee Approval: Animals used in this study were treated according to the ethical rules for the care of laboratory animals (Adiyaman University Animal Experiments Local Ethics Committee, protocol no: 2020/044).
Etik Kurul Onayı: Bu çalışmada kullanılan hayvanlar, laboratuar hayvanlarının bakımı için etik kurallara (Adıyaman Üniversitesi Hayvan Deneyleri Yerel Etik Kurulu, protokol no: 2020/044) göre tedavi edildi.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: Although doxorubicin (DOX) is a commonly used chemotherapeutic agent, it causes significant toxic side effects on many organs. This study aims to investigate the effects of vitamin D (VD) on DOX-induced lung injury and expression of transient receptor potential melastatin 2 (TRPM2), a Ca^{2+} permeable cation channel.

Methods: A total of 24 Wistar albino rats were separated into four groups of six rats, as follows: The control group received no medications. The VD group received 200 IU/kg VD via an oral dropper (o.d.) for 14-days. DOX group received a single dose of 10 mg/kg DOX intraperitoneally (i.p.) on day 8. DOX+VD group was administered 200 IU/kg VD via an o.d. for 14-days, and a single dose of 10 mg/kg DOX i.p. on day 8. At the end of the experiment, lung and serum samples from all rats were collected. Masson's trichrome staining and streptavidin-biotin-peroxidase complex were applied to the lung tissue sections. Serum total antioxidant status (TAS) and total oxidant status (TOS) were assessed by enzyme-linked immunosorbent assay (ELISA) method.

Results: Histopathological damage was observed in the DOX group compared to the control group, and biochemical and immunohistochemical evaluation revealed that TOS level and TRPM2 expression increased while TAS level decreased significantly ($P<0.001$). Additionally, compared to the DOX group VD administration significantly reversed these values in the DOX+VD group ($P<0.001$).

Conclusion: VD showed a protective effect on lung damage induced by DOX. Our data also suggest that TRPM2 channel may have a role in the pathophysiology of DOX-induced lung damage.

Keywords: Doxorubicin, Lung, Oxidative stress, Transient receptor potential melastatin 2, Vitamin D

Öz

Amaç: Doksorubusin (DOX), yaygın olarak kullanılan bir kemoterapötik ajan olmasına rağmen, birçok organda önemli toksik yan etkilere sebep olmaktadır. Bu çalışma, D vitamininin (VD), DOX ile indüklenen akciğer hasarı ve Ca2+ geçirgen katyon kanalı olan, geçici reseptör potansiyeli melastatin 2 (TRPM2) ekspresyonuna etkilerini araştırmayı amaçlamaktadır.

Yöntemler: 24 Wistar albino sıçan dört eşit gruba ayrıldı. Kontrol grubu; hiçbir uygulama yapılmadı. VD grubu; 14 gün boyunca oral damlalıkla (o.d.) 200 IU/kg VD uygulandı. DOX grubu; 8. günde tek doz 10 mg/kg DOX intraperitoneal (i.p.) olarak uygulandı. DOX + VD grubu; 14 gün boyunca o.d. ile 200 IU/kg VD uygulandı, 8. günde tek doz 10 mg/kg DOX i.p. olarak uygulandı. Deney sonunda tüm sıçanlardan akciğer ve serum örnekleri toplandı. Akciğer doku kesitlerine Masson'un trikrom boyama yöntemi ve streptavidin-biotin-peroksidaz kompleks yöntemi uygulandı. Serum toplam antioksidan seviyesi (TAS) ve toplam oksidan seviyesi (TOS) enzime bağlı immünosorbent testi (ELİSA) yöntemi ile değerlendirildi.

Bulgular: DOX grubunda kontrol grubuna göre histopatolojik hasar gözlenirken, biyokimyasal ve immünohistokimyasal değerlendirmede, TOS düzeyinin ve TRPM2 ekspresyonunun anlamlı olarak arttığı, TAS düzeyinin ise anlamlı olarak azaldığı saptandı ($P<0,001$). Diğer taraftan, VD uygulamasının, DOX grubuna kıyasla, DOX+ VD grubunda bu değerleri önemli ölçüde tersine çevirdiği gözlendi ($P<0,001$).

Sonuç: VD, DOX'un neden olduğu akciğer hasarı üzerinde koruyucu bir etki gösterdi. Verilerimiz ayrıca, TRPM2 kanalının DOX ile indüklenen akciğer hasarının patofizyolojisinde bir rolü olabileceğini düşündürmektedir.

Anahtar kelimeler: Doksorubusin, Akciğer, Oksidatif stres, Geçici reseptör potansiyeli melastatin 2, D vitamini

How to cite/Atıf için: Yalçın A, Türk A, Aydın H, Yılmaz E, Çelik İS, Üçkardeş F. Effects of vitamin D on doxorubicin-induced lung injury and TRPM2 immunoreactivity in rats. J Surg Med. 2020;4(12):1236-1239.

Introduction

Doxorubicin (DOX) (adriamycin) is a potent antineoplastic antibiotic [1] that is used with a wide variety of human cancers, such as breast, ovarian, and hepatocellular carcinoma, and acute lymphoblastic leukemia [2]. However, its side effects limit the clinical use of this drug [3]. The molecular mechanism by which DOX leads to cell death remains unclear [4]. DOX administration decreases the endogenous antioxidants that have important roles in the scavenging of free radicals [5]. DOX-induced release of free radicals may cause oxidative stress, resulting in DNA damage and cell death [6]. Transient receptor potential (TRP) channels are known as non-selective cation channels which are activated by different chemical and physical stimuli such as oxidative stress, heat, and osmotic pressure [7]. Transient receptor potential melastatin 2 (TRPM2) is a heat sensitive, Ca^{2+} permeable cation channel of the melastanine subgroup of TRP superfamily [8]. Oxidative stress stimulates Ca^{2+} flow in TRPM2 channels [9]. Vitamin D (VD) is a steroid hormone that is often obtained by diet and synthesized by the skin when exposed to the sun [10]. It is a membrane antioxidant, and includes Vitamin D_3 (cholecalciferol), 1,25-dihydroxycholecalciferol, 7-dehydrocholesterol (pro-Vitamin D_3) and Vitamin D_2 (ergocalciferol) [11]. VD is both a prooxidative and antioxidative agent [12], and has been reported to reduce chronic inflammation, suppress oxidative stress, and contribute to mitochondrial respiratory function [13].

The present study was devised to investigate the protective utilities of VD in DOX-induced lung tissue injury, and whether the TRPM2 ion channel might be a marker in lung damage.

Materials and methods

Animals

We used 10-12-week-old 24 male Wistar albino rats obtained from Adiyaman University Experimental Animal Production and Research Center. Rats were divided into four equal groups, housed at 22 (2) ºC with a 12 h light/dark cycle and given standard feed and water *ad libitum*.

Experimental design

Animals were treated according to the ethical rules for the care of laboratory animals (Adiyaman University Animal Experiments Local Ethics Committee, protocol no:2020/044). Experimental groups were designed as follows: Control group received no medications. The VD group received 200 IU/kg VD (DEVİT- 3® Deva, Istanbul, Turkey) via an oral dropper (o.d.) for 14-days. DOX group received a single dose of 10 mg/kg DOX (Doxorubicin® Koçak 50 mg, Kocak-Farma, Istanbul, Turkey) intraperitoneally (i.p.) on day 8. DOX+VD group was administered 200 IU/kg VD via an o.d. for 14-days, and a single dose of 10 mg/kg DOX i.p. on day 8. At the end of the experiment, all rats were fasted overnight, and after obtaining intracardiac blood samples under anesthesia with ketamine (75mg/kg, Ketalar®, Eczacıbası; Istanbul, Turkey) and xylazine (10mg/kg, Rompun®, Bayer Turk Chemistry Industry. Ltd. Corp., Istanbul, Turkey), they were decapitated. Next, the lungs were removed rapidly and fixed with 10% formaldehyde for histopathologic examination. Blood samples of rats were centrifuged at 1500 rpm for 15 minutes to separate the serums. Serum samples were placed at -80°C until biochemical analysis.

Light microscopy

Tissue preparation and histopathology

Fixed lung tissues were passed through a graded alcohol series, cleared with xylene, and placed in paraffin. Sections were cut at 5−6 μm and mounted on polylysine slides. After deparaffinization with xylol, sections were passed through descending concentrations of alcohol, and stained with Masson's trichrome. Following evaluation of stained sections, images were obtained using a Leica DM500 microscope (Leica DFC295).

Biochemical methods

Determining TAS and TOS levels

ELISA method was used for determining the levels of TAS and TOS in serum samples by using TAS (Rat TAS Catalog no: YLA3389Ra YL Biotechnology Co., Ltd, Shanghai, CHINA) and TOS (Rat TOS Catalog no: YLA1392Ra YL Biotechnology Co., Ltd, Shanghai, CHINA) kits according to the instructions of manufacturer. The measurement range of Rat TAS ELISA kit was 1-300 pg/ml, Intra-Assay and Inter-Assay CV values were <10% and <12%, respectively. Sensitivity was 0.54 pg/ml. The measurement range of Rat TOS ELISA kit was 0.02-60 U/ml, Intra-Assay and Inter-Assay CV values were <10% and <12%, respectively. Sensitivity was 0.013 U/ml. The unit of test results is specified in U/ml for serum samples.

Immunohistochemical examination

For antigen retrieval, following rehydration, sections were boiled in a microwave oven (750 W) seven times each in citrate buffer solution, pH 6 for 5 min. The sections were cooled at room temperature for 20 min, washed three times for five minutes each with phosphate-buffered saline (PBS) (P4417; Sigma Chemical Co.), then incubated with hydrogen peroxide block solution (TA-125-HP; Lab Vision Corp. USA) for five minutes to block endogenous peroxidase activity. Sections then were washed three times each with PBS. After five minutes of applying Ultra V Block (TA-125-UB; Lab Vision Corp.), sections were incubated with primary antibody (60 min) for TRPM2 (Anti TRPM2 polyclonal antibody, bs-2888R, Bioss, Inc. USA), secondary antibody (30 min) (biotinylated goat anti-mouse/rabbit Ig G, TP-125-BN; Lab Vision Corp.) and streptavidin peroxidase (30 min) (TS-125-HR; LabVision Corp.). 3-Amino-9-ethylcarbazole (AEC) substrate + AEC chromogen (AEC substrate, TA-015 and HAS, AEC Chromogen, TA-002-HAC; Lab Vision Corp.) solution was dripped on the sections. The sections were washed with PBS. Counterstaining of the sections were performed with Mayer's hematoxylin, passed through PBS, and distilled water, mounted with Large Volume Vision Mount (TA-125-UG; Lab Vision Corp). After evaluation of the sections, images were obtained with a Leica DM500 microscope (Leica DFC295). The histoscore, which reflects the prevalence of immunoreactivity of TRPM2 on the tissue, was based on the rating scale: 0.1, < 25%; 0.4, 26−50%; 0.6, 51−75%; 0.9, 76−100%, and intensity of immunoreactivity: 0, unstained; 0.5, little staining; 1, some staining; 2, moderate staining; 3, strong staining.

Statistical analysis

Statistical analysis was carried out with SPSS 15.0 for Windows (SPSS Inc.). For data with a normal distribution (TAS,

TOS, and immunoreactivity variables), the Shapiro Wilk test was used. For between-group comparisons of TAS, TOS, and immune variables, a one-way analysis of variance (ANOVA) was utilized. Levene's test was performed for testing the homogeneity of variances. Tukey's multiple comparison test was used to reveal differences between groups of significant variables. The results are presented as mean (standard deviation) (SD). $P<0.05$ was considered statistically significant.

Results

Histopathological results

In the histopathological evaluation of lung tissues (Figure 1) the control and VD groups exhibited normal histological structure. Degeneration in the bronchial epithelium, increased collagen fibers at perivascular and peribronchial areas, and alveolar collapse was determined in the DOX group. However, the DOX+VD group demonstrated normal histopathological findings when compared to the samples from the DOX group. Together, our data suggested that VD may protect DOX-induced injuries in the lung tissues.

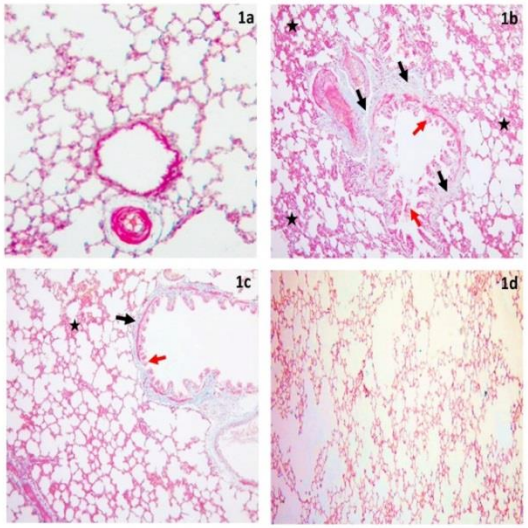


Figure 1: Masson trichrome stained lung tissues, magnification 200×. Normal histological appearance of control (1a) and VD (1d) groups. Degeneration in bronchial epithelium (red arrow), increased collagen at perivascular and peribronchial areas (black arrow) and alveolar collapse (black asterix) in DOX group (1b). Decreased degeneration in bronchial epithelium (red arrow), reduced collagen at perivascular and peribronchial areas (black arrow) and decreased alveolar injury (black asterix) in the DOX+VD group (1c).

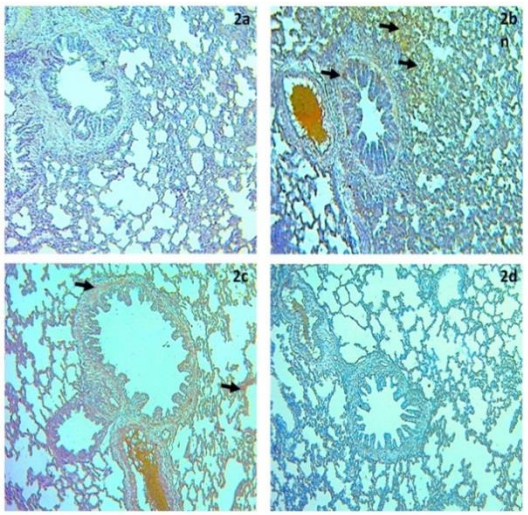


Figure 2: Lung tissues stained with Streptavidin biotin peroxidase complex method with Mayer's Hematoxylin counterstain for TRPM2 immunoreactivity, magnification 200×. Slightly TRPMP2 immunoreactivity in lung tissue of the control group (2a) and the VD group (2d). Increased TRPMP2 immunoreactivity (black arrow) in lung tissue of the DOX group (2b). Decreased TRPMP2 immunoreactivity (black arrow) in lung tissue of the DOX+VD group (2c).

Immunohistochemical results

Slight TRPM2 expression was observed in the control and VD groups ($P=0.097$) (Figure2). However, it was significantly increased in the DOX group when compared with the control group ($P<0.001$). Interestingly, when combined with DOX, VD decreased the expression of TRPM2 significantly in the DOX+VD group ($P<0.001$) (Table 1).

Table 1: Histoscore of TRPMP2 immunoreactivity in lung tissue

Groups	TRPM2 immunoreactivity
Control	0.79^{a} (0.07)
DOX	1.62^{c} (0.11)
DOX+ VD	1.19^{b} (0.04)
VD	0.68^{a} (0.06)
P-value*	<0.001

[a b c] Means within the same row with differing superscripts are significantly different ($P<0.05$, Tukey's test) *: One Way ANOVA

Biochemical results

TAS and TOS levels were similar in the control and VD groups ($P=0.124$, and $P=0.582$, respectively). In contrast, we observed significantly decreased TAS levels and increased TOS levels in the DOX group compared to the control samples ($P<0.001$, and $P<0.001$, respectively). TAS and TOS levels were reversed when we administered DOX in combination with VD in the DOX+VD group ($P<0.001$, and $P<0.001$, respectively) (Table 2).

Table 2: Serum levels of TAS and TOS

Groups	TAS (U/ML)	TOS (U/ml)
Control	1.48^{ab} (0.06)	15.67^{a} (0.44)
DOX	1.10^{c} (0.05)	20.64^{c} (0.97)
DOX+ VD	1.40^{b} (0.06)	18.04^{b} (0.29)
VD	1.53^{a} (0.05)	16.10^{a} (0.36)
P-value*	<0.001	<0.001

[a b c] Means within the same row with differing superscripts are significantly different ($P<0.05$, Tukey's test) *: One Way ANOVA

Discussion

Injuries induced by oxygen radicals in membrane lipids is the most important cause of DOX-induced toxicity [14]. Over-production of these radicals, especially the hydroxyl radicals, cause injury to macromolecules such as proteins, DNA, and membrane phospholipids [15].

DOX causes an increase in the collagen fibers on the alveolar wall of lung, degeneration of some cellular organelles [16], arterial endothelial and alveolar epithelial necrosis along with edema at periarterial and subpleural areas, and emphysema [17]. Consistent with the published reports, in the current study, DOX administration caused degeneration in the bronchial epithelium, increased collagen fibers at perivascular and peribronchial areas, and alveolar collapse in lung tissues of rats. These findings support the data that DOX is toxic to lung tissue due to increased lipid peroxidation and ROS production, which induces oxidative stress [16].

Deficiency of VD is related to decreased lung function, obstructive lung diseases such as chronic obstructive pulmonary disease and asthma [18]. VD is effective on the protection of pulmonary injury and tissue repair [19], and in preventing oxidative stress [20]. In this study, VD administration exhibited ameliorative utility by reversing the tissue structure, similar to the control group, as VD reduces tissue injury [21].

In 2017, Dietrich et al. [22] reported that as toxic sensors and effectors, TRP channels have roles in asthma, lung inflammation, fibrosis, and edema, along with Chronic Obstructive Pulmonary Disease (COPD). TRPM2 is an ion

channel located on the cell membrane. Oxidative stress [23] causes TRPM2 ion channels to open and increases intracellular Ca2+ ions [24]. In this process, intracellular influx of Ca2+ is considered the initiator of pathophysiological events that can lead to cell death [25]. In diabetic kidney tissue, increased TRPM2 immunoreactivity has been shown to decrease following administration of antioxidants, enalapril [26], and losartan [26]. Similarly, melatonin, a strong antioxidant, inhibits TRPM2 channel gated Ca2+ influx [28]. In the current study, increased TRPM2 expression in the DOX group could be related to DOX-induced oxidative stress. VD administration may have decreased the TRPM2 expression due to its antioxidant effect, in line with the literature.

An imbalance between ROS and the antioxidant defense system leads to oxidative stress, which is related to the pathogenesis of acute and chronic lung injury [29]. Oxidative stress occurs due to a disequilibrium between oxidants and antioxidants and causes tissue injury [30]. The total redox statuses of individuals were best evaluated with TAS and TOS levels combined [31,32]. DOX treatment has been reported to lead to an increase in TOS level and a decrease in TAS level in testis [33], and heart [34], and tissues. These findings show that DOX disrupted the oxidant-antioxidant balance and led to tissue damage. In the current study, a significant decrease in TAS level and a significant increase in TOS level in serum was observed in accordance with the literature, while VD administration decreased serum TOS and increased serum TAS levels in diabetic rats significantly [35]. Similarly, we observed decreased TOS level and significantly increased TAS level in the DOX+VD group. This restorative effect of VD could be attributed to antioxidative utility of VD [11,12].

Conclusion

VD could be a potential therapeutic agent for DOX-induced pulmonary toxicity. We suggest that increased TRPM2 immunoreactivity in the DOX group could be involved in the pathophysiological mechanism of pulmonary cytotoxicity and should be focused on as a therapeutic option to prevent chemotherapy induced cytotoxicity. Further studies are expected to explain the efficacy and role of VD and TRPM2 on chemotherapy induced cytotoxicity.

References

1. Chegaev K, Riganti C, Rolando B, Lazzarato L, Gazzano E, Guglielmo S, et al. Doxorubicin-antioxidant co-drugs. Bioorg Med Chem Lett. 2013;23(19):5307-10. doi: 10.1016/j.bmcl.2013.07.070.
2. Zheng J, Lee HC, Bin Sattar MM, Huang Y, Bian JS. Cardioprotective effects of epigallocatechin-3-gallate against doxorubicin-induced cardiomyocyte injury. Eur J Pharmacol. 2011;652(1-3):82-8. doi: 10.1016/j.ejphar.2010.10.082.
3. Munnier E, Cohen-Jonathan S, Hervé K, Linassier C, Souce´ M, Dubois P, et al. Doxorubicin delivered to MCF-7 cancer cells by superparamagnetic iron oxide nanoparticles: effects on subcellular distribution and cytotoxicity. J Nanoparte Res. 2011;13(3):959-71. doi: 10.1007/s11051-010-0093-1.
4. Gewirtz DA. A critical evaluation of the mechanisms of action proposed for the antitumor effects of the anthracycline antibiotics adriamycin and daunorubicin. Biochem Pharmacol. 1999;57(7):727–41. doi: 10.1016/s0006-2952(98)00307-4.
5. Singal PK, Siveski-Iliskovic N, Hill M, Thomas TP, Li T. Combination therapy with probucol prevents adriamycininduced cardiomyopathy. J Mol Cell Cardiol. 1995;27(4):1055-63. doi: 10.1016/0022-2828(95)90074-8.
6. Thorn CF, Oshiro C, Marsh S, Hernandez-Boussard T, McLeod H, Klein TE, et al. Doxorubicin pathways: pharmacodynamics and adverse effects. Pharmacogenet Genomics. 2011;21(7):440–6. doi: 10.1097/FPC.0b013e32833ffb56.
7. Matsumoto K, Takagi K, Kato A, Ishibashi T, Mori Y, Tashima K, et al. Role of transient receptor potential melastatin 2 (TRPM2) channels in visceral nociception and hypersensitivity. Exp Neurol. 2016;285(Pt A):41-50. doi: 10.1016/j.expneurol.2016.09.001.
8. Wehage E, Eisfeld J, Heiner I, Jüngling E, Zitt C, Lückhoff A. Activation of the cation channel long transient receptor potential channel 2 (LTRPC2) by hydrogen peroxide. A splice variant reveals a mode of activation independent of ADP-ribose. J Biol Chem. 2002;277(26):23150–6. doi: 10.1074/jbc.M112096200.
9. Wilkinson JA, Scragg JL, Boyle JP, Nilius B, Peers C. H2O2- stimulated Ca+2 influx via TRPM2 is not the sole determinant of subsequent cell death. Pflugers Arch. 2008;455(6):1141-51. doi: 10.1007/s00424-007-0384-2.
10. Caprio M, Mammi C, Rosano GM. Vitamin D: A novel player in endothelial function and dysfunction. Arch Med Sci. 2012;8(1):4-5. doi: 10.5114/aoms.2012.27271.
11. Wiseman, H. Vitamin D is a membrane antioxidant. Ability to inhibit iron-dependent lipid peroxidation in liposomes compared to cholesterol, ergosterol and tamoxifen and relevance to anticancer action. FEBS letters. 1993;326(1-3):285-8. doi: 10.1016/0014-5793(93)81809-e.
12. Timar A, Saberi-Karimian M, Ghazizadeh H, Parizadeh SMR, Sabbaghzadeh R, Emadzadeh M, et al. Evaluation of the serum prooxidant-antioxidant balance before and after vitamin D supplementation in adolescent Iranian girls. Adv Med Sci. 2019;64(1):174-80. doi: 10.1016/j.advms.2018.10.004.
13. Wimalawansa SJ. Vitamin D deficiency: Effects on oxidative stress, epigenetics, gene regulation, and aging. Biology. 2019;8(2):30. doi: 10.3390/biology8020030.
14. Olson RD, Mushlin PS. Doxorubicin cardiotoxicity: analysis of prevailing hypotheses. The FASEB Journal. 1990;4(13):3076–86.
15. Oz E, Erbaş D, Sürücü HS, Düzgün E. Prevention of doxorubicin-induced cardiotoxicity by melatonin. Mol Cell Biochem. 2006;282(1-2):31-7. doi: 10.1007/s11010-006-1153-9.
16. Take G, Yamaç D, Ozoğul C, Erdogan D. Ultrastructural damage in lung tissues in rats treated with doxorubicin and paclitaxel. Adv Ther. 2008;25(2):115-22. doi: 10.1007/s12325-008-0015-0.
17. Minchin RF, Johnston MR, Aiken MA, Boyd MR. The pharmacokinetics of doxorubicin in isolated lung of dog and main perfused in vivo. J Pharmacol Exp Ther. 1984;229(1):193-8.
18. Zosky GR, Berry LJ, Elliot JG, James AL, Gorman S, Hart PH. Vitamin D deficiency causes deficits in lung function and alters lung structure. Am J Respir Crit Care Med. 2011;183(10):1336-43. doi: 10.1164/rccm.201010-1596OC.
19. Tao S, Zhang H, Xue L, Jiang X, Wang H, Li B, et al. Vitamin D protects against particles-caused lung injury through induction of autophagy in an Nrf2-dependent manner. Environ Toxicol. 2019;34(5):594-609. doi: 10.1002/tox.22726.
20. Keles H. Yalcin A, Aydin H. Protective effect of Vitamin D on imidacloprid-induced testicular injury in rats. Arch Med Sci. 2019;15(1). doi: 10.5114/aoms.2019.86776.
21. Yalcin A, Aydin H, Turk A, Dogukan M, Eser N, Onderci M, et al. Vitamin D: An effective way to combat methotrexate-induced testis injury. Medicine, 2020;9(4):998-1003. doi: 10.5455/medscience.2020.10.222.
22. Dietrich A, Steinritz D, Gudermann T. Transient receptor potential (TRP) channels as molecular targets in lung toxicology and associated diseases. Cell calcium. 2017;67:123-37. doi: 10.1016/j.ceca.2017.04.005.
23. Naziroğlu M, Lückhoff A. Effects of antioxidants on calcium influx through TRPM2channels in transfected cells activated by hydrogen peroxide. J Neurol Sci. 2008;270(1-2):152-8. doi: 10.1016/j.jns.2008.03.003.
24. Hara Y, Wakamori M, Ishii M, Maeno E, Nishida M, Yoshida T, et al. LTRPC2 Ca2+-permeable channel activated by changes in redox status confers susceptibility to cell death. Mol Cell. 2002;9(1):163-73. doi: 10.1016/s1097-2765(01)00438-5.
25. Lange I, Yamamoto S, Partida-Sanchez S, Mori Y, Fleig A, Penner R. TRPM2 functions as a lysosomal Ca2+-release channel in beta cells. Sci Signal. 2009;2(71):ra23. doi: 10.1126/scisignal.2000278.
26. Kuloğlu T, Kocaman N. Determination of Renal TRPM2 Channels Immunoreactivities in Enalapril Administrated Diabetic Rats. F.Ü. Sağ. Bil. Tıp Derg. 2013;27(1):27-32. (In Turkish with English abstract)
27. Artaş G, Kuloglu, T. The Effects of Losartan on TRPV1 and TRPM2 Channels at Diabetic Rat Kidney Tissue Fırat Tıp Dergisi. 2014;19(3):116-21. (In Turkish with English abstract)
28. Celik O, Nazıroğlu, M. Melatonin modulates apoptosis and TRPM2 channels in transfected cells activated by oxidative stress. Physiol behav. 2012;107(3):458-65. doi: 10.1016/j.physbeh.2012.09.013.
29. Tasaka S, Amaya F, Hashimoto S, Ishizaka A. Roles of oxidants and redox signaling in the pathogenesis of acute respiratory distress syndrome. Antioxid Redox Signal. 2008;10(4):739–53. doi: 10.1089/ars.2007.1940.
30. Miller BA, Zhang W. Transient Receptor Potential Channels. Dordrecht: Springer; 2011. Chapter 29, TRP channels as mediators of oxidative stress; p. 531-44.
31. Feng JF, Lu L, Dai CM, Wang D, Yang YH, Yang YW, et al. Analysis of the diagnostic efficiency of serum oxidative stress parameters in patients with breast cancer at various clinical stages. Clin Biochem. 2016;49(9):692-8. doi: 10.1016/j.clinbiochem.2016.02.005.
32. Demirpençe O, Sevim B, Yıldırım M, Nurlu NA, Mert D, Evliyaoğlu O. Serum paraoxonase, TAS, TOS and ceruloplasmin in brucellosis. Int J Clin Exp Med. 2014;7(6):1592–7.
33. Öztürk E, Kaymak E, Akin AT, Karabulut D, Ünsal HM, Yakan B. Thymoquinone is a protective agent that reduces the negative effects of doxorubicin in rat testis. Hum Exp Toxicol. 2020;39(10):1364-73. doi: 10.1177/0960327120924108.
34. Karabulut D, Ozturk E, Kaymak E, Akin AT, Yakan B. Thymoquinone attenuates doxorubicin-cardiotoxicity in rats. J Biochem Mol Toxicol. 2020:e22618. doi: 10.1002/jbt.22618.
35. Gozel N, Genc F, Ozdemir FA, Kuloglu T, Kaya N, Yalcin MH, et al. Effects of Vitamin D on matrix metalloproteinase 9 and apoptosis in experimental diabetic rat kidney tissue. Fresenius Environ Bull. 2018;27(5 A):3766-75.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1240-1243.
DOI: 10.28982/josam.758402

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Clinicopathological assessment in orchiectomy materials

Orşiektomi materyallerinde klinikopatolojik değerlendirme

Leymune Parlak [1], Emine Zeynep Tarini [1]

[1] Department of Pathology, University of Health Science Turkey, Mehmet Akif İnan Training and Research Hospital, Şanlıurfa, Turkey

ORCID ID of the author(s)

LP: 0000-0002-5503-3067
EZT: 0000-0001-9874-5104

Corresponding author/Sorumlu yazar:
Leymune Parlak
Address/Adres: Department of Pathology, University of Health Science Turkey, Mehmet Akif İnan Training and Research Hospital, Şanlıurfa, Turkey
E-mail: leymune_38@hotmail.com

Ethics Committee Approval: The research was approved by Harran University Ethical Committee (27.01.2020/02/ no:18). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma Harran Üniversitesi Klinik Araştırmalar Etik Kurulu 27.01.2020 tarih, 02 nolu oturum ve 18 sayılı kararı ile onaylanmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract

Aim: Orchiectomy indicates excising the testicles unilaterally or bilaterally. The causes of excision include primary etiologies such as torsion/infarction, infection, malignancy, cryptorchidism, and therapeutic castration secondary to prostate cancer. The aim of this study is to determine the clinicopathological characteristics of patients undergoing orchiectomy and obtain regional data.

Methods: In this study, 316 orchiectomy specimen reports, stored in the archive of University of Health Science Turkey, Mehmet Akif İnan Training and Research Hospital, Pathology Laboratory between January 2015 and December 2019 were retrospectively evaluated. Histopathological diagnoses, right-left testicular localization, age range of patients and orchiectomy indication data were analyzed.

Results: While the ages of 316 patients included in the study ranged from 1 to 88 years, the mean age was 26 years. Among the orchiectomy materials, undescended testis was the most common cause with 129 (40.8%) cases. Three hundred (94.9%) cases underwent unilateral and 16 (5.1%) cases underwent bilateral orchiectomy. Orchiectomy was performed in 58 cases aged between 14-68 years (mean age: 33 years), with a pre-diagnosis of a mass. Tumor sizes ranged from 0.4 cm to 16 cm. The average tumor size was 5.1 cm. Histopathologically, 51 (87.9%) cases were diagnosed with germ cell tumor. The most common diagnosis among germ cell tumors was classical seminomas (n=23 (45.1%)).

Conclusion: Testicular orchiectomy surgery can be performed at any age depending on many different indications. Diagnoses vary from benign to malignant. Multiple sampling should be done to show the presence of GCNIS, which was highlighted in the last WHO 2016 classification, in testicular tumors, especially when diagnosing malignancy. Factors determining the prognosis such as lymphovascular invasion, rete testis invasion, and tumor size must be specified in the report.

Keywords: Testis, Orchiectomy, Cryptorchidism, Tumor

Öz

Amaç: Orşiektomi testisleri unilateral veya bilateral eksize etmek için uygulanan cerrahi işlemin adıdır. Eksizyon nedenleri arasında torsiyon/enfarktüs, enfeksiyon, malignite, kriptorşidizm gibi primer etyolojiler ile birlikte prostat kanserine sekonder yapılan terapötik kastrasyon sayılabilir. Bu çalışmanın amacı orşiektomi uygulanan hastaların klinikopatolojik özelliklerini belirlemek ve bölgesel verileri elde etmektir.

Yöntem: Bu çalışmada Ocak 2015 – Aralık 2019 tarihleri arasında SBÜ Mehmet Akif İnan Eğitim ve Araştırma Hastanesi Patoloji Labaratuvarı arşivinde kayıtlı 316 orşiektomi materyali retrospektif olarak tarandı. Histopatolojik tanılar, testis sağ-sol lokalizasyonu, hastaların yaş aralığı ve orşiektomi endikasyon verileri incelendi.

Bulgular: Çalışmaya alınan 316 adet olgunun yaşları 1 ile 88 arasında değişirken yaş ortalaması 26 idi. Orşiektomi materyalleri içinde inmemiş testis 129 (%40,8) olgu ile en sık neden olarak bulundu. 300 (%94,9) olguya unilateral, 16 (%5,1) adet olguya bilateral orşiektomi uygulandığı görüldü. Kitle ön tanısı ile 58 olguya orşiektomi uygulanmıştı. Yaş dağılımı 14-68 arasındaydı (ortalama yaş 33). Tümör boyutları 0,4 cm ile 16 cm arasında değişmekteydi. Ortalama tümör boyutu 5,1 cmdi. Histopatolojik olarak 51 (%87,9) olgu germ hücreli tümör tanısı aldı. Germ hücreli tümörler içinde de en sık tanı 23 (%45,1) olgu ile klasik seminomdu.

Sonuç: Testis orşiektomi cerrahisi her yaş da bir çok farklı endikasyona bağlı olarak yapılabilmektedir. Benignden maligniteye kadar değişen tanılar verilebilmektedir. Özellikle malignite tanısı konulurken son DSÖ 2016 testis tümörlerinde vurgulanan GCNIS varlığını gösterebilmek için çoklu örnekleme yapılmalıdır. Prognozu belirleyen lenfovasküler invazyon, rete testis invazyonu, tümör boyutu gibi faktörler raporda mutlaka belirtilmelidir.

Anahtar kelimeler: Testis, Orşiektomi, Kriptorşidizm, Tümör

How to cite/Atıf için: Parlak L, Tarini EZ. Clinicopathological assessment in orchiectomy materials. J Surg Med. 2020;4(12):1240-1243.

Introduction

Testis, a paired organ that lies within the scrotum, is suspended by the spermatic cord in which sperms are produced and the male hormone called testosterone is secreted. Each testis weighs between 15–19 grams in adults [1]. Some of the lesions of the testicles include cryptorchidism, epididymo-orchitis, testicular torsion and malignancies [2], depending on which, various symptoms such as abdominal mass, scrotal swelling, and pain may be observed [3].

Orchiectomy indicates surgical excision of the testicles unilaterally or bilaterally. The causes of excision include primary etiologies such as torsion/infarction, infection, malignancy, cryptorchidism, and therapeutic castration secondary to prostate cancer [2]. Testicular cancers constitute about 1-2% of all male malignancies. Although malignances peak between the ages of 15-40 years, they can be observed in all age groups [4-5]. Physical examination and anamnesis, serum tumor marker levels, and scrotal ultrasonography are used in diagnosis. Orchiectomy is important for both treatment and histopathological diagnosis, with which tumor subtypes can be identified. Lymphovascular invasion (LVI), tunica vaginalis invasion, spermatic cord invasion, and scrotal invasion can be detected by histopathological examination of orchiectomy materials to show the T stage of the tumor [6]. It is necessary to be aware of the variety of etiology and histopathological diagnoses of orchiectomy. The aim of this study is determining the clinicopathological features and patients undergoing orchiectomy and obtaining regional data.

Materials and methods

Approval for this study was granted by Harran University Ethical Committee (27.01.2020/02/ no:18). Histopathological diagnoses, right-left localization, age range of patients and causes of orchiectomy in 316 orchiectomy materials obtained in the University of Health Science Turkey, Mehmet Akif İnan Training and Research Hospital, between January 2015 and December 2019 were investigated through the pathology archive. Routine hematoxylin-eosin (H&E) stained slides and immunohistochemical studies of cases previously diagnosed with malignancy were re-evaluated. Classification and pathological staging were performed according to the 2016 World Health Organization classification of urinary system and male genital organ tumors. Findings with definitive diagnoses were presented to contribute to the literature.

Results

The mean age of 316 patients included in the study was 26 years (range: 1-88 years). Undescended testis was the most common cause of orchiectomy, with 129 (40.8%) cases (Figure 1). The other reasons included torsion in 71 cases (22.5%), mass in 58 cases (18.4%), and abscess/Fournier gangrene/orchitis in 42 cases (13.3%) (Table 1) (Figure 2).

Fifty-eight (18.4%) and two hundred and fifty-eight (81.6%) cases were operated for neoplastic and non-neoplastic indications, respectively. One hundred and thirty-nine cases (43.9%) underwent left, 96 (30.3%) cases underwent right, and 16 (5.1%) cases underwent bilateral orchiectomy. There were 67 cases (21.2%) without right-left localizations stated. Unilateral surgery was performed to all patients who were operated for neoplastic reasons, and 93.7% of patients were operated for non-neoplastic reasons. Indications for patients who underwent bilateral orchiectomy included prevention of increased libido in the mentally retarded patients, therapeutic castration for prostate cancer in older patients, infections, and gender determination for conditions such as testicular feminization and congenital adrenal hyperplasia.

Table 1: Distribution of orchiectomy indications

Causes of orchiectomy	n=316
Undescended testicle	129 (40.8%)
Torsion	71 (22.5%)
Mass	58 (18.4%)
Abscess / Fournier gangrene / orchitis	42 (13.3%)
Therapeutic castration due to prostate cancer	9 (2.8%)
Trauma	3 (1%)
Sex determination	2 (0.6%)
Preventing increase in libido	1 (0.3%)
Hernia	1 (0.3%)

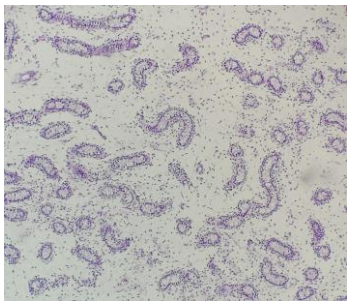


Figure 1: Undescended testicle: Atrophic testicle glands in edema stroma (HE, 100x)

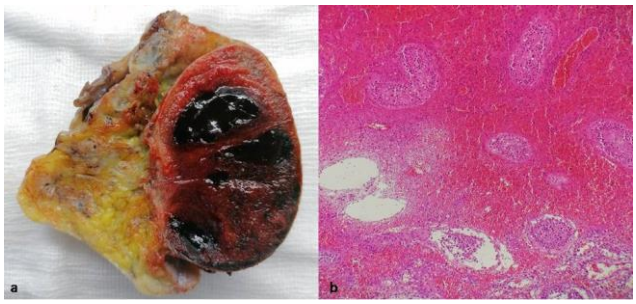


Figure 2: Torsion: Testicular bleeding and infarction in the glands (a: macroscopy, b: HE, 400x)

Orchiectomy was performed in 58 cases, whose age ranged between 14-68 years (Mean age: 33 years), with a pre-diagnosis of a mass. Tumor sizes ranged from 0.4 cm to 16 cm, with a mean tumor size of 5.1 cm. Based on 2016 World Health Organization Urinary system and male genital organ tumor classification, 51 (87.9%) cases were histopathologically diagnosed with germ cell tumor. The most common diagnosis among germ cell tumors was classical seminomas with 23 (45.1%) cases (Figure 3). Of the non-germ cell tumors, sex-cord stromal tumor was seen in 3 cases, mesenchymal tumors in 2 cases, hematologic malignancy in 1 case and simple cyst, in 1 case (Table 2).

Factors that have prognostic importance and affect staging in germ cell tumors were evaluated. Lymphovascular invasion was observed in 25 cases, perineural invasion in 3 cases, epididymis involvement in 6 cases, rete testicular involvement in 7 cases, tunica albuginea involvement in 5 cases, tunica vaginalis involvement in 6 cases, surrounding adipose tissue invasion in 2 cases, and spermatic cord involvement, in 5 cases. In tumors originating from in situ germ cell neoplasia, intratubular germ cell neoplasia was observed in 11 cases (Figure 4). According to the pathological tumor staging (pTNM) in the

eighth edition of the American Common Cancer Committee (AJCC), 19 cases were classified as pT1, 26 cases as pT2, 4 cases as pT3 and 2 cases as pT4. One case was at N1 stage with lymph node metastasis at the time of diagnosis. Also, during the follow-up, lung metastasis developed in one case in the third year after operation.

Table 2: Distribution of histopathological diagnoses of orchiectomies performed for neoplastic reasons

Tumors		n=58
Germ cell tumors		n=51 (87.9%)
Tumors derived from germ cell neoplasia in situ	Seminoma	23
	Embryonal Carcinoma	2
	Teratoma, Postpubertal Type	2
	Mixed Germ Cell Tumor	16
Tumors unrelated to germ cell neoplasia in situ	Spermatocytic Tumor	2
	Yolk Sac Tumor, Prepubertal Type	1
	Mixed Teratoma and Yolk Sac Tumor, Prepubertal Type	5
Non-Germ cell tumors		n=7 (12.1%)
Sex cord-stromal tumors	Sertoli cell tumor	1
	Leydig cell tumor	2
Mesenchymal tumors	Liposarcoma	1
	Inflammatory myofibroblastic tumor	1
Hematolymphoid tumors	Diffuse large B-cell lymphoma	1
Others	Simple cyst	1

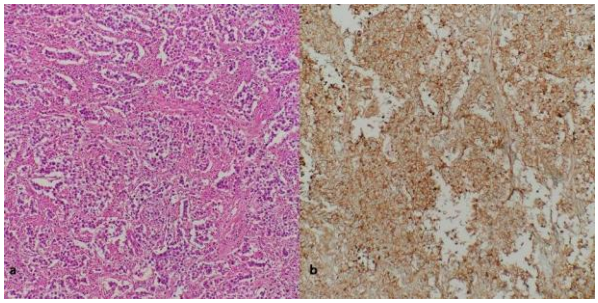


Figure 3: Seminoma: Tumor cells with fibrous septa and inflammatory cells (a: HE, 100x), PLAP positive stain (b: immunohistochemistry, 100x)

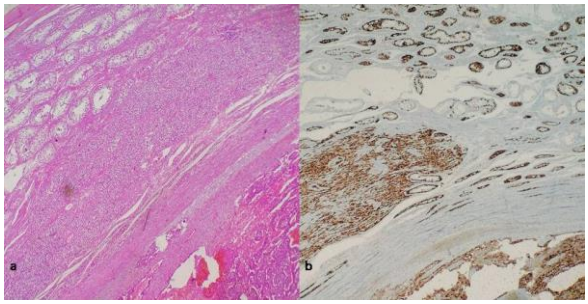


Figure 4: Intratubular germ cell neoplasia in embryonal carcinoma (a: HE, 100x) and PLAP positive stain (b: immunohistochemistry, 100x)

Discussion

Orchiectomy can be performed in any age group with various indications. In our study, we found that the most common orchiectomy reason was undescended testicle. Unlike ours, in the study of Nwafor et al. [7] evaluating testis biopsies performed after orchiectomy and for infertility, they found that 60.9% of 64 cases in their series underwent therapeutic castration due to prostate cancer. The ages of 64 cases ranged between 4-86 years, with a mean age of 54 years. Similarly, Latheef et al. [2] reported that the most common indication for orchiectomy in their 23-case orchiectomy series was therapeutic castration for prostate cancer. They reported that the ages of most cases ranged between 50-70 years, with the youngest being a newborn and the oldest being 89 years of age. In our study, age distribution was between 1 and 88 years old, and unlike these two publications, since our most frequent orchiectomy indication was undescended testicle, we found that our cases were younger, with a mean age of 33 years.

In their study investigating orchiectomy cases, Patel et al. [8] reported that 97.6% of orchiectomies performed for non-neoplastic reasons were unilateral, while orchiectomies for neoplastic reasons were completely unilateral. The most common indication for non-neoplastic orchiectomies was torsion. Sharma et al. [3] emphasized that all patients in their study underwent unilateral orchiectomy, and that right orchiectomy was performed in 58% of non-neoplastic lesions and 50% of neoplastic lesions. In their studies, the most common non-neoplastic orchiectomy indication was undescended testis with a rate of 39.6%. In our study, 139 (43.9%) cases underwent left, 96 (30.3%) cases underwent right, and 16 (5.1%) cases underwent bilateral orchiectomy. Unilateral surgery was performed in all patients operated for neoplastic reasons and 93.7% of patients operated for non-neoplastic reasons. Indications for patients who underwent bilateral orchiectomy were prevention of increased libido in mentally retarded patients, therapeutic castration for prostate cancer in older patients, infections, and gender determination for conditions such as testicular feminization and congenital adrenal hyperplasia. In the literature and the data in our study, the most common indications of laterality and orchiectomies vary.

Testicular cancers account for about 1-2% of all male malignancies. Although malignancy is mostly diagnosed between the ages of 15-40 years, it can be observed in all age groups [4,5]. Physical examination and anamnesis, serum tumor marker levels, scrotal ultrasonography are used in diagnosis, but orchiectomy is important for both treatment and histopathological diagnosis [6]. Yalçınkaya et al. [9] detected tumors in 139 (25.6%) cases in a series of 574 patients, and Bozkurt et al. [10] detected tumors in 45 (54.2%) of 83 orchiectomies. The mean ages of the cases reported by Yalçınkaya et al. [9] and Bozkurt et al. [10] were 32.94 ± 15.7 years and 38.8 years, respectively. In our study, orchiectomy was performed in 58 (18.4%) cases with a pre-diagnosis of neoplasia. Akin to the literature, our patients' mean age was 33 years.

Germ cell tumors constitute 90-95% of testicular tumors, among which seminoma is the most common, with a rate of 50%. In the study of Yalçınkaya et al. [9], 92% of testicular tumors were germ cell tumors, and the most common was seminoma with 47 (36.7%) cases. Bozkurt et al. reported that 86.7% of tumors were germ cell tumors and classical seminoma was the most common, with 41%. In our study, we found that 87.9% (n=51) of 58 cases operated for neoplasia were germ cell tumors, like the literature, and seminoma was the most common, with 23 cases (45.1%).

The etiology of testicular neoplasia includes undescended testicles, in situ germ cell neoplasia, germ cell tumor history in contralateral testicle, testicular dysgenesis, consuming a high calorie diet and sedentary lifestyle [9,11]. We did not detect neoplasia among 129 undescended testicles and 2 testicular dysgenesis cases. With the understanding of the importance of germ cell neoplasia in situ (GCNIS) as a precursor lesion in testicular tumors, several changes were made in the classification of germ cell tumors in the WHO Urinary and Male Genital System Tumors 2016 edition, according to the derivation

of tumor from GCNIS [12]. To determine the presence of GCNIS, non-tumor testicular tissue and tumor passage sampling should be increased [13]. In our study, 43 of 51 germ cell tumors (84.3%) derived from GCINS. In 11 (25.5%) of these tumors, intratubular germ cell neoplasia was observed.

There are several factors to determine the prognosis in testicular tumors, including tumor size, LVI, rete testis invasion, tumor histology and serum tumor markers [11,14]. Scandura et al. [15] showed that tumor size and epididymis invasion are strong predictors in metastatic seminomas. For tumor size, the cut-off was 4.25 cm. Based on their literature search, they stated that some publications determined the cut-off tumor size as 3-4 cm and emphasized the importance of rete testis invasion. Warde et al. [16] emphasized that tumor size above 4 cm and rete testis invasion are crucial factors in predicting relapse. In our study, tumor sizes ranged from 0.4 cm to 16 cm, with a mean of 5.1 cm. Lymphovascular invasion was observed in 25 cases, epididymis was involved in 6 cases, rete testicular was involved in 7 cases, tunica vaginalis in 6 cases, surrounding adipose tissue, in 2 cases, and spermatic cord, in 5 cases. There was lymphovascular, rete testis and spermatic cord invasion in our classical seminoma case with lymph node metastasis at the time of diagnosis. The tumor size was 8 cm.

Prognostic factors are also important in pathological T staging. According to the current TNM staging system, which was revised for the 8th time in 2016 by the American Joint Cancer Committee, pathological T stage increases from pT1 to pT2 if the tumor is limited to the testicle, invades the rete testis and LVI and LVI without tunica albuginea involvement or epididymis invasion or spermatic cord invasion are present. Spermatic cord involvement corresponds to pT3, and tumors that invade the tunica vaginalis layer of the testicle and spread to the scrotum correspond to pT4. Spermatic cord invasion with the presence of LVI in the spermatic cord can be considered distant organ metastasis and can increase the stage to pM1 [13,17]. In our study, germ cell tumors were classified as pT1 in 19 cases, pT2 in 26 cases, pT3 in 4 cases and pT4 in 2 cases. One case was at N1 stage with lymph node metastasis at the time of diagnosis.

Approximately 8% of non-seminomatous germ cell tumors in stage 1 can cause lung metastasis and 29.3% can metastasize to retroperitoneal lymph nodes. These tumors include embryonal carcinoma, teratocarcinoma, yolk sac tumor and choriocarcinoma [18]. Lung metastasis developed in the third year after orchiectomy in our case with mixed germ cell tumor (Seminoma + Embryonal carcinoma + Teratoma). This patient had a tumor size of 3.5 cm and lymphovascular invasion.

Limitation

Since we work as a central pathology laboratory in the province, despite enough cases, our study was limited because we could not access information such as serum tumor markers and survey of patients from the hospital registry.

Conclusion

Orchiectomy surgery can be performed at any age with varying indications, with histopathological examination results varying from benign to malignant. Multiple sampling should be done to show the presence of GCNIS, which was highlighted in the last WHO 2016 testicular tumors guideline, especially when diagnosing malignancy. Factors determining the prognosis such as lymphovascular invasion, rete testis invasion, and tumor size must be specified in the report.

References

1. In Juan Rosai: Rosai and Ackerman's Surgical Pathology 10th edition, Elsevier, Male reproductive system: Testis, 2011.pp.1334-74
2. Latheef DA, Nayak R, Nuzhath DT, Shetty DP, Nair DV. Histopathological Assessment of Orchidectomy Specimens in a Tertiary Care Center. International Journal of Innovative Research in Medical Science. 2019;4(03):183-7. doi:.10.23958/ijirms/vol04-i03/591
3. Sharma M, Mahajan V, Suri J, Kaul KK. Histopathological spectrum of testicular lesions- A retrospective study. Indian Journal of Pathology and Oncology. July-September 2017;4(3):437-41. 10.18231/2394-6792.2017.0094
4. Shanmugalingam T, Soultati A, Chowdhury S, Rudman S, Van Hemelrijck M. Global incidence and outcome of testicular cancer. Clin Epidemiol. 2013 Oct 17;5:417-27. doi: 10.2147/CLEP.S34430.
5. Park JS, Kim J, Elghiaty A, Ham WS. Recent global trends in testicular cancer incidence and mortality. Medicine (Baltimore). 2018 Sep;97(37):e12390. doi: 10.1097/MD.0000000000012390.
6. Stevenson SM, Lowrance WT. Epidemiology and Diagnosis of Testis Cancer. Urol Clin North Am. 2015 Aug;42(3):269-75. doi: 10.1016/j.ucl.2015.04.001.
7. Nwafor CC, Nwafor NN. Morphologic patterns of testicular lesions in Uyo: A university hospital experience. Sahel Med J. 2019;22:18-22.
8. Patel MB, Goswamy HM, Parikh UR, Mehta N. Histopathological study of testicular lesions. Gujarat Medical Journal. 2015;70(1):41-6.
9. Yalçınkaya U, Çalışır B, Uğraş N, Filiz G, Erol O, Testis tümörleri: 30 yıllık arşiv tarama sonuçları, Türk Patoloji Dergisi. 2008;24(2):100-6.
10. Bozkurt KK, Başpınar Ş, Akdeniz R, Bircan S, Koşar A. Testis tümörleri: 5 yıllık olgu serisi, Med J SDU / S.D.Ü. Tıp Fak. Derg. 2014;21(3):88-92.
11. Leman ES, Gonzalgo ML. Prognostic features and markers for testicular cancer management. Indian J Urol. 2010 Jan-Mar;26(1):76-81. doi: 10.4103/0970-1591.60450.
12. Williamson SR, Delahunt B, Magi-Galluzzi C, Algaba F, Egevad L, Ulbright TM, et al. The World Health Organization 2016 classification of testicular germ cell tumors: a review and update from the International Society of Urological Pathology Testis Consultation Panel. Histopathology. 2017 Feb;70(3):335-46. doi: 10.1111/his.13102.
13. Karabulut YY. Erkek Genital ve Üriner Sistem Kanserlerinde TNM Evrelemesinde Yapılan Değişiklikler. Güncel Patoloji Dergisi. 2018;2(2):57-63.
14. Facchini G, Rossetti S, Berretta M, Cavaliere C, D'Aniello C, Iovane G, et al. Prognostic and predictive factors in testicular cancer. Eur Rev Med Pharmacol Sci. 2019 May;23(9):3885-91. doi: 10.26355/eurrev_201905_17816.
15. Scandura G, Wagner T, Beltran L, Alifrangis C, Shamash J, Berney DM. Pathological risk factors for metastatic disease at presentation in testicular seminomas with focus on the recent pT changes in AJCC TNM eighth edition. Hum Pathol. 2019 Dec;94:16-22. doi: 10.1016/j.humpath.2019.10.004.
16. Warde P, Specht L, Horwich A, Oliver T, Panzarella T, Gospodarowicz M, et al. Prognostic factors for relapse in stage I seminoma managed by surveillance: a pooled analysis. J Clin Oncol. 2002;20:4448-52.
17. Evans AJ. An overview of recent WHO classification and AJCC pTNM staging changes for testicular neoplasms and their impact on the handling and reporting of orchidectomy specimens. Diagnostic Histopathology. 2018;24(6):pp.205-14. doi: 10.1016/j.mpdhp.2018.05.002
18. Pfannschmidt J, Hoffmann H, Dienemann H. Thoracic metastasectomy for nonseminomatous germ cell tumors. J Thorac Oncol. 2010 Jun;5(6 Suppl 2):S182-6. doi: 10.1097/JTO.0b013e3181dcf908.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(12):1244-1246.
DOI: 10.28982/josam.755373

Case report
Olgu sunumu

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Papillary carcinoma of the thyroglossal duct cyst: Is thyroidectomy necessary?

Tiroglossal duktus kisti papiller karsinomu: Tiroidektomi gerekli mi?

Selçuk Kuzu [1], Abdulkadir Bucak [1], Çağlar Günebakan [1], Murat Özdemir [1], Bilal Atilla Bezen [2]

[1] Department of Otorhinolaryngology, Afyonkarahisar Health Sciences University Medical Faculty, Afyonkarahisar, Turkey
[2] Department of Anesthesiology and Reanimation, Afyonkarahisar Health Sciences University Medical Faculty, Afyonkarahisar, Turkey

ORCID ID of the author(s)

SK: 0000-0002-0511-9874
AB: 0000-0003-3031-3465
ÇG: 0000-0003-3281-9785
MÖ: 0000-0003-0371-9128
BAB: 0000-0002-3435-9690

Corresponding author / Sorumlu yazar:
Selçuk Kuzu
Address / Adres: Afyonkarahisar Sağlık Bilimleri Üniversitesi Tıp Fakültesi Kulak Burun Boğaz Anabilim Dalı Posta Kodu: 03300, Afyonkarahisar, Türkiye
E-mail: dr.selcukkuzu@hotmail.com

Informed Consent: The authors stated that the written consent was obtained from the patient presented with images in the study.
Hasta Onamı: Yazarlar çalışmada görüntüleri ile sunulan hastadan yazılı onam alındığını ifade etmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 12/30/2020
Yayın Tarihi: 30.12.2020

Abstract
Thyroglossal duct cyst is the most frequent midline congenital neck anomaly. Carcinoma of the thyroglossal duct cyst is a rare entity, and papillary carcinoma is the most frequent malignancy of this uncommon entity. There are a limited number of studies on this subject in the literature, and in some series, it is associated with papillary thyroid carcinoma. There is no consensus on prophylactic thyroidectomy after diagnosis. In this study, a case, operated for thyroglossal duct cyst and diagnosed with papillary carcinoma and our approach consisting of follow-up without thyroidectomy are presented in light of the current literature.
Keywords: Thyroglossal duct cyst, Papillary carcinoma, Thyroidectomy

Öz
Tiroglossal kanal kisti en sık görülen orta hat konjenital boyun anomalisidir. Tiroglossal kanal kisti karsinomu nadir görülen bir durumdur. Papiller karsinom, bu nadir görülen varlığın en sık görülen malignitesidir. Literatürde bu konuyla ilgili kısıtlı sayıda çalışma vardır ve bazı serilerde bu durum tiroid papiller karsinomu ile birliktelik göstermektedir. Tanıdan sonra profilaktik tiroidektomi konusunda fikir birliği yoktur. Bu çalışmada, papiller karsinom tanısı konan tiroglossal kanal kisti için opere edilen ve tiroidektomi olmadan takip yaklaşımımız güncel literatür bilgisi ışığında sunulmuştur.
Anahtar kelimeler: Tiroglossal kanal kisti, Papiller karsinom, Tiroidektomi

Introduction

Thyroglossal duct cyst (TDC) is a congenital anomaly developing from thyroglossal duct residues and is encountered in 7% of the young adult population [1]. Carcinoma in the TDC is extremely rare and is diagnosed in less than 1% of cases [2,3]. The most frequent primary malignancy of TDC is papillary carcinoma [4]. It is usually diagnosed by the pathological examination of the removed tissue. In this study, a case operated for TDC and diagnosed with papillary carcinoma and our approach of follow-up without thyroidectomy is presented in light of the current literature.

How to cite / Atıf için: Kuzu S, Bucak A, Günebakan Ç, Özdemir M, Bezen BA. Papillary carcinoma of the thyroglossal duct cyst: Is thyroidectomy necessary? J Surg Med. 2020;4(12):1244-1246.

Case presentation

A nineteen-year-old female patient was admitted to our clinic with the complaint of swelling in the midline of her neck for three years. There was a painless mass of 2x1 cm (Figure 1). No pathological lymph nodes were detected in the neck. Thyroid function and laboratory tests were normal. Ultrasonography (US) identified a 2 cm multilocular cystic structure. To plan a potential surgical procedure, a computed tomography (CT) imaging scan was requested, which revealed similar evidence (Figure 2). No other pathological lesions were seen in the neck and the thyroid gland. Histopathological examination of the fine-needle aspiration sample showed cells of benign cytology. The patient was offered surgery with a preliminary diagnosis of TDC. The surgical procedure was uneventful. Pathologically, microscopic examination revealed a cystic tumor tissue with a fibrous wall lined with neoplastic-looking epithelium. Normal thyroid tissue was found in the cyst wall. The papillary structures were lined with neoplastic cells with clear nuclei and intranuclear inclusion bodies, and nuclear clefts. The tumor was encapsulated and had developed within the thyroid tissue, which showed neoplastic properties. Histopathological result of the specimen was reported as papillary carcinoma originating from the cyst floor. The patient was followed up in three to six month-intervals with neck and thyroid US and recently completed the 30-month follow-up uneventfully. Informed consent was obtained from the patient before surgery.

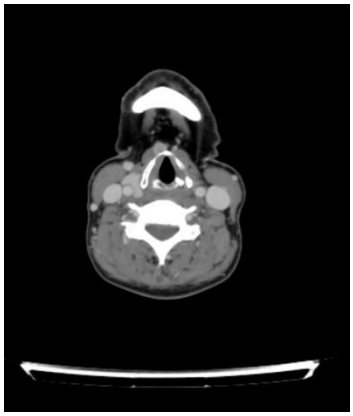


Figure 1: CT image of the patient

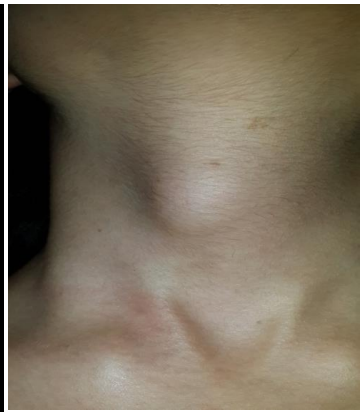


Figure 2: The mass in the middle of the neck

Discussion

The thyroid gland, the first endocrine gland that starts to develop in embryogenesis, completes its migration to the anatomical site of the tongue root at 7 weeks. The thyroglossal duct formed during this migration disappears by losing its channel feature over time. However, some parts of the duct may persist and TDCs develop between the hyoid and the thyroid gland because of continuing secretions of the cells that form the duct [5]. The TDC wall is covered with ciliated respiratory epithelium and / or squamous epithelium and contains more than 62% of regular thyroid tissue. Although the development of carcinoma in TDC is rare, 85% of malignant cases is constituted by papillary carcinoma, 7%, by mixed papillary follicular carcinoma, 5%, by squamous cell carcinoma, 2%, by adenocarcinoma and 1%, by anaplastic carcinoma [6]. Mechanism of thyroid malignancy in the TDC is still controversial. Some authors believe that it is caused by normal islets of thyroid in the remains of the thyroglossal duct. This theory is strengthened by the determination of ectopic thyroid clusters in histopathological results of 62% of the TDC. TDC papillary carcinoma can synchronously accompany the papillary carcinoma of the thyroid gland and can also be detected incidentally as an isolated focus [7].

For the diagnosis of primary papillary carcinoma of TDC, squamous or respiratory epithelium and normal thyroid follicles should be found on the cyst wall and the thyroid gland should be clinically normal [8,9]. The inner surface of the cystic lesion is surrounded by cuboidal and squamous epithelium, and the existence of normal thyroid tissue in the cyst wall show that papillary carcinoma originated primarily from the cyst floor. Since the benign cyst of the thyroglossal duct and carcinoma of the thyroglossal duct can hardly be distinguished, the diagnosis of carcinoma often remains after surgery [5].

However, preoperative fine-needle aspiration biopsy can diagnose papillary carcinoma. CT is important in the differential diagnosis, and solid cyst and calcification findings may be interpreted in favor of malignancy [5,8].

The treatment approach for papillary carcinoma of the TDC is also controversial. The debate on the origin of the tumor continues. The most common approach in benign cysts of the thyroglossal duct is the Sistrunk procedure. The discussion in the treatment of papillary carcinoma arising from the cyst focuses only on whether the Sistrunk procedure will be sufficient and what to do with the thyroid gland. In his study, Kristensen recommends Sistrunk procedure and thyroid suppression treatment in the postoperative period in cases where normal ectopic thyroid follicles are present in the cyst wall, there is no tumor invasion or spreading to the cervical lymph nodes beyond the cyst wall, and the thyroid gland is normal [3]. Defenders of the metastatic propagation theory recommend total thyroidectomy for long-term follow-up when there is no tumor invasion or signs of spread in the cyst wall. Doshi presented a large study (14 cases) in the literature [10]. According to the results of this study, only Sistrunk surgery is sufficient when a negative biopsy is obtained from a suspected lymph node or thyroid gland mass. As a result, primary papillary carcinoma developing on the background of TDC is very rare and its diagnosis is generally made postoperatively by histopathological examination. If the diagnosis of primary thyroglossal cyst carcinoma is trusted, Sistrunk operation is sufficient in treatment. In our case, we decided that only Sistrunk surgery would be sufficient due to the well-limited and smooth surface of the cyst, no tumor invasion outside the cyst wall, negative clinical and radiological lymphadenopathy in the neck, and findings that showed that the tumor originated primarily from the cyst floor. However, we concluded that a regular and close follow-up is essential for these cases.

References

1. Vincent S, Synhorst II J. Adenocarcinoma arising in a thyroglossal duct cyst. J. Oral Maxillofac Surg. 1989;47:633-5.
2. Allard R. The thyroglossal cyst. Head Neck Surg. 1982;5:134-46.
3. Fernandez J, Ordonez N, Shultz P, Samaan N, Hickey R. Thyroglossal duct carcinoma. Surgery. 1991;110:928-35.
4. Van Vuuren PA, Balm AJ, Gregor RT, Hilgers FJ, Loftus BM, Delprat CC, et al. Carcinoma arising in thyroglossal remnants. Clin Otolaryngol Allied Sci. 1994;19:509-15
5. Glastonbury CM, Davidson HC, Haller JR, Harnsberger HR. The CT and MR imaging features of carcinoma arising in thyroglossal duct remnants. AJNR Am J Neuroradiol. 2000;21:770-4.
6. Bdesha AS, Layer GT. Primary papillary carcinoma of a thyroglossal duct cyst: A report of a case and literature review. Br J Surg. 1992;79:1248-9.

7. Widström A, Magnusson P, Hallberg O, Hellqvist H, Riiber H. Adenocarcinoma originating in the thyroglossal duct. Ann Otol Rhinol Laryngol 1976;85:286-90.
8. Çayır D, Kulah B. Effects of preoperative fine needle aspiration biopsy on surgical strategy in patients with papillary thyroid carcinomas. J Surg Med. 2019;3(9):655-8.
9. Boswell WC, Zoller M, Williams JS, Lord SA, Check W. Thyroglossal duct carcinoma. Am Surg. 1994;60:650-5.
10. Doshi SV, Cruz RM, Hilsinger RL Jr. Thyroglossal duct carcinoma: a large case series. Ann Otol Rhinol Laryngol. 2001;110:734-8.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.