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Diagnostic value of angiopoietin-2 in the differentiation of malignant pleural effusions

Malign plevral efüzyonların farklılaşmasında anjiyopoietin-2'nin tanısal değeri

Dilaver Taş [1], Alaattin Köseler [2]

[1] Başkent University, Istanbul Hospital, Department of Pulmonology, Istanbul, Turkey
[2] Kayseri City Hospital, Department of Pulmonology, Kayseri, Turkey

ORCID ID of the author(s)
DT: 0000-0003-2785-2492
AK: 0000-0001-5835-0917

Abstract

Aim: Angiopoietins play an important role in the regulation of inflammation, angiogenesis and increased vascular permeability, which are the main steps in the pathogenesis of malignant pleural effusions (MPEs). The present study investigates the diagnostic value of pleural fluid angiopoietin-2 (Ang-2) levels in the differentiation of malignant pleural effusions from other effusions.

Methods: This research was designed as case-control study in a single-center. The study included a total of 66 patients (13 had transudate, 28 had benign exudate and 25 had malignant pleural effusions). The patient group involved 25 patients diagnosed with MPE, based on the criteria of lung cancer and other organ malignancies, and malignant pleural effusion. The control group consisted of 41 patients, 13 with transudate according to the Light criteria and 28 with exudate other than MPE (parapneumonic, tuberculous pleurisy, embolism, etc.).

Results: Pleural fluid Ang-2 levels were found to be higher in both the benign and malignant exudates than in the transudative pleural effusions (P=0.001). Pleural fluid Ang-2 levels were higher in the benign exudate group than in the malignant exudate group, although the difference was not statistically significant (P=0.874). A patient with an exudative pleural effusion and a pleural fluid Ang-2 level of higher than 13.84 was found to be 1.87 times more likely to have a malignant pleural effusion.

Conclusion: Despite the use of Ang-2 levels in the differentiation of transudative and exudative pleural effusions, the present study found that Ang-2 level cannot be used to differentiate between malignant and benign exudative pleural fluids.

Keywords: Angiopoietin-2, Malignant pleural effusion, Exudative pleural effusion

Öz

Amaç: Anjiopoietinler, malign plevral efüzyon (MPE) patogenezinde ana basamaklar olan inflamasyon, anjiyogenez ve vaskuler permeabilite artışının düzenlenmesinde önemli bir rol oynamaktadır. Çalışmamızda, malign plevral efüzyonların diğer efüzyonlardan ayrımında plevra sıvı anjiopoietin 2 (Ang-2) seviyelerinin tanısal değerini araştırdık.

Yöntemler: Bu çalışma, tek merkezli vaka kontrol çalışması olarak tasarlandı. Çalışmamıza, 13 transüda, 28 benign eksüda ve 25 malign plevral sıvıya sahip (malign eksüda) toplam 66 hasta alındı. Çalışmaya hasta grubu olarak olarak MPE tanısı konulmuş 25 hasta alındı. MPE tanılı hastalar; akciğer veya diğer organ maligniteleri mevcut olan ve plevral sıvının maligniteye bağlı olarak olarak geliştiği hastalardan oluştu. Kontrol grubu olarak, Light kriterlerine göre transüda olduğu saptanan 13 hasta ve MPE dışındaki eksüda vasıflı (parapnomonik, tüberküloz plörezi, emboli vb) 28 hasta olmak üzere toplam 41 hasta dahil edildi.

Bulgular: Plevral sıvı Ang-2 seviyeleri, hem benign eksüda hem de malign eksüda vasfındaki sıvılarda transüda vasfındaki plevral sıvılara göre belirgin olarak yüksek bulundu (P=0,001). Benign eksüda grubunda plevra Ang-2 seviyeleri malign eksüda grubuna göre yüksek olarak saptandı ancak bu durum istatistiksel olarak anlamlı değildi (P=0,874). Eksüda vasıflı plevral sıvılarda Ang-2 düzeyi 13,84 değerinin üzerinde saptanmış olan bir hastada malign plevral efüzyon olma riski, 13,84 değerinin altında olan bir hastaya göre 1,87 kat fazla bulundu.

Sonuç: Ang-2'nin, transüda ve eksüda özelliğindeki plevral sıvıların ayrımında kullanılabilir olmasına rağmen, eksüdatif plevral sıvılarda, malign ya da benign ayrımı yapmada yetersiz olduğu saptandı.

Anahtar kelimeler: Anjiopoietin 2, Malign plevral efüzyon, Eksüdatif plevral efüzyon

Corresponding author / Sorumlu yazar:
Dilaver Taş
Address / Adres: Başkent Üniversitesi, İstanbul Hastanesi, Göğüs hastalıkları Servisi, Kısıklı Cad., Oymacı Sokak No: 7, Altunizade, Üsküdar, İstanbul, Türkiye
e-Mail: dilavertas@gmail.com

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Introduction

Malignant pleural effusions (MPEs) are caused by a malignant disease affecting pleural fluid turnover, either directly or indirectly. Malignant pleural effusions constitute 28–61% of all pleural effusions, and lung cancer, breast cancer and lymphomas are held responsible for three-quarters of all malignant pleural effusions [1].

Although the exact pathogenesis of MPEs remains unknown, an increase in pleural vascular permeability, inflammation and angiogenesis are the main mechanisms in their development. Lymphatic obstructions caused by compression, and inflammatory and proangiogenic factors released from the tumor cells, are responsible for these mechanisms [1-3]. The most widely known of these factors is the vascular endothelial growth factor (VEGF), which is a growth hormone with proangiogenic and anti-inflammatory properties that plays a key role in increased vascular permeability [4,5].

Angiopoietins are glycoprotein molecules that possess regulatory effects on angiogenesis. To date, four angiopoietins have been identified, named Angiopoietin (Ang)) 1, 2, 3 and 4, all of which bind to the Tie-1 and Tie-2 receptors, which are members of the endothelium-specific tyrosine kinase family, and which exert their effects through the Tie-2 receptor [6]. By binding to the Tie-2 receptors, Ang-1 strengthens the connections between endothelial cells and with the surrounding supportive tissues (smooth muscle and extracellular matrix), thereby providing vessel stability and exerting negative effects on vascular permeability [7]. Ang-2 is competitive inhibitor of Ang-1 that destabilizes blood vessels by inhibiting the action of Ang-1 after binding to the Tie-2 receptor, and sensitizes the endothelium to inflammatory agents. Furthermore, it facilities VEGF-mediated angiogenesis and increases vascular permeability [8,9].

The role of Ang-2 in angiogenesis is mediated by VEGF-A, as in the presence of VEGF-A, Ang-2 destabilizes blood vessels and promotes vascular sprouting, but plays a suppressive role in accelerating vascular regression in the absence of VEGF-A [10]. The relationship between Ang-2 and VEGF-A is remarkable in tumor angiogenesis. The release of Ang-1 predominates in normal tissue, whereas the release of Ang-2 is more prominent in tumor tissue. This is considered to be a major step in tumor angiogenesis [11].

The Ang/Tie-2 pathway has been demonstrated to play an important role in the regulation of tumor-related angiogenesis, increased vascular permeability and inflammation, all of which are the main steps in the pathogenesis of MPE [11-13].

The present study investigates the diagnostic value of pleural fluid angiopoietin-2 levels in the differentiation of malignant pleural effusions from other effusions.

Materials and methods

This single-center case-control study was granted approval by the ethics committee. Between March 2012 and June 2013, Ang-2 levels were measured in patients with pleural effusion who were admitted to our chest disease clinic. The patient group involved 25 patients diagnosed with MPE, based on the criteria of lung cancer and other organ malignancies, and malignant pleural effusion. The control group consisted of 41 patients – 13 with transudate according to the Light criteria and 28 with exudate other than MPE (parapneumonic, tuberculous pleurisy, embolism, etc.). A diagnosis of pleural effusion was established by a physical examination, PA chest x-ray, computed tomography and thoracic ultrasound. Demographic characteristics, radiological findings, complete blood count, routine biochemistry, erythrocyte sedimentation rate (ESR) and C-reactive protein levels were recorded for all patients. A 50-ml pleural fluid was withdrawn by way of a pleural puncture. The appearance of the fluid, white blood cell count, glucose, total protein, albumin, and LDH and ADA levels were determined. The differentiation between transudate and exudate was based on Light's criteria. Patients with transudative pleural effusions underwent no further diagnostic procedure, while an inoculation into the Löwenstein-Jensen medium and nonselective medium was performed for exudative effusions. A cytologic examination was performed for all pleural effusions. Patients with an exudative effusion in whom the cytologic examination was non-diagnostic underwent a closed needle biopsy or video-assisted thoracoscopy (VATS).

Ang-2 measurement

The pleural fluid samples were centrifuged at 1,200 rpm for 7 minutes and stored at -80 degrees. The Human Ang-2 Enzyme-linked immunosorbent assay (ELISA) Kit (RayBiotech, New York, US) was used for the measurement of Ang-2 levels, with the results expressed as ng/ml.

Statistical analysis

SPSS for Windows version 14.0.0 (SPSS Inc., Chicago, Illinois, US) software was used for all statistical analyses. Along with descriptive statistics (mean, standard deviation, frequency, percent distribution) in the analysis of data, a one-way analysis of variance (ANOVA) was used to compare data with normal distribution between the groups, a Tukey's multiple comparison test was used in the comparison of subgroups, an independent samples t-test was used for the paired comparison of the groups, a Chi-square test was used for the comparison of qualitative data, and Pearson's correlation coefficient was used to evaluate the relationship between variables. The area under the curve (AUC) in a receiver operating characteristic (ROC) curve analysis was calculated to determine the sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio (LR+) and cut-off value of ang-2 in the differentiation of malignant pleural effusions. The significance of the results was evaluated at an alpha level of 0.05.

Results

Demographic characteristics

The study included 25 patients with MPE and 41 control patients, 13 of whom had transudative and 28 of whom had exudative pleural effusion. Of the patients with MPE, 64% were male (n=16) and 36% were female (n=9). Of the patients in the transudative effusion group, 84.6% were male (n=11) and 15.4% were female (n=2), whereas 92.9% of the patients in the benign exudative effusion group were male (n=26) and 7.1% were female (n=2). The mean age was 64.96 (16.25) years in the patient group, 77.92 (11.04) years in the transudative effusion

group and 41.61 (24.82) years in the benign exudative effusion group (Table 1).

There was a statistically significant difference in terms of age between the transudate, benign exudate and malignant exudate groups (P<0.001). The mean age was significantly lower in the benign exudate group than in the transudate and malignant exudate groups (P=0.001, P=0.002, respectively), whereas the mean age did not differ significantly between the transudate and malignant exudate groups (P=0.06). The number of female patients was significantly higher in the malignant exudate group than in the transudate and benign exudate groups (P=0.03).

Patient characteristics

The distribution of patients with MPE was as follows: 12 patients (48%) had lung cancer, three (12%) had breast, colon or gastric cancer, two (8%) had multiple myeloma, two had chronic lymphocytic leukemia, one (4%) patient had non-Hodgkin lymphoma and one had ovarian cancer. Of the patients with a benign exudate, 11 (39.3%) had parapneumonic effusion, 13 (46.4%) had tuberculous pleurisy, three (10.7%) had an undiagnosed effusion and one (3.6%) had an embolism. The pleural biopsy was inconclusive in three patients in whom a diagnosis could not be established. All transudative effusions were secondary to congestive heart failure.

Ang-2 levels in the pleural fluid

Pleural fluid Ang-2 levels were found to be higher in both the benign and malignant exudates than in the transudative pleural effusions (P<0.001) (Table 2, Figure 1). The mean pleural fluid Ang-2 levels was higher in the benign exudate group [17.84 (2.99) ng/ml] than in the malignant exudate group [17.37 (3.88) ng/ml], although the difference was not statistically significant (P=0.87) (Table 3). The Ang-2 level was useful in differentiating between transudative and exudative pleural fluids, but was of no value in the differentiation of malignant and benign effusions.

Across the different etiologies, the highest pleural fluid Ang-2 levels were observed in the tuberculous pleurisy, pulmonary embolism, idiopathic benign exudate, malignant pleural effusion, parapneumonic effusion and congestive heart failure cases, in respective order (Figure 2).

Relationship between pleural fluid Ang-2 levels and other laboratory parameters

In the analysis of correlation, a positive correlation was identified between Ang-2 level and adenosine deaminase (ADA), and protein and albumin values (r=0.377, r=0.443, r=0.509, P=0.003, P=0.001 and P=0.001, respectively). Likewise, a significant positive correlation was identified between Ang-2 levels and erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, and a negative correlation was found between Ang-2 and glucose levels (r=0.282, r=0.304, r=-0.298, P=0.03, P=0.02 and P=0.02, respectively) (Table 4).

Diagnostic value of Ang-2 in the differentiation of malignant exudate and benign exudate, exudate and transudate

The area under the curve in the ROC curve analysis for Ang-2 levels in the differentiation of exudative (malignant and benign exudates) and transudative effusions was 0.864 (0.758-0.936), which is above the desired threshold of 0.700. A cut-off value of >16.70 for Ang-2 yielded a sensitivity of 62.26%, a specificity of 92.31%, a positive predictive value of 97.1%, a negative predictive value of 37.5% and a likelihood ratio (LR) of 8.09 (Tables 5 and 6, and Figure 3).

The area under the curve in ROC curve analysis for Ang-2 in the differentiation of malignant and benign exudates was 0.515 (0.374-0.655), which is below the desired threshold of 0.700. A cut-off value of >13.84 for Ang-2 yielded a sensitivity of 20%, a specificity of 89.29%, a positive predictive value of 62.5%, a negative predictive value of 55.6% and a likelihood ratio (LR) of 1.87 (Tables 7 and 8, and Figure 4).

Table 1: Demographical characteristics of patients

		Transudate		Benign Exudate		Malignant Exudate		*P*-value [1]
Angiopoietin-2 ng/ml		77.92 (11.04)		41.61 (24.82)		64.96 (16.25)		<0.001
Gender	Male	11	84.6%	26	92.9%	16	64.0%	0.03
	Female	2	15.4%	2	7.1%	9	36.0%	

[1] One-Way analysis of variance, Chi-square test

Table 2: Angiopoietin-2 values in the transudate and exudate groups

	Transudate		Exudate		*P*-value [1]
	Mean.	SD	Mean.	SD	
Angiopoietin-2	11.86	3.49	17.62	3.41	<0.001

[1] Independent samples t-test

Table 3: Angiopoietin-2 values in the patient groups

	Transudate	Benign Exudate	Malignant Exudate	*P*-value
Angiopoietin-2 (ng/ml)	11.86 (3.49)	17.84 (2.99)	17.37 (3.88)	<0.001 [1]
	11.86 (3.49)	17.84 (2.99)	-	<0.001 [2]
	11.86 (3.49)	-	17.37 (3.88)	<0.001 [2]
	-	17.84 (2.99)	17.37 (3.88)	0.87 [2]

[1] One-Way analysis of variance, [2] Tukey's multiple comparison test

Table 4: Results of a correlation analysis

		Angiopoietin-2	ADA
Angiopoietin-2	r	1	0.377
	p		0.003
ADA	r	0.377	1
	p	0.003	
WBC	r	0.082	-0.079
	p	0.517	0.554
Glucose	r	-0.298	-0.482
	p	0.019	0.0001
Protein	r	0.443	0.637
	p	0.0001	0.0001
Albumin	r	0.509	0.556
	p	0.0001	0.0001
LDH	r	0.195	0.229
	p	0.129	0.083
ESR	r	0.282	0.198
	p	0.031	0.156
CRP	r	0.304	0.067
	p	0.021	0.641

Pearson's Correlation Coefficient, ADA: adenosine deaminase, LDH: lactate dehydrogenase, CRP: C-reactive protein

Table 5: The area under the curve (AUC) in the receiver operating characteristic (ROC) curve in the differentiation of the exudate (Malignant + Benign) and transudate groups

	AUC in the ROC curve
Angiopoietin-2	0.864 (0.758-0.936)

Table 6: Sensitivity, specificity and cut-off point for Angiopoietin-2 in the differentiation of exudate (Malignant + Benign) and transudate groups

Cut-off point	Sensitivity	Specificity	PPV	NPV	LR (+)
>16.70 (ng/mL)	62.26	92.31	97.1	37.5	8.09

PPV: positive predictive value, NPV: negative predictive value, LR (+): likelihood ratio

Table 7: The area under the curve (AUC) in the receiver operating characteristic (ROC) curve in the differentiation of the malignant exudate and benign exudate groups

	AUC in the ROC curve
Angiopoietin-2	0.515 (0.374-0.655)

Table 8: Sensitivity, specificity and cut-off point for Ang2 in the differentiation of the malignant exudate and benign exudate groups

Cut-off point	Sensitivity	Specificity	PPV	NPV	LR (+)
>13.84	20.00	89.29	62.5	55.6	1.87

PPV: positive predictive value, NPV: negative predictive value, LR (+): likelihood ratio

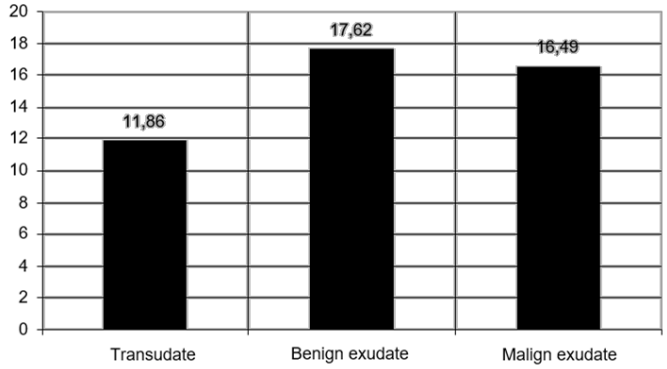

Figure 1: Distribution of Ang-2 values across the patient groups

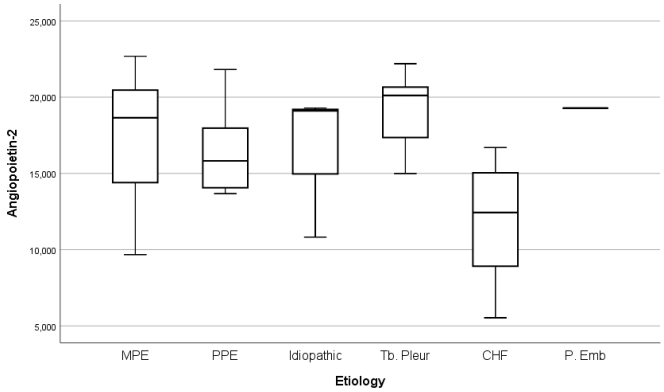

Figure 2: The highest pleural fluid Ang-2 levels according to the etiologies, MPE: Malignant pleural effusion, PPE: Parapneumonic effusion, Tb.Pleur: Tuberculosis pleuresy, CHF: Congestive heart failure, P. Emb: Pulmonary embolism

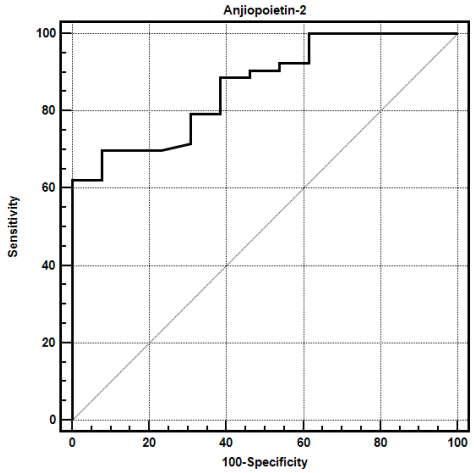

Figure 3: The ROC curve for the differentiation of the exudate (Malignant+Benign) and transudate groups

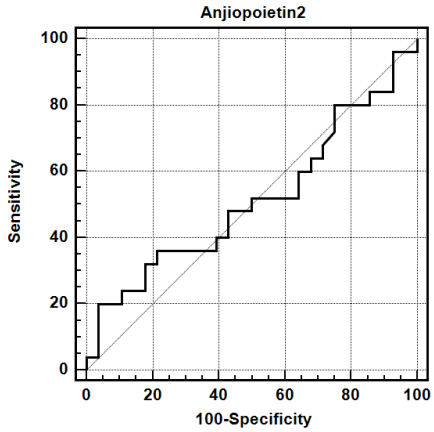

Figure 4: The ROC curve for the differentiation of the malignant exudate and benign exudate groups

Discussion

Ang-2 is known to affect the progression, invasion, metastatic characteristics and prognosis of a variety of tumors, and for this reason, recent studies have evaluated Ang-2 levels in such bodily fluids as serum, bronchial lavage fluid and pleural fluid, as well as in the tumor tissue, in order to identify any relationship between Ang-2 levels and tumor characteristics [14,15].

The present study investigates the diagnostic value of pleural fluid Ang-2 levels in the differentiation of malignant and benign pleural effusions. The results suggest that pleural fluid Ang-2 level was of no diagnostic value in the differentiation of malignant pleural effusions and benign pleural effusions, although it does have value in the differentiation of transudate and exudate.

Although it has been demonstrated that Ang-2 plays an important role in the regulation of tumor-related angiogenesis, increased vascular permeability and inflammation, all of which are important steps in the pathogenesis of MPE, no studies have found a significant difference in the pleural fluid Ang-2 levels of malignant pleural effusions and benign exudative effusions. Studies have even found higher pleural fluid Ang-2 levels in tuberculous pleural effusions and parapneumonic effusions than in malignant effusions [16-18].

Ioannis et al. identified significantly higher VEGF and Ang-2 levels in exudative pleural effusions than in transudative effusions [16]. The authors noted lower Ang-2 levels in malignant pleural effusions than in parapneumonic and tuberculous pleural effusions, and the highest Ang-2 levels were recorded in the pleural tuberculosis group. Similarly, Elhefny et al. [18] found significantly higher pleural fluid Ang-2 levels in exudative effusions than in transudative effusions, suggesting that Ang-2 levels are higher in benign exudative effusions than in malignant pleural effusions, with the highest Ang-2 levels being observed in the pleural tuberculosis group. Their study also found higher interleukin-8 (IL-8) levels, a marker of inflammation, in malignant effusions, and reported a positive correlation between pleural fluid Ang-2 and ADA levels in tuberculous pleural effusions. Similar to these two studies, the present study reports the highest pleural fluid Ang-2 levels in the pleural tuberculosis group and a significantly positive correlation was identified between pleural fluid Ang-2 levels and pleural fluid ADA levels. The present study also found a positive correlation between pleural fluid Ang-2 levels and ESR and CRP, which are markers of inflammation. The presence of a positive correlation between pleural fluid Ang-2 levels and such inflammatory markers as IL-8, ESR and CRP, and findings of higher Ang-2 levels in parapneumonic and tuberculous pleural effusions, suggest that Ang-2 is increased in pleural effusions in which inflammation is prominent.

Although studies have yet to detect any significantly increased Ang-2 levels in malignant pleural effusions, a study of mice showed a remarkable decrease in the amount of pleural fluid and pleural tumor foci with the inhibition of Ang/Tie-2 [19]. Fang et al. [20] further demonstrated that the combined inhibition of Ang-2 and VEGF showed synergistic effects in reducing the production of malignant pleural effusions and tumor

growth, and claimed that this combination could be used in the treatment of MPE in the future.

Other studies into pleural fluid Ang-2 levels showed higher Ang-2 levels in exudative effusions than in transudative effusions. In a similar study, and consistent with a previous study, Tomimoto et al. [17] found higher VEGF and Ang-2 levels in exudative pleural effusions than in transudative effusions. In a study by Sanad et al. evaluating pleural fluid Ang-1 and Ang-2 levels in 40 patients with transudative pleural effusion and 40 patients with exudative pleural effusion, the Ang-2 levels were reported to be significantly higher in the exudative pleural effusion group than in the transudative pleural effusion group [21].

Elhefny et al. [18] found significantly higher Ang-2 levels in benign exudative effusions than malignant exudative effusions. In their study, the mean Ang-2 level was 15.38 (6.33) in the benign exudative effusion group and 10.73 (4.22) in the malignant exudative effusion group. The present study, however, found no statistically significant difference in the pleural fluid Ang-2 levels between the benign and malignant exudative effusion groups. In the study of Elhefny et al. [18], the area under the curve in a ROC curve analysis for Ang-2 levels in the differentiation of malignant and benign exudative effusions was found to be 0.704, which is above the desired threshold of 0.700. A cut-off value of 15.67 ng/mL yielded a sensitivity of 91.3% and a specificity of 56.2%. In the present study, the area under the curve in the ROC curve analysis in the differentiation of malignant and benign exudative effusions was 0.515, which is below the desired threshold of 0.700. The cut-off value was found to be 13.84 ng/ml. Sensitivity was considerably low (62.26%), and specificity was 92.31%. In the differentiation between malignant exudative pleural effusions and benign exudative pleural effusions, the present study found that a patient with a pleural fluid Ang-2 level greater than 13.84 was found to be 1.87 times more likely to have a malignant pleural effusion than a patient with a pleural fluid Ang-2 level below 13.84. The study concludes that Ang-2 is of low value in the differentiation of malignant and benign exudates due to the likelihood of being less than 2 and an AUC of 0.515 in the ROC curve analysis.

Conclusion

Similar to the results reported in literature, the present study shows that pleural fluid Ang-2 level is valuable for differentiating between transudate and exudate, but is of no value in the differentiation of malignant and benign pleural effusions. The present study also found that Ang-2 levels are higher in pleural tuberculosis and parapneumonic effusions where inflammation is more prominent, and that Ang-2 levels positively correlate with CRP and ESR, which are the markers of inflammation. Despite the small number of study patients, the similarity of the results of the present study with those reported in literature increases their value.

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Comparative study of totally extra-peritoneal hernia repair versus open Lichtenstein hernioplasty for the treatment of primary inguinal hernia

Primer kasık fıtığı tamirinde total ekstraperitoneal yöntemle açık Lichtenstein yönteminin karşılaştırmalı çalışması

Yasin Kara [1]

[1] **Department of general surgery, Health Sciences University, Kanuni Sultan Süleyman Education and Research Hospital, Istanbul, Turkey**

ORCID ID of the author(s)
YK: 0000-0002-9723-1774

Abstract

Aim: There is still controversy over which inguinal hernia repair technique has the best postoperative results. Totally extra-peritoneal hernia (TEP) repair was compared with conventional open Lichtenstein (OL) herniorrhaphy in terms of postoperative pain, return time to work, recurrence rates and complications.

Methods: In this predesigned comparative study, total number of 97 patients who underwent TEP or Lichtenstein herniorrhaphy in Health Sciences University, Kanuni Sultan Süleyman Education and Research Hospital, in between January 2018 and September 2018 were evaluated and compared. Patients were divided in two groups as TEP group (n:50) and OL group (n:47). Demographic properties (age, sex), operation time, postoperative pain, hospital stay, return to work, recurrence rates and/or complications were analyzed and compared with each other.

Results: The mean operation time was 55.7 (19.90) minutes in TEP group, while it was 39.44 (10.69) minutes in OL group (P=0.001). Postoperative pain with VAS in TEP group on the first postoperative day was 3.2 (1.12) (range: 2-6), while it was 5.6 (1.02) (range: 2-8) in the OL group (P=0.001). The average time return to their routine work ranged from 6-18 days (mean 9.2 (2.03) in TEP group while it was 7-26 days (mean 14.8 (3.1)) in OL group (P=0.001). Postoperative complications as urinary retention, seroma, hematoma formation and paresthesia sensation were higher in OL group.

Conclusion: In our study, TEP repair was superior to OL repair in terms of postoperative pain, early return to work, chronic pain, postoperative urinary retention, seroma formation and postoperative paresthesia sensation. More studies with large case series and longer follow-up periods are still needed to judge the role of laparoscopy in repairing inguinal hernias.

Keywords: TEP, Lichtenstein, Recurrence rate, Pain, Postoperative complications

Öz

Amaç: Kasık fıtığı onarımda hangi tekniğin ameliyat sonrası daha iyi sonuçlar verdiği konusunda hala tartışmalar devam etmektedir. Laparoskopik total ekstraperitoneal herni (TEP) onarımı ameliyat süresi, postoperatif ağrı, işe dönüş zamanı, nüks oranları ve komplikasyonlar açısından konvansiyonel açık Lichtenstein (AL) yöntemle ile karşılaştırıldı.

Yöntemler: Bu önceden tasarlanmış karşılaştırmalı çalışmasında, Sağlık Bilimleri Üniversitesi, Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi'nde, 2018 Ocak-2018 Eylül tarihleri arasında TEP veya Lichtenstein herniorafisi yapılan toplam 97 hasta değerlendirildi ve birbirleriyle karşılaştırıldı. Hastalar TEP grubu (n: 50) Açık Lichtenstein (AL) (n: 47) olmak üzere iki gruba ayrıldı. Demografik özellikleri (yaş, cinsiyet), ameliyat süresi, ameliyat sonrası ağrı, hastanede kalış, işe dönüş süreleri ve komplikasyonlar analiz edildi.

Bulgular: Çalışmamızda TEP grubunda ortalama operasyon süresi 55.7 (19.90) dakika iken, OL grubunda 39.44 (10.69) dakika idi (P=0.001). Ameliyat sonrası ilk gün visual analog skoru (VAS) TEP grubunda 3.2 (1.12) (dağılım: 2-6) iken OL grubunda 5.6 (1.02) (dağılım: 2-8) (P=0.04) idi. TEP grubundaki işe dönme süresi 6-18 gün (ortalama 9.2 (2.03) iken OL grubunda 7-26 gün (ortalama 14.8 (3.1)) (P=0.001) idi. OL grubunda, idrar retansiyonu, seroma, hematom oluşumu, kronik ağrı ve parestezi hissi gibi postoperatif komplikasyonlar daha yüksek bulundu.

Sonuç: Çalışmamızda TEP onarımı postoperatif ağrı, erken işe dönüş, kronik ağrı, postoperatif idrar retansiyonu, seroma oluşumu ve postoperatif parestezi hissi açısından OL tamirinden daha üstündü. Laparoskopinin inguinal herni tamirindeki etkinliğini değerlendirmede daha uzun takip süreli ve geniş vaka serili çalışmalara ihtiyaç bulunmaktadır.

Anahtar kelimeler: TEP, Lichtenstein, Nüks oranı, Ağrı, Postoperatif komplikasyonlar

Corresponding author / Sorumlu yazar:
Yasin Kara
Address / Adres: Atakent Mahallesi, Halkalı, Altınşehir, İstanbul Cd. No:1, 34303, Küçükçekmece, İstanbul, Türkiye
e-Mail: yasinkara32@windowslive.com

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Introduction

While the inguinal hernia (IH) remains to be a serious health problem affecting community, IH repair is one of the most common surgeries in general surgery practice, performed on more than 20 million people annually throughout the world [1]. Although advanced techniques have been adopted in IH repair parallel to those in developing medical technologies, currently no consensus has been reached on the best method among all existing methods [1]. A Lichtenstein type tension free operation has now become the method of choice in the majority of countries around the world [1]. But the trends have changed in the last few decades with the introduction of laparoscopic inguinal herniorrhaphy (LIHR) with same or better outcomes. Nowadays in many hernia centers, LIHR is mainly applied by two operative techniques as totally extra-peritoneal (TEP) and transabdominal preperitoneal (TAPP) [2].

Opponents of LIHR proposed the possibility of a laparoscopic accident resulting in fatal complication such as bowel perforations or fatal vascular injuries, potential adhesive complications at sites where the peritoneum has been breached or prosthetic material has been placed, and the need for general anesthetics [2].

Nowadays controversy persists regarding the most effective IH repair. The aim of this study was to compare the open Lichtenstein (OL) and the TEP repairs in terms of operation time, hospital stay, postoperative pain, early and late complications and recurrences.

Materials and methods

In this predesigned comparative study, IH patients who were treated with TEP or OL herniorrhaphy techniques from January 2018 to September 2018 in our single tertiary center were evaluated and compared with each other in terms of operation time, postoperative and chronic pain, return time to work, early and late complications and/or recurrences.

A hundred and eighty five IH repairs were performed during the study period, 64 (34%) of which had TEP repair and 127 (66%) had OL. Patients operated with recurrent IH, conversion from TEP to OL repair and operation in emergency settings together with ones with incomplete data were excluded from the study. Among these cases, fifty TEP repairs were matched with forty seven OL repairs. Inclusion criteria were age over 18 years, primary IH, elective operation, with availability of data on 6 months follow-up.

Patients were divided into two groups as TEP group (n=50) and OL group (n=47). Data were obtained from patient files, polyclinic visits, phone calls and electronic hospital records which were included in the hospital archive. Ethics committee approval for the study was received from the local ethical committee. Study was carried out according to the principles of the Helsinki Declaration. All the patients were routinely informed and provided their written consent.

Patients were seen and parameters were recorded at 1th, 2nd, 4th, and 6th weeks, and 3th, and 6th months of operation. Postoperative pain was graded by using visual analogue score (VAS score). Patients were given VAS forms and asked to grade the severity of pain on 0-10 on the first, second day and first week of surgery. Operation time was noted as the time elapsed between first incision and last suturing and taken from anesthesia follow charts. Apart from VAS score, pain was graded as follows: level 1= no pain, 2= mild pain, 3= moderate pain, 4= severe pain, and 5=intolerable pain. Chronic pain was defined as level 4-5 pain lasting 3 months after the operation. Intraoperative complications (e.g., epigastric or testicular vascular bleeding, peritoneal, testicular, or nerve damages) and postoperative complications (e.g., hematoma, seroma, urinary retention, paresthesia, wound infection and recurrence) were recorded. An independent surgeon in the hospital saw the patients with any complaints, such as pain or a lump in the groin. Seroma or hematoma was defined as a collection of blood or serous fluid of more than 5 ml detected via ultrasonography in the subcutaneous tissues, inguinal canal, preperitoneal space or scrotum. Wound site infection was defined as presence of redness and pain with or without drainage from the incisions. The recurrence was defined as a bulge or weakness in the inguinal area exacerbated by a valsalva maneuver and necessitating further operation. Hospital stay time was the number of days in the hospital after the surgery.

TEP technique

Operations were performed with general anesthesia. Patients were in supine with slight trendelenburg position and both arms were tacked. Surgeon stands at the opposite side of hernia. Once infraumbilical is done, external fascia is opened and rectus muscle retracted laterally and a handmade balloon was used to open preperitoneal working space. Pressure was maintained at 10–12 mmHg by continuous insufflation of carbon dioxide. Midline two 5 mm working trocars were entered under direct vision of laparoscope. Symphysis pubis and Cooper ligament were made apparent by clearance of preperitoneal adhesions. Bogros space was opened and any cord lipoma was excised. Then direct, indirect, femoral and obturator spaces are examined to see any herniations. Triangles of death and pain are seen and no tacker is used at this places. Indirect hernias were retracted from inguinal channel to preperitoneal space and five cm below deep ring, direct herniation in Hasselbach's triangle peritoneum pulled back and transversalis fascia was tacked at the iliopubic tract to eliminate death space. Then potential hernia spaces were covered with 15x10 cm polypropylene mesh (Prolene; Ethicon, Inc., Somerville, NJ, USA) which anchored with 5 mm titanium spiral tacks (Tyco Healthcare, Norwalki CT, USA) to symphysis pubis, Cooper ligament routinely and occasionally further tacks were placed anteriorly on the under surface of rectus abdominus and the fascia transversalis laterally. Under direct camera vision, following a final inspection, desufflation was performed and trocars were removed.

Open Lichtenstein Technique

All Operations were performed under either spinal or general anesthesia. After the division of cremasters, the hernia sac was prepared to permit digital examination for the presence of a pantaloon hernia. The sac was then high ligated. A polypropylene mesh measuring 6x11 cm (Ethicon Inc., Somerville, NJ, USA) was placed with a interrupted 2/0 polypropylene suture overlapping the pubic tubercle by 2 cm. Laterally, a slit in the propylene mesh permitted passage of the spermatic cord and the ilioinguinal nerve.

Statistical analysis

SPSS 20.0 program was used for statistical evaluation. Absolute frequencies or mean (standard deviation) were used in data presentation. Student's t-test was used to determine whether a statistically significant difference exists between the groups regarding age and surgery duration. Fisher Exact test was used to examine the relationship between the categorical variables. ANOVA test was used for comparison of length of hospital stay between the TEP and OL groups. $P<0.05$ was considered to be statistically significant.

Results

Median age was 48.8 (range: 25-76) in TEP group and 52 (range: 19-81) in OL group ($P=0.117$). Of 50 cases, 49 were male and one was female with a ratio of 49/1 in TEP group and 43 were male and 4 were female with a M/F ratio of 11/1 in OL group ($P=0.022$). In TEP group, hernia types were Nyhus type 2 (44.2%), Nyhus type 3a (36.5%) and Nyhus type 3b (19.2%), on the other hand in OL group Nyhus type 2 (43.1%), Nyhus type 3a (43.1%) and Nyhus type 3b (13.8%). A total of 62 hernia defects were repaired in the TEP group and 58 hernias in the OL group.

The duration of surgery for the OL group was 39.44 (10.69) minutes (range: 25-70), a significantly lower value than for TEP group in which mean operation time was 55.7 (10.90) minutes (range: 35-110). Difference was statistically significant as $P=0.001$ (Table 1).

Complications in TEP and OL groups consist of hematoma (n:1, 2% vs n:3, 6.38%) ($P=0.01$), seroma (n:1, 2% vs n:12, 25%) ($P=0.001$), urinary retention (n:3, 6% vs n:10, 21%) ($P=0.001$), wound infection (n: 2, 4% vs n:3, 6.38%) ($P= 0.4$), paresthesia (n:9, %18 vs n:17, 36%) ($P=0.001$) in the distribution of the lateral femoral cutaneous nerve, suggestive of meralgia parasthetica, but did not require any specific treatment, recurrence (n: 2, 4% vs n:3, 6.38%) ($P=0.40$). Chronic inguinal pain was reported by 2 patients (4%) in TEP group. One patient required referral to the pain team and in other it is well controlled with simple analgesia. In OL group, 4 patients (8.5%) had suffered from chronic pain which had either resolved without treatment or were well tolerated with simple analgesia ($P=0.04$) (Table 2, 3).

Patients were followed for average 11 months (range: 6-13) in TEP group and average 10 months (range: 7-13) in OL group ($P=0.26$). Mean hospital stay did not differ significantly between two groups although it is slightly lower in TEP group ($P=0.112$). Hospital stay time was 22.6 (4.7) hours in TEP group and 25 (6.4) hours in OL group (Table 1).

Postoperative first day VAS was 3.2 (1.12) in TEP group and 5.6 (1.02) in OL group ($P=0.001$). At the second day, VAS score was 2.5 (0.75) in TEP group and 4.2 (0.85) in OL group ($P=0.03$) (Table 4). Bilateral repair patients reported more pain and reduced physical function versus unilateral repairs in both groups.

The average time in TEP group to return to their routine work ranged from 6-18 days (mean 9.2 (2.03)) while in OL group it was 7-26 days (mean 14.8 (3.1)) ($P=0.001$) (Table 5).

Table 1: Demographics, mean hospital stay, mean duration of operations and follow-up time in two groups

Characteristic	TEP	OL	*P*-value
Gender			
Male n (%)	49 (98)	43 (91.5)	** 0.02
Female n (%)	1 (2)	4 (8.5)	
Mean age of patients, years (range)	48.8 (25-76)	52 (19-81)	* 0.12
Mean hospital stay, mean (SD)	22.6 (4.7)	25 (6.4)	* 0.11
(range)	(15-27)	(17-36)	
Operation time (minutes), mean (SD)	55.68 (10.90)	39.44 (10.69)	* 0.001
(range)	(35-110)	(25-70)	
Mean follow-up time, months (range)	11 (6- 13)	10 (7-13)	* 0.26

SD: Standard deviation, * Student's t-test, ** Fisher's Exact test, TEP: Laparoscopic total extra-peritoneal herniorrhaphy, OL: Open Lichtenstein repair

Table 2: Early and late complications in TEP group

	24th hour n (%)	1st week n (%)	1st month n (%)	3rd month n (%)	6th month n (%)	*P*-value *
Chronic pain	-	-	-	2 (4)	1 (2)	0.04
Paresthesia	9 (18)	7 (14)	3 (6%)	1 (2)	1 (2)	0.001
Seroma	0	1 (2)	0	0	0	0.001
Hematoma	0	1 (2)	0	0	0	0.01
Urinary retention	3 (6)	0	0	0	0	0.001
Wound infection	0	2 (4)	0	0	0	0.40
Recurrence	0	1 (2)	0	1 (2)	0	0.40

TEP: Laparoscopic total extra-peritoneal herniorrhaphy, * Fisher's Exact test

Table 3: Early and late complications in OL group

	24th hour n (%)	1st week n (%)	1st month n (%)	3rd month n (%)	6th month n (%)	*P*-value *
Chronic pain	-	-	-	4 (8.5)	3 (6.38)	0.04
Paresthesia	17 (36)	11 (23.4)	4 (8.5)	2 (4)	1 (2)	0.001
Seroma	0	12 (25)	0	0	0	0.001
Hematoma	0	3 (6.38)	0	0	0	0.01
Urinary retention	10 (21)	0	0	0	0	0.001
Wound infection	0	3 (6.38)	0	0	0	0.4
Recurrence	0	0	0	3 (6.38)	0	0.4

OL: Open Lichtenstein repair, * Fisher's Exact test

Table 4: Comparison of VAS scores at postoperative 1st, 2nd day and 1st week

VAS scores	Technique	n	Mean	Min	Max	SD	*P*-value *
Postoperative 1st day	TEP	50	3.2	2	6	1.12	0.001
	OL	47	5.6	2	8	1.02	
Postoperative 2nd day	TEP	50	2.5	1	4	O.75	0.03
	OL	47	4.2	2	6	0.85	
Postoperative 1st week	TEP	50	0.8	0	3	0.3	0.01
	OL	47	2.5	1	5	0.8	

Min: Minimum, Max: Maximum, SD: Standard deviation, *Student's t-test, VAS: Visual analogue scale, TEP: Laparoscopic totally extra-peritoneal herniorrhaphy, OL: Open Lichtenstein

Table 5: Return to normal work in days

Group	≤1 week	≤ 2 weeks	≤3 weeks	≤4 weeks	Mean (SD) days
TEP (n=50)	15 (30%)	28 (56%)	7 (14%)	0	9.2 (2.03)
OL (n=47)	3 (6.3%)	12 (25.5%)	26 (55.3%)	6 (12.6%)	14.8 (3.1)
P-value *	0.001	0.001	0.001		0.001

*Student's t-test, TEP: Laparoscopic totally extra-peritoneal, OL: Open Lichtenstein

Discussion

The usage of prosthetic mesh materials was responsible from the abrupt decrease in the rate of recurrence after herniorrhaphy from 35-40% to less than 2%. OL technique is considered the "gold standard" for IH repair and is gained wide acceptance all over the world [3]. Usage of laparoscopy in hernia surgery has been increased tremendously with the introduction of new operating techniques during the past three decades. Nowadays, two laparoscopic operative techniques as TEP and TAPP have been used widely in many centers. Prolonged hospital stay and post-operative pain are of more concern for patients immediately after surgery. In many studies, surgeons performing laparoscopic hernioplasty pointed out that there is decreased post-operative pain and short postoperative hospital stay as compared to OL repair [4]. In our single tertiary center, laparoscopic herniorrhaphy (TEP, TAPP) have been applied for six years. Open Lichtenstein repair constitutes the 70% of all IH operations in our institute.

Myers et al. [5] in their prospective study comparing open Lichtenstein and Laparoscopic TEP repairs reported that TEP group had significantly increased operation time, higher recurrence rate but lower incidence of chronic pain and wound infection. In our study group, in TEP group, two (4%) of 50

cases developed recurrence one of which early at first week and other at third month following surgery. They were indirect and direct hernias and recurrences were guessed to be due to inadequate dissection and reduction of indirect hernia sac and slipping of the polypropylene mesh into the direct hernia pouch. In OL group, recurrence was seen in three (6.38%) at third month of follow-up. The difference between two groups were statistically insignificant (P=0.40). Choi et al. [6] reported that scrotal extension of the hernia, large hernia defects and male gender were major risk factors of seroma formation after laparoscopic TEP repair. In our study group, minor complications as seroma (2%), hematoma (2%) and wound infection (4%) were detected in TEP patients. Seromas all resolved spontaneously before the last office visit. Patients operated with OL technique had 12 (25%) seroma, 3 (6.38%) hematoma, 3 (6.8%) wound infection. Compared with the TEP group, OL group had more seroma, hematoma seroma formation (P=0.001, P=0.01). The choices of operations for the treatment of recurrences in TEP group and OL group were open Lichtenstein herniorrhaphy and TEP repair respectively.

Sevinç et al. [7] in their comparative prospective study, stated that TEP repair had belter outcomes than open Lichtenstein in terms of chronic pain as 3.4% to 25.2%, respectively (P=0.001). In laparoscopic IH repairs, limited or no use of tucker or any fixating devices has been recommended to avoid postoperative or chronic pain in numerous studies [8]. In some investigations, less chronic pain has been reported for hernia repairs that did not use tacks; but there is a controversy in literature at this subject. Tam et al. [9] in their series concluded those no-fixation methods significantly decrease operative time, operation costs, and hospital stay time, but no difference between mesh fixation and no-fixation methods in terms of postoperative pain, complications, and hernia recurrence. In our TEP group, the VAS score on the first postoperative day was 3.2 (1.12), on the second postoperative day it was 2.5 (0.75) and 0.8 (0.3) on the seventh postoperative day. In OL group, the score on the first postoperative day was 5.6 (1.02), on the second postoperative day it was 4.2 (0.85) and 2.5 (0.8) on the seventh postoperative day. VAS scores were found to be lower in TEP group compared to OL group, the differences were statistically significant (P=0.001, 0.03 and 0.01, respectively). In accordance with literature, chronic pain was higher in OL group compared to TEP group (8.5% vs. 4%) (P=0.04). We have selectively used tacks or fixation devices with a minimum number just to the two or three areas as cooper ligament and over the symphysis pubis. In TEP group, one patient required referral to the pain team and in other it was well controlled with simple analgesia. In OL group, 4 patients (8.5%) suffered from chronic pain either resolved without treatment or were well tolerated with simple analgesia.

Koning et al. [10] reported higher recurrence rates in TEP repairs. Langeveld et al. [11] reported similar recurrence rates with a follow-up of 49 months. The recurrences after TEP repair are more commonly seen at the beginning of learning curve (LC) [11]. Hasbahceci et al. [12] in their study with 39 cases reported that at least 20 cases are required to learn anatomical knowledge and surgical pitfalls for performing TEP without conversion in early phase. In the guidelines of the European Hernia Society, the required range of LC of each surgeon is reported to be between 50 and 100 patients [13]. In our series, the surgeons were experienced with at least 100 cases but two (4%) recurrences were encountered. We can say that as the surgeon gets experience to get self-confidence about discrimination of anatomy and dissection plans, the recurrence rates of TEP procedure may decrease.

In our study, operating time was higher in TEP group when compared to OL group, the difference was statistically significant (55.68 (10.90) vs 39.44 (10.69) (P=0.001). However, it is clear that the operation time not only depends upon the surgical technique applied but also surgeon's experience, types and size of hernia, availability of laparoscopic instrumentations and currently available materials for repair. It is apparent that there is a controversy about this subject in literature. Khury et al. [14] reported that the operating time for TEP repair was longer than OL. While Bracale et al. [15] in their meta-analysis attributed this increased time to the need of dissection to create the preperitoneal working space. However, Sevinc et al. [7] stated that the mean operation time was shorter in TEP group with 49.2 (15.5) min vs 54.3 (14.6) min in OL group (P=0.004).

Choi et al. [6] in their study comparing laparoscopic TEP repair with OL technique reported that mean hospital stay is lower in TEP repairs (1.6 days in TEP, 3.2 days in OL). In our series, although statistically insignificant, mean hospital stay was lower in TEP group when compared to OL (22.6 (4.7) vs. 25 (6.4)) (P=0.11). However, hospital stay may be affected not only from patients' physical condition but also the hospital's turnover rate, psychological factors and traditional beliefs.

The study of TEP patients conducted by Reiner et al. [16] (n=783) showed that 583 patients (74.7%) returned to normal work ≤3 days with a median 3 days (range:1-41 days). In their prospective randomized long term study, Bansal et al. [17] reported that convalescence times of LIHR were shorter than conventional Lichtenstein repair. In our study group, the average time in TEP group to return to their routine work was 9.2 (2.03) (ranged: 6-18 days) while in OL group it was 14.8 (3.1) days (range: 7-26 days). In TEP group, 30% of patients returned to work within the 1th week. Our study showed that patients operated with TEP technique had early return to work compared to OL patients, the difference was statistically significant (P=0.001). TEP patients have better postoperative outcomes in terms of postoperative pain, early return to work.

Small sample size, short follow up period and usage of different types of anesthesia (General or spinal) in both groups were limitations of our study.

Conclusion

In terms of return time to work, postoperative pain, chronic pain, postoperative urinary retention, seroma formation and postoperative paresthesia sensation, laparoscopic TEP repair was found to be superior to the OL herniorrhaphy. More studies with large series and longer follow-up periods are still needed on the role of laparoscopy in repairing inguinal hernias.

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Evaluation of information, expectation and satisfaction in hospitalized patients: Observational survey study

Yatan hasta bilgi, beklenti ve memnuniyetinin değerlendirilmesi: Gözlemsel anket çalışması

Yahya Kemal Çalışkan [1], Fatih Başak [2]

[1] Department of General Surgery, University of Health Science, Kanuni Education and Research Hospital, Istanbul, Turkey
[2] Department of General Surgery, University of Health Science, Umraniye Education and Research Hospital, Istanbul, Turkey

ORCID ID of the author(s)
YKÇ: 0000-0003-1999-1601
FB: 0000-0003-1854-7437

Corresponding author / Sorumlu yazar:
Yahya Kemal Çalışkan
Address / Adres: Genel Cerrahi Kliniği, Kanuni Eğitim ve Araştırma Hastanesi, Küçükçekmece, İstanbul, Türkiye
e-Mail: yahyakemalc@yahoo.com

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Abstract

Aim: Evaluating the satisfaction of hospitalized patients can be worth as much as the service quality provided. For the improvements to be made in this regard, satisfaction, knowledge and expectations should be determined. In this study we wanted to determine the current situation in a tertiary hospital.

Methods: Survey-based observational study was planned. A two-stage questionnaire was developed for hospitalization and discharge, respectively. After the number of samples was determined, the patients who were treated for at least three days in the surgical clinic were taken to the study. In the analysis, descriptive statistics (number, percent), mean (standard deviation) for appropriate numerical data for normal distribution were used.

Results: One-hundred-and-fifteen patients were included in the study and questionnaires were administered. The mean age of the patients was 43.2 (16.2), 44 were male and 71 were female. Education and monthly income were found to be low in most of the patients. The most important situation in choosing our hospital was found to be inadequate economic situation. Although 60% of patients do not admit that every procedure is a risk, only 35.7% of patients in any complication stated that they could trust their doctor. When the satisfaction of the hospital was questioned in the exit questionnaire, an average of 7.5 (2) out of 10 was found.

Conclusion: It is necessary to increase the level of satisfaction, to question different dimensions of services, to give importance to patient demands, to question quality work of hospital employees, to determine difficulties and to reevaluate patient satisfaction at regular intervals.

Keywords: Satisfaction, Hospitalized patients, Expectation

Öz

Amaç: Hastanede yatarak tedavi gören hastaların memnuniyetini değerlendirmek, verilen hizmet kalitesi kadar değer kazanabilmektedir. Bu konuda yapılacak iyileştirmeler için öncelikle hastanelerin; memnuniyet, bilgi ve beklentilerin belirlenmesi gerekli görülmektedir. Bu çalışmada bir üçüncü basamak hastanedeki mevcut durumu belirlemek istedik.

Yöntemler: Anket bazlı gözlemsel çalışma planlandı. Hastaneye yatış ve taburcu sırasında yapılmak üzere iki aşamalı anket oluşturuldu. Örneklem sayısı belirlendikten sonra cerrahi kliniğinde en az üç gün yatarak tedavi gören hastalar çalışmaya alındı. Analizde tanımlayıcı istatistikler (sayı, yüzde), normal dağılım için uygun sayısal verilerde ortalama (standart sapma) kullanılmıştır.

Bulgular: 115 hasta çalışmaya alındı ve anketler uygulandı. Hastaların yaş ortalaması 43,2 (16,2), 44'ü erkek, 71'i kadındı. Eğitim ve aylık gelir hastaların çoğunda düşük bulundu. Hastanemizi seçmedeki en önemli durumun yetersiz ekonomik durum olduğu görüldü. Hastaların %60'ı her ameliyatın riski olduğunu kabul etmesine rağmen, herhangi bir komplikasyonda hastaların sadece %35,7'si doktoruna güvenebileceğini ifade etti. Çıkış anketinde hastaneden memnuniyeti sorgulandığında 10 üzerinden ortalama 7,5 (2) olduğu görüldü.

Sonuç: Memnuniyet seviyesini arttırmak, hizmetlerin farklı boyutlarını sorgulamak, hasta taleplerine önem vermek, hastane çalışanlarının kaliteli işlerini sorgulamak, zorlukları tespit etmek ve hasta memnuniyetini düzenli aralıklarla yeniden değerlendirmek gerekmektedir.

Anahtar kelimeler: Memnuniyet, Hastanede yatan hastalar, Beklenti

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Introduction

"Patient satisfaction" by the authorities evaluating the expectations of the patient; It is taken as one of the basic criteria that shows the quality of patient care [1]. With the technology, audits and therapies developed in the healthcare sector, quality health care demand becomes widespread [2]. "Patient Satisfaction", which holds an important place in quality health care assessment, is seen as necessary evidence to determine the correct use of the resources to be allocated to this issue [3].

A low quality service, which cannot be provided with appropriate patient satisfaction, could lead to delays and increased cost in response to patients' treatment. This quality-free service, which can occur in the health system, has brought together the formation of some institutions and organizations such as "private health care" which prioritizes quality and patient satisfaction [4,5].

"Patient Satisfaction" is questioned at certain times in health institutions. The aim of these researches is to assess the quality of the service from the perspective of the patients, examine the factors affecting the satisfaction and create an improvement plan according to the determined situation [6]. Our study was conducted to assess patients' satisfaction levels, and to reveal associating factors.

Materials and methods

Questionnaire based observational study was planned for the study. This research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects". The hospital which is study conducted is a tertiary education hospital which trains assistants for specialties.

Patients who have been hospitalized at least three days and agreed to participate to the study were taken into study. Patients with limited cognitive abilities (forced to express themselves) were excluded from the study. The Turkish Ministry of Health had created a multiple-choice questionnaire to measure satisfaction of in-patients [7].

The study's questionnaires were created using this current questionnaire. Two questionnaires were prepared with 15 (for enter) and 16 (for exit) questions, respectively, and were applied to patients at entrance to and exit from the hospital.

The sample size has been identified as 106 to show 50% difference with 8% α - error in confidence interval of 90% to present 20,000 patients. Nine patients were added to reduce the margin of error, and a total of 115 patients were scheduled to work. First, the patients were informed about the study and after the notified consent was received, the questionnaires were administered to the patients face-to-face by the survey employees. Demographic data of the patients, the results of the survey were recorded.

Statistical analysis

SPSS (V20, SPSS Software, Inc., USA) program was used for statistical analysis. Descriptive statistics (number, rate) in analysis, mean (standard deviation) was used in numerical data that is suitable for normal distribution. T-test was used for comparison of descriptive variables with normal distribution and Mann-Whitney U test variables without normal distribution. The Chi-square test was used to assess an association between qualitative variables. Logistic regression analysis is occupied for detection of related factors in satisfaction. Differences were considered statistically significant if the *P* value was equal to or less than 0.05.

Results

After six patients were excluded from the study, questionnaire was administered to 115 patients after approval. The mean age of the patients was 43.2 (16.2), 44 were male and 71 were female.

Data of first questionnaire which was performed during hospitalization is summarized in table 1. The most (73.9%) of our patients had only a primary or secondary education. Monthly income in half of the patients was at the level of minimum wage defined by our government. 59.1% mentioned that detailed information was provided by the doctor.

Table 1: First questionnaire performed during hospitalization

Question	Answer n (%)	Answer n (%)	Answer n (%)	Answer n (%)
1. What is your level of education?	a. Primary-Secondary education 85 (73.9)	b. High School 25 (21.7)	c. University 5 (4.3)	
2. What is your monthly income?	a. Minimum wage 59 (51.3)	b. 2x Minimum wage 45 (39.1)	c. Over 2x minimum wage 10 (8.7)	
3. Do you have a social security?	a. Yes 110 (95.6)	b. No 5 (4.4)		
4. Do you have any information about the illness?	a. Yes, detailed information provided by the doctor 68 (59.1)	b. The doctor has not yet given information but has his own knowledge 34 (29.6)	c. As far as I am concerned, I have knowledge 8 (7)	d. No, I have no information about the disease. 5 (4.3)
5. What is the reason for choosing our hospital?	a. For being close to my home 30 (26.1)	b. I do not have the economic condition to meet the private hospital 61 (53)	c. I've been sleeping before and liked the service 14 (12.2)	d. Emergency (or transfer) came, I had no choice 10 (8.7)
6. Do you trust hospital and doctors?	a. Yes, I absolutely trust 81 (70.4)	b. I have some doubts in this regard 26 (22.6)	c. No, I do not trust, but I have no choice 8 (7)	
7. What are your hearings about our hospital from the audience and the television?	a. I have heard positive things 63 (54.8)	b. I heard negative things 52 (45.2)		
8. What do you expect from hospitals and doctors?	a. I expect to heal the patient completely 50 (43.5)	b. Make efforts to heal your illness as much as you can 44 (38.3)	c. I have no expectations 21 (18.3)	
9. Do you know that every operation is an acceptable risk?	a. Yes, I know and I accept them 69 (60)	b. Yes, I know, but I do not accept them, 34 (29.6)	c. No, this is absolutely unacceptable 12 (10.4)	
10. Do you have a vital risk of you or your patient?	a. Yes, I think it's a vital risk and I trust the hospital 29 (25.2)	b. I have no idea in this regard, but I trust the hospital and the doctors 48 (41.7)	c. No, I do not think it's a vital risk 38 (33)	
11. What do you do if patient (you) has a problem during surgery and treatment?	a. Trust until the end of the hospital and the doctor 41 (35.7)	b. I will take the patient to another hospital 21 (18.3)	c. Consult the doctor to other doctors 19 (16.5)	d. Applying legally 34 (29.6)
12. Do you know what an assistant doctor is?	a. A technician trained in a Specialization 26 (22.6)	b. Student who has not yet become a doctor 32 (27.8)	c. The doctor who just finished the university 25 (21.7)	d. The doctor who saw an area "Specialist training" 32 (27.8)
13. Our hospital is the "Education" hospital. Do you know what a education hospital is?	a. First plenary, Hospital aimed at patient service and satisfaction 43 (37.4)	b. First plan, hospital aimed at resident doctor training 50 (43.5)	c. Student Doctor's hospital 22 (19.1)	
14. What is the estimated salary of a doctor?	a. Minimum wage 37 (32.2)	b. 1-2x Minimum wage 38 (33)	c. 2-4x Minimum wage 23 (20)	d. Over 4x minimum wage 17 (14.8)
15. Do you think that doctors receive adequate respect and salary according to the job they are doing?	a. They are aware of the seriousness of their job, but they cannot take it as respect and salary 60 (52.2)	b. I think some of them do not deserve respect and this salary. 36 (31.3)	c. I think they get enough respect and salary 13 (11.3)	d. I think they get a lot of respect and salary 6 (5.2)

Table 2: Second questionnaire performed during discharge from hospital

Question	Answer n (%)	Answer n (%)	Answer n (%)	Answer n (%)
1. Have you ever been to a Private Hospital?	a. Yes 36 (31.3)	b. No 79 (68.7)		
2. What are your thoughts on the CLEANING of our hospital?	a. Good 53 (46.1)	b. Can be better 58 (50.4)	c. Bad 4 (3.5)	
3. What are your thoughts about our hospital food?	a. Good 50 (43.5)	b. Can be better 50 (43.5)	c. Bad 14 (12.2)	
4. What are your thoughts about the PERSONNEL-PATIENT CARE?	a. Good 71 (61.7)	b. Can be better 36 (31.3)	c. I'm bad, I'm not happy at all 8 (7)	
5. What are your thoughts about Nursing Nursing?	a. Well, they help in every way 87 (75.7)	b. Can be better 28 (24.3)	c. I'm bad, I'm not happy at all 0 (0)	
6. What are your thoughts about ASISTANT DOCTORS?	a. Well, they help in every issue, 76 (66.1)	b. Can be better, 37 (32.2)	c. I'm bad, I'm not satisfied at all 2 (1.7)	
7. What are your thoughts about our hospital's SPECIALIST DOCTORS?	a. Well, they help in every issue, 93 (80.9)	b. Can be better, 20 (17.4)	c. I'm bad, I'm not satisfied at all 2 (1.7)	
8. Are you satisfied with your treatment?	a. Yes, fully satisfied 92 (80)	b. I am not completely satisfied 21 (18.3)	c. I am not satisfied 2 (1.7)	
9. How does your hospital come to be?	a. Fully Remediation 26 (22.6)	b. Better 84 (73)	c. As it comes, there's no change 5 (4.3)	d. Worsened 0 (0)
10. Did you have enough information about your patient's illness while being a battalion?	a. Yes, the assistant doctor provided enough information 40 (34.8)	b. Yes, the expert doctor provided enough information 32 (27.8)	c. Very brief information, I think it is not enough 32 (27.8)	d. No, he did not give any information 11 (9.6)
11. What are the difficulties you experience at the hospital? (you can mark more than one)	a. Admission - Departure Procedures, Procedures 44 (38.3)	b. I feel uncomfortable because I am very sick in the rooms 54 (47)	c. Uncomfortable because the rooms are crowded during visiting hours 28 (24.3)	d. I feel uncomfortable with the attitude of doctors to me and the patient 6 (5.2)
12. What do you do if the patient's disease repeats itself?	a. Apply to this hospital again 97 (84.3)	b. I go to another hospital 13 (11.3)	c. Other 5 (4.3)	
13. Do you trust this hospital and the doctors?	a. Yes, I absolutely trust, there is no doubt already 89 (77.4)	b. I had some doubts in this regard, but I liked the service and the interest 23 (20)	c. No, I do not trust, but I have no choice 4 (3.5)	
14. Would you recommend our hospital to other people?	a. Yes 99 (86.1)	b. No 16 (13.9)		
15. Suggestions (you can mark more than one)	a. Do not take visitors out of the escort for the day the patient is operated 36 (31.3)	b. Doctors explain more about the patient 67 (58.3)	c. Increase the number of private rooms 59 (51.3)	D. Get bed for companion 60 (52.2)
16. Do you rate your Satisfaction from 1 to 10 in our hospital?	7,5±2 (min: 1 max:10)			

Main rationale of choosing our hospital was insufficient economic condition (53%) to spend in private hospital. Sixty percent of the patients accept that every operation had a risk of complication, and 70.4% stated that they trust the hospital and doctors. However 35.7% stated that they trust doctors until the end if the patient has a problem during surgery, and 52.2% expressed that “doctors are aware of the seriousness of their job, but they cannot take it as respect and salary”.

Data of second questionnaire was performed during discharge from the hospital, and it is summarized in table 2. The most of the patients (68.7%) stated that they had never admitted to a private hospital. Cleaning, food, personnel-patient care, nursing were found acceptable by 46.1, 43.5, 61.7 and 75.7 percent of the patients, respectively. Care of assistant doctors and specialist doctors were found helpful by 66.1 and 80.9 of the patients, respectively. 80% stated that they are satisfied with the treatment. 84.3% expressed that they will admit to this hospital again if the disease repeat itself. 86.1% of the patients stated that they will recommend our hospital to other people. From 1 to 10, satisfaction level for our hospital was 7.5 (2) (min: 1 max: 10). No difference was found between demographics and level of satisfaction (P=0.396). In logistic regression model, no association was found between level of satisfaction and age and gender (Table 3).

Table 3: Logistic regression model for estimating level of satisfaction

	Unstandardized Coefficients	Standardized Coefficients		
	B	Std. Error	Beta	*P*-value
(Constant)	8.176	0.842		0.000
Age	-0.007	0.012	-0.053	0.575
Gender	-0.250	0.388	-0.061	0.520

Discussion

Customer-centered service understanding in the Community has increasingly gained importance to the demands of individuals receiving healthcare services. However, due to the continuity and complexity of the individual's health needs, the criteria for satisfaction are different and complex than the criteria in a restaurant or other service areas in the community [4]. In other words, the health care service differs significantly from other industry and service enterprises in some important ways. In a competitive market, consumers can show their dissatisfaction by changing their shopping place.

However, it is limited to the choice of health care institutions due to the health care of individuals. This limitation is even more evident in institutions such as the social Insurance institution and the State Hospital where national health services are presented in our country [6].

With the concept of quality in healthcare services, the number of studies based on the measurement of patient satisfaction, which has been increasingly raised in recent years, is increasing. With the expectations of the patient's Hospital services and service team to prioritize their requirements with the determination of the patients ' service presentation, feedback and feedback, the quality of the facility and improvement in healthcare services is extremely important. At the same time, patient satisfaction has been seen as necessary evidence to decide on the effective use of existing resources due to the increasing cost of health care [8-11].

Patient satisfaction is a complex concept affected by various elements and is one of the most important indicators of quality patient care. In general, patient satisfaction is based on the service to meet the patient's expectations or to detect the services provided by patients. The quality of the service is basically determining the level of satisfaction of the patient and in this process all activities that pass through the patient's application, diagnosis, treatment and maintenance results play an important role. Elements that determine service quality; The environment in which the service is offered, the appearance, the timing of the service, the ability to provide services to the subjects of the service, the continuity of the service, reliable, accurate and flexible factors [10,11]. However, in determining and detecting the quality of health services; Waiting times of the patients, the courtesy and consistency of the employees, the availability of the service, the services offered at once and accurately, in an unlikely state that employees find and respond to the necessary solutions, and the service As a complete fulfillment, the elements play an important role. The most important determinants in determining these factors are the consumers [11,12]. For this reason, the determination, measurement and evaluation of patient satisfaction parameters is of paramount importance in order to ensure that hospitals and healthcare enterprises are able to gain and sustain competitive advantage [11]. Two basic methods are used indirectly and

directly in the Assessment and evaluation studies on patient satisfaction. Direct methods include methods such as a written questionnaire, face-to-face interview, telephone questionnaire, where satisfaction level is directly asked to the patient on the basis of pre-determined parameters. The indirect methods are that the satisfaction level is not directly asked to the patient, but the patient's spontaneous feedback, such as patient complaints and thanks, and the number of nurses per patient, affecting the patient, but it refers to the methods derived from the unknown values [12,13].

In studies of direct satisfaction measurements, patients were found to be more informed about the disease and drug interactions by the physician, affecting satisfaction [14]. In the study conducted on geriatric patients by Huber and his colleagues, the receipt of the patients ' opinions was determined to improve the effectiveness of the treatment and increase the level of patient satisfaction [15]. On the other hand, nurses were found to have a high level of meaningful relationship between the nursing rate per bed and the working years of nurses on the Patient satisfaction level [16].

Patient satisfaction affects various factors. These; related to the patient (age, gender, education, social security, diagnosis of illness, etc.), service (personnel behavior, information about the disease, patient interaction, etc.) and the properties related to the institution (physical and environmental conditions, bureaucracy, etc.) [17,18]. In this study we found some acceptable satisfaction levels (7.5 out of 10). Some aspect of this satisfaction might be a reason of obligatory, maybe mandatory, admission to our hospital. However, the findings in the literature may differ. In the study of Demir and et al. [19] the relationship with the level of satisfaction of gender and education has been examined and a meaningful relationship is noted. Konca and his colleagues [20] reported that they did not find a meaningful relationship between the patients' satisfaction levels and gender, education status, and duration of hospital stay. Ercan and his colleagues [9] have found significant correlation between ages, education level, income, social security status and scale score in their work using satisfaction scale. Hekkert and his colleagues [21] indicate that there is a meaningful correlation between age, gender, health condition and hospital type, size and satisfaction level. Quintana and his colleagues [22] have found a meaningful relationship with patient satisfaction in their studies, such as age, gender, and educational status.

Personality type, depression status and anxiety of a patient affect his/her health condition [23-25]. Depression and anxiety may also affect patient satisfaction level and judgement in various ways [26]. In our study, we found some obscure data in survey at some point. We didn't perform an evaluation of patients' psychiatric condition. This issue has to be planned to solve with later well designed studies.

This study has a number of limitations. In our study, we couldn't found any relation with age and gender with level of satisfaction. But we cannot perform other statistical calculation with remaining survey questions because we used a non-standard, non-validated questionnaire. The significance of findings of this study may be interpreted as unclear due to low statistical calculation and significance. Although this study was conducted in one region, the results may be generalizable to other areas. Future larger studies with statistical analyses to predict satisfaction would be of interest.

To increase the level of satisfaction, questioning the different dimensions of the services, giving importance to patient demands, adoption of quality work by hospital employees and re-evaluating the satisfaction at regular intervals have to be performed.

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A different perspective on the correlation between histopathological type and PET-CT SUVmax in non-small cell lung cancer: A retrospective cohort study

Küçük hücreli dışı akciğer kanserinde histopatolojik tip ile PET-BT SUVmax arasındaki korelasyon üzerine farklı bir bakış açısı, Retrospektif kohort çalışma

Özgur Ömer Yıldız [1], İlknur Aytekin Çelik [1]

[1] Yildirim Beyazit University, Faculty of Medicine, Department of Thoracic Surgery, Ankara, Turkey

ORCID ID of the author(s)
ÖÖY: 0000-0001-7314-3131
İAÇ: 0000-0003-0754-680X

Abstract

Aim: In recent years, alternative therapies targeting directly cancer cells and targeted agents have been developed. The aim of this study is to develop a new perspective on alternative therapies on local targets, as identify the correlation between positron emission tomography-computed tomography (PET-CT) SUVmax and histological type of the tumor in non-small cell lung cancers.

Methods: This study is based on the retrospective examination of patients who underwent PET-CT for preoperative staging with non-small cell lung cancer between January 2012 and May 2018. Statistical analyses are made between SUVmax values and histopathological types.

Results: The study is including 448 patients who underwent surgery for non-small cell lung cancer. The average size of the mass was 4.5 cm and the average SUVmax value was calculated as 13.3. The patients were classified into five groups according to their histopathological diagnosis. PET-CT fluorodeoxyglucose (FDG) involvement has been classified for different histopathological types. Statistically significant correlation was identified between the tumor size and histopathological diagnosis. It was found that the difference between SUVmax values of the adenocarcinoma tumors and other types are found statistically significant. SUVmax values have been found mostly between 5-10 in patients with adenocarcinoma and 10-15 in others.

Conclusion: Considering that there are statistically significant differences between PET-CT SUVmax values of tumor cell types, we argue that radiopharmaceuticals which could provide different and local treatment should be used in cancer treatment, they should be combined with alternative therapies such as loco-regional treatment methods, and the studies in that direction should continue in line with the technological developments.

Keywords: Lung cancer, PET-CT, Radiopharmaceutica

Öz

Amaç: Son yıllarda akciğer kanserinin moleküler biyolojisi konusunda yapılan araştırmalar ile kanser hücreleri yanında normal hücreleri de hedef alan sistemik konvansiyonel tedavi yöntemlerinin yanında direk kanser hücrelerini hedef alan tedaviler gelişmiş ve böylece lokal hedefe yönelik ajanlar başlığı altında yeni tedavi alternatifleri üzerine yoğunlaşılmıştır. Bizim çalışmamızda ise amaç lokal hedefe yönelik tedavi alternatifleri konusunda farklı bir kapı aralamak, küçük hücreli dışı akciğer kanserlerinde kitle Pozitron emisyon tomografi-bilgisayarlı tomografi (PET-BT) SUVmax değerinin tümör histolojik tipi ile korelasyon gösterip göstermediğini belirlemektir.

Yöntemler: Çalışmamız, ocak 2012 ile mayıs 2018 yılları arasında preoperatif evreleme amaçlı istenen PET-BT ve sonrasında opere edilen küçük hücreli dışı akciğer kanseri olgularının retrospektif incelenmesi ile oluşturuldu. PET-BT'deki kitlenin SUVmax değeri ve histopatolojik tip kaydedilerek istatistiksel değerlendirme yapıldı.

Bulgular: Çalışmaya KHDAK nedeni ile opere edilen 448 olgu dahil edildi. Olguların ortalama kitle boyutları 4,5cm, ortalama SUVmax değerleri 13,3 olarak hesaplanmıştır. Olgular histopatolojik tanılarına göre 5 grupta toplandı. PET-BT fluorodeoksiglikoz (FDG) tutulum SUVmax değerleri gruplandırıldı ve farklı histopatolojik türde malignitelerin ağırlıklı olarak gösterdikleri tutulum değerleri belirlenmeye çalışıldı. Tümör boyutu ve histopatolojik tanılar ile SUVmax değerleri arasında anlamlı ilişki tespit edildi. Adenokarsinom hücre türüne ait tümörlerin diğer karsinomlara göre PET-BT SUVmax değerlerinin anlamlı düzeyde farklılık gösterdiği tespit edildi. SUVmax değerlerinin ağırlıklı olarak adenokarsinom olgularında 5-10 arası düzeylerde, diğer türlerde genellikle 10-15 arası tutulum gösterdiği belirlendi.

Sonuç: Tümör hücre tiplerinin PET-BT SUVmax değerleri anlamlı düzeyde farklılık gösterdiklerinden yola çıkılarak PET'te farklı ve lokal tedaviyi sağlayacak radyofarmasötiklerin kullanılması ve değişik alternatifler oluşturulması konusunda teknolojik gelişmeler baz alınarak çalışmalar devam etmelidir.

Anahtar kelimeler: Akciğer kanseri, PET-BT, Radyofarmasötikler

Corresponding author / Sorumlu yazar:
Özgur Ömer Yıldız
Address / Adres: Yıldırım Beyazıt Üniversitesi, Tıp Fakültesi, Bilkent Şehir Hastanesi, Göğüs Cerrahisi Anabilim Dalı, Ankara, Türkiye
e-Mail: dr.ooyildiz@gmail.com

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Introduction

Lung cancer is one of the most important health issues in the world due to increasing incidents and mortality rates. Lung cancer accounts for one third of deaths from cancer. Only 15% of the patients live for 5 years or longer after they are diagnosed. Despite the developments in diagnosis methods and surgical and non-surgical methods, the tumors identified during the diagnosis are not limited to the lungs in the majority of the patients [1]. In patients with non-small cell lung cancer, there is mediastinal lymph node involvement at the time of the diagnosis, and less than 33% of the patients are suitable for surgical resection [2,3].

In recent years, new alternative therapies targeting directly the cancer cells and targeted agents have been developed, in addition to the studies on the molecular biology of lung cancer and systemic conventional therapies targeting both the cancer cells and normal cells. Biophysical methods in lung parenchyma aiming for higher dose medication include embolic confinement or chemo-embolization, selective pulmonary artery perfusion without controlling venous flow, lung suffusion and isolated lung perfusion in which the lung is completely separated from the systemic circulation [4]. The common aim of these techniques is to reduce systemic toxicity for the patients who will undergo chemotherapy in case there is a metastasis from non-small cell lung cancer (NSCLC) or other organ malignancies, as well as to enable higher dose local therapies without the systemic exposure of the chemotherapy agents [5].

The aim of our study is to develop new perspectives on alternative therapies for local targets, to identify whether there is any correlation between positron emission tomography-computed tomography (PET-CT) SUVmax values and the histological type of the tumor in non-small cell lung cancer, and to develop a new perspective for this correlation to support the use of radiopharmaceuticals labelled with molecules effective in local therapy in the foreseeable future.

Materials and methods

This study is based on the retrospective examination of the patients with non-small cell lung cancer, who underwent PET-CT for preoperative staging and surgery, in the clinics we have been working between January 2012 and May 2018. All PET-CT's were taken by the same center. All the evaluations were performed using standard methodology. In this retrospective study, 448 patients who underwent PET-CT for preoperative staging 406 of the patients were (90.6%) male and 42 were female (9.3%).

Preoperative assessment of all patients included anamnesis, physical examination, respiratory function tests, electrocardiography, blood biochemistry and hemogram tests, coagulation tests, postero-anterior and lateral lung graphics, thorax computed tomography and PET-CT. All patients whose tumor size was bigger than 3cm underwent cranial magnetic resonance imaging (MRI) for preoperative staging. Tests and invasive procedures were performed based on TNM staging. Age, gender, preoperative diagnostic tests, location of the mass, SUVmax values of masses and all intrathoracic lymph nodes in PET-CT, operations performed, lymph nodes which were sampled/excised in operation, size of the tumor lesion and tumor type of all patients were recorded in the database.

The areas of FDG accumulation outside normal biodistribution was identified through an evaluation of the F-18 fluorodeoxyglucose (FDG) PET-CT scans. The SUVmax values were calculated.

Statistical analysis

All data are examined statistically; Chi Square, Correlations and One-way Anova analysis methods have been used on SPSS 16 data analysis software. The findings under the $P<0.05$ have been accepted as statistically significant.

Results

The study included 448 patients that underwent surgery for non-small cell lung cancer. 406 of the patients were male (90.6%) and 42 of the patients were female (9.3%) with an average age of 58.9 (8.99) (26-87). In all patients, the size of the mass and FDG involvement (SUVmax) were recorded. According to this, the average size of the masses was calculated as 4.5 (2.3) cm (0.4-20) and the average SUVmax value was calculated as 13.35 (6.18). The patients were classified in 5 groups according to the histopathological diagnosis, which included squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, large cell carcinoma and other types. PET-CT FDG involvement SUVmax values have been classified and involvement values with malignancy in different histopathological types have tried to be identified (Table 1).

Table 1: PET-CT SUVmax values according to histopathological types

SUVmax groups	SCC n (%)	ADENO n (%)	ADENOSCC n (%)	LARGE n (%)	Others n (%)	Total n
0-5	2 (0.93)	18 (11.11)	1 (2.7)	0 (0.0)	0 (0.0)	21
5-10	46 (21.49)	55 (33.95)	4 (10.81)	4 (17.39)	3 (25)	112
10-15	78 (36.44)	61 (37.65)	13 (35.13)	10 (43.47)	5 (41.66)	167
15-20	57 (26.63)	19 (11.72)	12 (32.43)	5 (21.73)	1 (8.33)	94
20-25	20 (9.34)	6 (3.7)	5 (13.51)	3 (13.04)	1 (8.33)	35
25-30	6 (2.8)	1 (0.61)	0 (0.0)	1 (4.34)	2 (16.66)	10
30-35	3 (1.4)	1 (0.61)	2 (5.4)	0 (0.0)	0 (0.0)	6
35-40	0 (0.0)	1 (0.61)	0 (0.0)	0 (0.0)	0 (0.0)	1
40-45	2 (0.93)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2
Total	214 (100)	162 (100)	37 (100)	23 (100)	12 (100)	448

SCC: Squamous cell carcinoma, ADENO: Adenocarcinoma, ADENOSCC: Adenosquamous carcinoma, LARGE: Large cell carcinoma

Significant correlation was identified between the tumor size and the histopathological diagnoses and the SUVmax values. 214 of the patients (47.8%) was operated for small cell cancer, 162 of them (36.2%) adenocarcinoma, 37 of them (8.3%) for adenosquamous carcinoma and 23 (5.1%) for large cell carcinoma and 12 (2.7%) for other malignancies. PET-CT SUVmax values of the patients were compared with the histopathological diagnoses.

Significant relation was found between the tumor size and the diagnoses types, and the SUVmax values in Chi Square analysis. Positive correlation was found between the tumor diameter and the SUVmax values when compared with Correlations analysis (Table 2).

When the diagnoses types and SUVmax values were compared using the One-way Anova method, it was found that the difference between the PET-CT SUVmax values of tumors containing adenocarcinoma cell types and squamous or adenosquamous carcinoma is statistically significant (Table 2).

In the analysis done through classification of SUV values, it was found that the involvement level in all malignancy types is at 10 -15 SUVmax value level. In the second frequency,

it was found that adenocarcinoma patients showed involvement between 5-10 SUVmax values and other malignancies showed 15 SUVmax value.

Table 2: Comparison of SUV max values found in adenocarcinoma with other cell types

Dependent Variable	(I) Tumor type	(J) Tumor type	Mean Difference (I-J)	Std. Error	*P*-value	95% Confidence Interval	
						Lower Bound	Upper Bound
SUVmax	Adeno	SCC	-3.45*	0.62	<0.001	-5.14	-1.75
		Other	-3.91	1.78	0.18	-8.78	0.97
		Large	-3.72*	1.33	0.04	-7.35	-0.09
		Adeno-squamous	-4.51*	1.08	<0.001	-7.48	-1.54

SCC: squamous cell carcinoma

Discussion

Our knowledge on survival ways of tumor cells, their genetics and resistance to drugs have increased in recent years. Possible reason for the negative results on some tumors after surgery and chemotherapy is their resistance to chemotherapy agents and the failure of drugs to reach the effective concentration level in the tumor mass [4,5]. This shows that there is a need for new chemotherapy agents and a method to transfer them inside the lung tissue in a more effective way. There is an increasing interest in the methods aiming for higher drug doses in lung parenchyma.

Furthermore, PET-CT imaging is now a routine practice, based on the idea that cancer needs more energy, hence uses more glucose compared to the normal tissues. The most frequently used compound in PET imaging is FDG labelled with Fluorine (F)-18. SUVmax is a semi-quantitative indicator showing radioactively labelled glucoses uptake of the tumor tissue, and determining prognostic factors such as tumor differentiation. FDG PET-CT has been successful in identifying and monitoring malign tumors [6]. Other PET radiopharmaceuticals have been used in some tumors with lower FDG affinity and lower glucoses metabolism. Among the most typical examples are Ga-68 PSMA in prostate cancer, Ga-68 DOTA-TATE and F-18 FDOPA in neuroendocrine tumors and F-18 fluorocholine in hepatocellular cancer. PET-CT with different radiopharmaceuticals showing different biological features of neoplastic tissue is used for primary tumor diagnosis and characterization, in particular for staging, and re-staging, determining relapse, identifying response to therapy, and planning radiotherapy in thoracic tumors [7,8]. As it can be seen, specific radiopharmaceuticals are used for different tumors and there are new developments with significant progress in this area.

The main aim of the methods that aim for higher dose drug targeting in lung parenchyma, such as embolic trapping or chemoembolization, selective pulmonary artery perfusion without controlling venous flow (SPAP), lung suffusion and isolated lung perfusion in which lung is completely separated from systemic circulation, is to deliver chemotherapeutic agents to the isolated lungs and to eliminate systemic side effects, as well as to reach maximum concentration level in the target tissue [5]. Isolated perfusion methods in cancer treatment that was first published by Creech et al. in 1959 have been supported with other studies but these studies have not been popular to this date [4,9].

Changing SUVmax values according to the histological types in NSCLC, which we aimed to show in this study, can offer a new approach in developing targeted therapies. Such a study has not been conducted yet. Existing studies mostly focused on prognostic significance of SUVmax value and changes in SUVmax values according to histological types. There are studies evaluating the correlation between SUVmax and histological subtypes of NSCLC, which found SUVmax value of adenocarcinoma significantly low compared to other subtypes [10-12]. In Turkey, the study conducted by Yalcınkaya et al. [13] found that there is a statistically significant difference between the average SUVmax value of adenocarcinoma which is 13.27 and that of squamous carcinoma which is 16.11.

Similar to the other studies, the SUV max values in adenocarcinoma patients were significantly low in our study as well. Based on that, if the radiopharmaceutical agent accumulation in NSCLC subtypes show differences, we believe that chemotherapeutic agents can be delivered to the target tissue labelled with a radionuclide, and reach to a sufficient concentration level in the target tissue. Besides, if it is used together with methods such as isolated lung perfusion which aims to increase treatment success by reaching at maximum chemotherapeutic drug dose in the target tissue, it can be possible to provide treatment with the most efficient dose, by determining the chemotherapy dose in proportion to involvement level identified according to the tumor subtypes, and with minimum side effects.

Parallel to the developing technology, PET-CT modality which provides functional information at molecular level and in vivo, and enables us to conduct a non-invasive examination about the biological behavior of the tumor in both morphological and functional senses. This study supports the studies which argue that PET-CT images contain more information than considered and provide opportunities such as developing individualized treatment plans in the clinical practice.

Conclusion

Depending on the features of PET radiopharmaceuticals, different biochemical, metabolic or functional parameters can be imaged in vivo. But the routine practice is monitoring the glucose metabolism, which is the most accepted and used parameter. FDG compound labelled with F-18 is utilized for this reason. There are also radiopharmaceuticals specific to the organ and the tumor. It is possible to achieve the minimum dose, the minimum systemic side effects and the maximum response by combining special radiopharmaceuticals that have been developed for the treatment of target organs and chemotherapeutical agents.

Considering that there are statistically significant differences between PET-CT SUVmax values of tumor cell types, we argue that radiopharmaceuticals which could provide different and local treatment should be used in cancer treatment, they should be combined with alternative therapies such as loco-regional treatment methods, and the studies in that direction should continue in line with the technological developments.

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Predicting survival in gastric cancer: A prospective cohort study with 102 patients

Mide kanserinde sağkalımı tahmin etmek: 102 hasta ile prospektif kohort çalışma

Koray Koşmaz [1], Mustafa Taner Bostancı [2], Mehmet Ali Çaparlar [2], Fatih Başak [3], Abdullah Şişik [3], Süleyman Kalcan [3], Ali Ediz Kıvanç [3], Kemal Tekeşin [3], Gürhan Baş [4], Orhan Alimoğlu [4]

[1] Department of Gastroenterology Surgery, Ankara Education and Research Hospital, Ankara, Turkey
[2] Department of General Surgery, Dışkapı Yıldırım Beyazıd Education and Research Hospital, Ankara, Turkey
[3] Department of General Surgery, Health Science University, Umraniye Education and Research Hospital, Istanbul, Turkey
[4] Department of General Surgery, Medeniyet University, Goztepe Education and Research Hospital, Istanbul, Turkey

ORCID ID of the author(s)
KK: 0000-0003-2111-3162
MTB: 0000-0003-2876-2683
MAÇ: 0000-0001-6466-0348
FB: 0000-0003-1854-7437
AŞ: 0000-0002-7500-8651
SK: 0000-0002-0829-7334
AEK: 0000-0002-6359-0314
KT: 0000-0002-1688-0597
GB: 0000-0003-1702-0772
OA: 0000-0003-2130-2529

Corresponding author / Sorumlu yazar:
Koray Koşmaz
Address / Adres: Gastroenteroloji Cerrahisi Kliniği, Ankara Eğitim ve Araştırma Hastanesi, Ankara, Türkiye
e-Mail: koraykosmaz@hotmail.com

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Abstract

Aim: Gastric cancer is one of the most aggressive tumors of the gastrointestinal tract. Course of disease can be different in every case. The aim of this study was to evaluate prognosis of gastric cancer patients and factors affecting survival.

Methods: Observational cohort study was planned. Primary gastric cancer patients enrolled into study. Patients with rare tumors were excluded. Patients were divided in 4 groups; Group 1: patients suitable for surgery and underwent surgical resection, Group 2: patients that were discovered unresectable during operation, Group 3: patients that were radiological inoperable, Group 4: patients who refused the surgery. We analyzed survival among groups, and evaluated effecting factors.

Results: 102 patients were included in the study. Sixty-six patients underwent surgical resection (group 1). Five patients were diagnosed as inoperable during surgery (group 2). Six-teen patients were determined as inoperable by radiologic evaluation (group 3). Fifteen patients (group 4) were evaluated as operable; however they refused surgery. No differences were detected among groups in comparison of gender with p of 0.250 (table 1). However, age distribution was different between groups with p of 0.043 because group 4 is formed by older patients with mean age of 71.0 (10.0). Survival analysis showed that patients in group 1 (14.0 (5.1) months) had better survival than other groups (P=0.011). Male patients showed better survival than female patients (14 (1.9) vs 6 (1.8) months, P=0.002).

Conclusion: Although course of gastric cancer differs in every patient, proper surgery at certain stages seems to be a feasible treatment option with acceptable survival rates.

Keywords: Gastric cancer, Survival, Course of disease

Öz

Amaç: Gastrik kanser, gastrointestinal sistemin en agresif tümörlerinden biridir. Her durumda hastalık seyri farklı olabilir. Bu çalışmanın amacı, mide kanseri hastalarının prognozunu ve sağkalımı etkileyen faktörleri değerlendirmektir.

Yöntemler: Gözlemsel kohort çalışması planlandı. Primer mide kanseri hastaları çalışmaya alındı. Nadir tümörleri olan hastalar çalışma dışı bırakıldı. Hastalar 4 gruba ayrıldı; Grup 1: Cerrahiye uygun ve cerrahi rezeksiyon yapılan hastalar, Grup 2: Operasyon sırasında rezeke edilemeyen tespit edilen hastalar, Grup 3: Radyolojik olarak çalışmayan hastalar, Grup 4: Cerrahiyi reddeden hastalar. Gruplar arasında sağkalımı analiz ettik ve etkili faktörleri değerlendirdik.

Bulgular: Çalışmaya 102 hasta alındı. Altmış altı hastaya cerrahi rezeksiyon yapıldı (grup 1). Beş hastaya ameliyat sırasında çalışamazlık tanısı kondu (grup 2). Altı genç hasta radyolojik değerlendirme ile inoperabl olarak belirlendi (grup 3). On beş hasta (grup 4) uygun olarak değerlendirildi; ancak ameliyatı reddetti. Cinsiyete göre gruplar arasında fark bulunmadı (P=0,250) (Tablo 1). Bununla birlikte, yaş dağılımı, P=0.043 olan gruplar arasında farklıydı çünkü grup 4, yaş ortalaması 71.0 (10,0) olan yaşlı hastalar tarafından oluşturulmuştur. Sağkalım analizi, grup 1'deki hastaların (14.0 (5,1) ay) diğer gruplardan daha iyi sağkalım gösterdiğini gösterdi (P=0,011). Erkek hastalar kadınlara göre daha iyi sağkalım gösterdi (14 (1,9) vs 6 (1,8) ay, P=0,002).

Sonuç: Her ne kadar mide kanseri seyri farklı olsa da, belirli evrelerde uygun cerrahi işlem, kabul edilebilir sağkalım oranları ile uygulanabilir bir tedavi seçeneği gibi görünmektedir.

Anahtar kelimeler: Mide kanseri, Sağkalım, Hastalığın seyri

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Introduction

Gastric cancer is one of the most aggressive tumors of the gastrointestinal tract. While 5-year-survival of early gastric cancer is approximately 90%, it varies between 15-20% at advanced stage [1]. In Turkey, annual incidence of gastric cancer is 9.6/100,000 in men and 5.7/100,000 in women. Therefore, we expect to encounter 130,000 new cases each year. Gastric cancer's death rate is the second highest in male and third in female population [2]. Male incidence is higher than female and male/female ratio is 2/1. While it's rarely encountered before 40, its incidence gets higher with age and reaches its highest rate in around 60 years of age [3].

Gastric cancer can be diagnosed in early stage in Japan due to their advanced methods of screening. It is diagnosed in later stages and harder to cure in Western Countries due to rare incidence and infrequent and insufficient screenings [1].

There are various studies over factors effecting prognosis. These include, sex, age, blood type and blood transfusion, body-mass-index, tumor localization, size, macroscopic type, histological grade, stage, metastatic lymph node count, tumor markers (CEA, Ca19-9), pre-operative hemoglobin and albumin levels, surgical procedure method, lymph node dissection (D1, D2, D3) and chemo/radiotherapy [1-3]. Studies showed that gastric cancer prognosis is affected in almost all cases by some factors while different results are seen for some others [2].

Main treatment of most gastric cancer is surgical resection and lymph node dissection. However, palliative surgery may be performed for some gastric cancer patients diagnosed at later stage with pre-operative radiological evaluation or discovered as unresectable during surgical exploration. Some patients receive only chemo/radiotherapy if they refuse the operation. However, there is limited information in literature concerning the end of the course of treatments. The aim of this study was to evaluate prognosis of gastric cancer patients and factors affecting survival.

Materials and methods

Observational cohort study was planned to evaluate primary gastric cancer patients who were diagnosed between 2009 and 2012, retrospectively using prospective database. Local ethics committee of our hospital approved the study that was prepared according to ethical standards of 1975 Helsinki Declaration's Human Experiment Committee which was revised in 2000 (www.wma.netle/policy/b3.htm).

Patients with rare tumors (i.e., gastrointestinal stromal tumor, lymphoma, and neuroendocrine tumor) were excluded. After investigating gastric cancer patients to evaluate operability with radiologic techniques (computed tomography, positron emission tomography), we informed the patients about surgery. Patients were divided in 4 groups; Group 1: patients suitable for surgery and underwent surgical resection, Group 2: patients that were discovered unresectable during operation, Group 3: patients that were radiological inoperable, Group 4: patients who refused the surgery.

After evaluating the patient as operable radiologically and having the consent for operation, total or subtotal gastrectomy was performed according to tumor's location. Standard lymph node dissection (D2) was performed. All patients were sent to medical oncology post-operatively (chemoradiotherapy).

Demographic data, i.e., age, gender, of the patients were recorded. Tumor location and TNM stage of group 1 patients were recorded. Tumors located in corpus and cardia were defined as "proximal" and "distal" if located in the remaining portion of the stomach. All patients were followed-up by telephone and routine examinations every three months in first two years, every six months following three years, and every one year after five years of diagnosis of the cancer. Patients who failed to comply follow-ups were not evaluated in survival analysis. Main outcome of our study is survival. Firstly, we analyzed survival among groups. Further analysis was performed for group 1 patients to evaluate the effect of tumor location and TNM stage on survival.

Statistical analysis

NCSS (Number Cruncher Statistical System) 2007 & PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) were used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used to evaluate the study data. Mann Whitney U test was used in comparison of quantitative data with two groups, Kruskal Wallis test were used for three or more groups that aren't normally distributed. Fisher's Exact and Yates Continuity Correction test were used to compare qualitative data, Kaplan Meier Survival Analysis and Log Rank tests were used to evaluate survival. Median (standard error) was used to present the survival. Hazard ratio was calculated using Cox Regression Analysis to determine parameters affecting survival. Relevance was calculated as $P<0.05$ in the confidence interval of 95%.

Results

One-hundred and eleven patients with gastric cancer were evaluated in eligibility. Nine patients with rare tumors were excluded, and 102 patients were included in the study. Sixty-five were male, 37 were female (Male/Female ratio: 1.75). Mean age was 63.9 (12.3) years (ranging between 21 and 89). Flowchart of the study is shown in figure 1.

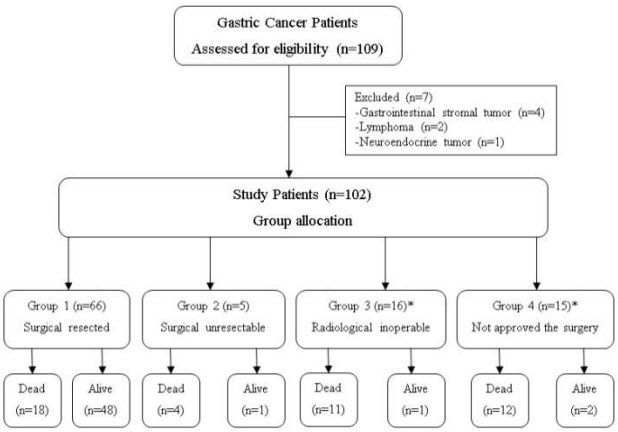

Figure 1: Flowchart of the study (* Five patients, four in group 3, one in group 4, left the follow-up, and their outcomes are unknown)

Sixty-six patients underwent surgical resection (group 1). Forty-two of these patients received total gastrectomy (proximal tumors) and 24 subtotal gastrectomy (distal tumors).

Additional operations were performed in six patients (three splenectomy, one distal pancreatectomy, one cholecystectomy and resection of liver segment 5, one nephrectomy). Average dissected lymph node count was 34.3 (10-65) and mean lymph node metastasis count was 10.9 (range 0-60). Five patients were diagnosed as inoperable during surgery (group 2) and only one of them received palliative gastro-enterostomy.

Post-operative complications occurred in 18 (25.4%) patients (11 surgical site infection, three pulmonary infection, two anastomosis leakage, one renal failure, one sub-phrenic abscess, one pulmonary emboli, one evisceration). Three patients (4.2%) died within the first month after operation, and accepted as surgical mortality.

Six-teen patients were determined as inoperable by radiologic evaluation (group 3). Fifteen patients (group 4) were evaluated as operable; however they didn't give consent for surgery and received only oncological treatment (chemo/radiotherapy). All patients operated or not, were directed to the medical oncology department for further treatment (chemo/radiotherapy).

No differences were detected among groups in comparison of gender with *P* of 0.250 (table 1). However, age distribution was different between groups with *P* of 0.043 because group 4 is formed by older patients with mean age of 71.0 (10.0).

Table 1: Demographics of study patients

		Group 1 (n=66)	Group 2 (n=5)	Group 3 (n=16)	Group 4 (n=15)	*P*-value
Age, Mean (SD)		63.2 (12.2)	66.8 (6.7)	59.0 (13.3)	71.0 (10.0)	[1] 0.043*
Gender, n (%)	Male	40 (60.6)	5 (100)	9 (56.3)	11 (73.3)	[2] 0.250
	Female	26 (39.4)	0 (0)	7 (43.8)	4 (26.7)	

SD: Standard deviation, [1] Anova test, [2] Chi-square test, *$P<0.05$

Survival analysis

Five patients abandoned the follow-up therefore 97 patients were evaluated in survival analysis. Median survival of all patients was 10.0 (1.5) months (range 0 - 79).

Survival analysis showed that patients in group 1 (14.0 (5.1) months) had better survival than other groups ($P=0.011$, table 2, figure 2). Male patients showed better survival than female patients (14 (1.9) vs. 6 (1.8) months, $P=0.002$, table 3, figure 3).

Table 2: Kaplan Meier survival analysis of groups

	Estimate (month)	Std. Error	95% Confidence Interval Lower Bound	Upper Bound	*P*-value (Log Rank)
Group 1	14.000	5.078	4.048	23.952	0.011
Group 2	5.000	2.191	0.706	9.294	
Group 3	4.000	0.569	2.884	5.116	
Group 4	6.000	0.617	4.790	7.210	
Overall	10.000	1.513	7.034	12.966	

Group 1: Resected surgically, Group 2: Surgically unresectable, Group 3: Radiological inoperable, Group 4: Not approved the surgery

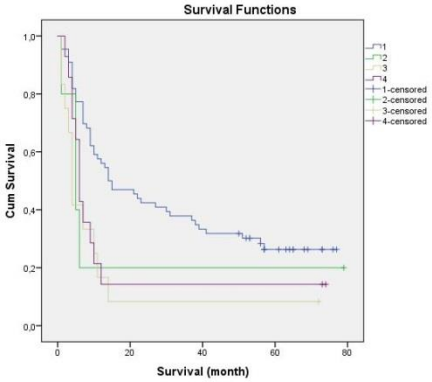

Figure 2: Survival analysis between groups (Group 1: Resected surgically, Group 2: Surgically unresectable, Group 3: Radiologically inoperable, Group 4: Not approved the surgery)

Further analysis was performed for group 1 patients as a subgroup analysis. No differences were detected in respect to location of the tumor ($P=0.884$, table 4, figure 4). Advanced TNM stages showed less survival ($P<0.001$, table 5, figure 5).

Table 3: Survival analysis of genders

Gender	n (%)	Median Estimate (month)	Std. Error	95% Confidence Interval Lower Bound	Upper Bound	*P*-value (Log Rank)
Male	65 (63.7)	14.000	1.935	10.207	17.793	0.002
Female	37 (36.3)	6.000	1.824	2.425	9.575	
Overall	102 (100)	10.000	1.228	7.593	12.407	

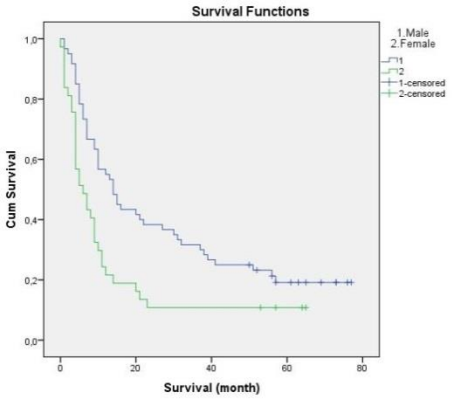

Figure 3: Survival analysis according to genders

Table 4: Survival analysis of tumor locations in group 1

Location	n (%)	Median Estimate	Std. Error	95% Confidence Interval Lower Bound	Upper Bound	*P*-value (Log Rank)
Proximal	42 (63.7)	14.000	3.780	6.590	21.410	0.884
Distal	24 (36.3)	9.000	13.472	0.000	35.405	
Overall	66 (100)	14.000	4.062	6.038	21.962	

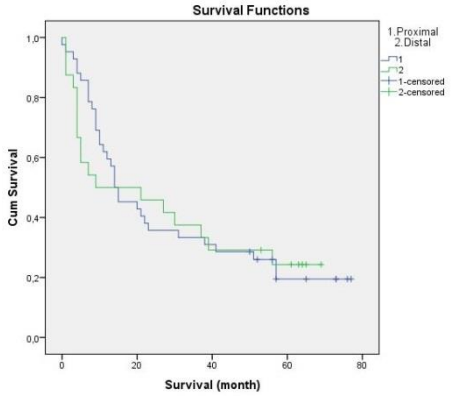

Figure 4: Survival analysis of tumor locations in group 1

Table 5: Survival analysis according to TNM stages in group 1

TNM stage	n (%)	Median Estimate (month)	Std. Error	95% Confidence Interval Lower Bound	Upper Bound	*P*-value (Log Rank)
Stage 1	5 (7.8)	.	.	.	.	<0.001
Stage 2	16 (23.4)	57.000	.	.	.	
Stage 3	38 (57.9)	9.000	1.539	5.984	12.016	
Stage 4	7 (10.9)	7.000	2.619	1.868	12.132	
Overall	66 (100)	14.000	5.078	4.048	23.952	

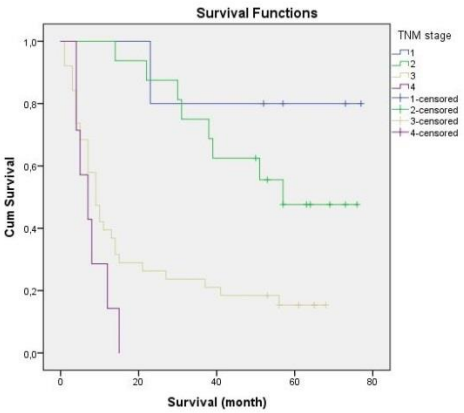

Figure 5: Survival analysis according to TNM stages in group 1

Discussion

In this study, we found that the patients with gastric cancer who were unresectable detected during operation, radiological inoperable detected preoperatively and refused the operation, has showed lesser survival than the patients who were suitable for surgery and underwent surgical resection.

Gastric cancer is still a significant cause of death among cancers even though its incidence reduced and resectability rate got higher since the second half of the 20th century in western countries. Prognosis is still poor despite the fact that post-operative mortality rate lowered from 14% to %6 in western countries. Poor survival time is mostly related to late diagnosis and local/regional recurrence (4). Excluding Japan, early gastric cancers' 5-year-survival-time is 25-40%. Male incidence is 1.8-2 times higher than female. Incidence gets higher with age and mostly seen in the 6th and 7th decades. Various retrospective multivariate analyses indicate that age is an irrelevant factor for prognosis [4-6]. In our study, we observed that most gastric cancer patients are diagnosed in an advanced stage and surgically resected patients' mortality rate is 3%, and male incidence is 1.75 times higher and 66.6% of the patients are the 6th and 7th decades of age, just as in literature.

Stage, lymph node metastasis and penetration through the gastric wall are significant for prognosis. Prognosis in early stage can be very good; however, 60% of the patients have already lost the chance to have surgery when diagnosed. Most of these patients are either in the 3rd or 4th stage [7]. Metastatic lymph node count and extent of serosa invasion negatively affect prognosis. Five-year-survival for stage IA is 90%, 80% for stage IB, 65% for stage II, 50% for stage IIIA, 30% for IIIB and 5% for stage IV, and operated stage I and IV patients' five-year-survival are found to be 88.2% and 3.7% respectively. These results were to be found relevant statistically in univariate and multivariate analyses [8]. In our study, we found tumor stage to be a significant factor for prognosis just as in literature. Mortality rate of our operated gastric cancer patients were found to be 0% for early stage, 18.2% for stage II, 67.8% for stage III and 100% for stage IV.

Lymph node metastasis is also an important prognostic factor. Huang et al.'s [9] retrospective analysis of 236 D2 resected patients with gastric cancer originating from cardia and fundus showed that adequate lymph node resection and low count of metastatic lymph nodes (lower than 30%) increase survival time. Know et al. [10] grouped patients according to their ratio of dissected lymph nodes to metastatic lymph nodes as 0%, 1-25%, 26-50 and higher than 50% and reported 5-year-survival as 83%, 66%, 30% and 23% respectively. In a multi-centric study, among retrospectively scanned 777 advanced stage gastric cancer patients' survival time, the most significant difference was found to be the threshold of 11 metastatic lymph node (chi-square value 42.88, HR:2,523, CI 95%, 1.913, 3.329 (P<0.001)-cox rational risk model). According to this conclusion, patients were divided into 2 groups, lymph node metastasis count 10 or below and above 10. Prognosis was found to be better in patients with lymph node metastasis count lower than 10 [11].

Stewart et al.'s [12] study with 1654 gastric cancer patients showed us lymph node involvement higher than 20% is the most important poor prognostic factor. It was stated that extended lymphadenectomy may increase the excised metastatic lymph node count and therefore prolong survival time. Metastatic lymph node count and stage is a very important prognostic factor.

Primary treatment of gastric cancer is surgery, and enough surgical resection margins are the most important prognostic factor [12]. Sixty-six patients have gone under resection and D2 lymph node dissection in our series. Average dissected lymph node count was 34.3 (10-65) and mean lymph node metastasis count was 10.9 (0-60). As we mentioned before, stage, lymph node metastasis and penetration through the gastric wall are significant factors for prognosis. Therefore, improvements in population screening for gastric cancer are of high importance to diagnose and treat in an early stage just like all cancer types. Screening programs like endoscopic procedures and tumor marker analysis's are found to be successful in diagnosis of gastric cancer in an early stage, especially in the Far East countries [13,14].

Adequate surgical resection is also an important prognostic factor for gastric cancer and most of cancer as stated in the literature [15-18]. This also means adequate lymph node dissection which makes it a surgical prognostic factor. We strongly believe that D2 lymph node dissection should be standardized for gastric tumors just as the Swedish studies made in meso-colic resection for rectum tumors.

In the United States, the reported overall 5-year relative survival rate of all people with stomach cancer is approximately 29%. The relative survival rate comes from comparison of the observed survival of stomach cancer to that expected for normal people. In our study, we found 5-year survival as 38.1% in all group. Since we did not studied to reveal relative survival, it is little higher from relative survival reported in the literature [15,19]. Further studies are needed to evaluate relative survival of all people with stomach cancer in our country.

Over the last 30 years, survival rate has improved gradually as new therapeutic modalities emerged. However the overall survival rate reported in the United States is poor due to most stomach cancers are diagnosed at an advanced stage. The stage of the cancer has been reported as the major factor on a patient's prognosis [19]. In our study, we demonstrated the same outcome as reported in literature.

The study has a number of possible limitations. The main limitation of this study is that the number of patients in study groups was small at some level. Future larger studies with definitive statistical results would be of interest. The other limitation was that stage of gastric cancer was not obvious in the patients who refused surgery. Although this study was conducted in one hospital in Turkey, the results may be generalizable to other areas.

Our findings suggest that patients should be more informed about the surgery to decrease refusal and late admissions with more advanced stage, and screening programs should be encouraged. With this study, comparing the study groups and judging a better course of disease may be little excessive interpretation of the statistical analysis. Several

questions remain to be resolved, and aforementioned data found in this study should be proven, in particular. Despite the limitations, this study demonstrates that surgery remains the most effective method in the treatment of gastric cancer.

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Anxiety, depression, type D personality, somatosensory amplification levels and childhood traumas in patients with panic disorders

Panik bozukluğu olan hastalarda anksiyete, depresyon, D tipi kişilik, bedensel duyumları abartma seviyeleri ve çocukluk çağı travmaları

Yasin Taşdelen [1], İbrahim Yağcı [2]

[1] Department of Psychiatry, Aydın State Hospital, Aydın, Turkey
[2] Department of Psychiatry, Kars Harakani State Hospital, Kars, Turkey

ORCID ID of the author(s)
YT: 0000-0003-4985-0690
İY: 0000-0003-0755-2695

Corresponding author / Sorumlu yazar:
Yasin Taşdelen
Address / Adres: Aydın Devlet Hastanesi, Psikiyatri Anabilim Dalı, Aydın, Türkiye
e-Mail: yasintasdelen@hotmail.com

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Abstract

Aim: Persons with type D personality have been shown to be predisposed to depression and anxiety disorders. However, to our knowledge, there are no studies which have investigated the relationship between panic disorder (PD) and type D personality. Our aim in the current study was to determine whether PD was associated with Type D personality, anxiety, depression, childhood trauma and somatosensory amplification by comparing the characteristics of patients with and without PD.

Methods: We designed a questionnaire based case-control study. The study group included 100 patients with panic disorder, and control group consisted of 100 healthy individuals. Sociodemographic Data Form, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Type D Personality Scale (DS14), Childhood Trauma Questionnaire (CTQ) and Somatosensory Amplification Scale (SSAS) were carried out for each participant.

Results: The patient and control groups were found to be similar in terms of sex, marriage status, education status and employment status. Compared to the control group, scores for BAI (P<0.01), BDI (P<0.01), CTQ (P<0.01), DS-14 (P<0.01) were found to be significantly higher in the patient group. The frequency of Type D personality was also higher in the patient group.

Conclusion: Our findings show that patients with PD have significantly higher scores in anxiety, depression, Type D Personality, CTQ total scores measures compared to controls. We did not find any associations between PD and somatosensory amplification. We believe our findings will contribute significantly to the limited literature on this topic.

Keywords: Panic disorder, Type D personality, Childhood trauma, Depression, Anxiety

Öz

Amaç: D tipi kişiliğe sahip kişilerin depresyon ve anksiyete bozukluklarına yatkın oldukları gösterilmiştir. Ancak, bildiğimiz kadarıyla panik bozukluğu ve D tipi kişilik arasındaki ilişkiyi araştıran hiçbir çalışma bulunmamaktadır. Bu çalışmada amacımız, Panik bozukluk tanısı olan ve olmayan hastaların özelliklerini karşılaştırarak Panik bozukluğun D Tipi kişilik, kaygı, depresyon, bedensel duyumları abartma ve çocukluk çağı travmaları ile ilişkili olup olmadığını belirlemekti.

Yöntemler: Anket bazlı bir vaka kontrol çalışması tasarladık. Çalışmaya panik bozukluğu olan 100 kişi ve 100 sağlıklı kişi dahil edildi. Her bir katılımcıya Sosyodemografik Veri Formu, Beck Depresyon Ölçeği (BDÖ), Beck Anksiyete Ölçeği (BAÖ), D Tipi Kişilik Ölçeği (DS-14), Çocukluk Çağı Travma Ölçeği (ÇÇTÖ) ve Bedensel Duyumları abartma Ölçeği (BDAÖ) yapıldı.

Bulgular: Olgu ve kontrol gruplarının cinsiyet, evlilik durumu, eğitim ve çalışma durumu açısından farklılık olmadığı bulundu. Hasta grubunda kontrol grubuna göre BAÖ (P<0.01); BDÖ (P<0.01); ÇÇTÖ (P<0.01); DS-14 (P<0.01) anlamlı olarak yüksek bulunmuştur. D Tipi kişilik sıklığı da hasta grubunda daha yüksekti.

Sonuç: Bulgularımız, Panik bozukluğu olan hastaların anksiyete, depresyon, D Tipi Kişilik, Çocukluk çağı travmatik yaşantıları toplam puanları kontrol grubuna göre anlamlı olarak yüksektir. Panik bozukluk ve bedensel duyumları abartma arasında anlamlı bir ilişki bulamadık. Bulgularımızın bu konudaki sınırlı literatüre önemli katkı sağlayacağına inanıyoruz.

Anahtar kelimeler: Panik bozukluk, D tipi kişilik, Çocukluk çağı travmaları, Depresyon, Anksiyete

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Introduction

Panic disorder (PD) is one of the anxiety disorders. It is a chronic or recurrent condition that significantly deprives the individual of social and functional ability [1]. The life-time prevalence of PD is reported to be 1.5–2.5%, while the prevalence of panic attack is around 7–9%. A systematic review which assessed studies from Europe reported a 12-month prevalence rate of 1.8% for PD, in 2005 [2]. Various studies have linked PD with major depression [3], higher anxiety (or sensitivity) [4], having suffered childhood abuse [5], neural fear triggers and several other psychosocial factors including personality traits [6]. Neuroticism, a major personality trait causing persons to disproportionately suffer from stressful events, has especially been associated with PD. Individuals with high neuroticism scores tend to have high levels of stress, are burdened heavily by stressful events, and experience sadness and depression more frequently. These characteristics are also exhibited by persons with type D personality, albeit at varying levels.

Individuals with type D personality are characterized by negative affectivity and social inhibition, meaning they are more likely to experience negative affect (similar to neuroticism) whilst also being less likely to express subsequent feelings in social environments [7]. For the sake of an example, this personality type may be likened to a psychological pressure cooker; outside effects cause significant pressure for the individual, however they are unable to express their feelings, leading to reduced quality of life and significant stress [8]. Persons with type D personality have been shown to be predisposed to depression and anxiety and stress disorders [9].

Our aim in the current study was to determine whether PD was affected by factors such as Type D personality, Somatosensory Amplification, depression, anxiety and a history of childhood trauma by comparing the characteristics of patients with and without PD.

Materials and methods

The study was a clinical observational study of case-control type. The characteristics of patients with panic disorder were compared with controls. Enrollment to the study was continued until a total of 100 persons with panic disorder and 100 controls were included into the study. Panic disorder diagnoses were made according to the DSM-5 diagnostic criteria by experienced psychiatrists (Table 1). Ethical approval was obtained from the Kafkas University Ethical Committee (no: 6, date: 25.04.2018).

Inclusion criteria were the fact that the patient was diagnosed with panic disorder by the psychiatric physician was to be over 18 years of age and the patients agreed to participate in the study. For the control group, the patient did not have any psychiatric disorder, accepted to participate in the study and was over 18 years of age. Exclusion Criteria were determined the refusal to participate after being informed and the presence of clinically detected mental retardation and illiteracy.

Measurements

The age, gender, marriage status, educational status and employment status of all patients and controls were recorded. Afterwards, all participants underwent the following questionnaires: Somatosensory Amplification Scale (SSAS), Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI) and the Childhood Trauma Questionnaire. All questionnaires were applied to patients under the management of a psychiatrist and in the presence of a single nurse, both of which were blinded to the study protocol. The scales used were evaluated by the psychiatrist. Each questionnaire was completed in 20–25 minutes.

Somatosensory Amplification Scale (SSAS)

Developed by Barsky et al. [10], this 10-item scale determines how patients interpret somatic symptoms and reports the level of somatization as a continuous variable. All items are equally weighted (1 to 5 points) and the total score from the questionnaire may range from 10 to 50. A higher score indicates greater somatic amplification.

Beck Anxiety Inventory (BAI)

Beck et al. [11] developed this 21-question inventory for the measurement of anxiety symptoms among patients. All items are scored on a scale of 0–3 points with possible total scores ranging between 0-63 points. A high total score reflects the presence of high anxiety in a patient.

Beck Depression Inventory (BDI)

This inventory was also developed by Beck et al. [12]. It is another 21-item questionnaire and determines the severity and risk of depression in an individual. Each item is scored between 0–3 and the resultant total scores range from 0 to 63 points.

The Childhood Trauma Questionnaire

This questionnaire was developed by Bernstein and colleagues for the evaluation of childhood maltreatment [13]. The 28-item test determines the presence and severity of 5 maltreatment types: emotional and physical neglect, and emotional, physical and sexual abuse. The points gathered in these subsections are then summed up, resulting in a final total score.

Evaluation of Type D personality

The assessment of type D personality was performed via the Type D Scale-14 (DS14) [14]. The DS14 questionnaire is comprised of two sets of questions which evaluate negative affectivity (7-items) and social inhibition (7-items). Each item is evaluated on a 5-point Likert scale ranging from 0 to 4 points (0=false, 1=rather false, 2=neutral, 3=rather true to 4=true). The possible total score of each section ranges between 0–28. Those with ≥10 points on both scales are classified as having type D personality.

Statistical analysis

The SPSS version 20 software package for windows was used to evaluate all data. Normal distribution was tested with the Shapiro-Wilk test. The Student's t-test was used to compare data with normal distribution, and the Mann-Whitney U-test was used to compare data without normal distribution. Analysis of Covariance (ANCOVA) with age as a covariate was used for comparing variables that correlated with age. Categorical data was analyzed using Chi-square tests. $P \leq 0.05$ values were considered statistically significant.

Results

The case and control groups were found to be similar in terms of sex (P=0.725), marriage status (P=0.388), education status (P=0.453) and employment status (P=0.118). The mean age of the control group (24.68 (5.62) years) was lower than that of the case group (29.26 (8.04) years) (P=0.001). The distribution of sociodemographic characteristics in both groups are shown in Table 2.

Compared to the control group, mean BAI (P=0.001), BDI (P=0.001), CTQ (P=0.001) and SSAS (P=0.007) scores were found to be higher in the case group. The frequency of Type D personality was also more frequent in the case group (P=0.001). However, after adjusting for age, SSAS was not found to be associated with panic disorder (P=0.061). The mean scores of both groups in terms of psychologic measurements are shown in Table 3.

In the PD group, patients with and without Type D personality were found to be similar in terms of BAI, BDI, CTQ and SSAS total scores. The distribution of psychologic measurements of the case group according to D type personality is shown Table 4.

Table 1: DSM-V Diagnostic Criteria for Panic Disorder

Diagnostic Criteria for Panic Disorder
1) Recurrent unexpected panic attacks
2) At least one of the attacks has been followed by a month or more of one or both of the following:
a) Persistent concern or worry about additional panic attacks or their consequences (eg, losing control, having a heart attack, "going crazy").
b) A significant maladaptive change in behavior related to the attacks (eg, behaviors designed to avoid having panic attacks, such as avoidance of exercise or unfamiliar situations).
3) The disturbance is not attributable to the physiological effects of a substance (eg, medication or illicit drug) or another medical condition (eg, hyperthyroidism, cardiopulmonary disorders).
4) The disturbance is not better explained by another mental disorder. As examples, the panic attacks do not occur only in response to:
a) Feared social situations, as in social anxiety disorder
b) Circumscribed phobic objects or situations, as in specific phobia
c) Obsessions, as in obsessive-compulsive disorder
d) Reminders of traumatic events, as in posttraumatic stress disorder
e) Separation from attachment figures, as in separation anxiety disorder

Table 2: The distribution of sociodemographic characteristics in the case and control groups

	Case group (n=100)	Control group (n=100)	*P*-value
Sex			
Male	51(47.2%)	57(52.8%)	0.725
Female	49(53.3%)	43(46.7%)	
Age	29.26±8.04	24.68±5.62	0.001
Marriage status			
Single	56(47.5%)	62(52.5%)	0.388
Married	44(53.7%)	38(46.3%)	
Education			
Primary School	16(51.6%)	15(48.4%)	
Secondary School	24(52.2%)	22(47.8%)	0.453
High School	45(53.6%)	39(46.4%)	
University	15(38.5%)	24(61.5%)	
Employment			
No	50(56.2%)	39(43.8%)	0.118
Yes	50(45.0%)	61(55.0%)	

Table 3: The distribution of psychiatric measurement scores in the case and control groups

	Case group (n=100) Mean(SD)	Control group (n=100) Mean(SD)	*P*-value
BAI	42.94(10.43)	6.96(3.27)	0.001*
BDI	25.44(11.47)	12.37(3.56)	0.001*
CTQ			
Physical Neglect	12.98(2.34)	11.85(3.33)	0.016*
Physical Abuse	18.34(2.48)	15.85(2.84)	0.001*
Emotional Neglect	11.53(1.49)	11.15(2.75)	0.779
Emotional Abuse	23.83(2.19)	21.19(3.24)	0.001*
Sexual Abuse	11.86(1.30)	11.96(2.85)	0.570
Total scale	78.54(6.13)	72.09(8.46)	0.001*
SSAS	32.66(8.31)	30.71(6.10)	0.061

SD: Standard deviation, DS-14: Type D Personality, BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory, SSAS: Somatosensory Amplification Scale, CTQ: Childhood Trauma Questionnaire, * P<0.05

Table 4: The distribution of psychiatric measurements in the case group according to D type personality

	Type D (n=84) Mean (SD)	Non-type D (n=16) Mean (SD)	*P*-value
BAI	7.00 (3.21)	6.75 (3.64)	0.677
BDI	12.27 (3.46)	12.88 (4.10)	0.613
CTQ	78.31 (6.15)	79.75 (6.04)	0.409
SSAS	30.73 (6.15)	30.63 (6.02)	0.854

SD: Standard deviation, BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory, SSAS: Somatosensory Amplification Scale, CTQ: Childhood Trauma Questionnaire

Discussion

In the current study, patients with panic disorder were compared with controls in terms of sex, age, marriage, education and employment status as well as psychological measurements. The results demonstrated that patients with PD were similar to controls in regard to sex, marriage, education and employment status, whereas, age was found to be significantly higher in the PD group. In regard to psychological measurements adjusted for age difference, those with PD were found to have higher total scores in the BAI, BDI and CTQ scales. SSAS scores were similar in both groups.

There are only a few studies in the literature that have focused on the relationship between psychiatric disease and Type D personality. In a study by Michal and colleagues, it was reported that those with Type D personality had higher risk for psychiatric problems such as social inhibition, depression, panic and somatization. The same study also reported that Type D personality immensely increased the risk for PD (OR: 5.09 (3.43-7.58), 2.2% vs 10.4%) [15]. Grande et al. reported that Type D personality was present in 62.5% of individuals who were followed by their psychiatry department with various types of mental distress [16]. In another study, in which patients with non-cardiac chest pain were assessed for panic disorder and depression, the authors reported that Type D personality was more frequent in those who had comorbid depression and panic disorder [17]. In the current study, 56 individuals from the PD group (56%) were found to have type D personality, while only 16 of those in the control group (16%) had Type D personality, as measured by DS14. In other words, 77.8% of patients who had Type D personality were patients with PD. This finding indicates the presence of an association between PD and Type D. Contrasting results also exist; one study reported the lack of an association between PD and Type D personality among 571 patients with chronic heart disease [18].

When we compared other psychological measurements, those with PD tended to have significantly higher scores in the anxiety (BAI), depression (BDI) and childhood trauma (CTQ) scales. Considering the differences between the groups in terms of BAI, BDI and CTQ scores, we decided to compare the results of PD patients with and without Type D personality; however, no differences were found between the groups in any of the psychological measures. This finding may be explained by the fact that the case group was comprised of PD patients; hence all would be expected to have high anxiety, leading to similarities in psychiatric measurements.

Psychiatric disease in adult age has been associated with a history of childhood adversities in a number of studies [19]. However, in terms of PD, several studies have shown that childhood adversity seems to have little –if any– effect on

disease frequency [20,21]. Nevertheless, a large meta-analysis of psychiatric studies demonstrated that individuals with PD had a higher frequency of physical trauma during their childhood, while there were no associations between PD and other childhood adversities, such as emotional trauma or sexual abuse [22]. A study by Bandelow and colleagues [23] reported an association between PD and three factors: anxiety disorders running in the family, experience of traumatic events in the childhood, and poor parentage. However, in a later study focused on anxiety disorders, they could not find any association between personality disorders and having a history of physical or sexual abuse in the childhood [24]. In a very informative study by Goodwin et al., the frequency of panic attack and panic disorder were found to be significantly increased among those who suffered childhood physical or sexual abuse [25]. In the current study, childhood adversities were evaluated with the CTQ which showed that those with and without PD had similar results for emotional neglect and sexual abuse subscales, while physical neglect, physical abuse, sexual abuse and total scores were higher among patients with PD. These results suggest that those who suffer physical and sexual adversities in their childhood may be predisposed to panic disorders in their adulthood. However, Segenfredo et al. [26] reported very interesting findings in their evaluation of patients with PD. They found that, compared to controls, emotional abuse, mother overprotection and father overprotection were higher among those with PD. This suggests that both childhood abuse and overprotection may increase the possibility of PD later on in life.

It is evident that the literature on this topic is very conflicted in regard to the associations between PD and childhood trauma. In the light of previous studies and our results, it is reasonable to assume that the risk of PD is increased among those who suffer childhood adversities, especially in the form of physical abuse. However, the fact that studies have associated PD with both ends of the spectrum of negative parental influences (abuse and overprotection) demonstrates the existence of a gap in knowledge regarding the influence of childhood adversities on psychiatric disease in the adulthood.

Clark et al. [27] have strongly argued that PD is associated with misinterpretation of bodily sensations. Furthermore, patients with anxiety disorder were shown to have significant somatosensory amplification in a very recent study [28]. However, studies on PD report highly conflicting results. While some have shown increased SSAS scores in patients with PD compared to controls and those with depression [29], others suggest that somatosensory amplification does not have a role in PD [30]. In our study, although the PD group was found to have higher SSAS scores initially, statistical significance disappeared after adjustment for age. The lack of difference between our groups supports the findings of studies which suggest there is no association between PD and somatosensory amplification.

This study was a self-reported case-control study and inherits all limitations associated with such studies. The number of patients may also be considered low for the generalization of results. However, although several studies have been performed for the evaluation of Type D personality and its effects, the most prominent among these were based on study groups with cardiac disease. This is one of the first studies to evaluate the effects of Type D personality on patients with a diagnosis of PD in the absence of other diseases. We also investigated the role of childhood adversity and somatosensory amplification. Another strength of the study is the fact that all evaluations were performed with widely accepted measures such as the BAI, BDI, CTQ and SSAS questionnaires.

Conclusions

Our results have shown that patients with PD have significantly high scores in childhood adversity, anxiety and depression measures compared to controls. Type D personality was found to be significantly more frequent among those with PD; however, there were no differences among PD patients with and without Type D personality in terms of psychiatric measurements. It was also interesting to observe that PD was not associated to somatosensory amplification. We believe our findings will contribute significantly to the limited literature on this topic. We also believe future studies will benefit from strengthening inclusion and exclusion criteria for patients and increasing the number of psychiatric measures in order to determine whether PD patients with and without Type D personality have significant differences in characteristics.

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Protective effects of krill oil on ischemic reperfusion injury in experimental model of priapism

Kril yağının deneysel priapizm modelinde iskemik reperfüzyon hasarı üzerine koruyucu etkileri

Engin Kölükçü [1], Nihat Uluocak [2], Velid Unsal [3]

[1] Tokat State Hospital, Department of Urology, Tokat, Turkey
[2] Gaziosmanpaşa University, Department of Urology, Tokat, Turkey
[3] Mardin Artuklu University, High School of Health and Central Research Laboratory, Mardin, Turkey

ORCID ID of the author(s)
EK: 0000-0003-3387-4428
NU: 0000-0001-8315-466X
VU: 0000-0003-1415-0563

Abstract

Aim: The aim of the study is to evaluate the effects of krill oil on priapism induced ischemia-reperfusion injury in priapism rat model.

Methods: Total of 24 rats were randomly divided into three groups with eight rats in each group. Group 1 was determined as the control group. Experimental priapism model was constructed in rats in Groups 2 and 3 for 1 hour and then priapism was terminated for 30 minutes to evaluate ischemia-reperfusion injury. The rats in Groups 1 and 2 were given tap water and standard chow pellets. Group 3: The same feeding procedure was applied to the experimental animals but supplemented with krill oil for one month. At the end of the experiment penectomy were performed, and blood samples were withdrawn from inferior vena cava of the rats to determine the levels of protein carbonyl (PC), malondialdehyde (MDA), nitric oxide (NO), glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) in systemic circulation, and cavernosal tissues.

Results: Biochemical examination of penile tissues showed that MDA and PC levels in Group 3 were significantly lower than group 2, while GSH-Px activities were significantly increased (P=0.001, P=0.005, P=0.003, respectively). Serum analysis results showed that MDA and NO levels in Group 3 were significantly lower than Group 2 and SOD activities significantly increased (P=0.011, P=0.001, P=0.009, respectively).

Conclusion: In this study, protective effect of krill oil against priapism induced ischemia-reperfusion injury in cavernosal tissue was observed based on biochemical evidence.

Keywords: Krill oil, Ischemia, Reperfusion, Priapism

Öz

Amaç: Mevcut çalışmanın amacı ratlara uyarlanmış priapizm modelinde krill yağının priapizm kaynaklı iskemi-reperfüzyon hasarı üzerindeki etkilerinin değerlendirilmesidir.

Yöntemler: Toplam 24 adet rat her bir grupta 8 rat bulunacak şekilde randomize edildi. Grup 1 kontrol grubu olarak belirlendi. Deneysel priapizm modeli Grup 2 ve 3'teki ratlara 1 saat süreyle uygulandı ve ardından iskemi-reperfüzyon hasarını değerlendirmek için priapizm 30 dakika süre ile sonlandırıldı. Grup 1 ve 2 deki ratlara standart yem ve musluk suyu verildi. Grup 3: Aynı beslenme prosedürü deney hayvanlarına uygulandı, ancak bir ay boyunca krill yağı ile takviye edildi. Deney sonunda süperoksit dismutaz (SOD), glutatyon peroksidaz (GSH-Px), malondialdehid (MDA), nitrik oksit (NO), protein karbonil (PC) düzeylerinin belirlenmesi amacı ile tüm ratlara penektomi uygulanarak vena kava inferiordan kan örneği alındı.

Bulgular: Penil dokuların biyokimyasal değerlendirmesinde Grup 3'teki MDA ve PC seviyeleri Grup 2'e göre anlamlı derecede düşük gözlemlenirken GSH-Px aktiviteleri anlamlı düzeyde yüksek olarak izlendi (sırasıyla P=0.001, P=0.005, P=0.003). Serum analiz sonuçları ise Grup 3'teki MDA ve NO seviyelerini Grup 2'e göre anlamlı derecede düşük olduğunu gösterirken SOD aktivitesini anlamlı düzeyde yüksek olduğunu ortaya koydu (sırasıyla P=0.011, P=0.001, P=0.009).

Sonuç: Bu çalışmada krill yağının; kavernosal dokuda gelişen priapizm ile indüklenen iskemi-reperfüzyon hasarına karşı koruyucu etkinliği biyokimyasal kanıtlara dayanılarak gözlenmiştir.

Anahtar kelimeler: Krill yağı, İskemi, Reperfüzyon, Priapzm

Corresponding author / Sorumlu yazar:
Engin Kölükçü
Address / Adres: Üroloji Bölümü, Tokat Devlet Hastanesi, Gültekin Topçam Bulvarı, Yeni Cadde, Tokat, Türkiye
e-Mail: drenginkolukcu@gmail.com

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Introduction

Priapism is defined as an ongoing erection lasting longer than 4 hours without sexual stimulation [1]. This term is derived from the Greek god Priapus [2,3]. According to the pathophysiology of priapism, which has an important place in urological emergency practices, is considered in three groups as stuttering (recurrent or intermittent), nonischemic (high-flow or arterial) and ischemic (low-flow or venous-occlusive) priapism. Nonischemic priapism which is not accompanied with findings of ischemia penile tissue, and stuttering priapism, which is characterized by painful erection periods constitute only 5% of all patients with priapism [1]. It is estimated that the annual incidence of ischemic priapism, also known as a compartment syndrome, is between 0.3 and 1.5 per 100,000 men, which constitutes 95% of cases diagnosed with priapism [4].

In ischemic priapism tissue blood supply becomes deficient and stasis occurs in the corpus cavernosum. This circulatory disorder occurring in the cavernous tissues results in the development of an acidic, anoxic, hypercarbia and glucopenic environment [4,5]. Ischemic priapism is one of the most important urological emergencies affecting the sexual life of couples in the short and long term. Application of treatment algorithms without wasting time is very critical in preventing tissue damage. Otherwise, cavernosal smooth muscle necrosis, corporal fibrosis and erectile dysfunction develop in patients with ischemic priapism [6]. The first administration involves aspiration and installation of the most common phenylephrine, α-adrenergic agonists, during an attempt to increase smooth muscle tone. Although there is no universally accepted treatment algorithm, surgical approaches are considered in patients who did not respond to treatment or seek medical help at a very late stage of the disease [7].

With the termination of ischemic priapism, the tissues are reperfused, but a very complex chain of reactions, called ischemia-reperfusion injury becomes manifest. Reperfusion carries a vital importance for ischemic tissues. However, this situation leads to a number of metabolic effects that, paradoxically, only lead to more serious consequences than ischemia-induced damage. In tissues that are deprived of high energy during ischemic period; alteration in electrolyte content results in a decrease in antioxidant enzyme level, increase in the production of proinflammatory cytokines and leukocyte adhesion molecules, and leads to the formation of a vulnerable environment against damage that may occur during reperfusion period [8]. In fact, with reperfusion of ischemic tissue, molecular oxygen enters into cells and initiates chain reactions where rapidly emerging reactive oxygen species play a main modulatory role in the induction of ischemia-reperfusion injury which damages important molecules as membrane lipids, genetic material, intracellular structural and functional proteins [9]. When we look at previous studies, it has been observed that many pharmacological agents have been investigated in order to protect the tissues from ischemia-reperfusion injury or to minimize the damage.

Krill oil is obtained from the Antarctic krill (Euphausia superba) which is a rich source of long-chain fatty acids [10]. Krill oil contains high concentrations of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA); there are many important functions such as preservation of membrane structures, modulating of an inflammatory response, and regulation of fetal development [10,11]. In addition, Krill oil also contains very effective antioxidants such as astaxanthin, vitamins E and A [12]. Thanks to all of these features, krill oil has been investigated in many different fields ranging from cardiovascular diseases to central nervous system disorders.

In this study, we aimed to determine the effect of krill oil against priapism induced ischemia-reperfusion injury in cavernosal tissue was observed based on biochemical evidence. To the best of our knowledge this is the first experimental study investigating the effects of krill oil on rat priapism model.

Materials and methods

Animals

A total of twenty-four 10 week-old-male Wistar-Albino rats weighing between 220 and 450 g were used in our study. The protocol of the experimental study were performed in compliance with the provision of 1986 Strasbourg Universal Declaration on Animal Welfare and approved by the local ethical committee (HAYDEK 2015-26). The rats were maintained in standard solid cages as three rats for each cage under 12 hours of light and dark cycle and, at a constant temperature of 22 ° C.

Experimental design

All surgical procedures were performed under an appropriate depth of anesthesia. To this end an anesthetic agent xylazine hydrochloride with sedative and muscle relaxation effects (Rompun 2%, Bayer, Turkey) was administered through the intraperitoneal route at a dose of 10mg/kg. Also ketamine hydrochloride with dissociative anesthetic effectiveness was also given via intraperitoneal route a dose of 50-60 mg/kg (Alfamine 10%, Ege Vet, Turkey). Priapism in experimental animals was performed according to the method described by Sanli et al [13]. Vacuum the erection was performed with the tip of the 5 cc syringes. Then 2 mm wide constriction bands prepared from 16 Fr Foley catheters were tied around the base of the rat's penis to sustain erection. Total of 24 rats were randomly divided into three groups with eight rats in each group. Group 1 was assigned as the control group. The rats only penectomy was performed and 3 cc blood samples were withdrawn form inferior vena cava to determine the baseline levels of protein carbonyl (PC), malondialdehid (MDA), nitric oxide (NO), glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) in systemic circulation, and cavernosal tissues. Group 2: Priapism was induced in compliance with the above-indicated priapism model. At the end of the first hour priapism was terminated and penile reperfusion was applied for 30 minutes [13,14]. Then penectomy were performed, and 3 cc blood samples were withdrawn from inferior vena cava of the rats to study the same parameters. The rats in these two groups were given tap water and standard chow pellets. Group 3: The same feeding procedure was applied to the experimental animals but supplemented with krill oil for one month. Krill oil (SuperbaTM Krill Oil, Aker Biomarine, Norway) was given to experimental rats at a dose of 0.5 ml-100g/kg [15]. In this group, the same ischemia-reperfusion model was applied to the second group. Penile and

blood samples were analyzed using the same procedure as in the other groups (Figure 1).

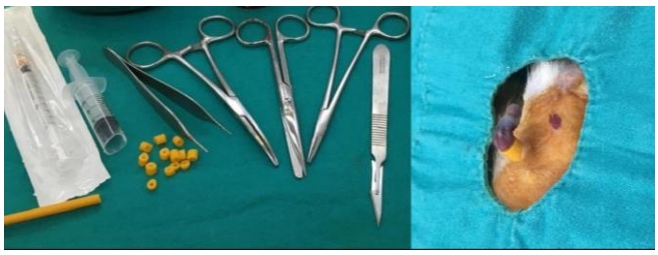

Figure 1: Priapism induced in rat model

Biochemical evaluations

Measurement of MDA levels

The reaction of the lipid peroxidation product MDA with thiobarbituric acid (TBA) yields a pink color at a wavelength of 532 nm during spectrophotometry [16].

Determination of SOD activity

Experimental principle is that the superoxide present in the xanthine/xanthine oxidase system is a byproduct of the reduction of nitro blue tetrazolium (NBT). This complex gives maximum absorbance at 560 nm in the spectrophotometer [17].

Determination of GSH-Px activity

The method is based on the measurement of GSH-Px activity and the reduction of absorbance at 340 nm due to the removal of NADPH present in the medium. In the experimental environment, there were reduced glutathione, sodium azide, glutathione reductase, NADPH and H2O2 as the last substrate [18].

Determination of PC levels

Based on the principle that the groups would react with 2.4-dinitrophenylhydrazine to form 2.4 dinitrophenylhydrazone, levels of PC group were measured spectrophotometrically at 370 nm [19].

Determination of NO levels

The determination of nitrite/nitrate, the stable end product of NO radicals, is often used as a measure of NO production. The total NO concentration is generally determined as the sum of nitrite and nitrate concentrations. The amounts of nitrite and nitrate were determined by spectrophotometric analysis at 540 nm with the Griess reaction [20,21].

Statistical analysis

The calculations were made by statistical software (IBM SPSS Statistics 21, SPSS inc., an IBM Co., Somers, NY). Data were shown as means±standard deviation, and Kruskal-Wallis test was used for analysis. If statistically significant results were obtained, then the Mann-Whitney U test was employed for comparisons of differences between the two independent groups. $P<0.05$ was accepted as the level of statistically significant.

Results

The results of biochemical analysis in penile tissues are presented in Table 1. Experimental animals were compared, and higher MDA, PC and NO values found in Group 2 relative to Group 1 without any statistically significant intergroup difference ($P>0.05$). The mean MDA and PC values in Group 3 were measured as 42.41 (8.4) nmol/g wet tissue and 2.15 (0.56) nmol/µg protein respectively. Although both values were considered to be low compared to Group 2 ($P=0.001$, $P=0.005$ respectively). On the other hand, no statistically significant correlation was found between Groups 2 and 3 when NO levels were evaluated in penile tissue samples ($P=0.12$). When the antioxidant enzyme activities of the experimental animals in Group 3 were investigated, SOD and GSH-Px values were measured as U/mg protein 0.15 (0.03) U/mg and 18.69 (7.22) U/mg protein respectively. GSH-Px value significantly increased relative to the other Groups 1 and 2 ($P=0.01$, $P=0.003$ respectively). No statistically significant correlation was found between the other two groups in terms of SOD values ($P= 0.14$).

Results of serum biochemical analysis are presented in Table 2. Accordingly, the mean NO value in the experimental animals in Group 3 was 71.14 (12.53) µmol/L which was significantly lower than Group 2 ($P=0.001$). The mean SOD and GSH-Px values in Group 3 were measured as 11.75 (1.24) U/ml and 760.87 (333.9) U/L respectively. Although both values were higher when compared with the other two groups, only SOD values were found to be statistically significantly higher ($P=0.009$). On the other hand, the mean MDA and PC values of the experimental animals in Group 3 were 1.65 (0.43) nmol/g and 712.1 (103.69) nmol/m, respectively. Although both values were considered to be low compared to Group 2, only mean MDA value was statistically significantly lower in Group 3 ($P=0.011$). On the other hand, no statistically significant relationship was found between the control group and the ischemia-reperfusion group in both serum and tissue biochemical examinations. This condition is thought to be related to the short duration of ischemia-reperfusion injury.

Table 1: Biochemical analysis results and comparisons in penile tissues of all groups

Groups (n:8)	SOD (U/mg protein)	GSH-Px (U/mg protein)	MDA (nmol/g wet tissue)	PC (nmol/µg protein)	NO (µmol/g wet tissue)
Group 1	0.11 (0.03)	7.15 (2.19)	53.49 (6.59)	3.87 (0.59)	3.17 (0.85)
Group 2	0.16 (0.03) [a]	6.75 (2.01)	69.42 (11.88)	4.21 (1.1)	3.62 (0.42)
Group 3	0.15 (0.03)	18.69 (7.22) [b]	42.41 (8.4) [c]	2.15 (0.56) [d]	5.61 (3.12) [e]

SOD: Superoxide dismutase, GSH-Px: Glutathione peroxidase MDA: Malonyldialdehyde, PC: Protein carbonyl, NO: Nitric oxide

The paired comparison of biomarkers in tissue between the study groups

a) In comparison between Group 1, and Group 2 $P=0.044$.
b) In comparison between Group 1, and Group 3 $P=0.01$ and between Group 2, and Group 3 $P=0.003$.
c) In comparison between Group 2, and Group 3 $P=0.001$.
d) In comparison between Group 1, and Group 3 $P=0.007$, and Group 2 and Group 3 $P=0.005$.
e) In comparison between Group 1, and Group 3 $P=0.037$.
A statistically significant difference was not found between other groups.

Table 2: The biochemical analysis results of all groups in serum and comparisons between the groups

Groups N: 8	SOD (U/ml)	GSH-Px (U/L)	MDA (µmol/l)	PC (nmol/ml)	NO (µmol/L)
Group-1	8.34 (1.34)	563.26 (153.99)	2.85 (0.74)	1098.37 (147.9)	325.83 (99.06)
Group-2	8.37 (1.09)	451.01 (97.11)	3.05 (0.94)	1058.28 (454.6)	432.74 (37.39)
Group-3	11.75 (1.24) [a]	760.87 (333.9)	1.65 (0.43) [b]	712.1 (103.69) [c]	71.14 (12.53) [d]

SOD: Superoxide dismutase, GSH-Px: Glutathione peroxidase MDA: Malonyldialdehyde, PC: Protein carbonyl, NO: Nitric oxide

The paired comparison of biomarkers in serum between the study groups

a) In comparison between Group 1, and Group 3 $P=0.007$ and between Group 2 and Group 3 $P=0.009$.
b) In comparison between Group 1, and Group 3 $P=0.02$, and between Group 2 and Group 3 $P=0.011$.
c) In comparison between Groups 1, and Group 3 $P=0.018$.
d) In comparison between Groups 2, and Group 3 $P=0.001$.
A statistically significant difference was not found between other groups.

Discussion

Ischemic priapism is a pathological condition requiring urgent intervention characterized by prolonged, painful and rigid erection. When evaluated clinically, the corpus cavernosum is completely rigid and painful, while the corpus spongiosum and glans penis are affected mildly or not at all [4]. Penile smooth muscle plays an effective role in both formation of tumescence,

and detumescence. The smooth muscles relax during erection which is the functional and active state of the penis. In case of detumescence this process is reversed. In dysregulation of penile smooth muscle functions, the tendency for relaxation increases which predisposes to ischemic priapism [1,4]. In only 40% of the diagnosed patients' history of etiologic factors such as hematological disorder, malignancy, neurological disease, or antihypertensive, psychotropic, vasoactive drug use have been detected [7].

Histopathological evaluations using electron microscopy to reveal histological changes in ischemic priapism; have shown that the destructive changes in the cavernosal smooth muscle manifest themselves as interstitial edema after 12 hours. At the end of the 48th hour, thrombus is evident in sinusoidal cavities and its presence in fibroblast-like cells indicates that smooth muscle necrosis is taking its effect [22]. Fibrosis that develops in smooth muscle directly plays a role in the emergence of erectile dysfunction, which is common in priapism patients. Patients presenting with a sustained erection without detumescence interval for longer than 4 hours should be treated immediately. Early intervention in ischemic priapism has a critical importance for functional recovery. Permanent erectile dysfunction may develop in 90% of the cases with priapism that persists for more than 24 hours [6]. On the other hand, it is evident that the majority of patients with priapism is very reluctant to resort to healthcare services because of predominantly felt embarrassment, and shame [23]. In parallel with the prolonged priapism period, an intense fibrosis occurs in the corpus cavernosum. It is known that this situation complicates implantation of penile prosthesis to be performed in the future [4]. Implantation of penile prosthesis is recommended for patients presenting with priapism for more than 36 hours according to current urology guidelines [14,23]. On the other hand untreated or prolonged priapism may present with severe clinical conditions, such as penile gangrene [24].

Ischemia-reperfusion injury is a common clinical entity that may develop as a consequence of many conditions including cerebrovascular accident, hemorrhagic shock, medical or surgical interventions as thrombolytic therapy, coronary angioplasty, and transplantation [9]. Similarly, ischemic reperfusion injury is seen with the treatment of compartment syndrome in ischemic priapism. With the reperfusion of the tissue, paradoxically, ischemia-reperfusion injury depending on the degree of the ischemic injury leads to severe tissue damage [5]. Ischemia is the state in which oxygen (O2) and other substances cannot reach the tissues adequately as a result of impairment of tissue perfusion. Along with hypoxia that occurs after ischemia, the energy level in the cell decreases. The increase in glycolytic rate and ATP consumption directly reduces the cytosolic pH due to the liberation of hydrogen (H+) from the damaged lysosomes. This results in an increase in cytosolic sodium (Na+) and calcium (Ca+2) concentrations and inhibit the activation of the sodium-potassium ATPase (Na-K ATPase) pump. Increase in cytosolic Ca+2 concentration activates hydrolases such as proteases and phospholipases. Hydrolases further enhance the destructive process. Increased intracellular Na+ causes an increase in osmotic pressure and contributes to the degradation of the plasma membrane [25]. Antioxidant enzyme formation decreases and the number of leukocyte adhesion molecules of proinflammatory cytokines increase with the changing ion concentration during the ischemic period. This condition makes the tissue more sensitive to damage during reperfusion period [26,27]. Though a small amount of free radicals are produced during ischemia following reoxygenization, in the reperfusion phase, much greater amounts of free radicals are produced and increase the severity of destructive changes. Following ischemia, inflammatory response begins with reperfusion. This inflammatory process involves endothelial cells, macrophages, neutrophils, platelets, lymphocytes, parenchymal cells as well as non-cellular complement system, blood clotting cascade, free radicals, NO, proinflammatory and anti-inflammatory cytokines, elements, mediators and thus the microvascular perfusion is disrupted [5,8,26,28].

Irreversible cellular damage occurs due to the destructive effects of oxidative stress which leads to an increase in MDA, one of the end products of lipid peroxidation [16]. In a study, Evliyaoglu et al. [29] reported that MDA levels increased in all experimental animals in which priapism were induced compared to the control group. Similar results have been obtained in many studies using ischemia reperfusion model [30]. In our study, MDA levels increased in both penile tissues and serum samples in rats with ischemia-reperfusion injury. But this was not statistically significant. On the other hand, protein metabolism is very adversely affected, as lipids, and also the level of a protein oxidation product, PC increases in ischemia-reperfusion injury [31]. In our study, though not statistically significant, increased tissue PC levels in rats with ischemia-reperfusion injury were detected. NO, is synthesized in smooth muscle, endothelial cells and many other cells as a result of the oxidation of guanidino nitrogen of the amino acid L-arginine via nitric oxide synthase. In low concentrations, decreased concentrations of NO plays a role in important physiological functions, but in cases where tissues are exposed to unaccustomed conditions as oxidative stress, concentrations of NO climb to higher levels and rapidly react with superoxide radicals leading to rapid the formation of peroxinitrite [20,21,32]. In a study, Ozkan et al. [33] reported that NO levels increased in all experimental animals in which intestinal ischemia-reperfusion was induced compared to the control group. In our study, though not statistically significant, NO levels in the penile tissue and serum samples of rats exposed to ischemia-reperfusion injury increased compared to the control group. The superoxide radicals produced in destructive conditions are reduced by an antioxidant enzyme, SOD to hydrogen peroxide. This reduced hydrogen peroxide is converted into water and oxygen by another antioxidant enzyme called GSH-Px [34]. In our study, positive changes were detected that antioxidant enzyme in Group 3 than in Group 2.

Krill in Norwegian means fry fish. It is a shrimp-like, red-crusted small sea creature that lives in the cold waters of the Antarctic Ocean. These creatures do not consume heavy metals and pollutants as opposed to other fish [35,36]. Krill oil is an important phospholipid which differs from other oil types with its omega-3 and astaxanthin content. Of the long-chain fatty acids found in krill oil, a large part of the omega-3 fatty acid is in the form of phospholipid such as phosphatidylcholine and

phosphatidylethanolamine. Omega-3 bound to phospholipids is soluble in water. Thanks to its phospholipid binding, omega-3 in krill oil is easily absorbed and used by the human body. Because of its bioavailability, krill oil is shown as a top source of omega-3 [37]. Omega-3 fatty acids compete to arachidonic acid which is an omega-6 fatty acid. Arachidonic acid is converted into prostaglandin H2 (PGH2) via some enzymatic pathways. PGH2 is converted to thromboxane A2, a pro-inflammatory lipid through thromboxane synthase. When the arachidonic acid is replaced by omega-3 fatty acids, this inflammatory effect decreases. For this reason, omega-3 fatty acids are called anti-inflammatory compounds. Omega 3 fatty acids are metabolized in the human body with EPA and DHA. In these molecules, there is evidence that they have many different positive effects on blood lipid profile, central nervous system, and regulation of immune reaction steps [11,36,38]. Krill oil also contains a very powerful natural antioxidant called Astaxanthin, which gives it its red color. Literature information has been analyzed about astaxanthin in previous years, many useful biologic effects of astaxanthin including suppression of carcinogenesis in some cancer types as bladder and colon cancer, prevention of cardiovascular diseases, protection against free radicals, reinforcement, and modulation of immunologic system may be seen [39-44].

In recent years, the protective effects of krill oil on human body have been the subject of many researches. For example in their multicenter study, Bunea et al. [45] evaluated krill oil in 120 patients with hyperlipidemia, and showed that krill oil contributed very favorably to the lipid profiles by reducing total cholesterol, LDL, and triglyceride levels and increasing HDL levels. In an experimental study, Ierna et al. [46] reported that enriching the diet with krill oil exerted very beneficial effects on the clinical and histopathological findings of inflammatory arthritis. Similarly, Deutsch [47] revealed that krill oil significantly inhibited inflammation and alleviated symptoms of arthritis in a short-term treatment. Çiftçi and Gevrek [48] evaluated effectiveness of krill oil in a rat model where they induced ischemia-reperfusion injury in skeletal muscle. In this study, they concluded that krill oil provided a strong protection against ischemia-reperfusion injury based on their both histological and biochemical evaluations. Gamoh [49] observed the effects of krill-derived phospholipids on adult rat memory, and found that lipid peroxidation was suppressed in plasma and brain tissues in the krill-derived phospholipids group. Similarly, in an animal experimental study, Mellouk et al. [50] detected that krill oil decreased oxidative stress.

Study limitations

Establishment of the study on biochemical basis and no histopathological examination of penile tissue samples.

Conclusion

We can say that priapism induced oxidative damage, adverse effects at penile tissue. This leads to sexual dysfunction that may affect patients presenting with priapism their lifetimes. Based on our literature review, our study was the first study to show the effectiveness of krill oil in the experimental priapism model and also it indicated that ischemic priapism plays an important role in the alleviation of ischemia reperfusion injury. However, we think that our study results should be supported with further prospective more randomized and controlled studies.

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Evaluation of preoperative neutrophil-lymphocyte ratio in differentiated thyroid carcinoma with lymph node metastasis

Preoperatif nötrofil–lenfosit oranı ile lenf nodu metastazı olan differansiye tiroid karsinomu arasındaki ilişkinin değerlendirilmesi

Serhat Özçelik [1], Mehmet Çelik [2], Melike Özçelik [3]

[1] Adıyaman Training and Research Hospital, Department of Endocrinology and Metabolism, Adıyaman, Turkey
[2] Antalya Kepez State Hospital, Department of Internal Medicine, Division of Endocrinology and Metabolism, Antalya, Turkey
[3] Adıyaman Training and Research Hospital, Department of Medical Oncology, Adıyaman, Turkey

ORCID ID of the author(s)
SÖ: 0000-0002-0521-5866
MÇ: 0000-0001-7364-370X
MÖ: 0000-0003-0406-715X

Corresponding author / Sorumlu yazar:
Serhat Özçelik
Address / Adres: Adıyaman Üniversitesi Eğitim ve Araştırma Hastanesi, Endokrinoloji ve Metabolizma Anabilim Dalı, Adıyaman, Türkiye
e-Mail: ozserhat1981@gmail.com

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Abstract

Aim: Systemic inflammatory response has been shown to play a critical role in all stages of tumor development, progression and metastasis. High neutrophil lymphocyte ratio (NLR) is thought to be an indicator of poor prognosis of tumors. In this study, we investigated the relationship between preoperative NLR and lymph node metastasis of differentiated thyroid carcinoma (DTC).

Methods: The study included a total of 74 patients diagnosed with DTC according to pathology results after thyroid surgery. The NLR was determined by dividing the absolute neutrophil count in the whole blood count by the lymphocyte count. Optimal cut-off value was estimated by means of ROC curve. The study was designed a cross-sectional study.

Results: With a 95% confidence interval, the area under the curve of 0.620 and the likelihood ratio of 3.2, the cut-off value for NLR was found to be 2.59 with 44.4% sensitivity and 86.2% specificity, respectively. There was a significant relationship between the current cut off value and the lymph node metastasis of DTC (P=0.03).

Conclusion: NLR was found to be significantly increased in lymph node-positive differentiated thyroid cancers. The neutrophil to lymphocyte ratio as an inflammation index is inexpensive for patients with differentiated thyroid carcinoma, easily available and easy to obtain from routine blood tests.

Keywords: Neutrophil, Lymphocyte, Thyroid, Carcinoma

Öz

Amaç: Sistemik inflamatuar yanıtın tümör gelişimi, ilerlemesi ve metastazının tüm aşamalarında kritik bir rol oynadığı gösterilmiştir. Yüksek nötrofil lenfosit oranının (NLO), tümörlerin kötü prognozunun bir göstergesi olduğu düşünülmektedir. Bu çalışmada, preoperatif NLO ile diferansiye tiroid karsinomunun (DTC) lenf nodu metastazı arasındaki ilişkiyi araştırdık.

Yöntemler: Çalışmaya tiroid cerrahisi sonrası patoloji sonuçlarına göre DTC tanısı alan toplam 74 hasta alındı. NLO, tam kan sayımındaki mutlak nötrofil sayısının lenfosit sayısına bölünmesiyle belirlenmiştir. En uygun cut-off değeri ROC eğrisi ile tahmin edilmiştir. Çalışma cross-sectional olarak dizayn edildi.

Bulgular: %95 confidence interval ile eğri altında kalan alan 0,620 olan analizde olabilirlik oranı 3,2 olarak hesaplandığında %44,4 sensivite ve %86,2 spesifite ile NLR için cut-off değer 2,59 olduğu saptandı. Mevcut cut-off değeri ile DTC'nin lenf nodu metastazı arasında anlamlı bir ilişki vardı (P=0,03).

Sonuç: NLO lenf nodu pozitif diferansiye tiroid kanserlerinde anlamlı olarak yüksek bulundu. İnflamatuar indeks olarak nötrofil lenfosit oranı, diferansiye tiroid karsinomu olan hastalar için ucuzdur, kolay kullanılabilir ve rutin kan testlerinden elde edilmesi kolaydır.

Anahtar kelimeler: Nötrofil, Lenfosit, Tiroid, Karsinom

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Introduction

Systemic inflammatory response has been shown to play a critical role in all stages of tumor development, progression and metastasis [1]. Many studies to date have shown that elevated inflammatory biomarkers can (such as CRP, TNFα, and IL-6) reliably predict poor prognosis in various malignant neoplasms (esophageal, gastric, pancreas, colonic, ovarian, kidney, and lung) [1-3]. High neutrophil lymphocyte ratio (NLR) is thought to be an indicator of poor prognosis of tumors [2,4]. There are many studies to conclude increased NLR in some types of cancer. A high NLR has been shown to correlate with high recurrence or mortality rates in a wide range of malignant neoplasms [5-7].

Thyroid cancer is the most commonly encountered endocrine tumor. The well-differentiated, slow-growing thyroid malignancies derived from follicular cells are called differentiated thyroid carcinoma (DTC). Within the category of DTC, papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) are the two subtypes, which are distinguished by their distinct cytological features [8]. Several studies have shown a higher incidence of differentiated thyroid cancers (DTC) in patients with thyroiditis [8]. The formation of thyroid cancers is associated with local and systemic inflammatory responses. Therefore, it is important to investigate the relationship between preoperative NLR and tumor characteristics in patients with DTC, to better understand tumor growth and prognosis of thyroid cancer. The detection of NLR in daily practice is inexpensive to be routinely measured and may be useful to identify high-risk patients [9-10]. In the literature, some authors found a significant relationship between NLR and DTC prognosis [11], while some reported no difference in NLRs among patients with benign or malignant thyroid nodules [12]. Therefore, the relationship between the NLR and the DTC is controversial. In this study, we investigated the relationship between preoperative NLR and lymph node metastasis of differentiated thyroid carcinoma.

Materials and methods

Patient population

This study was conducted between December 2016 and November 2018 in the Department of Endocrinology and Metabolism Diseases and the patients whose medical records were accessible were examined retrospectively. The ethical committee approval was not taken because the study nature was retrospective. Patients diagnosed with differentiated thyroid carcinoma were included according to the pathology results after thyroid surgery. Clinical parameters included age, gender, blood indexes (complete blood count, absolute neutrophil count, absolute lymphocyte count and hemoglobin, etc.), tumor size (largest lesion size measured during histopathological examination), lymph node metastasis, and pathological features. The neutrophil lymphocyte ratio was determined by dividing the absolute neutrophil count in the whole blood count by the lymphocyte count. Patients with conditions known 3 months before the operation and have potential to affect the white blood cell count like chronic medical disease, hematological disorders, past malignancy histories, coronary artery diseases, glucocorticoid use and acute infection were excluded from the study. In addition, no patients with WBC count outside the institutional reference range (4000-10.000 /ml) were allowed to be included in the study.

Statistical analysis

Descriptive statistical methods (percent, mean, median, range, standard deviation) were used to provide the basic features of the data. Data was reported as means or median (standard deviation). The Pearson Chi-Square test was used for comparison of qualitative data. Receiver operating characteristic (ROC) curve was constructed for NLR and the area under the ROC curve (AUC) value with 95% CI was calculated. Optimal cut-off value for NLR was determined. In all comparisons, $P<0.05$ was considered significant. Statistical analyzes were performed using the SPSS 23.0 program (SPSS for Windows, Inc., Chicago, Illinois, USA).

Results

Seventy-four patents with differentiated thyroid cancer were included in the study. The mean age of the patients was 46.1 (12.1) (min: 22, max: 73). While 64 (86.5%) of the patients were female, 10 (13.5%) were male. The mean preoperative basal leukocyte values of the patients were 7.42 (1.47) cells/μL, the mean of basal neutrophil values was 4.34 (1.10) cells/μL and the basal lymphocyte values were 2.31 (0.64) cells/μL (Table-1).

TNM staging of differentiated thyroid cancer cases was performed according to AJCC 7th edition [13]. When differentiated thyroid cancer cases were evaluated, papillary thyroid cancer (PTC) was detected in 69 cases (93.2%) and follicular thyroid cancer was detected in 5 patients (6.8%). When PTC cases were evaluated, 13 cases (41.9%) were in T1a stage, 11 cases (35.5%) were in T1b stage, 5 cases (16.1%) were in T2 stage and 2 cases (6.5%) were in T4a stage. Follicular variant was found in 28 cases (75.7%) in the T1a stage, in 5 cases (13.5%) in the T1b stage, in 3 cases (8.1%) in the T2 stage and in 1 case (2.7%) in the T4a stage. Histopathological results showed that both classical and follicular variant was detected together in 1 case in stage T1b. Minimally invasive follicular thyroid carcinoma was detected in 1 out of 4 cases (25%) with T1a stage and in 3 cases (75%) with T2 stage. One patient with extensive invasive follicular thyroid cancer was found to have T2 stage (Table 2).

Table 1: Demographic characteristics and hematological data of DTC patients

	n	%
Total	74	100
Sex		
Male	10	13.5
Female	64	86.5
Age (years)		
<45 years	33	44.5
≥45 years	41	55.5
	Mean (SD)	Normal range
WBC total (cells/mL)	7420 (1470)	4000–10.000
Neutrophils (cells/mL)	4340 (1100)	2000–8000
Lymphocytes (cells/mL)	2310 (640)	900–5200

DTC: Differentiated thyroid carcinoma, SD: Standard deviation

Table 2: The relationship between the thyroid cancer variants and T stage

Thyroid cancer variants	T1a	T1b	T2	T4a	Total
Papillary thyroid cancer classical variant	13	11	5	2	31
Papillary thyroid cancer follicular variant	28	5	3	1	37
Papillary thyroid cancer classical and follicular variant	0	1	0	0	1
Minimally invasive follicular thyroid carcinoma	1	0	3	0	4
Extensive invasive follicular thyroid cancer	0	0	1	0	1
Total	42	17	11	3	74

When evaluated according to lymph node involvement; 24 patients (77.4%) had N0, 4 patients (12.9%) N1a and 3 (9.7%) had N1b disease. The follicular variant was found to be N0 in 35 cases (94.6%), N1a in 1 (2.7%) and N1b level in 1 (2.7%) case. Histopathological results showed that in 1 patient with N0 disease, both classical and follicular variant were detected together. All of 4 patients with minimally invasive follicular thyroid carcinoma had N0 stage. One patient with diffusely invasive follicular thyroid cancer was in N0 stage (Table 3). Seventy-four patients were found to be in stage M0 in terms of metastasis in TNM staging. In terms of lymph node metastasis, ROC curve analysis was performed to determine the predictive value of neutrophil lymphocyte ratio.

When the likelihood ratio was calculated to be 3.2 in the analysis with 95% confidence interval and area under the curve of 0.620, it was found that the cutoff value for NLR was 2.59 with 44.4% sensitivity and 86.2% specificity (Figure1). There was a significant relationship between the current cut off value and the lymph node metastasis of differentiated thyroid cancer (P=0.03).

Table 3: The relationship between the cut off value of neutrophil lymphocyte ratio and DTC lymph node metastasis

		Stage N			
Cut 0ff		N0	N1a	N1b	Total
<2.59	Count	56	2	3	61
	% of Total	75.7	2.7	4.1	82.4
>2.59	Count	9	3	1	13
	% of Total	12.2	4.1	1.4	17.6
Total	Count	65	5	4	74
	% of Total	87.8	6.8%	5.4	100.0

DTC: Differentiated thyroid carcinoma

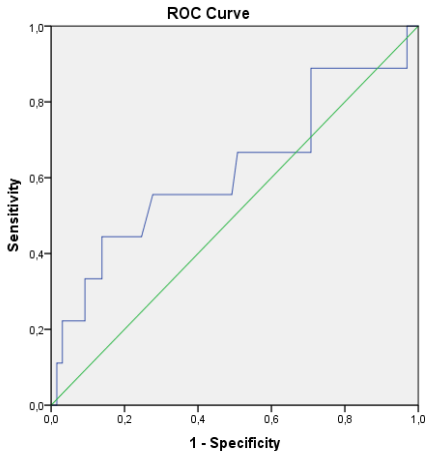

Figure 1: Receiver Operating Characteristic (ROC) Curves for Neutrophil-Lymphocyte

Discussion

Preoperative NLR is an inexpensive, easily accessible and frequently used parameter that reflects the systemic inflammatory response and the status of the immune system. High absolute neutrophil counts and low lymphocyte counts reflect higher inflammatory activity in patients. NLR may have a potentially important function in tumor progression and patient prognosis. In our study, we showed that preoperative NLR correlates positively with lymph node metastasis of differentiated thyroid carcinoma. Inflammatory cytokines (interleukin-1 receptor α, interleukin-6, 7, 8) may contribute to a tumor microenvironment that supports tumor invasion [14]. Neutrophils can inhibit tumor necrosis factor-α secretion (TNF-α) by producing vascular endothelial growth factor (VEGF). This is thought to play a role in tumor development and angiogenesis [15-16]. The reduction in lymphocyte count may reflect reduced specific antitumor immune activity [17]. In a meta-analysis involving patients with various solid tumors (breast, lung, liver, colon, and pancreas), Templeton et al. showed that high NLR is associated with negative overall survival [18]. Histopathological evaluation is accepted as the gold standard in the diagnosis of thyroid tumors. Recently, some laboratory parameters have been used as a marker for differentiation and prognosis of thyroid cancers. Examples include the use of the correlation between neutrophil lymphocyte ratio and tumor diameter, and the use of a neutrophil / lymphocyte ratio as a marker for papillary microcarcinoma screening [3]. Because the specificity of NLR is low, these values can only give an idea. When ROC curve analysis was calculated to define the predictive neutrophil lymphocyte ratio in terms of lymph node metastasis, in our study, 2.59 was found as threshold value with 44.4% sensitivity and 86.2% specificity. The optimal cutting level of the NLR is not yet standardized. Manatakis et al. [19] found a significant difference in the lymph node metastasis of PTCs when they determined the cut off level of NLR as 2.44. Koçer et al. [20] in their study compared the benign and malignant thyroid nodules and cut off value of NLR was suggested as 1.91. An interesting point that has been confirmed in our study is that the NLR values of differentiated thyroid cancer are relatively low compared to other solid tumors. A comprehensive meta-analysis investigating the relationship between NLR and various neoplasms' prognosis (gastrointestinal, gynecological, pulmonary, brain, breast, head and neck), up to 7.7 percent in NLR medians was detected [18].This study showed that high NLR in DTC patients was positively correlated with lymph node metastasis of AJCC TNM stage reflecting the malignancy degree of the tumor with.

In conclusion, preoperative high NLR in DTC patients was positively associated with lymph node metastasis of AJCC-TNM stage reflecting the degree of malignancy of the tumor. This work may give an idea for new therapies that aim to increase the lymphocyte value to reduce NLR and control tumor growth through immune reactions.

The use of single institution data, the retrospective nature and the small sample size are the main constraints of our study. Because of the fact that the non-invasive, encapsulated PTC follicular variant is classified as noninvasive follicular thyroid neoplasm with papillary-like nuclear properties, we think that this retrospective comparison between classical and follicular variants of PTC may possibly be subject to bias and error.

Conclusion

NLR was found to be significantly increased in lymph node positive differentiated cancers. The neutrophil to lymphocyte ratio as an inflammation index is inexpensive for patients with differentiated thyroid carcinoma, easily available and easy to obtain from routine blood tests.

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Is there any association between calcium values and otosclerosis?

Kalsiyum değerleri ve otoskleroz arasında bir ilişki var mı?

Erkan Yıldız [1], Orhan Kemal Kahveci [2], Şahin Ulu [2], Halit Buğra Koca [3]

[1] Department of Otorhinolaryngology, Şuhut State Hospital, Afyonkarahisar, Turkey
[2] Department of Otorhinolaryngology, University of Health Science, Afyonkarahisar School of Medicine, Afyonkarahisar, Turkey
[3] Department of Medical Biochemistry, University of Health Science, Afyonkarahisar School of Medicine, Afyonkarahisar, Turkey

ORCID ID of the author(s)
EY: 0000-0002-0265-7327
OKK: 0000-0002-6159-133X
ŞU: 0000-0003-0193-1942
BK: 0000-0002-5353-3228

Corresponding author / Sorumlu yazar:
Erkan Yıldız
Address / Adres: Afyonkarahisar Şuhut Devlet Hastanesi, 03800, Şuhut, Afyonkarahisar, Türkiye
e-Mail: dr.erkanyildiz@hotmail.com

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Abstract

Aim: Otosclerosis; is an idiopathic disease caused by the occupation of the otic capsule and the stapes base with the spongioform bone. It is the most common type of conductive hearing loss after otitis media in otorhinolaryngology. There are no studies in the literature showing the relationship between blood calcium levels and hearing loss. The aim of this study is to investigate the blood calcium levels and hearing loss of patients with otosclerosis diagnosed retrospectively.

Methods: The study was performed case-control study. Patients were divided into two groups: patient and control. The patient group consisted of 40 patients who were operated for otosclerosis in the otolaryngology clinic between 2013 and 2017. Calcium values in the blood biochemistry of these patients and preoperative hearing tests were recorded retrospectively. The control group admitted for any reason, the otolaryngology clinic and consisted of 40 patients with non-ear disease. Calcium values in blood biochemistry and hearing tests performed in outpatient clinic were recorded retrospectively. The hearing of the patients in both groups was recorded by taking the average of the right and left ear.

Results: The mean age of the control group was 28 (2.4) (18-60) years. The mean age for the patient group was 32 (2.6) (19-68). No significant difference was observed between the two groups in terms of age (P=0.061). The control group was 10.8 (1.2) dB on the right and the left ear. The mean calcium blood levels in the control group were 9.8 (0.4) mg/dL. The mean right and left ear audiometry of the patient group was 38 (0.6) dB. The mean blood calcium level of the patient group was 11.7 (0.9) dB. There was a significant difference between the control group and the patient group in the audiometry test (P=0.024). There was no significant difference between the patient group and the control group in terms of blood calcium (P=0.078).

Conclusion: There was a significant deterioration in hearing in patients with otosclerosis. However, there was no significant increase in blood calcium levels. Therefore, there was no significant relationship between blood calcium level and hearing in otosclerosis.

Keywords: Otosclerosis, Conductive hearing loss, Calcium, Stapedectomy

Öz

Amaç: Otoskleroz; otik kapsülün ve stapes tabanının spongioform kemik ile işgalinden kaynaklanan idiyopatik bir hastalıktır. Kulak burun boğazın pratiğinde otitis media sonrası en sık görülen iletim tipi işitme kaybı nedenidir. Literatürde kan kalsiyum düzeyleri ile işitme kaybı arasındaki ilişkiyi gösteren çalışma yoktur. Bu çalışmanın amacı, otosklerozlu hastaların kan kalsiyum seviyelerini ve işitme kaybını retrospektif olarak inceleyip arasındaki ilişkiyi saptamaktır.

Yöntemler: Çalışma vaka kontrol çalışması olarak yapıldı. Hastalar hasta ve kontrol grubu olmak üzere iki gruba ayrıldı. Hasta grubu, kulak burun boğaz kliniğinde 2013 ve 2017 yılları arasında otoskleroz ameliyatı geçirmiş 40 hastadan oluşuyordu. Bu hastaların kan biyokimyasındaki kalsiyum değerleri ve preoperatif işitme testleri retrospektif olarak kaydedildi. Kontrol grubu, herhangi bir nedenle, kulak burun boğaz kliniğinde için başvuran ve kulak hastalığı olmayan 40 hastadan oluşmaktadır. Kan biyokimyasında kalsiyum değerleri ve poliklinikte yapılan işitme testleri geriye dönük olarak kaydedildi. Her iki gruptaki hastaların işitmesi sağ ve sol kulağın ortalaması alınarak kaydedildi.

Bulgular: Kontrol grubunun yaş ortalaması 28 (2,4) (18-60) idi. Hasta grubunun yaş ortalaması 32 (2,6) (19-68) idi. Yaş açısından her iki grup arasında anlamlı fark izlenmedi. (P=0,061). Kontrol grubu sağ ve sol kulakta 10,8 (1,2) dB idi. Kontrol grubundaki ortalama kalsiyum kan seviyeleri 9,8 (0,4) mg/dL idi. Hasta grubunun sağ ve sol kulak odyometrisi ortalama 38 (0,6) dB idi. Hasta grubunun ortalama kan kalsiyum seviyesi 11,7 (0,9) dB idi. Odyometri testinde kontrol grubu ile hasta grubu arasında anlamlı fark vardı (P=0,024). Hasta grubu ile kontrol grubu arasında kan kalsiyum açısından anlamlı fark yoktu (P=0,078).

Sonuç: Otosklerozu olan hastalarda işitme duyusunda önemli bir bozulma vardı. Ancak, kan kalsiyum seviyelerinde önemli bir artış yoktu. Bu nedenle otoskleroz hastalığında kan kalsiyum seviyesi ile işitme arasında belirgin bir ilişki saptanmadı.

Anahtar kelimeler: Otoskleroz, İletim tipi işitme kaybı, Kalsiyum, Stapedektomi

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Introduction

Otosclerosis; is an idiopathic disease caused by the occupation of the otic capsule and the stapes base with the spongioform bone. For the first time, Politzer described stapes fixation in 1894. The disease is common in the white race and in women. The most common age is around 30-40. The etiology has not been fully elucidated. The most common causes of genetic, viral diseases and autoimmunity are discussed. Genetic transition is approximately 60% and autosomal dominant [1,2].

In otosclerosis, osteoblastic activity increases around the otic capsule. The most common place in the ear is the oval window, the second most often seen in the anterior of the round window. After the anterior of the capsule, the base is wrapped with sclerotic bone areas. After occupying the base of the Stapes, it holds the cochlea. Conductive hearing loss starts with stapes involvement and sensorineural loss is added with cochlea involvement. It is the most common type of conductive hearing loss after otitis media in otorhinolaryngology [3].

In 10% of the population there is only histological otosclerosis and in 10% clinical otosclerosis occurs. Histologically, spongiosis and sclerosis are two stages. It is primarily composed of avascular and soft bone. Then it becomes hardened and becomes vascular. Clinical otosclerosis is quite rare except for white race. Women are 3 times more common than men. It progresses mostly with pregnancy. Generally, involvement is bilateral. Firstly, the insidious progression begins as the type of hearing loss. Initially low frequencies keep all frequencies affected over time. Over time, resonance and dizziness are added depending on the effect of the cochlea. Otoscopic examination is common in most patients. Some patients may have a red reflex behind the eardrum (Schwartze Sign). Hypodense foci can be seen in the radiological involvement [4-6].

Medical or surgical treatment is used in the treatment of the disease, but its definitive treatment is surgery. Sodium fluoride (NaF) is the first choice for medical treatment and steroids can also be used. A significant number of patients benefit from the hearing aid. Stapedectomy or stapedetotomy is used for surgical treatment. Stapes are removed from the base and the piston is replaced. In stapedectomy, the stapes are completely removed [7-9].

There are no studies in the literature showing the relationship between blood calcium levels and hearing loss. An increase in blood calcium levels can be expected in this disease, which is characterized by abnormal bone formation. In our study, the relationship between the increase in hearing loss, which is an indicator of the progression of the disease, and the blood calcium levels, will be explained with the literature.

Materials and methods

The study was performed case-control study. Patients were divided into two groups: patient and control. The patient group consisted of 40 patients who were operated for otosclerosis in the otolaryngology clinic between 2013 and 2017. Calcium values in the blood biochemistry of these patients and preoperative hearing tests were recorded retrospectively. The control group admitted for any reason, the otolaryngology clinic and consisted of 40 patients with non-ear disease. Calcium values in blood biochemistry and hearing tests performed in outpatient clinic were recorded retrospectively. The hearing of the patients in both groups was recorded by taking the average of the right and left ear. Patients with one ear disease in the patient group, those with chronic disease that would impair calcium metabolism and those with sensorineural hearing loss due to age were excluded. In the control group, those with chronic disease that would impair calcium metabolism and those with sensorineural hearing loss due to age were excluded. Ethics committee approval was obtained (Afyon Kocatepe University Faculty of Medicine 2018-2).

Statistical analysis

SPSS 21.0 software (IBM, SPSS, Chicago, USA) was used for analysis. Continuous data were given as mean (standard deviation) and categorical data as number (n) and percentage (%). Student t test ın was used to compare independent data groups. Chi-square test was used for comparison between groups. $P<0.05$ was considered statistically significant.

Results

The mean age for the control group was 28 (2.4) (18-60). The mean age for the patient group was 32 (2.6) (19-68). No significant difference was observed between the two groups in terms of age ($P=0.061$). In the control group, male/female was 22/18, and patient group was 16/24. No significant difference was observed between the two groups in terms of gender ($P=0.094$). The mean right and left ear audiometry of the control group was 10.8 (1.2) dB. The mean calcium blood levels in the control group were 9.8 (0.4) mg/dl. The mean right and left ear audiometry of the patient group was 38 (0.6) dB. The mean blood calcium level of the patient group was 11.7 (0.9) mg/dl. There was no significant difference in blood calcium between the patient group and the control group ($P=0.078$). A significant difference was observed in the audiometry test between the control group and the patient group ($P=0.024$) (Table 1).

Table 1: Age, gender, calcium, audiometry test characteristics of working groups

	Control group	Patient group	*P*-value
Age	28 (2.4) (18-60)	32 (2.6) (19-68)	0.061
Gender (M/F)	22/18	16/24	0.094
Blood calcium level (mg/dl)	9.8 (0.4)	11.7 (0.9)	0.078
Left-right mean hearing level (dB)	10.8 (1.2)	38 (0.6)	0.024

Discussion

Otosclerosis is an inflammatory idiopathic disease that causes abnormal bone formation in the otic capsule. Genetic aspects are dominant and women are 3 times more than the average. The common characteristics of these patients are white race and female gender. Although it is seen as histological otosclerosis, it is not seen clinically. As a result, the staple and then holding the cochlea causes transmission and sensorinoral hearing loss. In a study related to otosclerosis imaging, it was found that the hypodense spongiotic foci in the CT were the main responsible area for hearing loss [10,11].

There are many studies related to inflammatory and biochemical analysis of otosclerosis. In otosclerosis, otic capsule contains abnormal bone. Therefore, osteoblastic activity increased. Thus, serum alkaline phosphatase activity also increases. It is possible that increased enzyme activity may

trigger calcium increase [12]. The effect of calcium and vitamin D deficiency on otosclerosis has been investigated and their hearing loss has been improved [13]. In another study conducted with otosclerosis, oxidative stress indicators increased in otosclerosis [14].

Otosclerosis is an idiopathic disease. But many reasons have been put forward. In the studies, it was observed that the inflammatory process, hormonal activity, measles virus and oxidative stress increased osteoblastic activity [15]. Aurbach et al. [16] observed an increase in enzyme activity by an increase in blood PTH (Parathormone) level. After an increase in osteoblastic activity, there is also an increase in calcium in the tissues. However, there are no studies for blood levels in the literature.

Hearing loss is the indicator of progression in otosclerosis. Initially, the stapes are kept and, depending on the fixation, conductive hearing loss occurs. Later, the stapes base and cochlea involvement begin. As a result, the sensorineural part of the hearing loss occurs. At the same time, the other indicator of progression is the increase in alkaline phosphatase with osteoblastic activity. Thus, calcium increase is expected in the blood [17,18]. Our claim in this study is to expect an increase in blood calcium levels with the increase of hearing loss. However, as the hearing loss increased, there was no significant increase in calcium levels. The increase in enzyme activity in the otic capsule did not lead to a regular increase of calcium in the blood.

In this study, we examined the relationship between blood calcium levels and degree of hearing in patients with otosclerosis. There was no significant difference between blood calcium levels and hearing degrees were different. However, the number of patients in these study groups was limited. If it is investigated in a larger population and larger patient series and can give more accurate results.

Conclusion

Otosclerosis is a progressive disease in which abnormal bone formation and enzyme activity is increased significantly. As the hearing loss increases, bone formation in the disease increases, but this increase is not reflected in the blood calcium levels.

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Evaluation of initial results of naïve HIV-infected patients regarding bone health

HİV ile enfekte naif hastaların ilk değerlendirme bulgularının kemik sağlığı açısından değerlendirilmesi

Ercan Yenilmez [1], Rıza Aytaç Çetinkaya [1]

[1] Sultan Abdulhamid Han Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey

ORCID ID of the author(s)
EY: 0000-0002-1145-8856
RAÇ: 0000-0002-5676-9527

Corresponding author / Sorumlu yazar:
Ercan Yenilmez
Address / Adres: Sultan Abdulhamid Han Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Servisi, Tibbiye Cad., Üsküdar, İstanbul, Türkiye
e-Mail: ercanyenilmez79@gmail.com

Ethics Committee Approval: Institutional Ethics Committee of Health Sciences University with approval number 18/72 on November 30th, 2018
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Abstract

Aim: HIV-infected patients have increased risk of osteoporosis due to both HIV and the treatment regimens in HIV. Our aim was to reveal the need of screening for bone health in HIV-infected patients, and to reveal the relationship between indirect serum markers of bone-condition, $CD4^+$ T lymphocyte counts and HIV RNA viral loads and DEXA screening results.

Methods: Naïve HIV positive patients over 18 years old who were under follow-up in our hospital between January 2014 and December 2018 were included in this retrospective cohort study. $CD4^+$ T cell counts, HIV RNA viral loads, body mass indexes (BMI), 25 (OH) vitamin D, serum calcium and corrected calcium (cCa) levels and DEXA screening results of these patients were recorded. For statistical analysis and interpretation, e-picos (https://www.e-picos.com) and SPSS (version 20.0; SPSS Inc., Chicago, IL, USA) were used.

Results: A total of 101 naive HIV-infected patients were included in the study. Vitamin D levels were within normal limits in only 9 (10.8%) patients, while 42 (50.6%) patients had insufficiency and 32 (38.5%) patients had deficiency. Serum calcium and cCa values were significantly lower in patients with < 40 years of age (P=0.04). According to the T-score assessment in DEXA screening, 19 patients (47.5%) had osteopenia findings in at least one of three regions (femoral neck, total hip and lumbar spine). A total of three male patients (7.5%) had osteoporosis. In terms of viral load, only BMD and T-score in women with viral load > 100,000 IU/mL were significantly lower in lumbar spine (P=0.01 and P=0.01, respectively). In terms of CD4 counts, only Z-scores in only lumbar spine and femoral neck were statistically lower in women with CD4 counts > 200 cells/µl (P=0.04 and P=0.03, respectively). There were not any significant differences in any other groups and region in terms of viral load and CD4 count. None of the factors including high viral load, low CD4 + count, low 25 (OH) vitamin D level or low cCa levels were directly related to T, Z-score and low BMD.

Conclusion: Osteopenia and osteoporosis are observed more frequently and at younger ages in HIV-infected patients than in the general population. Since we cannot make any prediction on bone health using one of the indirect markers in serum including 25 (OH) vitamin D levels and Ca levels or viral loads and CD4 counts in HIV-infected patients, BMD screening at younger ages may be beneficial.

Keywords: HIV, DEXA, Bone mineral density, Serum calcium, 25 (OH) vitamin D

Öz

Amaç: HIV-enfekte hastalarda hem HIV'in kendi etkisi hem de HIV'deki tedavi rejimlerinden dolayı osteoporoz riski artmıştır. Bu çalışmadaki amacımız, HIV ile enfekte hastalarda kemik sağlığı taramasının gerekliliğini ortaya koymak ve kemik durumuyla ilişkili indirek serum belirteçlerinin, $CD4^+$ T lenfosit sayılarının ve HIV RNA viral yüklerinin DEXA tarama sonuçları ile ilişkisini ortaya koymaktır.

Yöntemler: Bu retrospektif kohort çalışmasına Ocak 2014 ve Aralık 2018 tarihleri arasında hastanemizde takipte olan 18 yaş ve üstü HIV pozitif hastalar dahil edildi. CD4 + T hücre sayısı, HIV RNA viral yükleri, vücut kitle indeksleri (BMI), 25 (OH) D vitamini, serum kalsiyum ve düzeltilmiş kalsiyum (cCa) seviyeleri ve bu hastaların DEXA tarama sonuçları kaydedildi. İstatistiksel analiz ve yorumlama için e-picos (https://www.e-picos.com) and SPSS (version 20; SPSS Inc., Chicago, IL, USA) programları kullanıldı.

Bulgular: Çalışmaya toplam 101 naif HIV ile enfekte hasta dahil edildi. D vitamini düzeyleri sadece 9 (%10,8) hastada normal sınırlardayken, 42 (%50,6) hastada yetersizlik, 32 (%38,5) hastada eksiklik vardı. Serum kalsiyum ve cCa değerleri 40 yaşın altındaki hastalarda anlamlı olarak düşüktü (P=0,04). DEXA taramasındaki T skoru değerlendirmesine göre, 19 hastada (%47,5) üç bölgeden en az birinde (femur boynu, total kalça ve lomber omurga) osteopeni bulguları vardı. Toplam üç erkek hastada (%7,5) osteoporoz vardı. Viral yük açısından, viral yükü > 100.000 IU/mL olan kadınlarda sadece BMD ve T skoru lomber omurgada anlamlı derecede düşüktü (sırasıyla, P=0,01 ve P=0,01). CD4 sayıları açısından, sadece lomber omurga ve femur boynundaki Z skorları, CD4 sayısı> 200 hücre/µl olan kadınlarda istatistiksel olarak daha düşüktü (sırasıyla P=0,03 ve P=0,04). Diğer grup ve bölgelerde viral yük ve CD4 sayısı açısından anlamlı fark yoktu. Yüksek viral yük, düşük $CD4^+$ sayısı, düşük 25 (OH) D vitamini veya düşük cCa seviyeleri gibi faktörlerin hiçbiri doğrudan T, Z-skoru ve düşük BMD ile ilişkili değildi.

Sonuç: Osteopeni ve osteoporoz, HIV enfekte hastalarda genel popülasyona göre daha sık ve daha genç yaşlarda görülebilmektedir. HIV ile enfekte hastalarda 25 (OH) vitamin D düzeyleri ve Ca seviyeleri gibi kemik sağlığı ile ilgili indirek serum belirteçleri veya viral yükler ve CD4 sayılarını kullanarak kemik sağlığı konusunda herhangi bir öngörüde bulunamadığımız için, daha genç yaşlarda BMD taraması yararlı olabilir.

Anahtar kelimeler: HIV, DEXA, Kemik mineral yoğunluğu, Serum kalsiyum, 25 (OH) D vitamini

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Introduction

Osteoporosis, the most common metabolic bone disease, affects almost one-fourth of postmenopausal women. It is characterized by low bone mineral density (BMD), distortion of bone structure and bone tissue, and increased risk of fracture in bones. The life-long risk of bone fracture is 30-40% in women, while 20% in men [1].

In literature, the prevalence of spinal and hip fractures in patients infected with human immunodeficiency virus (HIV) is concluded to be 60% higher than normal population [2,3]. Low vitamin D levels, low body mass index and alcohol-tobacco use are concluded to be risk factors that increase the development of osteoporosis in HIV-infected populations. In addition, various agents in highly active antiretroviral therapy (HAART) regimen may contribute to the reduction of bone mineral density (BMD) in these patients [4,5].

Owing to successfully treatment of the HIV infection after HAART era, management of the comorbidities in boneskeletal, cardiovascular, neurological system, etc. arose as the main challenges in patients infected with HIV. In terms of bone health in HIV-infected patients, awareness about underlying-factors which reduce BMD, like vitamin D and calcium deficiency, has increased.

The aim of this study was to reveal the relationship between $CD4^+$ T cell counts, HIV RNA viral loads, body mass indexes (BMI), 25 (OH) vitamin D and serum calcium levels and bone mineral density (BMD) results in HIV-positive patients.

Materials and methods

A total of 101 naive HIV positive patients over 18 years old who had been follow-up in our hospital between January 2014 and December 2018 were included in the study. The study was approved by the Institutional Ethics Committee of Health Sciences University with approval number 18/72 on November 30th, 2018.

HIV RNA viral load, CD4 + T cell count, serum albumin, calcium, corrected calcium levels, thyroid stimulating hormone (TSH), T4 and alkaline phosphate (ALP) levels in naive HIV positive patients who were not receiving vitamin D or calcium supplement or any drugs that may affect BMD were recorded retrospectively. In addition, BMD results that were screened by dual energy X-ray absorptiometry (DEXA, Dual Energy X-Ray Absorptiometry) and initial BMIs of patients were retrospectively recorded.

Cases were evaluated in two groups; cases younger than 40 years of age were in the first group and older than 40 years of age were in the second group. The results of CD4 + T cell count, HIV RNA viral load, body mass index (BMI), 25 (OH) vitamin D and serum calcium levels and bone mineral density (BMD) were evaluated separately in two age-groups.

Exclusion criteria

HIV positive patients with endocrine, renal, gastrointestinal or hematological diseases like hyperparathyroidism, subclinical hyperthyroidism, Cushing's syndrome, idiopathic hypercalciuria, celiac disease, multiple myeloma, and patients receiving exogenous corticosteroids, vitamin or calcium supplementation were excluded from the study.

Definitions

The assessment of bone mineral density (BMD) test

BMD measurements were performed with DEXA (HorizonTM Wi S/N) and calculations were performed in software version 13602. The assessments of the results were based on World Health Organization (WHO) criteria.

According to WHO, the T-score is recommended for use in postmenopausal women or in men older than 50 years of age while Z-score is recommended for all other populations [1]. The T-score is a comparison of the patient's bone density with healthy, young individuals (ages between 20 and 29) of the same sex. A negative T-score of –2.5 or less at the femoral neck defines osteoporosis, while T score between –2.5 and –1 defines osteopenia and T score between –2.5 and –1 defines osteopenia and T score between –0.9 and 1 is the normal range [6,7]. The Z-score is a comparison with the bone density of people of the same age and sex as the patient. A negative Z-score of –2.0 or less defines osteoporosis.

Body mass index (BMI)

Patients with a body mass index less than 18.5 kg/m2 were considered to be underweight, 18.5-24.9 kg/m2 were normal or healthy, 25-29.9 kg/m2 were overweight, and ≥ 30 kg/m2 were considered obese. In our hospital, height weight measurements are performed before the measurement of BMD. Patients who have the data input in the HorizonTM Wi S/N system prior to BMD measurements were considered for BMI evaluation.

Corrected calcium (cCa) value

Since calcium is strongly bound to albumin in the blood, it should be considered that serum calcium levels can be mis-measured in patients with hypoalbuminemia. In our study, cCa values were calculated by Md+ calculator according to the serum calcium values of all the patients in order to prevent bias. In this calculation, cCa (mg/dL) =serum Ca (mg/dL) + 0.8 [4 - serum albumin (g/dL)] formula was used and the serum calcium reference ranges of the laboratory in our hospital were 8.4-10.5 mg/dL.

25 (OH) D vitamin

Serum 25 (OH) vitamin D levels less than ≤ 20 ng/mL was considered as deficiency, levels between 21 - 29 ng/mL was considered as insufficiency and higher than ≥ 30 ng/mL was considered normal.

Statistical analysis

For statistical analysis and interpretation, e-picos (https://www.e-picos.com) and SPSS (version 20.0; SPSS Inc., Chicago, IL, USA) were used. The values of minimum, maximum, mean, median and standard deviation were calculated as descriptive analyzes. Normality analysis was performed with Kolmogorov Smirnov test. Depending on whether parametric or nonparametric tests are applied; Chi-square / Fisher's exact test was used to analyze the relationship between two categorical variables. The Mann-Whitney U test was used to compare two independent samples. Values including $P<0.05$ in 95% confidence interval was considered to be statistically significant.

Results

A total of 101 naive HIV-infected patients were included in the study. Of the patients, 84 (83.1%) were male and 17 (16.8%) were female. The mean age of patients was 38 years of age (Minimum: 19, maximum: 75) (Table 1). Of the male cases, 56 were younger than 40 years-old and 28 were older than 40 years-old. The mean age among males was 37.4 years of age (Table 1). Among 17 female patients, 11 were younger than 40 years-old and 6 were older than 40 years-old. There was no significant difference between mean ages of the male and female cases (P=0.06).

The mean of $CD4^+$ T cell counts in male and female patients with < 40 years of age were 421 (243) and 282.2 (295) cells/µl, respectively. The mean of $CD4^+$ T cell counts in male and female patients with ≥ 40 years of age were 388.3 (286) and 329.7 (282) cells/µl, respectively. There were no significant differences in $CD4^+$ counts between age groups < 40 and ≥ 40 years of age among male and female cases (P=0.608, P=0.781, respectively).

In all patients, 17 (16.8%) had $CD4^+$ counts lower than 200 cells/µl, and the ratio of female and male patients with $CD4^+$ counts lower than 200 cells/µl were 47% and 13%, respectively (Table 1). The mean viral loads in males with < 40 and ≥ 40 years of age were 518784 (1184879) IU/mL and 1189756 (3744786) IU/mL, respectively. There was no significant difference in mean viral load and also in log2 mean viral load in male patients compared to age groups (P=0.798 and P=0.798, respectively). The mean viral load and mean viral loads in the log2 system were similar in the female cases compared to the age groups (P=0.940 and P=1, respectively) (Tablo 1).

The mean BMI in all cases was 23.7 (3.6) kg/m2. In terms of BMI, 70% of the patients were in normal or low-weight category; only two female patients with < 40 years of age were in the low-weight category. The mean BMI in < 40 and ≥ 40 age-groups was 22.1 (1.66) and 21.8 (1.1), respectively (Table 1). There were four cases in the obese category, and all were male. The number of patients with normal/low-weight and overweight/obese in the < 40 age-group was 22 to three, respectively, while it was six to nine in the ≥ 40 age-group, respectively. The ratio of overweight or obese patients was significantly higher in the ≥ 40 age-group (P=0.03) (Table 1).

25 (OH) vitamin D levels were screened in 83 patients. Vitamin D levels were within normal limits in only 9 (10.8%) patients, while 42 (50.6%) patients had insufficiency and 32 (38.5%) patients had deficiency. There was no significant difference in vitamin D levels between the age groups (P=0.796). In addition, there was no significant difference in serum albumin, TSH, T4 and ALP levels between the age groups (P=0.951, P=0.682, P=0.522, P=0.868, respectively) (Table 2).

However, mean serum calcium levels in < 40 and ≥ 40 age-groups was 8.9 (0.6) and 9.3 (0.7) mg/dL, respectively, and patients in < 40 years-old group had significantly lower levels of serum calcium (P=0.04). Accordingly, cCa values were significantly lower in patients in <40 years-old (Table 2). Only one patient had a slightly higher calcium level.

According to the T-score assessment in DEXA screening, 19 patients (47.5%) had osteopenia findings in at least one of three regions (femoral neck, total hip and lumbar spine). Of the patient, 15 (37.5%), nine (22.5%) and 17 (42.5%) had osteopenia findings in femoral neck, total hip and lumbar spine, respectively. A total of three male patients (7.5%), all of whom were younger than 50 years-old, had osteoporosis in the lumbar spine region.

We evaluated the differences in DEXA results according to HIV RNA and CD4+ counts in female and male patients. In terms of viral load, only BMD and T-score were significantly lower in lumbar spine in females with viral load > 100,000 IU/mL (P=0.01 and P=0.01, respectively). In terms of CD4 counts, only Z-scores in lumbar spine and femoral neck were significantly lower in women with CD4 counts > 200 cells/µl (P=0.03 and P=0.04, respectively). There were not any significant differences in any other groups and region in terms of viral load and CD4 count (Table 3).

In our study, we also investigated the effect of high viral loads (> 100000 IU/mL), low $CD4^+$ counts (< 200 cells), 25 (OH) vitamin D and cCa levels on DEXA parameters in patients with < 40 and ≥ 40 years of age. None of the factors including high viral loads, low $CD4^+$ counts, low 25 (OH) vitamin D levels and low cCa levels were directly related to T, Z-score and low BMD (Table 4).

Table 1: Baseline characteristics of the patients in the study regarding age-groups

Total n: 101	Age <40	Age ≥40	*P*-value
Patients (n)	67	34	N/A
Age (Median)	31	51	N/A
Male (n: 84; 83.1%)	56 (67.8%)	28 (%32.1)	N/A
Mean (SD)	29.1 (5.7)	52.1 (10.6)	N/A
Median	30	47	N/A
Female (n: 17; 16.8%)	11 (64.7%)	6 (35.2%)	N/A
Mean (SD)	31.4 (5.1)	56 (10.3)	N/A
Median	31	56	N/A
Body Mass Index			
Underweight or Normal (n: 28)	n:22 (88%)	n:6 (40%)	0.03
Overweight or obese (n: 12)	n:3 (12%)	n:9 (60%)	
$CD4^+$ T-cell count (cell/µl)			
Male (n: 73) Mean (SD)	421 (243)	388.3 (286)	0.608
Female (n: 17) Mean (SD)	282.2 (295)	329.7 (282)	0.781
HIV RNA (IU/mL)			
Male (n: 73) Mean (SD)	518784 (1184879)	1189756 (3744786)	0.798
Female (n: 17) Mean (SD)	151812 (234721)	62884 (50611)	0.940
Log_2 HIV RNA			
Male (n: 73) Mean (SD)	0.72 (0.03)	0.07 (0.02)	0.798
Female (n: 17) Mean (SD)	0.08 (0.03)	0.06 (0.01)	1

SD: Standard deviation, N/A: Non applicable

Table 2: Baseline laboratory results of the patients in the study

	Age <40 Mean (SD)	Age ≥40 Mean (SD)	*P*-value
25 (OH) vitamin D (ng/mL)	21.9 (11.7) (n:57)	22.9 (15.7) (n:26)	0.796
Serum Ca (mg/dL)	8.9 (0.6) (n:56)	9.3 (0.7) (n:25)	0.04
cCa (mg/dL)	8.7 (0.4) (n:56)	9.2 (0.7) (n:23)	0.006
ALP (U/L)	78.9 (46) (n: 61)	80.5 (30) (n:28)	0.868
Albumin (g/dL)	4.19 (0.6) (n:62)	4.16 (0.5) (n:25)	0.951
TSH (microIU/mL)	1.48 (0.9) (n:50)	1.35 (0.6) (n:25)	0.682
T4 (ng/dL)	0.99 (0.2) (n:38)	1.04 (0.1) (n:18)	0.522

Ca: Calcium, cCa: Corrected calcium, ALP: Alkaline phosphatase, TSH: thyroid stimulating hormone, T4: Thyroxine, SD: Standard deviation

Table 3: DEXA screening results of the patients in the study regarding sex, viral loads and CD4 counts

Region	Sex	Scores	HIV RNA (IU/mL) (n) Mean (SD) < 100,000	> 100,000	*P*-value	$CD4^+$ T (cell/µl) (n) Mean (SD) <200	≥ 200	*P*-value
Femoral neck	Female	T score	(4) 0.17 (1.2)	(4) -1.17 (0.9)	0.11	(2) 0.2 (2.4)	(6) -0.7 (0.7)	0.68
		Z score	(4) 0.35 (1.2)	(4) -0.57 (1.0)	0.28	(2) 1.20 (1.3)	(6) -0.55 (0.7)	0.04
		BMD	(4) 0.86 (0.1)	(4) 0.71 (0.1)	0.10	(2) 0.86 (0.3)	(6) 0.76 (0.1)	0.39
	Male	T score	(14) -0.49 (1.2)	(13) -0.02 (0.9)	0.28	(9) -0.9 (0.9)	(23) -0.1 (1.0)	0.05
		Z score	(14) -0.25 (1.2)	(13) 0.36 (0.9)	0.15	(9) -0.43 (1.1)	(23) 0.20 (1.0)	0.12
		BMD	(14) 0.85 (0.2)	(14) 0.85 (0.3)	0.95	(9) 0.79 (0.1)	(24) 0.87 (0.2)	0.35
Total Hip	Female	T score	(4) 0.50 (1.1)	(4) -0.92 (0.7)	0.06	(2) 0.6 (1.9)	(6) -0.4 (0.8)	0.27
		Z score	(4) 0.67 (1.0)	(4) -0.47 (1.1)	0.17	(2) 1.40 (0.9)	(6) -0.33 (0.9)	0.05
		BMD	(4) 1.00 (0.1)	(4) 0.82 (0.1)	0.06	(2) 1.01 (0.2)	(6) 0.88 (0.1)	0.26
	Male	T score	(15) -0.42 (0.8)	(14) 0.01 (0.7)	0.13	(9) -0.5 (0.1)	(25) -0.17 (0.8)	0.25
		Z score	(14) -0.35 (0.8)	(13) 0.29 (0.8)	0.05	(9) -0.20 (0.9)	(23) -0.06 (0.8)	0.71
		BMD	(14) 0.95 (0.1)	(13) 1.01 (0.1)	0.26	(9) 0.91 (0.1)	(23) 1.00 (0.1)	0.06
Lumbar spine	Female	T score	(4) 0.15 (0.9)	(4) -1.5 (0.1)	0.01	(2) 0.05 (0.2)	(6) -0.9 (0.7)	0.62
		Z score	(4) 0.45 (0.7)	(4) -0.92 (1.1)	0.08	(2) 1.15 (0.6)	(6) -0.70 (0.8)	0.03
		BMD	(4) 1.07 (0.1)	(4) 0.088 (0.0)	0.01	(2) 1.05 (0.2)	(6) 0.95 (0.1)	0.65
	Male	T score	(14) -0.70 (1.1)	(13) -0.41 (1.2)	0.52	(9) -0.4 (1.1)	(23) -0.8 (1.3)	0.38
		Z score	(14) -0.59 (1.1)	(13) -0.13 (1.3)	0.35	(9) -0.10 (1.1)	(23)-0.73 (1.4)	0.23
		BMD	(14) 0.99 (0.1)	(13) 1.04 (0.1)	0.34	(9) 1.01 (0.1)	(23) 0.98 (0.1)	0.61

SD: Standard deviation, BMD: Bone mineral density

Table 4: DEXA screening results of the patients in the study regarding age-group, viral loads and CD4 counts

Region	Age	Scores	HIV RNA (IU/mL) (n) Mean (SD)			$CD4^+$ T (cell/µl) (n) Mean (SD)			25 (OH) vitamin D (ng/mL) (n) Mean (SD)			cCa (mg/dL) (n) Mean (SD)		
			< 100,000	> 100,000	*P*-value	<200	≥ 200	*P*-value	< 21	≥21	*P*-value	Low	Normal	*P*-value
Femoral neck	<40 years	T score	(9) -0.65 (1.49	(10) -0.56 (1.1)	0.87	(8) -0.98 (0.9)	(13) -0.46 (1.3)	0.35	(10) -0.91 (1.4)	(11) -0.49 (1.0)	0.44	(3) -0.56 (0.9)	(15) -0.61 (1.3)	0.95
		Z score	(9) -0.41 (1.4)	(10) -050 (0.9)	0.52	(8) -0.37 (0.9)	(13) -0.20 (1.3)	0.75	(10) -0.63 (1.3)	(11) -0.45 (0.9)	0.27	(3) 0.06 (0.5)	(15) -0.26 (1.3)	0.68
		BMD	(9) 0.82 (0.2)	(11) 0.76 (0.3)	0.61	(8) 0.77 (0.1)	(14) 0.79 (0.3)	0.90	(10) 0.79 (0.2)	(11) 0.85 (0.1)	0.40	(3) 0.83 (0.2)	(16) 0.77 (0.3)	0.73
	≥40 years	T score	(9) -0.03 (0.9)	(7) 0.08 (0.8)	0.80	(3) 0.06 (1.7)	(16) -0.03 (0.65)	0.85	(10) -0.07 (0.8)	(8) 0.01 (0.9)	0.84	(2) 0.35 (0.5)	(10) 0.02 (0.9)	0.66
		Z score	(9) 0.17 (0.9)	(7) 0.41 (0.9)	0.62	(3) 0.50 (1.9)	(16) 0.25 (0.6)	0.84	(10) 0.21 (0.9)	(8) 0.40 (0.9)	0.66	(2) 0.70 (0.7)	(10) 0.42 (1.0)	0.72
		BMD	(9) 0.89 (0.1)	(7) 0.93 (0.1)	0.52	(3) 0.89 (0.2)	(16) 0.91 (0.1)	0.86	(10) 0.91 (0.1)	(8) 0.89 (0.1)	0.77	(2) 0.93 (0.1)	(10) 0.91 (0.1)	0.85
Total Hip	<40 years	T score	(10) -0.37 (0.9)	(11) -0.30 (0.9)	0.86	(8) -0.56 (0.7)	(15) -0.32 (1.0)	0.85	(10) -0.71 (1.0)	(12) -0.17 (0.8)	0.18	(3) -0.36 (0.5)	(17) -0.33 (0.9)	0.95
		Z score	(9) -0.32 (1.0)	(10) -0.02 (1.0)	0.53	(8) -0.22 (0.8)	(13) -0.25 (1.1)	0.95	(10) -0.60 (1.0)	(11) 0.07 (0.9)	0.13	(3) 0.13 (0.7)	(15) -0.22 (1.1)	0.60
		BMD	(9) 0.94 (0.2)	(10) 0.96 (0.2)	0.83	(8) 0.92 (0.1)	(13) 0.95 (0.2)	0.59	(10) 0.90 (0.2)	(11) 0.99 (0.1)	0.20	(3) 0.95 (0.1)	(15) 0.95 (0.2)	0.99
	≥40 years	T score	(9) -0.07 (0.9)	(7) -0.02 (0.6)	0.90	(3) 0.30 (1.4)	(16) -0.15 (0.6)	0.56	(10) -0.11 (0.6)	(8) -0.10 (0.9)	0.97	(2) -0.20 (0.7)	(10) 0.02 (0.9)	0.75
		Z score	(9) 0.06 (0.9)	(7) 0.30 (0.7)	0.60	(3) 0.93 (1.5)	(16) -0.01 (0.6)	0.39	(10) 0.00 (0.6)	(8) 0.27 (1.0)	0.51	(2) 0.00 (0.7)	(10) 0.28 (1.0)	0.72
		BMD	(9) 0.99 (0.1)	(7) 0.98 (0.1)	0.97	(3) 0.94 (0.2)	(16) 0.99 (0.1)	0.74	(10) 1.00 (0.1)	(8) 0.95 (0.1)	0.32	(2) 0.96 (0.2)	(10) 0.99 (0.1)	0.84
Lumbar spine	<40 years	T score	(9) -0.36 (1.0)	(10) -0.95 (1.2)	0.29	(8) -0.55 (1.2)	(13) -1.01 (1.3)	0.42	(10) -1.20 (0.9)	(11) -0.77 (1.4)	0.43	(3) -1.46 (0.1)	(15) -0.76 (1.3)	0.06
		Z score	(9) -0.18 (1.0)	(10) -0.53 (1.5)	0.57	(8) -0.50 (1.1)	(13) -0.87 (1.4)	0.18	(10) -1.01 (0.9)	(11) -0.40 (1.5)	0.31	(3) -0.76 (1.2)	(15) -0.53 (1.4)	0.80
		BMD	(9) 1.01 (0.13)	(10) 0.97 (0.14)	0.49	(8) 0.99 (0.1)	(13) 0.95 (0.2)	0.59	(10) 0.91 (0.1)	(11) 0.99 (0.2)	0.22	(3) 0.91 (0.0)	(15) 0.97 (0.2)	0.58
	≥40 years	T score	(9) -0.66 (1.2)	(7) -0.27 (0.8)	0.48	(3) 0.23 (1.20)	(16) -0.75 (1.12)	0.18	(10) -0.54 (0.9)	(8) -0.8 (1.4)	0.65	(2) -0.40 (1.7)	(10) -0.57 (1.2)	0.87
		Z score	(9) -0.53 (1.2)	(7) -0.02 (0.9)	0.40	(3) 0.60 (1.2)	(16) -0.60 (1.2)	0.12	(10) -0.42 (1.0)	(8) -0.51 (1.5)	0.88	(2) -0.25 (1.8)	(10) -0.35 (1.3)	0.93
		BMD	(9) 1.01 (0.1)	(7) 1.06 (0.1)	0.40	(3) 1.10 (0.1)	(16) 1.0 (0.1)	0.22	(10) 1.02 (0.1)	(8) 0.99 (0.2)	0.51	(2) 1.03 (0.2)	(10) 1.01 (0.1)	0.89

SD: Standard deviation, BMD: Bone mineral density

Discussion

HIV is a multisystemic disease with various complications depending on the affected system. Reduction in BMD is one of the most common complications and emerges as a result of both HIV infection and antiretroviral treatment [1].

Weight loss and low BMI are common signs in HIV-infected patients. However, none of the patients except for two women had low BMI in our study, and mean BMI was 23.7 (3.6) kg/m2 which was within the normal range. According to the study results of Gumuser et al. [8] including 72 naive HIV-infected patients, four patients had underweight, four were obese, and 64 patients had normal or overweight. Aydin et al. [9] revealed a BMI of 24.9 (3.7) kg/m2 in 126 HIV cases in Turkey. Vlot et al. [10] showed that the mean BMI of the patients in their study was 23.4. Cotter et al. [4] revealed that BMI in 210 naive HIV-infected patients was 26 kg/m2. Majority of the patients with HIV infection were normal or over-weighted in studies. Excluding the late presenters, we can conclude that patients with HIV infection do not have any difference from normal population in terms of body weight.

Vitamin D3 is required for the continuity of bone tissue, and its effects on bone structure are carried out through calcitriol (1,25 dihydroxyvitamin D) [11]. The rates for vitamin D deficiency in HIV positive patients vary between 60-90% in literature [12, 13]. In our study, the ratio of patients with vitamin D deficiency and insufficiency in all cases was 50.6% and 38.5%, respectively; total ratio was 89.1%. According to the results of Gumuser et al. [8] from Turkey, the ratio of vitamin D deficiency was 74.6% and the ratio for insufficiency was 14.5%, while the ratio of vitamin D deficiency and insufficiency was 14.6% and 68.8% in the study of Aydin et al. [9].

Dao et al. [13] from the United States revealed a vitamin D deficiency or insufficiency ratio of 70.3% in their observational cohort study including 673 HIV-infected patients, and the ratio of deficiency in the study of Gedela et al. [14] from England was 58.5%. However, the ratio of vitamin D deficiency in the study of Canuto et al. [15] from Brazil was remarkably the lowest in the literature with the rate of 1.6%; the low rate was attributed to the fact that the patients were exposed to sunlight for a long time because of long summer season in Brazil and very low rate of use of sunscreen. The high rate of osteopenia and osteoporosis in our study, despite the fact that Turkey has a long sunny summer season, may be related to the fact that patients were not staying in the sun enough and not wearing clothing that leaves their skin exposed.

Calcium is stored in the body at a rate of 99% combined with phosphate in the bone and is bound to plasma proteins at a rate of 40% [16]. Eight patients in our study had hypocalcemia, and one patient had mild hypercalcemia. Considering the low levels plasma proteins, especially low levels of albumin, in HIV-AIDS cases, cCa values should be calculated. In our study, all of the patients including eight patients with hypocalcemia had cCa levels within the normal range. It should be kept in mind that serum calcium levels may mislead clinicians for patients with low muscle mass, with metabolic disease, with impaired absorption or with AIDS; and cCa levels should be taken into consideration in such kind of patients.

Many factors may cause low BMD in patients with HIV infection. In vitro studies have shown that gp120 in the HIV virus structure increases the activity of osteoclasts, suppresses the function of osteoblasts, and also decreases ALP activity and calcium deposition by increasing primary apoptosis [11,17]. It is recommended to take calcium supplement and vitamin D to improve bone mass, especially in elderly individuals [16]. However, in our study, serum Ca and cCa levels were slightly lower in patients with younger-ages than the older, but the difference was not statistically significant. The results could be different if the age limit considered as 60 years of age instead of 40, but we did not have enough cases to design such a study (>60

age, n: 7). A more comprehensive study is needed to provide clearer conclusions.

ALP levels in our study, one of the bone turnover markers (BTMs), were also analyzed retrospectively. High levels of ALP were detected in only eight cases (7.9%) and there was no significant difference in ALP levels between both age groups. According to the study of Cotter et al. [4] including 210 cases, median ALP was 78 IU/L. And median ALP level was 66 U/L in the study of Vlot et al. [10]. These results were similar to our results.

Since BTMs reflect dynamic and short-term changes, DEXA is considered to be the gold standard for determining osteoporosis by providing to predict changes in BMD over the years [1]. The American National Osteoporosis Foundation recommends DEXA screening for all women over 65 years-old and for men over ≥ 70 years-old. The screening for individuals with HIV infection is recommended for postmenopausal women and for males over 50 years-old, however it is stated that the cost-effectiveness of this approach is not yet determined [18]. There is a contradiction standing out between these screening suggestions and our practices. According to the DEXA results in our study, the rate of osteopenia and osteoporosis were 47.5% and 7.5%, respectively. And the osteopenia was frequently seen in the lumber spine region while the minimum ratio of osteopenia or osteoporosis was in the hip. Only two of the patients with osteopenia had the findings in the regions other than lumbar spine. Hence, we may conclude that bone loss occurs first and highest in the lumbar spine region in both male and female cases. Studies in literature including HIV-infected male patients revealed that the ratio of osteopenia varied between 40% and 60% and the ratio of osteoporosis varied between 12% and 23% [19-22]. Similar to our study results, the ratio of osteopenia was 44.4%, while the ratio of osteoporosis was 11% in the study of Vlot et al. [10] including naive patients with a mean age of 39. The ratio of osteopenia in our study was similar to the results in literature, while the ratio for osteoporosis was lower than the results in literature. A meta-analysis including 10 studies with naïve patients and with a mean age of 31-44 years revealed 12 to 62.5% reduction in BMD [23]. When compared to non-HIV group, the ratio of osteopenia and osteoporosis were 6.4 and 3.6 fold higher in HIV-infected group according to the meta-analysis, respectively. So, even in a young-aged male predominant study group, osteopenia was common and there was a non-negligible risk of osteoporosis in the horizon in this group. Hence, these results may influence on the decision of antiretroviral treatment (ART) and such patients may require a prophylactic approach in terms of bone health.

One of the primary aims of this study was to search for the effect of viral loads, $CD4^+$ count, 25 (OH) vitamin D and cCa levels on the development of osteopenia and osteoporosis in HIV-infected cases. We revealed that only one of the factors including high viral load, low $CD4^+$ count, low 25 (OH) vitamin D level or low cCa levels were not directly related to T, Z-score and low BMD. Santi et al. [24] revealed in 1204 male patients infected with HIV that osteopenia ratio was 63.2%, osteoporosis ratio was 15.1% and 25 (OH) vitamin D deficiency ratio was 60.1%; these results were parallel with but slightly higher than our results. And similarly with our results, they also revealed that the relationship between viral load, $CD4^+$ count, 25 (OH) vitamin D and Ca levels and BMD were weak.

Relatively small size of the numbers of the patients in the study groups may have affected the statistical significance negatively; hence this may be considered as the limitation of the study.

Conclusion

As a result; osteopenia and osteoporosis are observed more frequently and at younger ages in HIV-infected patients than in the general population. Since we cannot make any prediction on bone health using one of the indirect markers in serum including viral load, CD4 count, 25 (OH) vitamin D levels or Ca levels in HIV-infected patients, BMD screening at younger ages may be beneficial. Thus, initial ART regimen can be determined considering the risk factors in terms of bone health. And also we believe that bone health can be better protected in HIV positive patients by proper recommendations like life style change or by providing vitamin D and calcium supplements in the early period if necessary.

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Risk factors for nasal septal perforation after septoplasty operation

Septoplasti sonrası nazal septal perforasyonlardaki risk faktörleri

Erkan Yıldız [1], Şahin Ulu [2], Orhan Kemal Kahveci [2]

[1] Department of Otorhinolaringology, Afyonkarahisar Şuhut State Hospital, Afyonkarahisar, Turkey
[2] Department of Otorhinolaringology, Healty Science University Hospital, Afyonkarahisar, Turkey

ORCID ID of the author(s)
EY: 0000-0002-0265-7327
ŞU: 0000-0003-0193-1942
OKK: 0000-0002-6159-133X

Corresponding author / Sorumlu yazar:
Erkan Yıldız
Address / Adres: Afyonkarahisar Şuhut Devlet Hastanesi, 03800 Şuhut, Afyonkarahisar, Türkiye
e-Mail: dr.erkanyildiz@hotmail.com

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Abstract

Aim: Nasal septal perforation is the most common complication in the long term after septoplasty. Nasal septal perforation is the partial opening of the wall between both nasal cavities. In this study, we will evaluate the causes of septal perforation after septoplasty.

Methods: 400 patients aged between 18 and 50 years who underwent septoplasty operation in Otorhinolaryngology clinic between 2016 and 2019 were evaluated. The study was performed as a retrospective cohort. These patients were divided into groups with and without perforation. Patients with perforation were evaluated in terms of age, gender, alcohol and cigarette use, and stabilization technique used in surgery.

Results: There were 280 male and 120 female patients in the study. 378 patients had no postoperative septal perforation. 22 had perforation after surgery. 19 of the patients in the perforated group were male and 3 were female. Male sex ratio was significantly dominant in perforated patients (19/3) (P=0.022). 21 of the patients were smoking and 1 patient was not drinking. (P=0.012). 11 of these patients were drinking alcohol and 10 of them did not drink alcohol. To stabilize the septum in patients with perforation while transseptal suturation + nasal splint was used in 14 patients, only nasal splint was used in 8 patients. The perforation rate after surgery was 22/400 (1.3%) (21/1) (P=0.012). There was no significant difference in the perforation rate among the patients with alcohol intake (P=0.082). There was significant difference between the methods used to stabilize the septum. The rate of perforation was significantly increased in patients who underwent transseptal suturation (P=0.023).

Conclusion: Patients with perforation after septoplasty were found to increase the risk of perforation by male sex, smoking and surgical technique as transseptal suturing technique.

Keywords: Nasal septal perforation, Septoplasty, Suturation, Smoking

Öz

Amaç: Septoplastinin sonrası uzun dönemde en sık görülen komplikasyon nazal septal perforasyonudur. Nazal septal perforasyon her iki nazal kavite arasındaki duvarın kısmen açılmasıdır. Bu çalışmamızda septoplasti sonrası ortaya çıkan septal perforasyonun nedenlerini inceleyeceğiz.

Yöntemler: Çalışma için 2016-2019 yılları arasında Kulak Burun Boğaz kliniğinde septoplasti operasyonu olan 18-50 yaş arası 400 hasta incelendi. Çalışma retrospektif-kohort olarak yapıldı. Bu hastalar perforasyonu olan ve olmayan iki gruba ayrıldı. Perforasyonu olan hastaların sigara ve alkol kullanımı, cinsiyet ve septum stabilizasyonu için kullanılan teknik açısından incelendi.

Bulgular: Hastaların 280 i erkek ve 120 si kadındı. Hastaların 378inde cerrahi sonrası septal perforasyon yoktu. 22sinde cerrahi sonrası perforasyon mevcuttu. Perforasyon olan gruptaki hastalardan 19u erkek 3 ü bayandı. Bu hastaların 21'i sigara içerken, 1 hasta içmiyordu. Bu hastaların 11 i alkol alırken 10 u alkol almıyordu. Perfore olan hastalarda septumu stabilize etmek için 14 hastada transseptal suturasyon + nazal doyle splint kullanılırken 8 hastada sadece nazal doyle splint kullanıldı. Yapılan cerrahi sonrası perforasyon oranı 22/400 (%1,3) idi. Perfore olan hastalarda erkek cinsiyet oranı anlamlı derecede baskındı (19/3) (P=0,022). Perfore olan gruptaki hastalarda sigara içen grup anlamlı derecede artmıştı (21/1) (P=0,012). Bu gruptaki hastalarda perforasyon oranı artışında, alkol alımı olanlarda anlamlı derecede farklılık izlenmedi (P=0,082). Septumu stabilize etmek için kullanılan yöntemler arasında anlamlı farklılık izlendi (P=0,023). Transseptal suturasyon yapılanlarda perforasyon oranı anlamlı derecede arttı (P=0,036).

Sonuç: Septoplasti sonrası perforasyonu olan hastalar incelendiğinde erkek cinsiyet, sigara kullanımı ve cerrahi teknik olarak transseptal suturasyonun perforasyon riskini artırdığı gözlendi.

Anahtar kelimeler: Nazal septal perforasyon, Septoplasti, Suturasyon, Sigara içmek

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Introduction

The nasal septum consists of the cartilage, the bone septum and the mucosal layer covering it. The bone septum consists of the vomer, the lamina perpendicular of the ethmoid bone and the maxillary crest. As a result of necrosis of the septum due to damage to these layers, there is a gap between the two nasal cavities. Therefore, the nasal airflow is disturbed and leads to deterioration in the quality of life of the patient [1].

Although the incidence of septal perforation is reported to be around 1%, it is actually much more. Septal perforations may occur due to iatrogenic, trauma, drug use (steroids, cocaine, etc.) and cauterization. The most common cause of septum surgery is secondary to infection [2].

The most common site of formation of septum perforations is the anterior region. The posterior or superior source is about 10%. Perforations in the anterior region lead to clinical symptoms, and Perforations in the posterior region do not produce much clinical signs. The most common cause of these patients is nose bleed, nasal congestion and nasal dryness. Rarely, there are complaints of sound extraction similar to whistling [1,2].

In the treatment, first of all, conservative method is observed. If the patient's complaints persist, surgical treatment is used. Topical washing, moisturizing and antibiotic creams are applied to the patient. Nasal septal buttons and endoscopic approaches are used for surgical treatment. Several flap techniques have been reported in relation to endoscopic approaches [3-5].

Materials and methods

Four-hundred patients aged between 18 and 50 years who underwent septoplasty operation in Otorhinolaryngology Clinic between 2016 and 2019 were evaluated. The study was performed as a retrospective cohort. These patients consisted of patients with septoplasty due to nasal septal deviation. All patients underwent septoplasty with closed technique. In some patients, transseptal suture technique was used at the end of septoplasty. In the transseptal suturation, 4.0 rapid vicryl was used. Nasal splints were used for all patients. These patients were divided into two groups with and without perforation. Demographic characteristics of the patients were recorded. Patients with perforation were evaluated in terms of age, gender, alcohol and cigarette use, and stabilization technique used in surgery. Approval was obtained from the local ethics committee (2015-3).

Statistical analysis

SPSS 21.0 software (IBM, SPSS, Chicago, USA) was used for analysis. The categorical data were given as number (n) and percentage (%). Chi-square test and Mann-Whitney U test were used to compare the characteristics of the data, smoking-alcohol use and the surgical method used. Regression analysis and Odds ratio were approved for risk factors. $P<0.05$ was considered statistically significant.

Results

There were 280 male and 120 female. 378 patients had no postoperative septal perforation. 22 had perforation after surgery. Of the patients in the perforated group, 19 male and 3 female were female. Male sex ratio was significantly dominant in perforated patients (19/3) ($P=0.022$). 21 of these patients were smoking and 1 patient was not drinking ($P=0.012$). 11 of these patients were drinking alcohol and 10 of them did not drink alcohol. To stabilize the septum in patients with perforation while transseptal suturation + nasal splint was used in 14 patients, only nasal splint was used in 8 patients. The perforation rate after surgery was 22/400 (1.3%) (21/1) ($P=0.012$). There was no significant difference in the perforation rate among the patients in this group and in those with alcohol intake ($P=0.082$). There was significant difference between the methods used to stabilize the septum. The rate of perforation was significantly increased in patients who underwent transseptal suturation ($P=0.023$) (Table 1).

Table 1: Comparison of age, gender, alcohol and cigarette use, and stabilization technique in patients with perforation

		P-value	Odds ratio
Gender	19 (Male) 3 (Female)	0.022	6.33
Use of smoke	21 (Smoking) 1 (Non-smoking)	0.012	21
Use of alcohol	11 (Drinking) 10 (Non-drinking)	0.082	1.1
Septum stabilization technique	14 (TSS + NS) 8 (Only NS)	0.023	1.75

TSS: Transseptal suturation, NS: Nasal splint

Discussion

The septum is the septic cartilage that separates the nasal cavity consisting of the bone at the back and the mucosa (mucoperikondrium, mukoperiostium) surrounding it. By providing nasal airflow from front to back, health provides a breath function. In septal perforations, this layer is primarily infected due to iatrogenic or surgical trauma, and then mucosal blood flow is impaired. Over time, small openings grow in this layer. Patients present with complaints such as nasal congestion, nasal bleeding, drying and crusting, whistling, and quality of life. Granulomatous diseases, topical drug use (steroids and cocaine), bilateral nasal cauterization, nasal tampons, and nose piercings. They are the most common anterior and rarely originate posterior and superior [6,7].

Septal perforation surgery is quite difficult. Conservative approach is recommended in the treatment. Vaseline moisturizing ointments, antibiotic ointments, postnasal drainage are the most common. Surgical treatment is used for patients who cannot relax with these methods. The most commonly used method was the nasal septal button method, and now the endoscopic flap translation method is the most common and successful treatment method. Although the nasal septal buttons have symptoms in a short time, they are not very successful in the long term. In flap methods, the success of experienced surgical hands is very high [8-10]. Generally extracorporeal technique is used in septoplasty repair [11].

Smoking and alcohol use are not required in patients undergoing nasal septum surgery. They have a negative effect on wound healing [12]. In a study conducted by Yazici et al. [13], cigarette smoking has been shown to decrease postoperative quality of life in patients undergoing septoplasty. In another study, it was observed that smoking increased the risk of perforation [14]. Increased suturing after septum surgery leads to crusting, causing infection and mucosal damage in that area of

the septum [15]. Therefore, suturation techniques for reducing crusting in septum surgery have been described. In addition, vaseline moisturizers and nasal washing are recommended. In the study on respiratory stress and complication of tamponade and septal suturation, the use of merosel buffer and smoking increased this risk [16]. In another study, no significant difference was observed between the use of tamponade and septal perforation relationship [17].

There is not much literature on the etiology of septum perforation. There are several studies suggesting that smoking increases perforation [18]. The effect of sex, alcohol use, surgical tamponade or suturation with perforation has not been investigated. In our study, a significant relationship was found between male sex and smoking and septal perforation. No significant increased risk was found in alcohol use. In the stabilization of septoplasty, the risk of septal perforation was not increased in the use of nasal tamponade alone, but the risk of septal perforation was increased in transseptal sutures.

However, the number of patients in these study groups was limited. If it is investigated in a larger population and larger patient series and can give more accurate results.

In conclusion, smoking and transseptal suturation technique are found to be risk factor for septal perforation in septum surgery.

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Bilateral endoscopic thoracic sympathectomy via single incision for the treatment of palmar and axillar hyperhidrosis

Palmar ve aksillar hiperhidrosis tedavisinde tek kesi ile bilateral endoskopik torakal sempatektomi

Hasan Oğuz Kapıcıbaşı [1]

[1] **Çanakkale Onsekiz Mart University, Faculty of Medicine, Department of Thoracic Surgery, Canakkale, Turkey**

ORCID ID of the author(s)
HOK: 0000-0001-7275-1039

Corresponding author / Sorumlu yazar:
Hasan Oğuz Kapıcıbaşı
Address / Adres: Çanakkale Onsekiz Mart Üniversitesi, Tıp Fakültesi, Göğüs Cerrahisi Anabilim Dalı, Çanakkale, Türkiye
e-Mail: droguzkapicibasi@gmail.com

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Abstract

Aim: Video-assisted thoracoscopic sympathectomy (VATS) is a safe, minimally invasive and effective procedure for primer hyperhidrosis. In this research, we aimed to present the advantages of uniportal endoscopic thoracic sympathectomy (ETS) surgery on patients who had palmar and axillary hyperhidrosis and did not respond to medical treatment.

Methods: Between February 2012 and November 2018, 46 ETS surgeries were performed on 23 patients (12 female patients and 11 male patients; the average age was 21 [16-27]) and the outcomes were evaluated in this retrospective cohort study. Uniport (Richard Wolf) sympathicotripsy and Kuntz nerve ablation were performed. We presented all the data about surgical techniques, perioperative-postoperative complications and patient satisfaction with their long-term results.

Results: During the long term follow-ups of our patients, compensatory hyperhidrosis was the most frequently observed finding. Hyperhidrosis occurred in multiple areas of the body in 11 of the patients (47%). 22 patients were completely satisfied with ETS surgery, and one of our patient with compensatory back sweats reported partial satisfaction. Recurrent hyperhidrosis was observed on the left side of one of our patients at 33 months post-operative examination. Minimal pneumothorax was observed in one of the patients, and it was regressed with medical treatment. The average operation duration was recorded as 21 minutes (15-31) per each hemithorax.

Conclusion: In conclusion, endoscopic thoracic sympathectomy is a treatment option with low mortality and morbidity. This approach should be considered for patients with palmar and axillar hyperhidrosis that medical treatment was not effective.

Keywords: Hyperhidrosis, Quality of life, Uniportal thoracoscopic surgery, Sympathectomy

Öz

Amaç: Video yardımlı torakoskopik cerrahi primer hiperhidroz tedavisinde güvenli, minimal invaziv ve etkili bir işlemdir. Biz bu çalışmamızda, medikal tedaviden fayda görmeyen palmar ve aksiller hiperhidroz hastalarında endoskopik torasik sempatektomi (ETS) operasyonlarının avantajlarını sunmayı amaçladık.

Yöntemler: 2012 Şubat-2018 Kasım arasında yirmi üç hastaya (12 kadın,11 erkek yaş ortalaması 21 [16-27] kırk altı ETS operasyonu uygulandı ve sonuçlar bu retrospektif kohort çalışmada değerlendirildi. Uniport (Richard Wolf) T2-T4 sempatik ganglionu ve Kuntz sinir ablasyonu yapıldı. Cerrahi teknik ve operasyon süresi ile ilgili tüm veriler, perioperatif ve postoperatif komplikasyonlar, hasta memnuniyeti ve uzun dönem sonuçları sunuldu.

Bulgular: Hastalarımızın uzun dönem takiplerinde en sık olarak vücudun çeşitli bölgelerinde kompansatuar terleme gördük ve 11 (%47) oranındaydı. Yirmi iki hasta ETS operasyonundan tamamıyla memnundu. Kompansatuar sırt terlemesi olan bir hasta kısmen memnunluk bildirdi. Otuz üç ay sonra hastalarımızdan birinin sol tarafında tekrarlayan hiperhidrozis gözlendi. Bir hastamızda minimal pnömotoraks izlendi ve medikal tedaviyle geriledi. Ortalama operasyon süresi her bir hemitoraks için 21 dk (15-31) olarak kaydedildi.

Sonuç: Medikal tedaviden fayda görmeyen hiperhidrozisli hasta grubunda, endoskopik torasik sempatektomi düşük mortalite ve morbidite ile yüksek hasta memnuniyeti sebebiyle tercih edilmesi gereken bir tedavi seçeneği olduğu sonucuna vardık.

Anahtar kelimeler: Hiperhidroz, Yaşam kalitesi, Uniportal torakoskopi, Sempatektomi

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Introduction

Hyperhidrosis is a disease with excessive sweating on skin because of overactive sympathetic ganglion innervations [1]. While primary hyperhidrosis can be seen on face, palm, axillary area and feet, secondary hyperhidrosis can be seen on any part of the body. Obesity, infections, endocrine disorders and malignancies can be considered as the etiological factors [2]. In addition to being observed between 0.3% and 4.5% of the general population, equally on both genders, conservative treatment is generally inadequate [3].

In primary hyperhidrosis treatment, endoscopic thoracic sympathectomy (ETS) is being used increasingly lately as an effective minimal invasive way [3,4]. The complication that is seen commonly besides ETS's positive sides is compensatory hyperhidrosis which is seen on various parts of the body [5].

In this study, we aimed to present surgery techniques, their durations, complications and long term results, on patients with palmar and axillary hyperhidrosis who had ETS surgery.

Materials and methods

Between February 2012 and November 2018, 46 ETS surgeries were performed on 23 patients (12 female patients and 11 male patients, the average age was 21 [16-27]), and the results were evaluated retrospectively. All these surgeries took place in İzmit Seka State Hospital and Canakkale Onsekiz Mart University Hospital.

The patients consisted of those who were examined in endocrinology and dermatology policlinics before the operation and did not respond to medical treatment. Routine biochemical blood tests (potassium, sodium, chloride, bicarbonate, blood urea nitrogen-BUN, magnesium, glucose, and creatinine), PA/L (posteroanterior/lateral) Chest x-rays and electrocardiography ECG of the patients were evaluated before the operation. Patients were intubated with double-lumen tube (Carlens numbered 32-36) and were placed at a-30-degree in a supine position under general anesthesia. One-lung ventilation was established. Camera and thoracic instruments were inserted from approximately 2 cm long incision, which was in the intersection of the right anterior axillary line with the third intercostal space. An operating thoracoscope with zero-degree lens (Richard Wolf) is routinely used in all patients. Sympathetic ganglion was electro-cauterized from T3-T4 and T2-T3 levels. An aspiration catheter was sent to the thoracic cavity from the 2 cm incision after bleeding control and 'U' suture was applied. The free end of the catheter was taken to a closed underwater drainage system in a sterile container. After drawing the air in the thoracic cavity by applying positive ventilation pressure, skin incision was closed by end of catheter. The same process was applied to the other side. All the patients were evaluated with PA chest radiography in the early postoperative period. The average operation duration was recorded from the first incision to the last suture as minutes.

Statistical analysis

Clinical findings, sociodemographic qualities and complications of the patients operated in our clinic were presented in numbers and percentages as descriptive data.

Results

Surgical mortality was not observed in any of our patients. Pain control was provided to our patients with paracetamol and tramadol hydrochloride until the post-operative discharge time. Right after the surgery, we observed that the hyperhidrosis of the hands and the axillary areas of our patients were improved. 5 patients said that s/he experienced pain during respiration, and 3 patients described local pain on trocar area. In one patient after observing hemorrhage while removing partial cohesive ness on a diseased lung's apical area by dissection, incision was enlarged to 4 centimeters for taking the control of the bleeding endoscopically and right tube thoracostomy was applied. After cohesiveness on the left side passed, sympathetic chain was cauterized endoscopically. In one patient, postoperative minimal pneumothorax was observed, and after oxygen treatment (4lt/min of O2 with nasal cannula) pneumothorax resolved and the patient was discharged. Recurrent hyperhidrosis was observed on the left side of one of our patients after 33 months (Table 1). In our follow-ups, even though increased sweating on various body parts of 11 patients at different levels was observed. One patient said the level of his excessive back sweating was so high that he had to change his clothes a couple of times during the day. Compensatory sweating was mostly observed on the back area (Table 2). The average duration of operation was 21 minutes (15-31) for each hemithorax.

Table 1: Minor complications

Complication	No (%) of patients
Pneumothorax (minimal)	1 (4)
Bleeding	1 (4)
Respiratory pain	5 (21)
Local pain (trocar site)	3 (13)
Recurrence (single-sided)	1 (4)
Bradycardia	1 (4)
Horner syndrome	-

Table 2: Compensatory hyperhidrosis

Location	No (%) of patients
Back	6 (26)
Face	3 (13)
Abdomen	1 (4)
Neck	1 (4)

Discussion

Primary hyperhidrosis (idiopathic/essential) is the most common type of hyperhidrosis and occurs in three different patterns: palmoplantar (most frequently), axillary and cranio-facial. In primary hyperhidrosis (PH) etiology, any kind of an underlying disease is ruled out, and it is triggered by emotional changes and stress rather than fever. Family history is present between 60-80% of these patients [6], and secondary hyperhidrosis is associated with underlying diseases like infections, genetic syndromes, malignancies, drugs, neurologic, metabolic and endocrine disorders. Secondary hyperhidrosis can also be localized or generalized [7]. The endocrinology and dermatology consultations of the patients were held before the operation, and our patient groups consisted of those who did not respond to the treatment and did not have any underlying disease history.

In order to diagnose primary idiopathic focal hyperhidrosis, the criteria developed by Homberger et al. [8] were used. Excessive sweating observed in certain parts of the body without a clear reason for at least six months and

experienced during sleep, hyperhidrosis more than once in a week, starting before the age of 25, affecting individuals' daily activities in a negative way and having a family history can be considered as a diagnostic finding especially if a patient has at least two of these symptoms. Due to excessive sweating on hands and armpits, social lives of patients with primary hyperhidrosis are affected. These patients look for many different solutions to get rid of these complaints. Medical treatment methods can be benefited for patients with hyperhidrosis. While surgical treatment can be benefited for patients for whom medical treatment is not effective. ETS has become the gold standard in surgical treatment [9,10]. Especially in the recent period, the use of double-lumen endotracheal intubation tubes has increased the practicability of ETS. We prefer double-lumen intubation tubes in our operations. Because of the fact that some parts of the research were conducted in a small state hospital and that anesthesiologists had less experience about double-lumen intubation compared to those in a much bigger center, the duration of anesthesia was partially longer. Thoracoscopic surgery was firstly performed by Kux in 1951 [11], but it was not used much until the 1980s [12].

Today, for palmar hyperhidrosis and vasospastic vascular diseases (Buerger, Raynoud syndrome etc.), video-assisted thoracoscopic sympathectomy (VATS) sympathectomy has been found to be absolutely superior to conventional thoracotomy due to the low duration and safety of the process, patient comfort and its shorter length of in-hospital stay after surgery [13]. Considering factors such as cosmetic concerns and postoperative pain, which affects patient comfort negatively, a decrease in surgical incision has also been aimed. In a prospective comparison study about using two ports or a single port in VATS for palmar hyperhidrosis, both procedures were found to be safe and minimally invasive. While single port method found out to be less painful, so it was should be preferred [14]. We also used a single port in all of our operations and received positive feedbacks from patients on lesser postoperative pain. Although there is not a common idea regarding which sympathetic ganglion should be cauterized in order to ensure ablation in primary hyperhidrosis, T2-T4 sympathectomy is performed for excessive sweating of the palms; many studies in the literature have reported that performing only T2-T3 sympathectomy increases compensatory hyperhidrosis [15]. In our research, ablation was performed through the cauterization of the T2-T3 and T3-T4 levels.

The most common side effect of primary hyperhidrosis surgery is compensatory hyperhidrosis which is reported to occur between 3% and 98% in the literature [16,17]. In our research, compensatory hyperhidrosis was the most frequent complication (47%) and showed similarities with other studies. Although nearly all of our patients experienced compensatory sweating at a level that would not embarrass them or would not urge them to change clothes one patient experienced serious compensatory sweating on the back area which led him to change clothes more than once.

Another serious complication in ETS is Horner syndrome which mostly affects one side of the face (unilateral) and is seen as ptosis, miosis, anhidrosis and enophthalmos. Temporary or permanent Horner syndrome reported after sympathectomy surgery was less than 5% [18]. Horner syndrome was not seen in any of our cases.

Bilateral sympathectomy can also cause cardiac sympathetic blockage and subsequently result in serious bradycardia [19]. That is why ECG findings of patients should be evaluated thoroughly before the operation. In one of our patients, temporary perioperative bradycardia occurred during the operation, and after a while it got better spontaneously. In a study conducted by Gossot et al. [13], it was reported that acute bleeding occurred due to intercostal vein injury in 5,3% of the cases and that these cases were taken under control through thoracoscopic methods.

In one of our cases, while the cohesiveness on apical lung was being removed, intercostal vein injury occurred and bleeding was taken under control endoscopically by enlarging the incision for a bit more. The cohesiveness on the left side of the same patient was removed through standard thoracoscopic method, and the sympathectomy was completed without complications. It should be kept in mind that our patient having a tuberculosis history in her family. It can be seen quite often due to chronic diseases and inappropriate antibiotic treatments in Turkey, that patients should be analyzed beforehand by taking this fact in to account.

Pleural effusion (1%), pneumothorax (1%), chylothorax and persistent intercostal neuralgia (<1%) were among the complications which were seen less [2,20]. In post-operative chest radiography of one of our patients, minimal pneumothorax was seen that did not require immediate intervention. Following the resorption of the pneumothorax by means of oxygen treatment, patient was discharged on the first day after the operation. Another potential side effect of hyperhidrosis surgery is recurrent hyperhidrosis. The incidence rate is between 0% and 65% and shows changes in different studies to a larger extent. The reason might be related to different techniques used, sympathetic chains levels and results of follow-ups [21]. In our follow-ups, recurrent hyperhidrosis on the left side of one of our patients was observed after 33 months.

Number of cases is limited in our study. Multiport VATS could not be compared with uniportal VATS. Recurrence rates between two groups, duration of hospital stay and patient satisfaction rates are not evaluated. Thereby, the advantages of uniportal VATS are not presented.

Conclusion

Endoscopic thoracic sympathectomy is a method that can be applied easily and effectively to patient groups that do not respond to medical treatment and do not have any underlying disease history. In our experience, uniportal bilateral sympathectomy could be easily done to treat palmar and axillary hyperhidrosis. We think that this operation is a reliable method with high level of patient satisfaction that does not have many potential complications.

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Approach to iatrogenic colon perforations due to colonoscopy: A retrospective cohort study

Kolonoskopiye bağlı gelişen iyatrojenik kolon perforasyonlarına yaklaşım: Retrospektif kohort çalışma

Yasin Kara [1]

[1] **University of Health Sciences, Kanuni Sultan Süleyman Education and Research Hospital, Department of General Surgery, Istanbul, Turkey**

ORCID ID of the author(s)
YK: 0000-0002-9723-1774

Abstract

Aim: Iatrogenic colonic perforation (ICP) is a serious complication that can increase mortality and morbidity in patients undergoing therapeutic or diagnostic colonoscopy. The aims of this study are to (1) evaluate the underlying mechanisms of ICPs; (2) discuss the ideal treatment approach and period between onset and treatment; (3) review the current literature regarding the management of ICPs and (4) share our experiences as a single tertiary center.

Methods: Patients who underwent colonoscopy between January 2012 and March 2019 at Kanuni Sultan Süleyman Training and Research Hospital's Endoscopy Unit were reviewed retrospectively. Interventions during which ICPs occurred were documented and analyzed.

Results: Between January 2012 and March 2019, 9857 patients underwent colonoscopy and 1320 patients underwent rectosigmoidoscopy at our center. Ten of these procedures were associated with perforation. The perforation rates were 0.06% and 0.23% in diagnostic and therapeutic colonoscopies respectively. The most frequent localizations of perforation were (a) Rectosigmoid junction (30%) (b) Sigmoid colon (30%) (c) Descending colon (20%) and (d) Transvers colon (10% (e) Cecum (10%). Managements included surgical treatment in eight patients two of whom were operated with late laparotomy, endoscopic clipping of perforation and conservative management in one patient, and conservative treatment in one patient. There was no mortality and eight patients discharged uneventfully but one of remaining two patients had acute hepatitis, one had enterocutaneous fistula. Conclusion: Iatrogenic colonic perforations are rare but most serious complications of colonoscopy procedures. Especially, special attention should be given to older and comorbid patients receiving therapeutic procedures during colonoscopy. High risk patients and their families must be informed about this complication. Difficult and tough colonoscopies should be monitored closely at least 24 hours as early diagnosis is vital for treatment. Comorbidities, age, general condition of patient, the size and location of the perforation, and the time interval between onset and diagnosis should be evaluated, and the treatment procedure should be planned. Conservative management, endoscopic clipping, laparoscopic or open operations from primary repair to Hartmann's procedure can be used, decision should be made on a case by case basis.

Keywords: Colonoscopy, Iatrogenic bowel perforation, Treatment, Emergency surgery, Laparoscopy

Öz

Amaç: İyatrojenik kolon perforasyonu (İKP), terapötik veya tanısal kolonoskopi uygulanan hastalarda mortalite ve morbiditeyi artırabilen ciddi bir komplikasyondur. Bu çalışmanın amacı (1) İKP'lerin oluş mekanizmalarını irdelemek (2) İdeal tedavi yaklaşımlarını ve zamanını tartışmak (3) Tedaviye yönelik güncel literatürü gözden geçirmek ve (4) üçüncü basamak tek merkez olarak tecrübelerimizi paylaşmaktır.

Yöntemler: Ocak 2012 ve Mart 2019 arasında Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi Endoskopi Ünitesinde, tanısal veya tedavi amaçlı yapılan tüm kolonoskopiler retrospektif olarak incelendi. İyatrojenik kolon perforasyonu gelişen işlemler kayıt altına alındı ve analiz edildi.

Bulgular: 2012 Ocak ve 2019 Mart arasında, merkezimizde 9857 hastaya kolonoskopi ve 1320 hastaya rektosigmoidoskopi işlemi yapılmıştır. Bu işlemlerden 10 tanesinde iyatrojenik kolon perforasyonu gelişmiştir. Perforasyon oranları tanısal işlemlerde %0.06, tedavisel işlemlerde %0.23 idi. Perforasyon alanları, sıklığına göre (a) rektosigmoid bileşke (%30), (b) sigmoid kolon (%30), (c) inen kolon (%20), (d) transvers kolon (%10), (e) çekum (%10). Sekiz hasta ikisi geç laparotomi olmak üzere ameliyat edildi, bir hastada perforasyona endoklipleme ve konservatif tedavi yine bir hastaya sadece konservatif tedavi uygulandı. Mortalite izlenmemiş olup sekiz hasta sorunsuz taburcu edilirken, kalan iki hastanın birinde akut hepatit tablosu ve diğerinde enterokütan fistül gelişmiştir.

Sonuç: İyatrojenik kolon perforasyonları kolonoskopi işleminin nadir ancak en ciddi komplikasyonudur. Özellikle girişimsel işlem uygulanan yandaş hastalığı olan yaşlı hastalara dikkat edilmelidir. Yüksek riskli hastalar ve aileleri perforasyon konusunda bilgilendirilmelidir. Zor geçen, şüpheli kolonoskopilerde, hastalar en az 24 saat müşahade altında takip edilmelidir. Perforasyon gelişen hastalarda yandaş hastalık, hastanın genel durumu, perforasyonun yeri ve büyüklüğü ve perforasyondan ameliyata kadar olan süre hesaba katılarak tedavi prosedürü belirlenmelidir. Her hasta vaka bazında değerlendirilerek konservatif takipten endoskopik kliplemeye, laparoskopik veya açık olarak primer rafiden Hartman prosedürüne kadar bir dizi tedavi yöntemi seçilebilir.

Anahtar kelimeler: Kolonoskopi, İyatrojenik kolon perforasyonu, Tedavi, Acil cerrahi, Laparoskopi

Corresponding author / Sorumlu yazar:
Yasin Kara
Address / Adres: Atakent Mahallesi, Halkalı Altınşehir İstanbul Cd. No:1, 34303 Küçükçekmece, İstanbul, Türkiye
e-Mail: yasinkara32@windowslive.com

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Introduction

Since colonoscopy was introduced in 1960s at the Department of Surgery of Medical Center in New York City, it is accepted as the gold standard method in diagnosis, prevention, treatment, and follow-up of colorectal cancers and diseases [1].

Currently, because of the extended therapeutic and diagnostic indications of colonoscopy, number of iatrogenic colonic perforations (ICP) is increased. As a major cause, it is estimated that the frequency of ICP is 0.019%-0.8% and 0.10%-3% for diagnostic and therapeutic colonoscopy respectively [2].

Perforation located at the colon can rapidly cause peritonitis and even sepsis depending upon bowel cleaning, the size and localization of perforation, age and comorbidities of patients. These complications imply high morbidity and mortality [3].

In the management of ICP, unfortunately there is not a gold standard method. The traditional management of ICP is surgical repair by either laparotomy or laparoscopy. Although most cases require urgent surgery, in some cases, ICP can be managed by endoscopic clipping and conservative management (CM). We aimed to evaluate the incidence of ICP, risk factors, patient management strategies, and the clinical consequences in our single tertiary center in the light of literature.

Materials and methods

Between January 2012 and March 2019, a total of 11177 lower gastrointestinal system endoscopies were performed at our single tertiary center. Patients with ICP were investigated retrospectively. All procedures were conducted under sedoanalgesia. The procedures were performed by 16 endoscopists, including 13 general surgeons and 3 gastroenterology specialists. The experience of the endoscopists varied between 3 and 17 years.

The data of the cases was obtained retrospectively from the patient files in hospital archive and from electronic hospital records. Local Ethics committee approval was not required because of the retrospective nature of the study. Written informed consent was obtained from all patients included in this study. The study was prepared in accordance with the principles of the Helsinki Declaration.

We evaluated and analyzed the demographics, comorbidities, American Society of Anesthesiologists (ASA) scoring of patients, the type of procedure (therapeutic or diagnostic), indications for colonoscopy, associated colonic pathologies, location and detection time of perforation, treatment strategies (operative or nonoperative), duration of hospitalization, and postoperative complications.

Patients who underwent surgery within the twelve hours after perforation are named as early laparotomy; those who underwent surgery after twelve hours were called as late laparotomy. Patients in whom perforation detected during colonoscopic examination were operated in the early period of emergency surgery team. Patients who were suspected to have colon perforation after colonoscopy were hospitalized in their clinics, the other service or outpatient patients were followed up by the emergency surgery team. Patients diagnosed with perforation following radiological evaluation and / or clinical follow-up were operated.

The perforations were detected either during colonoscopy by observing a visible defect in the colonic wall (mesenteric or antimesenteric side) or after the procedure by detecting free intra-abdominal air upon radiological examination. Appropriate stable patients were treated either conservatively or endoclipping plus conservative management. Patients who complained of abdominal pain or distention following colonoscopy were initially evaluated by abdominal x-ray, hemogram and C-reactive protein level. All patients with generalized peritonitis and free intra-abdominal air underwent surgical intervention either open or laparoscopically.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) (IBM Corp.; Armonk, NY, USA) 22.0 software package was used for statistical analysis. Data was presented with numbers and percentages.

Results

Between January 2012 and February 2019, a total of 11177 colorectal system endoscopies were performed in our endoscopy unit, 9857 of them were colonoscopy and 1320 of them were sigmoidoscopy. During these procedures, polypectomy was performed in 516 patients and biopsy was performed in 1171 patients. Iatrogenic colon perforation developed in 10 patients eight of which required surgical intervention. Seven (70%) of these patients were female and three (30%) were male and their mean age was 59 (40-73 years). While nine cases occurred during colonoscopy one case had ICP during rectosigmoidoscopy. ICP occurred during therapeutic procedure in 4 patients and due to diagnostic colonoscopy in 6 patients (Table 1).

Eight patients with ICP were diagnosed during endoscopic examination; others were diagnosed with acute abdominal symptoms during clinical follow-up, and / or were diagnosed with intra-abdominal free air in radiological examination. Patients who had ICP detected during endoscopy were operated on an average of 2.45 hours (1-5 hours), and patients diagnosed in late period after clinical endoscopy were operated on average of 60 hours (30-90 hours). The mean duration of the operation after colonoscopy was 13.95 hours (1-90 hours). Five patients underwent early, two patients underwent late laparotomy and one had early laparoscopic primary repair (Table 1).

In two of six patients operated in early period, primary suturing either laparoscopically or open was the treatment of choice. In four cases, open segmental colon resection plus end to end anastomosis was the operative procedure. One case that occurred after polypectomy was treated conservatively as bowel resting, intravenous fluid replacement and antibiotherapy. Another perforation detected during polypectomy was treated with endoclipping and conservative management. Two patients with ICP were detected in late period. In one of them, perforation was in cecum and due to argon plasma coagulation of cecal angiodysplasia, treatment of choice was right hemicolectomy and ileotransversostomy. Other late detected perforation was at 90th hour of diagnostic colonoscopy, she was in sepsis and emergency

laparotomy and Hartmann's procedure with abdominal vacuum-assisted closure (VAC) exchange procedure applied (Table 1).

The perforation area was the rectosigmoid in three (30%) patients and the sigmoid in three (30%), descending colon in two (20%), transvers colon in one (10%) and cecum in one (10%) patient. Considering all applications, the rate of ICP was found to be 0.09%. When evaluated separately, perforation rate was 0.06% in diagnostic colonoscopy and 0.23% in therapeutic ones. The reasons for perforation in interventional colonoscopy were snare polypectomy in three patients and argon plasma coagulation of bleeding angiodysplasia in one patient.

The diverticulosis was found in two patients who developed colon perforation due to diagnostic endoscopy, and the long-folded sigmoid colon anatomy and previous surgery were the predisposing factors in remaining 4 patients.

Patient who underwent Hartmann's procedure and abdominal VAC exchange procedure developed acute hepatitis during follow-ups in intensive care unit and one with right hemicolectomy ileotransversostomy developed enterocutaneous fistula.

Table 1: Demographics and properties of patients with ICP, localization of perforations, time of diagnosis, and treatment modalities of iatrogenic colon perforations

Age	Gender	Indication of colonoscopy	Perforation site	BMI	ASA score	Comorbidity	Procedure modality	Diagnosis	Operation time	Treatment
40	F	Chronic diarrhea	Sigmoid	27	2	No	Diagnostic	During endoscopy	2nd hour	Laparoscopic primary suturing
56	F	FOBT (+)	Rectosigmoid junction	26	3	HT, COPD	Therapeutic	During endoscopy	1st hour	Resection and anastomosis
67	F	Constipation	Rectosigmoid junction	26	3	CHF, HT	Diagnostic	In emergency room	4th day	Hartmann's procedure +Abdominal VAC
73	F	Lower gastrointestinal bleeding	Cecum	24	4	CAD, HT, DM	Therapeutic	In emergency room	1st day	Open right hemicolectomy
73	M	Iron deficiency Anemia	Rectosigmoid junction	20	3	HT, DM, CHF	Diagnostic	During endoscopy	2nd hour	Open primary suturing
63	F	FOBT(+)	Sigmoid colon	27	3	HT	Therapeutic	During endoscopy	Conservative	Conservative management
66	M	Iron deficiency anemia	Transvers colon	25	3	DM, MG	Diagnostic	During endoscopy	2nd hour	Segmental resection and anastomosis
53	F	FOBT(+)	Descending colon	22	2	No	Diagnostic	During endoscopy	3rd hour	Segmental resection and anastomosis
56	F	Constipation	Sigmoid colon	28	3	HT, DM	Therapeutic	During endoscopy	Conservative	Hemoclipping
46	M	Constipation	Descending colon	24	2	No	Diagnostic	During endoscopy	4th hour	Resection and anastomosis

BMI: Body Mass Index; CHD: Congestive Heart Failure; HT: Hypertension; CAD: Coronary Artery Disease; RA: Rheumatoid Arthritis; MG: Myasthenia Gravis; FOBT: Fecal Occult Blood Test; COPD: Chronic Obstructive Pulmonary Disease. ASA: American Society of Anesthesiologists; VAC: Vacuum - assisted closure

Discussion

Colonoscopy is being used for diagnostic, therapeutic and follow-up purposes of various colorectal diseases and lesions. Iatrogenic colonic perforation is the second and most serious complication that encountered in colonoscopy procedures. Therapeutic interventions (Endoscopic mucosal resection, endoscopic submucosal dissection, polypectomy or biopsies, etc.) during colonoscopy increase the risk of ICP [3].

In a recent study of 56,882 colonoscopies, full-thickness large bowel perforation occurred in forty patients, corresponding to an incidence rate of 0.05% in diagnostic/screening procedures and 0.17% in therapeutic colonoscopies [4]. A greater risk of ICP was associated with low-volume practices, female gender (due to greater colonic length and a more mobile transverse colon), advanced age (reduced wall strength), history of diverticular disease, previous abdominal surgery (especially pelvic), and colonic obstruction (risk of over-insufflation) [4]. In a Netherland's study including 30,366 endoscopic procedures found that ICP occurred in 35 patients (0.12%) [5]. The authors described a 4-fold higher risk of ICP in colonoscopies compared with sigmoidoscopies and a 5-fold greater risk of ICP in therapeutic compared with diagnostic procedures. In our case series, when evaluated separately, perforation rate was 0.06% in diagnostic colonoscopy and 0.23% in interventional colonoscopy which is compatible with literature. Our nine (90%) ICP occurred during colonoscopy and one (10%) during sigmoidoscopy. The reasons for perforation in interventional colonoscopy were snare polypectomy in three patients and argon plasma coagulation of bleeding angiodysplasia in one patient. The diverticulosis was found in two patients who developed colon perforation due to diagnostic endoscopy, and the long-folded sigmoid colon anatomy and previous surgery were the predisposing factors in remaining 4 patients.

Iqbal et al [6] study, the perforation rates were higher at the rectosigmoid junction and the sigmoid colon (52%). The perforation rates in other sites of the colon were 17% (cecum), 14% (ascending colon), 7% (transverse colon), 8% (descending colon) and 1% (rectum), respectively. In our series, the most frequent locations of perforation were rectosigmoid and sigmoid (60%) and descending colon was 20%, cecum and transvers colon were 20% together. This was appropriate with the literature. The managements included surgical treatment in eight patients, endoscopic clipping of perforation and conservative management in one patient, and conservative treatment in one patient.

Perforation may result from direct mechanic effects (sharp edge) of the colonoscope, barotrauma, or thermal burns during polypectomy [6]. While perforation resulting from direct mechanic effects is often seen in the recto-sigmoid junction and strictures, perforation resulting from direct barotrauma is most frequently seen in the cecum zone [7]. Mechanical injury leads to the largest perforations, while electrocautery injury causes the smallest perforations. The patient dependent risks were anticoagulation usage, suboptimal bowel cleaning, active malignancy, and steroid usage. Other factors were the existence of dense or wide-mouthed diverticula, incomplete bowel preparation and active hemorrhage. The diverticulosis, the long-folded sigmoid colon anatomy and previous surgery were the predisposing factors in ICP in our series.

Some researchers observed that the perforation rate is higher in patients with two or more comorbidities [8-10]. In case series, 60% of colonic perforation was observed in patients with ASA scores greater than 2. Handami et al. [8] also reported female gender, older age, comorbidities and hypoalbuminemia as risk factors of increased ICP rates patients. In their study, perforation rates have been found to be higher during procedures performed for diagnosing nonspecific abdominal pain, iron deficiency anemia, inflammatory bowel disease and bleeding. In our series, colonoscopy indications in patients with ICP were constipation, colon cancer screening, acute lower gastrointestinal bleeding, iron deficiency anemia and chronic diarrhea.

For management, there is no gold standard method. Comorbidities, age, size and location of the perforation, and the time interval between the onset and diagnosis should be evaluated, and the treatment procedure should be planned. Sagawa et al. [11] proposed a treatment algorithm for ICPs as shown in figure 1. Conservative management, endoscopic clipping, laparoscopic or open operations from primary repair to

Hartmann's procedure can be used decision should be made on a case by case basis. Selective patients are likely to improve under conservative management. Generally, conservative treatment can be conducted if the patient has a small perforation, is in good general condition, and shows only mild signs of peritonitis. Such treatment requires bowel rest, the rapid administration of intravenous fluid therapy and broad spectrum antibiotics. With such treatment, clinical symptoms have been reported to improve usually within 24 hours [12,13]. Patients successfully treated non-surgically must be clinically stable, and their abdominal symptoms should improve rapidly with no deterioration due to peritoneal signs [13]. Conservative management in appropriate patients results in a shorter length of hospitalization and lower morbidity. In our series, one patient with microperforation after snare polypectomy developed localized mild abdominal pain and pneumoperitoneum with a mild increase in leukocytosis and C-reactive protein. She was followed with bowel rest, broad spectrum antibiotics and intravenous fluid therapy. Clinical symptoms improved within 24 hours and she was discharged on the fifth day of his admission.

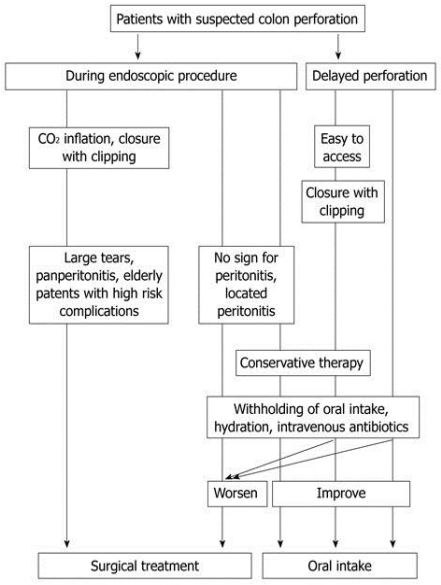

Figure 1: The management of iatrogenic colonic perforations

Intraoperative findings determine the surgical management [14]. Surgery may be primary closure or resection with primary anastomosis in cases of intra-abdominal contamination accompanied by normal tissues in order to limit the comorbidity. Due to the extensive contamination, poor tissue situation and a higher complication rate, stoma or fecal diversion after reparation is chosen. Iqbal et al [6] indicated that only two preoperative factors determined the type of procedure, the time after the perforation and mechanical injuries. Comparing patients who were diagnosed with perforation after 24 h, those within 24 h were more suitable for a primary closure because the latter was more likely to have extensive fecal contamination. Moreover, mechanical injury always induced larger perforations (average, 1.9 cm) which need fecal diversion after resection or resection and anastomosis. In our series, segmental colonic resection and anastomosis was treatment of choice in five patients because of large defects of perforation. In two late detected cases, more extensive operative procedures as right hemicolectomy and Hartmann's procedure with VAC were applied.

Currently the improvement of laparoscopic techniques and technology increase the practice of laparoscopic repair for ICP more widely [15]. In the Zhang et al [16] study, their experience in laparoscopic primary suturing of ICP indicated that laparoscopic perforation repair was a safe and feasible method. They reported that when compared with the open method, patients who underwent laparoscopic repair had a significantly shorter incision length (16 ± 15 mm vs 163 ± 54 mm), shorter length of hospital stay (5.1 ± 1.7 d vs 9.2 ± 3.1 d) and fewer perioperative complications (two vs five) [17]. Thus, they suggest that it is rational to regard laparoscopic therapy as the initial approach for repairing iatrogenic colorectal perforation. In our study group, one patient with sigmoid perforation detected during endoscopy operated at the 2nd hour of perforation laparoscopically. She had less pain and early mobilization and discharged at fourth day postoperatively. We think that in early detected perforations laparoscopic treatment might be safe and feasible.

In the recent study by Kim et al [18], 115285 diagnostic colonoscopies were performed with a total of 27 iatrogenic colon perforations (incidence of 0.02%). Endoscopic closure of the perforation site was attempted in 16 patients, with success in 13 patients. This suggests that immediate endoscopic closure with clips can be performed for diagnostic perforations as well as therapeutic colonoscopy-associated perforations. Jovanovic et al. [19] reported that endoscopic closure of colonic perforations could be performed when the perforation is < 1 cm. Some authors [22] have used the endoclips to treat perforations > 1 cm. Trecca et al. [20] reported 2 perforations > 3 cm that were managed by using endoclips successfully. Considering the technical challenge of endoclip application, an experienced endoscopist is the most important factor, as well as the site and size of the perforation. Clip closure was reported to be successful in 69% to 92% of cases [21]. In our series, one patient with sigmoid perforation of 0.5 cm size resulted from snare polypectomy was treated with endoclip application and conservative management as bowel resting, intravenous antibiotics and fluid resuscitation. She was discharged uneventfully on the sixth day of his admission

Experience of the endoscopist may decrease the perforation rates [22]. However, other than experience the various risk factors discussed previously contribute to the occurrence of ICPs. Lohsiriwat et al. [23] stated in their study of 10,124 patients that the experience of the endoscopist did not play a significant role in reducing complication rates. In our study, the experience of the endoscopists varied between 3 and 17 years. Of all cases in which perforations were documented, six were by endoscopists who had 6 to 8 years of experience, and four were by endoscopists who had 8 to 12 years of experience.

In our study, no significant difference in the rate of perforation between colonoscopies performed by gastroenterologists or surgeons has been noticed, so we may conclude that colonoscopies performed by surgeons are safe, with low morbidity and mortality.

In conclusion, ICPs are rare but most serious complications of both diagnostic and therapeutic colonoscopy procedures. All patients who will get colonoscopy and their families must be informed to be alert about this complication.

Special attention should be given to older and comorbid patients receiving therapeutic procedures during colonoscopy. Difficult and tough colonoscopies should be monitored closely at least 24 hours as early diagnosis is essential for treatment. For treatment there is no gold standard method, comorbidities, age, the size and location of the perforation, and the time interval between onset and diagnosis should be evaluated, and the treatment procedure should be planned. Conservative management, endoscopic clipping, laparoscopic or open operations from primary repair to Hartmann's procedure can be used, decision should be made on a case by case basis.

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Etiology of anemia in children aged between 6 months and 18 years

6ay-18 yaş arasındaki çocuklarda anemi etiyolojisi

Ömer Duyuran [1], Can Acıpayam [2], Nurten Seringeç Akkeçeci [3], Sevcan İpek [1], Rumeysa Duyuran [4]

[1] Department of Pediatrics, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey
[2] Department of Pediatric Hematology and Oncology, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey
[3] Department of Physiology, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey
[4] Department of Medical Biochemistry, Gaziantep University Medical Faculty, Gaziantep, Turkey

ORCID ID of the author(s)
ÖD: 0000-0003-3087-0587
CA: 0000-0002-6379-224X
NSA: 0000-0003-1915-2330
Sİ: 0000-0002-1406-4895
RD: 0000-0002-7110-0303

Corresponding author / Sorumlu yazar:
Can Acıpayam
Address / Adres: Kahramanmaraş Sütçü İmam Üniversitesi Tıp Fakültesi, Pediatrik Hematoloji Ve Onkoloji Anabilim Dalı, Avşar Kampüsü, 46100, Kahramanmaraş, Türkiye
e-Mail: cacipayam@hotmail.com

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Abstract

Aim: Anemia is an important public health problem that concerns human and community health. In this study, we aimed to determine the etiology of anemia in different age groups and create social awareness.

Methods: The study (retrospective cohort study) included anemia patients between 6 months and 18 years old who applied to the Pediatric Hematology and Oncology Outpatient Clinic of KSU Medical Faculty between January 2015 and January 2018.

Results: 1120 patients were included in the study. There were 873 with iron deficiency anemia, 184 with thalassemia minor, 25 with vitamin B12 deficiency anemia, 13 with autoimmune hemolytic anemia, 10 with hereditary spherocytosis and the other etiology of anemia. While 16.4% of all patients and 33.8% of patients aged 6-12 years had thalassemia minor. On the other side, 81.3% of patients aged 6 months-2 years, 74.3% of patients aged 2-6 years, 60.4% of patients aged 6-12 years and 85.0% of patients aged 12-18 years had iron-deficiency anemia. Iron deficiency anemia was common in males (60.2%) in the 2-6 years age group (P=0.002), but it was common in females (80.6%) in the 12-18 years age group (P<0.001).

Conclusion: As a result of this study, it has been concluded that screening and iron supplementation should be done in societies at risk.

Keywords: Anemia etiology, Iron-deficiency anemia, Thalassemia minor, Screening, Vitamin B12 deficiency

Öz

Amaç: Anemi, insan ve toplum sağlığını ilgilendiren önemli bir halk sağlığı sorunudur. Bu çalışmada farklı yaş gruplarında anemi etiyolojisini belirlemeyi ve sosyal farkındalık yaratmayı amaçladık.

Yöntemler: Çalışmaya (retrospektif kohort çalışması), Ocak 2015-Ocak 2018 tarihleri arasında, KSU Tıp Fakültesi Çocuk Hematoloji ve Onkoloji Polikliniğine başvuran 6 ay - 18 yaş arasındaki anemi hastaları dahil edilmiştir.

Bulgular: Çalışmaya 1120 hasta dahil edildi. 873 hastada Demir eksikliği anemisi, 184 hastada talasemi minör, 25 hastada vitamin B12 eksikliği anemisi, 13 hastada otoimmün hemolitik anemi, 10 hastada ise kalıtsal sferotositoz ve diğer anemi etiyolojileri vardı. Tüm hastaların %16,4'ünde, 6-12 yaş arası hastaların %33,8'inde talasemi minor vardı. Tüm hastaların %77,9'unda demir eksikliği anemisi vardı. 6 ay ile 2 yaş arası hastaların %81,3'ünde, 2-6 yaş arası hastaların %74,3'ünde, 6-12 yaş arası hastaların %60,4'ünde ve 12-18 yaş arası hastaların %85,0'inde demir eksikliği anemisi vardı. Demir eksikliği anemisi 2-6 yaş grubunda erkeklerde (%60,2) sık görülürken (P=0,002), 12-18 yaş grubunda kadınlarda (%80,6) yaygındı (P<0,001).

Sonuç: Bu çalışmanın sonucunda risk altındaki toplumlarda tarama ve demir takviyesinin yapılması gerektiği sonucuna varılmıştır.

Anahtar kelimeler: Anemi etiyolojisi, Demir eksikliği anemisi, Talasemi minor, Tarama, B12 vitamini eksikliği

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Introduction

Anemia is an important global public health problem that shows the socio-economic development of every nation and individual. The incidence of anemia worldwide is between 22.9-26.7%.The prevalence is over 40% in Turkey [1]. anemia is evaluated according to the mean erythrocyte volume (MCV) in three main headings: microcytic, macrocytic and normocytic anemia [2]. The most common anemia is iron-deficiency anemia [3].

Hemoglobin is generally high in new-born babies and mostly consists of hemoglobin F. The lifespan of hemoglobin F is shorter than that of adult hemoglobin and begins to collapse earlier. Exposed iron is stored. Iron stores are sufficient until the baby is 6 months old. After this time, iron supplementation with food is important to prevent anemia [2]. The iron demand is increasing in infancy and in puberty due to the higher growth rate at that period. The iron demand also increases due to menstrual bleeding in adolescent girls. Iron deficiency has an important effect on neurological development as well as anemia. Even if iron deficiency is treated, these developmental retardations can be irreversible [4].

As in all over the world, the prevalence of anemia and iron-deficiency anemia is high in our country and in our region. There are not enough studies showing the etiology of anemia in our region. In this study, it was aimed to raise awareness about the etiology of anemia and anemia itself for our region and to draw attention to this social problem by showing that anemia is common in our society. By that, it was aimed to attract patients, their relatives, and health professionals to take preventive measures before anemia occurs.

Materials and methods

This was a retrospective single-center cohort study. We started this study after we received the approval from the Kahramanmaras Sutcu Imam University (KSU) Faculty of Medicine Clinical Studies Ethics Committee (08.11.2017-2017/18). Patients with anemia between 6 months and 18 years of age who were admitted to the Department of Pediatric Hematology and Oncology between January 2015 and January 2018 were selected for this study. Patients with chronic diseases and migrants were excluded from the study.

The patients were divided into four age groups: 6 months-2 years (infantile), 2-6 years (pre-school), 6-12 years (school age), 12 -18 years (adolescence). Gender was divided into two groups: male and female. Demographic data and information about erythrocyte transfusions as well as hemoglobin electrophoresis, complete blood counts, biochemical profiles, LDH, folic acid, vitamin B12, ferritin levels and anemia etiologies of the patients included in our study were obtained from the medical records.

In our study, for the parameters evaluated, we worked with the complete blood count and reticulocyte fluorescent impotence method by using Sysmex XN-3000 brand fully automatic blood counting device.

Ferritin, folic acid, and vitamin B12 were studied by the chemiluminescence method on the Siemens Adevia Centaur XP fully automatic hormone analyzer. Iron, iron binding capacity, LDH, total bilirubin, and direct bilirubin were studied photometrically on Siemens Adevia 1800 Chemistry System.

Statistical analysis

Statistical analyses were performed using the SPSS (v. 22). Normality distribution was assessed by the Kolmogorov-Smirnov Test. The Independent Sample T-Test was used for two independent samples that fit the normal distribution. The Mann-Whitney U Test was used for samples that did not show normal distribution. The Two-Sample Chi-Square Test was used to analyze data with two variable frequencies, while the Single Sample Chi-Square Test was applied to data with single sampling frequency. Mean, standard deviation, minimum and maximum values of the data were calculated. $P<0.05$ was accepted as statistically significant.

Results

1120 patients between 6 months-18 years old with anemia and without chronic disease and foreign origin were included in the study. 30.6% of the patients (343) who participated in the study were 6 months-2 years, (304) 27.1% were 2-6 years, (139) 12.4% were 6-12 years and (334) 29.8% were 12-18 years old. There were more patients aged between 6 months - 2 years and 12 - 18 years ($P<0.001$). Of the patients who participated in the study, (566) 50.5% were female and (554) 55.5% were male. 120 (35%) of the patients between the ages of 6 months and 2 years were female and 223 (65%) were male ($P<0.001$). Of the patients aged 12-18 years, 255 (76.3%) were female and 79 (23.7%) were male ($P<0.001$). This difference was statistically significant. 58.2% of the patients aged 2 to 6 years were male which was statistically significant, too ($P=0.004$).

54.0% of the patients aged 6-12 years were male ($P=0.351$) (Table 1). Of all the patients, 81.3% aged between 6 months and 2 years, 74.3% aged between 2-6 years, 60.4% aged between 6-12 years and 85.0% aged 12-18 years had iron deficiency anemia.

Table 1: Distribution of patients by age and gender

Age groups	Female		Male		Total	
	n	%	n	%	n	%
6 months-2 years	120	35	223	65	343	30.6
2-6 years	127	41.8	177	58.2	304	27.1
6-12 years	64	46	75	54	139	12.4
12-18 years	255	76.3	79	23.7	334	29.8
Total	566	50.5	554	49.5	1120	100

It was noticed that the frequency of iron deficiency anemia increased in infants and adolescents.

77.9% of the patients were diagnosed with iron-deficiency anemia, 2.2% had vitamin B12 deficiency anemia, 0.2% had anemia due to folic acid deficiency, 0.3% had thalassemia major, 0.4% had thalassemia intermedia, 16.4% had thalassemia minor, 0.3% had congenital dyserythropoietic anemia, 0.2% had sickle cell anemia, 0.1% had G6PDH deficiency anemia, 1.2% had autoimmune hemolytic anemia and 0.9% had hereditary spherocytosis.

Iron-deficiency anemia was seen the most which was followed by thalassemia minor, vitamin B12 deficiency anemia, autoimmune hemolytic anemia, and hereditary spherocytosis, respectively. Of the 873 patients with iron-deficiency anemia, (452) 51.8% were female and (421) 42.2% were male. On the other side, of the 25 patients with vitamin B12 deficiency

anemia, (17) 68% were female and (8) 8% were male. The gender distribution of the patients with anemia due to folic acid deficiency (1) was equal ((1) 50% female and (1) 50% male). Of the 3 patients with thalassemia major (1) 33.3% were female and (2) 66.7% were male. In addition, (83) 25% of the patients with thalassemia intermedia were female and (101) 75% were male. Of the 3 patients with CDA, (2) 66.7% were female and (1) (33.3%) were male. The gender distribution of the patients with sickle cell anemia was equal, too ((1) 50% were female and (1) 50% were male). One patient with G6PDH deficiency anemia was male. Of the 13 patients with autoimmune hemolytic anemia (4) 30.8% were female and 9 were male (69.2%). Eventually, of the 10 patients with hereditary spherocytosis, (4) 40% were female and (6) 60% were male. The difference between them was not statistically significant (P=0.360).

The mean age of patients with iron deficiency anemia was 6.6 (6.1) years. The WBC, RBC, PLT, ferritin, folic acid and LDH levels of males were statistically higher than females (P<0.001). MCV, MCH, total bilirubin and direct bilirubin levels of the male patients were found to be statistically lower than that of the females (P<0.001). The mean age of males was younger than that of the girls (Table 2).

Table 2: Average laboratory characteristics according to gender of patients with iron deficiency anemia

Parameters	Minimum-Maximum		Mean (SD)		Mean (SD)	*P*-value
	Female (n:452)	Male (n:421)	Female (n:452)	Male (n:421)	(n: 873)	
Years (Age)	1-17	1-17	9.0 (6.3)	4.1 (4.7)	6.6 (6.1)	<0.001
WBC(mm^3)	2220-22580	1870-28330	8022 (3274)	8877(3394)	8443 (3362)	<0.001
RBC($10^6/mm^3$)	2.5-6.8	2.8-6.4	4.62 (0.64)	4.91 (0.58)	4.76 (0.63)	<0.001
HGB(g/dL)	3.1-11.9	4.0-12.1	8.88 (1.81)	8.88 (1.57)	8.88 (0.63)	0.634
HCT(%)	12-40.1	15.4-36.6	28.72 (5.00)	28.69 (4.17)	28.71 (4.62)	0.386
MCV(fL)	38.8-92.1	38.6-88.7	62.22 (9.27)	58.68 (8.29)	60.50 (8.98)	<0.001
MCH(pg)	2.7-29.5	10.6-28.9	19.17 (3.79)	18.18 (3.38)	18.68 (3.63)	<0.001
MCHC(g/dL)	22.4-37.9	9.0-39.7	30.79 (2.82)	30.9 (3.30)	30.84 (3.06)	0.234
RDW(%)	12.3-60.8	13.5-50.5	20.99 (7.63)	21.28 (6.80)	21.13 (7.24)	0.167
PLT($10^3/mm^3$)	108-1070	55-1420	375 (144)	417 (173)	397 (161)	<0.001
Iron(ug/dL)	3.0-73.0	4.0-55.0	17.4 (13.7)	17.6 (12.6)	17.5 (13.2)	0.876
Iron binding (ug/dL)	147-725	271-567	404.9 (88.9)	406.0 (62.0)	405.0 (78.0)	0.455
T.saturation(%)	1-17	1-13	4 (3)	3 (3)	4 (3)	0.852
Ferritin(ug/L)	0.00-72.90	0.10-90.00	6.80 (8.65)	10.39 (13.30)	8.68 (12.09)	<0.001
Vit. B12(ng/L)	63-1507	141-1624	392 (182)	435 (243)	404 (208)	0.165
Folic acid(ug/L)	1.8-64.1	2.6-78.9	10.96 (8.39)	13.41 (8.99)	12.13 (8.69)	<0.001
T. bil. (mg/dL)	0.06-1.90	0.06-3.40	0.44 (0.26)	0.37 (0.25)	0.40 (0.26)	<0.001
D. bil. (mg/dL)	0.00-1.10	0.00-0.56	0.16 (0.11)	0.14 (0.08)	0.15 (0.10)	<0.001
LDH(U/L)	99-713	122-771	240 (91)	283 (86)	260 (90)	<0.001
Reticulocytes	0.80-5.10	0.86-4.70	2.28 (1.12)	2.07 (1.12)	2.20 (1.11)	0.389

SD: Standard deviation, WBC: Number of leukocytes, RBC: Number of erythrocytes, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean erythrocyte volume, MCH: Mean erythrocyte hemoglobin, MCHC: Mean erythrocyte hemoglobin concentration, RDW: Erythrocyte distribution width, PLT: Platelet count, T. saturation: Transferrin saturation, Vit. B12: Vitamin B12, T. Bil: Total bilirubin, D. Bil: Direct bilirubin, LDH: Lactate dehydrogenase

The mean age of patients with thalassemia minor was 6.3 (4.9) years. The levels of MCV, RDW and iron binding capacity of patients with iron deficiency anemia were significantly higher than those with thalassemia minor (P<0.001). RBC, HGB, HCT, MCHC, iron, transferrin saturation, ferritin, total bilirubin, direct bilirubin (all P<0.001) and MCH (P=0.031) levels were statistically significantly lower There was no statistically significant difference in age (P=0.406), WBC (P=0.100), PLT (P=0.484), vitamin B12 (P=0.382), folic acid (P=0.571), LDH (P=0.386) and reticulocyte values (P=0.734) (Table 3).

Table 3: Laboratory features of patients with iron deficiency anemia and thalassemia minor diagnosis

Parameters	Minimum-Maximum		Mean (SD)		*P*-value
	Patients with iron deficiency anemia (n: 873)	Patients with T. minor (n: 184)	Patients with iron deficiency anemia (n: 873)	Patients with T. minor (n: 184)	
Years (Age)	1-17	1-17	6.6 (6.1)	6.3 (4.9)	0.406
WBC (mm^3)	1870-28390	4040-19270	8443 (3362)	8752 (2856)	0.100
RBC ($10^6/mm^3$)	2.5-6.8	3.23-6.89	4.76 (0.63)	5.51 (0.64)	<0.001
HGB (g/dL)	3.1-12.1	6.3-13.0	8.88 (0.63)	10.46 (1.00)	<0.001
HCT (%)	12.0-40.1	20.1-39.2	28.71 (4.62)	32.23 (3.28)	<0.001
MCV (fL)	38.6-92.1	41.4-90.2	60.50 (8.98)	58.8 (7.0)	0.006
MCH (pg)	2.7-29.5	12.8-29.4	18.68 (3.63)	19.08 (2.45)	0.031
MCHC (g/dL)	9.0-39.7	15.5-35.9	30.84 (3.06)	32.37 (2.10)	<0.001
RDW (%)	12.3-60.8	13.1-78.3	21.13 (7.24)	19.86 (7.17)	<0.001
PLT ($10^3/mm^3$)	55-1420	124-960	397 (161)	378 (122)	0.484
Iron (ug/dL)	3.0-73.0	21.0-146	17.5 (13.2)	59.47 (31.06)	<0.001
Iron binding (ug/dL)	147-725	290-592	405.0 (78.0)	343 (71)	<0.001
T. saturation(%)	1-17	6-56	4 (3)	8 (12)	<0.001
Ferritin (ug/L)	0.0-90.0	1.5-203	8.68 (12.09)	41.3 (40.3)	<0.001
Vit. B12 (ng/L)	63-1624	150-1068	404 (208)	387 (183)	0.382
Folic acid (ug/L)	1.8-78.9	1.5-41.3	12.13 (8.69)	12.42 (8.24)	0.571
T. bil. (mg/dL)	0.06-3.40	0.10-3.20	0.40 (0.26)	0.56 (0.44)	<0.001
D. bil. (mg/dL)	0.00-1.10	0.06-1.00	0.15 (0.10)	0.20 (0.15)	<0.001
LDH (U/L)	99-771	114-896	260 (90)	255 (90)	0.386
Reticulocytes(%)	0.80-5.10	0.96-2.30	2.20 (1.11)	1.78 (0.72)	0.734

SD: Standard deviation, WBC: Number of leukocytes, RBC: Number of erythrocytes, HGB: Hemoglobin HCT: Hematocrit, MCV: Mean erythrocyte volume, MCH: Mean erythrocyte hemoglobin, MCHC: Mean erythrocyte hemoglobin concentration, RDW: Erythrocyte distribution width, PLT: Platelet count, T. saturation: Transferrin saturation, Vit. B12: Vitamin B12, T. Bil: Total bilirubin, D. Bil: Direct bilirubin, LDH: Lactate dehydrogenase, IDA: Iron deficiency anemia, T. minor: Thalassemia minor

Discussion

Anemia is a serious public health problem as for the individual, family, and society. The development of countries and the frequency of anemia are related to each other. Anemia affects about half of society in developing countries. Children under the age of five are particularly at risk because of the rapid growth and development [5]. The prevalence of anemia worldwide is between 22.9-26.7% [1]. In our study; after migrants and those with chronic diseases were excluded, of the 5089 patients who applied to our outpatient clinic 22% had anemia. Between aged 6 months-2 years (30.6%) and between aged 12-18 years (29.8%) anemia is more common.

In 2011, Stevens et al. [6] found out in their worldwide study that 38% of pregnant women and 43% of children under five years of age were anemic. It is thought that 32 million pregnant women and 273 million children under the age of 5 are anemic around the world. In addition to that, Akkermans et al. [7] determined in their study (which included patients from the Netherlands, Germany, and England) that 18.9% of 1-3-year-old children were anemic. An estimated 20 percent of children in America are thought to have anemia [8]. Furthermore, the rate of anemia was detected as 22% in our study. Anemia is most common in the infant (6 months-2 years) and adolescents (12-18 years) period. In these periods, rapid growth and development, as well as the onset of menstruation in girls during adolescence, may increase the frequency of anemia.

Zuffo et al. [9] found out in Brazil that anemia was more common in boys in daycare centers and nurseries. The reason for the more frequent occurrence of anemia in men is due to their higher growth rates. Balcı et al. [10] observed in their study in Denizli that girls are more anemic in the adolescent period. It is thought that the increase in iron loss with menstruation may cause this [11]. In our study, no significant difference was found between girls (50.5%) and men (49.5%) in terms of the incidence of anemia. According to age groups, we detected that 65% of the patients aged between 6 months and 2 years, 58.2% of the patients between 2-6 years of age and 54% of the patients between 6-12 years old were male while 76.3% of the patients between 12-18 years of age were female. Muriuki et al. [12] found out in their study that 23.6% of children aged 0-7 years in Kenya and 17.6% of the same age group in Uganda had

iron deficiency anemia. Andre et al. [13] discovered in their review of iron deficiency anemia and nutrition in Brazilian children under 5 years of age that the frequency of iron deficiency anemia in children and boys younger than 24 months increased.

Schneider et al. [14] determined in a study in California that 12-36-month-old children of low-income families have evaluated risk factors for anemia; iron deficiency was found to be significantly higher in males than in females.

In our study, iron deficiency anemia is common in all age groups. 66.7% of patients aged 6 months to 2 years. Iron deficiency anemia was common in males (60.2%) in the 2-6 years age group, but it was common in females (80.6%) in the 12-18 years age group.

Koç et al. [15] found out in their study in Sanlıurfa that 58.9% of the children between 6-16 years with had iron-deficiency anemia, 19% had chronic disease anemia, 10% had the intestinal parasitic infection and 6.3% had thalassemia minor. They pointed out that iron deficiency and parasitic diseases are serious problems in school-age children.

The most common anemia in our study was with 873 (77.9%) patients iron deficiency anemia. Among the rest of the patients, the following data were obtained: 184 (16.4%) thalassemia minor, 25 (2.2%) anemia due to vitamin B12 deficiency, 13 (1.2%) OIDA, 10 (0.9%) hereditary spherocytosis, 4 (0.4%) thalassemia intermedia, 3 (0.3%) thalassemia major, 3 (0.3%) CDA and 2 (0.2%) anemia due to folic acid deficiency and 1 (0.1%) anemia due to G6PDH deficiency. On the other side, 81.3% of patients aged 6 months-2 years, 74.3% of patients aged 2-6 years, 60.4% of patients aged 6-12 years and 85.0% of patients aged 12-18 years had iron-deficiency anemia.

The first thing that stands out in our study is that iron deficiency anemia is seen above 80% in adolescence and infantile period. Hereditary spherocytosis is the fifth most common cause of anemia. Hereditary spherocytosis is common in Kahramanmaras province and has an important place in the differential diagnosis of anemia [16].

Thalassemia is a disease which is seen 1-4% all around the world [17]. Thalassemia is more common in the Mediterranean, Sub-Saharan Africa, the Middle East and India [18]. Kahramanmaras province as a Mediterranean region is located in the region where thalassemia is common and this is a reason why it should be considered for differential diagnosis of thalassemia in the microcytic anemia. While 16.4% of all patients and 33.8% of patients aged 6-12 years had thalassemia minor. One reason for the increase could be that children start school and come into contact with a wider environment and the rising attention of people in the social environment. All patients with thalassemia major are between 6 months and 2 years old and all patients with the diagnosis of thalassemia intermedia are between the ages of 2-6 years. Sickle cell anemia is not common in our region. Two patients diagnosed were siblings and migrated from Sırnak.

However, this study has some limitations. Firstly, the study was designed retrospectively. Secondly, patients who came to the hematology and oncology outpatient clinic were evaluated in this study and do not reflect the population.

As a result; in our study, we have shown that iron deficiency is common in Kahramanmaras province of Turkey. It is more common especially between 6 months-2 years of age and 12-18 years of age.

In terms of anemia, it is appropriate to educate the children, to perform screening in appropriate age groups and to run iron supplement for children at risk. In addition, the thalassemia minor prevalence is high in our region and it has an important role in the differential diagnosis of iron deficiency anemia. It is important to perform screening before marriage and to conduct family screening and genetic counselling when thalassemia trait is detected.

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Management of local anesthetic toxicity and importance of lipid infusion

Lokal anestezik toksisitesinin yönetimi ve lipid infüzyonunun önemi

Gökhan Kılınç [1]

[1] **Department of Anesthesiology and Reanimation, Balikesir Atatürk City Hospital, Balikesir, Turkey**

ORCID ID of the author(s)
GK: 0000-0001-7979-6993

Abstract

Local anesthetics (LA) are one of the groups that block the transmission of sensory, motor and autonomic nerve impulses commonly used in clinical anesthesia. All local anesthetic molecules in clinical use consist of three parts: a lipophilic (aromatic) end, a hydrophilic (amine) end, and a chain that provides the connection between the ends. Physicochemical properties determine the clinical efficacy of local anaesthetics The part that determines the lipid solubility of local anesthetics is the aromatic ring. A higher dose of local anesthetics is required for cardiovascular system (CVS) toxicity. Hypertension, tachycardia and ventricular arrhythmia are the first of the diseases of CVS. Hypotension, arrhythmia, bradycardia and cardiac arrest develop as local anesthetics increase in blood. The symptoms of central nervous system (CNS) toxicity associated with LA are related to the plasma levels of drugs. Initially, there are drowsiness, dizziness, sedation, disorientation, tinnitus, nystagmus, metallic taste, nausea and vomiting. Then, restlessness, irritability, tremors and muscle twitches occur. After this, the tonic-clonic seizure and loss of consciousness develops, finally, apnea, cardiovascular collapse and coma. In the treatment of local anesthetic toxicity, it is recommended to provide airway, avoid the propofol if seizure occurs and treat with benzodiazepine. If cardiac arrest develops, it is recommended to switch to advanced life support, to reduce the given dose of adrenaline, to administer lipid emulsion (20%) and to respond to treatment if cardiopulmonary bypass is not provided.

Keywords: Local anesthetic, Toxicity, Lipid infusion

Öz

Lokal anestezikler (LA), klinik anestezide yaygın olarak kullanılan duyusal, motor ve otonom sinir sinirlerinin iletimini engelleyen ilaçlardır. Klinik kullanımdaki tüm lokal anestezik moleküller üç bölümden oluşur: bir lipofilik (aromatik) uç, bir hidrofilik (amin) uç ve uçlar arasında bağlantı sağlayan bir zincir. Lokal anesteziklerin klinik etkinliğini fizikokimyasal özellikler belirler. Lokal anesteziklerin lipid çözünürlüğünü belirleyen kısım aromatik halkadır. Kardiyovasküler sistem (CVS) toksisitesi için daha yüksek dozda lokal anestezikler gerekir. Hipertansiyon, taşikardi ve ventriküler aritmi, ilk görülen CVS yanetkileridir. Hipotansiyon, aritmi, bradikardi ve kalp durması kanda lokal anesteziklerin artmasıyla gelişir. LA ile ilişkili merkezi sinir sistemi (CNS) toksisitesinin semptomları, ilaçların plazma seviyeleri ile ilişkilidir. İlk başta uyuşukluk, baş dönmesi, sedasyon, oryantasyon bozukluğu, kulak çınlaması, nystagmus, metalik tat, bulantı ve kusma vardır. Sonra, huzursuzluk, sinirlilik, titreme ve kas seğirmesi meydana gelir. Bundan sonra, tonik-klonik nöbet ve bilinç kaybı, sonunda apne, kardiyovasküler kollaps ve koma gelişir. Lokal anestezik toksisitesinin tedavisinde, hava yolunun sağlanması, nöbet meydana gelirse propofoldan kaçınılması ve benzodiazepin ile tedavi edilmesi önerilir. Eğer kardiyak arrest gelişirse, verilen adrenalin dozunu azaltmak, lipit emülsiyonu uygulamak (%20) ve kardiyopulmoner bypass sağlanamadığında tedaviye yanıt vermek için ileri yaşam desteğine geçilmesi önerilir.

Anahtar kelimeler: Lokal anestezik, Toksisite, Lipid emulsiyonu

Corresponding author / Sorumlu yazar:
Gökhan Kılınç
Address / Adres: Balıkesir Atatürk Şehir Hastanesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, Balıkesir, Türkiye
e-Mail: gkilinc35@hotmail.com

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Introduction

Local anesthetics (LA) are one of the groups that block the transmission of sensory, motor and autonomic nerve impulses commonly used in clinical anesthesia. When administered in therapeutic doses, these effects are reversible and the nerve function returns completely without any damage to the nerve fiber and cell [1].

The use of LA in neuraxial anesthesia is another important development of James Corning that began in 1885 with a spinal anesthesia experiment on a dog. It was not used clinically until August Bier until 1899. Lumbar epidural anesthesia was described by the Spanish military surgeon Fidel Pages in 1921 and was popularized by the Italian surgeon Dogliotti in the 1930s [2].

Chemical structure

All local anesthetic molecules in clinical use consist of three parts: a lipophilic (aromatic) end, a hydrophilic (amine) end, and a chain that provides the connection between the ends. The linkage comprises either an amino ester or an amino amide linkage and local anesthetics are defined as belonging to one of two groups: amino-ester linked local anesthetics or amino-amide bonded local anesthetics. Procaine is a prototype of amino-ester bound local anesthetics, and the prototype of amino-amide linked local anesthetics forms lidocaine [3].

Physicochemical properties

Physicochemical properties determine the clinical efficacy of local anesthetics. The part that determines the lipid solubility of local anesthetics is the aromatic ring. Lipid solubility is the most important feature affecting the potency of local anesthetics. The membranes of the nerve membranes and connective tissues are lipoprotein. Local anesthetics with high fat content are easier to pass than the membrane and require fewer molecules [4].

Binding to protein is associated with the duration of action of the local anesthetic; because the non-free form does not have pharmacological activity. The local anesthetic with a high affinity to the protein remains attached to the nerve membrane for a longer period of time and the duration of action is prolonged [5,6].

Local anesthetics at physiological pH are weak bases until the equilibrium between the lipid soluble base form and water soluble ionized form is established [4]. The effect of local anesthesia occurs when it passes through the lipid-soluble tertiary form at physiological pH (7.4). The ionization constant (pKa) determines the form of the local anesthetic. By definition, pKa represents the pH in which 50% of the local anesthetic is in the oil-soluble tertiary structure with 50% water-soluble quaternary structure. Given the low pKa of the given local anesthetic means higher lipid solubility. This form is a faster passing form of lipid cell membranes, so the onset time of the action is shortened[4].The pKa of all local anesthetics is 8.0-9.0. If the environment is acidotic due to various reasons, the water-soluble quaternary form increases the amount of local anesthetic that enters the nerve tissue, which explains why the effect is diminished especially in the infected tissues [7,8]. Similarly, alkalinity of the pH of the environment causes the lipid-soluble tertiary structure to increase and the amount of local anesthetic that can enter the nerve membrane. It is applied by adding bicarbonate to this local anesthetic in clinical practice [9].

Clinical Use

Local anesthetics are applied in topical anesthesia, infiltration anesthesia, intravenous regional anesthesia, central block, peripheral nerve blocks and sympathetic block in anesthesia practice.

The sensitivity of nerve fibers to local anesthetics is different. It depends on the diameter of the fibers and the degree of myelination. Classically, first the feeling of heat, then the sinking, and then the slight touching sensation disappears. Generally autonomic fibers, small non-myelinized C fibers and small myelinized A kappa are blocked first, while motor and proprioceptive fibers are blocked later [4].

During peripheral nerve block procedures, anesthesia specialists often add lidocaine epinephrine. This application has two advantages. First, it reduces the plasma concentration of local anesthesia and thus minimizes the likelihood of systemic toxicity. Second, it increases the quality of the block and prolongs the duration of the peripheral nerve block [10].

Pharmacokinetics

Local anesthetics are most commonly given to the extravascular tissue close to the target tissue. It determines the plasma concentration of local anesthetics, the rate of absorption from the injection site, the rate of distribution in the tissue and the rate of elimination specific to the local anesthetic. Patient-related factors that determine systemic toxicity include age, cardiovascular, renal and hepatic function, and plasma protein binding [11].

Local anesthetics are very safe when administered in appropriate doses for proper anatomical localization. Local or systemic toxic reactions may occur if high dose local anesthetic application or intravascular or intrathecal injection is performed [6].

In high perfusion tissues, retrieval is faster and more complete. Systemic absorption and peak plasma level (Cmax) increase as the given dose increases. The addition of adrenaline to the local anesthetic reduces systemic absorption and significantly reduces Cmax. The purpose of adrenalin addition to the local anesthetic is to prolong the duration of the local anesthetic and to keep it longer in the tissue [10].

Intravenously administered local anesthetics are initially distributed to organs with large blood supply, such as the brain, kidneys and heart; it follows less canned tissues such as skin, skeletal muscle and fat. Local absorption in these organs will be affected by lipid solubility of local anesthetic, binding to pKa and protein, binding affinity and clearance to tissue. Affects local absorption in patient-specific factors such as cardiac output and metabolic status [12].

The amino-ester bound local anesthetics are hydrolyzed by tissues and blood esterases. Amino-amide-induced local anesthetics are primarily biotransformed with cytochrome P450 enzymes in the liver. Metabolites often retain local anesthetic activity and toxicity potential with a lower force than the parent compound [13].

The location of injected local anesthetics has the highest peak levels at plasma levels, intercostal and caudal injections,

followed by lumbar epidural, brachial plexus, sciatica and femoral injections [12].

Lungs

Most of the local anesthetics are temporarily removed during the first pass in the lungs. This effect may be due to the low pH of the lung tissue relative to the plasma, resulting in a degree of ion retention [14,15].

As a result; lungs may relieve the toxic sequelae of accidental intravenous injections of local anesthetics. Patients with right to left heart shunts do not have this safety net and have an increased risk of toxicity. The local anesthetic is re-washed in a slower circulation following lung absorption [15,16].

Placenta transfer

Local anesthetics may spread to the placenta; however, ester local anesthetics are rapidly hydrolyzed in the blood, so they do not pass the placenta in significant amounts. Local anesthetics with amide structure vary significantly at placental transfer rates and fetal retention degrees. Increased protein binding in the mother reduces the amount of local anesthetic that can be released and released through the placenta. The fetus has low levels of α1-acid glycoprotein, so it has a low concentration of local anesthetic binding sites. Fetal pH is lower than the maternal pH, which results in ion retention of agents with higher pKa values [17].

Systemic side effects of local anesthetics

Allergic reactions

Allergic events due to local anesthesia are rare. It develops against ester type local anesthetics, which is more para-amino benzoic acid derivative. The reaction against amide group local anesthetics is rare. The cause of allergy in the amide group of drugs is methyl-paraben, which is incorporated in these solutions as a preservative, similar to para-amino benzoic acid [18].

Tissue toxicity

Local anesthetics used in the clinic, rarely cause localized nerve damage. Chlorprocaine may show neurotoxicity after epidural and caudal anesthesia. A 5% solution of lidocaine may lead to cauda-equina syndrome. Local anesthetics are prepared in physiological effective concentrations, but are used by diluting [19].

Methemoglobinemia

The only anesthetic that causes this is high doses of prilocaine. The metabolism of this agent in the liver results in the formation of orthotoluidin, which is responsible for converting hemoglobin into methemoglobin. Methemoglobin shifts the oxyhydrogen dissociation curve to the left, thus preventing the release of oxygen to the tissues. These effects are proportional to the concentration of methemoglobin and are reversible. The return of methemoglobinemia can be accelerated by IV given methylene blue (1 mg / kg) [20].

Cardiovascular side effects

A higher dose of local anesthetics is required for cardiovascular system (CVS) toxicity. In general, local anesthetics suppress myocardial automatism and reduce the duration of the refractory period. Hypertension, tachycardia and ventricular arrhythmia are the first of the diseases of CVS. Hypotension, arrhythmia, bradycardia and cardiac arrest develop as local anesthetics increase in blood. Ropivacaine and levobupivacaine are less cardiotoxic than bupivacaine[12].

The main mechanism of cardiovascular toxicity is the blockage of myocardial voltage-dependent sodium channels. PR interval provokes dose-dependent prolongation of QRS duration and conduction time, and spontaneously depressing cardiac activity. These electrophysiological effects combine with the direct negative inotropic effect of local anesthetic drugs [21].

Side effects in central nervous system

The symptoms of central nervous system (CNS) toxicity associated with LA are related to the plasma levels of drugs. Initially, there are drowsiness, dizziness, sedation, disorientation, tinnitus, nystagmus, metallic taste, nausea and vomiting. Then, restlessness, irritability, tremors and muscle twitches occur. After this, the tonic-clonic seizure and loss of consciousness develops, finally, apnea, cardiovascular collapse and coma. Rapid systemic administration of LA may cause death without signs of CNS stimulation or with very short-term symptoms [22,23]. In some cases, the risk of local anesthetic toxicity increases (Table 1).

Table 1: Risk factors for local anesthetic toxicity

Risk factors
Elderly or child patient
Hepatic dysfunction or altered hepatic perfusion
Low cardiac output
High cardiac output
Cardiac pathology
Reduction in plasma proteins
Pregnancy
Beta blockers, digoxin, calcium antagonists, cytochrome P450 inhibitors

The appropriate dose of LA should be the desired time and the lowest dose to achieve the degree of analgesia or anesthesia. A specific dose of LA will show inter-individual variation in plasma concentrations depending on the region and rate of administration or patient demography. These observations have been attempted to be standardized per kilogram in adults and with the recommended maximum doses, in particular the maximum weight-based dose varies between countries and texts. Maximum doses should be observed, especially in patients with low body weight [22].

Safety steps in the prevention of toxicity

Several security steps have been advocated to identify or reduce the risk of toxicity. For safe implementation of LA, the following has been proposed: limiting the cumulative dose, ultrasound or direct visualization for catheter insertion, test dosage, incremental injections, negative catheter aspiration, and adherence to guidelines [24].

Limiting the cumulative effects of anesthetics

Simultaneous administration of multiple local anesthetics contributes to a single systemic toxic threshold. Although specific serum concentration levels are associated with toxicity, weight based (mg / kg) dosing guides cannot reliably estimate these levels and cause potential toxicity at lower doses than expected [11].

For topical LA and subcutaneous solutions, doses higher than the substantially recommended levels are administered. Based on pharmacokinetic data, it appears that these routes of administration are associated with a lower risk of systemic toxicity, yet toxicity may occur. American Association of Regional Anesthesia and Pain Medicine (ASRA) recommend the use of the lowest concentration and dose required for neuraxial and non-neuro-axial analgesia [25].

In postoperative period, analgesic concentrations (<0.25% bupivacaine or ropivacaine) are used for continuous infusion. The anesthesia team is limited to the recommended doses after the anesthesia is applied simultaneously by the anesthesia team. Liposomal bupivacaine should not be administered with other local anesthetics due to the risk of toxicity [11].

Incremental injections and catheter aspiration

Lack of objective data, it is recommended that small doses (3-5 mL) of local anesthetic doses be administered to allow the anesthetist or surgeon to easily monitor for unwanted intravascular injection. Data on the reliability of this technique are lacking because it is not practical to expect a complete circulation time (30-45 seconds) between each 3 mL injection. Although recommended, the catheter aspiration of blood is not reliable for identifying intravascular catheters [26,27].

Intravascular Test Dose Application

Several studies have identified evidence-based techniques for catheter testing dosing, but test dosing with an intravascular marker is recommended when doses of potentially toxic LA are planned to be administered [28]. Potential test dose agents include epinephrine, local anesthesia, air, opioid and isoproterenol. Test solutions containing epinephrine are widely used during electrocardiography and when monitoring heart rate and blood pressure [29].

Regional anesthesia in ultrasound guidance

Ultrasound has been shown to reduce the risk of local anesthetic systemic toxicity (LAST) alone by 60% to 65% compared to peripheral nerve stimulation [30]. A lower dose of LA is used for ultrasound injection. At the same time, the incidence of vascular puncture decreases and visual indications indicating intravascular injection allow the termination of injection prior to administration of LA dose. However, despite the use of ultrasound, LAST events continue to occur and ultrasound guidance does not affect the risk of LAST caused by systemic absorption of LA [31].

Treatment of local anesthetic toxicity

Airway control and respiratory support are the basis of treatment. Benzodiazepines or a small amount of propofol administered IV are preferred to terminate seizures. The use of benzodiazepine in premedication may be used to increase the seizure threshold, but respiratory depression may cause acidosis with its excess sedation, which increases the concentration of free drug in the serum [19].

In 2010, ASRA published a guide on LAST management and revised in 2012 and 2017. Measures to be taken in accordance with this guideline include: applying the lowest effective dose, for example applying a test dose with adrenaline (5 mcg/mL) and taking the drug by aspiration before each injection. In the treatment of local anesthetic toxicity, it is recommended to provide airway, avoid the propofol if seizure occurs and treat with benzodiazepine. Local anesthetic, calcium channel blocker, beta-blocker, and vasopressin use should be avoided. If cardiac arrest develops, it is recommended to switch to advanced life support, to reduce the given dose of adrenaline (<1 mcg/kg), to administer lipid emulsion (20%) and to respond to treatment if cardiopulmonary bypass is not provided [25].

Lipid emulsion

20% lipid infusion is the first intravenous lipid emulsion safely used in parenteral nutrition since 1962 [32].Lipid emulsion consists mainly of soybean oil, glycerol, egg phospholipid, omega-3 and omega-6 essential fatty acids [33].

Weinberg et al. [32] he observed that intravenous lipid infusions not only increased the dose of bupivacaine needed to produce asystoles in rats, but also improved survival after bupivacaine intravenous bolus doses were taken in rats. They then applied this observation to dogs as a model of a species closer to humans and discovered that lipid infusions during boutsivacaine-induced cardiac arrest increased survival during resuscitation [34].

Rosenblatt et al. [35] successfully performed intravenous lipid emulsion (ILE) clinical practice in 2006, and many studies have supported the use of ILE for bupivacaine, levobupivacaine and ropivacaine cardiotoxicity [36-38].

ILE has been included in safety guidelines for management of cardiotoxicity in LA in the United States since 2007 in the United States and since 2008 in the United States(39, 40).In 2010, the American Regional Association of Regional Anesthesia and Pain Medicine (ASRA) published the application guide on LAST, emphasizing the importance of airway management and early cardiopulmonary resuscitation with the addition of ILE therapy [40]. In 2010, a special case of the American Heart Association (AHA) ACLS rules recommended the use of lipid emulsion for LAST-induced cardiac arrest [41].

The efficacy of ILE in treating cardiotoxicity not well defined, but in vitro studies are thought to form a lipid pool. This expanded intravascular lipid pool to absorb the circulating lipophilic toxin, thereby reducing the free toxin that is not able to bind to the myocardium [42]. Weinberg et al. [43] studied isolated rat heart on the mechanism of action of lipid emulsions. As a result of this study, it was found that lipid therapy accelerated the recovery in case of bupivacaine-induced cardiac arrest. It has also been found that this treatment helps to reduce the bupivacaine content in cardiac tissue and clear the tissue from the bupivacaine. This study demonstrates the efficacy of lipid therapy and supports the theory of fat precipitation. In addition, lipid therapy has been reported to have a positive inotropic and chronotropic effect on the heart under bupivacaine. Another theory is explained by the increase in lipid emulsion, increased fatty acid flow to cardiac cells and reduction of reduced fatty acid transport caused by bupivacaine [44].

The 2017 checklist simplifies the dosing of lipid emulsions to contain 100 mL of bolus fixed by 200 to 250 mL of infusion for 15 to 20 minutes for all patients weighing more than 70 ml.

Weight-based dosing is reserved for patients with less than 70 kg, but even these recommendations emphasize that the exact volume and flow rate are not critical. In response to the further indications of percepted lipid emulsion dosing proposals, the checklist suggests that a 30-minute resuscitation process may comprise lipid emulsion volumes approaching 1 L. As a result, the recommended content for a lipid LAST Rescue Kit is 1 total L lipid emulsion %20 (Table 2) [25].

Table 2: Lipid Emulsion Therapy

Lipid Emulsion %20	
>70kg	<70kg
100ml 20% lipid emulsion bolus (2-3 min)	1.5 ml/kg %20 lipid infusion (2-3 min)
Lipid emulsion infusion 200-250 ml (15-20 min)	Lipid emulsion infusion 0,25ml/kg/min (ideal body weight)
Patient unstable	
Re-bolus once or twice at the same dose and double infusion rate: be aware of dose limiting (12ml/kg)	
Total volume of lipid emulsion can approach 1 L in a prolonged resuscitation (<30 min)	

The American Society of Regional Anesthesia and Pain Medicine Checklist for Managing Local Anesthetic Systemic Toxicity: 2017 Version

AAGBI involves the introduction of a large initial intravenous bolus injection containing a 20% lipid emulsion at 1.5 mL/kg for 1 minute after administration of a LAST cardiac arrest; followed by an infusion of 15 mL/kg/h. Cardiopulmonary resuscitation should be continued. Two additional flakes (1.5mL/kg) can be given at 5-minute intervals in the absence of spontaneous circulation or deterioration after 5 minutes. The intravenous infusion rate should be doubled to 30 mL/kg/h. A maximum of three boluses can be given and a total dose of 12 mL/kg should not be exceeded. The ASRA guidelines differ only in terms of suggesting an additional bolus, and after the hemodynamic stability has been reached, the infusion at a maximum dose of 10 mL/kg should be continued for 10 minutes [39,40].

In response to candida, IN infusions modulate cytokine production by mononuclear white cells, which increase the risk of infection. With infusions, thrombophlebitis may develop during peripheral IV administration. They may cause impaired reticuloendothelial system function and altered inflammatory responses during prolonged treatment. They may cause allergic reactions, including anaphylaxis, especially if they contain soybean oil. If the fat particles are larger than 5 microns, they may result in pulmonary, splenic, placental and cerebral fat embolism. When administered at rates greater than 100 mg/kg/h, they can cause pulmonary hypertension; can cause warfarin resistance by facilitating binding of warfarin to albumin [45].

Conclusion

In clinical practice, local anesthetics are used quite frequently and the early diagnosis and treatment of toxicity is very important. LAST is a life threatening adverse event. The use of the lipid emulsion at the right time and at an effective dose will be life-saving. Therefore, each area where LA is used in potentially toxic doses should be equipped with a basic resuscitation device and a 20% lipid emulsion.

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Bladder leiomyoma: A case report and brief review of literature

Mesane leiomyomu: Olgu sunumu ve kısa literatür derlemesi

Engin Kölükçü [1], Bekir Süha Parlaktaş [2], Faik Alev Deresoy [3], Murat Beyhan [4], Latif Mustafa Özbek [5]

[1] Tokat State Hospital, Department of Urology, Tokat, Turkey
[2] Gaziosmanpaşa University, Department of Urology, Tokat, Turkey
[3] Gaziosmanpasa University, Department of Pathology, Tokat, Turkey
[4] Tokat State Hostpital, Department of Radiology, Tokat, Turkey
[5] Iğdır State Hospital, Department of Urology, Iğdır, Turkey

ORCID ID of the author(s)

EK: 0000-0003-3387-4428
BSP: 0000-0001-8754-4155
FAD: 0000-0002-2243-9394
MB: 0000-0002-8630-4632
LMÖ: 0000-0002-0680-4451

Corresponding author / Sorumlu yazar:
Engin Kölükçü
Address / Adres: Üroloji Bölümü, Tokat Devlet Hastanesi, Gültekin Topçam Bulvarı, Yeni Cadde, Tokat, Türkiye
e-Mail: drenginkolukcu@gmail.com

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Abstract

Leiomyomas are non-epithelial benign and rare lesions of bladder. Their symptoms vary considerably based on the size, localization and nature of the lesion. Recently, an optimal treatment option for bladder leiomyoma is still contradictive. Transurethral resection, segmental surgical excision or partial cystectomy are main treatment modalities. This study presents a 41 year-old male case who applied to our center with hematuria complaint and had leiomyoma diagnosis based on tissue sampling following transurethral resection.

Keywords: Bladder, Leiomyoma

Öz

Leiomyomlar mesanenin nonepitelyal benign lezyonları olup oldukça nadir olarak izlenmektedirler. Semptomatoloji olgular arasında lezyonun büyüklüğüne, lokalizasyonuna ve karakterine göre oldukça farklılıklar göstermektedir. Günümüzde mesane leiomyomu için optimal tedavi seçeneğinin konusundaki tartışmalar devam etmektedir. Transüretral rezeksiyon, segmental cerrahi eksizyon veya parsiyel sistektomi ana tedavi yöntemleri olarak gösterilmektedir. Bu çalışmada hematüri ile başvuran ve uygulanan transüretral rezeksiyon sonrası doku tanısı leiomyom olarak sonuçlanan 41 yaşındaki erkek olgunun sunulması amaçlanmıştır.

Anahtar kelimeler: Mesane, Leiomyom

Introduction

Leiomyomas are benign mesenchymal tumors originating from smooth muscles. They can be observed in any organ with smooth muscles. They frequently develop in one organ, and have a solitary character, but they may appear in several organs or as multiple lesions in one organ [1]. In genitourinary system, leiomyomas are most commonly found in renal capsule, but they are quite rare in bladder. They constitute less than 0.5% of all bladder tumors [2,3]. Some of the leiomyomas observed in bladder are diagnosed accidentally and these patients could have a wide range of clinical presentations such as hematuria, dysuria and pollakiuria [4].

Treatment of bladder leiomyomas is still controversial today. Localization, size and nature of these lesions are important for the treatment method of choice. Transurethral resection, segmental surgical excision or partial cystectomy are main treatment modalities used for the treatment of these cases [4-5]. The aim of the present study was to discuss in light of the literature a case who applied to our clinic with hematuria complaint and was diagnosed bladder localized leiomyoma.

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Case presentation

Forty-one year old male patient applied to our clinic with complaints of muscle pain, fatigue and tea-colored urine. The patient had no comorbidities or surgical history. No pathological finding other than microscopic hematuria was observed in laboratory examinations. In contrast-enhanced whole abdomen tomography, on the other hand, a mass of 2 cm size was observed in bladder lateral wall (Figure 1). In urethrocystoscopy, a solid lesion of about 2 cm size was found in right lateral wall of bladder. Except for this lesion, both ureter orifices, bladder neck and bladder mucosa excluding the area where mass was located appeared completely normal. Then, transurethral resection was performed under spinal anesthesia for the lesion observed in bladder. Catheter was removed on the third postoperative day and the patient was discharged without any problem. In microscopic examination of tissue specimens, a tumor development with poor cellularity extending in various directions as bundles and showing flow pattern (Figure 2). On the other hand, it was revealed that the lesion was composed of fine spindle cells with bipolar nuclei but had no mitosis and necrosis. However, adipose tissue foci and vascular structures were observed among cellular bundles. Besides, stromal myxoid changes were observed in background of some areas. Immunohistochemical analysis showed an extended and strong cytoplasmic expression of SMA (smooth muscle actin) stain applied to tissue (Figure 3). Based on all pathological data, case was diagnosed as bladder leiomyoma. The patient was taken to routine follow-up program and no recurrence was observed in follow-ups performed for two years.

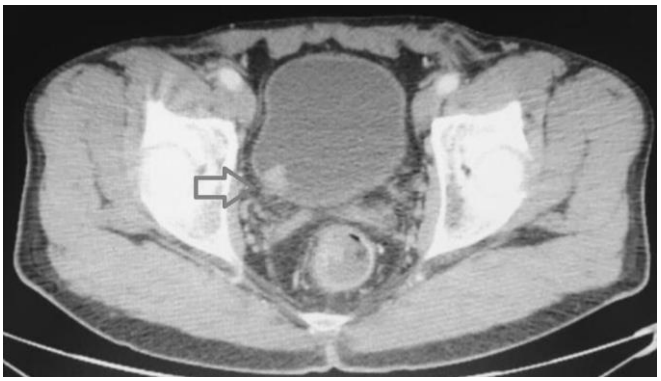

Figure 1: Computed tomography scan showing heterogeneously enhancing bladder mass (arrow)

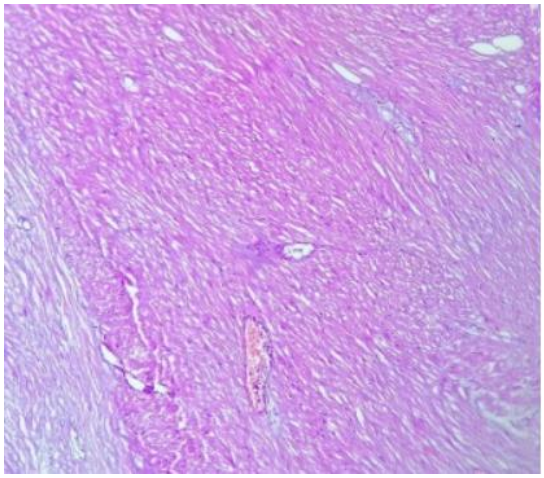

Figure 2: Histopathological examination of the bladder mass

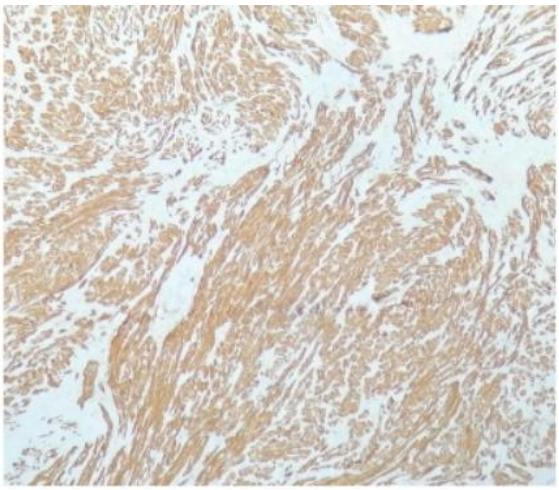

Figure 3: Immunohistochemical analyses of the bladder mass

Discussion

A detailed examination of the literature showed that many benign structures of bladder have been described such as inflammatory myofibroblastic tumor, postoperative spindle cell nodule, neurofibroma, schwannoma, leiomyoma and hemangioma [6]. However, most commonly observed benign mesenchymal tumors of these formations are leiomyomas [4]. Bladder leiomyoma was first described by Kretschmer et al. [7] in 1931. Nevertheless, etiology of leiomyomas has not been fully elucidated yet. Many factors such as infections, hormonal changes and chromosomal anomalies have been suspected in the etiology [4,8]. Leiomyomas could be found in all age groups. In women, they are more common in the third and fourth decade of the life [5]. Previous studies found that size of these benign lesions could vary enormously from millimeters to gigantic sizes of up to 30 cm [3,9]. Nature of these lesions in bladder could be of three types: endovesical, extravesical and intramural. Endovesical location is the most common form and is observed in 63-86% of the cases followed by extravesical form which is found in 11-30%. Intramural form, on the other hand, is least common one and constitutes 3-7% of all leiomyomas [9].

Clinical findings of bladder leiomyomas are closely associated with the location, size and nature of the lesion. The leiomyoma patients could present with hematuria, bacteriuria, frequently urinary system infection, flank pain and obstructive or irritative urinary symptoms. However, they can also be incidentally diagnosed [10,11]. Silva-Ramos et al. [12] performed a clinical study with 90 patients who had bladder leiomyoma and found that most frequent complaint of the patients was irritative urinary symptoms. Similarly, irritative urination was the most common complaint of the patients in another study by Jiang et al. [13]. Goluboff et al. [14], on the other hand, reported that obstructive symptoms were most common complaints of leiomyoma patients (49%). In the same study, 11% of the patients had hematuria and 38% had irritative urinary symptoms while 19% of them had incidental diagnosis.

Ultrasonography (USG), intravenous pyelography (IVP), computed tomography (CT) and magnetic resonance imaging (MRI) are major methods used for radiological evaluation of bladder leiomyomas. Leiomyoma is usually observed as homogeneous, hypoechoic and clearly bordered in USG and has small amount of hemorrhage in Doppler USG [16].

Intravesical or submucosal leiomyomas have a filling defect or bladder contour irregularity in IVP [17]. In CT, bladder leiomyoma generally has an appearance of round hypodense mass with clear borders while centripetal homogeneous contrasting is observed in contrast-enhanced CT. It is observed as a mass with smooth surface and low signal intensity. Use of MRI is suggested more frequently for the diagnosis because of its better tissue contrast and higher resolution [18]. In bimanual examination, on the other hand, it is a palpable, smooth surfaced mobile lesion with elastic structure. Cystoscopy and tissue examination are absolutely necessary for the diagnosis [14]. Leiomyomas are grossly clear-bordered, thin-capsuled solid masses with yellow colored sectional surface. Microscopically, leiomyoma is made of intersecting smooth muscle fascicles surrounding vascular structures lined with normal endothelium and arranged as bundles extending in various directions. No mitotic activity, hemorrhage or necrosis foci are observed in these lesions. Immunohistochemically, they have positive staining with SMA (smooth muscle actin), MSA (muscle-specific actin), desmin, h-caldesmon and vimentin. In general, they are negative with keratins and EMA (epithelial membrane antigens). Four major pathologies are important in differential diagnosis of leiomyoma. These are leiomyosarcoma, solitary fibrous tumor, postoperative spindle cell nodule and inflammatory myofibroblastic tumor. Detrusor muscle invasion is the most significant factor in differential diagnosis with leiomyosarcoma. However, findings such as presence of nuclear atypia, high level of mitosis and tumor necrosis also help for the differential diagnosis. Postoperative spindle cell nodules generally appear a few weeks after the transurethral resections. Histologically, they resemble sarcomas because of cellularity and high number of mitosis. Although spindle cells are considered to originate from mesenchymal cells, histochemically they are positively stained with LMWCK (low molecular weight cytokeratin), vimentin, actin and desmin, but not with EMA. Inflammatory myofibroblastic tumors (inflammatory pseudotumors) are usually observed as polypoid masses in bladder during childhood. Histologically, they are diagnosed with the presence of spindle cells on myxoid and inflammatory background. Immunohistochemically, they are LMWCK negative. Solitary fibrous tumors are distinguished from leiomyomas with their cellularity and mitosis number, and histochemically with the presence of CD34, EMA and bcl-2 expressions [18-19].

Treatment modalities vary based on size, location and character of the lesion. Transurethral resection and fulguration are used in clinical practice as extremely minimally invasive treatment modality for small sized lesions which could be identified endoscopically. On the other hand, previous studies showed that repeating surgical interventions could be needed as secondary to incomplete resection in 18% of endovesical leiomyomas resected by transurethral method [20]. Especially for leiomyomas of intramural or extravesical nature which may have large sizes, open, laparoscopic or robotic mass enucleation and partial or total cystectomy are among the treatment modalities [4,20].

In conclusion, it is extremely important to perform cystoscopic examination for patients applying with hematuria and to include benign lesions of bladder such as leiomyomas, though they are rare, in their differential diagnoses.

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Inguinal bladder hernia, a rare cause of inguinal herniation: Report of two cases

Nadir bir inguinal herniasyon nedeni olan inguinal mesane fıtığı: İki olgu sunumu

Aliou Zabeirou Oudou [1], Tenkorang Somuah [2], Belhaj Anas [1], Aissaoui Alae Eddine [1], Souiki Tarek [1], Farih Moulay Hassan [2], Ibn Majdoub Karim [1], Toughrai Imane [1], Mazaz Khalid [1]

[1] Department of Visceral and Endocrinological Surgery II, Chu Hassan II, Fes, Morocco
[2] Department of Urology, Chu Hassan II, Fes, Morocco

ORCID ID of the author(s)

AZO: 0000-0001-6152-210x
TS: 0000-0001-5657-7253
BA: 0000-0002-1118-1594
AAE: 0000-0001-5776-2709
ST: 0000-0002-2416-4355
FMH: 0000-0001-8997-5717
IMK: 0000-0002-0421-7296
TI: 0000-0003-0401-3012
MK: 0000-0001-7779-7802

Corresponding author / Sorumlu yazar:
Aliou Zabeirou Oudou
Address / Adres: Department of Visceral and Endocrinological Surgery II, Chu Hassan II, Fes, Morocco
e-Mail: ali.zabeirou@gmail.com

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Abstract

Hernia surgery is the most frequent in visceral surgery. The bladder is rarely involved in groin hernia. This is when a diverticulum or a part of the bladder wall is incarcerated within the hernia. This affection is often asymptomatic. The diagnosis is made per-or post-operatively following complications. We report 2 cases of inguinal hernia involving the bladder in which the first case was diagnosed preoperatively whereas the second was diagnosed intraoperatively.

Keywords: Bladder, Hernia, Inguinal

Öz

Fıtık cerrahisi viseral cerrahide en sık görülenidir. Mesane nadiren kasık fıtığı ile ilişkilidir. Bu, divertikülün veya mesane duvarının bir bölümünün fıtık içinde hapsedilmesidir. Bu durum genellikle asemptomatiktir. Tanı komplikasyonları takiben ameliyat sonrası veya sonrasında yapılır. Bu çalışmada iki kasık mesane fıtığı olgusunu sunuyoruz, mesane ilişkisi birinci vakada preoperatif tanı ile, ikinci vakada intraoperatif olarak teşhis edildi.

Anahtar kelimeler: Mesane, Fıtık, Kasık

Introduction

Bernard Levine was the first to describe bladder hernia in 1951 as a scrotal cystocele [1]. Bladder inguinal hernia is a rare pathology found in about 1-4% of inguinal hernias [2]. The diagnosis is usually done intraoperatively or sometimes postoperatively following the onset of complications. Surgery is the required treatment option; it involves reintegrating the herniated part of the bladder and performing a herniorrhaphy. Patients often have associated urological symptoms. Inguinal bladder hernia constantly remains unknown to the surgeon before diagnosis is made during surgery. We report two cases of inguinal hernia with bladder involvement in which diagnosis was obtained preoperatively for the first and intraoperatively for the second.

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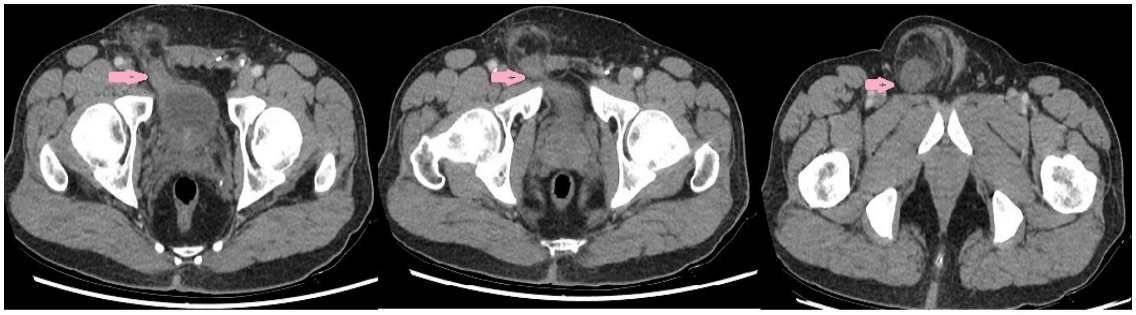

Figure 1: Axial computed tomography scan demonstrated the right upper part of the bladder herniated into the inguinal canal. Inguinal canal had not any bowel segment (arrows).

Case presentation

Case 1

A 50-year-old patient without any significant medical history who complained of dysuria, pollakiuria, urinary urgency associated with a burning sensation during micturition. The patient explained that the symptomatology had evolved during 6 months and had aggravated by the appearance of a right inguinal painless, reducible swelling which was impulsive to cough. It is important to note that the inguinal swelling increased in volume during pre-micturition and reduces after micturition "Mery's Sign". Digital rectal examination found a normal palpable prostate.

An abdominopelvic computed tomography (CT) scan was performed which revealed a right inguinal cystocele (Figure 1). The patient was scheduled for surgery. The Surgical exploration revealed a direct inguinal hernia associated with involved the bladder (Figure 2). The surgical treatment consisted of a repositioning of the bladder in an anatomical position and Lichtenstein tension free hernia repair. The postoperative course was uneventful.

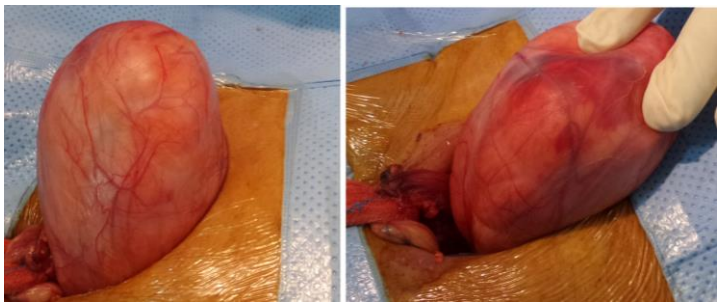

Figure 2: Image showing right inguinal bladder hernia intraoperatively.

Case 2

A 80-year-old patient, who was being treated in the department of urology for benign prostatic hypertrophy, was admitted to the emergency department for a painful swelling on the left groin. Clinical examination found an inguinal a painful, irreducible swelling with a negative cough impulse. The diagnosis of strangulated left inguinal hernia was retained. No radiological examination was performed. The patient was admitted to the operating room for an emergency surgery.

The surgical exploration revealed a thick hernia sac. Bladder involvement was ascertained as the after the hernia sac was incised making it possible to perceive the balloon of the urine catheter (Figure 3). The surgical treatment consisted of the suture of the injured bladder wall. The bladder was repositioned it's an anatomical position. Bassini technique was used to repair the hernia. The postoperative course was uneventful.

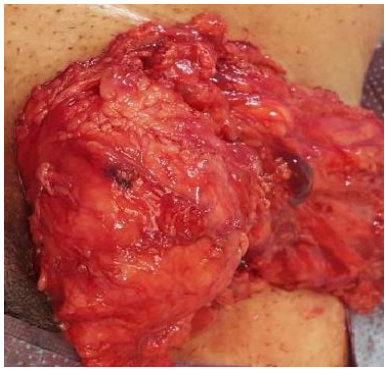

Figure 3: Image showing left inguinal bladder hernia intraoperatively

Discussion

Inguinal bladder hernia represents 1 to 4% of all inguinal hernias and mainly affects male patients aged between 50 and 80 years [1,3,4]. The existence of obstructive urinary tract disorders is a risk factor for the disease [5]. Although more this disorder may be frequently due to a prostatic pathology frequent in males. Bladder hernia can also occur in females [6].

Inguinal hernia of the Bladder can touch a bladder wall, a diverticulum or even the entire bladder. They are responsible for symptoms ranging from simple irritative symptoms to acute obstructive renal failure [7]. A two-step urination, facilitated by applying pressure on the hernia and the disappearance of the hernia after the voiding, constitutes a very revealing but inconstant clinical sign: Mery's Sign [8]. However, this pathology often remains asymptomatic. As a result, the diagnosis is usually made intraoperatively.

The diagnosis is often made preoperatively. Radiographic imaging can help obtain the diagnosis in order to reduce the risk of bladder injury during hernia repair when urinary symptoms are present. Indeed, less than 7% of bladder hernias are diagnosed before surgery, while in 16% of cases it is diagnosed postoperatively in the presence of parietal suppuration or vesico-cutaneous fistula [9].

Ultrasound or abdominal CT scan allows diagnosis of bladder hernia [10]. CT scan can identify the contents of the hernia (intestine / omentum / bladder) as well as the associated complications. Retrograde urethrocystography performed in search of stenosis of the urethra may objectify an inguinal bladder hernia. They appear as a rounded, unilateral, regular image of addition, communicating widely with the bladder [11].

The treatment consists of a hernia surgery with reintegration of the bladder in an anatomical position. In case of voluminous hernia, bladder diverticulum, or vesical necrosis, the herniated part can be resected. In case of preoperative diagnosis the treatment of a bladder hernia does not differ from that of other hernias and consists of a bladder repression associated with

a hernia repair. Resection of the bladder is required due to the risk of reduction of bladder capacity and ureteral injury [12].

BPH is a herniogenic factor. The prevalence of inguinal hernia is 15% to 25% in patients admitted for prostate adenoma [13]. In view of the relation between hernia and BPH, It is recommended to treat a BPH with alpha-blockers in the initial therapy. In case of satisfactory improvement of micturition, herniorrhaphy should be performed [14].

In Conclusion: Inguinal bladder hernia is a rare entity and occurs most often in a patient over 50 years of age with a history of urinary incontinence. The symptomatology is nonspecific; the diagnosis is suspected in a patient with an associated urinary disorder (Mery's Sign) and confirmed preoperatively or by computed tomography scan.

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Spontaneous inguinal enterocutaneous fistula, as an exceptional complication of incarcerated Richter's hernia: A case report

Spontan inguinal enterokutan fistül, hapsedilen Richter fıtığının istisnai bir komplikasyonu: Olgu sunumu

Aliou Zabeirou Oudou [1], Badri Mourad [1], Souiki Tarek [1], Ibn Majdoub Karim [1], Toughrai Imane [1], Mazaz Khalid [1]

[1] Department of Visceral and Endocrinological Surgery II, Chu Hassan II, Fes, Morocco

ORCID ID of the author(s)
AZO: 0000-0001-6152-210x
BM: 0000-0001-5085-0941
ST: 0000-0002-2416-4355
IMK: 0000-0002-0421-7296
TI: 0000-0003-0401-3012
MK: 0000-0001-7779-7802

Corresponding author / Sorumlu yazar:
Aliou Zabeirou Oudou
Address / Adres: Department of Visceral and Endocrinological Surgery II, Chu Hassan II, Fes, Morocco
e-Mail: ali.zabeirou@gmail.com

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Abstract

Richter's hernia may be defined as an abdominal hernia in which only part of the circumference of the bowel wall is entrapped and strangulated in the hernial orifice. It occurs at various positions with femoral ring being the most common. As the bowel continuity is maintained, the patients usually do not have intestinal obstruction. The spontaneous enterocutaneous fistula is a rare complication of inguinal Richter's hernia. We report a case of a 75 year old female patient with enterocutaneous fistula which occurred spontaneously in the right inguinal region. Abdominal computed tomography scan confirmed the diagnosis of enterocutaneous fistula. We performed a right celiotomy with resection and primary anastomosis of the fistulous bowel. Patient recovered uneventfully without any complications or recurrence.

Keywords: Enterocutaneous fistula, Femoral ring, Inguinal, Richter's hernia, Spontaneous

Öz

Richter fıtığı, bağırsak duvarının çevresinin sadece bir bölümünün fıtık deliğinde sıkışıp boğulduğu karın fıtığı olarak tanımlanabilir. Femoral halka en yaygın olanı olup, çeşitli pozisyonlarda ortaya çıkabilir. Bağırsak devamlılığı korunduğundan, hastalarda genellikle bağırsak tıkanıklığı yoktur. Spontan enterokutan fistül, inguinal Richter fıtığının nadir görülen bir komplikasyonudur. Bu çalışmada sağ inguinal bölgede spontan olarak ortaya çıkan enterokutan fistülü olan 75 yaşında bir kadın hasta sunuldu. Abdominal bilgisayarlı tomografi taraması enterokutan fistül tanısını doğruladı. Rezeksiyon ve sağ bağırsakta primer anastomoz ile sağ seliotomi yapıldı. Hasta herhangi bir komplikasyon veya nüks olmadan sorunsuz bir şekilde iyileşti.

Anahtar kelimeler: Enterokutan fistül, Femoral halka, İnguinal, Richter fıtığı, Spontan

Introduction

Richter's hernia is an incarceration of the antimesenteric circumference of bowel wall is within the hernia sac. This situation is responsible for the occurrence of ischemia, gangrene and perforation of the bowel [1]. It occurs at various positions with femoral ring being the most common. [2]. It is a more common disease in developing countries because of the delay in diagnosis [3].

We report a case of a 75 year old female patient with enterocutaneous fistula which occurred spontaneously in the right inguinal region. Abdominal computed tomography (CT) scan confirmed the diagnosis of enterocutaneous fistula.

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Case presentation

A 75 years old female admitted to surgery emergency for fecal fistula in the right inguinal region since 20 days. She developed 5 weeks ago a painful swelling of the right groin whose evolution is marked by the appearance of a fistula.

The clinical examination found an altered patient, dehydrated. Abdomen is soft and not painful. No symptoms of intestinal obstruction. The examination of the inguinal region finds a fistulous orifice with a fecal matter discharge (Figure 1). On CT scan showed communication of the cutaneous opening with a small gut loops (Figure 2).

The patient was admitted to the operating room for an emergency surgery and right inguinal region explored with a right celiotomy which confirmed a right sided Richter's femoral hernia with part of the small bowel wall as content which was gangrenous and opened up (Figure 3). Resection of gangrenous segment and end to end anastomosis was done in one layer. Mac VAY technique was performed to repair the femoral hernia. The fistulous tract was laid open and curetted. Post-operative period are uncomplicated.

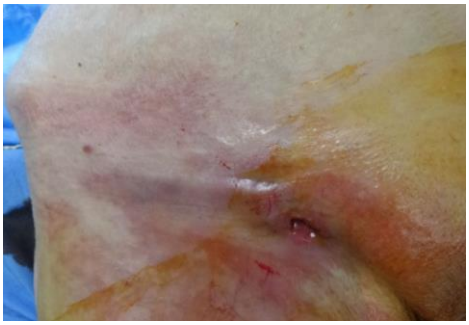

Figure 1: Image of the right groin showing opening of the enterocutaneous fistula

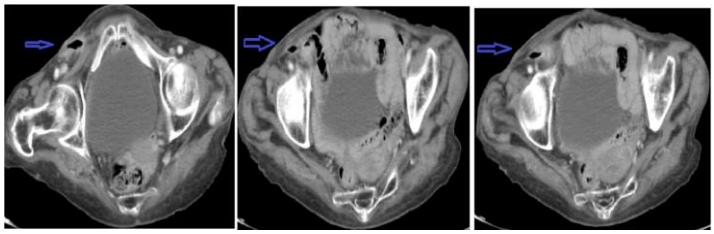

Figure 2: Abdominal computed tomography scan showing enterocutaneous fistula (arrow)

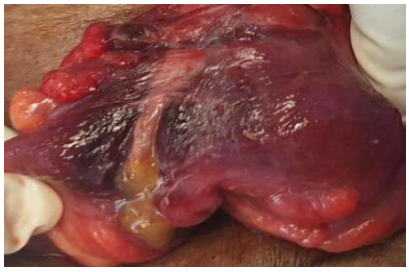

Figure 3: Image showing necrosis and perforation of small bowel

Discussion

Femoral hernias are diagnosed in more than 50% of cases during strangulation [4]. It is a more common pathology in women. Diagnosis of femoral hernias is difficult due to the configuration of the Femoral ring. The potential severity of a strangulated hernia is related to the risk of acute intestinal obstruction and intestinal gangrenous. Enterocutaneous fistula can complicate neglected groin hernia [5].

A Richter's hernia progresses more rapidly to gangrene due to constricting ring that exerts direct pressure on the bowel wall and hence compromised blood supply [6]. Making the diagnosis of Richter's hernia may be difficult because of the apparently innocuous initial symptoms and sparse clinical findings; the diagnosis may remain presumptive until clearly confirmed at surgery [7].

The CT scan with ingestion of gastrografin allows the diagnosis of a fistula [8]. Most of these spontaneous fecal fistulas have been reported from developing countries like India and Nigeria [9] and is usually the result of poverty, lack of knowledge, neglect, late presentation and lack of proper management [10].

In conclusion, an enterocutaneous fistula revealing a Richter's femoral hernia demonstrates a significant diagnostic delay. The treatment is surgical and should be adapted to local and parietal conditions.

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Laparoscopic cholecystectomy in left-sided gallbladder detected during operation

Ameliyat sırasında saptanan sol yerleşimli safra kesesinde laparoskopik kolesistektomi

Yahya Kemal Çalışkan [1], Fatih Başak [2], Abdullah Şişik [2]

[1] Department of General Surgery, University of Health Science, Kanuni Education and Research Hospital, Istanbul, Turkey
[2] Department of General Surgery, University of Health Science, Umraniye Education and Research Hospital, Istanbul, Turkey

ORCID ID of the author(s)
YKÇ: 0000-0003-1999-1601
FB: 0000-0003-1854-7437
AŞ: 0000-0002-7500-8651

Abstract

The case where the gallbladder was located on the lower face of the left lateral segment of the liver was defined as a left-sided gallbladder. It is a rare hereditary anomaly and can be seen with the right-sided ligamentum teres. Vascular and biliary anomalies can be seen in the cases of placement anomaly. Full dissection of the calot's triangle applied as a standard in laparoscopic cholecystectomy is important for the safety of the cases in anomaly cases. In this study, we aimed to present a laparoscopic cholecystectomy performed in a case of a left-sided gallbladder detected during surgery.

Keywords: Gallbladder, Variation, Laparoscopic cholecystectomy

Öz

Safra kesesinin karaciğerin sol lateral segmentinin alt yüzüne yerleşmesi durumu sol yerleşimli safra kesesi olarak tanımlanmıştır. Nadir görülen kalıtsal bir anomali olup, sağ yerleşimli ligamentum teres ile birlikte görülebilmektedir. Yerleşim anomalisi olgularında damarsal ve safra yolları anomalisi görülebilmektedir. Laparoskopik kolesistektomi ameliyatında standart olarak uygulanan kalot üçgeninin tam diseksiyonu anomali olgularında da ameliyat güvenliği için önemlidir. Bu çalışmada ameliyat esnasında saptanan sol yerleşimli safra kesesi olgusunda yapılan laparoskopik kolesistektomi ameliyatını sunmak amaçlanmıştır.

Anahtar kelimeler: Safra kesesi, Varyasyon, Laparoskopik kolesistektomi

Introduction

A left-sided gallbladder (LSG) is a gallbladder located on the left side of the liver, round ligament, and not on the right side, which is its mundane location. It is first described from Hochstetter in 1856. The reported incidence is between 0.1% and 1.2% [1-4]. The present case report demonstrates a case of LSG identified during laparoscopic cholecystectomy. Gallbladder is located in the lower left side of the left lateral segment of the liver. It is a rare hereditary anomaly and can be optically discerned with a right-sided ligamentum teres. In this study, we aimed to present challenges in a laparoscopic cholecystectomy performed in a case of a LSG detected during surgery.

Corresponding author / Sorumlu yazar:
Yahya Kemal Çalışkan
Address / Adres: Genel Cerrahi Kliniği, Kanuni Eğitim ve Araştırma Hastanesi, Küçükçekmece, İstanbul, Türkiye
e-Mail: yahyakemalc@yahoo.com

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Case presentation

A 55-year-old woman presented with abdominal pain and jaundice. She is hospitalized with the pre-diagnosis of cholangitis and choledocholithiasis due to occlusion of choledochus. He was discharged after medical treatment. Magnetic resonance cholangiography revealed no abnormality in the gallbladder or pathology in the biliary tract. The patient was prepared for elective cholecystectomy six weeks later. Operation revealed that the gallbladder was located in the left segment of the left lobe of the liver and left of the ligamentum teres (Figure 1, 2). It was decided to continue cholecystectomy without changing the places of entry. Cystic canal and cystic artery were revealed in the caliper dissection with technique of open window and critical view of safety. No major anomalies were observed in the dissection area. Standard retrograde (infundibulum-first) cholecystectomy was performed laparoscopically. The patient was discharged without any problems after one day. The pathological examination of the specimen was reported as chronic cholecystitis with gall stone.

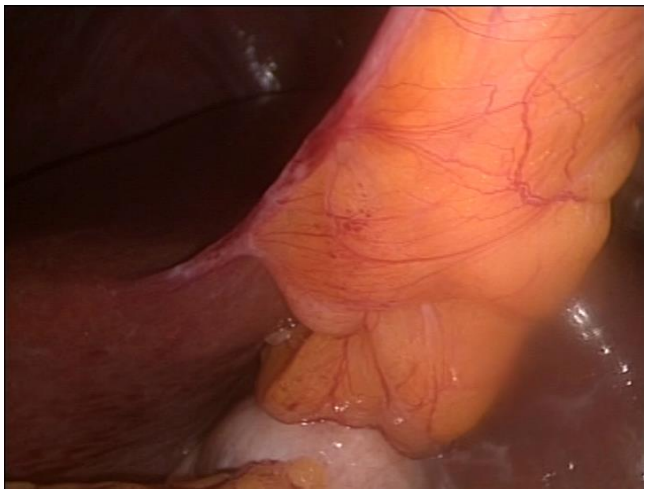

Figure 1: Intraoperative view of left-sided gallbladder

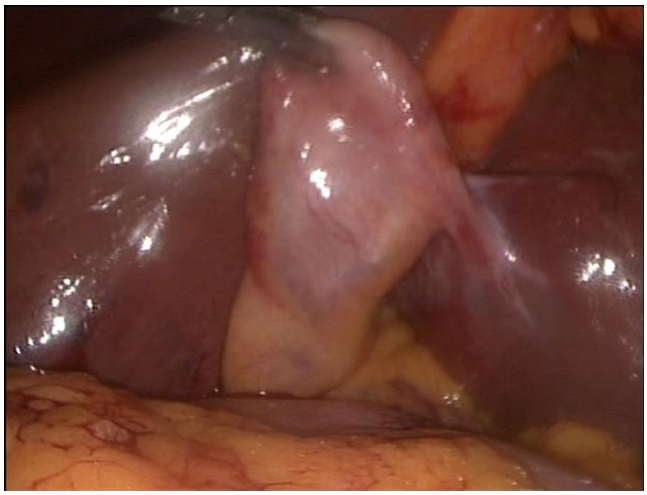

Figure 2: Gallbladder attached to the left lobe of the liver

Discussion

LSG is a rare anomaly. Vascular and biliary anomalies may be seen in these cases with placement anomaly. In laparoscopic cholecystectomy, for surgical safety, surgeon should complete dissection applied as a standard to reveal anomaly of the calot's triangle. Antegrade cholecystectomy (fundus-first) or, if necessary, conversion should be kept in mind when the association with the main bile duct is suspicious or in cases of such anomaly [3-5].

Aberrant gallbladder can be of 4 different types: Left-sided; intrahepatic; transverse; Retro settled. These are the most rarely seen gallbladder without situs inversus [5]. LSG can be found in two anatomic variants. The first is the actual LSG where the gallbladder is located in the left lobe of the liver. In this case, there may be subtypes depending on how the cystic channel is incorporated into the biliary tree [4-6]. The cystic channel is connected to the right bile duct (CBD) on the right side. The normal gallbladder bud does not go to the left and right of the left lobe, to the left and right of the left lobe, and to the left of the round ligament. Left cystic canal or left CBD connected. It accompanies failure in the development of the normal structure of the right and right side of the liver canal [7]. Second, the gallbladder is on the left side of the round ligament, but the round ligament is still in the right lobe of the liver because it is still attached to the right liver [6].

The inability to predict the cystic duct or the general bile duct may be challenging, and the selective use of selective intraoperative cholangiography might contribute to the safe laparoscopic management of this unusual problem [7,8].

In conclusion, left-sided gallbladder is a rare operative finding. Preoperative imaging may not detect the anomaly. Intraoperative cholangiography should be performed to detect anomalies associated with biliary trees. When the surgeon is suspicious, conversion to open surgery is recommended to prevent complications.

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