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## İÇİNDEKİLER / CONTENTS

### ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Deniz Esin TEKCAN ŞANLI Duzgun YILDIRIM COVID-19 Pandemisiyle Artış Gösteren Subakut Tiroidit [tr] Subacute Thyroiditis Exacerbated by the COVID-19 Pandemic [en] / Sayfa: 1-7 PDF

Hayrullah YAZAR Güler KUŞÇU GÜNAY Mustafa Baran İNCİ Süleyman KALELİ Mehmet ÇAKAR Anjiyografi Hasta Plazmalarında, Paraoxonase 1, Arylesterase ve Total Thiol İncelemesi [tr] / Paraoxonase1, Arylesterase and Total Thiol Investigation in Angiography Patient Plasmas [en] Sayfa: 8-12 PDF

Abdülhekim YARBAĞ Tip 2 Diabetik Makula Ödemli Hastalarda Tedavi Karşılaştırması [tr] / Comparison of Treatment in Patients with Type 2 Diabetic Macular Edema [en] / Sayfa: 13-18 PDF

Türkan AKYOL GÜNER Tuğçe GÜNTER Diyabetli Bireylerde Beslenme Okuryazarlığının Yaşam Kalitesi ve Metabolik Kontrol Üzerine Etkisi [tr] / The Effect on the Quality of Life and Metabolic Control of Nutritional Literacy in Individuals with Diabetes Mellitus [en] / Sayfa: 19-26 PDF

Fatih ŞAHİN Havva KOCAYİĞİT Fikret BAYAR Ayça TAŞ TUNA Sezaryen Doğumlarda Tek Doz Spinal ve Kombine Spinal Epidural Anestezinin Postoperatif Analjezi Kalitesinin Karşılaştırılması [tr] / Comparison of Postoperative Analgesia Quality of Single Dose Spinal and Combined Spinal Epidural Anesthesia in Cesarean Deliveries [en] / Sayfa: 27-31 PDF

Cihan AYDIN Şeref ALPSOY İlker YILDIRIM Ahmet GÜLTEKİN Cavidan ARAR Mesut ENGİN Bişar AMAÇ Genel Yoğun Bakım Ünitesinde Yatan COVID 19 Hastalarında Mortaliteyi Öngörmeye İntegrasyon İndekslerinin Prediktif Değerleri [tr] / Predictive Values of Inflammation Indexes in Predicting Mortality in Patients with COVID 19 Hospitalized in General Intensive Care Unit [en] / Sayfa: 32-39 PDF

Mehmet Hanifi TANYERİ Mehmet Emin BÜYÜKOKUROĞLU Pelin TANYERİ Rümeyza KELEŞ Şeyma Nur BAŞARIR BOZKURT Oguz MUTLU Firuzan AKAR Bekir Faruk ERDEN Güner ULAK Loksapin, İloperidon, Paliperidon'un İzole Farelerde Vas Deferens Kasılması Üzerine Kronik Etkileri [tr] / Chronic Effects of Loxapine, Iloperidone, Paliperidone on Mice Isolated Vas Deferens Contractility [en] / Sayfa: 40-46 PDF

Hale TOSUN Birgül ÖDÜL ÖZKAYA Ferište UZ Asiye GÜL Cerrahi Girişim Uygulanan Hastalarda Ağrı ve Konfor İlişkisi [tr] / The Relationship Between Pain and Comfort in Patients with Surgical Interference [en] / Sayfa: 47-52 PDF

Gamze FIŞKIN Zeynep ÖLÇER Annelerin Beslenme Davranışları ve Çocuklarının Beslenme Sürecine Yönelik Tutumları Arasındaki İlişki [tr] / The Relationship Between Mothers' Feeding Behaviors and Their Children's Attitudes Towards Feeding Process [en] / Sayfa: 53-61 PDF

Erhan HAFIZ Özgür ALTINBAŞ Kardiyak Cerrahi Sonrası Postoperatif Mediastinit Tedavisi Sonuçları: Yıkamalı ve Yıkamasız Metodlarla Yapılan Negatif Basıncılı Yara Tedavilerinin Karşılaştırılması [tr] / Treatment Outcomes of Postoperative Mediastinitis After Cardiac Surgery: A Comparison of Negative Pressure Wound Therapy Performed with Instillation Method and Non-Instillation Method [en] / Sayfa: 62-67 PDF

Kemine UZEL Filiz BİLİR Bahar SARIİBRAHİM ASTEPE Paşa ULUĞ Yusuf Kemal ARSLAN Tunay KİREMİTLİ Gebeliğin İntrahepatik Kolestazi ve Maternal-Fetal Sonuçları [tr] / Intrahepatic Cholestasis of Pregnancy and Maternal-Fetal Results [en] / Sayfa: 68-73 PDF

Güven KILIÇ Kursad ONEC Ömer POLAT Hemodiyaliz Hastalarında Spondilodiskitis [tr] / Spondylodiscitis in Patients under Haemodialysis [en] / Sayfa: 74-79 PDF

Hasan ERGENÇ Zeynep ERTÜRK Ahmet Tarık EMİNLER Hakan CİNEMRE Akut Pankreatit Hastalarında Nötrofil/Lenfosit ve Trombosit/Lenfosit Oranlarının Tanısal ve Prognostik Değeri [tr] / Diagnostic and Prognostic Value of Neutrophil/Lymphocyte Ratio and Platelet/Lymphocyte Ratios on Acute Pancreatitis Patients [en] / Sayfa: 80-85 PDF

Tamseel AWAN Farah KHALİD Tabeer AWAN Maliha ZAİDİ Karaçi'deki İşletme Öğrencilerinde Kendi Kendine İlaç Uygulamaları [tr] / Self-Medication Practices among Business Students in Karachi [en] / Sayfa: 86-92 PDF

Mukaddes TOZLU Diminutif Poliplerin Endoskopik Tedavisinde Jumbo Forceps ve Soğuk Snare ile Polipektomi Yöntemlerinin Karşılaştırılması [tr] / Jumbo Forceps Polypectomy Versus Cold Snare Polypectomy for Removal of Diminutif Colorectal Polyps [en] / Sayfa: 93-98 PDF

Neslihan ARICI Asu ÖZGÜLTEKİN Nilgün KANSAK Rıza ADALETİ Handan ANKARALI Sebahat AKSARAY Üçüncü Basamak Bir Hastanede Yatan COVID-19 Hastalarında Sekonder Enfeksiyonlar [tr] / Secondary Infections in COVID-19 Patients Hospitalized in A Tertiary Hospital [en] / Sayfa: 99-105 PDF

Mehmet Hanifi TANYERİ Mehmet Emin BÜYÜKOKUROĞLU Pelin TANYERİ Rümeyza KELEŞ Şeyma Nur BAŞARIR BOZKURT Oguz MUTLU Firuzan AKAR Bekir Faruk ERDEN Güner ULAK Haloperidol, Olanzapin, Risperidon ve Klozapinin Organ Banyosu Sistemi Kullanılarak Fare Detrusor Kası Üzerine Etkileri [tr] / Effects of Haloperidol, Olanzapine, Risperidone And Clozapine on Mice Detrusor Muscle Using Organ Bath System [en] / Sayfa: 106-111 PDF



Turan YILDIZ Necmettin AKPINAR Hasan ARIK Ahmet Taner ELMAS Sema UĞURALP Piyeloplasti Yapılan Ureteropelvik Bileşke Darlıklı Hastaların Epidemiyolojik Verileri: Tek Merkez Deneyimi [tr] / Epidemiological Data of Patients with Ureteropelvic Junction Stenosis Performed Pyeloplasty: A Single Center Experience [en] / Sayfa: 112-116 PDF

Asuman DEVECİ ÖZKAN Ayten HACIEFENDİ Fatih ÖZKAN Gamze GÜNEY ESKİLER Süleyman KALELİ Ecir Ali ÇAKMAK Özge TURNA Traf2 ve Nck Etkileşimli Protein Kinaz (TNIK) İnhibitörünün Metastatik Köpek Meme Tümör Hücrelerinde Apoptotik Etkisinin Belirlenmesi [tr] / Determination of the Apoptotic Effect of Raf2 and Nck-Interacting Protein Kinase Inhibitor on Metastatic Canine Mammary Gland Tumor Cells [en] / Sayfa: 117-122 PDF

Alper KURTOĞLU Alauddin KOCHAİ Erhan ŞÜKÜR Erkan İNANMAZ Ertunç ÖKSÜZĞLU Zafer ŞEN İsmail DALDAL Orhan BAŞOĞLU Tijjani MAGASHI Distal Ekstra-Artiküler Tibia Kırığının Tedavisinde Minimal İnvaziv Plak veya İntramedüller Çivi, Hangisi Daha İyi? [tr] / Minimally-Invasive Plate or Intramedullar Nail in the Management of Distal Extra-Articular Tibial Fracture, What Is Better? [en] / Sayfa: 123-129 PDF

Songül DOĞANAY Özcan BUDAK Askorbik Asit ve Sodyum Selenitin Renal İskemi-Reperfüzyon Hasarında İnflamatuar Cevap ve Apoptoz Üzerine Etkileri [tr] / Effects of Ascorbic Acid and Sodium Selenite on Inflammatory Response and Apoptosis in Renal Ischemia-Reperfusion Injury [en] / Sayfa: 130-136 PDF

Zafer ŞEN Alper KURTOĞLU Total Diz Artroplastisi Sonrası Ağrı Yönetimi: Kısa-Orta Dönem Sonuçlarımız [tr] / Pain Management after Total Knee Arthroplasty: Our Short-Medium Term Results [en] / Sayfa: 137-142 PDF

Esin AK İsmet Burcu TURKYILMAZ Aleyna MUHAN Refiye YANARDAĞ Sıçanlarda Amiodaronun Sebep Olduğu Akciğer Hasarında Beyaz Lahana Ekstraktının Koruyucu Rolü [tr] / Protective Role of White Cabbage Extract Against Amiodarone-Induced Lung Damage in Rats [en] / Sayfa: 143-150 PDF

## **OLGU SUNUMU / CASE REPORT**

Canatan TAŞDEMİR Yusuf AYDEMİR Hasan DÜZENLİ Covid-19'un Nadir Bir Komplikasyonu Olan Pnömomediastinum [tr] / Pneumomediastinum, A Rare Complication of Covid-19 [en] / Sayfa:151-155 PDF

## **DERLEME MAKALESİ / REVIEW ARTICLE**

Muhammad Lokman BIN MD. ISA Normalına ALIAS Mohamad Helmy JAAFAR Kapsam Belirleme İncelemesi: Malezya'daki Aborjinler Arasındaki Parazit Kontrol Uygulamaları Hakkında Sağlık Okuryazarlığı Açıklıkları [tr] / Scoping Review: Health Literacy Gaps about Parasites Control Practices among Aborigines in Malaysia [en] / Sayfa: 156-164 PDF

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## COVID-19 Pandemisiyle Artış Gösteren Subakut Tiroidit

### Subacute Thyroiditis Exacerbated by the COVID-19 Pandemic

<sup>1,2</sup>Deniz Esin TEKCAN SANLI, <sup>3</sup>Duzgun YILDIRIM

<sup>1</sup>Gaziantep University, Faculty of Medicine, Şahinbey Research and Practice Hospital, Department of Radiology, Gaziantep, TURKEY

<sup>2</sup>Istanbul Rumeli University, Vocational School of Health Services, Department of Medical Imaging Techniques, Istanbul, TURKEY

<sup>3</sup>Acibadem Mehmet Ali Aydınları University, Acibadem Taksim Hospital, Department of Radiology, Istanbul/ TURKEY

Deniz Esin Tekcan Sanli: <https://orcid.org/0000-0002-6545-5757>

Duzgun Yildirim: <https://orcid.org/0000-0002-5411-229X>

#### ÖZ

**Amaç:** Bu çalışmada SARS-CoV-2 virüsü ile subakut tiroidit (SAT) arasındaki etiyolojik ilişkiyi değerlendirmek ve bu iki antitenin benzer klinik özelliklere sahip olabileceğine dikkat çekmek amaçlandı.

**Materyal ve Metot:** Ülkemizde Coronavirus disease-19 (COVID-19) salgınının 4. ayında; klinik ve laboratuvar özelliklerine göre SAT şüphesi olan 5 hasta boyun ultrasonografi (USG) için kliniğimize sevk edildi. Bu olguların geçmiş tıbbi öyküsü, temas öyküsü ve COVID-19 Polimeraz Zincir Reaksiyonu (PCR) test sonuçları değerlendirildi.

**Bulgular:** Subfebril ateş, boğaz ağrısı, boğazda yanma hissi, yutma güçlüğü hastaların başvuru semptomlarıydı. Tüm olgularda anormal tiroid hormon değerleri ve yüksek eritrosit sedimentasyon hızı/C-reaktif proteini (CRP) değerleri vardı. USG'de dört hastada tiroid bezi hacmi artmıştı. Belirgin demarkasyon nodülü saptanmayan tüm hastalarda tiroid parankiminde hipovaskülarize heterojen hipoeoik düzensiz alanlar gözlemlendi. Ultrason elastografi-sinde parankimal heterojenite ve sertlik saptandı. PCR testi negatif olan olguların düşük doz kontrastsız toraks bilgisayarlı tomografi bulguları (BT) normaldi.

**Sonuç:** Etiyolojisinde viral ajanlar sıklıkla suçlanan subakut tiroidit SARS-CoV-2 ile de ilişkili olabilir. Subakut tiroidit ve COVID-19 enfeksiyonu arasındaki klinik ve laboratuvar bulgularının benzerliği tanılmal zorluklar yaratabilir.

**Anahtar Kelimeler:** COVID-19, elastografi, SARS-CoV-2, subakut tiroidit, ultrasonografi

#### ABSTRACT

**Objective:** It was aimed to evaluate the etiological relationship between the SARS-CoV-2 virus and subacute thyroiditis (SAT). We also wanted to point out the fact that these two entities may have similar clinical features.

**Materials and Methods:** During the 4th month of the Coronavirus disease-19 (COVID-19) pandemic in our country; five patients were referred to our clinic for neck ultrasonography (USG) with a suspected diagnosis of SAT based on clinical and laboratory features. Past medical history, contact history, and COVID-19 Polymerase Chain Reaction (PCR) test results of these cases were evaluated.

**Results:** Subfebrile fever, sore throat, burning sensation in the throat, difficulty in swallowing were the presenting symptoms of the patients. All cases had abnormal thyroid hormone values and elevated erythrocyte sedimentation rate/C-Reactive Protein (CRP) values. USG showed increased thyroid gland volume in four patients. Hypovascularized heterogeneous hypoechoic patchy areas in thyroid parenchyma were observed in all patients without discrete nodules. Ultrasound elastography revealed parenchymal heterogeneity and stiffness. Low-dose non-contrast chest computerized tomography (CT) findings was normal with negative Polymerase chain reaction (PCR) test results in patients.

**Conclusion:** Subacute thyroiditis, which is often accused by viral agents in etiology, may also be associated with SARS-CoV-2. The similarity of clinical and laboratory findings between subacute thyroiditis and COVID-19 infection may pose diagnostic challenges.

**Keywords:** COVID-19, elastography, SARS-CoV-2, subacute thyroiditis, ultrasonography

#### Sorumlu Yazar / Corresponding Author:

Deniz Esin Tekcan Şanlı  
Gaziantep University, Faculty of Medicine, Şahinbey Research and Practice Hospital, Üniversite Bulvarı P.K. 27310, Şehitkamil / Gaziantep, TURKEY  
Tel: +90 544 810 44 46  
E-mail: [tekcandenizesin@gmail.com](mailto:tekcandenizesin@gmail.com)

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## INTRODUCTION

Subacute thyroiditis (SAT) is a rare, self-limiting clinical condition that usually occurs after viral infections, and the etiology is unknown in the majority of cases.<sup>1,2</sup> It is more common in women and in the 40-50 age range.<sup>2,3</sup> The common presenting symptoms are fever, weakness, sore throat extending to the ear and jaw, painful swelling in the neck.<sup>2</sup> On physical examination, tenderness and warmth can be detected during neck palpation. In the acute period, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values are generally elevated high secondary to inflammation. SAT generally shows the triphasic fluctuation in thyroid hormone values as hyperthyroidism, hypothyroidism, and euthyroidism. Although most of these cases become euthyroid, permanent hypothyroidism may occur in the long term in a small number of cases.<sup>4</sup>

Although the diagnosis of SAT is usually based on clinical and laboratory findings, ultrasonography (USG) is frequently used in routine practice as a supportive diagnostic method.<sup>5,6</sup> Grayscale ultrasonography findings include increased thyroid gland size with heterogeneous, hypoechoic, nodular-patchy areas with decreased vascularization on Doppler sonography.<sup>4,7</sup> Elastography shows markedly elevated stiffness with heterogeneous parenchymal color-coding, with elasticity values typically higher than thyroid malignancies.<sup>8</sup> Treatment is often symptomatic and is based on the disease stage. Analgesic and anti-inflammatory medication usually alleviate patient symptoms while beta-blockers can be used for thyrotoxicosis findings.<sup>9</sup>

Although the etiology of subacute thyroiditis is not fully understood, it is the most accepted view is that viral agents activate the immune system, causing autoimmune reactions after a certain latent period and destroying the thyroid glands with these antibodies. Like other viral agents, the SARS-CoV-2 virus, which can cause multisystem and multiorgan involvement and exacerbate the immune system, causing intense cytokine release (cytokine storm), is very likely to cause autoimmune events and affect the thyroid gland in this way. This may then cause the activation of autoimmune diseases such as subacute thyroiditis. It is also possible for a condition of essentially autoimmune origin to arise, such as subacute thyroiditis.<sup>10-14</sup>

In this study, we aimed to highlight that SARS-CoV-2 may play a role in the etiology of subacute thyroiditis, which usually manifests clinically within a few weeks to months following upper respiratory tract infection or other viral infections. We also wanted to emphasize that SAT should be kept in mind in the clinical differential diagnosis of COVID-19 during the pandemic period.

## MATERIALS AND METHODS

This study was performed by the Acıbadem University Medical Research Ethics Committee (Date: 06.08.2020, decision no: 2020/17), and verbal informed consent form was obtained from all patients. This study was conducted according to the World Medical Association Declaration of Helsinki.

Patients who underwent neck USG with a pre-diagnosis of SAT in our clinic between June 14 and July 14, 2020 were included in the study. Clinical findings of the patients (fever, dry cough, sore throat, difficulty in swallowing, neck sensitivity, palpitations, tremor, irritability, sleep disorders, appetite disorders), laboratory findings [hemoglobin (Hb), hematocrit (Htc), leukocyte, neutrophil, lymphocyte, neutrophil/lymphocyte ratio (N/L), CRP, ESR], thyroid hormone panel [TSH, fT3, fT4, anti-thyroid peroxidase (TPO), anti-thyroglobulin (Tg) antibodies] were recorded. Grayscale and Doppler sonography features [volume, parenchymal heterogeneity, nodule, perithyroidal lymph node, vascularization] with elastography features [parenchymal heterogeneity, Vmean, Vmax, velocity standard deviation (VSD)] were evaluated on USG. The clinical history and relevant lab/imaging findings of these cases were evaluated in terms of COVID-19 [history of contact, clinical findings, chest x-ray, chest computed tomography (CT) examination, PCR].

All sonographic and elastographic examinations were performed with the same device (General Electric Healthcare 2016, LOGIQ S8, XDclear) by the same radiologist. The ML6-15 probe was used for grayscale, and the 9L probe for elastography. Reference values of thyroid volumes were based on the study by Seker et al.<sup>15</sup> ( $13 \pm 6.27$  ml). Gland vascularization was evaluated with the color Doppler feature of the device. For shear wave elastography (SWE), 2D shear software from the same device was used. The probe was placed with a gel pad precisely in the neck area, without any pressure on the skin during measurements. The patients were asked to hold their breath for 5 seconds during elastography. After the SWE stabilized, the sample box was placed in the middle of the hypoechoic areas. The region of interest (ROI) area was standardized not to exceed  $0.5 \text{ cm}^2$  and measurements were taken from the middle of the heterogeneous area in the sample box. The Vmean, Vmax, and VSD values were automatically calculated in m/s and recorded by the device. Elastographical evaluations and measurements were made separately for both lobes.

**Statistical Analysis:** SPSS 21 (SPSS Inc., IBM company, Chicago) program was used for statistical analysis. Descriptive data were presented as mean, standard deviation, minimum and maximum values, frequency and ratio. As the overall number of cases

was relatively small, no inferential statistical analysis was undertaken.

## RESULTS

Five patients were included in the study. All cases were female with a mean age of  $46 \pm 12.68$  (29-61y). All patients had subfebrile fever, tenderness in the neck, and difficulty in swallowing at the time of admission. The demographic and clinical characteristics

of the cases are shown in Table 1.

The CRP and ESR values were elevated in all cases and the N/L rates were high in two cases. In three cases, there was a significant decrease in TSH value with high FT3 and FT4 values. TSH was high in one case, although FT3 and FT4 values were normal. In the other case, all values including TSH were normal. Details of the laboratory features of the cases are shown in Table 2.

**Table 1.** Demographic data and clinical symptoms of patients.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age	39	29	55	46	61
Gender	F	F	F	F	F
Comorbidity	-	-	Breast cancer	-	-
Smoking	-	-	-	-	-
COVID-19 contact history	+	-	-	+	-
PA chest X-ray, Thorax CT	(no feature)			(no feature)	-
rRT-PCR	Negative	-	-	Negative	-
Fever	+	+	+	+	+
Cough	+	+	-	+	-
Sore throat	+	+	+	+	+
Difficulty in swallowing	+	+	+	+	+
Fullness in the throat	+	-	+	+	+
Tremor	+	-	+	-	+
Palpitation	+	-	+	-	+
Sleeping disorders	+	-	-	-	+
Duration of symptoms (day)	25	35	45	40	20

COVID-19, coronavirus disease 2019; CT, Computed tomography; PA, Posterior anterior; rRT-PCR, real-time reverse-transcriptase polymerase chain reaction.

**Table 2.** Laboratory values and thyroid hormone panel of the cases.

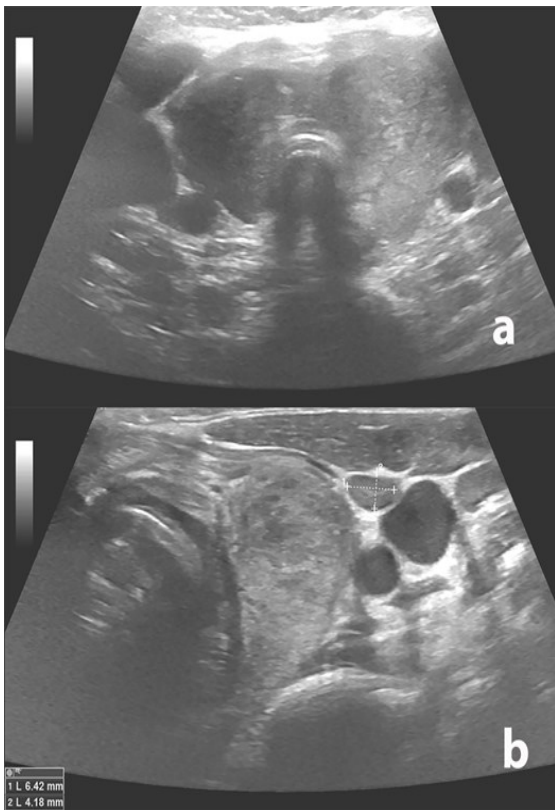
	Reference values	Case 1	Case 2	Case 3	Case 4	Case 5
Hemoglobin (g/dL)	11.9 - 14.9	10.9	13.4	9.6	11.4	-
Hematocrit (%)	35.5 - 44.2	32.7	37.5	29.5	35.1	-
Leukocyte ( $\times 10^3/\mu\text{L}$ )	4.06 - 10.6	8.35	5.88	10.69	7.63	-
Neutrophil ( $\times 10^3/\mu\text{L}$ )	1.9 - 7.0	6.56	3.2	8.67	5.1	-
Lymphocyte ( $\times 10^3/\mu\text{L}$ )	1.3 - 3.76	1.07	1.81	1.29	1.77	-
N/L ratio	<3.13	6.15	1.77	6.72	2.88	-
C-reactive protein (mg/dL)	<0.50	9.75	11.2	36	2.47	-
ESR (mm/sa)	<20	80	91	122	41	101
TSH (uIU/mL)	0.25 - 4.55	0.017	9.52	0.015	1.21	0.06
FT3 (pmol/L)	3.5 - 6.5	11.6	5.63	9.76	3.97	7.11
FT4 (pmol/L)	11.5 - 22.7	41.48	16.51	35.04	11.97	26.55
Anti-TG (pmol/L)	0 - 60	58.4	417	52.6	33.8	15
Anti-TPO (IU/mL)	0 - 60	22.9	1300	33.7	28	47

N/L, Neutrophil/Lymphocyte; ESR, Erythrocyte sedimentation rate; TSH, Thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; Anti-TG, anti-thyroglobulin; Anti-TPO, anti-thyroid peroxidase.

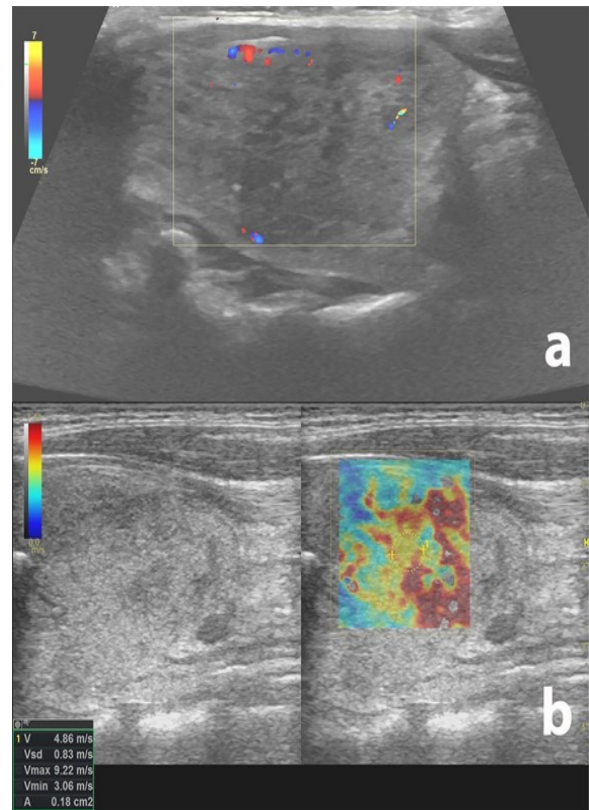
Ultrasonography revealed parenchymal heterogeneity in all cases, and increase in thyroid gland volumes in all cases except for a single case (Figure 1a). Within the parenchyma, there were heterogeneous hypoechoic patchy and nodular areas that did not give specific boundaries. There were multiple subcentimetric lymph nodes with a reactive appearance adjacent to the thyroid gland parenchyma in all cases (Figure 1b).

In Doppler sonography, heterogeneous hypoechoic areas were hypovascular in all cases (Figure 2a). In SWE evaluation, heterogeneous color coding and increased velocity values were detected supporting parenchymal heterogeneity and increased stiffness in all patients (Figure 2b).

The average elasticity values were: right lobe Vmean:  $2.88 \pm 0.37$  m/sec, Vmax:  $6.53 \pm 0.83$  m/sec, Vsd:  $1.18 \pm 0.43$ ; left lobe Vmean:  $2.89 \pm 0.58$  m/sec, Vmax:  $6.0 \pm 2.67$  m/sec, Vsd:  $0.97 \pm 0.55$ . Grayscale ultrasonography, Doppler sonography, and shear wave elastography features of cases are shown in Table 3. The cases were questioned retrospectively in terms of clinical complaints, contact history, and PCR results for COVID-19. There was suspicious contact history in two cases (one is a hospital staff). These two cases were assessed for COVID-19 since they had suspicious symptoms in the previous months. Chest radiographs and low-dose non-contrast chest CT were normal. The PCR results of the cases were negative.



**Figure 1.** a) Gray scale image of the thyroid gland in subacute thyroiditis; b) Perithyroidal lymphadenopathy.



**Figure 2.** Doppler and elastography examination of the thyroid gland parenchyma. a) Hypovascularity of the same thyroid tissue in color Doppler sonography; b) Parenchymal patchy heterogeneity and increased stiffness in elastographic examination.

**Table 3.** Grayscale ultrasonography, doppler sonography, and shear wave elastography features of cases.

	Case 1	Case 2	Case 3	Case 4	Case 5
<b>R lobe volume (ml)</b>	10.66	4.8	6.8	8.2	9.2
<b>L lobe volume (ml)</b>	11.24	3.2	14.8	5.7	6.2
<b>Total volume (ml)</b>	21.9	8	21.6	13.9	15.4
<b>Hypovascularization</b>	+	+	+	+	+
<b>Thyroid nodule</b>	-	-	-	-	-
<b>Perithyroidal LN</b>	+	+	+	+	+
<b>SWE</b>	Heterogeneous	Heterogeneous	Heterogeneous	Heterogeneous	Heterogeneous
<b>R-Vmean (m/sn)</b>	3.39	2.74	3.07	2.85	2.39
<b>R-Vmax (m/sn)</b>	6.78	6.9	7.45	5.22	6.31
<b>R-VSD</b>	1.15	1.1	1.89	0.69	1.1
<b>L-Vmean (m/sn)</b>	3.45	2.19	3.4	2.38	3.04
<b>L-Vmax (m/sn)</b>	8	2.63	9.25	4.39	5.76
<b>L-VSD</b>	1.45	0.23	1.54	0.62	1.02

LN, lymph node; R, right; L, left; SWE, shear wave elastography; VSD, velocity standard deviation.

## DISCUSSION AND CONCLUSION

The SARS-CoV-2 infection that started in China in late 2019 became a global health problem lead to a pandemic in a short amount of time. SARS-CoV-2 started in China in late 2019 and has affected the whole world by causing a pandemic in a short time.<sup>16</sup> The common presenting symptoms of viral infection include patients mainly present with symptoms of upper respiratory tract infection such as fever, dry cough, sore throat, and weakness.<sup>17,18</sup> Previous studies have reported that the virus progresses more severely in immunosuppressive, elderly, and male patients who have comorbid diseases.<sup>16-18</sup> It has higher mortality rates compared to other viral agents, due to severe acute complications such as ARDS, sepsis, and multiorgan failure.<sup>16-18</sup> However, the subacute and late complications of the disease have not been clarified yet.

SAT is a benign clinical condition with unknown etiology that usually occurs within weeks to months after exposure to viral agents especially with upper respiratory tract infections such as influenza, Epstein Barr virus (EBV), adenovirus, cytomegalovirus (CMV), Coxsackievirus A-B.<sup>1,19</sup> Also, SARS-CoV-2 too, which mainly affects the respiratory tract, The SARS-CoV-2, which also affects the respiratory tract, may cause SAT like other agents that are held responsible for the disease. Two different cases with SAT, who were evaluated in relation to SARS-CoV-2, have been reported in two recent publications.<sup>20,21</sup> This situation caught our attention at a similar time frame. SAT, which is a rare clinical condition, was encountered in five patients in the last month in our clinic. Although the disease is generally known to increase seasonally in the summer following a latent period after exposure to the viral agent, in our clinic, this high frequency for SAT has never been detected in such a short amount of time.<sup>3</sup> The high incidence

of SAT during the pandemic suggests that the disease may be associated with SARS-CoV-2. Also, four months have passed since the first case of the virus was detected in our country and this interval is consistent with the latent period of the disease. Although COVID-19 PCR was negative in our cases, it did not affect our suspicion as to the causative etiology of SARS-CoV-2 for SAT. The PCR sensitivity may vary depending on the time of sampling, method of sampling, and the person taking the sample. The false negativity rate can be quite high as 40-70%.<sup>22,23</sup> The fact that no radiological feature in terms of COVID-19 was detected in our cases does not refute our findings as CT may be negative in very early stages of the disease.<sup>23,24</sup> According to the literature, we also know that some patients may have the disease without showing any radiological or clinical findings.<sup>22,25</sup> In addition, considering the average age of our patients, there is a possibility that they underwent the disease asymptotically.<sup>26,27</sup> Therefore, although our cases did not show any COVID-19 related clinical or radiological findings in the past months, SARS-CoV-2 was a suspected factor in these patients. Similarly, the detection of widespread follicular damage and parenchymal destructions in the thyroid gland in the autopsy series after the SARS pandemic in 2002-2003 strengthens the relationship between SAT and SARS-CoV-2.<sup>28,29</sup> Moreover, many case reports and case series showing the relationship between SARS-CoV-2 and subacute thyroiditis have been published in the literature so far<sup>10-14</sup>. This relationship is so strong that there are cases that develop subacute thyroiditis even after vaccination.<sup>30</sup> The most common symptoms in subacute thyroiditis cases developing after COVID-19 is fever and sore throat (81%) as in other agents<sup>11</sup> Therefore, it is difficult to diagnose SARS-CoV-2-associated subacute thyroiditis based on symptoms

alone. In this case, it should be considered in patients with recent COVID-19 infection, those with a history of contact with people diagnosed with COVID-19, and those who have been vaccinated against SARS-CoV-2. It mustn't be developed immediately after the disease, but after a certain latent period like other agents.

Apart from all these, another point that should be emphasized is that both diseases can present with similar complaints of nonspecific upper respiratory tract infection, and the laboratory findings can be similar as well. In this respect, SAT should be kept in mind and included in the clinical differential diagnosis in patients with a pre-diagnosis of COVID-19 without specific laboratory and radiological imaging findings specific to the disease.

In conclusion, subacute thyroiditis is a clinical entity that usually occurs after a latent period following viral infections. The SARS-CoV-2 may cause subacute thyroiditis or autoimmune diseases like other viral agents. Subacute thyroiditis may clinically mimic SARS-CoV-2. Due to the similarity of clinical and laboratory findings, subacute thyroiditis should be considered in the differential diagnosis of COVID-19 infection, and SARS-CoV-2 should be considered as an etiologic agent for subacute thyroiditis.

**Ethics Committee Approval:** This study was performed after it was approved by the Acıbadem Healthcare Institutions Medical Research Ethics Committee (Date: 06.08.2020, decision no: 2020/17).

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Author Contributions:** Concept – DETS; Supervision – DY.; Materials – DETS; Data Collection and Processing – DETS; Analysis and Interpretation – DETS, DY; Writing – DETS, DY.

**Peer-review:** Externally peer-reviewed.

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## Anjiyografi Hasta Plazmalarında, Paraoxonase 1, Arylesterase ve Total Thiol İncelemesi

### Paraoxonase1, Arylesterase and Total Thiol Investigation in Angiography Patient Plasmas

<sup>1</sup>Hayrullah YAZAR, <sup>2</sup>Güler Kuşçu GÜNAY, <sup>3</sup>Mustafa Baran İNCİ,  
<sup>4</sup>Süleyman KALELİ, <sup>5</sup>Mehmet Akif ÇAKAR

<sup>1</sup>Sakarya Üniversitesi Tıp Fakültesi, Tıbbi Biyokimya, Sakarya, Türkiye  
<sup>2</sup>Sakarya Üniversitesi Sağlık Bilimleri Enstitüsü, Sakarya, Türkiye  
<sup>3</sup>Sağlık Bakanlığı, İstanbul Sağlık Müdürlüğü, Halk Sağlığı, İstanbul, Türkiye  
<sup>4</sup>Sakarya Üniversitesi Tıp Fakültesi, Tıbbi Biyoloji Anabilim Dalı, Sakarya, Türkiye  
<sup>5</sup>Sakarya Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Sakarya, Türkiye

Hayrullah Yazar: <https://orcid.org/0000-0001-9447-6322>  
Güler Kuşçu Günay: <https://orcid.org/0000-0002-5529-3061>  
Mustafa Baran İnci: <https://orcid.org/0000-0003-1893-5368>  
Süleyman Kaleli: <https://orcid.org/0000-0002-6043-2521>  
Mehmet Akif Çakar: <https://orcid.org/0000-0003-3216-4205>

#### ÖZ

**Amaç:** Radyal koroner anjiyografi uygulanan erişkin hastalarda; Paraoxonase-1 (PON 1), Arylesteraz (ARE) ve Total tiyol (TTL) değerlerinin, kan plazmasında tespit edilmesi amaçlandı.

**Materyal ve Metot:** Çalışmanın katılımcı sayısı, birisi kontrol diğeri hasta grubu olmak üzere, iki grupta toplam 68 oldu. Kontrol grubu 34 sağlıklı bireyden oluşurken, hasta grubu ise 34 radyal koroner anjiyografi hastasından oluştu. Kan numuneleri lityum heparinli tüplere alındıktan sonra laboratuvara transfer edildi ve burada santrifüj işleminden sonra ayrılan plazmaları, çalışma gününe kadar kapaklı eppendorf tüplerde -80°C de saklandı. Test parametreleri tam otomatik analizörde spektrofotometrik metot ile incelendi. Çalışmada elde edilen veriler SPSS 23 paket programı ile istatistiksel olarak analiz edildi. Anlamlılık düzeyi, p<0,05 olarak kabul edildi.

**Bulgular:** Hasta grubundaki ortalama TTL değerleri (360,29 µmol/L) kontrol grubuna göre (482,25 µmol/L) anlamlı derecede düşük bulundu (p<0,001). Benzer şekilde hastaların ortalama ARE değerleri (11,30 U/L) kontrol grubuna göre (14,28 U/L) anlamlı derecede düşük bulundu (p<0,001). Hasta grubu PON 1 (U/L) değerleri sırasıyla (medyan, Q1, Q3): 140,78; 100,06; 322,12 olarak bulundu. Kontrol grubu PON 1 (U/L) değerleri ise, sırasıyla: 153,65; 104,9Q8; 454,13 şeklinde bulundu. Bu değerler arasında anlamlı bir fark olmadığı görüldü (p=0,30).

**Sonuç:** Anjiyografi hastaları plazma değerleri, lipofilik antioksidan özelliklerde azalma olduğunu gösterdi. PON 1 değerleri, istatistiksel olarak anlamlı olmamasına rağmen bu görüşü destekledi. Öte yandan; hasta grubunda tespit edilen anlamlı TTL düşüklüğü, üzerinde daha geniş araştırmalar gerektiren bir sonuç olarak tespit edildi.

**Anahtar Kelimeler:** Arylesteraz, paraoxonase 1, renal anjiyografi, total tiyol

#### ABSTRACT

**Objective:** In adult patients undergoing radial coronary angiography; It was aimed to determine the values of paraoxonase-1, Arylesterase and Total thiol in blood plasma.

**Materials and Methods:** The number of participants in the study was 68 in two groups, one for the control group and the other for the patient group. While the control group consisted of 34 healthy individuals, the patient group consisted of 34 radial coronary angiography patients. After blood samples were taken into lithium heparin tubes, they were transferred to the laboratory and the plasma separated after centrifugation was stored at -80 °C in capped eppendorf tubes until the working day. Test parameters were analyzed by spectrophotometry method on a fully automated analyzer. The data obtained in the study were statistically analyzed with the SPSS 23 package program. Significance level was accepted as p<0.05.

**Results:** The mean TTL values in the patient group (360.29 µmol/L) were found to be significantly lower than the control group (482.25 µmol/L) (p <0.001). Similarly, the mean ARE values of the patients (11.30 U/L) were found to be significantly lower than the control group (14.28 U/L) (p<0.001). Patient group PON 1 (U/L) values, respectively (median, Q1, Q3): 140.78; 100.06; 322.12 were found. Control group PON 1 (U/L) values: 153.65; 104.9Q8; 454.13 were found. There was no significant difference between these values (p=0.30).

**Conclusion:** Angiography patients showed a decrease in plasma values, lipophilic antioxidant properties. PON 1 values supported this view, although it was not statistically significant. On the other hand; Significant low TTL detected in the patient group was determined as a result that requires further studies.

**Keywords:** Arylesterase, paraoxonase 1, renal angiography, total thiol

#### Sorumlu Yazar / Corresponding Author:

Hayrullah Yazar  
Sakarya Üniversitesi Tıp Fakültesi, Tıbbi Biyokimya, Sakarya,  
Türkiye  
Tel: 05323179702  
E-mail: drhyazar@hotmail.com

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## GİRİŞ

Paraoksonaz (Pon) enzimi ile ilgili en geniş kapsamlı araştırma hiç kuşkusuz Diepgen TL ve arkadaşlarının yaptığı çalışmadır.<sup>1</sup> Çalışma ile oldukça farklı ülkelerden toplanan insan serum örneklerinde Pon aktivitesi araştırılmıştır. Çalışmaya; Avrupa, Afrika ve Asya ülkeleri dahil edilmiştir.<sup>1</sup> İlave olarak belirtmeliyiz ki; paraoksonaz 1 (PON 1) araştırmaları, özellikle, Macaristan'da gerçekleştirilen "Paraoksonazlar Konferansı" ile artmıştır.<sup>2</sup> Konferansta Pon birçok hastalıkla ilişkilendirilmiş, bunlar arasında; kardiyovasküler hastalıklar, diabetes mellitus, romatizma, alzheimer yer almıştır.<sup>2</sup> Günümüzde ise PON 1 araştırmaları, oldukça geniş bir yelpazede artarak devam etmektedir.<sup>3-7</sup>

Arilesteraz (ARE) enzimi ile ilgili yapılan ilk çalışmalar içerisinde koyun plazmasında yapılan çalışma dikkat çekicidir.<sup>8</sup> Yapılan araştırmada, "nişasta jel elektroforez" yoluyla farklı ırkların koyunlarında kan plazma esterazları incelenmiş olup, esterazın en az üç enzimden oluşan bir "poli-enzim sistemi" olduğu gösterilmiştir. Bu enzimler; arilesteraz, karboksilesteraz ve kolin esteraz olarak ifade edilmiştir.<sup>8</sup> Günümüzde yapılan araştırmalarda ARE ve PON 1 aktivitesi, lipid profilleri ile birlikte incelenmektedir.<sup>9</sup>

İnsan plazma Total tiyol (TTL) havuzunda miktar olarak en fazla albümin ve diğer proteinler vardır. Plazma TTL havuzunun küçük bir kısmında sistein, sisteinil glisin, glutatyon, homosistein ve  $\gamma$ -glutamilsistein gibi düşük molekül ağırlıklı tiyoller bulunmaktadır.<sup>10</sup> Öte yandan; son yapılan araştırmalarda tiyollerin oksidatif stres ile ilişkileri tespit edilmiş olup, bu çalışmalar; çocuklardan hamile kadınlara kadar oldukça geniş bir yelpazede dikkat çekici sonuçlar ortaya koymuştur.<sup>11-13</sup>

Yapılan pek çok çalışmada gösterildiği gibi, koroner arter hastalığına (KAH) yol açan en önemli etken aterosklerozdur. Öte yandan; lipid profili bozukluğunun ateroskleroz ile ilişkisi de bilinen bir gerçektir. Dolayısıyla KAH riskinin teşhisi konusunda yapılan çalışmaların büyük kısmı kan lipidlerin düzeyi ile ilişkilidir. Ateroskleroza karşı korunmada rol oynayan yüksek yoğunluklu lipoprotein (HDL) ile ilişkili olan esteraz ise, PON 1 dir.<sup>14</sup> PON 1 ve HDL kolesterol seviyesi ile KAH ilişkisi arasındaki son araştırmalar, PON 1 in daha iyi bir indikatör olduğunu göstermiştir.<sup>15</sup> Bizim çalışmamızda, erişkinlerde, PON 1, ARE, TTL kan plazma değerleri; renal anjiyo yapılması gerekli görülen hastalar ile sağlıklı bireylerde karşılaştırılacaktır. Tespitlerimize göre çalışmamız literatürde ilk olma özelliğindedir; şöyle ki; PON 1, ARE ve TTL parametreleri, aynı anda anjiyo hastalarında ilk defa birlikte çalışılmıştır.

## MATERYAL VE METOT

**Etik Durum:** Sakarya Üniversitesi Tıp Fakültesi Girişimsel Olmayan Etik Kurulundan izin alınan (Tarih:14.3.2018, karar no: 64) bu çalışma, SAÜ BAP (no: 12017-08-06-003) birimi tarafından desteklenmiştir. Çalışmamız Uluslararası bildirgelerde ön görülen kriterlere göre yapılmıştır.

Yaklaşık 7 ay süren bu çalışmada, dahil edilen gönüllülerden aydınlatılmış onamlar alındı. Çalışmada kontrol grubu, gönüllü sağlıklı bireylerden oluşturuldu. Dahil edilme kriterleri: daha önceden dökümanite koroner arter hastalığı öyküsü olmaması, kronik böbrek ya da karaciğer yetersizliği olmaması, son 1 yıl içerisinde serebrovasküler olay geçirmemesi, ciddi periferik arter hastalığı bulunmaması olarak belirlendi. Ayrıca; kontrolsüz diyabet ve hipertansiyon ile, klinik hipertroidi ve erektil disfonksiyon, dışlama kriteri olarak belirlendi. Çalışmada 34 kontrol ve 34 anjiyografi hasta plazması; TTL, PON 1, ARE, tam otomatik analizörde incelendi (Beckman Coulter marka AU 680, seri no: 2016024580, Koutou-ku, Tokyo, Made In Japan). Kanlar tüm hastalardan yeşil kapaklı (lityum heparinli 4,5 cc, yeşil kapaklı BD) tüplere alındı ve numuneler derhal soğuk zincire uyularak transfer edildi. Laboratuvara gelen numuneler hemen santrifüj işlemine tabi tutularak (soğutmaltı, 1500 g 10 dakika), kapaklı eppendorf tüplerde (isolab centrifuge tubes 2.0 ml) -80 de saklandı. Çalışmada, Rel Assay Diagnostics marka kit kullanıldı. Çalışma gününden 24 saat önce -80 deki numuneler -20 ye yerleştirildi, çalışmadan 1 saat önce -20 den çıkarılan numuneler mikro-santrifüj işlemine tabi tutuldu.

**İstatistiksel Analiz:** Çalışmada elde edilen tüm verilere SPSS 23 paket programı uygulandı. Yapılan istatistiksel değerlendirmelerde; One Sample Kolmogorov Smirnov testi, Spearman korelasyon analizi, Independent Samples T Testi ve Mann-Whitney U testi kullanıldı. Anlamlılık  $p < 0,05$  düzeyinde değerlendirildi.

## BULGULAR

Yapılan bu çalışmada; One Sample Kolmogorov Smirnov testine göre, ARE ve TTL değerleri normal dağılım gösterirken PON 1 değerleri normal dağılım göstermedi. Tanımlayıcı istatistikler sonucunda hasta (n=34) ve kontrol grubundaki (n=34) TTL değerlerinin aritmetik ortalama ve standart sapma değerleri sırasıyla 360,29±75,50  $\mu\text{mol/L}$  ve 482,25±39,65  $\mu\text{mol/L}$  olarak hesaplandı. Gruplarda, TTL ve ARE değerleri anlamlı bir fark gösterdi (\*:  $p < 0,05$ ) (Tablo1).

Hasta ve kontrol grubundaki PON 1 değerlerinin aritmetik ortalama ve standart sapma değerleri sırasıyla 225,89 ± 163,09 U/L ve 271,39 ± 199,40 U/L olarak hesaplanırken, medyan değerleri sırasıyla

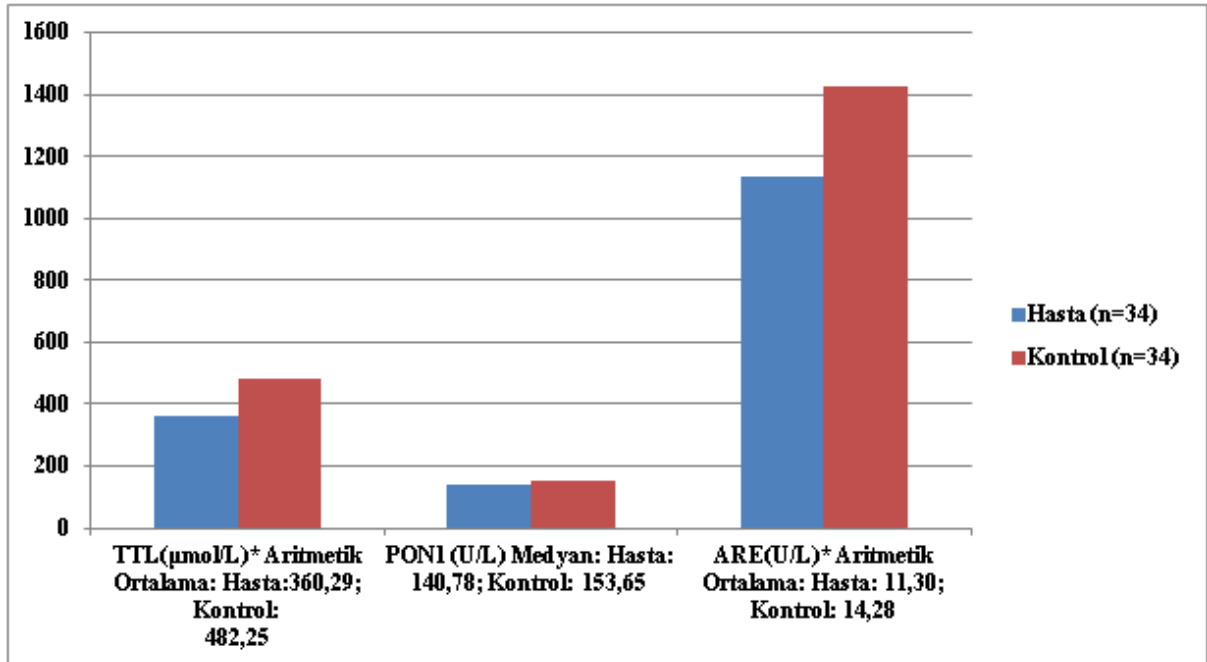
140,78 U/L ve 153,65 U/L olarak hesaplandı (Şekil 1).

Tablo 1 ve Şekil 1'de gösterildiği gibi; hasta ve kontrol grubundaki ARE değerlerinin aritmetik ortalama ve standart sapma değerleri sırasıyla  $11,30 \pm 2,88$  U/L ve  $14,28 \pm 2,49$  U/L olarak hesaplandı. Spearman korelasyon analizinde TTL ile PON 1 değerleri arasında anlamlı bir ilişki saptanmazken PON 1 ile ARE değerleri arasında pozitif yönde, orta düzeyde istatistiksel olarak anlamlı bir ilişki saptandı ( $n=68$ ,  $r=0,42$ ,  $p<0,001$ ). Ayrıca, TTL ile ARE değerleri arasında pozitif yönde, güçlü düzeyde, istatistiksel olarak anlamlı bir ilişki saptandı ( $n=68$ ,  $r=0,53$ ,  $p<0,001$ ). Hasta ve kontrol grubunun ARE ile TTL değerlerine Independent Samples T Testi uygulandı. Yapılan Independent Samples T testinde, hasta grubundaki TTL değerleri (Ortalama  $\pm$  Standart Sapma =  $360,29 \pm 75,50$   $\mu\text{mol/L}$ ) kontrol grubuna göre (Ortalama  $\pm$  Standart Sapma =  $482,25 \pm 39,65$   $\mu\text{mol/L}$ ) istatistiksel olarak anlamlı derecede düşük bulundu ( $p<0,001$ ). ARE değerleri, istatistiksel olarak anlamlı derecede kontrol grubuna göre daha düşük bulundu. Hasta grubu Ortalama  $\pm$  Standart Sapma =  $11,30 \pm 2,88$  U/L iken, kontrol grubu Ortalama  $\pm$  Standart Sapma =  $14,28 \pm 2,49$  U/L şeklinde oldu ( $p<0,001$ ). Hasta ve kontrol gruplarının normal dağılım göstermeyen PON 1 değerleri Mann-Whitney U testine göre değerlendirildi. Hasta grubu PON 1 (U/L) değerleri sırasıyla (median, Q1, Q3): 140,78; 100,06; 322,12 olarak bulundu. Kontrol grubu PON 1 (U/L) değerleri ise, sırasıyla: 153,65; 104,98; 454,13 şeklinde bulundu. Hasta grubundaki PON 1 değerleri kontrol grubuna göre düşük bulunsada, istatistiksel olarak anlamlı değildi ( $p=0,30$ ).

**Tablo 1.** TTL, ARE ve PON 1 değerlerinin karşılaştırması.

	Hasta (n=34)		Kontrol (n=34)	p
TTL ( $\mu\text{mol/L}$ )	360,29 $\pm$ 75,50		482,25 $\pm$ 39,65	<0,001*
PON 1 (U/L)	Medyan	140,78	153,65	0,30**
	Q1	100,06	104,98	
	Q3	322,12	454,13	
ARE (U/L)	11,30 $\pm$ 2,88		14,28 $\pm$ 2,49	<0,001*

\*: Independent Samples T testi uygulanmıştır. \*\*: Hasta ve kontrol grupları normal dağılım göstermeyen PON 1 için Mann-Whitney U testi uygulanmıştır.



**Şekil 1.** TTL, ARE ve PON 1 değerlerinin grafik üzerinde karşılaştırılması.

**TARTIŞMA VE SONUÇ**

PON 1'in, ilaçlar ve bitki ekstraktları ile fizyolojik rolünü ve modülasyonunu anlamak için yapılan en yeni çalışmalar gözden geçirilmiştir.<sup>16</sup>Yapılan incelemede; aterosklerozun Batı ülkelerinde önde gelen ölüm nedenlerinden biri olduğu vurgulanırken, düşük yoğunluklu lipoproteinlerin (LDL) oksidasyonunu engellemede HDL'nin önemli bir koruyucu rolü olduğu ifade edilmiştir. Yine aynı incelemede; HDL parçacıklarını oluşturan proteinlerden olan ARE ve PON 1'in, kardiyovasküler hastalıklardan muzdarip kişilerde önemli bir parametre olabileceği ve tedavi düzenlenmesine katkıda bulunabileceği ifade edilmiştir.<sup>16</sup> Bizim çalışmamızda anjiyo hastalarında tespit edilen ARE sonuçlarındaki ciddi düşüklük ( $p<0,001$ ) bu yaklaşım ile uyumluluk göstermektedir. Öte yandan; çalışmamızda PON 1 düşüklüğü her ne kadar istatistiksel olarak anlamlı olmasa da, ifade edilen bilimsel tespitler ile örtüşmektedir.

Pon enziminin insan vücudunda antioksidan savunmanın evrensel faktörü olduğunu ifade edilmiştir.<sup>17</sup> Pon'un gen ailesinin tandem olarak hizalandığı ve üç üyesinin tespit edildiği, bunların; PON 1, Pon2 ve Pon3 olduğu belirtilmiştir. Reaktif oksijen türlerindeki artan üretimin, ateroskleroz dahil olmak üzere birçok inflamatuvar hastalığın gelişiminde rol oynadığı çalışmalarda bildirilmektedir.<sup>17-18</sup> PON 1 ve Pon3 proteinlerinin; lipoproteinler, makrofajlar ve aterosklerotik lezyonlardaki bazı oksitlenmiş lipidleri hidrolize ederek, oksidatif strese karşı koruma sağlayabilecekleri ifade edilmiştir.<sup>17</sup> Bizim çalışmamızda kontrol grubundaki sağlıklı bireylerde yüksek çıkan PON 1 değerleri de bu bakış açısı ile benzerlikler göstermektedir.

Stabil koroner arter hastalığı tanısı konulan hastalarda yapılan bir başka çalışma ise, tıpkı bizim çalışmamız gibi, "anjiyo öncesinde göğüs ağrısı ve akut stres dönemi geçirilmiş olması" belirtecini kullanmıştır.<sup>18</sup> Ayrıca çalışmada, diyabet olmayan hastaların seçilmesi, bizim çalışmamızda da kontrolsüz diyabeti olan hastaların dışlanması ile örtüşmektedir.<sup>18</sup> Çalışmanın ortaya çıkardığı ARE ve PON 1 aktivitesi düşüklüğü, bizim çalışmamız ile benzer nitelikte olup ateroskleroz ile ilişkilendirilmiştir. İlaveten, çalışmamızda tespit ettiğimiz ARE düşüklüğü, bu ilişkiyi oldukça güçlü bir veri olarak desteklemektedir.

Koroner anjiyografi hastalarında doğal tiol/disülfid oranı ile koroner aterosklerozun şiddeti arasındaki ilişki araştırılmıştır.<sup>19</sup> Yapılan çalışmada, koroner anjiyografi hastalarında spektrofotometrik tiyol ölçümünün %73 hassasiyet ve %68 özgüllük gösterdiği tespit edilmiştir.<sup>19</sup> Öte yandan bizim çalışmamızda, anjiyografi hastalarında sadece tiyol ölçümü yapılmış, ilaveten ARE ve PON 1 değerlerine de bakılmıştır. Ancak çalışmamızda oksidatif stres belirteçlerinin daha geniş kapsamlı test parametreleri

ile birlikte incelenmemiş olması, hiç kuşkusuz sınırlılık oluşturmaktadır.

Sonuç olarak yapılan çalışmamızda; ARE plazma değerlerinin hasta grubunda anlamlı derecede düşük çıkması, anjiyo hastalarında lipofilik antioksidan özelliklerde azalma olduğunu göstermektedir. Nitekim, her ne kadar istatistiksel açıdan anlamlı olmasa da PON 1 düşüklüğü, bu görüşümüzü desteklemektedir. Yine çalışmanın bir başka sonucu olan hasta grubu TTL düşüklüğü, özellikle tiol/disülfid dengesinin içinde bulunduğu, daha geniş kapsamlı araştırmalara konu olacak nitelikte görülmektedir.

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## Tip 2 Diabetik Makula Ödemli Hastalarda Tedavi Karşılaştırması

### Comparison of Treatment in Patients with Type 2 Diabetic Macular Edema

<sup>1</sup>Abdülhekim YARBAĞ

<sup>1</sup> Sakarya Üniversitesi Eğitim ve Araştırma Hastanesi, Göz Hastalıkları, Sakarya, Türkiye

Abdülhekim Yarbağ: <https://orcid.org/0000-0002-4181-1884>

#### ÖZ

**Amaç:** Diyabetik makula ödemi (DMÖ) tanılı hastalarda; intravitreal triamsinolon asetonid (İVTA), laser fotokoagülasyon (LFK) ve LFK ile kombine İVTA tedavilerinde etkinlik araştırması yapmak amaçlanmıştır.

**Materyal ve Metot:** Hastalar rastlantısal olarak üç ayrı gruba ayrıldı: Grup 1, 22 hastanın 30 gözünden oluşmakta olup yaş ortalaması 63,2 yıl idi. Grup 2, 22 hastanın 34 gözünden oluşmakta olup yaş ortalaması 59,9 yıl idi. Grup 3 ise 21 hastanın 27 gözünden oluşmakta olup yaş ortalaması 64,5 yıl idi. Olgulara tedavi öncesi ve sonrası 1. 3. 6. ve 9. aylarda en iyi düzeltilmiş görme keskinliği, göziçi basınç (GİB) ölçümü ve fundus muayenesini içeren tam göz muayenesi yapıldı. PERG (Pattern Elektoretinografi) testi ile P50 amplitüdü, HRTII (Heidelberg Retina Tomograph II) testi ile ÖHD (Ödem Harita Değeri) ölçüldü.

**Bulgular:** Grup 1'de (İVTA+LFK) görme keskinliği 26 (%86,6) gözde artarken, 3 (%10) gözde değişmedi, 1 (%3,3) gözde azaldı. Grup 2'de (LFK) görme keskinliği 18 (%52,9) gözde artarken, 10 (%29,4) gözde değişmedi, 6 (%17,6) gözde azaldı. Grup 3'te (İVTA) görme keskinliği 20 (%74) gözde artarken, 7 (%25,9) gözde değişmedi, azalma hiçbir olguda gözlenmedi.

**Sonuç:** İVTA ile birlikte lazer FK kullanımının, tek başına İVTA ve lazer FK kullanımından daha etkili olduğunu gözlemledik.

**Anahtar Kelimeler:** Diabetik makula ödemi, intravitreal, laser fotokoagülasyon, triamsinolon asetonid

#### ABSTRACT

**Objective:** In the study, it was aimed to compare the effectiveness of intravitreal triamcinolone acetonide (IVTA), laser photocoagulation (LPC), and the LPC combined with IVTA treatments in patients with diabetic macular edema (DME).

**Materials and Methods:** The patients were randomly separated into three groups: Group 1 (IVTA+LFC) consisted of 30 eyes of 22 patients, and the average age was 63.2 years. Group 2 (LFC) consisted of 34 eyes of 22 patients and the mean age was 59.9 years. Group 3 (IVTA) consisted of 27 eyes of 21 patients with a mean age of 64.5 years. The complete eye examination including best-corrected visual acuity (BCVA), intraocular pressure (IOP) measurements, and the fundus inspection was carried out before and 1. 3. 6. and 9. months after the treatment. P50 amplitudes were measured with the PERG test, and edema map values (EMV) were measured with HRT II.

**Results:** In Group 1, the BCVA increased in 26 eyes (86.6%), did not change in 3 eyes (10%), and decreased in one eye (3.3%). In Group 2, the BCVA increased in 18 eyes (52.9%), did not change in 10 eyes (29.4%), and decreased in 6 eyes (17.6%). In Group 3, the BCVA increased in 20 eyes (74%) and did not change in 7 eyes (25.9%).

**Conclusions:** We observed the use of the laser FC combined with IVTA seems to be more effective than using each other of IVTA and laser FC solely.

**Keywords:** Diabetic macular edema, intravitreal, laser photocoagulation, triamcinolone acetonide

#### Sorumlu Yazar / Corresponding Author:

Abdülhekim Yarbağ  
Sakarya Üniversitesi Eğitim ve Araştırma Hastanesi,  
Göz Hastalıkları, Sakarya, Türkiye  
Tel: +05069221102  
E-mail: drabdulhekim@gmail.com

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## GİRİŞ

Diyabetes Mellitus (DM) insülinin biyolojik etkinliğinin veya miktarının azalması sonucu ortaya çıkan bir sistemik hastalıktır. Başlıca komplikasyonları damar endotelini direkt olarak etkilemesi ile böbrek, göz ve kalp üzerindedir.<sup>1-3</sup> Hastalığın prevalansı hasta yaşı ve hastalık süresi ile ilişkilidir. Tip1 Diyabetes Mellitus'de 20 yılda %99, Tip2 DM'de 20 yılda %60 oranında değişik derecelerde retinopati bulunmuştur.<sup>4-6</sup> Diyabetes mellitusun tedavisinin gelişmesiyle, bu hastaların yaşam süresi uzamış ve hastalığın uzun seyri boyunca gelişen dejeneratif damar değişiklikleri öne çıkmaya başlamıştır. Diyabetik mikroanjyopati ve nöropati adı altında böbrek, göz, uç kısım dokular gibi birçok doku ve organda başlayan değişiklikler ortaya çıkmakta; hastaların böbrek fonksiyonunun bozulmasına, görme fonksiyonunu kaybetmesine, cilt ve kas organlarının nekrozuna yol açmaktadır. Diyabetik bir kişi diyabet olmayan bir kişiye göre 50-80 kat daha fazla görme fonksiyonunu yitirme riskine sahiptir ve diyabet 30-60 yaş grubunda en yaygın körlük sebebidir.<sup>7</sup> Bu hastalarda körlük için önde gelen risk faktörü Diyabetik makula ödemi (DMÖ). Diyabetik retinopatinin (DR) şiddeti artarken, Diyabetik makulopatinin prevalansı da artmaktadır. Nonproliferatif Diyabetik retinopatili hastaların %3'ünde makula ödemi izlenirken, orta ve ağır nonproliferatif evrede bu oran %38, proliferatif retinopati evresinde %71'e ulaşmaktadır.<sup>8-9</sup> Makula ödemi, juvenil başlangıçlı DM ve insüline bağlı DM'de daha yaygın olarak görülmektedir. DMÖ gelişmesinde rolü olduğu anlaşılan biyokimyasal aracılardan sayıları gün geçtikçe artmaktadır. Vasküler endotelial büyüme faktörü (VEGF) endotel, pigment epitelyumu (PE), Müller ve glial hücreler tarafından yapılmakta ve protein kinaz C izoformunun uyarılmasıyla damar geçirgenliğini arttırmakta, aynı zamanda retina iskemisine yol açmaktadır.<sup>10</sup> Diyabetik retinada saptanan biyokimyasal değişiklikler; artmış oksidatif stres, protein kinaz C aktivasyonu, nonenzimatik glikolizasyon, poliyol yolu ve artmış nitrik oksit olarak özetlenebilir.<sup>11</sup> İlâveten belirtilirse, oksidatif stres son yıllarda pek çok konu ile ilişkilendirilmiş olup bunlar arasında göz hastalıkları da yer almaktadır.<sup>12</sup> Değişik araştırmacıların yaptıkları çalışmalarda da grid LFK (Laser fotokoagülasyon) etkinliğinin sınırlı olduğu görülmüş ve laser skarının progresif olarak büyümesi sonucu makulanın olumsuz etkilenebileceği gösterilmiştir.<sup>13</sup> Yapılan birçok çalışmada İVTA (İntravitreal Triamsinolon Asetonid) prezervan madde içermeyen preparatları tavşanlara uygulanmış ve belirgin bir toksisiteye rastlanmamıştır.<sup>14</sup> Şüphesiz İVTA enjeksiyonu öncesi yıkama işleminin povidon-iyodinin ile yapılması, bu duruma katkı sağlamıştır. Zira; povidon-iodin, her türlü grişimsel göz müdahalelerinde ve tedavilerinde

kullanımı giderek yaygınlaşan önemli bir preparattır.<sup>15</sup> Triamsinolon asetonid intravitreal enjeksiyonu ile maksimum biyoyararlanımla etki etmesi sağlanmaktadır. Subtenon uygulamaların yetersiz penetrasyon nedeniyle kan-retina bariyerine karşı pek etkili olmadığı gösterilmiştir.<sup>16</sup>

Bu çalışmada Göz Kliniğinde DMÖ tanısı konulan hastalarda İVTA + LFK, LFK, İVTA şeklindeki tedavilerin görme keskinliği, PERG (Pattern Elektoretinografi) (P50) ve HRTII (Heidelberg Retina Tomograph II) üzerindeki etkisini araştırmak amaçlanmıştır.

## MATERYAL VE METOT

Sakarya Üniversitesi Tıp Fakültesi Girişimsel Olmayan Etik Kurulundan izin alınan (Tarih:13.4.2021, karar no: 279) bu çalışma, uluslararası bildirelerde ön görülen kriterlere göre Erciyes Üniversitesi Tıp Fakültesi Göz Hastalıkları Kliniği'nde 2007 yılında yapılmış Uzmanlık Tezi'nden üretilerek gerçekleştirilmiştir.

Fundus muayenesi ve FFA (Fundus Floresein Anjiyografi) ile DMÖ tanısı konan, 6-13 ay takip edilmiş ve herhangi bir tedavi uygulanmamış 65 olgunun 91 gözü çalışmaya dahil edildi. Görme keskinliği 3 metreden parmak sayımı (mps)'nin altında olan, glokom veya kataraktı olan, tedavi sonrası takibi mümkün olmayacak sistemik hastalığı olanlarla, kontrol altına alınamayan HT ve DM olan olgular çalışma kapsamına alınmadı. Preoperatif dönemde olguların sistemik ve oftalmolojik hikayeleri alındı, detaylı oftalmolojik muayene yapıldı. Snellen eşeli ile en iyi düzeltilmiş görme keskinlikleri (sonrası logMAR değerine çevrildi), aplanasyon tonometresi ile göz içi basınçları ölçüldü, fundus lensiyle fundus muayenesi yapıldı. FFA, PERG, HRTII ödem haritası değeri ile DMÖ tipi ve derecesi belirlendi. Akabinde olgular randomize olarak üç gruba ayrıldı: Grup 1: İVTA ve LFK (İVTA'dan 6 hafta sonra) uygulanan olgular, Grup 2: LFK uygulanan olgular, Grup 3: İVTA uygulanan olgular. Makula laser tedavisinde fokal, grid ve modifiye grid tarzında yeşil argon laser (532 nm dalga boyu) kullanıldı. İVTA enjeksiyonu öncesi her göz povidon-iyodin ile yıkandı, blefarasto yerleştirildi. Tüm hastalara topikal anestezi uygulandı, retrobulber anesteziye ihtiyaç duyulmadı. Topikal anestezi sonrasında insülin enjektörü ile 4 mg/ 0,1 ml triamsinolon asetonid, üst temporal kadrandan limbusa 3-4 mm uzaklıktan intravitreal olarak ameliyathane koşullarında enjekte edildi. Enjeksiyon uygulanan göz antibiyotikli pomad ile kapatıldı ve komplikasyon açısından değerlendirilmek üzere 1 gün, 1 hafta, 2 hafta aralıklarla kontrole çağrıldı. Olgular tedaviden sonra 1. 3. 6. 9. aylarda kontrole çağrılarak oftalmolojik muayeneleri yapıldı. FFA ile MÖ tipi ve derecesi aynı kişi tara-



findan değerlendirildi. Tüm kontrollerde DGK (Düzeltilmiş Görme Keskinliği), GİB (Göz İçi Basınç) değeri, fundus muayenesi, PERG, HRTII, ve FFA yapıldı.

Pupil dilate edilmeden, cilt elektrodu olarak gümüş klorür kaplı elektrodlar kullanılarak referans elektrodlar dış kantüsün iki santimetre dışına, topraklama elektrodu iki kaşın orta noktasından 2cm yukarıya alına yerleştirildi. Topikal anestezi (% 0.5proprarakain hidroklorür) her iki göze damlatıldıktan sonra alt fornixe limbustan yaklaşık 5 mm alta HK-loop elektrodlar yerleştirilerek cilde tespit edildi. Hastanın gözlüklerini takması sağlanarak refraksiyonu düzeltildi. PERG yanıtını kaydetmek için düşük eşik filtresi 30 Hz olacak şekilde ayarlama yapıldı. Stimulus şekli dama tahtası, kontrastın %99, stimulus frekansı 1,02, dakikadaki stimulus sayısı 73,2, kazanç zamanı 204, alınacak stimulus sayısı 150 olarak belirlendi.

**İstatistiksel analiz:** Ölçülebilir verilerin normal dağılım uygunluğuna bakıldı. Dağılım  $x \pm SD$  olarak tanımlandı. Gruplar arasındaki farklılığa One Way Anova testi, zamanlar arasındaki farklılığa ise Tekrarlı Varyans analizi kullanıldı. Normal dağılıma uymayan verilerde gruplar arası Kruskal- Wallis Varyans analizi, zamanlar arasındaki farklılığa ise Friedman testi kullanıldı.  $p < 0,05$ 'den küçük değerler istatistiksel olarak anlamlı kabul edildi.

## BULGULAR

Araştırmaya dahil edilen olguların demografik bilgileri tablo 1'de gösterilmiştir. Tablo 1'de görüldüğü gibi çalışmaya dahil edilen hastaların 32'si erkek, (% 49,2), 33'ü kadın (%50,8) olup yaş ortalaması 62,5 yıl (49-80 yıl arasında) idi.

Grup 1: İVTA ve LFK İVTA'dan 6 hafta sonra LFK uygulanan olgulardan oluşan grup 1'in DGK, PERG P50 amplitüdü ve HRTII ÖHD sonuçları tablo 2'de gösterilmiştir.

Tablo 2'de görüldüğü gibi, tedavi öncesi ile sonrası ortalama görme keskinliği, PERG P50 değeri ve ÖHD'ler arasında istatistiksel olarak anlamlı fark bulundu ( $p < 0,05$ ). GİB değerleri tedavi öncesine göre 1. ay ve 3. ayda istatistiksel olarak yüksek iken 6. ay ve 9. ayda anlamlı fark gözlenmedi ( $p > 0,05$ ).

Birinci, 3., 6. ve 9. aylar arasında saptanan ÖHD'leri arasında istatistiksel anlamlı farklılık bulunmamasına rağmen ( $p > 0,05$ ) ÖHD'deki maksimum azalma 3. ayda gözlemlendi. Bu grupta DGK, P50 amplitüdü ve HRTII ÖHD'i açısından tedaviden önceki ve sonraki değerleri arasında istatistiksel olarak anlamlı fark mevcuttu ( $p < 0,05$ ). Enjeksiyon sonrası ortalama GİB değeri, başlangıç değerlerine göre artmış olarak saptandı ve tedavi öncesi ve sonrası 1. ay ve 3. ay GİB değerleri arasında istatistiksel olarak anlamlı farklılık mevcut idi ( $p < 0,05$ ).

Grup 2: LFK uygulanan olgulardan oluşmakta olup, laser FK tedavisi öncesi ve sonrası 1. 3. 6. ve 9. aylardaki DGK, P50 amplitüdü ve HRTII ÖHD ortalamaları tablo 3'te gösterilmiştir.

Tablo 3'te görüldüğü gibi, tedavi öncesi ile sonrası 1. ay, 3. ay, 6.ay ve 9. ay kontrollerinde saptanan ortalama görme keskinliği, PERG P50 değeri ve

**Tablo 1.** Araştırmaya katılanların demografik özellikleri.

Erkek	Kadın	Yaş Ort.	Erkek%	Kadın%
32	33	62,5	49,2	50,8

**Tablo 2.** Grup 1'in tedavi öncesi ve sonrası değerleri.

	TÖ	TS 1.ay	TS 3.ay	TS 6.ay	TS 9.ay	P
DGK	1,30± 0,32	0,94 ±0,36	0,70± 0,26	0,72± 0,31	0,78± 0,35	<0,05
P50	1,26 ±0,99	1,93 ±1,40	2,38± 1,20	2,26± 1,30	2,16 ±1,23	<0,05
HRTII-ÖHD	2,80± 0,90	1,85 ±0,53	1,42 ±0,30	1,50 ±0,38	1,60± 0,46	<0,05
GİB (mmHg)	14,67± 2,85	17,72 ±3,97	18,75 ±3,22	16,03 ±3,56	15,94± 3,11	<0,05

TÖ: Tedavi Öncesi; TS: Tedavi Sonrası; DGK: Düzeltilmiş Görme Keskinliği; PERG: Pattern Elektoretinografi; HRTII: Heidelberg Retina Tomograph II; ÖHD: Ödem Harita Değeri; GİB: Göz İçi Basınç; P değerleri <0,05 ve >0,05 şeklinde gösterildi; P<0,05 istatistiksel olarak anlamlı kabul edildi.

**Tablo 3.** Grup 2'in tedavi öncesi ve sonrası değerleri.

	TÖ	TS 1.ay	TS 3.ay	TS 6.ay	TS 9.ay	P
DGK	1,20± 0,32	1,05 ±0,45	0,98± 0,42	1,06± 0,50	1,10± 0,54	<0,05
P50	1,42 ±0,95	1,70 ±1,35	1,81± 1,43	1,72± 1,44	1,62 ±1,40	<0,05
HRTII-ÖHD	2,51± 0,72	1,94 ±0,56	1,85 ±0,60	1,96 ±0,63	2,08± 0,72	<0,05
GİB (mmHg)	14,68± 3,42	14,46 ±3,73	15,04 ±2,82	14,85 ±2,90	14,73± 3,05	>0,05

TÖ: Tedavi Öncesi; TS: Tedavi Sonrası; DGK: Düzeltilmiş Görme Keskinliği; PERG: Pattern Elektoretinografi; HRTII: Heidelberg Retina Tomograph II; ÖHD: Ödem Harita Değeri; GİB: Göz İçi Basınç; P değerleri <0,05 ve >0,05 şeklinde gösterildi; P<0,05 istatistiksel olarak anlamlı kabul edildi.

**Tablo 4.** Grup 3'ün tedavi öncesi ve sonrası değerleri.

	TÖ	TS 1.ay	TS 3.ay	TS 6.ay	TS 9.ay	P
<b>DGK</b>	1,23± 0,26	0,89 ±0,30	0,77± 0,33	0,82± 0,36	0,87± 0,38	<0,05
<b>P50 (mV)</b>	1,35 ±0,82	2,05 ±1,20	2,31± 1,13	2,10± 1,03	1,89 ±1,15	<0,05
<b>HRTII-ÖHD</b>	2,62± 0,64	1,74 ±0,42	1,58 ±0,36	1,70 ±0,46	1,94± 0,51	<0,05
<b>GİB (mmHg)</b>	14,82± 3,15	17,37 ±4,51	19,02 ±2,95	16,68 ±3,82	17,0± 3,56	>0,05

TÖ: Tedavi Öncesi, TS: Tedavi Sonrası, DGK: Düzeltilmiş Görme Keskinliği, PERG: Pattern Elektoretinografi., HRTII: Heidelberg Retina Tomograph II, ÖHD: Ödem Harita Değeri, GİB: Göz İçi Basıncı. P değerleri <0,05 ve >0,05 şeklinde gösterildi. P<0,05 istatistiksel olarak anlamlı kabul edildi.

ÖHD'leri arasında anlamlı fark mevcut iken (p<0,05), GİB değerleri tedavi öncesine göre 1. ay, 3. ay, 6. ay ve 9. ayda anlamlı fark göstermedi (p>0,05). Grup 2'de DGK, P50 amplitüdü ve HRTII ÖHD'i açısından tedaviden önceki ve sonraki değerleri arasında istatistiksel olarak anlamlı fark mevcuttu (p<0,05). PERG ile saptanan P50 değerlerinde, tedavi öncesi değere göre anlamlı artış tespit edildi. Takip muayeneleri esnasında GİB değerleri, hiçbir gözde 21 mmHg'in üzerine çıkmamış olup LFK tedavisi sonrası ortalama GİB değişikliği, başlangıç değerlerine göre istatistiksel olarak anlamlı farklılık göstermedi (p>0,05).

Grup 3'ün tedavi öncesi ve sonrası 1., 3., 6. ve 9. aylardaki DGK, PERG P50 amplitüdü ve HRTII ÖHD bulguları, tablo 4'te gösterilmiştir.

Tablo 4'te görüldüğü gibi, tedavi öncesi ile sonrası ortalama görme keskinliği, PERG P50 değeri ve ÖHD'leri arasında, istatistiksel olarak anlamlı fark bulundu (p<0,05). Tedavi sonrası ortalama ÖHD'leri, başlangıç değerlerine göre azalmış olarak saptandı. Bu grupta DGK, P50 amplitüdü ve HRTII ÖHD'i açısından tedaviden önceki ve sonraki değerleri arasında istatistiksel olarak anlamlı fark mevcuttu (p<0,05). PERG ile saptanan P50 değerleri tedavi öncesi değer ile karşılaştırıldığında anlamlı artış tespit edildi (p<0,05). GİB değişikliği, başlangıç değerlerine göre istatistiksel olarak anlamlı farklılık göstermedi (p>0,05).

## TARTIŞMA VE SONUÇ

Yapılan ilk çalışmalarda makula laser FK tedavisinin makula ödemi etkili olarak azalttığı tespit edilmiştir.<sup>17</sup> Tedavi edilmeyen gözlerin hiçbirinde ödem azalma göstermezken tedavinin etkili olarak görme kaybını önlediği, görme keskinliğini koruduğu hatta artmaya yol açabildiği görülmüştür. Tedavi edilen hastaların 2. yıl sonunda % 45'i görme keskinliğinde artma, % 45'i görme keskinliğini koruma, % 4'ü ise azalma gösterirken, bu tedaviyi görmemiş grupta sırasıyla artma % 8, durumunu koruma % 49 ve azalma % 43 olmuştur (112).<sup>17</sup> Bizim çalışmamızda sadece laser FK uygulanan grupta tedaviden sonra 9. ayda 18 (%52,9) olguda DGK'de artma, 10(%29,4) olguda durumunu koruma, 6(%17,6) olguda azalma görüldü.

Diabetik makula ödemi (DMÖ) diyabetes mellitusun

en ağır komplikasyonlarından biri olup diabetik hastalarda önde gelen körlük nedenidir.<sup>18-19</sup> DMÖ hiperglisemi etkisiyle vasküler endotelin bozulması, mikroanevrizma oluşumu, kan-retina bariyerinin bozulması ve vasküler geçirgenliğin artması sebebiyle, damardaki sıvının intraretinal ve subretinal boşluğa birikmesi sonucunda oluşur. DMÖ tedavisinde klasik yöntem makular laser fotokoagülasyon olup, fokal, grid ve modifiye grid olarak yapılmaktadır. Yapılan çalışmalar, laser fotokoagülasyon tedavisinin görmeyi koruma ve ödemi tedavi etmede etkili olduğunu göstermiştir.<sup>20-23</sup> Fotokoagülasyonun hastalıklı retina pigment epitelini ortadan kaldırıp yerini daha genç ve işlevsel hücrelerin almasını sağlayarak etki ettiğini ileri süren araştırmacılar da vardır.<sup>24</sup> Ayrıca grid laser fotokoagülasyonun yüksek oksijen tüketicisi fotoreseptörleri tahrip ettiği için iç retina tabakalarındaki oksijen miktarını arttırdığı ve böylece buraya olan kan akımını azalttığı da ileri sürülen bir başka etki mekanizmasıdır.<sup>24</sup>

Literatürde İVTA sonrası arka subkapsüler katarakt oranı %6-10 arasında bildirilmektedir.<sup>25</sup> Bizim çalışmamızda grup1'de 5 (%16,6), grup2'de 3(%8,8), grup3'te 9 gözde (%33,3) katarakt görüldü. Son zamanlarda yazarlar dirençli DMÖ tedavisinde İVTA ve laser FK'nin görmeyi artırma ve koruma özelliklerini göz önünde bulundurarak, İVTA ile kombine LFK uygulamayı önermektedirler. Araştırmacılar yaptıkları bir çalışmada, diffüz DMÖ'de İVTA'ya ilave olarak LFK uygulamasının görmeyi artırdığını ve makula ödeminin tekrarlamasını azalttığını göstermişlerdir.<sup>26</sup>

Bizim çalışmamızda DMÖ hastalarına uygulanan, İVTA ile kombine LFK, LFK ve İVTA tedavi yöntemlerini tüm grupların tedavi öncesi ve sonrası görme keskinlikleri göz önüne alınarak karşılaştırılınca, İVTA ile kombine LFK grubu, en yüksek ve stabil görme keskinliği göstermekteydi. Yalnızca LFK uygulanan grupta görme keskinliğinde artış daha düşük olarak saptandı. Sadece İVTA uygulanan grupta 1. ve 3. aylarda anlamlı şekilde artma mevcut ise de 6. ve 9. aylarda azalma olduğu görüldü.

Yine çalışmamızda İVTA ile kombine LFK tedavisinin düzeltilmiş görmeyi anlamlı şekilde artırdığı ve bu tedavi ile makular ödemin nüks oranının düşük olduğu tespit edilmiştir. Yalnız LFK uygulamasında, düzeltilmiş görme korunmakta ise de görme keskin-

liğinde artma oranı düşük olarak bulunurken, makula ödeminin uzun süre nüks etmediği görülmüştür. Sadece İVTA uygulamasında ise ilk dönemlerde görme anlamlı oranda artmakta, ancak MÖ nüks oranı yüksek olması nedeniyle tekrarlayan enjeksiyonlara ihtiyaç duyulmaktadır.

Sonuç olarak;

1) DMÖ tedavisinde her üç grupta da başlangıç görme keskinliğine kıyasla başarı elde edilmesine karşın uzun dönem etkinliği göz önüne alındığında laser FK ile kombine İVTA uygulamasının sadece İVTA veya laser FK uygulanan olgulara kıyasla daha etkin olduğu gözlenmektedir.

2) PERG P50 amplitüdü ve HRTII-ÖHD, DMÖ'ü olan olgularda uygulanan tedavinin etkinliğini değerlendirmede kullanılabilecek olan testlerdir.

**Etik Komite Onayı:** Sakarya Üniversitesi Tıp Fakültesi Girişimsel Olmayan Etik Kurulundan alınmıştır (Tarih:13.4.2021, karar no: 279).

**Çıkar Çatışması:** Yazarlar çıkar çatışması bildirmemişlerdir.

**Yazar Katkıları:** Fikir – AY; Denetim, Malzemeler, Veri Toplanması ve/veya İşleme - ; Analiz ve/veya Yorum -AY; Yazıyı yazan – AY.

**Hakem Değerlendirmesi:** Dış bağımsız.

**Finansal Destek:** Bu çalışma, Erciyes Üniversitesi tarafından tıpta uzmanlık tezi olarak desteklenmiştir.

**Teşekkür:** Uzmanlık tez danışmanı olan Prof. Dr. Abdullah ÖZKIRIŞ'a katkılarından dolayı teşekkür ederiz.

**Diğer Bilgi:** Bu çalışma Abdülhekim YARBAĞ'ın "Diabetik makula ödemi olan olgularda intravitreal triamsinolon enjeksiyonu, laser fotokoagülasyon ve intravitreal triamsinolon enjeksiyonu ile kombine laser fotokoagülasyon tedavilerinin karşılaştırılması" adlı uzmanlık tezinden üretilmiştir.

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## Diyabetli Bireylerde Beslenme Okuryazarlığının Yaşam Kalitesi ve Metabolik Kontrol Üzerine Etkisi

### The Effect on the Quality of Life and Metabolic Control of Nutritional Literacy in Individuals with Diabetes Mellitus

<sup>1</sup>Türkan AKYOL GÜNER, <sup>2</sup>Tuğçe GÜNTER

<sup>1</sup>Zonguldak Bulent Ecevit University, Faculty of Health Sciences, Zonguldak, Turkey

<sup>2</sup>Zonguldak Bulent Ecevit University, Ahmet Erdogan Vocational School of Health Services, Zonguldak, Turkey

Türkan Akyol Guner: <https://orcid.org/0000-0003-0138-0669>

Tuğçe Gunter: <https://orcid.org/0000-0001-7416-2967>

#### ÖZ

**Amaç:** Bu çalışmanın amacı diyabetli bireylerde beslenme okuryazarlığı düzeyinin yaşam kalitesi ve metabolik kontrol üzerine etkisini incelemektir.

**Materyal ve Metot:** Tanımlayıcı ve kesitsel tipteki bu çalışma, Türkiye'nin kuzey batısında bir şehir merkezinde faaliyet gösteren bir aile sağlığı merkezinde Kasım 2020-Nisan 2021 tarihleri arasında 423 diyabetli birey ile yapılmıştır. Veriler, "Sosyodemografik ve sağlığa ilişkin veri formu", "Yetişkinlerde beslenme okuryazarlığı değerlendirme aracı" ve "Dünya Sağlık Örgütü-Beş İyilik hali indeksi" ile toplanmıştır. Metabolik değerlendirmede Hemogloblin A1C, açlık kan şekeri, kolesterol, trigliserid, düşük dansiteli lipoprotein kolesterol, yüksek dansiteli lipoprotein kolesterol ve beden kütle indeksi sonuçları kullanılmıştır.

**Bulgular:** Diyabetli bireylerde, beslenme okuryazarlığı ile yaşam kalitesi ve yüksek dansiteli lipoprotein kolesterol düzeyi arasında pozitif yönlü yüksek ve anlamlı; beden kütle indeksi, hemogloblin A1C, açlık kan şekeri ve kolesterol arasında negatif yönlü yüksek ve anlamlı ilişki bulunmuştur.

**Sonuç:** Diyabetli bireylerde yetersiz/sınırlı beslenme okuryazarlığı düzeyi, metabolik kontrol değerlerini ve yaşam kalitesini olumsuz etkilemektedir.

**Anahtar Kelimeler:** Beslenme, diyabet, okuryazarlık, yaşam kalitesi

#### ABSTRACT

**Objective:** This study aims to examine the effect on the quality of life and metabolic control of nutritional literacy in individuals with diabetes.

**Materials and Methods:** This descriptive and cross-sectional study was conducted with 423 individuals with diabetes in a family health center operating in a city center in northwest of Turkey between November 2020 and April 2021. The data were collected using the "Socio-demographic and health-related data form", "Evaluation instrument of nutrition literacy on adults" and "The World Organization-Five Well-being index". Metabolic control was evaluated using the results of Hemogloblin A1C, fasting blood glucose, cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and body mass index.

**Results:** It was found that there was a high and positive significant correlation between nutritional literacy with quality of life and high-density lipoprotein cholesterol, there was a high and negative significant correlation between nutritional literacy and body mass index, hemogloblin A1C, fasting blood glucose, and cholesterol of individuals with diabetes.

**Conclusion:** It was found that there was a high and positive significant correlation between nutritional literacy with quality of life and high-density lipoprotein cholesterol, there was a high and negative significant correlation between nutritional literacy and body mass index, hemogloblin A1C, fasting blood glucose, and cholesterol of individuals with diabetes.

**Keywords:** Diabetes mellitus, literacy, nutritional, quality of life

#### Sorumlu Yazar / Corresponding Author:

Türkan Akyol Güner  
Address: Zonguldak Bulent Ecevit University, Faculty of Health Sciences, Assist. Prof. Dr., Kozlu- Zonguldak / Turkey  
Tel: +9005057336954  
E-mail: akyol\_turkan@hotmail.com

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## INTRODUCTION

Diabetes mellitus (DM) is an important public health problem that develops due to increased blood glucose levels as a result of insulin deficiency, insulin resistance, or a combination of both, and may cause acute and chronic complications.<sup>1</sup> Effective individual follow-up is required for the control and treatment of DM and to prevent or delay the complications that may occur. The most important individual measure that patients can take and the key factor in the control of this disease are having adequate nutritional literacy.<sup>2</sup> Nutritional literacy is defined as the ability of individuals to have and apply knowledge about food, nutrients, adequate and balanced nutrition, choosing and consuming healthy food, and cooking and storing foods correctly. In other words, it is defined as the degree to which individuals can obtain, process, understand, and convey to others the necessary information to make informed decisions about nutrition.<sup>3</sup> Nutritional knowledge and skills play an important role in choosing the right foods for individuals with DM, making their quality of life consistent with their metabolic self-management and providing metabolic control of their body mass index (BMI).<sup>4,5</sup> Increasing the quality of life of individuals and keeping metabolic parameters within the appropriate limits is associated with learning about the right diet; that is, with improving nutritional literacy.<sup>6</sup>

As a result of a study investigating the relationship of health literacy with diabetes mechanisms, it was reported that nutritional literacy is very important in diabetes and that there is a limited number of studies examining the relationship between nutritional literacy, metabolic control, and quality of life.<sup>7</sup>

This study aims to help fill the gap in the literature by examining the effect of nutritional literacy on metabolic control and quality of life in individuals with DM.

## MATERIALS AND METHODS

**Ethics Committee Approval:** In this research, ethical approval was obtained from the Human Research Ethics Commission of University (Date:09.10.2020, decision no:897), and institutional permission was received from the Provincial Directorate of Health (Date:16.11.2020–95762934-799). Informed consent was obtained from the diabetic individuals who agreed to participate in the study.

**Study Setting and Selection Criteria:** This descriptive and cross-sectional study was conducted with 423 individuals with diabetes in a family health center operating in a city center in northwest of Turkey between November 2020 and April 2021. The population of the study is 512 individuals with diabetes registered to the FHC. The sample of the study con-

sisted of 423 individuals with diabetes who met the inclusion criteria and volunteered to participate in the study. The inclusion criteria were: being over 18 years of age, having been diagnosed with DM for at least one year, having at least an elementary education, and having volunteered to participate in the study. The exclusion criteria were: being visually and/or hearing impaired, having any neuropsychological disease had been diagnosed.

**Data Collection:** The data were collected using the Socio-demographic and health-related data form, Evaluation instrument of nutrition literacy on adults (EINLA), and The World Organization-Five (WHO-5) Well-being index. Metabolic control was evaluated using the results of Hemoglobin A1C (HbA1c), fasting blood glucose (FBG), cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and body mass index (BMI). The metabolic control evaluations of the participants were based on the blood results obtained in the last 1 month. For those without blood results, venous blood was taken to assess metabolic control. Data collection forms were filled in by the participants in FHC. The height and weight of the participants were measured for BMI calculation.

**Socio-demographic and Health-Related Data Form:** This form was created by the researchers by scanning the literature (3-5,7). It consists of 12 questions about age, gender, educational status, marital status, employment status, income status, health status, nutritional status, and nutritional education status. by Mearns et al

**WHO-5 Well-being index:** This scale, which was developed by Bech et al,<sup>8</sup> was rearranged as 5 items within the scope of the project carried out by the WHO in order to measure the quality of life of patients.<sup>9</sup> It consists of 5 items. Each item is evaluated between 0 and 5. 0 represents the “worst possible” and 5 represents the “best possible” quality of life. The Turkish adaptation studies of the scale and its validity and reliability studies were carried out by Eser et al.<sup>10</sup> This scale is a means of measuring the quality of life of the participants for the last two weeks. An increase in the scores obtained from the scale indicates an increase in the quality of life.

**EINLA:** This scale was developed by Cesur, Koçoğlu, and Sümer as a tool for understanding and evaluating the nutritional information read by adults.<sup>11</sup> A total score of 0-11 points indicates “inadequate”, 12-23 points “limited”, and 24-35points “adequate” nutritional literacy.<sup>10</sup> The Cronbach's Alpha reliability coefficient of the original scale was 0.75, and it was found to be 0.81 as a result of its use in our study.

**Metabolic Control Data:** BMI was classified using

the WHO standardization.<sup>11</sup> Recent blood results for HbA1c, FBG, cholesterol, LDL, HDL, and triglycerides were also obtained from medical records were based on the guidelines from the American Diabetes Association (ADA).<sup>12</sup>

**Statistical Analysis:** Statistical analysis of the data was performed using SPSS 22.0 (IBM Corporation, Armonk, NY, USA) package program. In data analysis, percentage, mean±SD, t-test, ANOVA, Tukey test, and Pearson Correlation Coefficient were used. Multiple regression analysis was used to determine the effects of independent variables on dependent variables. The significance level in the tests was taken as p <0.05.

**RESULTS**

The socio-demographic and health-related characteristics of the participants are given in Table 1. 52.2%

of the participants were male, 43.0% were between the ages of 59-69, 75.4% were married, 56.4% were employed, 62.6% had middle income, 38.8% had diabetes for 1-5 years, 59.8% had not received any education about nutrition in diabetes, and 71.6% of them requesting nutrition education in diabetes (Table 1).

The metabolic evaluations of the individuals with DM according to their level of nutritional literacy are given in Table 2. The BMI, HbA1c, FBG, cholesterol, and HDL values of those individuals with DM who had adequate nutritional literacy were statistically significantly lower than those with inadequate and limited levels.

Table 3 shows the comparison of demographic and health-related characteristics of the individuals with DM according to scale mean scores. The EINLA mean scores of those who were sex (p=0.001), age

**Table 1.** Some demographic and health-related characteristics of individuals with DM.

Variables	n	%	Variables	n	%
<b>Sex</b>			<b>Diabetes duration</b>		
Female	202	47.8	1-5 years	164	38.8
Male	221	52.2	6-10 years	142	33.6
<b>Age (years)</b>			≥ 11 years	117	27.7
37-47	104	24.6			
48-58	137	32.4	<b>Co-morbidities</b>		
59-69	182	43.0	Yes	189	44.7
<b>Education status</b>			No	234	55.3
Primary school	134	31.7	<b>Regular breakfast</b>		
Middle school	84	19.9	Yes	288	68.1
High school	92	21.7	No	98	23.2
University	113	26.7	Sometimes	37	8.7
<b>Marital status</b>			<b>Skipping meals</b>		
Married	319	75.4	Yes	63	14.9
Single	49	11.6	No	66	15.6
Widow	55	13.0	Sometimes	294	69.5
<b>Working status</b>			<b>Nutrition education status</b>		
No	184	43.5	Yes	170	40.2
Yes	239	56.5	No	253	59.8
<b>Income status</b>					
Good	124	29.3	<b>Requesting nutrition education</b>		
Middle	265	62.6	Yes	303	71.6
Poor	34	8.1	No	120	28.4

**Table 2.** Metabolic evaluation according to nutrition literacy levels of individuals with DM.

Variables	Inadequate Mean ±SD	Limited Mean ±SD	Adequate Mean ±SD	F	p
<b>BMI (kg/m2 )</b>	29.18±10.18	25.58±10.99	20.65±8.30	<b>13.759</b>	<b>0.000**</b>
<b>HbA1c (%)</b>	8.63±2.61	7.52±2.03	6.98±2.66	<b>12.203</b>	<b>0.001*</b>
<b>FBG(mg/dL)</b>	167.28±87.12	148.52±45.19	138.56±40.15	<b>17.170</b>	<b>0.000**</b>
<b>Cholesterol (mg/dL)</b>	204.26±48.35	195.48±31.81	180.65±53.33	<b>3.701</b>	<b>0.025*</b>
<b>Triglycerides (mg/dL)</b>	175.09±102.08	165.85±112.54	163.34±86.79	4.123	0.128
<b>HDL (mg/dL)</b>	44.86±10.74	45.10±11.58	46.98±9.25	<b>8.379</b>	<b>0.015*</b>
<b>LDL (mg/dL)</b>	123.41±40.65	120.98±38.74	118.56±45.89	1.580	0.228

\*p<0.05; \*\*p<0.001; F: ANOVA; BMI: Body mass index; HbA1c: Glycated hemoglobin; FBG: Fasting blood glucose; LDL: Low-density lipoprotein cholesterol; HDL: High-density lipoprotein cholesterol; mg/dL: milligram/deciliter.

(p=0.000), education status (p=0.012), marital status (p=0.000), working and income status (p=0.000), diabetes duration (p=0.000), co-morbidities (p=0.000), regular breakfast (p=0.001), skipping meals (p=0.000) and nutrition education status (p=0.012) were found to be statistically significant. In examining the quality of life according to the socio-demographic and health-related characteristics of the individuals with DM no significance was found according to sex (p=0.781), while age (p=0.000), educational status (p=0.023), marital status (p=0.015), working status (p=0.000) and in-

come status (p=0.021), co-morbidities (p=0.000) and nutrition education status (p=0.018) were found to be statistically significant (p<0.05) (Table 3). It was determined that there was a high and significant positive correlation between the nutritional literacy and quality of life (r: 0.820; p=0.001) and the HDL (r: 0.580; p=0.003) of individuals with DM. There was a high and negative significant correlation between nutritional literacy and BMI (r:-0.698; p=0.000), HbA1c (r:-0.712; p=0.001), FBG (r:-0.690; p= 0.000) and, Cholesterol (r:-0.754; p=0.008) (Table 4).

**Table 3.** Comparison of socio-demographic and health-related characteristics according to scales means of individuals with DM.

Variables	EINLA		WHO-5 Well-being index	
	Mean ±SD	Statistics	Mean ±SD	Statistics
<b>Sex</b>				
Female	25.08±8.87	t=0.318	9.42±4.48	t=0.278
Male	21.85±7.71	<b>p=0.001***</b>	8.64±4.12	p=0.781
<b>Age (years)</b>				
37-471	29.66±3.49	F=257.42	13.25±2.56	F=90.684
48-582	25.14±5.99	<b>p=0.000**</b>	11.89±2.45	<b>p=0.000**</b>
59-693	15.17±6.15	*Difference=1>2, 1>3, 2>3	10.25±6.23	*Difference=1>3
<b>Education status</b>				
Primary school1	12.51±2.63	F=351.68	9.35±4.38	F=91.564
Middle school2	21.46±7.22	<b>p=0.012***</b>	10.52±3.59	<b>p=0.023***</b>
High school3	26.86±3.31	*Difference=4>3,2,1	12.45±5.63	*Difference=4>2,1
University4	29.55±4.20	3>2,1; 2>1	13.57±4.45	
<b>Marital status</b>				
Married1	22.96±7.87	F=75.397	14.63±3.45	F=85.658
Single2	27.18±5.47	<b>p=0.000**</b>	12.36±2.96	<b>p=0.015***</b>
Widow3	11.52±1.52	*Difference=2>1,3; 1>3	9.96±3.85	*Difference=1>3
<b>Working status</b>				
No	15.03±5.33	t=-22.502	8.95±4.62	t=-22.240
Yes	27.30±5.83	<b>p=0.000**</b>	15.56±2.85	<b>p=0.000**</b>
<b>Income status</b>				
Good1	30.66±2.78	F=256.224	13.52±2.23	F=90.479
Middle2	18.51±6.73	<b>p=0.000**</b>	10.36±3.69	<b>p=0.021***</b>
Poor3	11.54±1.31	*Difference=3>2,1; 2>1	7.63±4.35	*Difference=1>3
<b>Diabetes duration</b>				
1-5 years1	29.42±3.50	F=281.966	13.54±2.85	F=89.523
6-10 years2	19.55±6.63	<b>p=0.000**</b>	12.23±3.45	p=0.235
>11 years3	14.43±5.97	*Difference=3>2,1; 2>1	10.67±3.56	
<b>Co-morbidities</b>				
Yes	15.40±6.27	t=-20.881	8.12±2.56	t=-20.881
No	27.26±5.40	<b>p=0.000**</b>	14.45±4.25	<b>p=0.000**</b>
<b>Regular breakfast</b>				
Yes1	25.91±6.28	F=198.388	11.56±5.84	F=91.325
No2	13.41±5.67	<b>p=0.001***</b>	11.28±3.56	p=0.156
Sometimes3	13.89±3.38	*Difference=1>2,3	10.85±3.74	
<b>Skipping meals</b>				
Yes	13.98±6.71	F=86.221	11.35±4.52	F=88.564
No	30.13±3.22	<b>p=0.000**</b>	12.84±3.43	p=0.458
Sometimes	21.84±7.62	*Difference=2>3,1	11.97±4.62	
<b>Nutrition education status</b>				
Yes	24.70±7.81	t=5.787	14.39±3.94	t=-20.150
No	20.12±8.09	<b>p=0.012***</b>	10.75±3.63	<b>p=0.018***</b>

t: Independent Samples t test; F: ANOVA; \*Tukey test; \*\*: p<0.001; \*\*\*: p<0.05; EINLA: Evaluation instrument of nutrition literacy on adults.



**Table 4.** Correlation with metabolic control and WHO-5 Well-being index of Nutritional literacy of individuals with DM.

Variables	r	p
HbA1c (%)	-0.712**	0.001*
FBG (mg/dL)	-0.690**	0.000*
Cholesterol (mg/dL)	-0.754**	0.008*
HDL (mg/dL)	0.580**	0.003*
BMI (kg/m <sup>2</sup> )	-0.698**	0.000*
WHO-5 Well-being index	0.820**	0.001*

Pearson correlation coefficient; \*:p<0.01; \*\*: correlation coefficient; HbA1c: Glycated hemoglobin; FBG: Fasting blood glucose; LDL: Low-density lipoprotein cholesterol; HDL: High-density lipoprotein cholesterol; BMI: Body mass index.

In the regression table constructed to explain the effect on the Well-being index, BMI, and HbA1c results of the nutritional literacy level of the individuals with DM, it was found that nutritional literacy affected the quality of life, BMI, and HbA1c. It was determined that the quality of life explained 84.7% ( $R^2 = 0.847$ ) of the nutritional literacy level, BMI explained 48.7% ( $R^2 = 0.487$ ), and HbA1c explained 48.6% ( $R^2=0.486$ ) (Table 5).

#### DISCUSSION AND CONCLUSION

It is thought that this study will contribute to the literature as it is the first study to examine the effect of nutritional literacy on metabolic control values and quality of life in individuals with DM registered in FHC. This study examined the level of nutritional literacy of individuals with diabetes and found that they had a limited level of nutritional literacy. In one study examining the effect of nutritional literacy level on the self-care activities of individuals with diabetes, it was determined that one out of every five individuals had a limited level of nutritional literacy, similar to our study.<sup>3</sup> The lack of any other study evaluating nutritional literacy in individuals with diabetes necessarily limits the discussion of this specific finding of the study.

In this study, it was determined that there was a statistically significant difference in the level of nutri-

tional literacy in terms of all socio-demographic characteristics except for sex. Examining other study evaluating the relationship between nutritional literacy and socio-demographic characteristics, it was determined that they had similar findings to the current study, in that there was a negative correlation with age, and a positive correlation with education level.<sup>13</sup> Examining the literature in terms of the effect of sex and marital status on nutritional literacy, results were found that were similar to those of the current study.<sup>14</sup>

Nutritional literacy was also affected by the health characteristics of the individuals with diabetes.<sup>15,16</sup>

In the current study, it was observed that individuals with diabetes who had a longer period of diagnosis and had a comorbid disease had lower nutritional literacy levels. In addition, it was determined that the nutritional literacy of those who did not eat breakfast regularly, skipped meals, and did not receive education about nutrition in diabetes was also found below. These findings were also supported by some studies in the literature. In these studies, it was found that the presence of a diagnosed chronic disease and an increase in the duration of diagnosis had a negative impact on nutritional literacy,<sup>17</sup> that individuals who did not skip meals had a higher level of nutritional literacy,<sup>18</sup> and nutrition-related education increased the level of nutritional knowledge.<sup>19</sup>

**Table 5.** Regression table of the effect on WHO-5 Well-being index, BMI, and HbA1c of EINLA.

Dependent variable	Independent variable	$\beta$	t	p	$R^2$	Adj. $R^2$	F
Model 1	Constant		5.893	0.00*	0.847	0.846	324.432
WHO-5 Well-being index	EINLA	0.820	48.212	0.00*			
	Constant		103.948	0.00*	0.487	0.486	399.273
BMI	EINLA	-0.698	-19.982	0.00*			
	Constant		31.176	0.00*	0.486	0.485	382.294
HbA1c(%)	EINLA	-0.712	-21.245	0.00*			

\*p: 0.00; R: Regression coefficient; EINLA: Evaluation instrument of nutrition literacy on adults; BMI: Body mass index; HbA1c: Glycated hemoglobin.

There is an increasing prevalence of many diseases and their accompanying complications, especially obesity, in individuals with inadequate nutritional literacy.<sup>20</sup> In individuals with diabetes, for whom nutritional behaviors are very important, BMI values can be kept within appropriate limits by sufficient nutritional literacy. BMI may increase as a result of negative nutritional behaviors due to inadequate/limited nutritional literacy as well as medical and individual factors in individuals with diabetes.<sup>21</sup> When the BMIs of the diabetic individuals who participated in this study were examined, it was seen that they were in the overweight category with a mean of  $27.36 \pm 3.24$ , and there was a significant relationship between nutritional literacy and BMI. In similar studies investigating the relationship between nutritional literacy and BMI conducted with different sample groups, was determined that nutritional literacy significantly affected the BMI value and that the BMI of individuals who had inadequate nutritional literacy was higher.<sup>22,23</sup> An increase in BMI is associated with increased complications from diseases, a more negative body image, and thus a negative effect on the quality of life.

It has been reported that approximately 86.2% of individuals with DM have poor metabolic control.<sup>23</sup> The relationship between metabolic parameters and nutritional literacy was also examined in the current study. It was determined that there was a significant correlation between nutritional literacy and the HbA1c, FBG, cholesterol, and HDL values, while there was no significant correlation between nutritional literacy and triglyceride and LDL values. Similar to the current study, the study conducted by Mearns et al showed that there was a significant relationship between nutritional literacy and cholesterol, HbA1c, FBG, and HDL values.<sup>24</sup> These results are similar to the findings of the current study, which indicate that nutritional literacy may have a potential impact on blood glucose and lipid values.

This study also evaluated the quality of life of individuals with diabetes using the WHO-5 Well-being index. Quality of life is an important criterion for evaluating the health status and the effects of the treatment given to an individual with diabetes.<sup>25</sup> The quality of life means a score of the individuals who participated in the study was found to be  $15.28 \pm 2.56$  and this was determined to be moderate in terms of how the scale is evaluated. Another study found that the quality of life of individuals with diabetes was similarly low.<sup>26</sup>

In the current study, it was found that the individuals of a lower age, higher education level, who were married, employed, had a good income, had no comorbid disease, and had received education about nutrition in diabetes had higher quality of life scores than the others. Similarly, other studies have found

that factors such as a lower education level, lower-income level, not being married, and having a comorbid disease negatively affected the quality of life.<sup>27,28,29</sup> As seen from these parameters, quality of life is affected by a wide variety of factors.

This study investigated the relationship between nutritional literacy, metabolic parameters, and quality of life: it was concluded that there was a negative correlation between nutritional literacy and metabolic values (HbA1c, FBG, cholesterol, HDL) and BMI and that there was a positive correlation between nutritional literacy and the quality of life of the individuals with diabetes. Similarly, in a study examining the effect of health literacy and nutritional status on the glycemic values of individuals with diabetes, it was found that there was a negative correlation between glycemic values and BMI and the level of nutritional knowledge.<sup>30</sup>

In this study, it was observed that inadequate/limited nutritional literacy negatively affected the metabolic control values and quality of life. Accordingly, a range of educational policies should be developed to increase the nutritional literacy levels of individuals with diabetes. It is recommended that initiatives such as education, seminars, and conferences be planned, with an initial focus on primary health care institutions and an evaluation of the health and nutritional literacy of individuals who use their services.

**Ethics Committee Approval:** In this research, ethical approval was obtained from the Human Research Ethics Commission of University (Date:09.10.2020, decision no:897), and institutional permission was received from the Provincial Directorate of Health (Date:16.11.2020-95762934-799). Informed consent was obtained from the diabetic individuals who agreed to participate in the study.

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## Sezaryen Doğumlarda Tek Doz Spinal ve Kombine Spinal Epidural Anestezinin Postoperatif Analjezi Kalitesinin Karşılaştırılması

### Comparison of Postoperative Analgesia Quality of Single Dose Spinal and Combined Spinal Epidural Anesthesia in Cesarean Deliveries

<sup>1</sup>Fatih ŞAHİN, <sup>1</sup>Havva KOCAĞİT, <sup>1</sup>Fikret BAYAR, <sup>2</sup>Ayça TAŞ TUNA

<sup>1</sup> Sakarya Üniversitesi Eğitim ve Araştırma Hastanesi Anesteziyoloji ve Reanimasyon Kliniği, Sakarya, Türkiye  
<sup>2</sup> Sakarya Üniversitesi Tıp Fakültesi Anesteziyoloji ve Reanimasyon Ana Bilim Dalı, Sakarya, Türkiye

Fatih Şahin: <https://orcid.org/0000-0002-8501-0675>

Havva Kocayigit: <https://orcid.org/0000-0002-8719-7031>

Fikret Bayar: <https://orcid.org/0000-0001-9953-4018>

Ayça Taş Tuna: <https://orcid.org/0000-0001-6764-2647>

#### ÖZ

**Amaç:** Sezaryen doğum analjezisinde sıkça kullanılan intratekal morfin ve epidural morfinin analjezik etkilerinin karşılaştırılması amaçlanmıştır.

**Materyal ve Metot:** Hastalar tek doz spinal (TDS) ve kombine spinal epidural (KSE) anestezi grubuna ayrıldı. TDS anestezi standart olarak 10 mg %0,5 hiperbarik bupivakain, 10 µg fentanyl, 100 µg morfin, KSE’de ise morfin eklenmeden subaraknoid aralığa enjekte edildi. KSE grubundaki hastalara 2. saat ve 24. saatte epidural kateterden 3 mg morfin 10 mL hacimde uygulandı. Ağrı şiddetinin hesaplanması için visual analog skala (VAS) kullanıldı.

**Bulgular:** Çalışmaya toplam 144 hasta dahil edildi. 71 hastaya TDS, 73 hastaya ise KSE anestezi uygulandı. VAS skorlarının karşılaştırılmasında 2., 12. ve 48. saat skorlarında anlamlı fark bulundu. 2.saat VAS skorunda TDS anestezi grubunda daha düşük VAS skoru mevcutken 12., 24., ve 48. saat VAS skorlarında KSE anestezi grubunda daha düşük VAS skoru bulundu.

**Sonuç:** Her iki tedavide iyi analjezi sağladı. Özellikle mobilizasyon sonrasında epidural analjezi uygulaması intratekal opioid kullanımına göre daha iyi sonuçlar vermektedir.

**Anahtar Kelimeler:** Kombine spinal epidural anestezi, morfin, sezaryen doğum, spinal anestezi

#### ABSTRACT

**Objective:** It is aimed to compare the analgesic effects of intrathecal morphine and epidural morphine, which are frequently used in cesarean delivery analgesia.

**Materials and Methods:** Patients were divided into single-dose spinal (SDS) and combined spinal epidural (CSE) anesthesia groups. While 10mg 0.5% hyperbaric bupivacaine, 10µg fentanyl, 100µg morphine were administered to SDS anesthesia group as standard, the aforementioned drugs without morphine were injected into the subarachnoid space in CSE group. The patients in CSE group, 3mg morphine in a volume of 10mL was administered through the epidural catheter at the 2nd and 24th hour. Visual analog scale (VAS) was used to calculate pain intensity.

**Results:** Total of 144 patients were included in the study. It was observed that 71 patients were applied SDS anesthesia and 73 patients were applied CSE anesthesia. In the comparison of VAS scores, significant difference was found in the scores at 2nd, 12th and 48th hours. While the 2nd hour VAS score was lower in SDS anesthesia group, 12th, 24th, and 48th hour VAS scores were lower in CSE anesthesia group. The highest difference was found in the 48th hour VAS scores.

**Conclusion:** Both treatments provided good analgesia. Especially after mobilization, application of epidural analgesia gives better results than intrathecal opioid use.

**Keywords:** Both treatments provided good analgesia. Especially after mobilization, application of epidural analgesia gives better results than intrathecal opioid use

#### Sorumlu Yazar / Corresponding Author:

Fatih Şahin

Adres: Sakarya Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi Anesteziyoloji ve Reanimasyon Kliniği 54100, Sakarya / Türkiye

Tel: +05062607219

E-mail: tyflfatih16@hotmail.com

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## GİRİŞ

Türkiye’de sezaryen doğum oranı 2017 yılında % 53,1 oranında olup, dünyada ilk sırada yer almaktadır.<sup>1</sup> Sezaryen doğumların anestezi yönetiminde nöroaksiyel uygulamalar öncelikli tercih edilen yöntemlerdir.<sup>2</sup> Sezaryen doğumda uygulanabilen analjezik/anestezik teknikler çok çeşitli olup; karmaşık doğumlar için nöroaksiyal (yani spinal veya epidural) kateterin erken yerleştirilmesi, sürekli infüzyon epidural analjezi, opioidlerle birlikte epidural lokal anesteziklerin kullanımı, yüksek veya düşük konsantrasyonlarda lokal anestetik kullanımı, lokal anestezikli veya lokal anesteziksiz tek enjeksiyonlu spinal opioidler, kalem uçlu spinal iğneler, kombine spinal epidural (KSE) analjezi ve hasta kontrollü epidural analjezi (HKEA) gibi pek çok teknik uygulanabilmektedir.<sup>3</sup> Bunların içerisinde intratekal morfin, epidural morfin veya HKEA sezaryen doğum sonrası analjezi tedavisinde en sık kullanılan yöntemlerdendir. Dichtwald ve ark.<sup>4</sup> yaptıkları randomize kontrollü bir çalışmada epidural ve spinal uygulamalarda lokal anesteziklere ek olarak morfin ve fentanil kullanımının postoperatif analjezide oldukça önemli olduğunu ve biyoyararlanımının yüksek olduğunu göstermişlerdir. HKEA ve intratekal morfinin birlikte kullanımının tek başına intratekal morfin kullanıma göre postoperatif ilk 12 ve 24 saatte daha iyi analjezi sağladığı gösterilmiştir.<sup>5</sup> Analjezi için epidural kateter kullanıldığında ise opioid kullanımını lokal anestezik kullanımını azaltıp analjezi kalitesini artırmaktadır.<sup>3</sup> Otao ve arkadaşları sadece lokal anestezik ile tek doz spinal (TDS) anestezi ve değişen dozlarda opioidli TDS anestezi uygulanan hastaların postoperatif HKEA kullanımlarını karşılaştırmışlardır. Sadece lokal anestezik ile TDS anestezi uygulanan hastalarla değişen dozlarda opioidli TDS anestezi uygulanan hastalara göre anlamlı derecede yüksek HKEA kullanımı bildirilmiştir.<sup>6</sup> Düşük doz lokal anestezik ve opioid kullanılan TDS aneste-

zi ve KSE anestezinin, tek doz spinal anestezi uygulamasına göre daha düşük yan etki insidansı oluşturduğu da gösterilmiştir.<sup>7</sup>

Bu çalışmanın primer amacı sezaryen doğumdan sonraki ilk 48 saat içerisinde TDS ve KSE anestezi uygulanmış hastaların postoperatif analjezi etkilerinin karşılaştırılması ve değerlendirilmesidir. Sekonder amacı ise uygulanan iki teknik arasında gelişen komplikasyon oranının karşılaştırılmasıdır.

## MATERYAL VE METOT

**Çalışmanın Etik Yönü:** Sakarya Üniversitesi Tıp Fakültesi yerel etik kurul onayı (Tarih: 29/01/2021, karar no: 6050-28) alındıktan sonra Sakarya Üniversitesi Eğitim ve Araştırma Hastanesi’nde Mart 2020 - Aralık 2020 tarihleri arasında sezaryen doğum yapmış olan, TDS ve KSE anestezi uygulanan hastaların dosya verileri kullanıldı. Hasta verileri hastanenin elektronik veri programı Karmed, Kardelen Yazılım (Kardelen Software, Mersin, Türkiye)’dan elde edildi. Çalışma Helsinki bildirgesine uygun olarak yapıldı.

## BULGULAR

Çalışmaya sezaryen doğum uygulanmış toplam 144 hasta dahil edildi. 71 hastaya TDS anestezi uygulanırken, 73 hastaya ise KSE anestezi uygulandığı gözlemlendi. Hastaların yaş, boy, kilo ve VKİ değerleri iki grup arasında karşılaştırıldığında gruplar arasında anlamlı bir fark bulunamadı (Tablo 1).

İki grubun VAS skorlarının karşılaştırılmasında 2., 12. ve 48. saat skorlarında anlamlı fark bulundu (p değeri sırasıyla; <0,001, <0,006, <0,001). 2.saat VAS skorunda TDS anestezi grubunda daha düşük VAS skoru mevcutken 12., 24., ve 48. saat VAS skorlarında KSE anestezi grubunda daha düşük VAS skoru bulundu. En yüksek fark 48. saat VAS skorlarında mevcuttu (p<0,01) (Grafik 1) (Tablo 2).

**Tablo 1.** Demografik veriler.

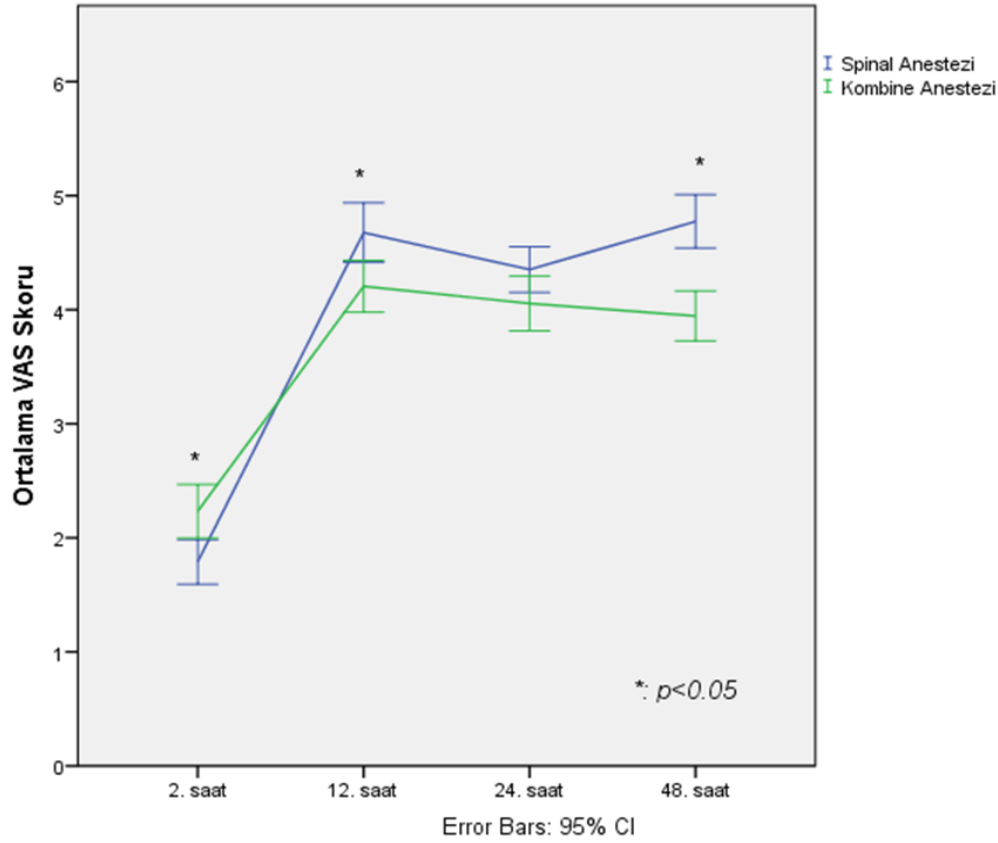
	Tek Doz Spinal Anestezi (n=71)	Kombine Spinal Epidural Anestezi (n=73)	p
Yaş (yıl)	29,8±6,6	29,8±5,6	0,965
Boy (cm)	163,2±12,5	162,2±3,7	0,517
Vücut Ağırlığı (kg)	79,5±12,5	76,2±10,1	0,095
VKI	30,0±4,9	28,9±3,5	0,141

Student-t Testi kullanılmıştır; Ortalama ± SD; VKİ: Vücut Kitle İndeksi (kilo/boy<sup>2</sup>); cm: Santimetre; kg: Kilogram.

**Tablo 2.** Tek doz spinal anestezi ve kombine spinal epidural anestezi grubunun VAS Skorları açısından karşılaştırılması.

VAS Skorları	Tek Doz Spinal Anestezi (n=71)	Kombine Spinal Epidural Anestezi (n=73)	p
2. saat	2 [1-2]	2 [2-2]	<0,01*
12. saat	5 [4-5,5]	4 [4-5]	0,006*
24. saat	4 [4-5]	4 [4-5]	0,077
48. saat	5 [4-6]	4 [3-5]	<0,01*

Mann-Whitney U test kullanılmıştır; Median [IQR]; VAS: Visual Analog Skala; \*: p<0.05.



**Grafik 1.** VAS skorlarının 48 saatlik takibi.

KSE anestezi uygulanmış olan 1 hastada thuy iğnesi ile dural ponksiyon gözlenmiş fakat hastanın postspinal baş ağrısı olmamıştır. 5 hastada postspinal baş ağrısı gelişmiş olup bu hastalar TDS anestezi uygulanan hastalardı. Postspinal baş ağrısı gelişen 5 hastanın 4'ünde medikal tedavi (hidrasyon, aminokardol ve kafein) yeterli olurken 1 hastanın şikayetlerinin devam etmesi üzerine epidural kan yaması uygulandı. TDS anestezi uygulanan hastalarda baş ağrısı daha fazla gözlenirken KSE anestezi uygulanan hastalarda omuz ağrısı, gaz sancısı ve kaşıntı

şikayetinin daha fazla olduğu gözlemlendi. Tüm komplikasyonlar değerlendirildiğinde ise gruplar arasında anlamlı fark bulunmadı ( $p=0,067$ ) (Tablo 3).

#### TARTIŞMA VE SONUÇ

Çalışmamızda sezaryen doğum sonrasında ağrının erken saat değerlendirmesinde TDS anestezi uygulanan hastalarda daha iyi postoperatif analjezi sağlandığı ve sonraki takiplerinde ise KSE anestezi uygulananlarda postoperatif epidural kateterden uygula-

**Tablo 3.** Komplikasyonlar.

	Tek Doz Spinal Anestezi (n=71)	Kombine Spinal Epidural Anestezi (n=73)	p
Post-spinal baş ağrısı	5 (7,04 %)	-	0,067
Omuz ağrısı	1 (1,41 %)	3 (4,11 %)	
Gaz sancısı	1 (1,41 %)	2 (2,74 %)	
Kaşıntı	-	4 (5,48 %)	

Ki-kare Test; n (%).

nan opioid tedavisinin geç dönemde daha iyi analjezi sağlayarak daha düşük VAS skorları sağladığı gözlemlendi.

Sezaryen doğum sonrası analjezinin nöroaksiyel yoldan sağlanması için genellikle epidural kateter aracılığıyla sürekli opioid ve lokal anestezi uygulaması veya intratekal opioid uygulaması kullanılmaktadır.<sup>8,9</sup> Bizim kliniğimizde rutin olarak sezaryen doğum analjezisinde KSE anestezi ve sonrasında epidural kateterden aralıklı opioid enjeksiyonu veya lokal anesteziğe morfin ve fentanil eklenerek TDS anestezi uygulaması kullanılmaktadır.

Postoperatif analjezi için intratekal ve epidural opioid kullanımının hangisinin daha üstün olduğuyla ilgili farklı görüşler mevcuttur.<sup>2,5,10</sup> Kaufner ve ark.<sup>2</sup> 179 hasta üzerinde yaptıkları prospektif randomize kontrollü çalışmada postoperatif 6. saatte dinlenme sırasında intratekal morfin ile TDS anestezi yapılan hastalarda, sadece epidural yol ile analjezi sağlanan hastalara göre VAS skorlarının anlamlı derecede düşük olduğunu göstermişlerdir. Mobilizasyon sonrasında ise 6., 24. ve 48. saatte intratekal morfin uygulanan hasta grubunda epidural analjezi uygulanan hastalara göre anlamlı derecede daha düşük VAS skorları olduğunu bildirmişlerdir. Bu çalışmaya göre intratekal morfin uygulaması epidural uygulamaya göre daha başarılı analjezik etki oluşturduğu bildirilmiştir. Zıt bir görüş olarak ise başka bir randomize kontrollü çalışmada intratekal ve epidural morfin analjezisi karşılaştırılmış ve dinlenme sırasında ilk 21 saatte aralarında anlamlı bir fark bulunamamıştır. Hareket başladığında ise epidural morfin uygulananların intratekal morfin uygulananlara göre daha düşük VAS skorlarına sahip olduğu gözlenmiştir. VAS skorları arasında fark saptanmasına rağmen tüm hastaların %90'ında tatmin edici bir ağrı tedavisi sağlandığı bildirilmiştir.<sup>10</sup> Bizim çalışmamızda ise VAS skoru ortalamalarının TDS anestezi uygulananlarda ortalama 2 ile 5 arasında, KSE uygulananlarda ise ortalama 2 ile 4 arasında olduğu gözlemlendi. Yukarıdaki çalışmalarda görüldüğü üzere intratekal morfin uygulamasının epidural analjeziye üstün olduğu gösterildiği gibi tam tersinin olduğu durumlarda görülmektedir. Bu farklılığın oluşmasındaki en önemli sebebin farklı çalışma metodolojileri ve özellikle epidural analjezi sırasında kullanılan ilaçların farklı doz ve çeşitlilikte olmasından kaynaklandığını düşünmekteyiz. Bizim çalışmamızda ise postoperatif ilk saatlerde tıpkı Kaufner ve ark.<sup>2</sup> yaptıkları çalışmaya benzer şekilde postoperatif 2. saatte dinlenme sırasında intratekal morfin ile TDS anestezi uyguladığımız hastalarımızda VAS skoru anlamlı derecede düşüktü. Hareket başladıktan sonra ise özellikle 24 ve 48. saatteki VAS skoru KSE grubunda Sarvelo ve ark.<sup>10</sup> çalışmalarında gösterdiği gibi anlamlı olarak daha düşüktü. Hastalar hareket etmeye başladıktan sonra 12. saatte ise VAS skorları arasında anlamlı

bir fark bulunamadı. Bu durum bize özellikle hareket başlayana kadar postoperatif ilk saatlerde intratekal morfin uygulamasının, hareket başladıktan sonra ise postoperatif süre uzadıkça epidural analjezik uygulamasının daha iyi analjezi sağladığını gösterdi. Nöroaksiyel analjezinin etkisinin ve süresinin uzatılması için kullanılan farklı adjuvan opioid ilaçların yan etkileri de olabilmektedir. Yapılan çalışmalarda epidural yolla sağlanan analjezi ile alt ekstremitte uyuşukluğu ve zayıflığı insidansının az olduğu; intratekal yolla sağlanan analjezinin hızlı şekilde başladığı, etkin bir analjezi sağladığı fakat yüksek bulantı kusma insidansına neden olduğu bildirilmiştir.<sup>11-13</sup> Sarvelo ve ark.<sup>10</sup> postoperatif bulantı veya kusmayı intratekal 100 µg morfin uygulanan hastaların %16'sında, epidural morfin uygulananların %26'sında ve intratekal 200 µg morfin kullanılan hastaların ise %28'inde meydana geldiğini göstermişlerdir; ameliyat sonrası 3. saatte epidural grubunda daha az kaşıntı görülürken, 24. saatte intratekal 200 µg uygulanan daha çok kaşıntı oluştuğu gösterilmiştir. Bizim çalışmamızda ise kaşıntı şikayeti sadece epidural analjezi uygulanan hastaların %5,5'inde görülmüştür. Bu bize kaşıntı sebebinin epidural kateterden uygulanan morfin olduğunu düşündürmüştür.

Farklı çalışmalarda 27 gauge quinke iğne ile TDS anestezi uygulanan hastalarda %3,8 oranında, 25 gauge quinke iğne ile ise %8,3 oranında KSE anestezi uygulanan hastalarda ise %1,34 oranında postspinal baş ağrısı geliştiği gösterilmiştir.<sup>14,15</sup> Bizim çalışmamızda da benzer şekilde TDS anestezi sonrasında %7 oranında postspinal baş ağrısı gelişti. Epidural iğne yerleştirilirken bir hastada dural delinme yaşanmasına rağmen baş ağrısı gelişmedi. KSE grubunda uyguladığımız epidural enjeksiyonların postspinal baş ağrısı gelişimini azalttığını düşünmekteyiz.

Intratekal morfin uygulamasında ciddi komplikasyonlarından birinin solunum depresyonu olduğu gösterilmiştir.<sup>16</sup> Bizim çalışmamızda her iki grupta da kullanılan morfin dozunun düşük olmasından dolayı herhangi bir solunum depresyonu olgusu gelişmemiştir. TDS anestezi sonrasında %26,6 oranında, genel anestezi sonrasında ise %43,9 omuz ağrısı olduğu gösterilmiştir.<sup>17</sup> Bizim çalışmamızda ise %2,8 oranında omuz ağrısı geliştiği görüldü. Literatüre göre omuz ağrısında bu kadar fark çıkmasının en önemli sebebi VAS 4 üzeri olduğunda kortaracı analjezik olarak parasetamol kullanılması ve bu ağrının hastalarda rahatsızlık vermemesidir.

Sonuç olarak hem intratekal morfin hem de epidural morfin sezaryen doğum analjezisinde başarılı sonuçlar sağlamaktadır. Mobilizasyonun ardından özellikle epidural analjezi uygulaması intratekal opioid kullanımına göre daha iyi sonuçlar vermektedir.



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## Genel Yoğun Bakım Ünitesinde Yatan COVID 19 Hastalarında Mortaliteyi Öngörmeye İlişkili İndekslerin Prediktif Değerleri

### Predictive Values of Inflammation Indexes in Predicting Mortality in Patients with COVID 19 Hospitalized in General Intensive Care Unit

<sup>1</sup>Cihan AYDIN, <sup>1</sup>Şeref ALPSOY, <sup>2</sup>İlker YILDIRIM, <sup>2</sup>Ahmet GÜLTEKİN, <sup>2</sup>Makbule Cavidan ARAR, <sup>3</sup>Mesut ENGİN, <sup>4</sup>Bişar AMAÇ

<sup>1</sup>Namık Kemal University Faculty of Medicine, Department of Cardiology, Tekirdağ, Turkey.

<sup>2</sup>Namık Kemal University Faculty of Medicine, Department of Anesthesia and Reanimation, Tekirdağ, Turkey.

<sup>3</sup>Health Sciences University Bursa Yüksek İhtisas Training, and Research Hospital, Department of Cardiovascular Surgery, Bursa, Turkey.

<sup>4</sup>University of Health Sciences, Mehmet Akif İnan Training and Research Hospital, Department of Perfusion, Şanlıurfa, Türkiye

Cihan Aydın: <https://orcid.org/0000-0002-1401-5727>

Şeref Alpsoy: <https://orcid.org/0000-0003-3720-0076>

İlker Yıldırım: <https://orcid.org/0000-0002-4245-1163>

Ahmet Gültekin: <https://orcid.org/0000-0001-8551-7815>

Makbule Cavidan Arar: <https://orcid.org/0000-0003-1952-427X>

Mesut Engin: <https://orcid.org/0000-0003-2418-5823>

Bişar Amaç: <https://orcid.org/0000-0003-0320-4239>

#### ÖZ

**Amaç:** Küresel bir pandemiye neden olan koronavirüs hastalığı 2019 (COVID-19), milyonlarca insanın enfekte olmasına ve birçok insanın ölmesine neden oldu. Bu çalışmada rutin olarak değerlendirilen klinik ve laboratuvar değerlerinin COVID-19 hastalığı olan hastaların mortalitesini tahmin edip edemeyeceğini araştırmayı amaçladık.

**Materyal ve Metot:** Çalışmamızda COVID 19 tanısı ile genel yoğun bakım ünitesinde yatırılan 89 hastanın rutin laboratuvar parametreleri retrospektif olarak incelendi. Sistemik inflamasyonun agregat indeksi (AISI) ve diğer inflamatuvar değerler COVID-19 polimeraz zincir reaksiyonu testi pozitif olan ve akciğer tomografisinde buzlu cam opasitesi olan hastalarda yapılan kan testlerinden hesaplandı. Hastalar yoğun bakım takiplerinde ölenler (sağ kalamayanlar) ve taburcu olanlar (sağ kalanlar) olarak iki gruba ayrıldı.

**Bulgular:** Çalışmamızda takipte ölen 48 hastada AISI, diğer inflamatuvar parametreler, ferritin, troponin I, d-dimer ve prokalsitonin gibi biyokimyasal parametreler taburcu edilen hastalardan anlamlı derecede yüksekti. Hipertansiyon ve daha yüksek AISI ve ferritin seviyeleri, Cox regresyon analizinde azalmış sağkalım ile istatistiksel olarak ilişkiliydi (Sırasıyla: Risk oranı (RO)=3,176;%95 Güven aralığı (GA), 1,122-8,991,P=0,03, RO=1,114; %95 GA, 1,060-1,348, P=0,042 ve RO=1,072;95% GA,1,014-1,242, P=0,011).

**Sonuç:** Kan testlerinden elde edilen inflamasyon indeksleri ile ferritin gibi akut faz reaktanları, yoğun bakım takiplerinde COVID-19'lu hastalarda tedavi stratejisini ve risk sınıflandırmasını planlamada bize yol gösterebilir.

**Anahtar Kelimeler:** İntlamasyon, kan parametreleri, koronavirüs 2019 hastalığı, pandemi

#### ABSTRACT

**Objective:** Causing a global pandemic, the coronavirus disease 2019 (COVID-19) has caused millions of people to become infected and many more to die. In this study we aimed to investigate whether routinely evaluated clinical and laboratory values can predict the mortality of patients with COVID-19 disease.

**Materials and Methods:** In our study, routine laboratory parameters of 89 patients hospitalized in the general intensive care unit with the diagnosis of COVID 19 were retrospectively analyzed. The aggregate index of systemic inflammation (AISI) and other inflamatuvar values were calculated from blood tests in patients with positive COVID-19 polymerase chain reaction test and with ground-glass opacity on lung tomography. Patients were divided into two groups as those who died (non-survivors) and those who were discharged (survivors) during the intensive care follow-ups.

**Results:** In our study, in 48 patients who died during follow-up, the indexes of AISI, other inflamatuvar parameters and the biochemical parameters such as troponin I, d-dimer, ferritin and procalcitonin were significantly higher than in discharged patients. Hypertension and higher AISI and ferritin levels were statistically associated with reduced survival in Cox regression analysis (Hazard ration (HR): 3.176; 95% Confident interval (CI): 1.122-8.991, p=0.03, HR: 1.114; 95% CI: 1.060-1.348, p=0.042, HR=1.072;95% CI: 1.014-1.242, p=0.011, respectively.

**Conclusion:** Inflammation indexes derived from blood tests and acute phase reactants such as ferritin can guide us in planning the treatment strategy and risk stratification in patients with COVID-19 in intensive care follow-ups.

**Keywords:** Blood parameters, coronavirus 2019 disease, inflammation, pandemic

#### Sorumlu Yazar / Corresponding Author:

Bişar Amaç

University of Health Sciences, Mehmet Akif İnan Training and Research Hospital Department of Perfusion, Esentepe Town, Ertuğrul Street, Postal zipcode: 63200 Karaköprü/Şanlıurfa, Türkiye  
Tel: 0414 318 60 00

E-mail: amacbisar@gmail.com

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## INTRODUCTION

The Coronavirus disease 2019 (COVID-19) outbreak, which caused the death of 2.2 million patients by infecting 100 million people worldwide, was first identified as pneumonia of unknown origin in Wuhan, China.<sup>1</sup> In June 2020, the outbreak reported in Japan then spread to Europe and America. The disease has been declared as a global pandemic by the world health organization (WHO). Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the pathogen of coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome-CoV (SARS-CoV), and Middle East Respiratory Syndrome-CoV (MERS-CoV), are viruses, that belong to the  $\beta$  genus CoV family.<sup>2</sup> Although most people have mild symptoms, it can cause acute respiratory distress syndrome (ARDS) in some patients.<sup>3</sup>

COVID-19 can cause cytokine storms, multi-organ failure, sepsis, and thrombosis. Long-term damage has been observed in organs, especially the lungs and heart. Despite having gone through the acute phase of the disease, many patients continue to experience various effects for months.<sup>4</sup> The severity of the disease in patients with COVID-19 is evaluated as mild, moderate, and severe according to the laboratory tests, clinical symptoms, and the level of involvement in the lung tomography. While the majority of patients (average 81%) have mild or moderate symptoms, such as subfebrile fever and cough, twenty percent of them have to be followed up in the intensive care unit.<sup>3</sup> The mortality rate of intensive care units is around 61.5%.<sup>5</sup> There is a need for inexpensive, useful biomarkers that can determine the severity of the disease in early diagnosis and help early aggressive treatment. Routine blood analysis, which is easily studied in all kinds of hospital conditions, can guide us in the diagnosis and treatment of the inflammatory process.<sup>6</sup>

Complete blood analysis can easily give us information about the number and structure of defense cells such as lymphocytes, neutrophils, and monocytes. Furthermore, combined ratios of these parameters can be useful for diagnosis, treatment, and risk stratification. In several studies,<sup>7</sup> It has been determined that the neutrophil to lymphocyte ratio (NLR), derived NLR (dNLR), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), and systemic inflammation response index (SIRI) were useful for the diagnosis and severity assessment of COVID-19.<sup>8-9</sup>

In our study, we examined the value of parameters such as ferritin, procalcitonin, and troponin I in predicting prognosis in intensive care patients, in addition to these indexes.

## MATERIALS AND METHODS

Patients hospitalized in Faculty of Medicine, Tekirdag Namık Kemal University anesthesia intensive care unit (ICU) with the diagnosis of covid 19 between 1 November 2020 and 30 January 2021 were included in our study retrospectively. The study was carried out under the Helsinki declaration and was approved by Tekirdag Namık Kemal University hospital ethics committee (Date: 27/04/2021, decision no: 2021.107.04.02). In all patients, the diagnosis of COVID-19 disease was made by evaluating reverse transcription-polymerase chain reaction test (PCR) and lung tomographies. Intubated patients admitted to the ICU and patients with critical disease, malignancy, known systemic inflammatory disease, and serum creatinine values above 2 mg/dL were excluded from the study. For all our patients hospitalized in the intensive care unit with the diagnosis of COVID-19; ceftriaxone 1x2 grams intravenous, clarithromycin 2x500 milligrams intravenous, enoxaparin 2x0.6 cc subcutaneous, 3x300 milligrams intravenous acetylcysteine, 1x 500 mg ascorbic acid intravenously were given.

Then, a 2x600 mg oral loading dose of favipiravir, 2x1600 mg oral continued. 6 milligrams of dexamethasone intravenously was added to the treatment of patients with severe respiratory distress. Tocilizumab 400 milligrams intravenously was given to 3 patients in the non-survivor group, and immune plasma was given to one patient in the survivor group and two patients in the non-survivor group.

The demographic clinical characteristics and laboratory results of the patients were obtained from the electronic database of our hospital. Systemic inflammation indexes, respectively; NLR (neutrophil/lymphocyte ratio), dNLR (neutrophils/(white blood cells -neutrophils)), PLR (platelet/lymphocyte ratio), MLR (monocyte/lymphocyte ratio), SIRI ((neutrophils  $\times$  monocytes)/lymphocytes), systemic immune inflammation index (SII) ((neutrophils  $\times$  platelets)/lymphocytes) and aggregate index of systemic inflammation (AISI) ((neutrophils  $\times$  monocytes  $\times$  platelets)/lymphocytes), LCR

((lymphocyte/C reactive protein (CRP) ratio)) were calculated from whole blood assays. The patients were divided into two groups as those who died (non-survivors) and those who were discharged (survivors) during the intensive care follow-ups.

Discharge criteria for patients were: (i) absence of fever for at least 3 days; (ii) signs of improvement on chest computed tomography scan or X-ray; (iii) the presence of two consecutive negative PCR tests performed at least 24 hours apart.

Blood parameters of the patients were measured from blood samples obtained from antecubital veins during ICU hospitalization. Whole blood counts

were performed with an automated whole blood analyzer, and biochemical values were measured with an automatic device. Systemic inflammation indexes were calculated.

**Statistical Analysis:** SPSS for Windows Vers 22.0 (SPSS Inc., IL, USA) was used for all statistical analysis. Continuous variables with normal distribution were expressed as mean±standard deviation (SD) and categorical variables were expressed as a percentage. Non-normally distributed data were expressed as median and IQR (interquartile range). Descriptive analysis was performed for categorical data. Independent samples T-test was performed for data conforming to a normal distribution, and Mann-Whitney U test was used for data not compatible with a normal distribution. Whether the parameters conformed to the normal distribution was evaluated with the Kolmogorov Smirnov test. Differences between categorical variables were appropriately evaluated by the Fisher test or chi-square test. Receiver operating characteristics (ROC) curve analysis was performed to estimate optimal cut-off values of inflammation indexes. Cox regression analysis was used for hazard ratios of the indexes and other parameters.  $P < 0.05$  was considered statistically significant.

## RESULTS

A total of 89 (54 men and 35 women) patients who were hospitalized in the ICU and diagnosed with COVID-19 by PCR test and lung tomography were included in the study (Table 1). The median age was 68 (IQR:28-93) years. Forty-one (46%) patients were discharged alive. The remaining 48 (53.9%) patients died during the intensive care follow-up. Most of the patients hospitalized in the intensive care unit had an accompanying chronic disease. Sixty (67.4%) of the patients had a history of hypertension. 37 (41.5%) of the patients were diabetic. Of the 89 patients, 22 (24.7%) had coronary artery disease, 9 (10.1%) had cerebrovascular disease, 17 (19.1%) had heart failure, and 15 (16.8%) had respiratory disease, respectively. The median hospitalization duration was 4 (1-26) days. The non-survivor group was older, although there was no statistically significant difference in age. (70 years, IQR: 41-93 years vs 66 years, IQR: 28-88 years  $p=0.052$ ). When we look at the demographic characteristics of the patients, there was no difference between the two groups in terms of heart failure, diabetes, coronary artery disease, cerebrovascular disease, age, and gender distribution (Table 1).

**Table 1.** Demographic, clinical, and hematological features of COVID-19 survivors and non-survivors.

Variables	All Patients (n=89)	Survivors (n=41)	Non-Survivors (n=48)	P-value
Age(Years)	68 (28-93)	66 (28-88)	70 (41-93)	0.052
Gender(F/M)	35/54	20/21	15/33	0.09
Hospital stay(days)	4(1-26)	4(1-19)	4(1-26)	0.87
Respiratory Disease (No/Yes)	74/15	34/7	40/8	0.95
Diabetes(No/Yes)	52/37	25/16	27/21	0.65
Cerebrovascular disease (No/Yes)	80/9	36/5	44/4	0.54
Cardiovascular disease(No/Yes)	67/22	31/10	36/12	0.94
Heart Failure	72/17	32/9	40/8	0.52
Hypertension(No/Yes)	29/60	13/28	16/32	0.87
Wbc( $\times 10^9$ )	12.9(0.79-36.7)	12(1-24)	14.67(4-37)	<0.001
Monocytes( $\times 10^9$ )	0.781(0.12-23)	0.56(0.1-1)	0.82(0.12-23)	<0.001
Neutrophils( $\times 10^9$ )	10.5(0.32-32.5)	8.8(0.32-20)	12.39(4-33)	<0.001
Platelets( $\times 10^9$ )	200(16-776)	173(100-334)	225.5(16-776)	0.029
Lymphocytes( $\times 10^9$ )	0.8(0.15-6.53)	0.9(0.2-2.2)	0.63(0.15-6.5)	0.051
CRP (mg/L)	120(1.97-476)	82.04(2-338)	150.5(4-476)	0.004
D-dimer(mg/L)	2.17(0.19-35.2)	1.78(0.19-35)	2.37(0.19-35)	0.043
Fibrinogen(mg/dl)	407(56.1-935)	397.3(150-935)	421(56-900)	0.62
Ferritin(ng/ml)	730(25.3-72852)	361.7(25-6260)	1906(74-72852)	<0.001
Procalcitonin(ng/ml)	0.44(0.02-10.95)	0.18(0.02-5)	0.71(0.18-11)	<0.001
Troponin I(ng/l)	25(3-1100)	17(3-1100)	32.5(5-437)	0.007
AST (IU/L)	39(8-1459)	23(8-106)	78.5(24-1459)	<0.001
ALT (IU/L)	34( 6-869)	23(9-128)	43(6-869)	0.003
INR	1.23(0.87-10.9)	1.13(1-10.9)	1.3(1-3)	<0.001

F;Female, M;Male, Wbc: White blood cell, CRP: C reactive protein, AST: Aspartate aminotransferase ALT: Alanine aminotransferase, INR: International normalized ratio. All continuous variables are reported as medians and interquartile ranges.

When we look at the cell rates in complete blood count, in the non survivor group, white blood cells (WBC,) monocytes, neutrophils, platelets were higher, WBC WBC (median  $12 \times 10^9$  L, IQR: (1-24) vs  $14.67 \times 10^9$  L, IQR: (4-37)  $p < 0.001$ ), monocytes (median  $0.82 \times 10^9$  L, IQR: (0.12-23) vs  $0.56 \times 10^9$  L, IQR: (0.1- 1)  $p < 0.001$ ), neutrophils median  $12.39 \times 10^9$  L, IQR: (4-33) vs  $8.8 \times 10^9$  L, IQR: (0.32-20)  $p < 0.001$ ), platelets (median  $173 \times 10^9$  L IQR: (100-334) vs  $225.5 \times 10^9$  L, IQR: (16-776)  $p = 0.029$ ) respectively (Table 1).

Although lymphocyte counts were low in the non survivor group, it was not statistically significant (median  $0.63 \times 10^9$  L, IQR: (0.15-6.5) vs  $0.9 \times 10^9$  L (0.2-2.2), IQR: (0.2-2.2)  $p=0.051$ ). The ratios of acute phase reactants such as CRP, ferritin were significantly higher in the non survivor group. CRP (median 150.5 mg/L, IQR: (4-476) vs 82.04 mg/L, IQR: (2-338),  $p=0.004$ ), ferritin (median 1906 ng/ml IQR: (74-72852) vs 361.7 ng/ml, IQR:(25-6260),  $p<0.001$ ). Likewise, procalcitonin levels, an inflammation marker, were higher in the non-survivor

group (median 0,71(ng/ml) IQR: (0.18-11) vs 0.18 (ng/ml) (0.02-5) , $p=0.000$ ). D dimer levels were statistically higher in non-survivor group (median 2.37(mg/L) IQR:(0.19-35) vs 1.78(mg/L) IQR: (0.19 -35)  $p=0.043$ ) (Table 1).

When we look at the inflammation indexes derived from complete blood tests, it was found to be significantly higher in the non-survivor group (SII, AISI, MLR, NLR, PLR, SIRI, LCR, dNLR)  $p<0.001$ ,  $p<0.001$ ,  $p<0.001$ ,  $p<0.001$ ,  $p<0.001$ ,  $p=0.004$ ,  $p<0.001$ , respectively) (Table 2).

The roc analyzes cut-off values for survival for each inflammatory index were as follows; AISI, 1318.12; dNLR, 6.03; MLR, 0.76; NLR, 16.82; PLR, 250.4; SII, 2189.55; SIRI, 7,43. ROC curve analysis cut-off values for troponin I and ferritin parameters related to survival were; 24.5 and 707.8 respectively (Table 3).The values of area under the curve (AUC) were 0.922 (0.859-0.984) for AISI, 0.737(0.635-0.839) for dNLR, 0.903(0.838-0.967) for MLR, 0.93 (0.877-0.984) for NLR, 0.757 (0.655-0.860) for PLR, 0.922 (0.859-0.984) for SII, 0.946 (0.902-0.990) for SIRI (Table 3).

**Table 2.** Inflammation indexes of COVID-19 patients.

Indexes	Survivors	Non- Survivors	P value
SII	1472.5(126-2811)	3963(296-24413)	<0.001
AISI	831.08(15.13-1590)	3235(1167-20261)	<0.001
MLR	0.5(0.15-1.15)	1.16(0.32-18.42)	<0.001
NLR	8.48(0.97-19.2)	16.8(9-56.9)	<0.001
PLR	164.2(71.43-609.52)	360.17(10.46-1616)	<0.001
SIRI	4.1(0.12-12.06)	14.5(3.47-426.3)	<0.001
LCR	0.017(0.01-048)	0.0047(0.0007-0.25)	0.004
dNLR	4.5(0.68-11.14)	7(1.63-26.91)	<0.001

AISI: Aggregate index of systemic inflammation, COVID-19: Coronavirus disease 2019; dNLR: derived neutrophil to lymphocyte ratio, MLR: monocyte to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, SII: systemic immune-inflammation index, SIRI: systemic inflammation response index, LCR: lymphocyte to C-reactive protein ratio. All variables are reported

**Table 3.** ROC curves and prognostic accuracy of inflammation indexes and biochemical parameters.

	AUC	95% CI	P Value	Cut off	Sensitivity(%)	Specificity(%)
SII	0.922	(0.859-0.984)	<0.001	2189.55	85.4	85.4
SIRI	0.946	(0.902-0.990)	<0.001	7.43	87.5	87.8
NLR	0.93	(0.877-0.984)	<0.001	16.82	50	50
dNLR	0.737	(0.635-0.839)	<0.001	6.03	62.5	63.4
MLR	0.903	(0.838-0.967)	<0.001	0.76	83.3	82.9
PLR	0.757	(0.655-0.860)	<0.001	250.4	72.9	73.2
AISI	0.992	(0.981-1.000)	<0.001	1318.12	93.8	92.7
Troponin I	0.667	(0.550-0.784)	0.007	24.5	60.4	61
Ferritin	0.841	(0.757-0.926)	<0.001	707.8	75	75.6

AISI: Aggregate index of systemic inflammation, dNLR: derived neutrophil to lymphocyte ratio, MLR: monocyte to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, SII: systemic immune-inflammation index, SIRI: systemic inflammation response index

Hypertension and higher AISI and ferritin levels were statistically associated with reduced survival in Cox regression analysis (Hazard ratio (HR)=3.176; 95% Confident interval (CI), 1.122-8.991, p=0.03, HR=1.114; 95% CI, 1.060-1.348, P=0.042, HR=1.072; 95% CI,1.014-1.242, p=0.011, respectively) (Table 4).

## DISCUSSION AND CONCLUSION

The COVID-19 pandemic, which affects all humanity, has caused many problems in the fields of economy, social and health in the world, and the spread of the new mutant form seen in England, America, and South Africa while vaccination studies continue, worries all humanity. Furthermore, many questions about whether we will be able to keep ahead of future variants of COVID-19, which will certainly arise.<sup>8</sup> Vaccination, early diagnosis, and treatment are important to cope with this urgent problem. COVID-19 (RNA virus,) and its mutants can mutate faster than DNA viruses. Such new mutations could make them more deadly, more transmissible, or both.<sup>9</sup> It makes it difficult to immunize people against the new mutant virus with the vaccine. We planned our study for predicting mortality and directing treatment. Our study adds new ones to the inflammation markers in COVID-19.

In studies performed, a decrease in peripheral T cell subsets is frequently observed in patients with severe

acute respiratory syndrome(SARS). In healed patients, peripheral T Cell subsets were found to normalize rapidly; this can be used as a diagnostic tool for SARS.<sup>10</sup> SARS-CoV-2 disrupts the immune system, causing an uncontrollable immune response in the body. Lymphopenia, lymphocyte activation and dysfunction, granulocyte and monocyte abnormalities are seen in these patients. There are high cytokine levels and an increase in immunoglobulin. Patients with severe COVID-19 are more likely to show lymphopenia on admission, indicating an important predictor for severe patients.<sup>11,12</sup> Although there was a significant decrease in the number of CD4 + T, CD8 + T, NK, and B cells, there was a greater decrease in the number of CD8 + T cells in severe cases than in mild ones.<sup>13-16</sup>

Therefore, these data show that lymphopenia, or inflammatory markers to be derived, can be used as an indicator of disease severity and prognosis in patients with COVID-19. An extreme increase in inflammatory cytokines is seen in severe cases. In this cytokine storm, there is an increase in cytokines such as IL-1 $\beta$ , IL-2, IL-6, IL-7, IL-8, IL-10, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), interferon-inducible protein-10 (IP10), monocyte chemotactic protein 1 (MCP1), macrophage inflammation protein-1 $\alpha$ , IFN- $\gamma$ , and TNF- $\alpha$ . In particular, IL-1 $\beta$ , IL-6, and IL-10 are the three most

**Table 4.** Hazard ratios of the indexes and other parameters obtained by Cox regression analysis.

	HR	95% CI	P value
Diabetes Mellitus	0.750	0.293-1.918	0.548
Cerebrovascular disease	0.657	0.138-3.123	0.597
Cardiovascular disease	1.897	0.685-5.257	0.218
Heart Failure	0.363	0.112-1.178	0.092
Hypertension	3.176	1.122-8.991	0.030
Respiratory Disease	1.455	0.531-3.987	0.465
Gender (Male)	0.866	0.371-2.019	0.739
Age	1.029	0.999-1.061	0.059
CRP (mg/L)	1.002	0.997-1.006	0.438
D-dimer(mg/L)	1.012	0.973-1.053	0.545
Ferritin(ng/ml)	1.072	1.014-1.242	0.011
Procalcitonin(ng/ml)	1.099	0.943-1.279	0.226
Troponin I(ng/l)	1.002	0.998-1.005	0.330
SII	1.000	0.999-1.000	0.249
AISI	1.114	1.060-1.348	0.042
MLR	0.679	0.314-1.468	0.326
NLR	1.046	0.997-1.098	0.069
PLR	1.003	0.999-1.006	0.172
SIRI	1.014	0.988-1.041	0.299
dNLR	0.965	0.874-1.065	0.476

AISI: Aggregate index of systemic inflammation, CI: confidence interval, COVID-19: coronavirus disease 2019, CRP: C-reactive protein, dNLR: derived neutrophil to lymphocyte ratio, HR: hazard ratio, MLR: monocyte to lymphocyte ratio, NLR: neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: systemic immune-inflammation index, SIRI: systemic inflammation response index.

elevated cytokines in severe cases.<sup>17,18</sup> CD4 + T cells infected with covid 19 transforms into pathogenic T helper (Th) 1 cell and secrete GM-CSF, IL-6. This situation stimulates CD14 + CD16 + monocytes and promotes inflammation.<sup>19</sup>

Lymphopenia caused by COVID-19 can cause new infections caused by microbes. New bacterial infections trigger neutrophil supplementation and an increase in neutrophil counts in tissues. The COVID-19 virus binds with S proteins (Spike glycoprotein) to angiotensin-converting enzyme 2 receptors (ACE2) on human respiratory epithelial cells and T cells. COVID-19 can directly infect T cells and macrophages and reduce their numbers. High levels of TNF $\alpha$ , IL-6, and IL-10 have also been shown to reduce the number of T cells.<sup>20</sup> Therefore, targeting the IL-6 / IL-6 receptor (IL-6R) signaling pathway is a promising strategy for alleviating inflammation symptoms. Tocilizumab, an anti-IL-6 receptor antibody, and Sarilumab, a monoclonal antibody, are used in severe cases to stop cytokine storm. Lymphopenia, high cytokine levels, and neutrophil levels appear to be parameters that can help us in the progression of the disease. In our study, as in other studies, we found that leukocytosis, lymphopenia, and increased neutrophil count are associated with disease severity in terms of hematological parameters.

NLR values were reported to be a more sensitive biomarker of inflammation than the individual levels of neutrophils and lymphocytes.<sup>21</sup> We found higher NLR and dNLR values in patients with severe COVID-19 disease, consistent with previous studies.<sup>22,23</sup> In a recent study by Sayar et al., the relationship between inflammatory parameters and COVID-19 disease was investigated. In this study, a significant relationship was found between high d-dimer and ferritin levels and the need for intensive care. In addition, a significant relationship was found between NLR and leukocyte elevation and lung involvement rates.<sup>24</sup> In our study, we found that inflammatory indexes (SIRI, AISI, MLR, NLR, PLR, SIRI, LCR, dNLR) that can be easily calculated and used in the follow-up of patients with COVID-19 are related to the severity of the disease. In the Kaplan-Meier survival curves, which were obtained from the cut-off values of the inflammatory indexes in the roc curve analysis, survival was found to be associated with inflammatory indexes. High ferritin and troponin levels were also found to be associated with mortality.

However, these significant inflammatory indexes can be detected high in septic shock, rheumatological diseases, and some types of cancer. For instance, the SII has also been shown to be associated with poorer survival in small cell lung cancer, hepatocellular carcinoma, colorectal cancer, and stomach cancer.<sup>25,26</sup> In a study conducted by Aksu et al., the rela-

tionship between inflammatory parameters and the need for invasive intervention in patients with non-ST myocardial infarction during the COVID-19 pandemic period was investigated. At the end of the study, the authors found high SII values to be significantly higher in patients who needed invasive intervention.<sup>27</sup> In another study, a significant relationship was found between high CRP and in-hospital mortality in COVID-19 patients with coronary artery disease.<sup>28</sup> In our study, CRP and SII values were significantly higher in patients with mortality.

The limitations of our study are the retrospective nature of our study, including a small patient group, and the change in the blood picture during the hospitalization of the patients.

In our study, it was found that especially being hypertensive, having high AISI and ferritin levels were associated with mortality. In the first publications made in patients who died due to COVID-19, diabetes and hypertension rank first among additional diseases. However, in recent studies, it has been accepted that this condition is not only associated with the course of the disease and the risk of death but increases the risk due to accompanying cardiovascular and kidney diseases. Unlike other indexes, the AISI index is an inclusive index derived from platelet, lymphocyte, neutrophil, and monocyte levels. As a result, these indexes, which can be easily calculated, may be useful for patient follow-up. However, more new multi-center, prospective studies with large numbers of patients are needed.

**Ethics Committee Approval:** The study was approved by the Ethics Committee of the Medical Faculty of Namık Kemal University (Date: 27/04/2021, decision no: 2021.107.04.02). The study was carried out in accordance with international declaration, guideline, etc.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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## Loksapin, İloperidon, Paliperidon'un İzole Farelerde Vas Deferens Kasılması Üzerine Kronik Etkileri

### Chronic Effects of Loxapine, Iloperidone, Paliperidone on Mice Isolated Vas Deferens Contractility

<sup>1</sup>Mehmet Hanifi TANYERİ, <sup>2</sup>Mehmet Emin BUYUKOKUROĞLU, <sup>2</sup>Pelin TANYERİ, <sup>2</sup>Rümeysa KELEŞ KAYA, <sup>2</sup>Şeyma Nur BAŞARIR, <sup>3</sup>Oğuz MUTLU, <sup>3</sup>Fürüzan YILDIZ AKAR, <sup>3</sup>Bekir Faruk ERDEN, <sup>4</sup>Güner ULAK

<sup>1</sup>Yenikent Government Hospital, Department of Urology, Sakarya/Turkey

<sup>2</sup>Sakarya University, Faculty of Medicine, Department of Pharmacology, Sakarya/Turkey

<sup>3</sup>Kocaeli University, Faculty of Medicine, Department of Pharmacology, Kocaeli/Turkey

<sup>4</sup>Üsküdar University, Faculty of Medicine, Department of Pharmacology, Istanbul/Turkey

Mehmet Hanifi Tanyeri: <https://orcid.org/0000-0003-2654-2724>

Mehmet Emin Buyukokuroglu: <https://orcid.org/0000-0002-1452-3879>

Pelin Tanyeri: <https://orcid.org/0000-0002-2987-5834>

Rumeysa Keles Kaya: <https://orcid.org/0000-0002-5554-1918>

Seyma Nur Basarir Bozkurt: <https://orcid.org/0000-0002-2986-5089>

Oguz Mutlu: <https://orcid.org/0000-0003-0952-0742>

Furuzan Akar: <https://orcid.org/0000-0003-0948-3857>

Faruk Erden: <https://orcid.org/0000-0002-2542-5158>

Guner Ulak: <https://orcid.org/0000-0002-6132-6712>

#### ÖZ

**Amaç:** Erektile disfonksiyon, antipsikotiklerin olağan bir yan etkisidir; bu da hastaların ilaç kullanmaktan kaçınmasına neden olur. Bu çalışmanın amacı iloperidon, paliperidon ve loksapin'in farelerde serotonin (5-HT), noradrenalin (NA), adenosin trifosfat (ATP) ve potasyum klorür (KCl) ile indüklenen vas deferens kasılmaları üzerindeki etkilerini araştırmaktır.

**Materyal ve Metot:** Fareler rastgele deney gruplarına ayrıldı ve 21 gün boyunca ip enjeksiyonu ile tedavi edildi. Tedaviden sonra, ilaçların farelerin vas deferens şeritlerinin epididimal ve prostatik bölümlerinde 5-HT, ATP, NA ve KCl ile indüklenen kasılma tepkileri üzerindeki etkileri araştırıldı.

**Bulgular:** İloperidon, paliperidon ve loksapin ile tedavi edilen gruplardan elde edilen vas deferensin her iki bölümünde 5-HT ile indüklenen kasılma tepkileri önemli ölçüde artarken ATP ile indüklenen kasılma tepkileri önemli ölçüde azaldı. Bununla birlikte, bu ilaçların, fare vas deferens'in NA ve KCl ile indüklenen kasılmaları üzerinde önemli bir etkisi olmamıştır.

**Sonuç:** Bu sonuçlar, iloperidon, paliperidon ve loksapin'in kronik tedavilerinden serotonin ve ATP kaynaklı vas deferens kasılmalarının etkilendiğini göstermiştir. Bu ilaçlarla kronik olarak tedavi edilen farelerde, serotonerjik ve purinerjik reseptörler, erektil disfonksiyona neden olan vas deferens kasılmalarındaki değişikliklere katkıda bulunabilir.

**Anahtar Kelimeler:** Erektile disfonksiyon, iloperidon, in vitro, loksapin, paliperidon

#### ABSTRACT

**Objective:** Erectile dysfunction is a usual side effect of antipsychotic medications; this causes patients to avoid using drugs. The aim of this study to investigate the effects of iloperidone, paliperidone and loxapine on serotonin (5-HT), noradrenaline (NA), adenosine triphosphate (ATP) and potassium chloride (KCl)-induced contractions of the vas deferens in mice.

**Materials and Methods:** The mice were randomly divided into experimental groups and treated by ip injection of drugs for 21 days. After the treatment, the effects of drugs were investigated on 5-HT, ATP, NA and KCl-induced contractile responses in the epididymal and prostatic portions of mice vas deferens strips.

**Results:** 5-HT-induced contractile responses were significantly increased while ATP-induced contractile responses were significantly decreased in the both portions of the vas deferens obtained from the iloperidone, paliperidone and loxapine-treated groups. However, these drugs had no significant effect on NA- and KCl-induced contractions of mice vas deferens.

**Conclusion:** These results showed that serotonin and ATP-induced contractions of vas deferens were affected by the chronic treatments of iloperidone, paliperidone, and loxapine. In mice chronically treated with these drugs, serotonergic and purinergic receptors may contribute to changes in vas deferens contractions that cause erectile dysfunction.

**Keywords:** Erectile dysfunction, iloperidone, in vitro, loxapine, paliperidone

#### Sorumlu Yazar / Corresponding Author:

Pelin Tanyeri

Department of Pharmacology, Faculty of Medicine, Sakarya University, 54100 Sakarya-Turkey.

Tel: +(90) 530 512 55 90

E-mail: pelintanyeri@yahoo.com

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## INTRODUCTION

Sexual dysfunction is a significant public health problem of patients with schizophrenia.<sup>1,2</sup> Erectile dysfunction is the usual side effect of antipsychotic medications.<sup>1,3,4</sup> Moreover, sexual dysfunctions may diminish a person's quality of life and cause sexual problems.<sup>5</sup>

Inhibition of testosterone secretion due to high prolactin levels affects sexual function, which causes a reduction in sexual desire. On the other hand, hypothalamic dopamine has an inhibitory effect on prolactin release. Antipsychotic drugs that reduce dopaminergic activity lead to an increase in prolactin levels. Contrary to the suppressive effect of dopamine on prolactin, an increase in 5-HT activity causes prolactin release.<sup>6,7</sup>

Ejaculation is provided by both the autonomic and somatic nervous systems; it consists of two phases as emission and expulsion. The emission phase is generally under the control of sympathetic nervous system through noradrenaline (NA), ATP, NO, vasoactive intestinal peptide (VIP), and neuropeptide-Y neuromediators. On the other hand, the expulsion phase is under the influence of the autonomic and somatic nervous system through the NA, acetylcholine, ATP, NO, and VIP neurotransmitters.<sup>8</sup>

Iloperidone is a second-generation "atypical" antipsychotic. Its primary mechanism of action is combined D2/5HT2A antagonism.<sup>9</sup> Iloperidone has a high affinity for both D2 and 5HT2A receptors.<sup>10</sup>

Paliperidone or 9-hydroxy risperidone is the major active metabolite of risperidone. Paliperidone acts on dopamine D2 and serotonin 5HT2A receptors as an antagonist and also antagonizes the  $\alpha$ 1- and  $\alpha$ 2-adrenergic receptors and H1-histaminergic receptors.<sup>11</sup>

Loxapine is a post-synaptic antagonist at the D2 receptor and antagonist at the serotonin 5-HT2A, histaminergic H1, cholinergic M1, and adrenergic  $\alpha$ 1 receptors. Loxapine binds to the D4 receptor with higher affinity than to other dopaminergic receptors in human and animal models.<sup>12</sup> Also, loxapine has effects on Na-K and K-ATP channels, inhibits TREK1 and TREK2 of K channels.<sup>13</sup>

Sexual dysfunction is an important side effect of antipsychotic drugs; however, pharmacology studies about ejaculatory disorders is limited to clinical studies with registered drugs affecting the ejaculation process; therefore animal studies seems essential. According to these knowledge, the aim of this

work was to investigate the effects of chronic iloperidone, paliperidone, and loxapine usage on serotonin, adenosine triphosphate (ATP), noradrenaline and KCl-induced contractions of the vas deferens in order to evaluate the effect of iloperidone, paliperidone and loxapine on the motility of the vas deferens in mice.

## MATERIALS AND METHODS

**Ethical Status:** All procedures involving animals were in compliance with the European Community Council Directive of 24 November 1986, and ethical approval was granted by the Kocaeli University Ethics Committee (Date: 22.07.2014, decision no: KOÜ HADYEK 7/4-2014).

**Animals:** Male inbred BALB/c ByJ mice (Animal Research Center, Bursa-Turkey) aged 7 weeks upon arrival to the laboratory were used in this study. Animals (4–5 per cage) were kept in the laboratory at  $21 \pm 1.5$  °C with 60% relative humidity under a 12 h light/dark cycle (light on at 8.00 p.m.) for 2 weeks before experimentation. Tap water and food pellets were available ad libitum.

**Drugs:** Iloperidone, paliperidone, loxapine, serotonin, adenosine triphosphate, noradrenaline, and potassium chloride were obtained from Sigma Chemicals (St Louis, Mo, USA). All drugs were dissolved in 0.9 % physiological saline. Saline was used as the vehicle controls. Loxapine, iloperidone, and paliperidone were given intraperitoneally (i.p.) in a volume of 0.1 ml per 10 g body weight of mice. Drugs were prepared freshly on the day of the experiment.

**Experimental Design:** The mice were randomly divided into experimental groups (n=7) as follows: saline; iloperidone 0.5 mg/kg; iloperidone 1 mg/kg; paliperidone 0.25 mg/kg; paliperidone 0.5 mg/kg; loxapine 2.5 mg/kg; loxapine 5 mg/kg. Chronic treatment was carried out by intraperitoneal drug injection (i.p.) for 21 days. The control group mice were received ip (0.9% saline) during the experiment.

Mice were sacrificed by decapitation after 21 days of treatment, followed by the removal of vas deferens from each side. Later, each vas deferens were separated into prostatic and epididymal portions of 1–2 cm in length defined by Ventura (1998).

Epididymal and prostatic portions of vas deferens were surgically dissected free and soaked in 20 mL organ baths containing Krebs'solution with a composition (mM): 113 NaCl, 4.8 KCl, 2.5 CaCl<sub>2</sub>, 1.2 KH<sub>2</sub>PO<sub>4</sub>, 1.2 MgSO<sub>4</sub>, 25 NaHCO<sub>3</sub>, 11.7 glucose equilibrated with 95%O<sub>2</sub> /5%CO<sub>2</sub> at 37°C during the

study. The upper end of the tissues was attached to an isometric force transducer (FDT 10 A Commat İletisim, Ankara, Turkey) to measure the isometric force, and the lower end was fixed. Changes in isometric tension were continuously recorded on a computer via a four-channel transducer data acquisition system (MP150 Biopac Systems Inc. Goleta) using software (ACQ4.0 Biopac Systems Inc. Goleta) capable of analyzing data.

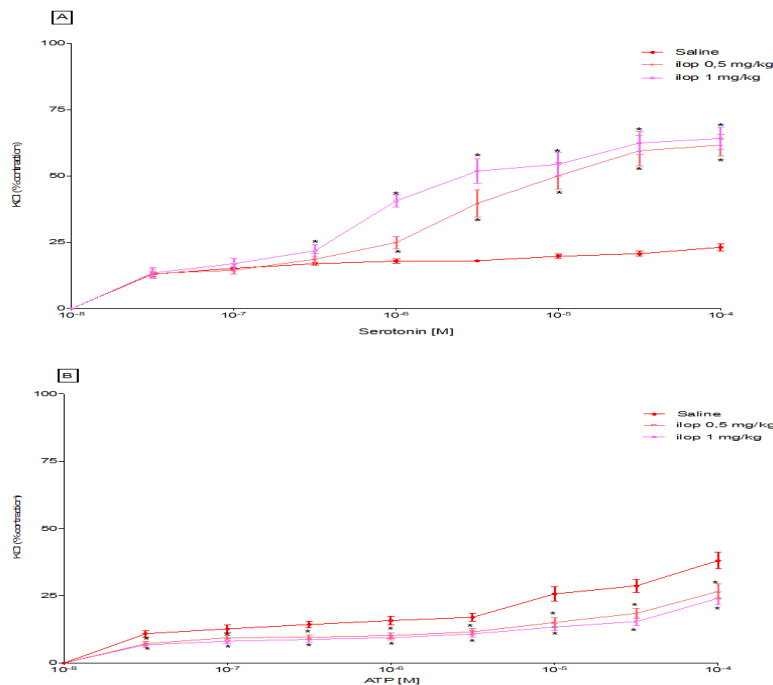
Equilibration was done that each strip was exposed with a basal tension of 1 g for 1 hour was done after the assembly. At the end of the equilibration, the strips were depolarized in Krebs solution with 80 mM KCl and left to equilibrate for 30 minutes. The Krebs Henseleit solution was replaced with a new solution every 15 minutes. After equilibration, the concentration–response curves to serotonin ( $10^8$  to  $10^4$  M), NA ( $10^8$  to  $10^4$  M) and ATP ( $10^8$  to  $10^4$  M) were obtained cumulatively. Each response was expected to plateau, then the next drug bolus was added. After the concentration-response graphs of the drugs were completed, the tissues were washed for another 30 minutes.

**Analysis of Data:** Results are expressed as the mean±standard error mean (S.E.M.) of different

experiments. Contractile responses to serotonin, ATP and noradrenaline were calculated as a percentage of the maximal contraction caused by KCl (80 mM). Statistical comparison between the groups was performed by GraphPad Prism 9 statistical program using ANOVA supported by Dunnett’s post hoc test. Results were considered to be significantly different at a p-value of <0.05.

**RESULTS**

We showed that serotonin-induced contractions were significantly increased and ATP-induced contractions were significantly decreased in both prostatic and epididymal portions of the mice vas deferens obtained from iloperidone (0.5 and 1 mg/kg) groups compared with the control group, epididymal data are shown in figure (p<0.05; Figure 1). The Emax value for serotonin was significantly higher in prostatic and epididymal portions of the mice vas deferens obtained from iloperidone treated groups than in the control group (p<0.05; Table 1). The Emax value for ATP was significantly lower in prostatic and epididymal portions of the mice vas deferens obtained from iloperidone treated groups than in the control group (p< 0.05; Table 1).



**Figure 1.** A: Serotonin concentration-responses curves of iloperidone in the isolated epididymal segment of mice vas deferens smooth muscle. B: ATP concentration-responses curves of iloperidone in the isolated epididymal segment of mice vas deferens smooth muscle. Each point is expressed as a percentage of the contraction induced by 80 mM KCl is given as the mean ± standard error of the mean (SEM). ilop: iloperidone; \* p< 0.05.

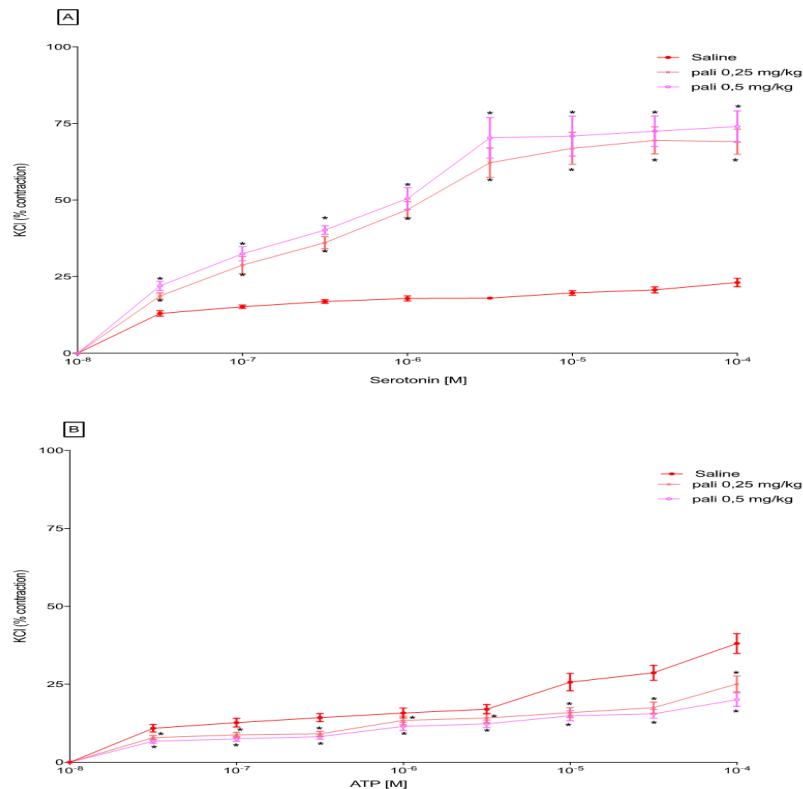
**Table 1.** The Emax (% of 80 mM KCl) values for serotonin, noradrenaline, and ATP, and Emax value (mg) for 80 mM KCl in vas deferens obtained from iloperidone, paliperidone, and loxapine treatment and control mice

	Control	Ilop 0.5	Ilop 1	Pali 0.25	Pali 0.5	Lox 2.5	Lox 5
<b>epididimal</b>							
KCl	1534±184	1412±166	1394±212	1296±234	1498±241	1462±176	1386±198
serotonin	23±2	64±5*	66±6*	71±7*	74±7*	48±4*	53±5*
ATP	38±4	28±3*	24±3*	26±3*	21±2*	30±3*	28±3*
NA	42±4	41±4	40±4	40±4	39±4	44±4	42±4
<b>prostatic</b>							
KCl	2044±314	1984±216	1896±228	1998±224	2034±246	2156±292	2324±286
serotonin	16±2	36±4*	40±4*	32±3*	34±3*	27±3*	28±3*
ATP	28±3	22±2*	19±2*	15±2*	14±2*	18±2*	16±2*
NA	19±2	16±2	15±2	18±2	17±2	17±2	16±2

Data are the mean ± standard error of the mean (SEM). NA: noradrenaline; KCl: potassium chloride; ilop: iloperidone, pali: paliperidone, lox: loxapine; \* p<0.05.

Also, serotonin-induced contractions were significantly increased and ATP-induced contractions were significantly decreased in both prostatic and epididymal portions of the mice vas deferens obtained from paliperidone (0.25 and 0.5 mg/kg) groups compared with the control group, epididymal data are shown in figure (p<0.05; Figure 2). The Emax value for serotonin was significantly higher in prostatic and epididymal portions of the mice vas deferens obtained from paliperidone treated groups than in the control group (p<0.05; Table 1).

The Emax value for ATP was significantly lower in prostatic and epididymal portions of the mice vas deferens obtained from paliperidone treated groups than in the control group (p<0.05; Table 1).

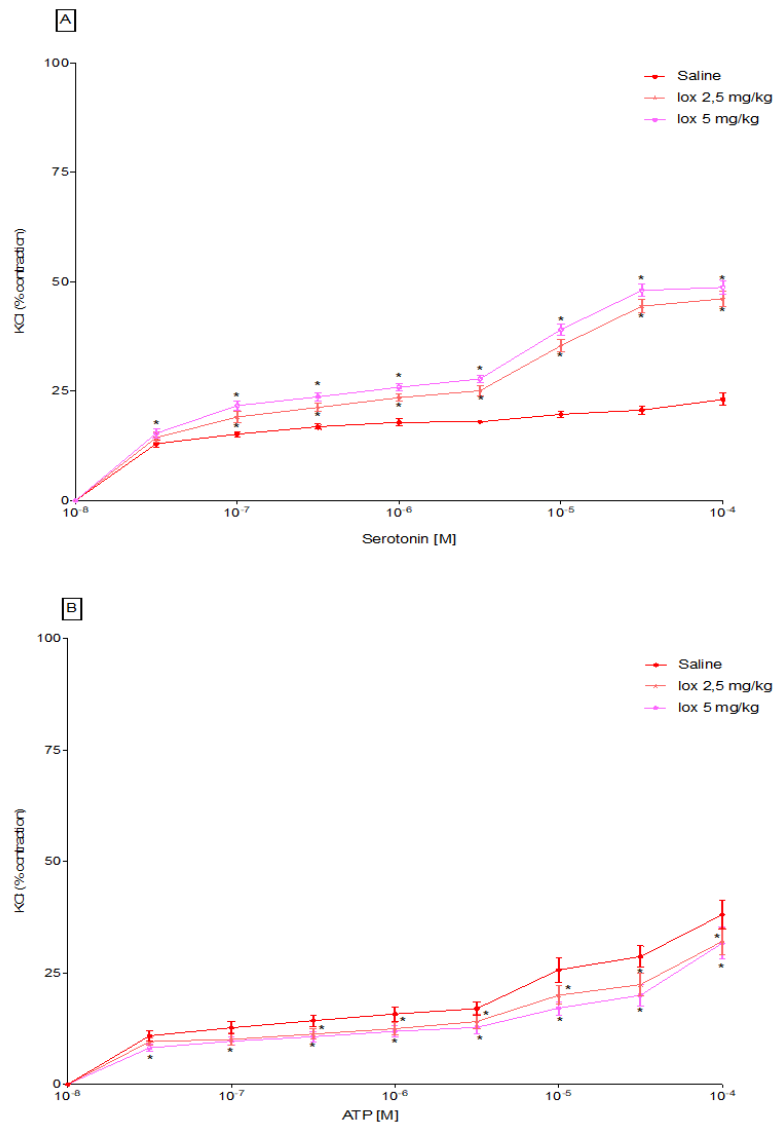


**Figure 2.** A: Serotonin concentration-responses curves of paliperidone in the isolated epididymal segment of mice vas deferens smooth muscle. B: ATP concentration-responses curves of paliperidone in the isolated epididymal segment of mice vas deferens smooth muscle. Each point is expressed as a percentage of the contraction induced by 80 mM KCl is given as the mean ± standard error of the mean (SEM). pali: paliperidone; \* p<0.05.

In addition, serotonin-induced contractions were significantly increased, and ATP-induced contractions were significantly decreased in both prostatic and epididymal portions of the mice vas deferens obtained from loxapine (2.5 and 5 mg/kg) groups compared with the control group, epididymal data are shown in figure ( $p < 0.05$ ; Figure 3). The Emax value for serotonin was significantly higher in prostatic and epididymal portions of the mice vas deferens obtained from loxapine treated groups than in the control group ( $p < 0.05$ ; Table 1). The Emax value for ATP was significantly lower in prostatic

and epididymal portions of the mice vas deferens obtained from loxapine treated groups than in the control group ( $p < 0.05$ ; Table 1).

The results of the study demonstrated that, iloperidone (0.5 and 1 mg/kg), paliperidone (0.25 and 0.5 mg/kg) and loxapine (2.5 and 5mg/kg) treatments had no effect on the noradrenaline-induced contractile responses in either portion of the vas deferens. The Emax value for noradrenaline had no effect in iloperidone, paliperidone and loxapine-treated groups than in the control group ( $p > 0.05$ ; Table 1). There were no significant differences in KCl-



**Figure 3.** A: Serotonin concentration-responses curves of loxapine in the isolated epididymal segment of mice vas deferens smooth muscle. B: ATP concentration-responses curves of loxapine in the isolated epididymal segment of mice vas deferens smooth muscle Each point is expressed as a percentage of the contraction induced by 80 mM KCl is given as the mean  $\pm$  standard error of the mean (SEM). lox: loxapine; \*  $p < 0.05$ .

induced contractile responses among the groups.

## DISCUSSION AND CONCLUSION

Psychological, pharmacological, traumatic, and hormonal factors are the cause of premature ejaculation. Erectile dysfunction is characterized by sexual reluctance, erectile dysfunction, orgasmic disorders, premature ejaculation, and/or painful ejaculation can be congenital or acquired, pervasive or situational, psychological, organic, or combined.<sup>14</sup> Neurological diseases such as autonomic neuropathy, Parkinson's disease, spinal cord trauma, usage of antihypertensive, antipsychotic, antidepressant, and alpha-blocker drugs, bladder, neck, and prostate diseases may cause sexual disorders. Premature ejaculation may be psychological or organic. For treatment of premature ejaculation, psychosexual and behavioural therapy, topical applications, antidepressants, alpha-blockers and/or sildenafil are used. Delayed ejaculation is usually psychological and may occur after SSRI usage, neuropathy, and spinal trauma.<sup>15</sup>

The importance of 5-HT pathways in the control of male sexual function has been demonstrated in previous publications. 5-HT is an inhibitory transmitter in the control of sex drive and high levels of 5-HT are associated with ejaculation inhibition. Therefore, SSRIs can be the therapy of choice for premature ejaculation because they can cause a slowing of ejaculation.<sup>16</sup>

In our study, we investigated the effects of iloperidone, paliperidone, and loxapine on vas deferens. Serotonin-induced contractions were significantly increased in both prostatic and epididymal portion of the mice vas deferens obtained from iloperidone (0.5 and 1 mg/kg) paliperidone (0.25 and 0.5 mg/kg) and loxapine (2.5 and 5mg/kg) groups compared with the control group. SSRT inhibitors impair sexual function demonstrated in a previous study.<sup>17</sup> The reason for this deterioration is the disruption of the erectile pathways in the spinal cord with the increase of 5-HT receptors.<sup>18</sup>

ATP-induced contractions were significantly decreased in both prostatic and epididymal portions of the mice vas deferens obtained from iloperidone (0.5 and 1 mg/kg) paliperidone (0.25 and 0.5 mg/kg) and loxapine (2.5 and 5mg/kg) groups compared with the control group. On the other hand, iloperidone, paliperidone, and loxapine treatments had no significant effect on NA- and KCl-induced contractions of the prostatic and epididymal portions of the mice vas deferens. It is assumed that the contraction caused by potassium is 100% contraction, the contractions of

vas deferens are evaluated according to this; these contractions are calculated as the percentage of potassium. We use potassium to test if there is a problem in the contractile mechanisms of the tissue. And also, the lack of effect of iloperidone, paliperidone or loxapine treatment on NA-induced contractions may be explained by serotonergic receptors or postreceptor mechanisms being more sensitive to these treatments than noradrenergic receptors or postreceptor mechanisms.

In summary, loxapine, iloperidone, and paliperidone increased serotonin response and decreased ATP response. These results may show the effect of these drugs on male reproductive function in patients using antipsychotic drugs. In addition, these drugs can be used in the treatment of delayed ejaculation, as they stimulate ejaculation by stimulating 5-HT neurons. Further studies can be done on this subject.

**Ethics Committee Approval:** Our study was approved by the Kocaeli University Local Ethics Committee for Animal Experiments (Date: 22.07.2014, decision no: KOÜ HADYEK 7/4-2014).

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Author Contributions:** Concept – MHT, MEB; Supervision – MHT, MEB, PT; Materials – MHT, MEB, PT; Data Collection and/or Processing – MHT, MEB, PT, RKK, ŞNBB; Analysis and/ or Interpretation – OM, FYA, BFE, GU; Writing – MHT, MEB, PT.

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## Cerrahi Girişim Uygulanan Hastalarda Ağrı ve Konfor İlişkisi

### The Relationship Between Pain and Comfort in Patients with Surgical Interference

<sup>1</sup> Hale TOSUN, <sup>2</sup> Birgül ÖDÜL ÖZKAYA, <sup>2</sup> Ferište UZ, <sup>3</sup> Asiye GÜL

<sup>1</sup> Sağlık Bilimleri Üniversitesi, Hamidiye Sağlık Bilimleri Fakültesi, İstanbul, Türkiye  
<sup>2</sup> Sağlık Bilimleri Üniversitesi, Bakırköy Dr Sadi Konuk Eğitim Araştırma Hastanesi Genel Cerrahi Kliniği, İstanbul, Türkiye  
<sup>3</sup> İstanbul Kültür Üniversitesi, Sağlık Bilimleri Fakültesi, İstanbul, Türkiye

Hale Tosun: 0000-0001-5362-6793  
Birgül Ödül Özkaya: 0000-0003-1016-5469  
Ferište Uz: 0000-0003-2781-0305  
Asiye Gül: 0000-0002-4440-5769

#### ÖZ

**Amaç:** Çalışma cerrahi girişim uygulanan hastalarda ağrı ve konfor ilişkisini değerlendirmek amacıyla yapıldı.

**Materyal ve Metot:** Bir eğitim ve araştırma hastanesinde cerrahi girişim uygulanan hastalar araştırma evrenini oluşturdu. Tanımlayıcı olan çalışmada örnekleme cerrahi girişim uygulanmış ve çalışmaya katılmayı kabul eden 132 hasta alındı. Veriler hasta tanım formu, Sayısal Derecelendirme Ölçeği ve Genel Konfor Ölçeği kullanılarak elde edildi.

**Bulgular:** Örnekleme alınan hastaların yaş ortalamaları 42,64±17,27, %53'ü erkek, %58,3'ü evlidir. Katılımcıların %72'sinin herhangi bir kronik hastalığı bulunmamaktadır. Daha önce cerrahi bir girişim uygulananların oranı %16,7'dir. Çalışmada en fazla uygulanan cerrahi işlemin laparoskopik kolesistektomi (%19,7) ve laparoskopik apendektomi (%16,7) olduğu belirlendi. Genel anestezi %80,3'üne uygulandı. Hastaların ağrı puan ortalaması 3,68±1,37, Genel Konfor Ölçeği toplam puanı 136,46±11,20 olarak belirlendi. Ameliyat sonrası hastaların %59,1'inin orta derecede ağrısı bulunmaktaydı. Ağrı ile Genel Konfor Ölçeği toplam puan ortalaması arasında negatif yönlü çok zayıf bir ilişki belirlendi ( $r=-0,175$ ;  $p=0,045$ ).

**Sonuç:** Ameliyat sonrası ağrı rahatsızlık yaratan bir durumdur. Ağrı ve konfor düzeyinin belirlenmesi, bakımın kalitesini ve hasta memnuniyetini arttırmak için önemlidir.

**Anahtar Kelimeler:** Ağrı, bakım, cerrahi, hasta, konfor

#### ABSTRACT

**Objective:** The study was conducted to evaluate the relationship between pain and comfort in patients undergoing surgical intervention.

**Materials and Methods:** Patients who underwent surgical intervention in a training and research hospital formed research universe. In the descriptive study, 132 patients who agreed to participate in study after surgery were included in sample. The data were obtained using the patient description form, Numerical Rating Scale and General Comfort Scale.

**Results:** Their mean age is 42.64±17.27, 53% are male, 58.3% are married. 72% do not have any chronic disease. The number of those who have undergone a surgical operation before is 16.7%. The most common surgical intervention in study were laparoscopic cholecystectomy (19.7%) and laparoscopic appendectomy (16.7%). General anesthesia was applied to 80.3%. The mean pain score of patients was determined as 3.68±1.37, and total score of General Comfort Scale was 136.46±11.20. Postoperatively, 59.1% of patients had moderate pain. A very weak negative correlation was found between pain and total score of General Comfort Scale ( $r=-0.175$ ;  $p=0.045$ ).

**Conclusion:** Postoperative pain is an uncomfortable situation. Determining pain and comfort level is important to increase quality of care and patient satisfaction.

**Keywords:** Pain, care, surgery, patient, comfort

#### Sorumlu Yazar / Corresponding Author:

Hale Tosun  
Mek-teb-i Tıbbiye-i Şahane, Selimiye Mah. Tıbbiye Cad. No:38  
Üsküdar, İstanbul, Türkiye 34668  
Tel: +90 216 346 36 36  
E-mail: hale.tosun@sbu.edu.tr

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## GİRİŞ

Ağrı terimi, Uluslararası Ağrı Çalışmaları Derneği tarafından her zaman rahatsız edici ve "gerçek veya potansiyel doku hasarı ile ilişkili" olarak tanımlanır.<sup>1</sup> Cerrahi işlem vücut dokusuna zarar veren, hasara neden olan ve genellikle ağrının eşlik ettiği hastalar ve sağlık profesyonelleri için sorun olan bir durumdur.<sup>2</sup> Cerrahi hastasının çoğu, mevcut tüm analjezik ilaçlara ve modern cihazlara rağmen ameliyat sonrası orta düzeyden şiddetli düzeye değişen ağrı yaşamaktadır.<sup>3</sup> Ameliyat sonrası ağrının; hasta memnuniyetini azalttığı, yaşam kalitesini düşürdüğü ve sosyal etkileşimi bozduğu, hastanede kalış süresini uzattığı, morbidite ve mortalite düzeylerini arttırdığı bildirilmektedir.<sup>3-5</sup>

Konfor, hastada stresli bir sağlık durumu olduğunda; ferahlama, rahatlatma veya üstünlük için temel ihtiyaçlarının karşılanması olarak tanımlanmaktadır.<sup>6</sup> Konfor kavramı; siyasi, teknik, bilimsel, sosyal ve dini olarak farklı anlamlara sahip olmakla birlikte sağlık bilimleri ile özellikle hemşirelikle yakından ilgilidir.<sup>7,8</sup> Konfor bakımla ilişkili karmaşık bir kavramdır. Türk Dil Kurumu konforu "günlük hayatı kolaylaştıran maddi rahatlık" olarak tanımlamıştır.<sup>9</sup> Konfor, rahatsızlığın ortadan kaldırılması ve rahatlatılması ile sağlanır.<sup>10</sup> Konfor kavramı bireyseldir ve temel bir insan ihtiyacı olarak kabul edilmektedir.<sup>6,8</sup> Konfor kişinin dinamik ve çok yönlü durumunu yansıtan bütünsel bir sonuçtur.<sup>6</sup> Kolcaba'nın konfor teorisi, hemşireleri, hastaların fiziksel, psiko-manevi, çevresel ve sosyokültürel alanlarda rahatlık ihtiyaçlarını karşılamaya teşvik etmektedir.<sup>6,8,11</sup>

Günümüzde yaygın olarak yapılan cerrahi girişimlerin hasta konforu üzerinde önemli etkisi bulunmaktadır.<sup>12</sup> Cerrahi her ne kadar yaşamı kurtarıcı/iyileştirici girişimler olsa da hastayı fiziksel ve psikososyal yönden etkilemektedir.<sup>10</sup> Ameliyat sonrası akut ağrı insidansının yüksek olduğu bildirilmektedir.<sup>5</sup> Bu durum hastanın konforunu etkiler.<sup>12</sup>

Cerrahi girişim uygulanan hastalarda konforun sağlanması ve sürdürülmesi hemşirelik bakımının amaçları arasındadır.<sup>13</sup> Ağrı, ameliyat sonrası dönemde hastaların en sık yaşadığı problemlerden biri olup yeterli ağrı yönetimi, sağlık bakımında evrensel bir gerekliliktir.<sup>14</sup>

Konfor gereksinimlerini karşılamaya yönelik hemşirelik bakımının hasta memnuniyeti ve yaşam kalitesini arttırdığı belirtilmektedir.<sup>10</sup>

Klinik uygulamada, ameliyat sonrası ağrı değerlendirmesi için tipik olarak sözlü ve sayısal derecelendirme skorları (Verbal Numerical Rating Scale [VNRS]) veya görsel analog ölçek (Visual Analog Scale [VAS]) gibi ölçüm araçları yaygın olarak kullanılması yanı sıra geçerli ve güvenilirdir.<sup>15</sup> Sıfır ila 10 arasında derecelendirilmiş bir ölçekte, konforu sağlamak için 3 veya daha düşük bir puan hedeflen-

mektedir.<sup>16</sup>

Günümüzde sağlık profesyonelleri, hastaların ağrılarını azaltmak ve konforunu sağlamak konusunda daha fazla çaba göstermektedir.<sup>17</sup> Bu nedenle çalışmada cerrahi girişim uygulanan hastalarda ameliyat sonrası ağrı ve konfor düzeyi arasındaki ilişkiyi değerlendirmek amaçlanmıştır.

## MATERYAL VE METOT

**Araştırmanın Etik Yönü:** Çalışma için kurum ve etik kurul izni (06.05.2019 tarih, karar no:2019-09) alındı. Çalışma sırasında Helsinki İnsan Hakları Bildirgesi'ne uyuldu. Araştırmanın örneklemini oluşturan hastalara araştırmanın amacı hakkında bilgi verildi. Araştırmaya katılma istekliliği ve gönüllülük ilkesi dikkate alınarak onayları alındı.

**Araştırmanın Türü:** Tanımlayıcı bir çalışmadır.

**Araştırmanın Evreni ve Örnekleme:** İstanbul Avrupa yakasında bir eğitim ve araştırma hastanesinde cerrahi girişim uygulanan hastalar oluşturdu. Örnekleme; 1 Kasım-30 Aralık 2019 tarihleri arasında cerrahi girişimin birinci gününde olan, 18 yaş ve üzeri, kronik ağrı öyküsü ve opioid kötüye kullanımı olmayan ve çalışmaya katılmayı kabul eden 132 hasta alındı.

**Veri Toplama Araçları:** Veriler hasta tanılama formu, Genel Konfor Ölçeği (GKÖ) ve Sayısal Derecelendirme Ölçeği (Numeric Rating Scale, [NRS]) kullanılarak elde edildi. Veriler ameliyat sonrası 1. günde klinikte çalışan iki hemşire tarafından hasta ile yüzyüze görüşme yöntemiyle elde edildi. Ağrının tüm cerrahi girişimlerde deneyimlenmesi nedeni ile, yapılan ameliyata bakılmaksızın, araştırmaya katılmayı kabul eden tüm hastalar örnekleme alınmıştır.

**Hasta Tanılama Formu:** Araştırmacılar tarafından oluşturulan yaş, cinsiyet, medeni durum, kronik hastalık varlığı, geçirilen cerrahi operasyon, anestezi türü, uygulanan cerrahi operasyon sorularını içermektedir.

**Genel Konfor Ölçeği (GKÖ):** Kolcaba tarafından geliştirilmiş, Kuşuoğlu ve Karabacak tarafından Türkçeye uyarlanmıştır. GKÖ dördü/altı Likert tipinde ve 24 pozitif, 24 negatif soru olmak üzere 48 maddeden oluşmaktadır. Çalışmada dördü/altı Likert tipi kullanım kolaylığı açısından tercih edilmiştir. Ölçek alt boyutları; ferahlama (16 madde), rahatlatma (17 madde) ve sorunların üstünden gelmedir (15 madde). Pozitif ifadelerde yüksek puan (4) yüksek konforu, düşük puan (1) düşük konforu, negatif maddelerde ise düşük puan (1) yüksek konforu, yüksek puan (4) ise düşük konforu işaret etmektedir. Ölçekteki negatif ifadeler ters kodlanarak toplam puan elde edilir. Ölçekten en düşük 48, en yüksek 192 puan alınabilir. Toplam puan ölçek maddelerinin sayısına bölünerek 1-4 arasında bir aralıkta belirtilir.

GKÖ'nün Cronbach's alpha katsayısı 0,85 olarak saptanmıştır.<sup>11</sup> Bu çalışmada ise Cronbach's alpha katsayısı 0,78 olarak belirlendi.

**Sayısal Derecelendirme Ölçeği:** Katılımcılar ağrılarını 0-10 cm'lik ölçek üzerinde 0 puan hiç ağrının olmaması, 10 puan en şiddetli ağrı olarak işaretlediler. Sıfır ile 10 arasındaki bir ölçekte 0 olan bir ağrı derecelendirmesi ağrısının olmadığı, 1 ile 3 arasında hafif ağrıyı, 4 ile 6 orta dereceli ağrıyı ve 7 veya daha yüksek bir ağrı derecelendirmesi ise şiddetli ağrısının olduğu anlamına gelmektedir.<sup>18</sup>

**İstatistiksel Analiz:** Verilerin değerlendirilmesinde SPSS 21.0 paket (Statistical Package for the Social Sciences) programı kullanıldı. Ölçeklerden elde edilen verilerin normal dağılıma uygunluğu Kolmogorov-Smirnov testi ve basıklık-çarpıklık değerleri ile incelendi. Hastaların tanımlayıcı verileri, ağrı ve Genel Konfor Ölçeği puanları sayı, yüzde, ortalama, standart sapma, minimum-maksimum değerleri ile gösterildi. Ölçekler arasındaki ilişkiyi belirlemek için Pearson korelasyon analizi yapıldı. Ağrı derecesine göre Genel Konfor Ölçeği puan ortalamaları arasındaki fark Kruskal Wallis varyans analizi ile değerlendirildi. Araştırma sonuçlarında %95

güven aralığında,  $p < 0,05$  değeri istatistiksel olarak anlamlı kabul edildi.

## BULGULAR

Örneklem grubunun yaş ortalaması  $42,64 \pm 17,27$ , 70'i erkek (%53), 77'si (%58,3) evlidir. Katılımcıların 95'inin (%72) herhangi bir kronik hastalığı yoktur. Daha önce cerrahi bir operasyon geçirenlerin sayısı 22 (%16,7)'dir. Çalışmada en fazla uygulanan cerrahi işlemin laparoskopik kolesistektomi (%19,7;  $n=26$ ), laparoskopik apendektomi (%16,7;  $n=22$ ) ve total tiroidektomi (%12,1;  $n=16$ ) olduğu belirlendi. Genel anestezi %80,3'üne ( $n=106$ ) uygulandı (Tablo 1).

Hastaların ameliyat sonrası birinci günde ağrı puanı ortalaması (NRS puan ortalaması)  $3,68 \pm 1,37$  (min=0; maks=9), Genel Konfor Ölçeği toplam puanı  $136,46 \pm 11,20$  (min=105; maks=176) olarak belirlendi. Genel Konfor Ölçeği puanları 1-4 arasında derecelendirildiğinde ortalama puanın  $2,84 \pm 0,23$  (min=2,19; maks=3,67) olduğu saptandı (Tablo 2) Ağrı ile Genel Konfor Ölçeği toplam puanı arasında negatif yönlü istatistiksel olarak anlamlı çok zayıf bir ilişki belirlendi ( $r=-0,175$ ;  $p=0,045$ ) (Tablo 3). Ağrı derecesine göre Genel Konfor Ölçeği toplam

**Tablo 1.** Hastaların sosyo-demografik bilgileri.

Özellikler	$\bar{x} \pm SS$ (Min-Maks)	n (%)
Yaş	$42,64 \pm 17,27$ (18-87)	
Kadın		62 (47,0)
Erkek		70 (53,0)
Evli		77 (58,3)
Bekar		55 (41,7)
Kronik hastalığı var		37 (28,0)
Kronik hastalığı yok		95 (72,0)
Daha önce cerrahi operasyon uygulanan		22 (16,7)
Daha önce cerrahi operasyon uygulanmayan		110 (83,3)
Anestezi türü		
Genel		106 (80,3)
Spinal		26 (19,7)
Uygulanan cerrahi operasyon		
Laporoskopik kolesistektomi		26 (19,7)
Laporoskopik apendektomi		22 (16,7)
Total troidektomi		16 (12,1)
Pilonidal sinüs		14 (10,6)
Mastektomi		11 (8,3)
Herni		11 (8,3)
Total gastrektomi		7 (5,3)
Tamamlayıcı laparoskopik		5 (3,8)
Kolektomi		5 (3,8)
Diğer*		15 (11,4)

\*Whipple, hemoroidektomi, gastrektomi, gastrointestinal kanama, fistülektomi, omentoplasti

**Tablo 2.** Ağrı ve Genel Konfor Ölçeği puan ortalamaları ( $n=132$ ).

	$\bar{x} \pm SS$	Min-maks
<b>Ağrı puanı</b>	$3,68 \pm 1,37$	0-9
<b>Genel Konfor Ölçeği puanı</b>	$136,46 \pm 11,20$	105-176
<b>Genel Konfor Ölçeği (1-4)</b>	$2,84 \pm 0,23$	2,19-3,67

**Tablo 3.** Sayısal Derecelendirme Ölçeği ve Genel Konfor Ölçeği arasındaki korelasyon katsayılarının dağılımı.

	n	r	p
Sayısal Derecelendirme Ölçeği (Ağrı Seviyesi)	132	-,175	,045
Genel Konfor Ölçeği			

**Tablo 4.** Ağrı derecesine göre Genel Konfor Ölçeği puanları.

Ağrı düzeyi	Genel Konfor Ölçeği puanları					
	n (%)	$\bar{x} \pm SS$	Median	min-maks	Kw	p
Ağrı yok (0)	4 (3,0)	139,0 $\pm$ 7,30	139	131,0-147,0	3,473	0,324
Hafif ağrı (1-3)	49 (37,1)	137,48 $\pm$ 9,99	138	123,0-176,0		
Orta derecede ağrı (4-6)	78 (59,1)	136,08 $\pm$ 11,62	136,5	111,0-163,0		
Şiddetli ağrı (7 ve üstü)	1 (0,8)	105,0	105	105,0		

puanları arasında istatistiksel olarak anlamlı bir fark belirlenmedi (Kw=3,473; p=0,324) (Tablo 4).

### TARTIŞMA VE SONUÇ

Ağrı, "rahatsız edici" ve "gerçek veya potansiyel doku hasarıyla ilişkili" olarak tanımlanmaktadır.<sup>19</sup> Fiziksel ağrı psikolojik, sosyal ve ruhsal sıkıntı ile yakından ilgilidir.<sup>20</sup> Postoperatif ağrı kontrolü için doğru ve güvenilir değerlendirme yöntemlerinin kullanılmasının gerekli olduğu bildirilmektedir.<sup>16</sup> Çalışmada grubun yarısından fazlasının orta derecede ağrı yaşadığı belirlenmiştir. Ameliyat sonrası dönemde hastaların sıklıkla orta ila şiddetli derecede ağrıları olmaktadır, bu ağrıyı değerlendirmek de hemşirelerin sorumluluğundadır.<sup>4</sup> Ağrı deneyimi karmaşıktır ve doğru sonuçlar için doğru bir ölçüm aracı gereklidir. Klinik uygulamada ağrının değerlendirilmesinde Görsel Analog Ölçek (VAS) veya Sayısal Derecelendirme Ölçeği (NRS) gibi basit ölçekler yaygın olarak kullanılmaktadır.<sup>21</sup>

Gürkan ve ark. Sayısal Derecelendirme Ölçeğinin ameliyat sonrası akut ağrının değerlendirilmesinde ilk tercih edilebilecek ölçüm aracı olabileceğini bildirmişlerdir.<sup>5</sup> Bu çalışmada orta derecede ağrısı olanlar çoğunlukta olmakla birlikte hafif ağrısı olanların sayısı da azımsanmayacak kadar yüksektir. Ayhan ve Kursun abdominal cerrahi sonrası, Görsel Analog Ölçeğine göre hastaların ortalama ağrı puanını 4,40 $\pm$ 2,7 olarak belirlemişlerdir.<sup>4</sup> Ağrı değerlendirmesinde fizyolojik göstergelerin geçerliliğine yönelik olarak ağrının, kan basıncı ve nabız gibi hemodinamik ölçümlerde de anlamlı farklar oluşturduğu tespit edilmiştir.<sup>22</sup>

Subramanian ve ark. (ameliyat sonrası ilk 24 saatte hastaların tamamının ciddi ağrıları olduğunu saptamışlardır.<sup>3</sup> Karabulut ve ark. açık kalp cerrahisi uygulanan hastalarda ağrı puanlarını ameliyattan hemen sonra 7,07 $\pm$ 2,6, ameliyat sonrası ilk mobilizasyonunda 6,71 $\pm$ 2,7 olarak saptamışlardır.<sup>23</sup> Ağrı fizyolojisi, farmakoloji, cerrahi teknikler ve ameliyat öncesi ve sonrası bakımdaki ilerlemelere rağmen, bazı çalışmalar hala cerrahi işlemleri takiben ağrı kontrolünün yetersiz olduğunu ve ameliyat sonrası hastaların %50-90'ının orta ila şiddetli ağrı yaşadığını bildirmektedir.<sup>4</sup> Çalışma sonuçları literatürle uyumludur. Bununla birlikte, her hastanın bireysel olarak değerlendirilip ağrı kontrollerinin sağlanması gerektiği açıktır. İyi bir değerlendirme ve bireyselleştirilmiş ağrı giderici yaklaşımların uygulanması hasta konforunu arttıracaktır.<sup>20</sup>

Kolcaba konforu; "bireyin gereksinimlerine yönelik yardım etme, huzur sağlama ve sorunların üstesinden gelebilmeye ilişkin fiziksel, psikospiritüel, sosyal ve çevresel bütünlük içinde karmaşık bir yapıya sahip beklenen bir sonuç" olarak tanımlamıştır.<sup>6</sup> Hasta, cerrahi girişimler sonucu konforunun bozulmasına neden olan fizyolojik, psikolojik ve sosyal yönden birçok sorunla karşılaşır.<sup>10</sup> Bu çalışmada ameliyat sonrası konfor düzeyi orta düzeyde bulunmuştur. Büyükcünal Şahin ve Rızalar'ın çalışmasında ameliyat sonrası dönemde konfor düzeyleri orta ve üzerinde bulunmuştur.<sup>10</sup> Yılmaz ve ark. ameliyat sürecinde hastaların konfor düzeyinin orta düzeyde olduğunu belirlemişlerdir.<sup>24</sup> Kubat Bakır ve Yurt'un çalışmasında cerrahi işlem sonrası konfor puan ortalamasının 128,91 olduğu saptanmıştır.<sup>12</sup> Genel olarak çalışmalarda ameliyat sonrası hastaların orta düzeyde konfora sahip olduğu ve cerrahinin hasta konforunun bozulmasında önemli bir faktör olduğu görülmektedir.

Ağrı, konfor gereksiniminin karşılanmasında ortaya çıkan ilk sorundur.<sup>12</sup> Çalışmada ağrı ile konfor arasında negatif yönlü zayıf bir ilişki bulunmuştur. Bu durum örneklem grubunun farklı cerrahi operasyon geçiren hastalardan oluşmasının yanı sıra konfor algıları ve ağrı deneyimi gibi bireysel farklılıklardan

kaynaklanabileceği düşünülmektedir. Miu ve ark. konfor ve ağrı skorları arasında orta düzeyde bir ilişki olduğunu saptamışlardır. Ayrıca ağrıyı spontan olarak ifade etmeyen hastalara ameliyat sonrası değerlendirilmenin bir parçası olarak konforunun sorulabileceğini, bu yaklaşımın, "ağrı" kelimesinden ve olası nosebo (nocebo) etkilerinden kaçınma avantajı da sağlayabileceğini ileri sürmüşlerdir. Nosebo, plasebonun (placebo) tersi, negatif beklentilerin hastayı negatif etkilemesidir.<sup>1</sup> Bu etkiler, farmakolojik tedavinin etkinliğini ve psikolojik/fiziksel girişimlerin etkinliğini önemli ölçüde azaltma potansiyeline sahiptir.<sup>25</sup> Karabulut ve ark. açık kalp cerrahisi uygulanan hastalarda taburculuk öncesi ağrı ve konfor seviyesi arasında istatistiksel olarak anlamlı bir ilişki saptamamışlardır.<sup>23</sup> Büyükünül Şahin ve Rızaların çalışmasında şiddetli ağrısı olan hastaların konfor düzeyinin düşük olduğu belirlenmiştir.<sup>10</sup> Ağrı hasta konforunu etkilemektedir.<sup>16</sup> Bu nedenle, ağrı kontrolünün sağlanması için hemşirelik girişimlerinin uygulanması hasta konforu açısından önemlidir. Sonuç olarak; ağrı ve konfor birbiri ile yakından ilişkilidir. Ameliyat sonrası ağrı ve konfor düzeyinin belirlenmesi, bakımın kalitesini ve hasta memnuniyetini arttırmak için gereklidir. Hastaların bireysel olarak değerlendirilip ağrısının azaltılması konforunu da arttırmada etkili olabilir. Çünkü ağrı ve konfor algısı bireysel özellikler ve deneyimler ile ilişkilidir. Araştırma sadece bir eğitim araştırma hastanesinde yapılmış olmasından dolayı sonuçlar genellenemez.

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**Çıkar Çatışması:** Yazarlar çıkar çatışması bildirmemişlerdir.

**Yazar Katkıları:** Fikir ve tasarım: HT, AG; Veri toplama ve işlenmesi: BÖÖ, FU; Analiz ve yorum: HT, AG; Kaynak tarama: HT, AG; Makaleyi yazan: HT, AG, BÖÖ, FU.

**Hakem Değerlendirmesi:** Dış bağımsız.

**Teşekkür:** Bu çalışmada yer alan tüm katılımcılara teşekkür ederiz.

**Diğer Bilgi:** Tüm katılımcılardan onam alınmıştır.

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## Annelerin Beslenme Davranışları ve Çocuklarının Beslenme Sürecine Yönelik Tutumları Arasındaki İlişki

### The Relationship Between Mothers' Feeding Behaviors and Their Children's Attitudes Towards Feeding Process

<sup>1</sup>Gamze FIŞKIN, <sup>2</sup>Zeynep ÖLÇER

<sup>1</sup>Amasya Üniversitesi Sağlık Bilimleri Fakültesi, Ebelik Bölümü, Amasya, Türkiye  
<sup>2</sup>Ankara Medipol Üniversitesi Sağlık Bilimleri Fakültesi, Hemşirelik Bölümü, Ankara, Türkiye

Gamze Fışkın: <https://orcid.org/0000-0003-3065-6484>

Zeynep Ölçer: <https://orcid.org/0000-0003-0594-2606>

#### ÖZ

**Amaç:** Araştırma kapsamında annelerin sağlıklı beslenme tutumlarının değerlendirilerek çocuklarına yönelik beslenme tutumları arasındaki ilişkinin incelenmesi amaçlanmıştır.

**Materyal ve Metot:** Ağustos 2021 tarihleri arasında araştırmaya dâhil edilme kriterlerini karşılayan anneler oluşturulmuştur (n=233). Veriler anne bilgi formu, Sağlıklı Beslenmeye İlişkin Tutum Ölçeği (SBİTÖ) ve Beslenme Süreci Anne Tutumları Ölçeği (BSATÖ) kullanılarak toplanmıştır. Oluşturulan anketler pandemi tedbirleri gereği online olarak sosyal medya üzerinden dağıtılmıştır.

**Bulgular:** Annelerin SBİTÖ ve BSATÖ'den aldıkları toplam puan ortalamaları sırasıyla 83,862 ±9,158 ve 61,660 ±18,929'du. Annelerin yaşı, eğitim ve gelir düzeyleri, beslenme davranışları, çocukların yaşları gibi değişkenlerin beslenme tutum ve davranışlarını etkilediği, fakat annelerin beslenme tutumlarıyla çocuklarının beslenmesine yönelik tutumları arasındaki anlamlı bir ilişkinin olmadığı tespit edilmiştir (r= -0,040 p= 0,545).

**Sonuç:** Araştırmadaki annelerin sağlıklı beslenmeye yönelik bilgi düzeylerinin zayıf olduğu, çocuklarının beslenmesinde kısmen olumsuz tutum sergiledikleri ve kendi beslenme davranışlarıyla çocuklarına yönelik sergiledikleri davranışlar arasında ilişki olmadığı sonucuna varılmıştır.

**Anahtar Kelimeler:** Anne, beslenme davranışı, çocuk, tutum

#### ABSTRACT

**Objective:** It was aimed to evaluate the healthy nutrition attitudes of mothers and to examine the relationship between nutritional attitudes towards their children.

**Materials and Methods:** The sample of the descriptive, cross-sectional and correlational study consisted of mothers who met the inclusion criteria between 05 June-05 August 2021 (n=233). The data were collected using the mother information form, the Attitude Scale for Healthy Nutrition (ASHN) and the Mother's Attitudes Towards the Feeding Process Scale (MATFPS). The questionnaires created were distributed online via social media due to pandemic measures.

**Results:** The mean total scores of the mothers in ASHN and NATFPS were 83.862 ±9.158 and 61.660 ±18.929, respectively. It has been determined that variables such as mothers' age, education and income levels, nutritional behaviors, and children's age affect nutritional attitudes and behaviors, but there is no significant relationship between mothers' nutritional attitudes and their attitudes towards feeding their children (r= -0.040 p= 0.545).

**Conclusion:** It was concluded that the mothers in the study had a less level of knowledge about healthy nutrition, they have partially a negative attitude towards the nutrition of their children, and there was no relationship between their own nutritional behaviors and the behaviors they displayed towards their children.

**Keywords:** Child, feeding behavior, mother, attitude

#### Sorumlu Yazar / Corresponding Author:

Gamze Fışkın  
Amasya Üniversitesi Sağlık Bilimleri Fakültesi İpekköy Yerleşkesi  
05100 Amasya, Türkiye  
Tel: +9 0358 218 1767  
E-mail: gamzefiskin@gmail.com

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## GİRİŞ

Sağlıklı beslenme; bireyin yaşı, cinsiyeti ve fizyolojik durumu göz önünde bulundurularak ihtiyacı olan tüm besin öğelerinin yeterli miktarda karşılanması, yağ oranı düşük, lif açısından zengin, meyve ve sebze tüketimi yüksek bir diyet olarak tanımlanmaktadır.<sup>1</sup> Bu beslenme şekli çocukluk sürecinden itibaren bireylerin kazanarak yaşam boyu sürdürmeleri gereken bir sağlık davranışı olarak bilinmektedir. Dengeli ve sağlıklı beslenme çocukların bü-yüme ve gelişmelerini sağlıklı bir şekilde sürdürebilmesi, hastalıklardan korunması ve kaliteli bir yaşam sürdürebilmelerinde son derece önemlidir.<sup>2</sup> Yetersiz beslenen çocuklar zihinsel sağlık problemlerinin yanı sıra okul başarısında düşme, okulu bırakma gibi birçok durum açısından risk altındadır.<sup>3</sup> Ayrıca çocukluk dönemdeki yanlış veya yetersiz beslenme yetişkinlik dönemindeki obezite, hipertansiyon ve kardiyovasküler hastalıklar ya da diyabet gibi endokrin hastalıkların temelini de oluşturmaktadır.<sup>4</sup> Pek çok faktörün beslenme alışkanlıklarını etkilediği bilinmektedir.<sup>5</sup> Sağlıklı beslenme davranışının ilk adımı olarak görülen tutum geliştirme sürecinde çocukların ebeveynlerinin yeme davranışlarını, yaşam tarzlarını ve beden imajıyla ilgili memnuniyet durumlarını model aldıkları bildirilmektedir.<sup>1,5</sup> Yapılan çalışmalarda; aile üyelerinin çocuklar için olumlu model olmaları, sağlıklı gıda tüketimi yapmaları ve sağlıklı beslenme davranışları kazandırmaları konusunda destekleyici tavır sergilemeleri gerekliliği üzerinde durulmaktadır.<sup>5</sup> Örneğin, Bowne'nin çalışmasında; çocukların yeme alışkanlıklarıyla ebeveyn tutumları arasında bir ilişki bulunduğu, bu alışkanlıkların üzerinde ise otoriter tutumun çok etkili olduğu gösterilmiştir.<sup>6</sup> Beslenme üzerinde etkili olan bir diğer faktör de ebeveynlerin cinsiyetidir. Babaların ve annelerin beslenme konusunda çocuklarına karşı farklı davrandıkları görülmektedir. Babaların genellikle çocuklarına karşı daha hoşgörülü davrandıkları ve gıda alımı üzerinde daha az aktif kontrol uyguladığı annelerin ise daha kontrolcü ve otoriter olduğunu gösteren kanıtlar sunulmuştur. Bu kanıtlarda, annelerin yemek zamanlarında beslenme sürecinde olan çocuklarını doğrudan etkilediği ve diğer çocukları da beslenme konusunda dolaylı olarak etkilediği görülmektedir.<sup>5</sup> Ebeveyn beslenme uygulamaları ve beslenme bilgisi de çocukların beslenme davranışları ve yiyecek tercihleri üzerinde etkili olmaktadır.<sup>7</sup> Bireyler kendi sevmediği besinleri çocuklarına sunmadıklarından çocukların bu besin-leri deneme şansı

olmamaktadır. Bu bakımdan annenin beslenme biçiminin çok erken yaşlardan itibaren çocuğun beslenme biçimini de etkilediği söylenebilmektedir.<sup>8</sup>

Araştırma kapsamında; annelerin sağlıklı beslenme davranışlarını belirlemek, çocuklarının beslenme sürecine yönelik tutumlarını anlamak ve kendi beslenmeleriyle çocuklarına sergiledikleri tutum arasındaki ilişkiyi görebilmek amaçlanmıştır.

## MATERYAL VE METOT

**Etik Durum:** Bu araştırma Amasya Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu tarafından onaylanmış olup (Tarih: 06.05.2021, karar no: 69) Helsinki deklarasyonuna uygun şekilde gerçekleştirilmiş ve katılımcıların onamları alınmıştır.

Tanımlayıcı, kesitsel ve ilişki arayıcı tipte tasarlanmış olan araştırmanın evrenini; Türkiye'deki 2-6 yaş arası çocuğu bulunan anneler, örneklemini ise; 5 Haziran 2021-5 Ağustos 2021 tarihleri arasında araştırmaya katılmayı kabul eden anneler oluşturmuştur. Örneklem kriterlerini karşılayan 242 annenin 9 tanesi araştırmaya katılmayı kabul etmediğinden çıkartılmış ve araştırma toplam 233 anneyle tamamlanmıştır (n=233). Pandemi tedbirleri nedeniyle internet tabanlı anket yazılımı olan google forms aracılığıyla toplanan veriler istatistik programına aktarılarak analizleri yapılmıştır.

**Veri Toplama Araçları:** Veriler anne bilgi formu, Sağlıklı Beslenmeye İlişkin Tutum Ölçeği (SBİTÖ), Beslenme Süreci Anne Tutumları Ölçeği (BSATÖ) kullanılarak toplanmıştır.

**Anne Bilgi Formu:** Araştırmacılar tarafından literatür incelemesi sonucunda hazırlanan form sosyodemografik, obstetrik ve araştırmayla ilişkili olduğu düşünülen toplam 28 sorudan oluşmaktadır.<sup>2,9,10</sup>

**Sağlıklı Beslenmeye İlişkin Tutum Ölçeği (SBİTÖ):** 21 maddeden oluşan anket 5'li likert tipte olup 4 faktörden oluşmaktadır. Bu faktörler, Beslenme Hakkında Bilgi (BHB), Beslenmeye Yönelik Duygu (BYD), Olumlu Beslenme (OB) ve Kötü Beslenme (KB) olarak adlandırılmıştır. Ölçekten alınabilecek puanlar 21-105 arasında değişmektedir. Demir ve Cicioğlu tarafından geçerliği yapılan ölçekten alınan yüksek puanlar sağlıklı bir beslenme biçimine sahip olduğunu göstermektedir.<sup>1</sup> Ölçeğin güvenilirlik katsayıları, BHB faktöründe 0,90, BHB faktöründe 0,84, OB faktöründe 0,75 ve KB faktöründe 0,83 olarak bildirilmiştir. Ölçeğe ait cronbach alfa katsayısı 0,90 olup bu çalışmada 0,80



olarak belirlenmiştir. Alt faktörlerin güvenilirlik katsayıları ise; BHB 0,93, BYD 0,71, OB 0,80 ve KB 0,77 şeklinde hesaplanmıştır.

**Beslenme Süreci Anne Tutumları Ölçeği (BSATÖ):** Dilsiz ve Dağ tarafından geçerliliği yapılan ölçek 5’li likert tipte olup 27 maddeden oluşmaktadır. Ölçeğin alt faktörleri ve güvenilirlik katsayıları ise şöyledir; “Öğün Sırasındaki Negatif Duygu Durumu (ÖSNDD)” 0,92, “Yetersiz/Dengesiz Beslenmeye İlişkin Tutumlar (YDBİT)” 0,84, “Negatif Besleme Stratejileri (NBS)” 0,72, “Zorla Besleme (ZB)” 0,70 ve “Diğerlerinin Görüşüne Tepki (DGT)” 0,91’dir. BSATÖ’den alınabilecek puanlar 27 ve 135 arasında değişmektedir. BSATÖ’nün her bir faktör ve ölçek toplam puanı açısından artması, annelerin beslenme sürecine dair göstermiş olduğu tutumlarda sorun olduğunu ifade etmektedir.<sup>11</sup> Ölçeğe ait cronbach alfa iç tutarlılık katsayısı 0,91, bu çalışma için ise 0,93 olarak belirlenmiştir. Ölçek alt faktörlerinin güvenilirlik katsayıları ise sırasıyla; ÖSNBD 0,90, YDBİT 0,90, NBS 0,84, ZB 0,87 ve DGT 0,74’tür.

**Verilerin Analizi:** Araştırma verileri SPSS 15.0 (Statistical Package for the Social Sciences) kullanılarak analiz edilmiştir. Tanımlayıcı veriler; sayı, yüzde, ortalama, standart sapma, minimum, maksimum değerler ile gösterilmiş ve verilerin normal dağılıma uygunluğu test edilmiştir. İstatistiksel anlamlılık düzeyi 0,05 olarak kabul edilerek bağımlı ve bağımsız değişkenlerin arasındaki fark non-parametrik analizlerden Kruskal Wallis ve Mann Whitney U testi kullanılarak incelenmiştir. Değişkenler arasındaki ilişkinin belirlenmesi için Spearman korelasyon testi kullanılmıştır.

## BULGULAR

Araştırmaya katılan annelerin yaş ortalamalarının  $33,523 \pm 3,758$  (min= 26, max= 40), eşlerinin yaş ortalamalarının ise;  $36,077 \pm 4,114$  (min= 29, max= 44) olduğu tespit edilmiştir. Annelerin çoğunluğunun lisans mezunu (%60,5) olduğu ve çalışmadığı (%73,8), gelirlerinin giderlerine eşit (%54,9) olduğu saptanmıştır. %65,2’sinin sigara, %58,8’inin alkolü hiç kullanmadığı, eşlerinin %49,8’inin lisans me-

**Tablo 1.** Bağımsız değişkenlere ait verilerin dağılımı.

Değişkenler		n	%
Eğitim durumu	Lise	22	9,4
	Lisans	141	60,5
	Lisansüstü	70	30,1
Çalışma durumu	Çalışmıyor	61	26,2
	Çalışıyor	172	73,8
Gelir durumu	Gelir giderden az	26	11,2
	Gelir gidere eşit	128	54,9
	Gelir giderden fazla	79	33,9
Sigara kullanma durumu	Hiç kullanmayan	152	65,2
	Artık kullanmayan	33	14,2
	Hala kullanan	48	20,6
Alkol kullanma durumu	Hiç kullanmayan	137	58,8
	Artık kullanmayan	21	9,0
	Sosyal kullanıcı	75	32,2
Eşin eğitim durumu	Lise	62	26,6
	Lisans	116	49,8
	Lisansüstü	55	23,6
Eşin çalışma durumu	Çalışmıyor	8	3,4
	Çalışıyor	225	96,6
Aile tipi	Çekirdek	228	97,9
	Geniş	5	2,1
Planlı gebelik	Evet	220	94,4
	Hayır	13	5,6
Gebe kalma şekli	Spontan	218	93,6
	Tedaviyle	15	6,4
Toplam gebelik sayısı	Bir	104	44,6
	İki ve üzeri	129	55,4
Yaşayan çocuk sayısı	Bir	127	54,5
	İki ve üzeri	106	45,5
Çocukların yaşları	2	64	27,5
	3	56	24,0
	4	52	22,3
	5	43	18,5
<b>Total</b>		233	100

zunu olduğu ve %96,6'sının çalıştığı bulunmuştur. %97,9'u çekirdek aile yapısında olup %94,4'ünün planlı gebelik geçirdiği, %55,4'ünün iki ve üzerinde gebelik yaşadığı, %54,5'inin ilk yaşayan çocuğu olduğu ve %27,5'inin 2 yaşında çocuğa sahip olduğu belirlenmiştir (Tablo 1).

Araştırmadaki kadınların SBİTÖ toplam puan ortalaması 83,862 ±9,158 (min: 58 max: 100) olarak hesaplanmış ve beslenme hakkında bilgi 22,137±2,805 (min: 10, max: 25) alt faktöründen en yüksek ortalamaya sahip olduğu saptanmıştır (Tablo 2). Araştırmadaki kadınların BSATÖ toplam puan ortalaması 61,660±18,929 (min: 27 max: 117) olarak hesaplanmış ve yetersiz/dengesiz beslenmeye ilişkin tutum 23,939 ±7,949 (min: 8, max: 40) alt faktöründen en yüksek ortalamaya sahip olduğu saptanmıştır (Tablo 2).

Tablo 3'e göre; SBİTÖ toplam puan ortalamasının annelerin gelir durumu, eşlerinin çalışma durumu, gebeliğin planlı olması gibi faktörlerle ilişkili olduğu tespit edilmiştir. İkidenden fazla gruplu olan değişkenlerde anlamlılığın neden olduğu grubu belirlemek için Tamhane's T2 post hoc analizi uygulanmıştır.

Annelerin çocuklarının beslenme sürecine yönelik tutumları; yaş, çalışma durumu, gelir durumu, eşin eğitim düzeyi ve çocukların yaşlarıyla ilişkili olduğu görülmüştür (Tablo 4).

Araştırmaya katılan annelerin beslenme tutumlarıyla çocuklarının beslenmesine yönelik tutumları arasındaki ilişki Spearman korelasyon testiyle analiz edilmiş ve istatistiksel olarak anlamlılık görülmüştür ( $r = -0,077$   $p = 0,239$ ).

## TARTIŞMA VE SONUÇ

Bu araştırmamız, annelerin sağlıklı beslenme durumlarıyla çocuklarının beslenme sürecine yönelik tutumları arasındaki ilişkiyi belirlemek amacıyla yapılmıştır. Çocukların beslenmesinden birinci derecede sorumlu olan ebeveynlerin kendi beslenmelerine yönelik sergiledikleri tutumun çocuklarını da etkileyebileceği fikrinden yola çıkılmıştır. Araştırmamızın sonucunda; annelerin beslenme hakkında bilgi düzeylerinin yüksekliği olumlu etki yaratırken, yetersiz ve dengesiz beslenmeye ilişkin tutum ortalamalarının yüksek olması çocukların beslenme davranışlarını olumsuz etkileyebileceğine işaret etmektedir. Literatürde ebeveynlerin kendi inançları, beslenme tutumları, besin tüketim uygulamaları, bakış açıları ya da bilgilerinin çocuklarının beslenme sürecinde önemli bir etkiye sahip olduğu bildirilmiştir.<sup>12</sup> Hatta annelerin beslenme bilgisinin artmasıyla çocuklar için daha sağlıklı diyet seçimleri yaptıkları görülmektedir.<sup>7</sup> Bu nedenle çocukluk çağından itibaren sağlıklı ve dengeli beslenme konusunda ebeveynlerin bilgilendirilmesi son derece önem taşımaktadır. Prekonsepsiyonel ve gebelik döneminde devam ettirilen bilgilendirme eğitimlerine postpartum süreçte bebek ve çocuk beslenmesi konularının eklenmesi ebeveynler için yol gösterici olacaktır.

Ebeveynlerin sosyo-ekonomik düzeylerinin yetersiz olması sağlıklı yiyeceklere erişim ve alma konusunda ciddi sorunlar yaratacağından çocuk beslenmesini de olumsuz şekilde etkileyebilmektedir.<sup>7,13</sup> Bu araştırmamızda geliri giderine eşit olan kadınlarda BYD faktörünün ortalamasının yüksek olduğu, geliri fazla

**Tablo 2.** Ölçekler ve alt faktörlerinin puan ortalamaları.

	Ölçekler ve alt faktörleri	X ± SS	Min-Max
Sağlıklı Beslenmeye İlişkin Tutum Ölçeği	Beslenme hakkında bilgi	22,137±2,805	10-25
	Beslenmeye yönelik duygu	19,532±4,172	10-30
	Olumlu beslenme	20,532±3,841	6-25
	Kötü beslenme	21,660±3,459	6-25
	Toplam ortalama	83,862±9,158	58-100
Beslenme Süreci Anne Tutumları Ölçeği	Öğün arasındaki negatif duygu durumu	13,549±5,337	6-27
	Yetersiz/dengesiz beslenmeye ilişkin tutumlar	23,939±7,949	8-40
	Negatif beslenme stratejileri	10,283±4,810	5-25
	Zorla besleme	5,068±2,182	4-16
	Diğerlerinin görüşüne tepki	8,819±3,822	4-20
	Toplam ortalama	61,660±18,929	27-117

Tablo 3. Annelerin bağımsız değişkenlerinin SBİTÖ toplam puan ve alt faktörleriyle karşılaştırılması.

Değişkenler	BHB			BYD			OB			KB			SBİTÖ		
	Sıra Ort.SD	Z/X <sup>2</sup> p	Sıra Ort. SD	Z/X <sup>2</sup> p	Sıra Ort. SD	Z/X <sup>2</sup> p	Sıra Ort. SD	Z/X <sup>2</sup> p	Sıra Ort. SD	Z/X <sup>2</sup> p	Sıra Ort. SD	Z/X <sup>2</sup> p			
Yaş	26-30	115,75	<b>X<sup>2</sup>=10,305</b>	113,50	<b>X<sup>2</sup>=7,212</b>	115,42	<b>X<sup>2</sup>=5,603</b>	105,78	<b>X<sup>2</sup>=3,411</b>	110,73	<b>X<sup>2</sup>=0,632</b>				
	31-35	129,13	<b>p=0,006</b>	107,93	<b>p=0,027</b>	126,43	<b>p=0,061</b>	115,73	<b>p=0,182</b>	119,57	<b>p=0,729</b>				
	36-40	97,06		135,48		101,99		128,20		117,59					
Gelir durumu (Gelir gidere göre)	Az	106,02	<b>X<sup>2</sup>=4,748</b>	105,27	<b>X<sup>2</sup>=7,029</b>	<b>90,10</b>	<b>X<sup>2</sup>=6,653</b>	77,23	<b>X<sup>2</sup>=12,246</b>	80,73	<b>X<sup>2</sup>=8,744</b>				
	Eşit	111,40	<b>p=0,093</b>	127,56	<b>p=0,030</b>	115,30	<b>p=0,036</b>	117,09	<b>p=0,002</b>	119,71	<b>p=0,013</b>				
	Fazla	129,68		103,75		128,61		129,94		124,54					
Eşin çalışma durumu	Evet	118,22	<b>Z=-1,530</b>	116,29	<b>Z=-0,851</b>	120,11	<b>Z=-3,761</b>	120,32	<b>Z=-4,034</b>	119,82	<b>Z=-3,388</b>				
	Hayır	82,63	<b>p=0,126</b>	136,88	<b>p=0,395</b>	29,50	<b>p=0,000</b>	23,63	<b>p=0,000</b>	37,75	<b>p=0,001</b>				
Planlı gebelik	Evet	119,60	<b>Z=-2,525</b>	117,56	<b>Z=-0,525</b>	119,64	<b>Z=-2,476</b>	118,70	<b>Z=-1,607</b>	119,99	<b>Z=-2,790</b>				
	Hayır	73,00	<b>p=0,012</b>	107,50	<b>p=0,600</b>	72,31	<b>p=0,013</b>	88,15	<b>p=0,108</b>	66,38	<b>p=0,005</b>				
Çocukların yaşları	2	139,84		101,34		119,57		109,95		114,54					
	3	126,76		144,87		121,36		108,71		133,95					
	4	106,51	<b>X<sup>2</sup>=19,739</b>	113,94	<b>X<sup>2</sup>=16,359</b>	114,20	<b>X<sup>2</sup>=6,136</b>	149,84	<b>X<sup>2</sup>=19,203</b>	122,48	<b>X<sup>2</sup>=9,144</b>				
	5	97,59	<b>p=0,001</b>	101,55	<b>p=0,003</b>	125,65	<b>p=0,189</b>	113,03	<b>p=0,001</b>	104,86	<b>p=0,058</b>				
	6	82,11		131,75		81,72		82,47		86,19					

Z: Mann Whitney U Test; X<sup>2</sup>: Kruskal Wallis Test; Sıra Ort. SD: Sıra Ortalaması ve serbestlik derecesi; p<0,05: istatistiksel anlamlılık düzeyi.

Tablo 4. Annelerin bağımsız değişkenlerinin BSATÖ toplam puan ve alt faktörleriyle karşılaştırılması.

Değişkenler	ÖSNDD		YDBİT		NBS		ZB		DGT		BSATÖ		
	Sıra Ort. SD	Z/X <sup>2</sup> p	Sıra Ort. SD	Z/X <sup>2</sup> p	Sıra Ort. SD	Z/X <sup>2</sup> p	Sıra Ort. SD	Z/X <sup>2</sup> p	Sıra Ort. SD	Z/X <sup>2</sup> p	Sıra Ort. SD	Z/X <sup>2</sup> p	
Yaş	26-30	95,66	X <sup>2</sup> =9,128 p=0,010	95,65	X <sup>2</sup> =7,396 p=0,025	104,78	X <sup>2</sup> =2,754 p=0,252	100,85	X <sup>2</sup> =6,105 p=0,047	110,73	X <sup>2</sup> =10,500 p=0,005	96,65	X <sup>2</sup> =8,870 p=0,012
	31-35	128,93		125,98		123,24		124,24		130,87		129,17	
	36-40	113,52		118,63		116,04		117,47		98,17		112,32	
Eğitim durumu	Lise	80,25	X <sup>2</sup> =7,358 p=0,025	102,86	X <sup>2</sup> =1,876 p=0,391	87,61	X <sup>2</sup> =5,157 p=0,076	99,20	X <sup>2</sup> =6,190 p=0,045	79,57	X <sup>2</sup> =7,602 p=0,022	85,36	X <sup>2</sup> =5,864 p=0,053
	Lisans	121,77		121,40		117,76		124,26		121,56		122,63	
	Lis.üst	118,94		112,57		124,70		107,98		119,59		115,60	
Çalışma durumu	Evvel	122,22	Z=-1,992 p=0,046	124,82	Z=-2,976 p=0,003	123,18	Z=-2,360 p=0,018	119,29	Z=-1,031 p=0,303	118,58	Z=-0,603 p=0,547	123,77	Z=-2,575 p=0,010
	Hayır	102,29		94,96		99,57		110,54		122,55		97,91	
Gelir durumu (Gelir gidere göre)	Az	131,42	X <sup>2</sup> =3,887 p=0,143	146,19	X <sup>2</sup> =6,836 p=0,033	132,44	X <sup>2</sup> =1,588 p=0,452	151,29	X <sup>2</sup> =10,717 p=0,005	137,31	X <sup>2</sup> =2,753 p=0,253	143,96	X <sup>2</sup> =6,225 p=0,044
	Eşit	109,35		109,09		115,78		113,74		113,47		109,05	
	Fazla	124,65		120,22		113,90		110,99		116,04		121,01	
Eşin eğitim durumu	Lise	89,12	X <sup>2</sup> =15,768 p=0,000	103,92	X <sup>2</sup> =3,189 p=0,203	94,36	X <sup>2</sup> =9,651 p=0,008	102,93	X <sup>2</sup> =5,392 p=0,067	104,56	X <sup>2</sup> =4,356 p=0,113	93,60	X <sup>2</sup> =10,757 p=0,005
	Üni.	123,22		121,72		124,49		123,56		125,77		122,79	
	Lis.üst	135,31		121,79		126,72		119,03		112,54		131,15	
Çocukların yaşları	2	106,30		116,19		126,91		117,92		118,21		115,69	
	3	138,66		130,79		147,12		127,06		115,62		137,91	
	4	124,72	X <sup>2</sup> =11,628 p=0,020	116,24	X <sup>2</sup> =8,670 p=0,070	96,22	X <sup>2</sup> =24,214 p=0,000	107,66	X <sup>2</sup> =6,353 p=0,174	107,68	X <sup>2</sup> =2,055 p=0,726	111,98	X <sup>2</sup> =10,784 p=0,029
	5	105,03		117,85		102,10		123,06		127,12		112,49	
	6	93,92		77,17		83,67		94,92		119,75		81,89	

Z: Mann Whitney U Test; X<sup>2</sup>: Kruskal Wallis Test; Sıra Ort. SD: Sıra Ortalaması ve serbestlik derecesi; p<0,05: istatistiksel anlamlılık değeri.

olan kadınlarda OB, KB ve SBİTÖ toplam puan ortalamasının anlamlılık gösterdiği belirlenmiştir. Konuya ilişkin yapılan farklı bir çalışmada aileleri yüksek gelir düzeyine sahip olan öğrencilerin sağlıklı beslenme davranışları gösterdiği ifade edilmiştir.<sup>14</sup> Literatürle karşılaştırıldığında bu araştırmanın bulguları diğer çalışmalarla benzerlik göstermektedir.

Araştırmamızda, eşleri çalışan kadınların BHB hariçindeki tüm alt faktör ve ölçek toplam puan ortalamalarının yüksek olduğu bulunmakla birlikte örnekleme alınan kadınların büyük çoğunluğunun çalışan olması beslenme hakkında bilgilerinin yüksek olmasına rağmen zaman sıkıntılarında dolayı beslenme konusunda olumsuz davranışlara yönelmiş olabileceklerini düşündürmüştür. Son yıllarda yapılan farklı bir çalışmada; babaların genellikle gıda alımı üzerinde daha az aktif kontrol uyguladıkları annelerin ise çocuklarının beslenme sürecinde doğrudan etkili oldukları belirtilmiştir.<sup>5</sup> Benzer şekilde yapılan diğer çalışmalarda ülkemizde evde yemeğin hazırlanması ve sunulması işlerinde genellikle kadınların rol aldığı, çalışan erkeklerin ev içi görevlere çok fazla dahil olmadığı ve beslenmeye yönelik tüm sorumluluğun kadınlara yüklendiği üzerinde durulmuştur.<sup>15,16</sup> Bu açıdan literatürle benzer sonuçlar elde edilmiştir.

Gebeliğin planlanması kadınların hayat tarzı değişiklikleri yapmalarını, sağlıklı beslenmelerini ve yaşam standartlarını düzenlemelerini sağlamaktadır. Bu araştırmamızda gebeliği planlı olan kadınlarda beslenmeye yönelik olumlu alt faktörler içeren tüm alanlardan yüksek puanlar elde edilmesi gebeliklerin planlı olmasının pozitif sonuçlar doğurduğu anlamına gelmektedir. Konuya ilişkin yapılan diğer çalışmalarda planlanmamış gebelik yaşayan kadınların kafeinli içecek tüketimine devam ettiği, vitamin kullanımında eksikliklerin olduğu ve yetersiz beslenmenin görüldüğü bildirilmiştir.<sup>17</sup> Bu sonuçlar araştırma sonuçlarıyla paralel özellikler göstermektedir.

Erken çocukluk döneminde; çocukların sağlıklı gelişim sürecinin devam edebilmesi, bakımından sorumlu olan kişilerin özellikle ebeveynlerinin sergiledikleri tutum ve davranışlara bağlıdır.<sup>7,18</sup> Araştırmamızda annelerin çocuklarını besleme tutumlarının yaş, gelir seviyesi, eşlerin çalışma durumu, gebeliklerinin planlı olması ya da çocukların yaşları gibi faktörlerle ilişkili olduğu görülmüştür. 3-5 yaş arası çocuklar ve ebeveynleriyle yapılmış bir çalışmada, annelerin çocuklarını besleme tarzlarının yaş, gelir ve eğitim durumu, çocuk sayısı gibi değişkenlerle ilişkili olmadığı görülmüştür.<sup>9</sup> Çok ırklı bir mahallede ilkökul çağındaki çocuklarla yapılan başka bir araştırmada

ihmalkâr ebeveynlere sahip olanların ve beslenme süreçlerine müdahalede bulunulmayanların sağlıksız alışkanlıklar tüketme ihtimallerinin yüksek olduğu bulunmuştur.<sup>19</sup> Bu durum ebeveynler tarafından sergilenen tutumların çocukların beslenme süreci üzerindeki önemini vurgulamaktadır. 2-12 aylık bebeği olan 29 anneye yapılmış nitel bir çalışmada annelerin çocukları için en iyi olduğuna inandığı besinleri vermek istediklerini, sağlıksız gıdalardan kaçındıklarını ve besleme tutumlarını önceki deneyimlerine göre şekillendirdiklerini ifade etmişlerdir.<sup>10</sup> Senegal'de emziren 171 anneye yapılmış başka bir çalışmada beslenme bilgi ve tutumlarının yüksek oranda eğitim ve gelir düzeyiyle ilişkili olduğu bildirilmiştir.<sup>20</sup> Literatürdeki çalışmalar bu araştırmanın sonucuyla kısmen benzer özellikler göstermektedir. Sonuçların kısmen farklı çıkması, araştırmaların yapıldığı kültürel ve sosyoekonomik şartların veya örneklem gruplarının çeşitliliğinden kaynaklanıyor olabilir.

Bu araştırmamızda, 61,660±18,929 BSATÖ toplam puan ortalamasıyla annelerin besleme konusunda orta düzeyde sorun yaşadıkları ve bu sorunların en çok YDBİT alt faktöründe olduğu tespit edilmiştir. Literatürde 9 ay-6 yaş arası çocuğu olan 217 anneye yapılan bir çalışmada annelerin BSATÖ'den ortalama 75,20±17,49 puan aldıkları, beslemeye ilişkin gösterdiği tutumlarda orta düzeyde sorunları olduğu ve YDBİT alt faktöründen yüksek puanlar aldıkları görülmüştür.<sup>21</sup> 168 bebeğin ebeveynleriyle yapılan başka bir araştırmada da, BSATÖ toplam puan ortalamalarının 9. ayda 89,51±12,75, 12. ayda 89,00±12,77 olması annelerin besleme tutumlarında yüksek düzeyde sorun yaşadığına ve zaman içerisinde bu sorunlarda azalma olmadığına işaret etmektedir. Ayrıca annelerin YDBİT alt faktöründen en yüksek ortalamaya sahip olmaları bu araştırmamızla benzer niteliktedir.<sup>22</sup> Bir anaokulunda 248 öğrenci velisini kapsayan araştırmada ise, annelerin 54,00±16,00 BSATÖ toplam puan ortalamasıyla orta düzeyde sorun yaşadıkları tespit edilmiştir.<sup>23</sup> İncelenen tüm çalışmalarda annelerin orta-yüksek düzeyde çocuklarını besleme sorunu yaşamaları sağlık profesyonelleri tarafından değerlendirilmesi ve desteklenmesi gereken bir konu olduğunu göstermektedir. Aile ortamı, ebeveyn beslenme alışkanlıkları, sosyoekonomik durum, medya vb. birçok faktör çocukların yeme davranışlarını etkilemektedir.<sup>24</sup> Bu araştırmamızda annelerin beslenme durumuyla çocuklarına sergiledikleri beslenme tutumları arasında anlamlı bir ilişki bulunamamıştır. Literatürde 6-23 aylık çocuğu olan 326 Nijeryalı annenin beslenme bilgisi ve

çocuk besleme uygulamaları üzerine yapılmış bir araştırmada annelerin zayıf düzeyde beslenme bilgisine sahip olduğu ve çocuklarını beslemek konusunda da yeterli olmadıkları görülmüştür.<sup>25</sup> 169 çocuğun ve annelerinin beslenme durumu ilişkisini inceleyen farklı bir araştırmada, maternal beslenme yetersizliği olan kadınların çocuklarında da ciddi beslenme sorunları olduğu belirtilmiştir.<sup>26</sup> Diyet çeşitliliği ve beslenme durumu ile ilgili Hindistan'da yapılan başka bir çalışmada da, anne diyetinin çocuklara uyguladığı rejimle direkt ilişkili olduğu vurgulanmıştır.<sup>27</sup> 1396 katılımcının olduğu farklı bir araştırmada annelerin kendi diyetlerinde ağırlık verdiği besin türlerinin çocukların tükettiği besinlerle benzer özellikte olduğu belirlenmiştir.<sup>28</sup> Ancak Endonezya'da 136 anneyle yapılan başka bir çalışmada annelerin beslenme rolü ve bilgisi ile küçük çocuklarının yeterli beslenme durumu arasında anlamlı bir ilişki olmadığı gösterilmiştir.<sup>24</sup> Genel olarak incelenen tüm çalışmalarda annelerin beslenme bilgisinin çocukların beslenme durumuyla pozitif olarak ilişkili olduğu görülmekle birlikte araştırmamızın bulgularıyla zıt sonuçlar elde edilmiştir. Çalışmaların genelde anaerkil toplum yapısına sahip ülkelerde yapılması, ancak Türkiye'nin ataerkil yapıda olması toplumsal cinsiyete özgü atfedilen bir farklılık olarak nitelendirilmiştir. Ataerkil toplumlarda kadının statü olarak ikinci sınıf insan özelliğinde olması sağlıklı beslenmelerine neden olurken, erkek cinsiyeti, çocuk ve yaşlı sınıfa ait olanlara en iyi besinlerin sunulduğu bilinmektedir. Bu durumun araştırma sonuçlarımıza da yansımış olabileceği düşünülmüştür. Yine tartışmaya dâhil edilen ülkelerin sosyoekonomik ve eğitim seviyelerinin düşük olması bu ülkelerde yaşayan annelerin çocuklarını da sağlıklı şekilde beslemiş olduğuna işaret etmektedir. Araştırmamızdaki annelerin eğitim ve sosyoekonomik seviyelerinin daha yüksek olması literatürle farklı sonuçların ortaya çıkmasına neden olmuş olabilir.

Sonuç olarak; annelerin sağlıklı beslenme ve çocuklarının beslenme sürecine yönelik tutumlarının zayıf olduğu tespit edilmiştir. Bu iki olumsuz sonuç arasında istatistiksel bir anlamlılığın olmaması sevindirici bir bulgu olarak değerlendirilmiştir. Literatürde çocukların beslenme konusunda ebeveynlerinden etkilendiklerine dair kanıtların bulunması konunun göz ardı edilmemesi gerektiğine işaret etmektedir. Bu bakımdan sağlık profesyonellerinin prekonsepsiyonel dönemden başlayarak ebeveynlere sağlıklı beslenme alışkanlıkları kazandırmak, olumlu bir rol model olma konusunda cesaretlendirmek ve kazandırılan beslenme alışkanlıklarını sürdürebilmek

için farkındalıklarını arttırmaya yönelik girişimlerde bulunulması önerilmektedir.

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**Yazar Katkıları:** Fikir – GF, ZÖ; Denetleme-GF, ZÖ; Veri toplanması ve/veya işlemesi- GF, ZÖ; Analiz ve/veya yorum – GF; Yazıyı yazan – GF, ZÖ.

**Hakem Değerlendirmesi:** Dış bağımsız.

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## Kardiyak Cerrahi Sonrası Postoperatif Mediastinit Tedavisi Sonuçları: Yıkamalı ve Yıkamasız Metodlarla Yapılan Negatif Basıncılı Yara Tedavilerinin Karşılaştırılması

### Treatment Outcomes of Postoperative Mediastinitis After Cardiac Surgery: A Comparison of Negative Pressure Wound Therapy Performed with Instillation Method and Non-Instillation Method

<sup>1</sup>Erhan HAFIZ, <sup>2</sup>Özgür ALTINBAŞ

<sup>1</sup>Department of Cardiovascular Surgery, Medical Faculty, Gaziantep University, Gaziantep, Turkey

<sup>2</sup>Department of Operating Room Services, Vocational School of Health Services, Gaziantep University, Gaziantep, Turkey

Erhan Hafiz: <https://orcid.org/0000-0002-0801-3194>  
Özgür Altınbaş: <https://orcid.org/0000-0002-6819-2454>

#### ÖZ

**Amaç:** Kalp cerrahisi sonrası gelişen mediastinit potansiyel olarak yıkıcı bir komplikasyondur. Bu klinik durum için çeşitli tedavi modaliteleri önerilmiştir ve vakum yardımcı kapatma bunlardan biridir. Bu çalışmada yıkamalı ve yıkamasız yöntemlerle gerçekleştirilen vakum destekli kapatmanın sonuçlarını karşılaştırmayı amaçlanmıştır.

**Materyal ve Metot:** Ocak 2015-Haziran 2019 tarihleri arasında sternotomi ile kalp cerrahisi gerçekleştirilen ve sonrasında mediastinit gelişen toplam 60 hasta çalışmaya dahil edildi. Grup 1 ve Grup 2, sırası ile yıkamasız ve yıkamalı negatif basınçlı yara tedavisi uygulanan 30 hastadan oluşturuldu. Gruplar arasında demografik özellikler ve tedavi sonuçları karşılaştırıldı.

**Bulgular:** Hastaların demografik verileri benzerdi. Bakteriyolojik kültürler, her iki gruptaki hastaların büyük çoğunluğunda stafilocok varlığını gösterdi (Grup 1, % 61,6; Grup 2, %70). Tedavi, enfeksiyon eradikasyonu, yara kapanma ve hasta taburculuğu süreleri Grup 2'de istatistiksel olarak daha düşüktü ( $p<0,05$ ) Yara kapanma oranı Grup 2'de istatistiksel olarak daha yüksekti ( $p<0,05$ ).

**Sonuç:** Yıkama metodu kullanılarak uygulanan vakum destekli negatif basınç tedavisi, mediastinit tedavisinde uygulanabilen bir yöntemdir ve yıkamasız yöntemle göre üstünlükleri mevcuttur.

**Anahtar Kelimeler:** Enfeksiyon, mediastinit, negatif basınçlı yara tedavisi, vakum yardımcı kapatma, yara iyileşmesi

#### ABSTRACT

**Objective:** Mediastinitis following cardiac surgery is potentially devastating complication. Various treatment modalities were suggested for this clinical situation and vacuum assisted closure is one of them. In the study it was aimed to compare outcomes of vacuum assisted closure performed with instillation and non-instillation methods.

**Materials and Methods:** From January 2015 to June 2019, a total of 60 patients who had mediastinitis after cardiac surgery performed via sternotomy were included to the study. Both Group 1 and Group 2 was consisted of 30 patients to whom negative pressure wound therapy performed without and with instillation, respectively. Demographic characteristics and treatment outcomes were compared between the groups.

**Results:** Demographic data of the patients were similar. Bacteriologic cultures showed the presence of staphylococci in the majority of the patients in both groups (Group 1, 61.6%; Group 2, 70%). Duration of treatment, eradication of the infection, wound closure and patients discharge were statistically lower in Group 2 ( $p<0.05$ ). Rate of the patients with healed wound was statistically significantly higher in Group 2 ( $p<0.05$ ).

**Conclusion:** Vacuum assisted negative pressure therapy via instillation is a reliable method that can be performed in the treatment of mediastinitis and has superiority over non-instillation method.

**Keywords:** Infection, mediastinitis, negative pressure wound therapy, vacuum-assisted closure, wound healing

#### Sorumlu Yazar / Corresponding Author:

Özgür Altınbaş  
Department of Operating Room Services, Vocational School of Health Services, Gaziantep University, Gaziantep, Turkey  
Tel: +90505 657 05 77  
E-mail: ozgur\_altinbas@yahoo.com

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## INTRODUCTION

Deep sternal wound infections (DSWI), known as mediastinitis, is a major complication after cardiac operations performed with sternotomy. Mediastinal fascia and the deep-seated retrosternal tissues are the involved areas.<sup>1</sup> The incidence of the mediastinitis was reported between 0.6% and 5% in different series and despite adequate medical and surgical treatments it has mortality rates ranging from 10% to 45%.<sup>2</sup> Multifactorial process involves in the pathogenesis of the mediastinitis that includes various risk factors and pathogenic microorganisms. These factors related to either patient characteristics or the procedure.<sup>3</sup>

Different treatment modalities can be performed for mediastinitis. Prophylactic and/or microorganism-oriented antibiotherapy is one of the most important tools in the treatment regimens. Besides, surgical revision with primary closure or open dressings, closed irrigation, reconstruction with soft tissue flaps, and negative pressure wound therapy (NPWT) are the other treatment alternatives for mediastinitis.<sup>4</sup> NPWT can be performed with instillation method or standard method without instillation.<sup>5</sup>

Purpose of this study is to evaluate the treatment outcomes of the NPWT with and without instillation methods in patients with mediastinitis after cardiac surgery performed via sternotomy.

## MATERIALS AND METHODS

**Ethical Status:** Written informed consent was taken from all participants and this single center retrospective study was approved by Gaziantep University Ethics Committee of Clinical Trials (Date: 03/07/2019, decision no: 2019/196) and complies with the declaration of Helsinki.

From January 2015 to June 2019, hospital records of the patients who were treated with NPWT after cardiac operation performed via sternotomy were investigated. Patients performed emergent surgery, re-do surgery, beating heart surgery, underwent thoracic aortic surgery extended to the descending aorta, more than one valve interventions, coronary artery bypass with valve interventions, under 18 years old, diagnosed any kind of neoplasia, had evidences related to the infection but with negative substernal bacterial wound culture or without mediastinitis were not included to the study. A total of 60 patients diagnosed with mediastinitis after cardiac surgery and treated with NPWT with or without instillation methods were involved to the study.

Study was consisted of two groups. Both Group 1 and Group 2 were consisted of 30 patients to whom NPWT was performed without or with instillation method. Demographic data, laboratory findings and echocardiographic results in terms of ejection frac-

tion of the patients, comorbidities, kind of operations performed (coronary artery bypass graft operation, aort valve replacement, mitral valve replacement), classification of the wound, duration of operation and aortic cross-clamp, results of bacterial wound cultures and treatment outcomes of NPWT were compared. Cefazolin sodium 1gr was administered to the patients during induction of anesthesia via venous way and ordered three times a day after postoperative period. Antibiotherapy was revised to suitable one which of the detected pathogen in the surgical site was sensitive. Sternum was closed in classical way after operation but Robitschek method was performed for sternal fixation in the necessity of revision surgery.

Mediastinitis was defined according to Centers for Disease Control and Prevention guidelines.<sup>6</sup> Diagnosis of mediastinitis requires at least one of the following criteria; presence of organisms cultured from mediastinal fluid or tissue, evidence of mediastinitis on histopathological and gross anatomical examination, and at least one of the signs or symptoms including fever ( $>38^{\circ}\text{C}$ ), sternal instability or chest pain and additionally at least one of the following; mediastinal widening on imaging or purulent drainage from mediastinal site. El Oakley<sup>7</sup> classification was used for post-sternotomy mediastinitis.

**Statistical Method:** The normality of distribution of continuous variables was tested by Shapiro Wilk test. Mann-Whitney U test was used for comparison of two independent groups of variables with a non normal distribution. Chi-square test was used to assess relation between categorical variables. The categorical variables were expressed as percentages and continuous variables were expressed as the mean SD. SPSS 22.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Statistical significance was defined as  $p<0.05$  with a two tailed test.

## RESULTS

Both groups were consisted of 30 patients and there were no statistically differences in demographic, laboratory and clinical data prior to the treatment (Table 1).

In addition to the data above, there were no statistically significant differences in body mass index (BMI) (Group 1,  $n=17$ ; Group 2,  $n=18$ ) and immunosuppressive treatment between the groups.

All the patients were underwent open heart surgery by using cardiopulmonary bypass pump. Type of operations, duration of cross-clamp and operations were given in Table 2.

Post-sternotomy wound classification was evaluated according to the recommendations of El-Oakley et al and summarized in Table 3.

**Table 1.** Comparison of pre-treatment status between groups.

Variables*	Group 1 (n =30)	Group 2 (n = 30)	p
Age (years)	59.40 ± 10.29	57.13 ± 11.64	0.571
Gender (male/female)	13/17	12/18	0.835
Patients with DM	11	10	0.837
Patients with COPD	6	7	0.726
Patients with renal failure	2	2	>0.99
EF (%)	47±2.3	49±2.7	0.784
Wound area (cm <sup>2</sup> )	173.00 ± 123.73	127.33 ± 137.87	0.341
Albumin (gr/dL)	2.364 ± 0.325	2.350 ± 0.823	0.954
CRP (mg/L)	42.44±8.52	46.56±7.61	0.896
WBC count/ml	13.9	13.7	0.965

NPWT; negative pressure wound therapy, DM; diabetes mellitus, WBC; white blood cell \*Mean ± SD.

**Table 2.** Type of operations and duration of operations and cross-clamp.

	CABG(n)	AVR(n)	MVR(n)	Duration of Operation (min)	Duration of cross-clamp (min)
Group 1	18	5	7	160.3±12.4	45.2±3.7
Group 2	19	4	7	156.6±11.7	43.4±4.1
P	0.844	0.786	>0.99	0.934	0.925

CABG; coronary artery bypass graft, AVR; aortic valve replacement, MVR; mitral valve replacement.

**Table 3.** Post-sternotomy El-Oakley mediastinitis classification.

El Oakley Class	Group 1 (n=30)		Group 2 (n=30)	
	N	%	N	%
I	-	-	-	-
II	6	20.0	5	16.6
IIIA	9	30.0	9	30.0
IIIB	15	50.0	16	53.4
IVA	-	-	-	-
IVB	-	-	-	-
V	-	-	-	-

Bacteriologic wound cultures revealed the presence of staphylococci in the majority of the patients in both groups and results were given in Table 4.

Duration of treatment, bacterial eradication, wound closure, and hospital discharge were statistically

significantly lower in Group 2. Wounds of all patients totally healed in Group 2 however, 66.7% of the patients had totally healed wounds in Group 1 (Table 5).

**Table 4.** Culture-verified deep sternal wound infection pathogens.

Bacterial strains	Group 1 (n=30)		Group 2 (n=30)	
	N	%	N	%
Staphylococcus aureus	12	40.0	13	43.3
Escherichia coli	1	3.3	-	-
Staphylococcus epidermidis	6	20.0	7	23.3
Metisin resistance Staphylococcus aureus	6	20.0	5	16.6
Pseudomonas aeruginosa	3	10.0	2	6.6
Acinetobacter baumannii	2	6.6	3	10.0

**Table 5.** Comparison of treatment outcomes between groups.

Outcomes	Group 1 (n =30)	Group 2 (n = 30)	p
Days treated*	36.47 ± 13.07	9.87 ± 4.31	0.001**
Days wound eradicated from clinical infection*	26.40 ± 6.58	6.05 ± 1.48	0.001**
Wound healed (%)	65.7	100	0.006**
Days to wound closure*	28.65 ± 6.62	13.24 ± 6.58	0.001**
Days to patient discharge*	39.28 ± 12.14	14.76 ± 9.25	0.001**

NPWT, negative pressure wound therapy. \*Mean ± SD. \*\* p < 0.05 compared with control group.

## DISCUSSION AND CONCLUSION

Mediastinitis is a life-threatening complication after median sternotomy. Several risk factors have been defined in the literature and of those obesity and diabetes remain the most important.<sup>8</sup> Most of the participants in our study were involved in overweighted and obesity class I groups according to the BMI classification and DM was the most prevalent concomitant disease. Besides, advanced age, COPD, left ventricular dysfunction, female sex and renal failure were additional preoperative risk factors mentioned in the literature.<sup>2</sup> Most of the patients were female and had decreased EF and advanced age in our study. COPD was the second prevalent concomitant disease and there were four patients with renal failure. Prolonged duration of surgery and aortic-cross clamp time was accepted as intra-operative risk factors for mediastinitis.<sup>9</sup> Duration of operation and aortic cross-clamp time was within normal limits parallel with the literature in our study, because of exclusion of surgeries required more than one cardiac structure interventions and redo.

Use of bilateral internal mammarian artery for vascular graft in coronary artery bypass graft operations is also associated with postoperative mediastinitis. Harvesting of both mammarian arteries damages to sterna collateral blood supply and increases the vulnerability to infections.<sup>10</sup> In our study only left internal mammarian artery was used in patients who underwent coronary artery bypass graft operation.

Mediastinitis was classified into five categories according to time of presentation and presence of risk factors by El-Oakley et al.<sup>7</sup> All of the participants in both groups in our study were involved in group II, IIIA and IIIB.

The most common microorganism detected in wound infections is staphylococcus aureus and causing up to 80% of mediastinitis after cardiac surgery.<sup>11</sup> Similarly, S.aureus was the major pathogen detected in the bacteriologic wound cultures of the patients in both groups in our study.

Various treatment modalities were defined in the

literature for mediastinitis. Despite the choice of antibiotic, optimal dose, duration and timing remain controversial, preoperative antibiotic prophylaxis is one of the most important tools in the treatment.<sup>12</sup> Surgical debridement, drainage, irrigation, plastic reconstruction and NPWT are the other techniques established previously.<sup>13</sup>

NPWT is a newer method consists of an open-cell foam dressing covered with an adhesive drape. Sub-atmospheric pressure is created and maintained by the dressing connected to a vacuum pump.<sup>14</sup> It can be used in different wound types including acute wounds such as traumatic or dehisced surgical wounds and flaps and grafts, and chronic wounds such as diabetic, pressure and vascular ulcers.<sup>15</sup> Wound drainage, stabilization of the chest wall, isolation of the chest cavity to prevent contamination, granulation stimulation, maintenance of a moist environment, and increased blood flow to the tissues can be achieved by using NPWT when applied for the mediastinitis after sternotomy.<sup>16</sup> It also plays a critical role in cell proliferation, modulation of inflammation and decreasing in bacterial levels.<sup>15</sup> NPWT with antibiotic was suggested as a first line therapy for mediastinitis in a study conducted by Kaul.<sup>17</sup> In addition, initiation of NPWT is a class II recommendation by the guidelines of American Association of Thoracic Surgery (AATS) in patients to whom delayed sternal closure is planned following mediastinitis.<sup>18</sup> Cefazolin sodium (iv) was administered to the patients before operation and antibiotic therapy was regulated according to the microorganisms detected in the bacterial wound culture in post-operative period in our study.

NPWT can be performed by a standard way without instillation or with instillation method which allows automated, intermittent, volume controlled instillation of a topical wound solution during the therapy. Although several solutions were recommended in the literature for instillation, saline was the preferred one because of the outcomes similar to other types of solutions.<sup>19</sup> Saline was used for instillation in our study.

NPWT with instillation has been suggested in the treatment of infected or contaminated wounds in necrotizing fasciitis, upper and lower extremity wounds, ulcers, breast reconstruction and other complex wounds as well as mediastinitis.<sup>20</sup> Singh et al.<sup>21</sup> compared the outcomes of patients with mediastinitis treated with NPWT with and without instillation. Control of wound infection and early granulation tissue formation was better in patients treated with NPWT with instillation. Similarly, in a study designed by Chowdhry et al.<sup>20</sup>, days to wound closure and the number of therapy days were fewer in NPWT with instillation group. In our study, days to wound closure were significantly fewer and the duration of the treatment were significantly lesser in the patients treated via NPWT with instillation. Karaca et al.<sup>22</sup> reported a case of mediastinitis caused by *Mycoplasma hominis*. NPWT with instillation method was performed and patient was treated with a success in that study. Gabriel et al.<sup>23</sup> emphasized that NPWT with instillation has a positive impact on decreasing the bacterial colonization in acute or chronic wounds. Thus, this method can be useful for the eradication of infection in mediastinitis with appropriate antibiotics. Duration of the eradication of the wound was lesser in NPWT with instillation group in our study. According to the study designed by Hehr et al.<sup>24</sup>, successful clearance of infection and healed wounds in 89% of the patients were achieved with sternal, spinal and extremity infections via NPWT with instillation. Sternal wounds were healed in all of the patients treated via NPWT with instillation in our study. NPWT with instillation has also been shown to shorten the overall hospital stay.<sup>25</sup> Patients were statistically significantly discharged earlier to whom NPWT with instillation method was performed in our study.

Underlying mechanism of NPWT with instillation on wound healing and bacterial eradication can be explained as follows; NPWT with instillation allows to lower wound fluid viscosity, enabling the washout of necrotic tissue, clots and fibrin in addition to removal of excess fluid and increased granulation. NPWT alone supplies a mechanical stress for stimulation of underlying cell proliferation, while NPWT with instillation allows new cells to be set on healthy tissue. It removes inhibitory factors such as metalloproteases and destroys glycocalyx responsible for resistance to antiseptics.<sup>26,27</sup>

In conclusion, efficiency of NPWT on the treatment of mediastinitis after sternotomy was known previously. NPWT with instillation is a recently introduced treatment modality and performed NPWT with irrigation solution. Evidences are available in the literature related to its positive effects on cell proliferation and granulation which maintain wound healing and prevention of drug resistance. It has su-

periority over NPWT without instillation in the terms of duration of the therapy, wound closure, eradication of the infection and patient discharge. Further studies with larger population are required for additional effects of this therapy.

**Ethics Committee Approval:** Our study was approved by Gaziantep University Ethics Committee of Clinical Trials (Date: 03/07/2019, decision no: 2019/196).

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Author Contributions:** Concept- EH; Supervision- OA, EH; Materials- OA; Data collection and processing- EH, OA; Analysis and interpretation- OA; Writing- OA, EH.

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## Gebeliğin İntrahepatik Kolestazi ve Maternal-Fetal Sonuçları

### Intrahepatic Cholestasis of Pregnancy and Maternal-Fetal Results

<sup>1</sup>Kemine UZEL, <sup>2</sup>Filiz BILIR, <sup>3</sup>Bahar ASTEPE, <sup>4</sup>Paşa ULUĞ, <sup>5</sup>Yusuf Kemal ARSLAN, <sup>4</sup>Tunay KIREMITLI

<sup>1</sup>Department of Gynecology and Obstetrics, Erzincan Binali Yıldırım University Mengucek Gazi Training and Research Hospital, Erzincan, Turkey

<sup>2</sup>Department of Gynecology and Obstetrics, Kocaeli University, Kocaeli, Turkey

<sup>3</sup>Department of Gynecology and Obstetrics, University of Health Sciences Kocaeli Derince Training and Research Hospital, Kocaeli Turkey

<sup>4</sup>Department of Gynecology and Obstetrics, Erzincan Binali Yıldırım University, Medical Faculty, Erzincan, Turkey

<sup>5</sup>Department of Biostatistics, Erzincan Binali Yıldırım University, Medical Faculty, Erzincan, Turkey

Kemine Uzel : <https://orcid.org/0000-0002-4615-5601>

Filiz Bilir: <https://orcid.org/0000-0002-8961-1304>

Bahar Astepe: <https://orcid.org/0000-0002-9012-4802>

Paşa Uluğ: <https://orcid.org/0000-0001-9870-0109>

Yusuf Kemal Arslan: <https://orcid.org/0000-0003-1308-8569>

Tunay Kiremitli: <https://orcid.org/0000-0002-4531-827X>

#### ÖZ

**Amaç:** Sıklıkla ikinci trimesterin sonlarından itibaren ortaya çıkan intrahepatik gebelik kolestazi, gebelik döneminde görülen yaygın bir karaciğer hastalığıdır. Coğrafi varyasyonlara bağlı olarak genel insidansı %1 -%27,6 arasında değişmektedir. Bu çalışma, üniversite hastanemizde Gebeliğin İntrahepatik Kolestazi tanılı kadınların maternal ve fetal sonuçlarını bildirmeyi amaçladı.

**Materyal ve Metot:** Çalışma Eğitim ve Araştırma Hastanemizde, Haziran 2018-Aralık 2020 tarihleri arasında Gebeliğin İntrahepatik Kolestazi (GİK) ile komplike olan 44 gebede retrospektif olarak yapıldı. Çalışmaya dahil edilen olguların (n=44) demografik özellikleri, karaciğer enzimleri, tanı aldığı gebelik haftası, doğum şekli ve zamanı, doğumda APGAR skorları, yenidoğanın kilosu ve hasta bilgileri hastane kayıtlarından alındı.

**Bulgular:** Primipar kadın sayısı 27 (%61) idi. 4 (%9,1) kadında preeklampsi ve 4 (%9,1) kadında gestasyonel diabetes mellitus (GDM) izlendi. Yenidoğanlardan sadece birinde doğumda 1. ve 5. dakika APGAR skorları sırasıyla 0 ve 0 idi.

**Sonuç:** Çalışmamızda herhangi bir olumsuz maternal sonuç gözlenmemesine rağmen, bir perinatal ölüm izlendi. GİK'nin bireysel olarak yönetilmesini öneririz. Komplasyonların önlenmesinde yakın takip ve aktif yönetim gereklidir.

**Anahtar Kelimeler:** Gebelik, intrahepatik kolestaz, perinatal sonuçlar

#### ABSTRACT

**Objective:** Occurring frequently after the late second trimester intrahepatic cholestasis of pregnancy (ICP) is a widespread liver disease in the period of pregnancy. The general incidence of IC depending on the geographic variations, is probably to vary from 1% to 27.6%. In the study, it was aimed to report the maternal and fetal outcomes of women with ICP at our university hospital center.

**Materials and Methods:** The study was performed retrospectively on 44 pregnancies complicated by ICP between June 2018 and December 2020, at our Education and Research Hospital. Demographic characteristics, liver enzymes, a gestational week at diagnosis, type and time of delivery, APGAR scores at birth, and newborn weight and information about the patients included in the study were obtained from hospital records.

**Results:** The number of primiparous women was 27 (61%). In 4 (9.1%) women had preeclampsia and 4 (9.1%) women had gestational diabetes mellitus (GDM). Only one of the neonates had Apgar at the birth 1/5, 0 and 0 respectively.

**Conclusion:** In our study one perinatal death was observed, although no adverse maternal outcomes were observed. We recommend that ICP be managed individually. Close monitoring and active management are required in the prevention of complications.

**Keywords:** Intrahepatic cholestasis, perinatal outcomes, pregnancy

#### Sorumlu Yazar / Corresponding Author:

Kemine Uzel  
Erzincan Binali Yıldırım University, Mengucek Gazi Training and Research Hospital, Erzincan, Turkey  
Tel: +90 5413142510  
E-mail: kemineuzel@hotmail.com

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## INTRODUCTION

Occurring frequently after the late second trimester intrahepatic cholestasis of pregnancy (ICP) is a widespread liver disease in the period of pregnancy. The general incidence of IC depending on the geographic variations, is probably to vary from 1% to 27.6%, show differences between environmental factors and ethnic groups.<sup>1-3</sup> In comparison 1.24% in the Indian population, while this number is 1.46% in the Pakistani population, white population has a low incident of 0.62%.<sup>4</sup> in primarily Latina Los Angeles population, it is 5.6%.<sup>5</sup>

Although there is no definite data reported for Turkey, it was reported as 0.86% in one study and 0.45% in another study.<sup>6,7</sup>

ICP is defined by biochemical cholestasis with abnormal liver functions, and elevated levels of serum bile acids (BA) in the absence of other liver diseases, a pregnancy-specific liver disease characterized by maternal pruritus without any skin rash. P23 region of chromosome 2, the gene-related with ICP has been reported.<sup>8</sup>

With satisfying maternal results, symptoms and abnormal liver function are spontaneously decreasing after delivery. It has been reported that the most successful pharmacological agent used in ICP treatment ursodeoxycholic acid (UCDA) (500 mg, twice a day or 15 mg/kg/day).<sup>9,10</sup>

There is a high percentage of perinatal morbidity-mortality and it has been found that the rate of fetal complications like as preterm delivery, fetal distress, is increased in ICP.<sup>9,10</sup> Fetal birth weights were properly with gestational age and it was reported that there was no difference in fetal malformation and abortion rates. The incidence of meconium-stained is 25-45% of the amnios. Intrauterine fetal losses, preterm birth, and acute fetal distress are encountered in 2%, 44%, and 22% of in order of cases with ICP.<sup>11</sup> High BA levels have a harmful impact on cardiomyocytes, a few experimental animal types of research have shown that.<sup>12</sup> Therefore, ICP might stimulate foetal arrhythmia that may lead to still-birth.

Thus far, both ideal time to delivery and prenatal management stay uncertain. No method to decrease their risk of fetal monitoring has been described to either predict adverse perinatal results. For time to deliver in ICP-complicated pregnancies is also unclear, and the advice of various national expert societies is different. It has to be considered that induction of labor is associated with a higher frequency of complications such as surgical delivery compared to spontaneous labor.<sup>13</sup> Active management of labour protocols for ICP is recommended by the American College of Obstetricians and Gynecologists.<sup>14</sup>

In the study, it was aimed to report the maternal and fetal outcomes of women with ICP at our university hospital center.

## MATERIALS AND METHODS

**Ethical Status of the Study:** Our study was approved by Erzincan Binali Yildirim University Clinical Research Ethics Committee (Data: 26/04/2021, decision no: 06/ 33). This study was carried out per the Declaration of Helsinki.

Pregnant women who presented with the complaint of itching, who did not have any liver and skin pathology, and increased bile acids ( $\geq 10$   $\mu\text{mol/L}$ ) in the maternal blood, were considered as intrahepatic cholestasis of pregnancy (ICP). Demographic characteristics, liver enzymes, a gestational week at diagnosis, type of delivery, time of delivery, APGAR scores at birth, and newborn weight and information about the patients included in the study (n=44) were obtained from hospital records.

**Research Design:** The study was performed retrospectively on 44 pregnancies complicated by ICP between June 2018 and December 2020, at our Education and Research Hospital, a tertiary care maternity center.

**Cholestasis was diagnosed:** by the

1. Onset second or third trimester of pregnancy pruritus and cholestasis
2. BA  $\geq 10$   $\mu\text{mol/L}$
3. Normalization of biochemical parameters after delivery
4. Absence of other diseases that cause pruritus

Also, to exclude other causes of liver diseases in all patients prior to the record, the serological analysis of viral hepatitis was done. Detected normal ultrasonography of the liver and biliary tract for all women, which performed ultrasonography.

**Exclusion criteria were;** liver viral infections, fatty liver of pregnancy, patients with chronic liver diseases, skin diseases, cholelithiasis and allergic disorders.

**Statistical Analysis of Data:** Statistical analysis was performed with IBM SPSS ver. 22 (Armonk, NY: IBM Corp). For categorical variables results were shown as count (n) and percentage (%), for continuous variables as mean standard deviation or median (minimum-maximum) according to the distribution. Normality of the variables was checked with Shapiro-Wilks's test. Paired samples t test was used when comparing preop-postop hemoglobin and hematocrit levels. A p-value less than 0.5 was considered as statistically significant for all tests.

## RESULTS

Maternal and fetal outcomes were evaluated in 44 women with ICP during the study period.

Descriptive statistics are presented in Table 1 and Table 2.

Patient characteristics are shown in Table 1. Delivery type of 37 (84.1%) cases was a caesarean section. Antenatal corticosteroid was given to 4 (9.1%) of the women with ICP for the prevention of respiratory distress syndrome (RDS) in preterm infants. The number of primiparous women was 27 (61%). In addition, 4 (9.1%) women had preeclampsia and 4 (9.1%) women had gestational diabetes mellitus (GDM).

The median week of delivery was 37, and the median period of diagnosis to delivery interval was 1 week. One woman (%2) delivered spontaneously at  $\leq 36$  weeks' gestation. The number of fetuses with birth weight under 2500 g were 4 (9.1%). Nine fetuses (%20) had a pH of  $< 7.2$  level and they hospitalised in neonatal intensive care unit.

Only one of the neonates had Apgar at 1 and 5 minutes after birth, 0 and 0 respectively and this case was reported as intrauterine death with unknown

ethology, which was in 38 gestational ages (Table 1).

The follow-up and delivery outcomes are presented in Table 2. Liver alanine transaminase (ALT) were lowest value 6, and highest value 709 with median 59.5 (6-709). Aspartate transaminase (AST) value was 41.5 (10-923), and total bilirubin levels were 0.6 (0.3-10) in women. Hemoglobin values in Table 2 decreased after births in pre-post measurements and it was statistically significant ( $p < 0.001$ ). Similarly, hematocrit values also decreased, and it was statistically significant ( $p < 0.001$ ).

Neonatal mortality or neonatal morbidity such as sepsis, polycythaemia, hypothyroidism, neonatal convulsion, meningitis, pneumonia, pulmonary hypertension, pneumothorax, necrotizing enterocolitis, retinopathy of prematurity, congenital heart disease, intracranial haemorrhage, periventricular leukomalacia, congenital anomalies, metabolic diseases were not determined. Also, all women had eventless postpartum course.

**Table 1.** Socio-demographic parameters of the patients.

		Mean $\pm$ SD or Median(min-max)	
Age		28.7 $\pm$ 4.7	
BMI		25.6 $\pm$ 2.6	
Gravidity		1(1-5)	
Parity		0(0-3)	
Gestational age		37(34-41)	
Birth weight		2989.1 $\pm$ 358.4	
Apgar1		8(0-8)	
Apgar5		9(0-10)	
		<b>n</b>	<b>%</b>
Alcohol drinking	Never	34	85.0
	Drinking	6	15.0
Smoking status	Non-smoker	26	65.0
	Smoker	14	35.0
Season	Spring	7	15.9
	Winter	16	36.4
	Fall	11	25.0
	Summer	10	22.7
Type of Birth	Caesarean	37	84.1
	NSD	7	15.9
Betamethasone	No	40	90.9
	Yes	4	9.1
Preeclampsia	No	40	90.9
	Yes	4	9.1
Gestational diabetes mellitus	No	40	90.9
	Yes	4	9.1
Neonatal intensive care	No	35	79.5
	Yes	9	20.5
Phototherapy	No	41	93.2
	Yes	3	6.8
Ursodeoxycholic acid treatment	No	33	75.0
	Yes	11	25.0

Results were shown as Mean $\pm$  SD or Median(min-max) for numerical data and as count (n) and percentage (%) for categorical variables.



**Table 2.** Patients' clinic and laboratory results.

	Mean± SD or Median(min-max)	p*
Total bilirubin	0.6(0.3-10)	-
Direct bilirubin	0.3(0-1.7)	-
ALT	59.5(6-709)	-
AST	41.5(10-923)	-
ALP	236.1±97	-
Uric Acid	4.3±1.4	-
Hemoglobin (pre)	11.9±1.3	<0.001
Hemoglobin (post)	10.7±1.2	
Hematocrit (pre)	35.8±3.3	<0.001
Hematocrit (post)	32.4±3.4	

ALT: Alanine transaminase; AST: Aspartate transaminase; ALP: Alkaline phosphatase; \*p value of pre-op and post-op comparison; BMI: body mass index. Results were presented as mean±SD (standard deviation) or median (minimum-maximum); Paired samples t test was used when comparing preop-postop hemoglobin and hematocrit levels.

## DISCUSSION AND CONCLUSION

Two extensive retrospective cohort studies conducted in Sweden and Australia recently reported positive results with regard to ICP.<sup>2,15</sup> The study conducted in Sweden did not report the risk of stillbirth associated with ICP, but reported some increased risk of preterm birth, gestational diabetes and preeclampsia.<sup>2</sup> Generally positive results associated with ICP, such as mild or severe results without stillbirth, were reported in the study conducted in Australia.<sup>15</sup> A higher incidence of gestational diabetes, preeclampsia, and spontaneous preterm birth has been reported in women with ICP compared to the general population.<sup>15</sup> These higher rates of preterm births compared to stillbirths should be taken into account in the management of ICP. In both cohort studies, no increase in stillbirth rate and high rates of preterm delivery was considered secondary to medical treatment. The American College of Obstetricians and Gynecologists (ACOG) recommends active management protocols for the ICP.<sup>16</sup>

In our study, 4 (9.1%) women had preeclampsia and 4 (9.1%) women had gestational diabetes mellitus (GDM) and the median week of delivery was 37, and the median period of diagnosis to delivery interval was 1 week. One woman (2%) delivered spontaneously at ≤36 weeks' gestation. In addition, one stillbirth was observed in our study.

A high serum bile acid concentration is essential for diagnosis.<sup>17</sup> For women with ICP and markedly elevated BA, defined as >40 μmol/L and doubling of the levels of BA correlated with a 200% increase in risk of intrauterine fetal demise.<sup>18</sup> Several studies showed treatment with UCDA did not seriously reduce the risk of their primary outcome, which was a composite of perinatal death, preterm delivery, or neonatal unit admission.<sup>19</sup> We observed that, ursodeoxycholic acid treatment was given to 11 (20 %) of the women with ICP in our clinic. Clinically, ICP associated with elevated serum levels of bile acids,

and is often accompanied by elevation of serum levels of alanine aminotransferase (ALT) and/or aspartate aminotransferases (AST). In our study - liver alanine transaminase (ALT) was lowest value 6, and highest value 709 with median 59.5 (6-709). Aspartate transaminase (AST) value was 41.5 (10-923), and total bilirubin levels were 0.6 (0.3-10) in women.

One study reported that bile acids above 100 μmol/L were related to increased mortality despite twice-weekly antenatal testing.<sup>20</sup> A study by Kohari et al. investigates the efficacy of an intensive surveillance system for women with total bile acids >40 μmol/L at <36 weeks. The intensive surveillance included inpatient admission and continuous fetal heart rate (FHR) monitoring with delivery between 36 and 37 weeks. The authors reported a meaningful decrease in the stillbirth rate with this intensive surveillance strategy.<sup>21</sup>

Most women gave birth at ≥36 weeks' gestation in our study.

Delivery is mostly suggested at 37 weeks' without an amniocentesis for fetal lung maturity due to raised risk of fetal mortality, or after an amniocentesis for delivery prior to 37 weeks' gestation. If meconium is existing at the time of amniocentesis, delivery is indicated regardless of the fetal lung maturity results. Delivery can proceed without amniocentesis if the fetal monitoring is non-reassuring. Some providers are now waiting until 38-39 weeks gestation to deliver if there is the resolution of pruritus symptoms with treatment and bile acid levels are not significantly elevated (<40 micromol/L).

Antenatal corticosteroid was given to 4 (9.1%) of the women with ICP for the prevention of respiratory distress syndrome (RDS) in preterm infants in our study.

The ACOG, in their committee opinion detailing medically indicated late-preterm and early-term deliveries, recommends delivery at 36 to 37 weeks'

gestation. They also state that delivery before 36 weeks may be indicated related to laboratory and clinical conduction.<sup>14</sup>

In our study maternal and fetal demographic data and results were evaluated in 44 women with ICP. Spontaneous preterm delivery and preterm delivery ( $\leq 37$  weeks gestation) rates were low. The incidence of SGA fetuses was low. Low preeclampsia and GDM rate were recorded. One perinatal death was observed, although no adverse maternal outcomes were observed.

In conclusion; The sample size and retrospective nature of our study limited the results. However, these concerns apply to all available literature on ICP. The incidence of ICP is low; this is the limiting factor for future studies. We believe it is necessary to clarify whether prematurity associated with ICP is because of spontaneous or iatrogenic preterm birth. Given that there is no substantial evidence to suggest that ICP increases the rate of stillbirths, we recommend that ICP be managed individually rather than a routine preterm delivery. The planned caesarean rate was significantly higher in ICP cases, regarding maternal outcomes. Increases the emergency caesarean was as result of induction of labour for women with ICP. At the same time, inadequate response to iatrogenic induction as a result of early labour, and fetal distress during labour in ICP more common causes leading to an increasing number of caesarean sections.

**Ethics Committee Approval:** Our study was approved by Erzincan Binali Yildirim University Clinical Research Ethics Committee. (Data: 26/04/2021, decision no: 06/ 33).

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Author Contributions:** Concept – KU; Supervision – KU, FB, BA, PU; Materials -KU, FB, BA, PU; Data Collection and Processing -KU, YKA, TK; Analysis and Interpretation -KU, YKA; Writing – KU.

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## Hemodiyaliz Hastalarında Spondilodiskitis

### Spondylodiscitis in Patients under Haemodialysis

<sup>1</sup>Güven KILIÇ, <sup>2</sup>Kürşad ÖNEÇ, <sup>1</sup>Ömer POLAT

<sup>1</sup>Düzce University Faculty of Medicine, Department of Neurosurgery, Düzce, Turkey

<sup>2</sup>Düzce University, Faculty of Medicine, Department of Nephrology, Düzce, Turkey

Güven Kılıç: <https://orcid.org/0000-0001-5050-7908>

Kürşad Öneç: <https://orcid.org/0000-0003-3866-2838>

Ömer Polat: <https://orcid.org/0000-0003-4521-4312>

#### ÖZ

**Amaç:** Hemodiyaliz immünyüpresyon yaratmasının yanı sıra hastaların damar girişimlerine ve operatif prosedürlere daha sık maruz kalmaları nedeniyle enfeksiyon riskini arttırmaktadır. Amacımız hemodiyaliz hastalarında spondilodiskitis oranını, olası etkenleri ve hastalığa erken tanı konmasına yardımcı olabilecek parametreleri ortaya koymaktır.

**Materyal ve Metot:** 2010-2020 tarihleri arasında hemodiyaliz ünitesinde tedavi alan hastalar çalışmaya dahil edildi. Bel ağrısı şikayeti olan hastaların verilerine Mia-Med hasta kayıt sisteminden retrospektif olarak ulaşıldı.

**Bulgular:** Spondilodiskitis sıklığı %2,3 idi. Diyaliz süresinin uzaması ( $p<0,001$ ), kateter kullanımı ( $p=0,005$ ), diabetes mellitus ( $p=0,029$ ) ve kalp yetmezliği ( $p=0,005$ ) varlığının diskitis riskini arttırdığı saptandı. Spondilodiskitis bulunanlarda lökosit ( $p<0,001$ ), nötrofil lenfosit oranı (NLO) ( $p=0,006$ ), trombosit lenfosit oranı (TLO) ( $p=0,001$ ), sedimentasyon ( $p<0,001$ ) ve C-reaktif protein (CRP) ( $p<0,001$ ) değerleri anlamlı olarak yüksek idi.

**Sonuç:** Spondilodiskitis komorbiditesi olan, hemodiyaliz süresi uzun, kateter kullanılan ve ileri yaştaki hastalarda daha sık ortaya çıkmaktadır. Hızlı tanı için lökositöz, CRP, sedimentasyon gibi tetkikler kullanılabilir. Ayrıca tam kan tetkik sonuçlarından kolaylıkla hesaplanabilen NLR ve TLR, tanıda kullanılacak parametrelerdir.

**Anahtar Kelimeler:** Hematolojik parametreler, hemodiyaliz, spondilodiskitis

#### ABSTRACT

**Objective:** In addition to causing immunosuppression, hemodialysis may increase the risk of infection, given that the patients are more frequently exposed to vascular interventions and operative procedures. The present study aims to reveal the prevalence of spondylodiscitis in patients on hemodialysis, potential factors, and parameters that may help in the early diagnosis of the disease.

**Materials and Methods:** Patients who received treatment in the hemodialysis unit between 2010 and 2020 were included in the present study. Data of patients with low back pain were obtained retrospectively from the Mia-Med patient registry system.

**Results:** The frequency of spondylodiscitis was 2.3%. Findings showed that the prolonged dialysis duration ( $p<0.001$ ), catheter use ( $p=0.005$ ), diabetes mellitus ( $p=0.029$ ), and heart failure ( $p=0.005$ ) increased the risk of discitis. Leukocyte ( $p<0.001$ ), neutrophil-to-lymphocyte ratio (NLR) ( $p=0.006$ ), platelet-to-lymphocyte ratio (PLR) ( $p=0.001$ ), sedimentation ( $p<0.001$ ) and C-reactive protein (CRP) ( $p<0.001$ ) levels were significantly higher in patients with spondylodiscitis.

**Conclusion:** Spondylodiscitis occurs more prevalently in patients with comorbidity, have long hemodialysis duration, use catheters and in elderly patients. Leukocytosis, CRP, sedimentation can be used for rapid diagnosis. In addition, NLR and TLR, which can be easily calculated from the results of whole blood tests, are parameters that can be used in diagnosis.

**Keywords:** Hematological parameters, hemodialysis, spondylodiscitis

#### Sorumlu Yazar / Corresponding Author:

Ömer Polat

Department of Neurosurgery, Faculty of Medicine, Düzce University, Düzce, Turkey.

Tel: +905326953088

E-mail: polatnrs@gmail.com

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## INTRODUCTION

Spondylodiscitis is an inflammatory disease that impacts the spine, discs, and paraspinal tissue. In the adult age group, it mainly manifests itself as an infection that develops after discectomy. Albeit it has been argued in the literature that factors, such as trauma, viral infection and low-grade inflammation, are effective in the etiology of spondylodiscitis, the etiological factor that almost everyone agrees on is a bacterial infection.<sup>1</sup> It is considered that the agent spreads from the infection site to the disc by a hematogenous route. Infection typically begins in the adjacent end plate and the disc becomes secondarily infected. Predisposing factors for spondylodiscitis that occurs without surgical procedure to that area include past/current infectious diseases (skin, soft tissue, endocarditis and pneumonia), diabetes mellitus (DM), collagen-vascular diseases, steroid use, intravenous drug use, alcohol addiction, and other recent surgery or surgical interventions.<sup>2-4</sup>

Hemodialysis is a frequently used treatment method in patients with chronic renal failure. However, various complications may occur due to hemodialysis. The complication that is expected to occur more frequently in patients on hemodialysis is infection. In addition to conditions, such as uremia, malnutrition, vitamin D deficiency, and hyperparathyroidism, operative procedures, such as a central venous catheter, placement of vascular grafts, and opening of arteriovenous fistulas, may also increase the risk of infection in patients undergoing hemodialysis.<sup>5</sup>

In the study, it was aimed to reveal the rate of spondylodiscitis, potential factors, and parameters that could help in the early diagnosis of the disease in patients receiving hemodialysis treatment in our hospital.

## MATERIALS AND METHODS

**Ethics Committee Approval:** The present study was approved by Düzce University Clinical Research Ethics Committee (Date: 01.02.2021, decision no: 11/2021). All patients who received treatment in the Hemodialysis Unit of the Department of Internal Medicine, Department of Nephrology during the 10-year period between January 2010 and December 2020 were included in this study.

Data of patients with low back pain were obtained retrospectively from the Mia-Med patient registry system. Each patient's age, sex, smoking-alcohol use, duration of hemodialysis, whether there is an additional disease other than the reason for hemodialysis, the way of performing hemodialysis (arteriovenous fistula-catheter), examination findings for low back pain, and the results of the tests were noted down. Of the hemogram tests performed during the period of low back pain, leukocyte, eryth-

rocyte, thrombocyte, and hemoglobin data were recorded. The neutrophil-to-lymphocyte ratio (NLR) was computed by dividing the neutrophil count by the lymphocyte count, while the platelet-to-lymphocyte ratio (PLR) was calculated by dividing the platelet count by the lymphocyte count. Also, the C-reactive protein (CRP)-Sedimentation value was recorded as well. The blood culture results of the patients diagnosed with spondylodiscitis and the vertebral level that developed the disease were noted down. The results of patients with a diagnosis of spondylodiscitis were compared with those without.

**Statistical Analysis:** The software of SPSS for Windows version 21 was utilized for data analysis. Data were analyzed via Mann-Whitney U test and  $\chi^2$  or Fisher's exact tests, where applicable. Continuous variables were presented as mean (SD), median, minimum, and maximum. Model for logistic binary regression analysis using the Ward method and keeping the main discitis variable in the model was used to obtain Odds Ratios for the presence of diabetes, heart failure, catheter, hemogram parameters, NLR, and PLR. The results were considered statistically significant at  $p < 0.05$ .

## RESULTS

Of the 898 dialysis patients, 65 had low back pain (7.2%). Spondylodiscitis was found in 21 of the patients. The prevalence of spondylodiscitis was 2.3% (21/898). The prevalence of spondylodiscitis among those with low back pain was 32.3% (21/65). Complete blood count, CRP, sedimentation, blood culture, and Magnetic Resonance Imaging (MRI) were requested from all patients with low back pain, and these findings were utilized in the diagnosis.

When patients with low back pain were divided into two groups, those with spondylodiscitis ( $n=21$ ) and those without ( $n=44$ ), the mean age of the patients with dysthymia was  $69.6 \pm 1.2$ , and the median age was 70 years. The mean age of those without spondylodiscitis was  $69.8 \pm 1.2$  years, and the median age was 71.5 years, and no significant difference was found between the two groups ( $p=0.638$ ). Of the patients with spondylodiscitis, 61.9% (13/21) were female, and 38.1% (8/21) were male ( $p=0.465$ ). While 27.6% (8/29) of males had spondylodiscitis, 36.1% (13/36) of females had spondylodiscitis, and the difference between the two groups was not significant ( $p=0.465$ ) (Figure 1).

In the group of patients with spondylodiscitis, the localization of infection was found in the lumbar region in 14 (66.6%) patients and the thoracic region in seven (33.33%) patients. The number of patients with the upper-level lumbar region localization was 10 (71.42%). The findings showed that localization was in the lower thoracic region in all patients with

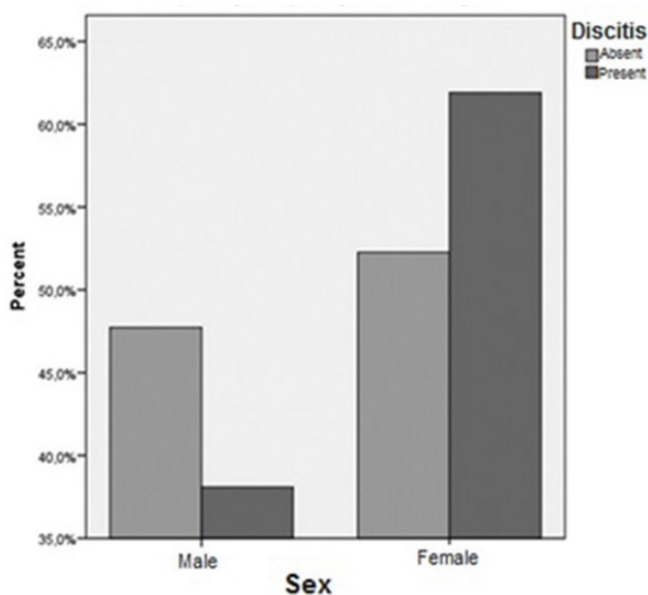


Figure 1. Frequency of spondylodiscitis by sex.

spondylodiscitis located in the thoracic region. It was observed that spondylodiscitis occurred close to the thoracolumbar junction level in 17 (81%) of the patients.

Dialysis duration was  $6.3 \pm 5.8$  years in people with spondylodiscitis, while it was  $2.3 \pm 2.0$  years in people without spondylodiscitis, and the difference was significant ( $p < 0.001$ ). It was revealed that increasing dialysis duration increased the incidence rate of spondylodiscitis (Figure 2).

While dialysis was performed via a catheter in 15 (71.43%) patients with spondylodiscitis, six (28.57%) had arteriovenous (AV) fistulas. The pres-

ence of a catheter significantly increased the rate of spondylodiscitis ( $p = 0.005$ ) (Table 1). In the blood culture results of the patients with discitis, growth was observed in 6 (28.57%) patients, *Staphylococcus aureus* was grown in 5 of these patients, and *Escherichia coli* was grown in 1 patient. The relationship between the presence of diabetes mellitus, the presence of heart failure, smoking, and alcohol use in patients with spondylitis is presented in Table 1. There were no other predisposing factors (soft tissue infection, endocarditis, pneumonia, collagen vascular disease, steroid use, IV drug use, history of surgery) in spondylodiscitis patients.

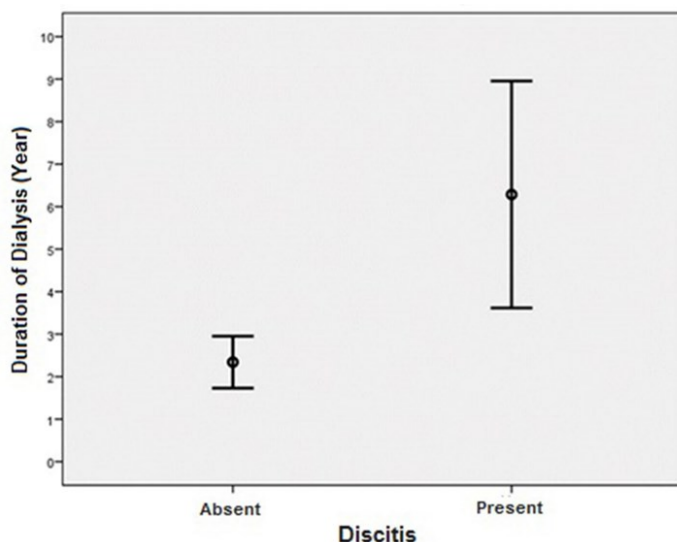


Figure 2. Relationship between duration of dialysis and spondylodiscitis.

**Table 1.** Potential predisposing factors in patient groups.

	Spondylodiscitis (+) n=21 (%)		Spondylodiscitis (-) n=44 (%)		P
<b>Dialysis technique</b>					
Catheter (n=30)	15	(71.3)	15	(34.1)	<b>0.005</b>
AV Fistula (n=35)	6	(28.57)	29	(65.9)	<b>0.005</b>
<b>Diabetes</b>					
Present	11	(52.38)	11	(25)	<b>0.029</b>
Absent	10	(47.62)	33	(75)	
<b>Heart failure</b>					
Present	12	(57.14)	7	(15.9)	<b>0.001</b>
Absent	9	(42.86)	37	(84.1)	
<b>Smoking</b>					
Present	6	(28.58)	12	(27.3)	0.913
Absent	15	(71.42)	32	(72.7)	
<b>Alcohol use</b>					
Present	1	(4.77)	3	(6.82)	0.747
Absent	20	(95.23)	41	(93.18)	

AV: Arteriovenous

The mean, median leukocytes, NLR, PLR, sedimentation, and CRP values were significantly higher in patients with spondylodiscitis, whereas erythrocyte and hemoglobin values were significantly lower. Difference between the hemogram parameters of patients with and without spondylodiscitis was not significant (Table 2).

## DISCUSSION AND CONCLUSION

Spondylodiscitis is defined as an infection of the intervertebral disc and adjacent vertebrae. The age group in which it occurs more prevalently is early childhood and the sixth decade.<sup>6</sup> Ages of the patients in our study were compatible with the literature. Males are affected twice more than females.<sup>7</sup> The gender of the patients in our study was not compati-

**Table 2.** Hematological parameters in the patient groups.

	Spondylodiscitis (+)	Spondylodiscitis (-)	P
<b>Leukocytes (K/uL)</b>			
Mean±SD (Min-max)	13.666 ± 0.93 (7.500-26.900)	7.400 ± 0.39 (4.000-16.400)	<b>&lt;0.001</b>
<b>Erythrocyte (M/uL)</b>			
Mean±SD (Min-max)	3.58 ± 0.13 (2.50 – 4.40)	4.02 ± 0.12 (2.60 – 5.03)	<b>0.018</b>
<b>Platelet (K/uL)</b>			
Mean±SD (Min-max)	212.85 ± 15.53 (81.00-371.00)	199.59 ± 10.18 (111.00-406.00)	0.407
<b>Hemoglobin (g/dL)</b>			
Mean±SD (Min-max)	10.62 ± 0.44 (6.70-13.40)	11.95 ± 0.40 (7.40-15.50)	<b>0.025</b>
<b>NLR</b>			
Mean±SD (Min-max)	7.12 ± 1.81 (0.20-32.00)	3.29 ± 0.65 (0.44-21.80)	<b>0.006</b>
<b>PLR</b>			
Mean±SD (Min-max)	178.50 ± 17.95 (35.20-331.00)	116.70 ± 11.87 (30.60-406.00)	<b>0.001</b>
<b>Sedimentation (mm/h)</b>			
Mean±SD (Min-max)	78.57-7.21 (33-141.00)	28.45 ± 2.50 (11.00-87.00)	<b>&lt;0.001</b>
<b>CRP (mg/L)</b>			
Mean±SD (Min-max)	16.08 ± 1.67 (4.50-32.90)	4.97 ± 1.14 (0.16-39.00)	<b>&lt;0.001</b>

NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; CRP: C-reactive protein.

ble with the literature. There were more female patients. Spondylodiscitis is most common in the lumbar region (58-68%), followed by thoracic (27-30%) and cervical vertebrae (5-11%).<sup>4,5,8</sup> In our study, the mean age of the patients was  $69.6 \pm 1.2$  years, which corresponds to the expected age range. However, although it was expected to occur mostly in males, 61.9% (13/21) of our spondylodiscitis patients were females, although the difference between the two groups was not significant. We are of the opinion that this difference may be due to hemodialysis and other predisposing factors. Concerning vertebral localization, infection was detected in the lumbar region in 66.6% of our patients and the thoracic region in 33.33%, which is consistent with the literature.

Hemodialysis applications have remarkably increased the survival time of patients with kidney failure thanks to improved materials and advanced techniques in recent years. Moreover, hemodialysis patients have a cumulative risk of infection since they are frequently exposed to vascular interventions and operative procedures, such as internal shunts, vascular grafts, and being in an immunologically dangerous condition.<sup>9</sup> Bacteremia is a common complication among hemodialysis patients and often develops due to the use of contaminated vascular instruments.<sup>5,10</sup> In our study, dialysis duration was significantly higher in patients diagnosed with spondylodiscitis than the patients without spondylodiscitis, and an increase in dialysis duration increased the incidence rate of spondylodiscitis.

It has been revealed that the most common pathogen detected in infectious spondylodiscitis is *S. aureus* (20-84%).<sup>11,12</sup> In their study, Lu et al.<sup>4</sup> detected the incidence of *S. aureus* at a rate of 38.9% and they underscored that this was associated with a low rate of positive culture. In our study, the most common causative agent was *S. aureus*, consistent with the literature. However, our culture positivity rate was remarkably low, which is consistent with Lu et al.<sup>4</sup>'s study.

Although the frequent occurrence of spondylodiscitis in hemodialysis patients is associated with bacteremia, the suppressed immunity of these patients, their advanced age, and comorbidities, such as DM increase the incidence of spondylodiscitis.<sup>5,10</sup> Furthermore, when examined concerning factors that may predispose to bacteremia, as well as the presence of catheter/fistula, presence of additional disease, and cigarette-alcohol use, the prolongation of the dialysis period, the use of catheters, and the presence of concomitant DM and heart failure increase the risk.<sup>5,8,13,14</sup> Lu et al.<sup>4</sup>, in their study of 18 patients, reported that 50% of the patients had diabetes, 55.6% had hypertension, and 55.6% had coro-

nary heart disease. In the same study, 27.8% of the patients used fistula, 22.2% used arteriovenous graft, 44.4% used catheter, and 5.6% femoral double lumen. Likewise, in our study, diabetes was 52.38%, heart disease was 57.14%, and the rate of those with both diseases was 38.09%. Besides, the rate of patients using a catheter was 71.43%. The incidence rate of spondylodiscitis was increasing with the use of a catheter.

The fact that spondylodiscitis is more common in the thoracolumbar region results in a late diagnosis of the disease and a higher mortality and morbidity rate.<sup>10</sup> High leukocyte, CRP, and sedimentation values, among the blood tests required for rapid diagnosis, are emphasized in all studies.<sup>12,15</sup> In our study, NLR and PLR values of the patients were also calculated, considering that parameters, such as sedimentation and CRP, that would accelerate the diagnosis of spondylodiscitis in patients with low back pain, and parameters that can be easily calculated from complete blood count, could reduce the delay in diagnosis.

NLR and PLR are described as markers of systemic inflammation used in inflammatory diseases and malignancies.<sup>16-18</sup> It has not been studied before in patients diagnosed with spondylodiscitis, but it has been studied in many diseases along with infection markers CRP and sedimentation. In our study, NLR and TLR values were significantly higher in spondylodiscitis patients, as were leukocyte, sedimentation, and CRP values.

Regarding the limitations of the present study, the data used in this study are single-centered. The data involves data for outpatients and does not involve treatment and follow-up data.

In conclusion, spondylodiscitis is a devastating condition that occurs more prevalently in hemodialysis patients due to predisposing factors. Affected patients are often patients with multiple comorbidities, long hemodialysis duration, catheter use, and advanced age. A history of low back pain, increased CRP, positive blood cultures, and characteristic MRI findings are safe findings for the diagnosis of leukocytosis. Moreover, concerning rapid diagnosis, NLR and TLR, which are easily calculated from the results of complete blood count, are parameters that can be used in the diagnosis before blood culture and MRI examination results, which require more time, in addition to routine and known tests, such as leukocytosis, CRP, and sedimentation.

**Ethics Committee Approval:** Our study was approved by the Düzce University, Clinical Research Ethics Committee (Date: 01/02/2021, decision no: 2021/11).

**Conflict of Interest:** No conflict of interest was



declared by the authors.

**Author Contributions:** Concept - GK, KÖ, ÖP; Supervision - GK, KÖ, ÖP; Data Collection and Processing - GK, KÖ, ÖP; Analysis and Interpretation - GK, KÖ, ÖP; Writing - ÖP.

**Peer-review:** Externally peer-reviewed.

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## Akut Pankreatit Hastalarında Nötrofil/Lenfosit ve Trombosit/Lenfosit Oranlarının Tanısal ve Prognostik Değeri

### Diagnostic and Prognostic Value of Neutrophil/Lymphocyte Ratio and Platelet/Lymphocyte Ratios on Acute Pancreatitis Patients

<sup>1</sup>Hasan ERGENC, <sup>1</sup>Zeynep ERGENC, <sup>2</sup>Ahmet Tarık EMINLER, <sup>3</sup>Hakan CINEMRE

<sup>1</sup>Department of Internal Medicine, Ayancık Government Hospital, Sinop, Turkey

<sup>2</sup>Department of Gastroenterology, Faculty of Medicine, Sakarya University, Sakarya, Turkey

<sup>3</sup>Department of Internal Medicine, Faculty of Medicine, Sakarya University, Sakarya, Turkey

Hasan Ergenç: <https://orcid.org/0000-0003-0519-0264>

Zeynep Ergenç: <https://orcid.org/0000-0001-7598-4508>

Ahmet Tarık Eminler: <https://orcid.org/0000-0003-1402-5682>

Hakan Cinemre: <https://orcid.org/0000-0001-7076-4012>

#### ÖZ

**Amaç:** Bu çalışmada, pankreatit hastalarının hastalık şiddetinin izlenmesinde nötrofil-lenfosit oranı (NLO) ve trombosit-lenfosit oranlarının (TLO) bir parametre olarak kullanılıp kullanılmayacağını göstermeyi amaçladık.

**Materyal ve Metot:** Akut pankreatit tanısı ile gastroenteroloji servisinde yatan ve takip edilen, dosyaları retrospektif olarak incelenen toplam 200 hasta çalışmaya dahil edildi. Akut pankreatitin şiddeti ve prognozu Atlanta sınıflaması ile değerlendirildi.

**Bulgular:** NLO ortalaması hasta grubunda  $9,84 \pm 9,60$ , kontrol grubunda ise  $2,00 \pm 0,86$  idi. Hasta grubunda NLO düzeyi yüksek saptandı ve cut-off değeri 2,85 olarak bulundu (Duyarlılık: %86 ve özgüllük: %81). Hastalık şiddetine göre NLO ortalamasında anlamlı bir değişiklik bulunmamasıyla birlikte, gruplar arasında NLO ortalamasındaki düşüş 48 saatte anlamlı bulundu.

**Sonuç:** Sadece ilk 48 saatteki NLO düzeyindeki değişikliğin hastalık şiddeti ile ilişkili olabileceğini bulduk. NLO'nun kullanılabilir, uygulanabilir ve kolay ulaşılabilir bir parametre olduğunu gördük.

**Anahtar Kelimeler:** Akut pankreatit, platelet, prognostik faktörler, NLO ve TLO

#### ABSTRACT

**Objective:** In this study, we aim at demonstrating whether we can use neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratios (PLR) as a parameter in monitoring the disease severity of Pancreatitis Patients.

**Materials and Methods:** A total of 200 patients diagnosed with acute pancreatitis, hospitalized and monitored in gastroenterology service, whose files had retrospectively been studied, were included in the study. The severity and prognosis of acute pancreatitis were evaluated with the Atlanta classification.

**Results:** The average of NLR was  $9.84 \pm 9.60$  in the patient group but  $2.00 \pm 0.86$  in the control group. The NLR level was found higher in the patient group. The cut-off value was found as 2.85 (Sensitivity: 86% and specificity: 81%). Although no significant change was found in terms of the average of NLR concerning the disease severity, the decrease in the average of NLR among the groups was found significant in 48 hours.

**Conclusion:** We have found that only the change in NLR level in the first 48th-hour could be associated with the disease severity. We found NLR as a parameter that can be used, applied, and accessed easily.

**Keywords:** Acute pancreatitis, platelet, prognostic factors, NLR and PLR

#### Sorumlu Yazar / Corresponding Author:

Hasan Ergenç  
Department of Internal Medicine, Ayancık Government Hospital,  
Sinop, Turkey  
Tel: +903686131027  
E-mail: dr.hasanergenc@hotmail.com

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## INTRODUCTION

Acute pancreatitis is characterized by the activation of pancreatic enzymes, amylase, and lipase, in the pancreas for various reasons and the digestion of pancreatic tissue itself.<sup>1</sup> It is an inflammatory disease characterized by abdominal pain and elevated serum pancreatic enzyme levels. Gallbladder and bile duct stones, alcohol, drugs, infections, trauma, ischemia, and genetic factors are the leading causes of acute pancreatitis etiology. In 80% of cases, gallstones and alcohol are the most common etiologic agents.<sup>2</sup>

Complete inhibition of pancreatic cathepsin B in an in vitro environment inhibits the activation of trypsinogen. Trypsin catalyzes the conversion of proenzymes and activates quinine and complement systems. These activated enzymes cause autodigestion in the pancreas, releasing more active enzymes.<sup>3</sup> Trypsinogen is typically activated in the pancreas in a small amount spontaneously, but by intrapancreatic mechanisms, this active trypsin is removed. Pancreatic secretory trypsin inhibitor inactivates by binding 20% of the active trypsin.<sup>4</sup> The pancreas also includes nonspecific antiproteases such as alpha-1-antitrypsin, alpha-2-macroglobulin.<sup>5</sup>

In literature, there have been researches on diagnostic values of neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte (PLR) ratios in some clinical diseases and health problems. According to these researches, NLR and PLR ratios may give clinicians an idea of potential disease and health conditions.<sup>6</sup>

Although there has been some research on NLR, PLR, and pancreatitis individually, there have not been enough studies on NLR and PLR on acute pancreatitis. Thus, it was aimed to evaluate diagnostic values of NLR and PLR ratios for acute pancreatitis.

## MATERIALS AND METHODS

**Ethical Status of the Study:** Our study was approved by the Sakarya University Ethics Committee (Date: 17.07.2014, decision no: 71522473/050.01.04/64 ). The study was carried out in accordance with the international declaration and guidelines.

**Study Group:** The present study was conducted with 200 patients, who were admitted to the RT Ministry of Health, Sakarya University, Faculty of Medicine, Education and Research Hospital Gastroenterology Clinic between 15.09.14-15.01.15, who met the inclusion criteria, and who were diagnosed with acute pancreatitis clinically and radiologically (the Patient Group). A total of 35 healthy individuals matched by gender and age were included in the study as the Control Group. The standard study form

was prepared previously for clinically diagnosed with acute pancreatitis, and the laboratory was filled. The patients' age, gender, medical history (diabetes, hypertension, ischemic heart disease, arrhythmias, hyperlipidemia), and the hemogram and biochemistry parameters were recorded on this form.

**Diagnosis and evaluating of the severity of Acute Pancreatitis:** The diagnosis of acute pancreatitis is made by the criteria of abdominal pain and serum amylase or three times the normal lipase level, determined with Atlanta classification. Many different terminologies have been defined in the definition of acute pancreatitis and its complications. In order to avoid these confusions, a consensus statement was written and published at a meeting held in Atlanta, the USA, in 1992.<sup>2</sup> According to this classification, our patients were divided into mild and severe pancreatitis. The number of patients in the severe group was 41, and the number in the mild group was 159.

Hemogram and extensive biochemistry tests were performed at admission and 48th hour for hospitalized patients. Especially hemoglobin (Hgb), neutrophil, lymphocyte, platelet, C-reactive protein (CRP), sedimentation, calcium, triglyceride (TG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and glucose values of the patients also were recorded. Each patient was evaluated with abdominal ultrasonography imaging (USI) regarding biliary/nonbiliary distinction after hospitalization.

**Statistical analysis:** The statistical package for social sciences for Windows 18.0' (SPSS 18 Inc.) program was used for statistical analysis in evaluating the data obtained in the study. Descriptive statistical methods (i.e., mean, standard deviation, frequency distribution, and %) were used to evaluate the study data, and ANOVA and Fischer's Test were used to compare the categorical data. Before the quantitative data were analyzed, it was tested whether the data showed normal distribution with the help of the Kolmogorov Smirnov Test. The data with normal distribution were evaluated using the ANOVA test to compare two independent groups, and the data that did not show normal distribution were evaluated using the Mann-Whitney U Test. The Kruskal Wallis Test was used to compare more than two groups. The Non-Parametric Spearman Test was used for correlation analyses, and the results were evaluated at a 95% Confidence Interval and the significance level was taken as  $p < 0.05$ .

## RESULTS

A total of 200 patients who had acute pancreatitis and 35 healthy volunteers who met inclusion criteria were included in the present study, and 72 (36%) of

these 200 patients were male, 128 (64%) were female, 18 (51%) of 35 healthy volunteers were male, and 17 (49%) were female. No statistically significant differences were detected between the two groups in terms of gender ( $p>0.05$ ) (Table 1). The mean age of the Patient Group was  $60.17\pm 17.19$ , and the mean age of the Control Group was found to be  $46.68\pm 16.96$ . Statistically significant differences were detected between the two groups in terms of age ( $p<0.05$ ) (Table 1).

The patient and control groups were compared with each other regarding the admission lymphocyte levels, neutrophil levels, platelet levels, 48<sup>th</sup>-hour lymphocyte levels, 48<sup>th</sup>-hour neutrophil levels, and 48<sup>th</sup>-hour platelet levels. The lymphocyte, platelet, 48<sup>th</sup>-hour lymphocyte, and 48<sup>th</sup>-hour platelet levels were lower in the Patient Group at statistically significant levels when compared to the Control Group ( $p<0.05$ ). The neutrophil and 48<sup>th</sup>-hour neutrophil levels were higher in the patient group at statistically significant levels when compared to the control group ( $p<0.05$ ) (Table 1).

The mean NLR was found to be  $9.84\pm 9.60$  in the Patient Group and  $2.00\pm 0.86$  in the Control Group, and the NLR level was higher in the Patient Group at a statistically significant level compared to the Control Group ( $p<0.05$ ). The mean PLR was found

to be  $0.23\pm 0.18$  in the Patient Group and  $0.12\pm 0.04$  in the Control Group, and the PLR level was higher in the patient group at a statistically significant level when compared to the Control Group ( $p<0.05$ ) (Table 2).

The mean arrival NLR was 9.18 in the mild group, the mean 48<sup>th</sup>-hour NLR was 5.42, and a statistically significant difference was detected between the two mean values ( $p=0.00$ ). The mean NLR was 11.99 at the end of the 48<sup>th</sup>-hour in the severe group, the mean NLR at the 48<sup>th</sup>-hour was 11.82, and no statistically significant differences were detected between the two mean values ( $p=0.15$ ) (Table 3).

In the present study, when the cut-off value was taken as 2.85 for the admission NLR parameter, the diagnostic value of the test was found to be 86% sensitive and 88% specific in terms of disease severity (Figure 1) ( $p=0.02$ ,  $R2:0.61$ ).

In the mild group, the mean PLR was 0.23 at admission and 0.17 at 48<sup>th</sup>-hour. No significant difference was found between groups ( $p=0.13$ ). The mean PLR was 0.24 at admission in the severe group and 0.20 at the 48<sup>th</sup>-hour. No statistically significant difference was detected between the mean PLR at 48<sup>th</sup>-hour and the mean PLR at admission ( $p=0.15$ ) (Table 4).

**Table 1.** Some demographic and biochemical characteristics of the patient and control group.

Variable	Patient (mean±sd)	Control (mean±sd)	P-value
Male gender n (%)	72 (36%)	18(51%)	0.08***
Female gender n (%)	128(64%)	17(49%)	0.06***
Age (years)	60.17±17.19	46.68±16.96	0.01*
Lymphocyte (K/uL)(admission)	1420.58±813.34	2869.37±3183.09	0.01**
Neutrophil (K/uL)(admission)	9410.15±4883.12	4532.86±1402.27	0.01**
Platelet (K/uL)(admission)	240.76±80.03	285.71±69.08	0.01*
Lymphocyte (K/uL)(48 <sup>th</sup> -hour)	1705.61±1155.63	2869.37±3183.09	0.01*
Neutrophil (K/uL)( 48 <sup>th</sup> -hour)	7898.22±4970.14	4532.86±1402.27	0.01**
Platelet (K/uL)( 48 <sup>th</sup> -hour)	212.92±72.38	285.71±69.08	0.01*

\*: ANOVA; \*\*: Mann-Whitney U; \*\*\*: Chi-Square.

**Table 2.** Relation between NLR and PLR levels of the patient and control group at admission.

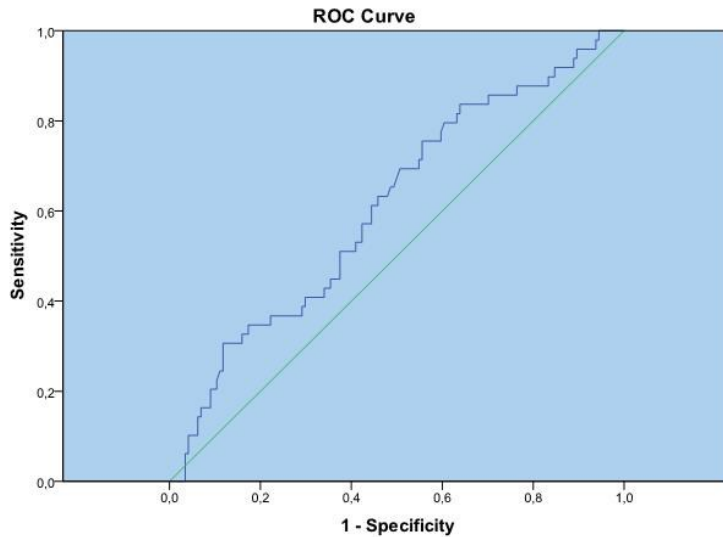
Variables (mean±sd)	Patient	Control	P-value
NLR	9.84±9.60	2.00±0.86	0.01*
PLR	0.23±0.18	0.12±0.04	0.01*

\*: Mann Whitney U.

**Table 3.** The relation between admission and 48<sup>th</sup>-hour values of NLR mean in the mild and severe group.

NLR (mean)	Admission	48 <sup>th</sup> -hour	P-value
Mild n:159	9.18	5.42	0.01*
Severe n:41	11.99	11.82	0.15*

\*: Wilcoxon.



**Figure 1.** Admission NLR ROC Curve according to disease severity.

**Table 4.** Relation between PLR mean admission and 48<sup>th</sup>-hour values in the mild and severe group.

PLR (mean)	Admission	48 <sup>th</sup> -hour	P-value
Mild	0.23	0.17	0.13*
Severe	0.24	0.20	0.15*

\*: Wilcoxon.

## DISCUSSION AND CONCLUSION

Acute pancreatitis is a significant disease of the pancreas drawing attention with high mortality and morbidity rates, its incidence varying between 4.9-35/100.000.<sup>7,8</sup> The fact that the disease is sometimes very mild and very severe clinically makes it challenging to diagnose, which may cause avoidable causes to be missed and mortality with second attacks that may develop. A total of 80% of the cases are mild and without serious morbidity, and 20% are severe. A decrease has not been observed over the years in the frequency of severe pancreatitis.<sup>9,10</sup>

Its pathophysiology consists of acute inflammation causing changes in regional tissues and other organs. The inflammation cascade was explained in previous clinical and experimental studies. According to the degree of inflammation, the histopathology of the disease exhibits a broad spectrum that ranges from mild interstitial edema to severe hemorrhagic gangrene and necrosis.<sup>8,11,12</sup>

Gallbladder stones and alcohol make up 70-80% of the etiology. Etiology differs among countries. For example, although alcohol ranks first in western countries, biliary causes are the first.<sup>13,14</sup> Other causes include abdominal trauma, hypertriglyceridemia, ampulla of Vater, pancreatic tumor, infectious causes, drugs, ERCP, or surgical interventions. Also, the etiologic cause cannot be

detected in 10% of the cases called "idiopathic pancreatitis".<sup>15,16</sup> When the literature was reviewed, many studies on the etiology of acute pancreatitis in our country came to the forefront. Especially in a study with 129 patients, biliary (64.3%) and idiopathic (26.4%) causes made up the first two lines.<sup>17-19</sup> Similarly, in a study with 84 patients, biliary causes accounted for 66% of the cases and idiopathic causes 31%.<sup>20-22</sup>

The severity of acute pancreatitis occurs in different degrees, and the main reasons for determining the severity are usually multifactorial. In general, it is thought that tissue damage is triggered by the activation of digestive zymogens in acinar cells as the mechanism of emergence of the clinic and causes acute pancreatitis.<sup>23-26</sup> On the other hand, there is no sufficient and definite information about the exact mechanism of pancreatitis.

Even if the severity and complications vary widely, the causes of acute pancreatitis are similar to clinical and laboratory findings. It can be argued that all causes of acute pancreatitis meet at a common point.<sup>27-29</sup> However, this idea needs to be proven by clinical and scientific research.

From this point of view, the idea of looking at the diagnostic value in diseases by making easy access to the values obtained in the routine tests and the results of the clinical tests has made significant

contributions to clinical applications. Although there is not enough literature base for diagnosis based on NLR and PLR rates and only based on these data, such studies may be important sources for further research and meta-analysis.

Early diagnosis is essential in pancreatitis and in evaluating the underlying ideas and findings. Therefore, any clinical practice that may express diagnostic value may be considered valuable. Although the findings obtained in the study are not sufficient for the diagnosis of pancreatitis, NLR and PLR ratios are essential in providing a basis for clinical studies and meta-analyses and guiding clinical applications. In the study, applying a high sample according to the studies in the field may contribute to the NLR and PLR studies in diagnosing pancreatitis.

In conclusion, there is a need for an easily accessible and inexpensive biomarker to indicate the diagnosis and clinical progression of acute pancreatitis, which may have different clinical manifestations. In our study, the purpose was to show the relations between NLR and PLR, which were shown in previous studies to increase inflammatory diseases and have prognostic importance, and acute pancreatitis. A significant increase was detected in NLR and PLR levels in the diagnosis of acute pancreatitis. However, it was found that only the change in NLR levels in the first 48 hours was associated with disease severity. Based on this finding, in our study, we would like to draw attention to NLR as an easily applicable and accessible parameter, which can be used similarly to the Atlanta classification. One of the limitations of this study is the small number of samples and the single center of the data. It is suggested that future studies be conducted with a larger number of samples from several medical centers.

**Ethics Committee Approval:** Our study was approved by the Sakarya University Ethics Committee (Date: 17.07.2014, decision no: 71522473/050.01.04/64).

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Author Contributions:** Concept – HE, ZE; Supervision – HE, ATE, HC; Materials – HE, ATE, HC; Data Collection and/or Processing – HE, ZE; Analysis and/ or Interpretation – ATE, HC; Writing – HE, HC.

**Peer-review:** Externally peer-reviewed.

**Other Information:** This study was produced from the thesis titled "The Role of Neutrophil/Lymphocyte and Platelet/Lymphocyte Ratio in the Evaluation of Acute Pancreatitis Severity" prepared by Hasan Ergenç on 17.07.2014.

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## Karacı'daki İşletme Öğrencilerinde Kendi Kendine İlaç Uygulamaları

### Self-Medication Practices among Business Students in Karachi

<sup>1</sup>Tamseel TANWIR AWAN, <sup>2</sup>Maliha ABBAS ZAIDI, <sup>3</sup>Farah KHALID, <sup>4</sup>Tabeer TANWIR AWAN

<sup>1</sup>Dow University Of Health Sciences, Professional Development Centre, Karachi, Pakistan

<sup>2</sup>Research Assistant, Institute of Medical Technology, Karachi, Pakistan

<sup>3</sup>Aga Khan University Hospital, Centre for Innovation and Medical Education, Karachi, Pakistan

<sup>4</sup>Research Assistant, Institute of Physical therapy and Medical Rehabilitation, Karachi, Pakistan

Tamseel Tanwir Awan: <https://orcid.org/0000-0002-4931-5658>

Maliha Abbas Zaidi: <https://orcid.org/0000-0002-5168-8883>

Farah Khalid: <https://orcid.org/0000-0003-3653-7741>

Tabeer Tanwir Awan: <https://orcid.org/0000-0003-4374-220X>

#### ÖZ

**Amaç:** Bu çalışmanın amacı, Karacı'deki işletme öğrencileri arasında kendi kendine ilaç uygulamalarını ve yaygınlığını bulmaktır.

**Materyal ve Metot:** Bu kesitsel bir çalışmadır ve Aralık 2018 – Aralık 2019 tarihleri arasında yürütülmüştür. Pakistan, Karacı İşletme Enstitüsü'nden veri elde etmek için uygun örnekleme tekniği kullanılmıştır. Veri analizi ve veri yönetimi SPSS sürüm 16.0 kullanılarak yapıldı.

**Bulgular:** Kendi kendine ilaç uygulama yaygınlığı %81 olarak elde edildi. Kendi kendine ilaç kullanmanın en yaygın nedeni, geçmişte başarılı bir şekilde ilaç tüketme (%46,2) ve doktora gitme zahmetinden kaçınma (%43,7) idi. Öğrencileri kendi kendine ilaç tedavisine yönelten en yaygın şikayetler ateş (%55,7), öksürük (%49,2) ve ağrı (%46) idi. En sık kullanılan ilaçlar ağrı kesici (%73,4) ve ateş düşürücü ilaçlar (%41,0) idi. Öğrencilerin ilaçları en büyük temin kaynağı serbest eczaneler (%67,6) olmuştur. Cinsiyet ve lisans programı gibi demografik faktörler ile kendi kendine ilaç tedavisi arasında anlamlı bir ilişki yoktu (sırasıyla p=0,061, p=0,747).

**Sonuç:** Karacı'deki işletme üniversitesi öğrencileri arasında %81'lik yüksek bir kendi kendine ilaç prevalansı bulundu ve bu, erkekler ve kadınlar arasında önemli bir fark olmaksızın endişe verici derecede yüksekti.

**Anahtar Kelimeler:** Farkındalık, kendi kendine ilaç tedavisi, öğrenciler, tıp, yaygınlık

#### ABSTRACT

**Objective:** The aim of this study is to find out the self-medication practices and its prevalence amongst business students of Karachi.

**Materials and Methods:** This is a cross-sectional study and was carried out from Dec 2018 – Dec 2019. Convenient sampling technique was used to obtain data from a Business Institute of Karachi, Pakistan. Data analysis and data management was done using SPSS version 16.0.

**Results:** Prevalence of self-medication practice was obtained to be 81%. The commonest reason for practicing self-medication was past successful consumption of the medicine (46.2%) and avoiding hassle to go to a doctor (43.7%). The commonest complaints that drove students to self-medicate were fever (55.7%), cough (49.2%) and pains (46%). Commonly used medicines were pain killers (73.4%) and fever relieving medicines (41.0%). The major source of obtaining the medicines was community pharmacies (67.6%) by the students. There was no significant association between the demographic factors such as gender and degree program and self-medication (p=0.061, p=0.747 respectively).

**Conclusion:** An 81% high prevalence of self-medication was found among the business university students in Karachi which is alarmingly high, with no significant difference between males and females.

**Keywords:** Aware, medicine, prevalence, self-medication, students

#### Sorumlu Yazar / Corresponding Author:

Tamseel Tanwir Awan  
C-280 PECHS-1, Karachi/ Pakistan  
Tel: +923232264111  
E-mail: tamseel.tanwir@gmail.com

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## INTRODUCTION

Self-medication is being considered as usage of medicines without consultation of qualified medical practitioner to deal with the self-diagnosed symptoms, or disorders, or constant usage of the prescribed medicines for a prolonged/repeated symptoms or disease.<sup>1,2</sup> Also defined as consumption of medications with no prescription, taking the medicines on advice of friends or the relatives, the reutilizing of an old prescription, or consuming the leftover medicines.<sup>3</sup>

There are many factors by which the self-medication is influenced, for instance the local legislation and accessibility of the medicines, the advertisements by pharmaceutical groups, education status of an individual, cultural norms, and the total number of family members and their income.<sup>4</sup> The widespread availability of over-the-counter (OTC) medications promotes self-medication as a result of recent development of pharmaceutical industry.<sup>5</sup> Analgesics, antibiotics, cough syrups, antimalarial, antipyretics are the drugs that are prone to self-medication.<sup>6</sup>

Every individual indulged in self-medication must be mindful about the risks and benefits of the product being used for self-medication. Certain dangers may perhaps be connected with self-medication, for example, drug resistance, drug associations, antagonistic medication responses, expanded polypharmacy, inaccurate finding and medication reliance.<sup>7-10</sup> Frequency of self-medication has escalated after 1980 when World Health Organization declared some drugs as safe to use without any prescription as a way to reduce the load on doctors. The patient starts self-medication with whatever suits them by taking information and processing it in his own way.<sup>11</sup>

In Pakistan and many developing countries, selling drugs without a prescription is seen. General populace tries to approach several other portals rather than that of a doctor to try to find aid for an illness due to the insufficiency of a proper fundamental system of health care together with budget issues. Despite this, in Pakistan, certainly no steps have been thought about to look into this difficulty.<sup>3</sup>

The idea behind this study was to educate and create awareness among the students who were unaware about the negative impact of self-medication, and this is the reason we had taken business students as participants. By conducting this study, an estimate of our young adult population that is practicing self-medication would be found as well as the sources from where they might have gotten these OTC drugs. This might be helpful in reducing rate of self-medication, its potential risk and decreasing the rate of drug resistant bacterial infections. Purpose of this study was to inquire the self-medication practices

along with its prevalence amongst business students of Karachi.

## MATERIALS AND METHODS

**Ethical Status of Study:** The current study was approved by H.E.J Research Institute, University of Karachi (Date: 12/09/2019, decision no: IAC/Ex/2019). This study was performed under Helsinki Declaration of Good Clinical Practice.

**Study Design and Study Setting:** The present study was a cross-sectional and was conducted to assess prevalence and practices of self-medication amongst business students in Karachi. The current study was conducted in a Business institute of Karachi. Target population included all students who were enrolled in undergraduate and master's courses in Karachi University Business School, University of Karachi. All healthcare students and personnel were being excluded from this research.

**Sampling Method and Sampling Size:** Non-probability sampling technique was implemented for this research. Participants were being informed and instructed regarding objective of this study before questionnaire administration. A sample of 400 business students was taken for this study. Sample size calculation was done by means of Slovin's formula with confidence level of 95%. Students related to healthcare field of academics were excluded from this study.

**Method of Data Collection:** Paper based questionnaire was used for the data collection. Questionnaire was adapted from research done by Correa da Silva et al, 2012 in Brazil and was modified as per needs of this study by the permission of the authors. The questionnaire had three sections (A, B and C). Self-medication was briefly defined at the start of the questionnaire. Section A contains the demographic variables. Section B assessed the self-medication practices and prevalence. Section C assessed attitude of students regarding the self-medication.

**Statistical Analysis:** Management of data and data analysis was being carried out by SPSS v.16. The descriptive analysis by calculating means and proportions for discrete and continuous data individually was performed. Moreover, inferential analysis was carried out by utilizing Pearson chi square test for recognizing association among the variables. The p-value <0.05 was being considered as significant in this study.

## RESULTS

Response rate of 100% was achieved for data collection. Business university students participated in the current study with many students falling in the age group of 18-23 years old (67.5%). There were 49% (196) male students and 51% (204) female students.

Amongst them 291 were undergraduate students while 109 were postgraduate students, detailed information can be seen in Table 1.

Pain killers (73.4%), Fever relieving meds (41.0%), Anti-allergy (30.2%) and Anti-biotics (26.0%) were the most frequently used drugs as elaborated in Table 2.

Most frequent reasons for self-medication were the past successful use of the medicine (46.2%), avoiding hassle to go to a doctor (43.7%) and saving time (30.6%) highlighted in Fig 1. Table 3. shows that the commonest complaints that drove students to opt for self-medication were fever (55.7%), cough (49.2%) and pains (46%). Majority of students selected the medication by opinion of family members (48.8%), previous doctor’s prescription (39%) and their own experience (35%). Majority of students considered the indication of medicine (40.5%) and type of medicine (38%) while selecting a medicine.

The major source of obtaining the medicines was

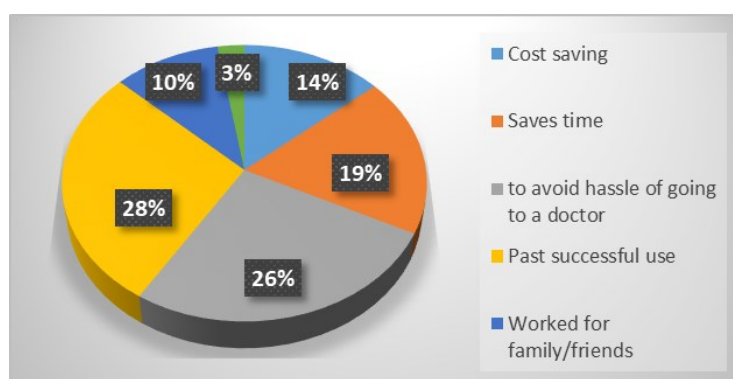
community pharmacies (67.6%) by the students. Only one hundred and seventy-two (52.8%) students said they checked the instructions that come with the packaging of medicine and one hundred and forty (54.1%) students partly understood those instructions. Students knew the dosage of medicine by consulting a doctor (32.6%), by checking the package insert (28.9%) and their own previous experience (26.1%). Moreover, 198 (60.7%) students sometimes changed the dosage of medicine during the course of self-treatment major reason being the improving condition (58%). Two hundred and fifteen (66%) students sometimes switched the medicine during the course of treatment with the major reason being the non-effectiveness of the former medicine (57.5%). Majority of students stopped taking the medicine after the symptoms of their ailment disappeared (44.3%). Two hundred and seventy (83.1%) students never experienced any adverse reaction by self-medicating.

**Table 1.** Baseline characteristics of participants.

	Demographics	Frequency	Percentage
<b>Age</b>	18-23	270	67.5%
	24-28	95	23.8%
	29-33	19	4.8%
	34-38	10	2.5%
	39-43	6	1.5%
<b>Gender</b>	Male	196	49.0%
	Female	204	51.0%
<b>Degree program</b>	Undergraduate	291	72.8%
	Masters	109	27.2%

**Table 2.** Most common drugs used to self-medicate.

Drugs	Frequency (%)
Pain killers	240 (73.4%)
Fever relieving meds	134 (41.0%)
Anti-allergy	98 (30.2%)
Anti-biotics	85 (26%)
Vitamins	73 (22.0%)
Pills for indigestion	41 (12.5%)
Sleeping pills	22 (6.7%)
Herbal / homeopathic	40 (12.2%)
Tonics	7 (2.1%)
Birth control pills	3 (.9%)



**Figure 1.** Reasons for self-medication.

**Table 3.** Practices and attitude towards self-medication.

Survey Questions	Feedback from participants	(n)	%
<b>Most common complaints for self-medication</b>	Runny nose	20	6.7%
	Nasal congestion	5	6%
	Cough	61	9.2%
	Sore throat	4	8.7%
	Fever	82	5.7%
	Aches and pains	50	6%
	Vomiting	5	6.8%
	Diarrhoea	6	0.2%
	Skin wounds	7	1.3%
<b>Selection of medicine</b>	Recommended by community pharmacist	2	5.1%
	Opinion of family members	59	8.8%
	Opinion of friends	9	8.1%
	Own experience	14	5%
	Recommended by net citizen	5	0.6%
	Previous doctor's prescription	27	9%
	Advertisement	5	0.6%
<b>Characteristic of medicine</b>	Type of medicine	24	8%
	Brand of medicine	8	3.1%
	Price of medicine	6	7.2%
	Indication for use	32	0.5%
	Adverse reaction	3	6.3%
<b>Source for obtaining medicine</b>	Community pharmacies	19	7.6%
	From a friend or relative	1	1.8%
	Leftovers from previous prescription	5	6.2%
	Online / e-shopping	1	0.5%
<b>Checking instructions</b>	Yes, always	9	4.2%
	Yes, sometimes	72	2.8%
	Never	5	3.0%
<b>Understanding instructions</b>	Fully understood	2	9.4%
	Partly understood	40	4.1%
	Did not understand at all	7	0.6%
<b>Dosage of medicine</b>	By checking package insert	3	8.9%
	By consulting a doctor	5	2.6%
	By consulting a pharmacist	2	2.4%
	By consulting a family member/ friend	9	7.6%
	By newspaper, books, magazines or tv	2	0.7%
	From internet	7	0.3%
	From my own previous experience	4	6.1%
	By guessing the dose myself	3	0.1%
<b>Changing dosage</b>	Yes, always	5	0.7%
	Yes, sometimes	98	0.7%
	Never	3	1.6%
<b>Reason for changing dosage</b>	Improving condition	30	8%
	Worsening condition	1	2.8%
	To reduce adverse reactions	1	3.8%
	Drug insufficient for complete treatment	3	4.7%
<b>Switching medicines</b>	Yes, always	8	0.6%
	Yes, sometimes	15	6.0%
	Never	2	5.2%
<b>Reason for switching medicine</b>	Former med did not work	42	7.5%
	Former med ran out	8	7.5%
	Latter one was cheaper	5	8.2%
	To reduce adverse reactions	9	1.7%
<b>Reason for stopping medicine</b>	After few days regardless of outcome	7	6.8%
	After symptoms disappear	44	4.3%
	A few days after recovery	8	7.1%
	After the medicine ran out	7	0.3%
	At completion of the course	3	3.2%
	After consulting the doctor	7	0.3%
<b>Adverse reaction due to self-medication</b>	No	70	3.1%
	Yes	5	6.9%
<b>Practice of self-medication</b>	Good practice	01	5.2%
	Acceptable practice	12	3.0%
	Not acceptable practice	7	1.8%
<b>Treating common diseases yourself</b>	Yes, i can	72	3.0%
	Not sure	77	4.2%
	No, i cannot	1	2.8%
<b>Attitude towards self-medication</b>	I encourage friends and family to self-medicate	94	8.5%
	Discourage friends and family to self-medicate	5	1.2%

Majority of students thought that self-medication is an acceptable practice (53%). One hundred and seventy-seven (43%) students thought that they can treat common diseases by self-medication whereas 172 (44.2%) students were not sure about it. 205 (51.2%) students responded that they would discourage while 194 (48.5%) would encourage friends and family for the self-medication.

Prevalence of the self-medication among study population was found to be 81% (N=327). There was no significant association between age and self-medication (p=0.059), gender and self-medication practices (p=0.061), degree program and the self-medication practices (p=0.747) were found out as shown in Table 4.

**DISCUSSION AND CONCLUSION**

Prevalence of the self-medication practice in business students in current research was 81%. There were many studies that showed consistency with the current research regarding prevalence rate, for instance 88% in Croatia,<sup>12</sup> 78% in Lahore,<sup>13</sup> 76% Karachi.<sup>3</sup> Several studies gave opposing frequency rate in comparison like 47.6% in Islamabad<sup>5</sup> and 45% in Turkey.<sup>14</sup> There was no significant association between the demographic factors such as gender and degree program with the self-medication. This result is in correspondence to a research performed in Karachi in which there was not much difference found between either gender or study year to be practicing self-medication more than the other.<sup>3</sup> There were several other studies done in Palestine, Iraq, and Bangladesh that reported no difference regarding self-medication practice in either gender.<sup>15-17</sup> A Kuwaiti study, on the other hand, indicated that girls self-medicate much more than the males (mainly because of painkillers for menstrual pain relief); the significant differences were also reported for age and grade in that study.<sup>18</sup>

The commonest purpose of self-medication should

have been ‘urgency of the problem’ because it is the only justifiable rationale, but among our study participants it was not found to be the most prevalent reason. Instead ‘past successful use of medicine’ (46.2%) and ‘avoiding the hassle to go to a doctor’ (43.7%) were found to be the commonest reason of self-medication in our study. Angamo and Wabe in year 2012 also found quick relief as the reason for self-medication.<sup>19</sup> This is practically identical with the study led on Pakistani mothers, which showed that 61.3% participants had great previous experience with drug which was fundamental purpose behind self-medication.<sup>20</sup> Such approaches show that even our knowledgeable youth is oblivious of the threats that can be caused by such practices, and this certainly is an alarming situation.

Although the reality of the matter is that the self-medication could treat minor illness that did not require curative discussion and consequently decrease the weight on medicinal administrations especially in the underprivileged nations with restricted human services means, accessibility of complex drugs, for example, anti-biotics without prescription is a well-spring of incredible concern.<sup>14</sup> A disturbing rate, 26%, of undergraduates had taken anti-biotics without legitimate clinical assessment. These outcomes are in congruent to research studies led in Karachi, Southern Spain and on undergraduates in Croatia where 35.6%, 41%, 38% individuals consumed anti-biotics without counseling a specialist respectively.<sup>3,21,14</sup> A major issue connected with this is of antibiotic resistance creating after some time with such unpredictable use.<sup>22</sup> Furthermore, the complaints that were frequent among students due to which they took medications were fever (55.7%), cough (49.2%) and pains (46%). In line with our results, the same complaints were in great numbers in research conducted in Bangladesh.<sup>17</sup> Painkillers (73.4%) was the most common drug that was used by students without any prior prescription. Analgesics were the drug

**Table 4.** Relationship between demographic variables and prevalence of self-medication among business students in Karachi.

Variable	Have you ever self-medicated		Total	P-value
	Yes n=387 (81.8%)	No n=73 (18.2%)		
<b>Age</b>				
18-23	229 (84.8%)	41 (15.2%)	270	0.059
24-28	68 (71.6%)	27 (28.4%)	95	
29-33	17 (89.5%)	2 (10.5%)	19	
34-38	8 (80%)	2 (20%)	10	
39-43	5 (83.3%)	1 (16.7%)	6	
<b>Gender</b>				
Male	153 (78.1%)	43 (21.9%)	196	0.061
Female	174 (85.3%)	30 (14.7%)	204	
<b>Degree program</b>				
Undergraduate	239 (82.1%)	52 (17.9%)	291	0.747
Masters	88 (80.7%)	21 (19.3%)	109	

of choice for the self-medication as seen in previous research.<sup>23</sup> High pervasiveness of the students regarding the self-medication with painkillers highlights the requirement for strategical and administrative mediations.<sup>15</sup>

The major source where the medicines were obtained were community pharmacies (67.6%) by the students while the leftover medicines were ranked second (26.2%). This was consistent with research done in Karachi that too on university students.<sup>24</sup> The latter source can be associated with the risk of consuming expired medicines, drugs that have indications for some other conditions and medicines that are actually meant for someone else.<sup>3,14</sup> This raises a concern as to why community pharmacies provide such easy access to medications, and this might be a strong reason in recording of high prevalence rate of self-medication. Students would never have received medications if community pharmacies declined to sell them without a prescription, which raises questions about pharmacy profession regulation enforcement.<sup>25</sup> Students should be educated about medication safety in a classroom setting. Strict measures could be implemented to govern the acquisition of pharmaceuticals and ban them from being purchased without a prior prescription by encouraging the pharmacists to allot these medications under strict supervision. There should be a proper check and balance system and medicine which do not lie in the category of over-the-counter medicines should never be provided without a prescription so that this problem can be prevented from escalating.<sup>26</sup> Despite the fact that it was not examined in this research, past studies have shown that advertising specifically influences young people to self-medicate.<sup>27</sup> In addition, the act of self-medication regularly has numerous antagonistic impacts and can prompt to numerous issues, including the worldwide development of Multi-Drug Resistant pathogens, medicate reliance and addiction, drug interactions, tragedies identifying with the reaction profile of particular drugs, danger of misdiagnosing and issues identifying with over and under dosing.<sup>19,28-30</sup>

In conclusion, prevalence of the self-medication (81%) was high among business students of Karachi which is alarmingly elevated, with no significant difference found between either males or females. Pattern towards expanded self-care and, with it, self-medication with ever more powerful medications appear to be relentless. The potential advantages of this practice, with the expanding strengthening of patients, are numerous. Though advancements in self-medication should be precisely overseen whether the advantages are to be amplified while potential dangers are kept to a minimum. Rigorous actions are required to screen notices of medications in printed electronic media.

**Ethics Committee Approval:** The study was approved by H.E.J Research Institute, University of Karachi (Date: 12/09/2019, decision no: IAC/Ex/2019). This study was performed under Helsinki Declaration of Good Clinical Practice.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Author Contributions:** Concept- TTA, MAZ; Supervision- TTA, FK; Materials- TTA, MAZ; Data collection and processing- TTA, MAZ; Analysis and Interpretation- TTA; Writing- TTA, FK, TTA.

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## Diminutif Poliplerin Endoskopik Tedavisinde Jumbo Forceps ve Soğuk Snare ile Polipektomi Yöntemlerinin Karşılaştırılması

### Jumbo Forceps Polypectomy Versus Cold Snare Polypectomy for Removal of Diminutive Colorectal Polyps

<sup>1</sup>Mukaddes TOZLU

<sup>1</sup> Sakarya Üniversitesi Tıp Fakültesi Gastroenteroloji Bölümü, Sakarya, Türkiye

Mukaddes Tozlu: <https://orcid.org/0000-0002-8534-8027>

#### ÖZ

**Amaç:** Kolonoskopi sırasında bulunan poliplerin çoğu 5 mm'nin altındadır. Polipektomi teknikleri endoskopistler arasında çok değişkendir ve endoskopistin tercihine göre belirlenmektedir. Bu çalışmada diminutif polip (DP) olarak adlandırılan, ≤5 mm poliplerde, jumbo forceps (JFP) ve soğuk snare (CSP) ile yapılan polipektomilerin tam rezeksiyon oranları ve komplikasyonlar yönünden karşılaştırılması amaçlanmıştır.

**Materyal ve Metot:** Kliniğimizde herhangi bir nedenle kolonoskopi yapılan ve ≤5 mm polip saptanan hastalar; JFP ve CSP grubu olarak iki gruba randomize edildi. Polipektomi yöntemleri komplikasyon ve rezeksiyon açısından karşılaştırıldı.

**Bulgular:** Toplam 100 polipektomi işlemi (JFP grubu=50 ve CSP grubu=50) analiz edildi. Ortalama hasta yaşı 59,1±11,2 yıldır ve 54'ü (%54) erkekti. Hastaların demografik özellikleri ve polip karakteristikleri gruplar arasında benzerdi. DP'ler için genel tam rezeksiyon oranı, JFP ve CSP grupları arasında önemli ölçüde farklı değildi (%90'a karşı %82, P=0,38). ≤3 mm poliplerde polipektomi süresi CSP grubunda anlamlı olarak uzundu (p=0,008). CSP grubunda %4 minör kanama izlendi ve 4 polip (%8) çıkartılmadı. Komplikasyon oranı CSP grubunda anlamlı olarak yüksek saptandı (p=0,01).

**Sonuç:** ≤5 mm kolorektal poliplerin eksizyonunda, rezidü açısından JFP ve CSP yöntemlerinin birbirlerine üstünlük sağladıkları gösterilmemiştir, ancak JFP yöntemi ile komplikasyon oranları daha düşük saptanmıştır.

**Anahtar Kelimeler:** Biyopsi, forceps, kolon polipleri, kolonoskopi

#### ABSTRACT

**Objective:** Most polyps found during colonoscopy are diminutive (≤5 mm). Polypectomy techniques are highly variable and determined by the endoscopist's preference. The aim of this study was to compare the efficacy and safety of jumbo forceps polypectomy (JFP) and cold snare polypectomy (CSP) for the removal of diminutive polyps (DP).

**Materials and Methods:** Patients who underwent colonoscopy for any reason in our clinic and were found to have DP were randomized into two groups as JFP and CSP. The main outcome was complete polyp resection and complication rate.

**Results:** A total of 100 polypectomies (50 in each group) were analyzed. The mean age of the patients was 59.1±11.2 years. Demographic characteristics of the patients were similar between groups. The overall rate of complete resection for DPs was not significantly different between JFP and CSP groups (90% versus 82%, p=0.38). Polypectomy time was significantly longer in the CSP group for polyps ≤3 mm (p=0.008). 4% minor bleeding and 8% tissue retrieval failure were noted for polyps resected by CSP. The complication rate was significantly higher in the CSP group (p=0.01).

**Conclusion:** JBF and CSP are not statistically different in completely removing DPs. However, the complication rate was lower in the JFP group.

**Keywords:** Biopsy, colonic polyps, colonoscopy, forceps

#### Sorumlu Yazar / Corresponding Author:

Mukaddes Tozlu  
Sakarya Üniversitesi Tıp Fakültesi Korucuk eğitim ve Araştırma Hastanesi  
Korucuk/Adapazarı/Türkiye  
Tel: 05337711802  
E-mail: mukaddestozlu@sakarya.edu.tr

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## GİRİŞ

Kolon kanseri için malignite potansiyeline sahip poliplerin çoğu kolonoskopi sırasında saptanarak çıkarılabilir.<sup>1</sup> Kolonoskopi sırasında bulunan poliplerin çoğu (%75-82) 5 mm'nin altındadır.<sup>2</sup> 5 mm altındaki kolon polipleri diminitif polip (DP) olarak adlandırılmaktadır.<sup>3</sup>

Tüm neoplastik poliplerin tam rezeksiyonu gereklidir. DP'ler sık saptanan polipler olduğundan, bu poliplerin tamamen çıkarılması için uygun polipektomi tekniği seçimi çok önemlidir. Polipektomi teknikleri endoskopistler arasında değişkendir ve endoskopistin tercihinine ve yöntemin ulaşılabilirliğine göre belirlenmektedir.<sup>4</sup>

Polipler çeşitli endoskopik tedavi yöntemlerinden biri ile alınabilir. Soğuk forseps polipektomi yöntemi, ulaşılabilirliği, kullanım kolaylığı ve snare ile alınması zor olabilecek küçük poliplerin çıkarılması kolaylığı nedeniyle bazı avantajlara sahiptir. Fakat forseps ile birden fazla ısırma ihtiyacı duyulması ve ilk ısırıktan sonra kanama ve ödemin polipektomi alanını gizleyerek rezidü kalma riskini artırması dezavantajlarıdır. Yapılan çalışmalarda polipektomi sonrası, tam endoskopik eradikasyondan sonra histolojide %29 ila %38 oranında rezidüel adenomatöz doku görülmüştür.<sup>5,6</sup> Soğuk snare polipektomi (CSP), DP'lerin yönetiminde standart forsepslerden daha etkili görünmektedir.<sup>7</sup> Jumbo biyopsi forsepsleri (JBF), standart forsepslere kıyasla daha fazla polip dokusu yakalayabilen bir tür soğuk forsepstir.

Son yıllarda standart forsepslere göre daha büyük olan jumbo forsepslerin etkili bir tedavi yöntemi olduğu bildirilse de DP'lerin endoskopik tedavisinde halen fikir birliği yoktur<sup>8</sup> ve kullanılan yöntemlerin doğrudan karşılaştırmasını içeren az sayıda çalışma yapılmıştır.

Bu çalışmada DP'lerde, jumbo forseps ve soğuk snare ile yapılan polipektomilerin tam rezeksiyon oranları ve komplikasyonlar yönünden karşılaştırılması amaçlanmıştır.

## MATERYAL VE METOT

Çalışma, Helsinki İlkeleri Bildirgesi'ne uygun olarak gerçekleştirildi ve Sakarya Üniversitesi Tıp Fakültesi, Klinik Araştırmalar Etik Kurulu'ndan onay alındı (Tarih: 17.05.2021, karar no: 117).

**Materyaller:** Çalışmaya, Mayıs ve Kasım 2021 tarihleri arasında Sakarya Üniversitesi Tıp Fakültesi Gastroenteroloji Kliniği'nde rutin kolonoskopi/rektosigmoidoskopi (tarama, surveyans veya tanı) uygulanan ve işlem esnasında kolon mukozasında diminitif polip ( $\leq 5$ mm) saptanan, 18 yaşın üzerindeki hastalar dahil edildi. İşlem öncesi tüm hastalardan yazılı bilgilendirilmiş onam alındı. 18 yaş altı, bilinen koagülopati, inflamatuvar bağırsak hastalığı, gebelik, polipozis sendromları olanlar ve kolon te-

mizliği yetersiz olanlar dışlandı.

**Yöntemler:** Hastalar jumbo forseps ve soğuk snare grubu olarak 2 gruba ayrıldı. Hastada polip saptandığında 1:1 randomizasyon ile polipektomi yöntemi seçildi. Bir hastada bir veya daha fazla polip varsa, uygun olan tüm polipler, başlangıçta atanan polipektomi yöntemi kullanılarak çıkarıldı. Polipler boyutlarına göre  $\leq 3$ mm ve 4-5 mm olarak 2 kategoriye ayrıldı. Polipektomiye başlamadan önce polip boyutu standart biyopsi forsepsini kullanılarak ölçüldü. Polipler; Paris sınıflandırmasına göre flat veya sesil olarak sınıflandırıldı. Polipektomi süresi, forseps/snare'in endoskop ucundan çıkışı ile biyopsi örneğinin çıkarılması arasında geçen süre olarak tanımlandı. Yaş, cinsiyet, kolonoskopi endikasyonu, antikoagulan kullanımı, komorbidite, polip boyutu, lokalizasyonu, sayısı, işlem süresi ve diğer demografik bilgiler kaydedildi.

Polipektomi işlemi; CSP grubunda 10 mm açıklık genişliğine sahip mikro-oval bir snare ve JFP grubunda 8,5 mm ağız açıklığına sahip jumbo forseps kullanıldı. Soğuk snare grubunda; soğuk snare ile polip çevresinde en az 1 mm normal dokuyu içerecek şekilde alındıktan sonra polipektomi yapıldı. Jumbo forseps grubunda; gerektiği kadar ısırık ile polip çıkarıldı. Her iki grupta polipektomi bölgesi 30 saniye hemoraji açısından izlendi. Daha sonra serum fizyolojik ile yıkandı ve rezidü açısından endoskopist tarafından değerlendirildi. Rezidü şüphesi olan yerlerden, rezidü şüpheli görünüm yoksa polipektomi bölgesi sağ ve sol kenarlarından tam açılmış standart forseps ile iki adet kontrol biyopsi alındı.

**Analizler:** Çalışmanın birincil amacı, iki grup arasında tam histolojik polip eradikasyon oranını karşılaştırmaktır. İkincil sonuçlar, polipektomi işlem süresi, doku çıkarma oranı ve polipektomiye bağlı komplikasyon oranları idi. Polipektomi yöntemleri komplikasyon ve polibin komplet/inkomplet çıkarılması açısından karşılaştırıldı.

**İstatistiksel Analiz:** Daha önceki çalışmalardaki verilere dayanarak CSP grubu için %93, jumbo forseps grubu için %75'lik, tahmini başarı oranlarına dayanarak, 0,05  $\alpha$  değerinde ve %80 güç ile çalışma kolu başına 54 hastalık bir örneklem boyutu belirlendi. Kategorik değişkenler, uygun olduğunda  $\chi^2$  testi veya Fisher exact testi kullanılarak değerlendirildi. Sürekli değişkenler için Student's t -testi veya Mann-Whitney U testi kullanıldı.  $P < 0,05$  istatistiksel olarak anlamlı kabul edildi. Tüm veriler toplandıktan sonra SPSS 24.0 programı ile uygun istatistiksel yöntemlerle analiz edildi.

## BULGULAR

İki grup arasında başlangıç özelliklerinde anlamlı bir farklılık yoktu. Hastaların demografik özellikleri Tablo 1'de görülmektedir.

Toplam 100 polipektomi işlemi (JFP grubu=50 ve



CSP grubu=50 hasta) analiz edildi. Ortalama hasta yaşı  $59,1 \pm 11,2$  yıldır. Hastaların 54'ü (%54) erkekti. Hastaların demografik özellikleri, komorbiditeleri, kolonoskopi endikasyonu, kolon temizlik skoru, anti-koagulan kullanımı her iki grup arasında benzerdi (Tablo 1).

Polip özelliklerine bakıldığında; poliplerin %62'si  $\leq 3$  mm, %38'i 4-5 mm büyüklüğünde idi. Paris sınıflandırmasına göre poliplerin %59'u sesil, %41'i flat olarak saptandı. 2 grup arasında polip özellikleri açısından anlamlı fark yoktu (Tablo 2).

Polipektomi yöntemlerinin etkinlik ve güvenilirliğinin karşılaştırılması Tablo 3'de gösterilmiştir.

DP'ler için genel tam rezeksiyon oranı %86 (86/100) idi. Tam rezeksiyon oranı, JFP ve CSP grupları ara-

sında önemli ölçüde farklı değildi (%90'a karşı %82,  $p=0,38$ ). Rezeke edilen poliplerin histopatolojik incelemesinde %45 tübüler adenom, %3 tübülovillöz adenom, %2 serrated adenom, %36 hiperplastik, %8 inflamatuvar psödopolip, %2 karsinom metastazı saptandı. 4 polip, polipektomi sonrası kaybolması nedeniyle patolojik değerlendirme yapılamadı. Polipektomi süresi 2 grup arasında önemli ölçüde farklı değildi ( $p=0,28$ ). CSP grubunda 2 hastada (%4) minör kanama izlendi ve 4 polip (%8) çıkartılmadı. JFP grubunda 1 hastada (%2) inkomplet rezeksiyon izlendi. Komplikasyon oranı CSP grubunda anlamlı olarak yüksek saptandı ( $p=0,01$ ) (Tablo 3).

Polip boyutlarına göre polipektomi sonuçlarının karşılaştırılması Tablo 4'de gösterilmiştir.

**Tablo 1.** Hastaların demografik özellikleri.

	Toplam n=100	Jumbo Forseps n=50	Soğuk Snare n=50	p
Yaş (ortalama $\pm$ SS)	59,1 $\pm$ 11,2	59,2 $\pm$ 11,1	58,9 $\pm$ 11,6	0,93
Erkek cinsiyet, n (%)	54 (54)	25 (50)	29 (58)	0,54
Komorbidite, n (%)	45 (45)	23 (46)	22 (46,8)	1
Kolonoskopi endikasyonu, n (%)				0,36
Anemi	15 (15)	7 (14)	8 (16,3)	
Karın ağrısı	14 (14)	6 (12)	8 (16,3)	
Kabızlık	7 (7)	5 (10)	2 (4,1)	
Malignite şüphesi	52 (52)	29 (58)	23 (46,9)	
Diğer	11 (11)	3 (6)	8 (16,3)	
Antikoagulan kullanımı, n (%)	17 (17)	12 (24)	5 (10,2)	0,1
Kolon temizlik skoru-İyi, n (%)	54 (54)	27 (54)	27 (54)	1

SS: Standart sapma.

**Tablo 2.** Polip özellikleri.

	Toplam n=100	Jumbo Forseps n=50	Soğuk Snare n=50	p
Polip Boyutu, n (%)				1
$\leq 3$ mm	62 (62)	31 (62)	31 (62)	
4-5 mm	38 (38)	19 (38)	19 (38)	
Paris Sınıflaması, n (%)				0,83
Sesil: Ip	3 (3)	2 (4)	1 (2)	
Is	36 (36)	20 (40)	16 (32)	
Isp	20 (20)	9 (18)	11 (22)	
Flat: IIa	38 (38)	18 (36)	20 (40)	
IIb	3 (3)	1 (2)	2 (4)	
Polip Lokalizasyonu, n (%)				0,95
Rektum	22 (22)	11 (22)	11 (22)	
Sigmoid	34 (34)	15 (30)	19 (38)	
İnen kolon	14 (14)	8 (16)	6 (12)	
Transvers kolon	18 (18)	10 (20)	8 (16)	
Çıkan kolon ve çekum	11 (11)	5 (10)	6 (12)	

## TARTIŞMA VE SONUÇ

Kolorektal poliplerin erken tanı ve tedavisine yardımcı olan kolonoskopi ve polipektomi işlemleri, kolorektal kanser riskini azaltan önemli minimal invaziv işlemlerdir. Kolonoskopi sırasında bulunan poliplerin çoğu DP'dir ve DP'lerin %50 ila %64'ünün adenom olduğu bildirilmektedir.<sup>9</sup> DP'ler malign potansiyelleri nedeniyle tamamen rezeksiyon edilmelidir. Daha önceki çalışmalarda, 5 ila 20 mm arasındaki polipler için yaklaşık %10'luk tam olmayan rezeksiyon oranları rapor edilmiştir.<sup>10</sup> Bu nedenle tam rezeksiyon oranını iyileştirmek için polipektomi tekniklerinin standardizasyonuna ihtiyaç vardır.

Standart forseps, sıcak ve jumbo biyopsi forsepsi, soğuk snare ve sıcak snare gibi çeşitli polipektomi yöntemleri vardır. DP'lerde sıcak yöntemlerde koter artefaktı nedeniyle histopatolojik değerlendirme zorluğu ve gecikmiş kanama ile karşılaşabileceği

bildirilmiştir.<sup>11</sup> Standart forseps, jumbo forseps, soğuk snare polipektomi gibi soğuk yöntemlerde bu risklere nadiren rastlanır. Standart biyopsi forsepsleri (SBF), kullanım kolaylığı ve güvenliği nedeniyle DP'lerin çıkarılmasında tercih edilmiştir. Ancak çalışmalarda, SBF'nin tam olmayan polipektomi oranı %29 ile %61 arasında rapor edilmiştir<sup>6</sup> ve özellikle >3 mm poliplerde tam rezeksiyon oranlarının, CSP ve JFP'den daha düşük olduğu bildirilmiştir.<sup>12,13</sup> DP'lerin çıkarılmasında JFP'nin etkinliği konusunda tartışmalar mevcuttur. Bir meta-analiz, JFP'nin toplam işlem süresini artırmadan yetersiz polip rezeksiyon oranlarını %60 oranında azaltabildiğini bildirmiştir.<sup>14</sup> SBF ile karşılaştırıldığında, jumbo forsepsin daha az ısırma ile tam rezeksiyon sağlayabilen daha geniş bir ağız açıklığı vardır. DP'lerin tedavisinde bir diğer tedavi seçeneği de CSP yöntemidir. CSP, polip tabanının etrafındaki 2-3 mm normal mukozanın yakalanması gibi teknik bir avantaja sahiptir. Bu da daha yüksek en-blok tam

**Tablo 3.** Polipektomi yöntemlerinin etkinlik ve güvenilirliğinin karşılaştırılması.

	Toplam n=100	Jumbo Forseps n=50	Soğuk Snare n=50	p
Tam rezeksiyon	86 (86)	45 (90)	41 (82)	0,38
Rezidü var, n(%)	14 (14)	5 (10)	9 (18)	0,38
Polipektomi süresi, sn (ortalama±SS)	55,4±46,2	53,8±48,9	57,1±43,6	0,28
Polip patoloji, n(%)				0,1
Hiperplastik	36 (36)	19 (38)	17 (34)	
Tubuler adenom	45 (45)	24 (48)	21 (42)	
Tubulovillöz adenom	3 (3)	1 (2)	2 (4)	
Yok-kayıp	4 (4)	-	4 (8)	
İnflamatuvar	8 (8)	4 (8)	4 (8)	
Serrated	2 (2)	-	2 (4)	
Karsinom metastazı	2 (2)	2 (4)	-	
Komplikasyon, n(%)				<b>0,01</b>
Yok	93 (93)	49 (98)	44 (88)	
Kanama	2 (2)	-	2 (4)	
Polip bulunamadı	4 (4)	-	4 (8)	
İnkomplet rezeksiyon	1 (1)	1 (2)	-	

SS: Standart sapma.

**Tablo 4.** Polip boyutlarına göre polipektomi sonuçlarının karşılaştırılması.

≤ 3mm	Toplam n=62	Jumbo Forseps n=31	Soğuk Snare n=31	p
Polipektomi süresi, sn (ortalama±SS)	48,6±37,8	37,1±28,1	60,6±43,1	<b>0,008</b>
Rezidü, n (%)	8 (12,9)	2 (6,5)	6 (19,4)	0,25
4-5 mm	Toplam n=38	Jumbo Forseps n=19	Cold Snare n=19	p
Polipektomi süresi, sn (ortalama±SS)	66,9±56,4	81,2±62,6	50,8±45,2	0,14
Rezidü, n (%)	6 (30,8)	3 (15,8)	3 (15,8)	0,34

SS: Standart sapma.

rezeksiyon sağlar. Bu tekniğin ana dezavantajı, polipektomiden sonra polip çıkarmanın başarısız olabilemesidir. Özellikle doku gayta ve kan ile karıştığında, çıkarılan polip bazen aspire edilmeden önce kolonda kaybolabilir.<sup>15,16</sup>

JFP ile CSP yöntemlerinin rezeksiyon oranlarını doğrudan karşılaştıran az sayıda çalışma vardır. DP'lerin çıkarılması için CSP'yi öneren son kılavuzlara rağmen, endoskopistler arasında soğuk forseps polipektomisi tercih edilen teknik olmaya devam etmektedir.<sup>17,18</sup> Bu muhtemelen birkaç faktörden kaynaklanmaktadır. Soğuk forseps hemen tüm endoskopi üniterlerinde mevcuttur, kullanımı kolaydır ve snare polipektomiye kıyasla endoskopist ve asistan arasında daha az koordinasyon gerektirir. Ek olarak, forseps, polipin küçük boyutu veya konumu nedeniyle, snare ile yakalanması zor olabilecek polipleri kolayca kavrayabilir. Ayrıca, snare polipektominin aksine, forseps ile elde edilen doku örneğinin kaybolma olasılığı daha düşüktür ve hemen alınabilir. Fakat biyopsi ile yüksek tam olmayan histolojik rezeksiyon oranı önemli bir endişe kaynağıdır.<sup>5,13</sup>

Bu nedenle, bu çalışmada diminutif polipektominin etkinliği ve güvenliği açısından CSP ile JFP'yi doğrudan karşılaştıran bir randomize kontrollü çalışma yaptık.

Çalışmamızda tüm DP'lerin >%90'ı JFP veya %82'si CSP ile tamamen rezeke edildi. CSP grubunun doku çıkarma oranı, JFP grubuna göre daha düşüktü, ancak istatistiksel olarak anlamlı değildi (p=0,38). Tüm polipler değerlendirildiğinde iki grup arasında polipektomi süresi açısından anlamlı bir fark yoktu. Polip boyutlarına göre yapılan analizde, ≤3 mm poliplerde toplam rezidü oranı %12,9 ve 4-5 mm boyutunda polipler için toplam rezidü oranı %30,8 olarak saptandı ve gruplar arasında anlamlı farklılık izlenmedi. ≤3 mm poliplerde polipektomi süresi JFP grubunda anlamlı olarak daha kısaydı (p=0,008). 4-5 mm polipler için polipektomi süresi JFP grubunda daha yüksek saptanmasına rağmen gruplar arasında farklılık göstermedi (p=0,14).

Çalışmalarda CSP tekniği ile küçük ama önemli sayıda doku alma başarısızlığı bildirilmiştir, bu da gereksiz polipektomi sonrası sürveyansa yol açabilir.<sup>16,19</sup> Yine, soğuk snare veya biyopsi sonrası minör kendi kendini sınırlayan mukozal kanama olabilir. CSP, diğer yöntemlerle karşılaştırıldığında, özellikle polipektomi sonrası kanama gibi yan etkilerle ilişkilendirilmiştir. Bizim çalışmamızda; CSP grubunda 2 hastada (%4) minör kanama izlendi ve 4 polip (%8) çıkartılmadı. JFP grubunda 1 hastada (%2) inkomplet rezeksiyon izlendi. Komplikasyon oranı CSP grubunda anlamlı olarak yüksek saptandı (p=0,01). Sonuçlarımıza göre, DP'lerin polipektomisinde, JFP yöntemi polipektomi materyalinin kolonda kaybolmadan forseps içinde çıkarılması için kolay ve etkili bir endoskopik tedavi seçeneği olarak

düşünülebilir.

Bu çalışmanın çeşitli kısıtlılıkları vardır. Birincisi, polipektomi yapan kolonoskopistin rezeksiyon yöntemine kör olmamasıdır. Bu, biasa neden olmuş olabilir. Bununla birlikte, yöntemlerin belirgin görünümü nedeniyle böyle bir körleme muhtemelen imkansızdır. İkincisi, polipektomi bölgesinden alınan iki ek biyopsi örneği rezidü dokuları tespit etmek için yetersiz olabilir. Narrow band imaging (NBI) veya chromoendoscopy ile polipektomi bölgesinin değerlendirilmesi rezidü dokuların tespit edilmesine katkıda bulunabilir. Son olarak, çalışmamız nispeten küçük bir örneklem büyüklüğüne sahiptir.

Sonuç olarak; ≤5 mm kolorektal poliplerin eksizyonda JFP ve CSP güvenilir yöntemlerdir. Rezidü açısından bu iki yöntemin birbirlerine üstünlük sağladıkları gösterilmemişse de, JFP yöntemi ile komplikasyon oranları daha düşük saptanmıştır. DP'lerin çıkarılması için forseps düşünülürse, bu çalışmanın sonuçlarına göre JFP önerilebilir. Polipektomi yöntemlerinden bağımsız olarak soğuk polipektomi sonrası rezidü polip riski devam ettiği için, polipektomi bölgesinin detaylı incelenmesi gerekmektedir.

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## Üçüncü Basamak Bir Hastanede Yatan COVID-19 Hastalarında Sekonder Enfeksiyonlar

### Secondary Infections in COVID-19 Patients Hospitalized in A Tertiary Hospital

<sup>1</sup>Neslihan ARICI, <sup>2</sup>Asu ÖZGÜLTEKİN, <sup>1</sup>Nilgün KANSAK, <sup>1</sup>Rıza ADALETİ, <sup>3</sup>Handan ANKARALI, <sup>4</sup>Sebahat AKSARAY

<sup>1</sup>University of Health Science, Haydarpaşa Numune Training and Research Hospital, Department of Medical Microbiology, Istanbul, Turkey

<sup>2</sup>University of Health Science, Haydarpaşa Numune Training and Research Hospital, Department of Anesthesiology and Reanimation, Istanbul, Turkey

<sup>3</sup>Medeniyet University, Faculty of Medicine, Department of BioStatistic, Istanbul, Turkey

<sup>4</sup>University of Health Science, Faculty of Medicine Hamidiye, Department of Medical Microbiology, Istanbul, Turkey

Neslihan ARICI: <https://orcid.org/0000-0003-4788-0044>

Asu ÖZGÜLTEKİN: <https://orcid.org/0000-0003-4307-9604>

Nilgün KANSAK: <https://orcid.org/0000-0002-1117-3906>

Rıza ADALETİ: <https://orcid.org/0000-0001-9576-6794>

Handan ANKARALI: <https://orcid.org/0000-0002-3613-0523>

Sebahat AKSARAY: <https://orcid.org/0000-0002-0552-1337>

#### ÖZ

**Amaç:** Bu çalışmada hastanede yatan COVID-19 hastalarında sekonder enfeksiyonların oranları, etiyolojik ajanları ve klinik sonuçlara etkisinin belirlenmesi amaçlanmıştır.

**Materyal ve Metot:** RT-PCR yoluyla COVID-19 tanısı doğrulanmış hastanede yatan 150 yetişkin hasta arasında sekonder enfeksiyonu olan ve olmayan hastaların özelliklerinin retrospektif olarak karşılaştırmalı analizi yapıldı.

**Bulgular:** Dahil edilen hastaların 20'sinde (%13,3) en az bir sekonder enfeksiyon tespit edildi. Yoğun bakım hastalarında sekonder enfeksiyon oranı (%72) genel serviste yatan hastalardan (%1,6) anlamlı derecede yüksek bulundu ( $p<0,001$ ). Ventilatör ilişkili pnömoni (VİP) prevalansı YBÜ hastalarında %52 idi. İzole edilen toplam 31 mikroorganizmanın çoğunluğunu gram negatif bakteriler oluşturmaktaydı. Genel olarak, 147 (%98) hasta, hastaneye yatışları esnasında en az bir kez antibiyotik tedavisi aldı. Sekonder enfeksiyonu olan hastalarda mortalite oranı, olmayanlara göre istatistiksel olarak anlamlı derecede yüksek bulundu ( $p<0,001$ ).

**Sonuç:** Genel serviste yatan COVID-19 hastalarında sekonder enfeksiyon oranı çok düşük olduğu için, antibiyotiklerin akılcı kullanımına gereği, bu hastalara ampirik antibiyotik tedavisi başlanmaması gerektiğini düşünüyoruz. Ayrıca VİP enfeksiyonlarının hem ampirik hem de hedefe yönelik tedavisinde çoklu ilaca dirençli bakterilerin dikkate alınmasının önemli olduğunu düşünüyoruz.

**Anahtar Kelimeler:** Antibiyotik kullanımı, COVID-19, sekonder enfeksiyonlar, ventilatör ilişkili pnömoni

#### ABSTRACT

**Objective:** In this study, it was aimed to describe rates, etiological agents of the secondary infections and its effect on clinical outcomes among hospitalized patients with COVID-19.

**Materials and Methods:** A retrospective comparative analysis of the characteristics of patients with and without secondary infection was carried out among 150 hospitalized adult patients with a confirmed diagnosis of COVID-19 via RT-PCR.

**Results:** Among included patients, 20 (13.3%) had at least one secondary infection. Secondary infection rate in ICU patients (72%) was significantly higher than patients in the general ward (1.6%) ( $p<0.001$ ). The prevalence of ventilator-associated pneumonia (VAP) was 52% in ICU patients. The majority of 31 microorganisms isolated were gram negative bacteria. Overall, 147 (98%) patients received at least one antibiotic during their hospitalization. A significantly higher mortality rate was present in patients with secondary infection compared to those without.

**Conclusion:** Since the rate of secondary infection in hospitalized COVID-19 patients in the general ward is very low, we consider that empirical antibiotic therapy should not be initiated in these patients in accordance with the rational use of antibiotics. Besides, we recommend that multidrug-resistant bacteria be taken into account both in the empirical and targeted antimicrobial therapy of VAP infections.

**Keywords:** Antibiotic use, COVID-19, secondary infections, ventilator-associated pneumonia

#### Sorumlu Yazar / Corresponding Author:

Neslihan Arici  
University of Health Science, Haydarpaşa Numune Training and Research Hospital, Medical Microbiology, Tıbbiye cad. No:23  
34668 Uskudar, Istanbul, Turkey  
Tel: +90-553-3496680  
Fax: +90-216-3360565  
E-mail: dr.neslihan.cicek@gmail.com

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## INTRODUCTION

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide, and due to severity of the disease, some patients need to be hospitalized and some severe cases may require intensive care with non-invasive or invasive respiratory support.<sup>1,2</sup> Patients with moderate or severe COVID-19 often have serious comorbidities, prolonged hospitalizations, and need for mechanical ventilation, which may pose a high risk for secondary infections.<sup>3,4</sup> Although rates of these infections in hospitalized COVID-19 patients are generally low (10-15%), it was emphasized in many studies that the presence of these infections is associated with unfavorable outcomes in critically ill ICU-patients.<sup>5-7</sup> Therefore, microbiological data are valuable in guiding evidence-based treatment of secondary bacterial infections in patients with COVID-19. International guidelines regarding antimicrobial stewardship recommend clinicians to collect blood cultures as well as respiratory samples for bacterial cultures to confirm the secondary infection.<sup>8,9</sup> However, in some studies, it has been reported that routine microbiological examinations cannot be performed due to the risk of exposure of healthcare workers to SARS-Cov-2 during sample collection and processing, which may cause serious disruptions in the diagnosis and treatment of secondary infection.<sup>3,5,10</sup> Furthermore, due to the difficulty of ruling out bacterial co-infection on presentation and also secondary infection during the course of the illness, empiric antibiotics, including broad spectrum agents, are frequently prescribed for patients both in the general wards and in the ICU.<sup>11</sup> However, recent World Health Organization (WHO) guidelines, and most researchers report that antibiotic prescription should be limited only to severe COVID-19 patients in order to avoid the widespread use of empirical antibiotics that could lead to the development of multidrug-resistant bacteria.<sup>7-9,12</sup>

Although there are studies on the clinical management of COVID-19 in our country, data on the secondary infections are scarce. In this study, performing a comparative analysis of the characteristics of patients with and without secondary infection, we aimed to describe rates, etiological agents of the secondary infections, and its effect on clinical outcomes among hospitalized patients with COVID-19.

## MATERIALS AND METHODS

**Ethics Committee Approval:** A retrospective observational analysis was carried out on hospitalized adult patients admitted to a tertiary hospital between 11/03/2020 and 31/05/2020 with a confirmed diagnosis of COVID-19 via reverse transcriptase-

polymerase chain reaction assay (RT-PCR) performed on nasopharyngeal throat swab specimens. Approvals were received by the Ministry of Health and the ethics committee of Haydarpaşa Numune Research and Training Hospital (Date: 29/06/2020, decision no:115).

**Study Design, Participants, and Data Collection:** A total of 150 patients with complete data of white blood cells (WBC), neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), and procalcitonin (PCT) results were included in the study. All data were collected from the hospital electronic record and included patient demographics, comorbidities, clinical parameters, laboratory findings, microbiology data (including culture of blood samples, endotracheal aspirate (ETA), urine, and antimicrobial susceptibility), ICU admission, mechanical ventilation (MV), patterns of antibiotic use, and outcome (length of hospital stay, discharge, and died). Secondary infection was determined by the presence of characteristic clinical features, and at least one positive blood, sputum/endotracheal aspirate, and urine culture results after 48 h of admission. Ventilator-associated pneumonia (VAP) was defined as the sum of infectious ventilator associated condition and a quantitative pulmonary infection (endotracheal aspiration growing  $>10^5$  CFU/mL) in patients exposed to invasive mechanical ventilation for at least 48 h.<sup>13</sup>

**Laboratory Procedures:** Laboratory confirmation of SARS-CoV-2 was achieved by RT-PCR (Biospeedy, Turkey) using nasopharyngeal throat samples at an authorized central laboratory. Routine blood examinations consisted of white blood cells (WBC), neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), and procalcitonin (PCT). For blood culture, blood was inoculated into aerobic and anaerobic media and culture bottles were incubated in an automated blood culture system (BactAlert, Biomerieux, France) for 5 days according to the manufacturer's recommendations. Blood cultures positive for skin flora [coagulase-negative staphylococci (CoNS), gram-positive bacilli, micrococci e.g.,] that did not grow in multiple cultures or on separate dates were excluded. For ETA culture, microorganisms grown  $\geq 10^5$  CFU/mL in ETA samples showing on gram stain  $>25$  neutrophils and  $<10$  epithelial cells per low power field were considered as etiological agents for secondary infection. Pathogen identification was performed by matrix assisted laser desorption ionisation-time of flight mass spectrometry (MALDI-TOF VITEK MS, bioMerieux, France). Antimicrobial susceptibility testing was carried out on VITEK-2 automated system (bioMerieux, France), and all the results were interpreted according to the criteria of the European Committee on Antimic-

robial Susceptibility Testing (EUCAST 2020).<sup>14</sup>

**Statistical Analysis:** Descriptive statistics of the obtained data were given in tables as mean, standard deviation (SD), median, number and % frequencies. The compliance of numerical data to the normal distribution was examined using the Shapiro-Wilks test. While the relationship of secondary infection status with numerical type features was examined with the Mann-Whitney U test, its relationship with the categorical features was evaluated with the Pearson chi-square test.  $p < 0.05$  was accepted as the statistical significance level and Statistical Package for the Social Sciences (SPSS ver. 23) program was used in calculations.

**RESULTS**

A total of 150 hospitalized patients with confirmed COVID-19 were analyzed. Among them 95(63.3%) patients were males and the mean age was 56 years (21-92). Among included patients, 20 (13.3%) had at least one microbiologically documented secondary infection and 130 (86.7%) had no secondary infection. The study population was divided into two subgroups as patients with and without secondary infection. The median age in patients with secondary infection (71.5 vs 54.5) was significantly higher than

those without ( $p < 0.001$ ). When laboratory values examined, median WBC (10.3 versus 5.5), NLR (11.3 versus 2.3), CRP (18 versus 2.4), and PCT (1.8 versus 0.05) levels were significantly higher among patients with secondary infection compared to those without ( $p < 0.001$ ). Thirteen of the 25 ICU-patients received MV for at least 48 hours had significant bacterial growth, indicating a 52% prevalence of ventilator-associated pneumonia (VAP) in these patients. The mean time of total MV duration was 9 days in patients with bacterial growth, and the mean time of ETA positivity after tracheal intubation was found to be 6.8 days. In comparison to patients who underwent invasive mechanical ventilation, and did not have secondary infection, patients with secondary infection received significantly longer mechanical ventilation with a median duration of 9 (5.75–17.5) days ( $p < 0.001$ ). Overall, 147 (98%) patients received at least one antibiotic during their hospitalization, regardless of the presence of any secondary infection. The median antibiotic days of therapy was 12 days (9.25–21) for the patients with secondary infection. Besides, patients with secondary infection had a median duration of hospital stay for 12 days (10–24.75), which was significantly higher than those without ( $p < 0.001$ ) (Table 1).

**Table 1.** Comparison of numerical properties between patients with and without secondary infection.

Parameters	Secondary infection	N	Mean±SD	Percentiles			p*
				25th	Median	75th	
Age	No	130	54.14±15.03	44.00	54.50	65.00	<0.001
	Yes	20	68.30±11.17	58.50	71.50	77.75	
WBC	No	130	6.39±3.36	4.50	5.55	7.33	<0.001
	Yes	20	13.18±7.33	9.00	10.30	18.75	
NLR	No	130	3.99±5.86	1.58	2.35	3.80	<0.001
	Yes	20	13.10±8.83	4.85	11.30	19.50	
CRP	No	130	4.90±5.19	0.80	2.45	7.73	<0.001
	Yes	19	19.61±9.70	11.00	18.00	29.00	
PCT	No	99	0.472±0.03	0.05	0.05	0.08	<0.001
	Yes	19	5.93±7.42	0.61	1.80	9.30	
Length of antibiotic therapy (day)	No	130	7.35±3.88	5.00	7.00	8.25	<0.001
	Yes	20	14.65±7.41	9.25	12.00	21.00	
Length of hospital stay (day)	No	130	9.27±4.58	6.00	8.00	11.25	<0.001
	Yes	20	16.20±9.23	10.00	12.00	24.75	
Length of ICU stay (day)	No	7	8.57±4.20	6.00	9.00	13.00	0.523
	Yes	18	13.22±9.59	7.00	10.00	18.25	
Length of mechanical ventilation (day)	No	4	7.00±2.70	4.25	8.00	8.75	0.005
	Yes	18	12.67±9.94	5.75	9.00	17.50	

WBC: white blood cells; NLR: neutrophil-to-lymphocyte ratio; CRP: C-reactive protein; PCT: procalcitonin; ICU: intensive care unit

\*Mann-Whitney U test

Considering all patients, most common comorbidities included hypertension, diabetes mellitus, and coronary heart disease, respectively. Patients with hypertension, coronary heart disease, and malignancy have had significantly higher secondary infection rate. Overall, 125 (83.3%) patients were treated in the general ward, and 25 (16.7%) patients were in the ICU. Secondary infection rate in ICU patients [18, (72%)] was significantly higher than patients in the general ward [2, (1.6%)] ( $p<0.001$ ). Among 130 patients without secondary infection, 123 (94%) of whom in the general service, the antibiotic regimen

most commonly used was azithromycin with or without ceftriaxone with a median duration of 7 (5–8.25) days. Among twenty patients with secondary infection, the most common antibiotics used were teicoplanin (12, 60%), meropenem [10, (50%)], and piperacillin-tazobactam (5, 25%), except of ceftriaxone and azithromycin administered before ICU admission. Generally, 127 (84.7%) of 150 patients were discharged, and 23 (15.3%) were died. A significantly higher mortality rate [18, (78.3%)] was present in patients with secondary infection compared to those without ( $p<0.001$ ) (Table 2).

**Table 2.** Comparison of categorical properties between patients with and without secondary infection.

		Secondary infection			p*
		Total	No (n=130)	Yes (n=20)	
		n (%)	n (%)	n (%)	
<b>Sex</b>	Male	95 (63.3)	81 (85.3)	14 (14.7)	0.506
	Female	55 (36.7)	49 (89.1)	6 (10.9)	
<b>Service</b>	General	125 (83.3)	123 (98.4)	2 (1.6)	<0.001
	ICU	25 (16.7)	7 (28.0)	18 (72.0)	
<b>Comorbidities</b>					
Hypertension	No	110 (73.3)	99 (90.0)	11 (10.0)	0.046
	Yes	40 (26.7)	31 (77.5)	9 (22.5)	
Diabetes	No	119 (79.3)	103 (86.6)	16 (13.4)	0.937
	Yes	31 (20.7)	27 (87.1)	4 (12.9)	
Coronary heart disease	No	133 (88.7)	121 (91.0)	12 (9.0)	<0.001
	Yes	17 (11.3)	9 (52.9)	8 (47.1)	
Chronic obstructive pulmonary disease	No	136 (90.7)	120 (88.2)	16 (11.8)	0.078
	Yes	14 (9.3)	10 (71.4)	4 (28.6)	
Chronic renal failure	No	140 (93.3)	123 (87.9)	17 (12.1)	0.109
	Yes	10 (6.7)	7 (70.0)	3 (30.0)	
Malignancy	No	142 (94.7)	126 (88.7)	16 (11.3)	0.002
	Yes	8 (5.3)	4 (50.0)	4 (50.0)	
<b>Antibiotics</b>					
Azithromycin	No	34 (22.7)	23 (67.6)	11 (32.4)	<0.001
	Yes	116 (77.3)	107 (92.2)	9 (7.8)	
Ceftriaxone	No	41 (27.3)	29 (70.7)	12 (29.3)	<0.001
	Yes	109 (72.7)	101 (92.7)	8 (7.3)	
Cefixime	No	139 (92.7)	121 (87.1)	18 (12.9)	0.623
	Yes	11 (7.3)	9 (81.8)	2 (18.2)	
Piperacillin-tazobactam	No	138 (92.0)	123 (89.1)	15 (10.9)	0.003
	Yes	12 (8.0)	7 (58.3)	5 (41.7)	
Colistin	No	146 (97.3)	130 (89.0)	16 (11.0)	<0.001
	Yes	4 (2.7)	0 (0.0)	4 (100.0)	
Meropenem	No	138 (92.0)	128 (92.8)	10 (7.2)	<0.001
	Yes	12 (8.0)	2 (16.7)	10 (83.3)	
Teicoplanin	No	129 (86.0)	121 (93.8)	8 (6.2)	<0.001
	Yes	21 (14.0)	9 (42.9)	12 (57.1)	
Vancomycin	No	149 (99.3)	130 (87.2)	19 (12.8)	0.011
	Yes	1 (0.7)	0 (0.0)	1 (100.0)	
No antibiotic administered	No	147 (98.0)	127 (86.4)	20 (13.6)	0.493
	Yes	3 (2.0)	3 (100.0)	0 (0.0)	
<b>Mechanical ventilation</b>	No	128 (85.3)	126 (98.4)	2 (1.6)	<0.001
	Yes	22 (14.7)	4 (18.2)	18 (81.8)	
<b>Outcome</b>	Discharge	127 (84.7)	125 (98.4)	2 (1.6)	<0.001
	Died	23 (15.3)	5 (21.7)	18 (78.3)	

\* Pearson chi-square test



A total of 86 samples, including 54 blood, 25 ETA, and 7 urine were obtained for microbiological culture from 43 of 150 COVID-19 patients. While no ETA samples were sent from 8 out of 22 mechanically ventilated patients in the ICU, a total of 25 ETA samples were collected from the remaining 14 patients during their hospital stay. A total of 21 bacteria were isolated from 18 ETA samples with significant growth. Among the detected twenty-one microorganisms, gram negative bacteria accounts for 19 (90.4%), and the most common bacteria isolated was *Acinetobacter baumannii* (n=11), followed by *Pseudomonas aeruginosa* (n=5), and *Klebsiella pneumoniae* (n=3), respectively. All of *A. baumannii* isolates were multi-drug resistant, and susceptible only against colistin. Any mold that could cause invasive pulmonary aspergillosis was not detected by Gram/Giemsa staining or by ETA culture. For diagnosis of bacteremia, no growth was occurred in any of the blood cultures from patients in the general wards, while in 10 (32%) of the blood cultures from ICU patients growth was detected. The microorganisms isolated were *Staphylococcus epidermidis* (n=3), *Enterococcus faecalis* (n=3), *Acinetobacter baumannii* (n=2), *Klebsiella pneumoniae* (n=1), and *Candida glabrata* (n=1) in order of frequency. As for gram positive bacteria, methicillin resistance was present in all *Staphylococcus epidermidis* isolates, and no vancomycin resistance was found in *Enterococcus spp.* While no growth was observed in urine samples sent from the ICU, *E.coli* was isolated in a sample from the general service.

## DISCUSSION AND CONCLUSION

Secondary infection is a serious complication in patients hospitalized with COVID-19, which is associated with worse outcomes and high mortality.<sup>6,15</sup> So far, many studies have been published reporting frequency and the features of these infections from different countries around the world.<sup>7,11</sup> As stated in some studies,<sup>16,17</sup> we also observed that patients with secondary infections were older and had multiple underlying comorbidities, mostly hypertension and coronary heart disease, compared to those without secondary infection. Overall, 127 of 150 hospitalized COVID-19 patients were discharged, and 23 were died in our study. We found that patients with secondary infection had significantly prolonged length of hospital stay and a higher mortality rate, compared to those without infection, which was consistent with previous studies.<sup>2,18</sup>

In the current literature, the rate of secondary infection in hospitalized COVID-19 patients varies widely between 3.8% and 83.3%, by emphasizing that it is noticeably more often in ICU-patients than those in the general service.<sup>2,6,11,18</sup> In accordance with this data, we found the secondary infection rate

to be 13.3% among all 150 hospitalized COVID-19 patients. In service-based evaluation, we observed that this rate was very high as 72% in ICU patients, while it was very low as 1.6% in non-ICU-patients. Besides, compared with patients without secondary infection, use of MV were more common in patients with secondary infections (81.8% vs 18.2%) and these patients received significantly longer mechanical ventilation with a duration of 12 versus 7 days. Given that secondary infections closely related with the use of mechanical ventilation, it is expected that the majority of secondary respiratory infections reported in critically ill COVID-19 patients are ventilator-associated pneumonia.<sup>11,16,19,20</sup> We also observed that 21 of 31 secondary infection episodes were lower respiratory tract infections, mostly VAP. In recent studies,<sup>18,19,21</sup> the rate of VAP in COVID-19 patients was reported being as high as 25–54%. Similarly, we found the prevalence of VAP as 52% (13) in mechanical ventilated COVID-19 patients. Our data indicated a significant rate of VAP, with a predominance of Gram-negative bacteria, mostly non-fermenters (*A.baumannii*, *P.aeruginosa*), compatible with previous studies of COVID-19 patients in ICU.<sup>1,6,20-22</sup> However, in contrast to a current study,<sup>23</sup> which reported that there have been several cases of COVID-19-associated pulmonary aspergillosis (CAPA), we didn't observed such a case, possibly due to the small number of ICU patients in our study population. Besides, we should state that the frequency of VAP may be slightly higher and secondary respiratory tract infection may have been overlooked, since respiratory samples were not sent from eight patients who were mechanically ventilated and died, and microbiological examination could not be performed. This observation is in agreement with previous studies which indicated that respiratory cultures from COVID-19 patients were obtained on a limited basis due to extreme workloads and risk for aerosolization, and thus the rates of secondary infection potentially affected.<sup>3,5</sup> Therefore, we recommend performing respiratory samples from mechanically ventilated COVID-19 patients with suspected secondary respiratory infection, taking all precaution to prevent possible transmission, due to provide an effective treatment and better prognosis of the patients.

Regarding blood cultures, culture positivity was detected as 16.5% (9/54), all of them in ICU patients. Among isolated microorganisms, gram positive pathogens were the most frequent cause of bacteremia, being coagulase negative *Staphylococcus (CNS)* and *Enterococcus spp.* the most common detected. The pathogen distribution was similar to some COVID-19 studies, which reported that *Enterococcus* strains especially may have been selected in bacteremia detected in intensive care patients due to previous

empirical use of ceftriaxone, as in our ICU-patients.<sup>18,22,24</sup>

Evaluating the antimicrobial resistance data of isolated microorganisms, it was remarkable that all *A. baumannii* isolates, which are the main bacterium of VAP infections, were resistant to all antibiotics except colistin. Therefore, for centers with similar epidemiological features to our hospital, in cases considered to develop possible or probable VAP, empirical treatment adequately covering the multidrug-resistant *A. baumannii* strains should be implemented. Switching to targeted antibacterial treatment upon microbiological results is highly appreciated. As stated in previous studies<sup>3,5,9,11,18</sup> conducted at the onset of the pandemic, oral or i.v empirical antibiotic therapy was initiated for all hospitalized COVID-19 patients. However, most researchers subsequently emphasized that there is a significant discrepancy between antibiotic use and bacterial infections in these patients. Similarly, almost all patients (98%) in our study routinely received ceftriaxone and azithromycin, but only 13% of them had a microbiologically proven bacterial infection. The WHO also currently recommends that antibiotics should not be prescribed unless there is clinical suspicion of a bacterial infection, and the use of empiric antimicrobials should be limited only for patients with severe COVID-19, based on patient host factors and local epidemiology.<sup>8</sup>

In our study, when laboratory values examined, it was found that median WBC (10.3 vs 5.5), NLR (11.3 vs 2.3), CRP (18 vs 2.4), and PCT (1.8 vs 0.05) levels were significantly higher among patients with secondary infection compared to those without. Thus, the fact that these parameters are within the normal range can help the clinician to predict that patients are unlikely to have secondary infection, even if it cannot be completely ruled out. Given that the incidence of secondary bacterial infection is very low (1.6%) for patients hospitalized in the general wards in our study, we consider that the widespread use of antibiotics is not necessary, and antibiotic stewardship programmes should be implemented among all COVID-19 patients to avoid both the side effects of antibiotics and the spread of antimicrobial resistance in hospital.

In conclusion, the rate of secondary infection in hospitalized COVID-19 patients differs widely among patients in the general ward and in the ICU. We consider that empirical antibiotic therapy should not be initiated in patients hospitalized in the general ward, as the rate of secondary infection is very low. On the other hand, due to the high rate of VAP, we recommend sending respiratory samples regularly from COVID-19 patients hospitalized in the ICU for targeted antimicrobial therapy, and considering multidrug-resistant bacteria in empirical treatment. Our

study have several limitations. First, we performed a single-centre retrospective study with a small sample size, which may limit generalizability. Second, in the diagnosis of secondary infection, we could not perform any additional tests other than culture, such as respiratory RT-PCR techniques or detection of pulmonary aspergillosis by galactomannan. Besides, although it is known that the use of steroids increases the risk of secondary infection, we could not comment on this issue in our study, since steroids were not used in the treatment of COVID-19 patients at the time of the study.

**Ethics Committee Approval:** Our study was approved by the Haydarpaşa Numune Training and Research Hospital Ethics Committee (Date:29/06/2020, decision no: 115).

**Conflict of Interest:** No conflict of interest was declared by the authors.

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## Haloperidol, Olanzapin, Risperidon ve Klozapinin Organ Banyosu Sistemi Kullanılarak Fare Detrusor Kası Üzerine Etkileri

### Effects of Haloperidol, Olanzapine, Risperidone And Clozapine on Mice Detrusor Muscle Using Organ Bath System

<sup>1</sup>Mehmet Hanifi TANYERI, <sup>2</sup>Mehmet Emin BUYUKOKUROĞLU, <sup>2</sup>Pelin TANYERI, <sup>2</sup>Rümeysa KELES KAYA, <sup>2</sup>Şeyma Nur BASARIR BOZKURT, <sup>3</sup>Oğuz MUTLU, <sup>3</sup>Füruzan YILDIZ AKAR, <sup>3</sup>Bekir Faruk ERDEN, <sup>4</sup>Güner ULAK

<sup>1</sup>Department of Urology, Yenikent Government Hospital, Sakarya/Turkey

<sup>2</sup>Department of Pharmacology, Faculty of Medicine, Sakarya University, Sakarya/Turkey

<sup>3</sup>Department of Pharmacology, Faculty of Medicine, Kocaeli University, Kocaeli/Turkey

<sup>4</sup>Department of Clinical Pharmacology, Faculty of Medicine Üsküdar University, İstanbul/ Turkey

Mehmet Hanifi Tanyeri: <https://orcid.org/0000-0003-2654-2724>

Mehmet Emin Büyükokuroğlu: <https://orcid.org/0000-0002-1452-3879>

Pelin Tanyeri: <https://orcid.org/0000-0002-2987-5834>

Rümeysa Keleş Kaya: <https://orcid.org/0000-0002-5554-1918>

Şeyma Nur Başarır Bozkurt: <https://orcid.org/0000-0002-2986-5089>

Oğuz Mutlu: <https://orcid.org/0000-0003-0952-0742>

Füruzan Akar: <https://orcid.org/0000-0003-0948-3857>

Bekir Faruk Erden: <https://orcid.org/0000-0002-2542-5158>

Güner Ulak: <https://orcid.org/0000-0002-6132-6712>

#### ÖZ

**Amaç:** Mesane normalde dolum fazı sırasında herhangi bir kasılma veya aktivite göstermez. Aşırı aktif mesanede, dolum aşamasında spontan kasılmalar ve detrusör instabilitesi görülür ve idrar kaçırma meydana gelir. Bu çalışma, birinci kuşak antipsikotik olan haloperidol ve ikinci kuşak antipsikotikler olan olanzapin, risperidon ve klozapinin, organ banyosu sistemi kullanılarak izole edilmiş fare mesanesi üzerindeki etkilerini göstermeyi amaçlamaktadır.

**Materyal ve Metot:** 63 tane kendi içinde yetiştirilmiş erkek fareye salin, haloperidol 0,125 mg/kg, haloperidol 0,25 mg/kg, olanzapin 1 mg/kg, olanzapin 2 mg/kg, risperidon 0,25 mg/kg, risperidon 0,5 mg/kg, klozapin 1,25 mg/kg ve klozapin 2,5 mg/kg uygulandı ve gruplara ayrıldı. Fareler 21 gün boyunca ilaçlarla tedavi edildi. Daha sonra, izole edilmiş fare detrusör şeritlerinde karbakol ile indüklenen kasılmaların, izoproterenol ile indüklenen gevşeme tepkileri üzerinde ilaçların etkileri araştırıldı.

**Bulgular:** Olanzapin, risperidon ve klozapin ile tedavi edilen gruplardan elde edilen fare detrusör şeritlerinde karbakol kaynaklı kasılmaların, izoproterenol ve papaverin tarafından gevşediğini gösterdik. Gruplar arasında KCl'nin neden olduğu kasılma tepkilerinde önemli bir fark yoktu.

**Sonuç:** Olanzapin, risperidon ve klozapin, mesane kapasitesini artıran detrusor kasının izoproterenol kaynaklı gevşemelerini arttırdı. Bu ilaçlar, antipsikotik ilaç kullanması gereken hastalarda aşırı aktif mesane tedavisinde klinik olarak faydalı olabilir.

**Anahtar Kelimeler:** Aşırı aktif mesane, haloperidol, klozapin, olanzapin, risperidon

#### ABSTRACT

**Objective:** The bladder normally shows no contractility or activity during the filling phase. In the overactive urinary bladder, spontaneous contractions and detrusor instability are seen in the filling phase and urinary incontinence occurs. This study aims to demonstrate the effects of first-generation antipsychotic haloperidol and second-generation antipsychotics olanzapine, risperidone, and clozapine on mice isolated bladder using the organ bath system.

**Materials and Methods:** 63 male inbred mice were divided as saline, haloperidol 0.125 mg/kg, haloperidol 0.25 mg/kg, olanzapine 1 mg/kg, olanzapine 2 mg/kg, risperidone 0.25 mg/kg, risperidone 0.5 mg/kg, clozapine 1.25 mg/kg and clozapine 2.5 mg/kg groups. Mice were treated with drugs for 21 days. Then, the effects of drugs were investigated on isoproterenol-induced relaxation responses of carbachol-induced contractions in isolated detrusor strips.

**Results:** We showed that carbachol-induced contractions relaxed by isoproterenol and papaverine in mice detrusor strips obtained from olanzapine, risperidone, and clozapine treated groups. There were no significant differences in KCl-induced contractile responses among the groups.

**Conclusion:** Olanzapine, risperidone, and clozapine increased the isoproterenol-induced relaxations of the detrusor muscle that increased the bladder capacity. These drugs might be clinically useful for the treatment of overactive urinary bladder in patients that should use antipsychotic drugs.

**Keywords:** Clozapine, haloperidol, olanzapine, overactive urinary bladder, risperidone

#### Sorumlu Yazar / Corresponding Author:

Oğuz Mutlu

Department of Pharmacology, Faculty of Medicine, Kocaeli University, Kocaeli/Turkey.

Tel: +(90) 535 505 04 88

E-mail: oguzmutlu80@hotmail.com

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## INTRODUCTION

Overactive urinary bladder has a high prevalence. Although it can be seen in all age groups and in both sexes, symptoms generally increase with age. The most prominent symptom of overactive urinary bladder is urgency.<sup>1</sup>

The normal function of the urinary bladder is controlled by the central and peripheral nervous systems. These two systems must work in harmony for the bladder to function properly. Unfortunately, some problems such as emotional distress, anxiety, depression, sleep disturbances and issues with sexuality, and avoiding social relationships may occur in patients. In addition, it has been suggested that there is a relationship between depression and anxiety associated with overactive urinary bladder and urgency incontinence and nocturia.<sup>2</sup>

Haloperidol exerts its effects through dopamine D2 receptors which are targets for antipsychotic drugs.<sup>3</sup> It is shown that olanzapine has high affinity for 5-HT<sub>2A/2C</sub>, dopamine receptors D<sub>1-4</sub>, M<sub>1-5</sub> muscarinic receptors, H<sub>1</sub> histaminergic receptors and  $\alpha$ -1 receptors.<sup>4</sup> Other atypical antipsychotic clozapine also affects some receptors, including dopamine D<sub>4</sub>, serotonin 5-HT<sub>2A</sub>, and 5-HT<sub>2C</sub>,  $\alpha$ 1- and  $\alpha$ 2-adrenergic, cholinergic, and histamine H<sub>1</sub>, similar to olanzapine.<sup>5</sup> Risperidone is also currently used in the treatment of psychiatric diseases. The main pharmacological activities of risperidone are shown its effects mediated by antagonism of serotonergic 5-HT<sub>2A</sub> and dopaminergic D<sub>2</sub> receptors.<sup>6</sup>

The atypical antipsychotics such as olanzapine, risperidone and clozapine that we used in this study; the incidence of extrapyramidal side effects is lower than classical antipsychotics such as haloperidole. It is more effective in curing the negative symptoms of schizophrenia and is used in the treatment of schizophrenia unresponsive to classical neuroleptics. Therefore, we aimed to demonstrate whether the long-term use of first-generation antipsychotic haloperidol and second-generation antipsychotic risperidone, olanzapine and clozapine may affect the contraction-relaxation responses on the detrusor muscle, *in vitro* in mice.

## MATERIALS AND METHODS

**Ethical Status:** All procedures involving animals complied with the European Community Council Directive of 24 November 1986, and ethical approval was granted by the Kocaeli University Ethics Committee (Date: 22.07.2014, decision no: KOÜ HADYK 7/4-2014 Kocaeli, Turkey). All authors comply with NIH guidelines for use of laboratory animals.

**Animals:** Male inbred BALB/c ByJ mice (Animal Research Center, Bursa-Turkey) aged 7 weeks upon

arrival to the laboratory were used in this study. Animals (4–5 per cage) were kept in the laboratory at 21 ± 1.5 °C with 60% relative humidity under a 12 h light/dark cycle (light on at 8.00 p.m.) for 2 weeks before experimentation. Tap water and food pellets were available *ad libitum*.

**Drugs:** Haloperidol, olanzapine, risperidone, clozapine, carbachol, isoproterenol, papaverine, and potassium chloride were purchased from Sigma Chemicals (St Louis, Mo, USA). All drugs were dissolved in 0.9 % physiological saline. Saline was used as the vehicle control. Haloperidol, olanzapine, risperidone and clozapine were given intraperitoneally (i.p.) in a volume of 0.1 ml per 10 g body weight of mice. Drugs were prepared freshly on the day of the experiment.

**Experimental Design:** They randomly divided into five experimental groups (n=7) as follows: saline; haloperidol 0.125 mg/kg, haloperidol 0.25 mg/kg, olanzapine 1 mg/kg, olanzapine 2 mg/kg, risperidone 0.25 mg/kg, risperidone 0.5 mg/kg, clozapine 1.25 mg/kg and clozapine 2.5 mg/kg. We determined the doses of drugs from the previous studies.<sup>7,8</sup> Mice were treated by i.p. injection of haloperidol, olanzapine, risperidone or clozapine for 21 days.<sup>8</sup> Mice receiving only the vehicle (0.9% saline, i.p.) during 21 days served as the control group. After removing adhering fat and connective tissue, the bladder was opened and divided into longitudinal strips, weighed, and placed in physiological saline solution of the following composition (mmol/l): NaCl 118; KCl 4.7; CaCl<sub>2</sub> 2.5; MgSO<sub>4</sub> 1.2; KH<sub>2</sub>PO<sub>4</sub> 1.18; NaHCO<sub>3</sub> 24.88; glucose 5.55. The detrusor smooth muscle strips were suspended in a 10-ml water-jacketed (37 °C) tissue bath, containing physiological saline solution continuously gassed with 95% O<sub>2</sub> and 5% CO<sub>2</sub>, resulting in a pH of 7.4. The resting tension on the tissues was maintained at 1 g during which the solution was replaced for 15 min intervals before adding drugs. The tissues were connected to an isometric force transducer (FDT 10 A Commat İletisim, Ankara, Turkey) for the measurement of isometric force, which was continuously recorded on a computer via a four-channel transducer data acquisition system (MP150 Biopac Systems Inc. Goleta) using software (ACQ4.0 Biopac Systems Inc. Goleta) that also could analyze the data. The upper end was connected to the transducer and the lower end was fixed. After mounting, each strip was allowed to equilibrate with a basal tension of 1 g for 1 h, with the Krebs Henseleit solution replaced every 15 min with fresh solution. At the end of the equilibration, strips were depolarized with 80 mM KCl in Krebs solution and allowed to equilibrate for 30 min. Then, the effects of drugs were investigated on isoproterenol-induced relaxation responses of carbachol-

induced contractions in isolated detrusor strips. First, the detrusor strips were stimulated with 80mM KCl, then tissues were washed for a further 30 min and precontracted with a submaximal concentration of carbachol ( $3 \times 10^{-6}$  M). After the contraction reached a plateau, cumulative concentration-response curves to isoproterenol ( $10^{-8}$  to  $3.10^{-4}$  M) then papaverine ( $10^{-4}$  M) were obtained.

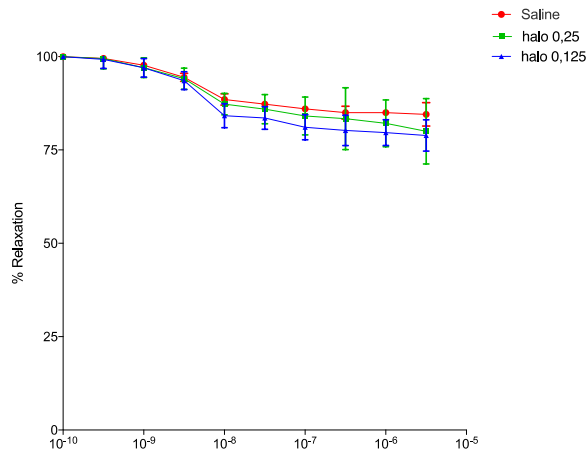
**Analysis of Data:** Statistical analysis of the data procured from the tests was made by Graphpad Prism 9 statistical program. Results are expressed as the mean  $\pm$  S.E.M. of different experiments. Relaxation responses to isoproterenol calculated as percentage of the maximal relaxation caused by papaverine ( $10^{-4}$  M). The significance of differences was tested by one-way ANOVA with a post-hoc Tukey's-Kramer test. Results were considered to be significantly different at a  $p$ -value of  $<0.05$ .

cantly different at a  $p$ -value of  $<0.05$ .

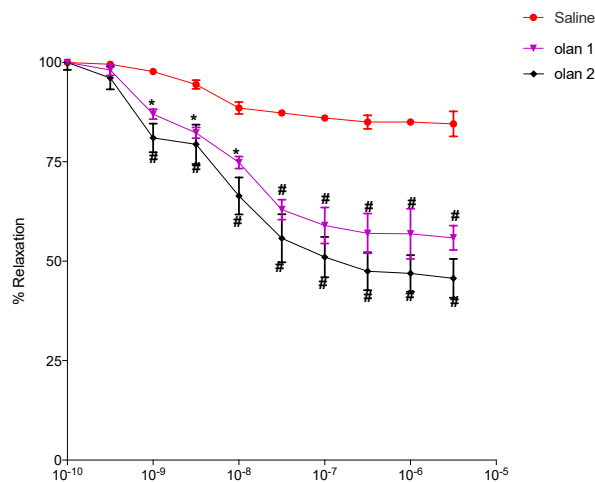
**RESULTS**

The findings of the study clearly showed that carbachol-induced contractions significantly don't relaxed by isoproterenol ( $10^{-8}$  to  $3.10^{-4}$  M) then papaverine in mice detrusor strips obtained from haloperidole treated group in Figure 1. However haloperidole treatment had no effect on KCl responses of mice bladder.

Results of isolated organ bath experiments demonstrated that carbachol-induced contractions relaxed by isoproterenol ( $10^{-8}$  to  $3.10^{-4}$  M) then papaverine in mice detrusor strips obtained from atypical neuroleptic drug olanzapine treated group shown in Figure 2. However, olanzapine treatment had no effect on KCl responses of mice bladder.



**Figure 1.** Isoproterenole concentration-responses (shown in x-axis) curves of haloperidole in isolated mice detrusor smooth muscle. Each point is expressed as a percentage of the relaxation (shown in y-axis) induced by papaverine ( $10^{-4}$  M) is given as the mean  $\pm$  standart error of the mean (SEM). Number of mice in each group is 7.

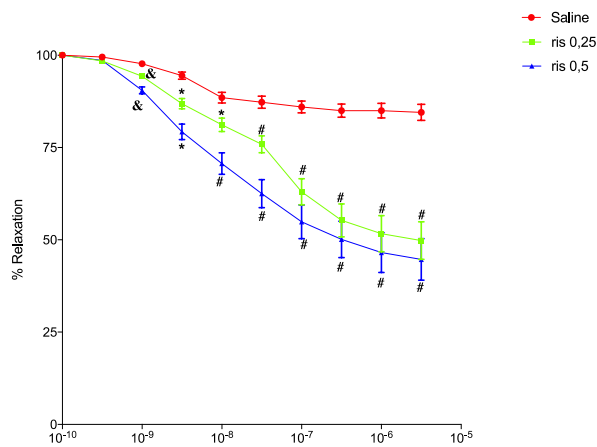


**Figure 2.** Isoproterenole concentration-responses (shown in x-axis) curves of haloperidole in isolated mice detrusor smooth muscle. Each point is expressed as a percentage of the relaxation (shown in y-axis) induced by papaverine ( $10^{-4}$  M) is given as the mean  $\pm$  standart error of the mean (SEM). Number of mice in each group is 7. (\* =  $p < 0,05$ ), (# =  $p < 0,001$ )

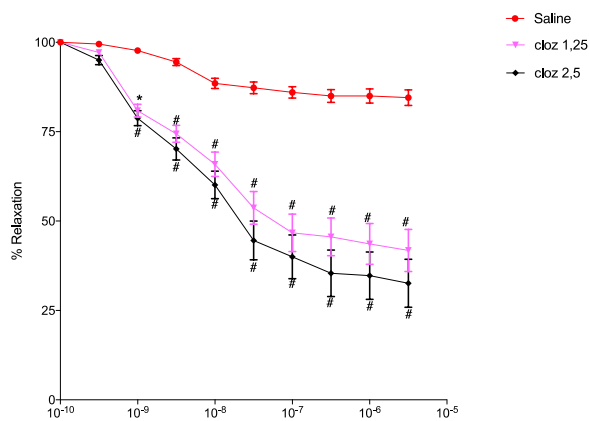
In addition we showed that carbachol-induced contractions dose-dependently relaxed by isoproterenol ( $10^{-8}$  to  $3.10^{-4}$  M) in mice detrusor strips obtained from atypical neuroleptic drugs risperidone and clozapine treated group shown in Figure 3 and Figure 4, respectively. However, neither risperidone nor clozapine treatment had no effect on KCl responses of mice bladder. In this research, the ranking of their relaxing potencies of the mice detrusor strips was clozapine > olanzapine > risperidone. Also, there were no significant differences in KCl-induced contractile responses among the groups.

**DISCUSSION AND CONCLUSION**

Normally, there is no activity in the bladder during the filling phase, but strong contractions of the bladder are seen when starting to urinate. These contractions continue until the bladder is completely empty. In an overactive bladder, spontaneous contractions and detrusor hyperreflexia occur during the filling phase. Incontinence can occur when these contractions are severe and cannot be prevented.<sup>9,10</sup> In overactive urinary bladder syndrome, detrusor contractions begin before the bladder is filled. This situation causes the bladder to be emptied before it is filled and frequent urination.<sup>11</sup> The overactive



**Figure 3.** Isoproterenole concentration-responses (shown in x-axis) curves of haloperidole in isolated mice detrusor smooth muscle. Each point is expressed as a percentage of the relaxation (shown in y-axis) induced by papaverine ( $10^{-4}$  M) is given as the mean  $\pm$  standart error of the mean (SEM). Number of mice in each group is 7. (& =  $p < 0,05$ ), (\* =  $p < 0,01$ ), (# =  $p < 0,001$ )



**Figure 4.** Isoproterenole concentration-responses (shown in x-axis) curves of haloperidole in isolated mice detrusor smooth muscle. Each point is expressed as a percentage of the relaxation (shown in y-axis) induced by papaverine ( $10^{-4}$  M) is given as the mean  $\pm$  standart error of the mean (SEM). Number of mice in each group is 7. (\* =  $p < 0,05$ ), (# =  $p < 0,001$ )

urinary bladder is a complex illness. It involves both peripheral and central nervous system factors.<sup>12,13</sup> All the drugs we use in practice today are peripheral acting agents. And there is not enough data and studies on central-acting drugs.

Antimuscarinic and beta 3 mimetic agents are used in first-line pharmacotherapy to prevent contractions and detrusor hyperreflexia in the filling phase.<sup>14</sup> In the use of antimuscarinic, side effects such as dry mouth, constipation and blurred vision can be seen in a dose-dependent manner.

Voiding control is done by the pontine urination center. In the overactive urinary bladder, contractions also occur beyond the control of this center.<sup>15</sup>

This study clearly showed that carbachol-induced contractions significantly don't relaxed by isoproterenol (10–8 to 3.10–4 M) then papaverine in mice detrusor strips obtained from haloperidole treated group; on the other hand we showed that carbachol-induced contractions dose-dependently relaxed by isoproterenol (10–8 to 3.10–4 M) in mice detrusor strips obtained from atypical neuroleptic drugs olanzapine, risperidone and clozapine treated group. Atypical antipsychotic drugs olanzapine, risperidone, and clozapine were found to relax by directly affecting the bladder muscle outside the central system in our study. Its use as the first choice, especially in patients who need to use antipsychotics and have overactive urinary bladder, makes it possible to treat two diseases with a single drug. These findings may open a new perspective to develop drugs in the treatment of overactive urinary bladder in the future. In conclusion; we showed that carbachol-induced contractions relaxed by isoproterenol then papaverine in mice detrusor strips obtained from atypical neuroleptic drug olanzapine, clozapine, risperidone treated group but not typical neuroleptic haloperidol. The findings of our study demonstrated that olanzapine, risperidone and clozapine increased the isoproterenol-induced relaxations of the detrusor smooth muscle that increased the bladder capacity. We showed that olanzapine, risperidone, and clozapine may offer a potential drug for patients with overactive urinary bladder. Olanzapine, risperidone, and clozapine can be used alone or in combination with anticholinergic and beta 3 receptor agonists for the treatment of overactive urinary bladder to minimize side effects. These three drugs might be clinically useful for the treatment of overactive urinary bladder in patients that should use antipsychotic drugs.

**Ethics Committee Approval:** Our study was approved by the Kocaeli University Local Ethics Committee for Animal Experiments (Date: 22.07.2014, decision no: KOÜ HADYK 7/4-2014).

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Author Contributions:** Concept – MHT, MEB; Supervision – MHT, MEB, PT; Materials – MHT, MEB, PT; Data Collection and/or Processing – MHT, MEB, PT, RKK, ŞNBB; Analysis and/ or Interpretation – OM, FYA, BFE, GU; Writing – MHT, MEB, PT.

**Peer-review:** Externally peer-reviewed.

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## Piyeloplasti Yapılan Ureteropelvik Bileşke Darlıklı Hastaların Epidemiyolojik Verileri: Tek Merkez Deneyimi

### Epidemiological Data of Patients with Ureteropelvic Junction Stenosis Performed Pyeloplasty: A Single Center Experience

<sup>1</sup>Turan YILDIZ, <sup>1</sup>Necmettin AKPINAR, <sup>2</sup>Hasan ARIK, <sup>3</sup>Ahmet Taner ELMAS, <sup>1</sup>Sema UĞURALP

<sup>1</sup> İnönü Üniversitesi Tıp Fakültesi Çocuk Cerrahi AD, Malatya, Türkiye

<sup>2</sup> Malatya Eğitim Araştırma Hastanesi Anestezi Ve Reanimasyon Bölümü, Malatya, Türkiye

<sup>3</sup> İnönü Üniversitesi Tıp Fakültesi Çocuk Nefroloji Bilim Dalı, Malatya, Türkiye

Turan Yıldız: <https://orcid.org/0000-0001-5317-7537>

Necmettin Akpınar: <https://orcid.org/0000-0001-7212-684X>

Hasan Arık: <https://orcid.org/0000-0001-7935-6832>

Ahmet Taner Elmas: <https://orcid.org/0000-0002-9749-6115>

Sema Uğuralp: <https://orcid.org/0000-0002-7628-0550>

#### ÖZ

**Amaç:** Antenatal hidronefrozun bebeklerde sık nedeni geçici ve kalıcı ureteropelvik bileşke darlığı (UPD)'dir. Renal hasar oluşturan veya oluşturma potansiyeli olan tüm hastalara piyeloplasti uygulanır. Biz bu çalışmada piyeloplasti yaptığımız hastalarımızın epidemiyolojik verilerini paylaşmak istedik.

**Materyal ve Metot:** Çalışmamızda 2011-2021 yılları arasında UPD nedeni ile opere edilen 131 hastayı değerlendirdik. Hastaların tanı zamanı, operasyon yaşı, takip süresi, cinsiyet, patolojinin tarafı, başvuru şikâyetleri, patolojinin etiyojisi ve karşı böbrek patolojisi kaydedildi.

**Bulgular:** Çalışmaya 109 hasta dâhil edildi. Hastaların %76,1'i erkek, %23,9'u kızdı. Erkek çocuklarda patoloji daha sıklıkla solda (%65,1) görülürken, kız çocuklarında patoloji daha sıklıkla sağda (%57,7) idi (p=0,036). Ortalama piyeloplasti yaşı 39,27±48,01 aydı. Antenatal tanıli hastaların ortalama piyeloplasti yaşı 15,74±23,48 aydı, geç dönem tanıli çocukların ortalama piyeloplasti yaşı 82,52±51,97 aydı (p=0,003). Aberan damar basılı UPD hastalarının %66,7'si geç dönemde tanı alırken, intrinsik nedenli hastaların %29,8'i geç dönemde tanı almıştı (p=0,005).

**Sonuç:** Ureteropelvik bileşke darlığı sıklıkla antenatal dönemde tanı almakta, erkek çocuklarında ve solda sık görülmektedir. Çalışmamızda kız çocuklarında sağ piyeloplastinin daha sık yapıldığı görülmüştür. Aberan damar basılı hastalar antenatal dönemde de tanı alabilmektedir. Bununla birlikte ilerleyen yaşlarda başvuran hastalarda aberan basılı UPD daha sık görülmektedir.

**Anahtar Kelimeler:** Çocuk, epidemiyoloji, piyeloplasti, ureteropelvik bileşke darlığı

#### ABSTRACT

**Objective:** The common cause of antenatal hydro-nephrosis in infants is temporary and permanent ureteropelvic junction stenosis (UPJS). Pyeloplasty is applied to all patients who have or have the potential to cause renal damage. This study, it was aimed to share the epidemiological data of our patients who underwent pyeloplasty.

**Materials and Methods:** In our study, we evaluated 131 patients who were operated for UPJS between 2011 and 2021. The time of diagnosis, age of operation, duration of follow-up, gender, side of the pathology, complaints on admission, etiology of the pathology and contralateral kidney pathology were recorded.

**Results:** 109 patients were included in the study. 76.1% of the patients were male and 23.9% were female. While pathology was more common on the left (65.1%) in boys, pathology was more common on the right (57.7%) in girls (p=0.036). The mean age of pyeloplasty was 39.27±48.01 months. The mean age of pyeloplasty in patients with antenatal diagnosis was 15.74±23.48 months, and the mean age of pyeloplasty in children with late diagnosis was 82.52±51.97 months (p=0.003). While 66.7% of UPD patients with aberrant vein pressure were diagnosed in the late period, 29.8% of the patients with intrinsic causes were diagnosed in the late period (p=0.005).

**Conclusion:** Ureteropelvic junction stenosis is frequently diagnosed in the antenatal period and is common in boys and on the left. In our study, it was observed that right pyeloplasty was performed more frequently in girls. Patients with aberrant vascular pressure can also be diagnosed in the antenatal period. However, UPJS with aberrant vascular pressure is seen more frequently in patients admitted at older ages.

**Keywords:** Child, epidemiyoloji, pyeloplasty, ureteropelvic junction stenosis

#### Sorumlu Yazar / Corresponding Author:

Turan Yıldız  
İnönü Üniversitesi Çocuk Cerrahi AD, Malatya  
Tel: +90 507 457 42 22  
E-mail: tyildiz44@gmail.com

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## GİRİŞ

Prenatal dönemde bebeklerin %1-5'inde ultrasonografi (US) ile tespit edilen en yaygın patoloji hidronefrozdur.<sup>1</sup> Üreteropelvik bileşke darlığı (UPD) ise konjenital hidronefrozun en sık nedenidir. UPD hastalarının önemli bir kısmı konservatif takip ve tedavi ile iyileşmektedir ancak UPD idrar akımını engeller ve yeterli akım sağlanamaz ise hidronefroz daha da ilerlemektedir. Tedavisiz kalan hastalarda ilerleyici böbrek hasarı ve böbrek fonksiyon kaybı ortaya çıkar. Zamanında gerekli cerrahi müdahale yapılan hastalarda geri dönüşümsüz böbrek hasarının önüne geçilmiş olur.<sup>2,3</sup> UPD hastalarının cerrahi tedavisinde dismembered piyeloplasti altın standarttır.<sup>4</sup> Üreteropelvik bileşke darlığının epidemiyolojik verileri değerlendirildiğinde literatür de yeterli verinin olduğu görülmektedir.<sup>5</sup> Bu hastaların 1/3'ünün opere edildiği,<sup>4</sup> önemli bir kısmının ise konservatif tedavi ile iyileştiği göz önüne alındığında cerrahi geçiren hastaların verilerinin tekrardan paylaşılması gerektiği gözlenmektedir. Bu amaçla biz daha önce bölgede epidemiyolojik verileri değerlendirilmeyen UPD nedeni ile piyeloplasti yapılan hastalarımızın epidemiyolojik verilerini değerlendirip, piyeloplasti planlamasında faydalı olabileceğini düşündüğümüz verilerimizi paylaşmak istedik.

## MATERYAL VE METOT

**Etik Komite Onayı:** Çalışmamızda Ocak 2011 ile Ocak 2021 yılları arasında UPD nedeni ile opere edilen 0-18 yaş arası 131 hasta geriye dönük olarak değerlendirildi. Bu çalışma için İnönü Üniversitesi yerel etik kurulundan onay alındı (Tarih30.11.2021, karar no: 1673). Uluslararası Helsinki beyannamesine uyularak çalışma gerçekleştirildi.

Çalışmaya hastaların dâhil edilme kriteri; piyeloplasti nedeni ile opere edilen 0-18 yaş aralığındaki tüm hastalardı. Hariç tutulma kriterleri ise yeterli veri toplanamayan, sekonder piyeloplasti vakaları ve nüks eden vakalardı. Ayrıca patolojinin etiyojisi olarak dinamik segment dışındaki intrinsik nedenler ve aberan damar basısı dışındaki ekstrinsik nedenler çalışma dışında tutuldu.

Hastaların tanı zamanı, operasyon yaşı, tanıya kadar olan takip süresi, cinsiyet, patolojinin tarafı, başvuru

şikâyetleri, karşı böbrekte patoloji olup olmaması ve cerrahi esnasında tespit edilen patolojinin etiyojistik tipi kayıtlardan alınarak not edildi.

Antenatal tanı alan hastalar doğum öncesi UPD'ye ait pozitif US verisi olup, doğum sonrası US ile tanısı doğrulanan hastalardı. Geç tanı alan hastalar ise ilk tanısını doğum sonrası dönemde alan hastalardı. Antenatal hidronefrozlu hastaların ameliyat yaşı ve preoperatif takip süresi olarak doğum sonrasında ameliyata kadar geçen süreler kaydedildi. Geç tanı alan hastalarda ise tanı zamanı ile operasyon arasındaki süre preoperatif takip süresi olarak kaydedildi. Üreteropelvik bileşke darlığı tespit edilen böbreğin karşı böbrekte tespit edilen patolojiler kaydedildi. Cerrahi esnasında tespit edilen etiyojistik nedenler intrinsik ve ekstrinsik nedenler olarak ayırt edildi. İntrinsik nedenlerin tümü dinamik segmentli UPD iken, ekstrinsik nedenlerin tümü aberan damar basısına bağlı hastalardı.

**İstatistiksel Analiz:** Analizler (IBM SPSS Statistics, Version 22.0; IBM Corp.; Armonk, NY, ABD) kullanılarak yapıldı. Sayısal verilerin normal dağılım gösterip göstermediği Shapiro Wilk testi ile değerlendirildi. Normal dağılım gösteren verileri karşılaştırmak için 2 grup arasındaki farkın önemlilik testi (independent t test) kullanıldı. Veriler ortalama±standart hata olarak sunuldu. Kategorik veriler kıkare testi kullanılarak karşılaştırıldı. Kategorik değişkenler sayı ve yüzde değerleri olarak sunuldu. Bir p değeri <0.05 istatistiksel olarak anlamlı kabul edildi.

## BULGULAR

UPD nedeni ile opere edilen 131 hastadan, 109'u bu çalışmaya dâhil edildi. Hastaların %76,1 (n=83)'i erkek, %23,9 (n=26)'u kız çocuğuydu. Ortalama ameliyat yaşı 39,27±48,01 ay idi. Erkek ve kızlarda ameliyat edilme yaşı arasında anlamlı fark yoktu (p=0,128). Hastaların %58,7 (n=64)'sinde patoloji solda iken; %37,6 (n=41)'sında sağda tespit edildi. Hastaların %3,7 (n=4)'sinde bilateral UPD nedeniyle piyeloplasti uygulandı. Erkek çocuklarda patoloji daha sıklıkla solda (%65,1; n=54) görülürken, kız çocuklarında patoloji daha sıklıkla sağda (%57,7; n=15) saptandı (p=0,036) (Tablo 1).

**Tablo 1.** Hastaların cinsiyetine göre yaş ve patoloji tarafı arasındaki ilişki.

	Erkek	Kız	Total	p
<b>Ortalama ameliyat yaşı</b>	35,11±36,12	51,54±55,59	39,27±48,01	0,128
<b>Taraf</b>	Sol n (%)	54 (65,1)	64 (58,7)	<b>0,036</b>
	Sağ n (%)	26 (31,3)	41 (37,6)	
	Bilateral n (%)	3 (3,6)	1 (3,8)	
<b>Toplam n (%)</b>	83 (100)	26 (100)	109 (100)	

Hastaların %65,1'i (n=71) antenatal tanıli hasta iken, %34,9'i (n=38) geç tanı alan hastalardı. Antenatal tanıli hastaların ortalama operasyon yaşı ve preoperatif takip süresi 15,74±23,48 ay iken; geç tanı alan hastaların ameliyat yaşı 82,52±51,97 ay, preoperatif takip süresi ise 14,44±3,10 ay olarak saptandı. İki grup arasında preoperatif takip süreleri arasında anlamlı fark yoktu (p=0,774). Geç dönemde başvuran çocukların ameliyat yaşı 82,52±51,97 ay olarak tespit edildi. Antenatal tanı alan hastaların %98,6 da karın ağrısı mevcut değilken, geç tanı alan hastaların %55,3'de karın ağrısı mevcuttu (p<0,001). Hastaların etiyolojik nedenleri göz önüne alındığında ante-

natal dönemde tanı alan hastaların %92,9'un da intrinsik nedenler tespit edilirken, %7,1'inde aberan damar basısına bağlı UPD görülmüştür (p=0,005) (Tablo 2).

Geç dönemde başvuran hastalar genellikle semptomatik hastalar olup, en sık görülen semptomu karın ağrısı (%55,3) idi. Başka sebeple yapılan US esnasında rastlantısal olarak tespit edilen UPD ise ikinci sıklıkta en sık başvuru nedeni idi (Tablo 3).

Hastaların %68,8 de karşı böbrekte herhangi bir patoloji görülmezken, %31,2 de patoloji mevcuttu. Karşı böbrekte en sık görülen patoloji UPD idi. İkinci sıklıkta VUR görüldü (Tablo 4).

**Tablo 2.** Tanı zamanı ile epidemiyolojik verilerin ilişkisi.

	Antenatal tanı	Geç tanı	p
<b>Operasyon yaşı (ay)</b>	15,74±23,48	82,52±51,97	<b>0,003</b>
<b>Takip süresi (ay)</b>	15,74±23,48	14,44±3,10	0,774
<b>Cinsiyet n (%)</b>			
Erkek	58 (81,7)	25 (65,8)	0,063
Kız	13 (18,3)	13 (34,2)	
<b>UPD tarafı n (%)</b>			
Sol	42 (59,2)	22 (57,9)	0,629
Sağ	25 (35,2)	16 (42,1)	
<b>Karşı böbrekte patoloji n (%)</b>			
Pozitif	23 (32,4)	11 (28,9)	0,442
Negatif	48 (67,6)	27 (71,1)	
<b>Karın ağrısı n (%)</b>			
Pozitif	1 (1,4)	21 (55,3)	<b>&lt;0,001</b>
Negatif	70 (98,6)	17 (44,7)	
<b>Cerrahi patoloji n (%)</b>			
İntrinsik	66 (92,9)	28 (73,7)	<b>0,005</b>
Aberan damar	5 (7,1)	10 (26,3)	
<b>Toplam</b>	<b>71 (65,1)</b>	<b>38 (34,9)</b>	

UPD: Üreteropelvik bileşke darlığı; (ay): Ay cinsinden yaş; n(%): Hasta sayısı (yüzde); p: <0.05 anlamlı.

**Tablo 3.** Geç tanı alan hastalarda başvuru nedenleri.

Başvuru nedenleri	n (%)
Karın ağrısı	21 (55,3)
Rastlantısal	10 (26,3)
İdrar yolu enfeksiyonu	5 (13,2)
İdrar kaçırma	1 (2,6)
Kilo alamama	1 (2,6)
<b>Toplam</b>	<b>38 (100)</b>

**Tablo 4.** Piyeloplasti yapılan hastalarda karşı böbrek patolojileri.

Karşı böbrek patolojisi	n (%)
Patoloji yok	75 (68,8)
Patoloji mevcut	34 (31,2)
UPD	19 (17,5)
VUR	6 (5,5)
Taş	4 (3,7)
Multistikistik displastik böbrek	2 (1,8)
Komplet ureter duplikasyonu	1 (0,9)
Atnalı Böbrek	1 (0,9)
UVD	1 (0,9)
<b>Toplam</b>	<b>109 (100)</b>

UPD: Üreteropelvik bileşke darlığı; VUR: Vezikoureteral reflü; UVD: Üreterovezikal darlık.

## TARTIŞMA VE SONUÇ

Çalışmamızda piyeloplasti sonrası 109 hastanın verileri analiz edildi. Hastaların büyük çoğunluğunda tanı antenatal dönemde konulmuştu. Piyeloplasti tüm hastalarda ve erkeklerde daha sıklıkla solda yapılırken, kız hastalarda daha sık olarak sağ piyeloplasti uygulandığı görülmüştür. Geç tanı alan hastalar sıklıkla karın ağrısı şikâyeti ile başvurmuşlardı. Karşı böbrekte patoloji tüm hastaların %31,2'inde görüldü. Karşı böbrekte en sık görülen patoloji geçici UPD idi. Piyeloplasti yapılan hastaların etiolojisinde intrinsik nedenler sık olmakla birlikte hastaların %13,8'de aberan damar basısına bağlı patoloji görüldü. Damar basısına bağlı patolojisi olan hastalar geç tanı almakta olup yaşları anlamlı olarak yüksekti.

Üreteropelvik bileşke darlığı 750-2000 canlı doğumda bir görülür ve konjenital hidronefrozun en sık nedenidir.<sup>2,5</sup> Erkeklerde kızlardan 2-3 kat daha sık görüldüğü bildirilmiştir. Üreteropelvik bileşke darlığı daha sıklıkla solda görülmekle birlikte, %20-30 vakada patoloji bilateral olarak raporlanmıştır.<sup>5</sup> Ceyhan ve ark<sup>6</sup> ise UPD nedeni ile piyeloplasti yapılanların %63,9'na sol piyeloplasti uygulandığını belirtmişlerdir. Ancak literatür taramamızda hiçbir çalışmada patolojinin yönü ve cinsiyetin birlikte değerlendirilmediği görülmüştür. Bizim çalışmamızda ilginç bir şekilde kız çocuklarında anlamlı olarak sağ piyeloplastinin daha fazla yapıldığı göze çarpmaktadır. Bu durum kızlarda sağ UPD'nin dikkatli değerlendirilmesini bize telkin etmektedir.

Günümüzde obstetrik US'nin sık kullanılmaya başlanması ve ailelerin düzenli kontrollerini yaptırması nedeni ile antenatal dönemde birçok renal patoloji erken tespit edilmektedir.<sup>7</sup> Antenatal US'larda tüm gebelerin %1-5'inde hidronefroz görülmektedir.<sup>8</sup> Bunların %41-88'i geçici veya fizyolojik hidronefroz olarak isimlendirilen spontan düzelen hidronefrozlardır.<sup>1</sup> Literatürde yaptığımız araştırmalara göre piyeloplasti yapılan hastaların ne kadarının antenatal tanı aldığına ait verilere ulaşılamamıştır. Bizim hastalarımızın ise %65,1'de antenatal tanı almıştı.

Üreteropelvik bileşke darlığı olan hastaların etiolojisinde intrinsik ve ekstrinsik faktörler yer alır. İntrensik nedenler, ureter kas sisteminin gelişiminin kesintiye uğramasına veya kas liflerini ayıran kollajen liflerinin anormal gelişimine bağlıdır. Bu sorunların her ikisi de kasılma yetersizliğine neden olur. Ekstrinsik obstrüksiyonlar, böbrek alt kutbundan geçen aberan damar basısına bağlı, fibröz bant adezyonlarına veya normal üreteropelvik bileşkenin kıvrılmasına bağlı olabilir. Aberan damar basısı ise en sık ekstrinsik nedenlidir. İntrensik nedenler daha sıklıkla antenatal dönemde tanı alıp, hayatın erken döneminde opere edilen hasta grubunu oluşturur.<sup>9</sup> Antenatal tanıli hastalarımızın %92,9'u intrinsik nedenli UPD olan hastalardı. Ekstrinsik nedenli has-

talar ise daha sık geç çocukluk döneminde tanı alan, daha çok semptomlar ile başvuran hastalardan oluşmaktadır.<sup>10</sup> UPD li hastaların %4,7-15 aberan damar basısı tespit edilirken semptomatik hastaların %49-58'inde aberan damar basısı tespit edilmiştir.<sup>4,6,10-14</sup>

Çalışmamızda 15 (%13,8) hastada aberan damar basısı tespit edilmişti. Esposito ve ark<sup>10</sup> yaptığı çalışmada aberan damar basısı olanların normal perinatal hikâyeye sahip olduğunu belirtmiştir. Yine Miscia ve ark<sup>9</sup> yaptığı meta analizde bu grup hastalarda sıklıkla doğum öncesi hidronefroz öyküsünün olmadığını belirtmiştir. Buna karşılık Weiss ve ark<sup>12</sup> ise aberan damar basılı hastaların %25,6'sında antenatal hidronefroz tanısının mevcut olduğunu vurgulamıştır. Bizim aberan damar basılı hastalarımızın %33'ünde prenatal hidronefroz tanısı mevcuttu.

Semptomatik hastalar aralıklı karın ağrıları, idrar yolu enfeksiyonu, bazı gecikmiş vakalarda hipertansiyon ile başvurabilirler.<sup>4,5</sup> Bizim serimizde hastaların %33,9'u geç yaşlarda başvuran hastalardan oluşmaktaydı. Bu grup hastalarımız semptomatik olmaları sonucu veya rastlantısal olarak US ile tanı alan hastalardan oluşmaktaydı. Bizim hastalarımızda karın ağrısı en sık görülen başvuru nedeniydi.

UPD hastalarında ek bir ürolojik anomali oranı %50'ye varan oranlarda bildirilmiştir.<sup>5</sup> Karşı böbrekte UPD birlikte en sık görülen patolojidir(%10-40). Bu hastaların büyük çoğunluğunun cerrahi ihtiyacı olmamakla birlikte yaklaşık %20'sine cerrahi uygulanmıştır. Hedge ve ark.<sup>15</sup> UPD hastalarında preoperatif ve postoperatif dönemde toplam %9-14 vakada VUR bildirmiştir. Çalışmalarda UPD ile birlikte görülen VUR'un %40'nın spontan düzeldiği gözlenmiştir. Vezikoüreteral reflüyü takiben renal displazi, multikistik displastik böbrekler ve renal agenezi diğer görülen karşı böbrek patolojileridir.<sup>4</sup>

Sonuç olarak, kız çocuklarında daha çok sağ UPD opere edilmesi kız çocuklarında sağ patolojilere dikkat edilmesini bize hatırlatmaktadır. Ayrıca aberan damar basılı UPD hastalarının düşük oranda antenatal tanı alması bize bu hastaların düşük dereceli hidronefroz nedeni ile gözden kaçmış olabileceğini düşündürmektedir. Bu çalışmanın retrospektif bir çalışma olması, konservatif takip edilen hastaların verilerinin olmaması, sadece bir merkeze ait verilerin olması, ve geç tanı alan hastaların prenatal hikayesinin ayrıntılarına ulaşılmaması kısıtlamaları olarak sayabiliriz Bu konuda prospektif bir çalışmaya ihtiyaç bulunmaktadır.

**Etik Komite Onayı:** Çalışmamız İnönü Üniversitesi Yerel Etik Kurulu tarafından onaylandı (Tarih:30.11.2021, karar no: 1673). Çalışma uluslararası deklarasyon, kılavuz vb uygun gerçekleştirilmiştir.

**Çıkar Çatışması:** Yazarlar çıkar çatışması bildir-

memişlerdir.

**Yazar Katkıları:** Fikir-TY; Denetleme-SU-ATE-YT; Veri toplama ve işlemesi-NA-TY; Analiz ve yorum-TY-HA; Yazı yazılması-TY-ATE-NA.

**Hakem Değerlendirmesi:** Dış bağımsız.

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## Traf2 ve Nck Etkileşimli Protein Kinaz (TNIK) İnhibitörünün Metastatik Köpek Meme Tümör Hücrelerinde Apoptotik Etkisinin Belirlenmesi

### Determination of the Apoptotic Effect of Raf2 and Nck-Interacting Protein Kinase (TNIK) Inhibitor on Metastatic Canine Mammary Gland Tumor Cells

<sup>1</sup>Asuman DEVECİ ÖZKAN, <sup>2</sup>Ayten HACIEFENDİ, <sup>2</sup>Fatih ÖZKAN, <sup>1</sup>Gamze GÜNEY ESKİLER, <sup>1</sup>Süleyman KALELİ, <sup>1</sup>Ecir Ali ÇAKMAK, <sup>3</sup>Özge TURNA

<sup>1</sup>Department of Medical Biology, Faculty of Medicine, Sakarya University, Sakarya, Turkey

<sup>2</sup>Department of Medical Biology, Institute of Health Science, Sakarya University, Sakarya, Turkey

<sup>3</sup>Department of Obstetrics and Gynaecology, Faculty of Veterinary Medicine, Istanbul University-Cerrahpasa, Istanbul, Turkey

Asuman Deveci Özkan: <https://orcid.org/0000-0002-3248-4279>

Ayten Hacıefendi: <https://orcid.org/0000-0001-7071-5624>

Fatih Özkan: <https://orcid.org/0000-0002-4658-8968>

Gamze Güney Eskiler: <https://orcid.org/0000-0002-2088-9914>

Süleyman Kaleli: <https://orcid.org/0000-0002-6043-2521>

Ali Ecir Çakmak: <https://orcid.org/0000-0003-2735-2105>

Özge Turna: <https://orcid.org/0000-0002-7638-0519>

#### ÖZ

**Amaç:** Köpek meme tümörleri (KMT) dışı köpeklerde en sık görülen tümörlerdir ve kullanılan başlıca tedavi seçeneği olarak cerrahi ciddi komplikasyonlara neden olmaktadır. Bu nedenle KMT için yeni tedavi seçeneklerine ihtiyaç duyulmaktadır. Traf2 ve Nck ile etkileşime giren serin protein kinaz (TNIK) WNT hedef genlerinin transkripsiyonel bir düzenleyicisidir ve meme kanseri gelişiminde yüksek oranda eksprese edilmektedir. TNİK'in inhibisyonu, anormal WNT sinyali olan kanserlerde yeni bir terapötik hedef olabilir. Bu nedenle, bu çalışmada NCB-0846'nın metastatik sarkom KMT alt tipi üzerindeki potansiyel terapötik etkisini ilk kez araştırılması amaçlanmıştır.

**Materyal ve Metot:** NCB-0846'nın KMT hücreleri üzerindeki sitotoksik ve apoptotik etkileri, WST-1, Annexin V, hücre döngüsü, akrinin oranj (AO) ve DAPI boyama ile analiz edilmiştir.

**Bulgular:** Elde edilen verilere göre NCB-0846, doza ve zamana bağlı anlamlı bir şekilde KMT hücre canlılığını azaltmış ve nükleer hasara sebep olmuştur. Ayrıca, NCB-0846, G0/G1 fazında hücrelerin birikmesi yoluyla apoptotik hücre ölümünü indüklemiştir.

**Sonuç:** Sonuç olarak elde ettiğimiz bulgular, NCB-0846'nın potansiyel olarak KMT için yeni bir terapötik anti-kanser ajan olabileceğini göstermektedir. Bununla birlikte KMT hücreleri üzerinde NCB-0846'nın TNİK ve Wnt sinyalinin inhibe edici aktivitesinin aydınlatılmasına yönelik daha ileri araştırmalara ihtiyaç duyulmaktadır.

**Anahtar Kelimeler:** Köpek meme tümörleri, apoptoz, TNİK inhibitörü

#### ABSTRACT

**Objective:** Canine mammary gland tumors (CMGTs) are the most common tumors in female dogs and the main treatment options used in CMGTs are surgery caused some complications. Therefore, new treatment options are needed for the CMGTs. Traf2 and Nck-interacting serine protein kinase (TNIK) as a transcriptional coregulator of Wnt targeted genes is highly expressed in breast cancer development. The inhibition of TNİK may be a new therapeutic target in cancers with abnormal WNT signaling. Therefore we aimed to investigate the potential therapeutic effect of NCB-0846 on metastatic sarcoma CMGTs subtype, for the first time.

**Materials and Methods:** The cytotoxic and apoptotic effects of NCB-0846 on CMGT cells were analyzed by WST-1, Annexin V, cell cycle, acridine orange (AO) and DAPI staining.

**Results:** NCB-0846 significantly inhibited cell viability in a dose and time dependent manner ( $p < 0.05$ ) and induced nuclear damage in CMGT cells. Furthermore, NCB-0846 caused apoptotic cell death through the accumulation of cells in the G0/G1 phase.

**Conclusion:** Our findings demonstrated that NCB-0846 could be potentially a new therapeutic anti-cancer agent in the treatment of CMGTs. However, further investigations need to be performed in order to elucidate the inhibitory activity of TNİK and Wnt signaling by NCB-0846 on CMGT cells.

**Keywords:** Canine mammary gland tumor cells, apoptosis, TNİK inhibitor

#### Sorumlu Yazar / Corresponding Author:

Asuman Deveci Ozkan  
Department of Medical Biology, Faculty of Medicine, Sakarya University, 54290, Korucuk, Adapazarı, Sakarya, Turkey.  
Tel: +902642954297  
E-mail: [deveci@sakarya.edu.tr](mailto:deveci@sakarya.edu.tr)

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## INTRODUCTION

Canine mammary gland tumors (CMGTs) are the most common tumors after skin tumors in female dogs and account for approximately 52% of all tumors.<sup>1-4</sup> CMGTs are subclassified (sarcomas, carcinomas, and carcinosarcomas) according to histopathological differentiation.<sup>5</sup> Mammary gland sarcomas with clear borders, hard consistency and a large area in dogs account for approximately 10-15% of all CMGTs.<sup>6</sup> The main treatment options used in CMGTs are surgery, radiotherapy, chemotherapy and immunotherapy whereas surgery that causes some complications is the first choice.<sup>7</sup> Therefore, new treatment options are needed for the increasing incidence of CMGTs, which have very similar properties with human breast tumors.

Traf2 and Nck-interacting serine protein kinase (TNIK) as a transcriptional coregulator of Wnt targeted genes is a center kinase that encodes 1360 amino acids and highly expressed in breast cancer development.<sup>8,9</sup> Studies have shown that an increase in TNIK expression and the abnormal activation of the Wnt/ $\beta$ -catenin signaling pathway plays an important role in the formation and development of breast cancer.<sup>10-12</sup> Therefore, the inhibition of TNIK may be a new therapeutic target in cancers with abnormal WNT signaling.<sup>13</sup>

Furthermore, increased TNIK expression in various types of cancer (pancreatic, colorectal and hepatocellular carcinoma) is associated with poor prognosis in patients.<sup>10,14,15</sup> Based on these findings, TNIK inhibition is important and various classes of TNIK inhibitors have been developed for this purpose.<sup>13,16</sup> In this context, many studies have been conducted to develop new TNIK inhibitors, recently.<sup>8,13,17</sup> Padgaonkar et al. report that ON108600 is a dual inhibitor of CK2 and TNIK and shows inhibitory activity in MDA-MB-231 cells.<sup>17</sup> Additionally, Masuda et al. demonstrate that NCB-0001 induces the expression of LC3 that is a marker of autophagy in PAMC82 human gastric cancer and T47D human breast cancer cell lines.<sup>13</sup> As a new TNIK inhibitor NCB-0846 inhibits the TGF $\beta$ 1-induced EMT in NSCLC cells.<sup>8</sup> However, there is no study in the literature evaluating the effects of NCB-0846 as a TNIK inhibitor on CMGT cells.

Therefore, in our study, the potential therapeutic effect of NCB-0846, a new type of TNIK inhibitor, was investigated for the first time on metastatic sarcoma CMGTs subtype. CMGT cells were diagnosed as liposarcoma with high metastatic capacity based on the criteria defined by Goldschmidt et al.<sup>18</sup>

## MATERIALS AND METHODS

**Ethical Statement:** The female dog was operated for cancer treatment, not for experimental procedure.

Tissue material removed by operation was used in the study. This was in conformity with the "Regulation on Working Procedures and Principles of Animal Experimental Ethics Committees Prepared by the Turkish Ministry of Environment, Urbanisation and Climate Change published in the Official Gazette of the Republic of Turkey dated February 2014 and numbered 28914".

**Cell Culture Conditions:** CMGT which was used in this study was a 22-year-old intact French Bulldog female dog, weighing 16 kg with an 8-month history of mammary mass (>5 cm) and diagnosed as metastatic liposarcoma. Primary cell isolation and culture from CMGT tissue was conducted as described by Turna et al.<sup>19</sup>

**Cell Viability Assay:** To determine the cytotoxic effects of NCB on CMGT cell, we performed WST-1 assay. For this purpose, the equal number of cells ( $2 \times 10^4$  cell/well) were cultured in 96 well plate. Then the cells were incubated with different concentrations of NCB-0846 (1, 2, 2.5, 3, 4 and 5  $\mu$ M) as a TNIK inhibitor for 24 and 48h. After treatment of NCB-0846, WST-1 dye was added into each well and incubated for 45 min at 37 °C in the dark and the absorbance was obtained with the microplate reader (Allsheng, China) at 450 nm. According to WST-1 results, the most effective NCB-0846 concentrations and incubation time (reduced viability by approximately 50%) were determined for further experiments. Each experiment was performed in triplicate.

**Annexin V Assay:** To determine the apoptotic effects of NCB-0846 on CMGT cell, we performed Annexin V assay. For this purpose, the equal number of cells ( $1 \times 10^5$  cell/well) were cultured in 6 well plate. Then the cells were incubated with the most effective concentrations of NCB-0846 (2.5 and 5  $\mu$ M) for 48h according to the WST-1 assay results. After treatment of NCB-0846, the cells were stained with Annexin V reagent (Millipore, Germany) and incubated for 30 min. Stained cells were analyzed with Muse Cell Analyzer (Millipore, Germany). Each experiment performed was in triplicate.

**Cell Cycle Assay:** To further analyze the effects of NCB-0846 on cell cycle arrest in CMGT cells, the equal number of cells ( $5 \times 10^5$  cell/well) were cultured in 6 well plate. Then the cells were incubated with the most effective concentrations of NCB-0846 (2.5 and 5  $\mu$ M) for 48h according to the WST-1 assay results. After treatment of NCB-0846, the cells were fixed with 70% ethyl alcohol and fixed cells were stained with Cell Cycle Kit (Millipore, Germany). After incubation for 30 min, the stained cells were analyzed with Muse Cell Analyzer (Millipore, Germany). Each experiment was performed in triplicate.



**Acridine Orange (AO) and 4',6-diamidino-2-phenylindole (DAPI) Staining:** To determine the morphological changes of cell and nucleus on CMGT cells, we performed AO and DAPI staining. For this purpose the equal number of cells ( $5 \times 10^5$  cell/well) were cultured in 6 well plate. Then the cells were incubated with the most effective concentrations of NCB-0846 (2.5 and 5  $\mu\text{M}$ ) for 48h according to the WST-1 assay results. After treatment of NCB-0846, the cells were fixed with 4% paraformaldehyde (PFA) for 30 min and fixed cells were stained with AO or DAPI dye for 30 min in the dark, separately. Stained cells were visualized by EVOS Fluid Cell Imaging System (Thermo Fisher Scientific).

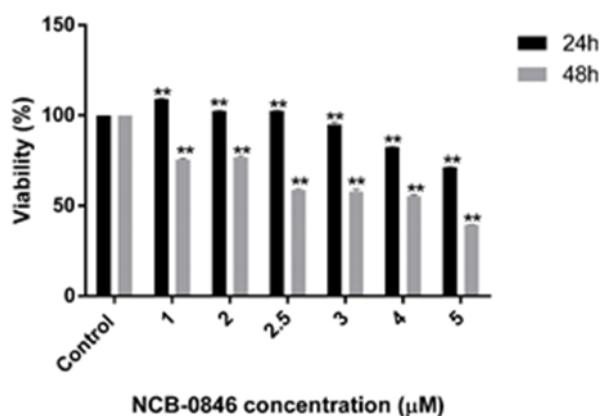
**Statistical Analysis:** All statistical analysis was performed by GraphPad Prism Version 8. One-way ANOVA with the Post-hoc Tukey test was used for

multiple comparisons.  $p < 0.05$  was considered significant.

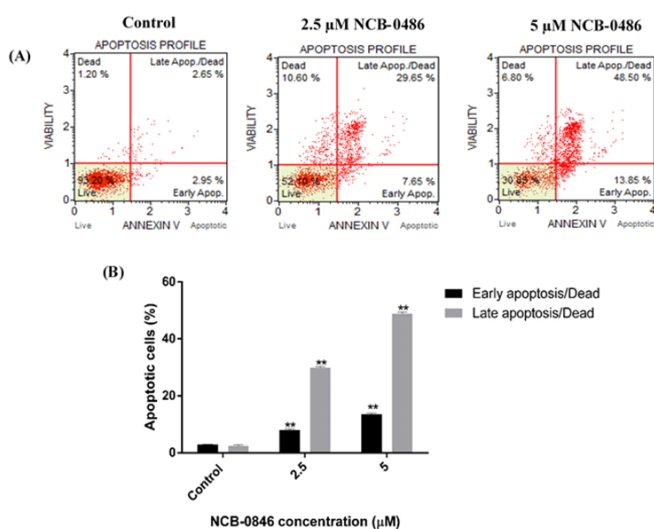
**RESULTS**

According to the WST-1 analysis results, the viability of cells were decreased in a dose and time dependent manner and shown in Figure 1. The viability of CMGT cells significantly reduced to  $76.05 \pm 1.93\%$ ,  $77.34 \pm 0.82\%$ ,  $59.08 \pm 0.21\%$ ,  $58.69 \pm 0.74\%$ ,  $55.73 \pm 1.69\%$  and  $39.48 \pm 1.23\%$  at concentration of 1, 2, 2.5, 3, 4 and 5  $\mu\text{M}$  NCB-0846, respectively for 48 h as shown in Figure 1. Thus, we selected 2.5 and 5  $\mu\text{M}$  NCB-0846 within 48 h for further experiments, in CMGT cells.

To determine the apoptotic effect of NCB-0846 on CMGT cells, we conducted Annexin V assay and shown in Figure 2.



**Figure 1.** The cytotoxic effects of NCB-0846 was determined by WST-1 analysis on CMGT cells and the cells were treated with different concentrations of NCB-0846 (1, 2, 2.5, 3, 4 and 5  $\mu\text{M}$ ) for 24 and 48h ( $p < 0.01^{**}$ ).

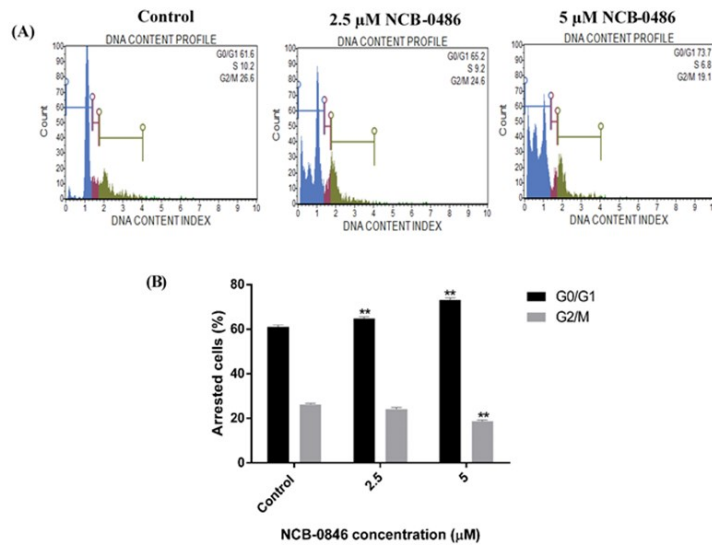


**Figure 2.** The apoptotic effect of NCB-0846 on CMGT cells was determined by Annexin V analysis (A) Annexin V histograms of CMGT cells treated with 2.5 and 5  $\mu\text{M}$  concentration of NCB-0846, (B) Statistical comparison of the NCB-0846-induced apoptotic cell death ( $p < 0.01^{**}$ ).

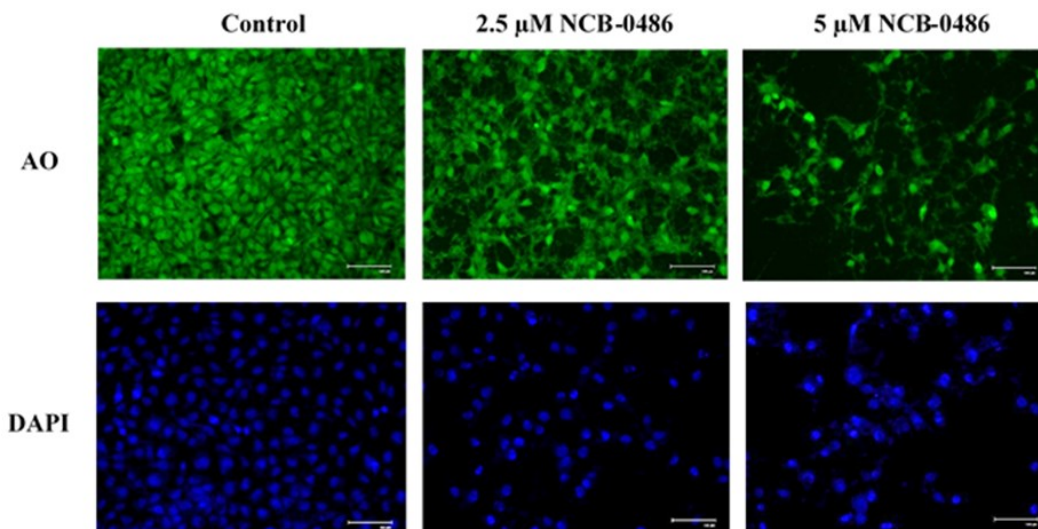
Our results demonstrated that NCB-0846 increased the proportion of total apoptotic cells especially late apoptotic cells as shown in Figure 2A. Following administration of 2.5 and 5  $\mu$ M NCB-0846, the late apoptotic cells were significantly increased from  $2.65 \pm 1.87\%$ , to  $29.65 \pm 1.53\%$  and  $48.50 \pm 2.13\%$  respectively for 48h as shown in Figure 2B. Therefore, these results were consistent with the WST-1 results. Our results indicated that NCB-0846 treatment resulted in G0/G1 arrest for 48 h in CMGTs cells as shown in Figure 3A. The accumulation of CMGT cells in the G0/G1 phase increased significantly from  $61.6 \pm 1.47\%$  to  $65.2 \pm 0.79\%$  and  $73.7 \pm 1.86\%$ , at 2.5 and 5  $\mu$ M NCB-0846 for 48 h as shown in

Figure 3B. Therefore, the NCB-0846 treatment resulted in G0/G1 phase arrest and apoptotic cell death.

After treatment with NCB-0846, typical apoptotic morphological changes were observed such as membrane blebbing and cell shrinkage in the cell especially at 5  $\mu$ M concentration for 48h as shown in Figure 4. The DAPI staining results demonstrated that irregular nuclear shrinkage and condensation were observed in CMGT cells after treatment with both 2.5 and 5  $\mu$ M NCB-0846. Therefore our findings were consistent with the Annexin V and cell cycle assay results.



**Figure 3.** The effect of NCB-0846 on cell cycle arrest was determined by cell cycle analysis (A) Cell cycle histograms of CMGT cells treated with 2.5 and 5  $\mu$ M concentration of NCB-0846, (B) Statistical comparison of the NCB-0846-induced cell cycle arrest level ( $p < 0.01$  \*\*).



**Figure 4.** To determine the morphological changes of cell and nucleus on CMGT cells, we performed AO and DAPI staining. CMGT cells were treated with 2.5 and 5  $\mu$ M concentration of NCB-0846 and stained with AO and DAPI dye (Scale bar: 100  $\mu$ m).

## DISCUSSION AND CONCLUSION

In this study, the potential cytotoxic and apoptotic effects of NCB-0846 were revealed in CMGT cells. According to our findings, NCB-0846 inhibited cell viability in a dose and time dependent manner and exhibited nuclear damage on CMGT cells. Furthermore, NCB-0846 induced apoptotic cell death through the accumulation of cells in the G0/G1 phase. Therefore, our findings demonstrated that NCB-0846 could be potentially a new therapeutic anti-cancer agent on CMGTs.

CMGTs are more aggressive than tumors in humans, and therefore chemotherapy is insufficient as a treatment option and only surgical intervention can be performed. For this reason, chemotherapy used in the treatment of CMGTs is not preferred due to the excess of side effects and thus there is an urgent need to new treatment options for better outcome. According to our results, NCB-0846 showed anti-cancer properties via the inhibition of cell proliferation, the induction of apoptosis, G0/G1 cell cycle arrest and nuclear damage in CMGT cells. The therapeutic effects of TNIK inhibition with small-molecule compounds have been demonstrated in the literature.<sup>8,20-22</sup> Kim et al.<sup>22</sup> state that NCB-0005 inhibits TGFβ1-induced activation of Wnt signaling in A549 lung adenocarcinoma cells and Sawa et al.<sup>21</sup> demonstrate that ON108600 which is a CK2 (casein kinase-2)/TNIK dual inhibitor targets stem-like cancer cells. On the other hand, NCB-0846 is a newly identified small molecule compound with high inhibitory activity against TNIK and shows anti-tumoral properties by inhibiting Wnt signaling.<sup>20</sup> Sugano et al.<sup>8</sup> shows that NCB-0846 inhibits TGFβ/SMAD signaling and EMT induction in A549 cells. Additionally, NCB-0846 suppresses the expression of Wnt targeted genes and Wnt-driven tumorigenesis in colorectal cancer cells. Therefore, our results were inconsistent with the literature.

In conclusion, we evaluated the therapeutic effect of NCB-048 at different concentrations on metastatic CMGT cells, for the first time. Our results indicated that the administration of NCB-0846 in CMGT cells induced early apoptosis and G0/G1 arrest. Consequently, as a new TNIK inhibitor, NCB-0846 has an anti-cancer potential agent on CMGT cells. However, further investigations need the elucidation of the inhibitory activity of TNIK and Wnt signaling by NCB-0846 on CMGT cells as well as human breast cancer.

**Ethics Committee Approval:** The study does not need an ethical approval. The bitch was operated for cancer treatment, not for experimental procedure. Tissue material removed by operation was used in the study. This was in confor-

mity with the "Regulation on Working Procedures and Principles of Animal Experimental Ethics Committees Prepared by the Turkish Ministry of Environment, Urbanisation and Climate Change published in the Official Gazette of the Republic of Turkey dated February 2014 and numbered 28914".

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Author Contributions:** Concept - ADO, AH, FO; Supervision - GGE, OT, AEC, SK; Materials - ADO, AH, FO; Data Collection and/or Processing - ADO, GGE, OT, AEC, SK; Analysis and/or Interpretation - ADO, AH, FO, GGE; Writing - ADO, OT, AEC, SK.

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## Distal Ekstra-Artiküler Tibia Kırığının Tedavisinde Minimal İnvaziv Plak veya İntramedüller Çivi, Hangisi Daha İyi?

### Minimally-Invasive Plate or Intramedullar Nail in the Management of Distal Extra-Articular Tibial Fracture, What Is Better?

<sup>1</sup>Alper KURTOĞLU, <sup>1</sup>Alauddin KOCHAI, <sup>1</sup>Erhan ŞÜKÜR, <sup>1</sup>Mustafa ERKAN İNANMAZ, <sup>1</sup>Ertuğ ÖKSÜZOĞLU, <sup>2</sup>Zafer ŞEN, <sup>3</sup>İsmail DALDAL, <sup>3</sup>Tijjani MAGASHI, <sup>4</sup>Orhan BAŞOĞLU

<sup>1</sup>Sakarya University Research and Training Hospital, Sakarya, Turkey

<sup>2</sup>University of Health Sciences Konya City Hospital Orthopedics and Traumatology, Konya, Turkey

<sup>3</sup>Lokman Hekim Akay Hospital, Department of Orthopaedic and Traumatology, Ankara, Turkey

<sup>4</sup>Toyatasa Hospital Orthopedics and Traumatology, Sakarya, Turkey

Alper Kurtuğlu: <https://orcid/0000-0001-9890-1330>

Alauddin Kochai: <https://orcid/0000-0002-5775-102X>

Erhan Şükür: <https://orcid/0000-0002-4697-7904>

Mustafa Erkan İnanmaz: <https://orcid/0000-0002-9555-0325>

Ertuğ Öksüzöğlü: <https://orcid/0000-0002-7007-8060>

Zafer Şen: <https://orcid/0000-0003-0807-6715>

İsmail Daldal: <https://orcid/0000-0003-1124-4409>

Tijjani Magashi: <https://orcid/0000-0002-9170-1683>

Orhan Başoğlu: <https://orcid/0000-0003-40381277>

#### ÖZ

**Amaç:** Bu çalışmanın amacı, intramedüller çivileme (IMN) veya minimal invaziv plak osteosentezi (MIPO) ile tedavi edilen distal tibia ekstraartiküler kırıklı hastaların klinik ve fonksiyonel sonuçlarını karşılaştırmaktır.

**Materyal ve Metot:** Bu retrospektif çalışma, IMN ile tedavi edilen 47 hastayı ve MIPO ile tedavi edilen 41 hastayı içermektedir. Klinik ve radyografik sonuçlar son takipte değerlendirildi. Klinik ölçüm olarak ön diz ağrısı, Amerikan Ortopedik Ayak ve Ayak Bileği Derneği (AOFAS) Ayak Bileği-Arka Ayak Ölçeği puanı ve Lysholm diz puanlama ölçeği kullanıldı.

**Bulgular:** İki gruptaki hiçbir hastada kaynamama gelişmedi. IMN grubunda kaynama süresi ve operasyon süresi MIPO grubuna göre anlamlı olarak daha yüksek olmasına rağmen ( $p<0,001$ ), MIPO grubunda tam yük taşıma süresi ve hastanede kalma süresi daha yüksekti ( $p<0,001$ ). Gruplar arasında yara sorunu, yanlış pozisyon, enfeksiyon ve greftleme oranları açısından istatistiksel olarak fark yoktu ( $p>0,05$ ). AOFAS skoru IMN grubunda istatistiksel olarak daha yüksek olmasına rağmen ( $p=0,031$ ), Lysholm diz skoru MIPO grubunda daha yüksekti ( $p<0,001$ ).

**Sonuç:** MIPO, erken kaynama, kısa operasyon süresi ve diz eklemine zarar vermemesi ile avantajlıyken, IMN daha erken tam yük taşımaya, daha kısa hastanede yatmaya ve daha iyi ayak bileği fonksiyonel sonuçları elde etmeyi sağlamaktadır.

**Anahtar Kelimeler:** Distal tibia kırıkları, intramedüller çivi, minimal invaziv plak osteosentezi

#### ABSTRACT

**Objective:** The aim of this study was to compare the clinical and functional outcomes of patients with distal tibia extraarticular fractures treated with Intramedullary nailing (IMN) or Minimally invasive plate osteosynthesis (MIPO).

**Materials and Methods:** This retrospective study included 47 patients treated with IMN and 41 patients with MIPO. Clinical and radiographic results were evaluated at last follow-up. Anterior knee pain, American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale score and Lysholm knee scoring scale were used as clinical measurement.

**Results:** Although the union time and operation time were significantly higher in the IMN group compared to the MIPO group ( $p<0.001$ ), the full weight bearing time and the hospital time were higher in the MIPO group ( $p<0.001$ ). There were no statistical differences between wound problem, malposition, infection and grafting rates in both groups ( $p>0.05$ ). Although the AOFAS score was statistically higher in the IMN group ( $p=0.031$ ), the Lysholm knee score was higher in the MIPO group ( $p<0.001$ ).

**Conclusion:** While MIPO is advantageous with low union time, low operating time and no damage to the knee joint, IMN allows earlier full weight bearing, lower hospitalization and has better ankle functional results.

**Keywords:** Distal tibial fractures, intramedullary nail, minimally invasive plate osteosynthesis

#### Sorumlu Yazar / Corresponding Author:

Alper Kurtuğlu  
Consultant Orthopaedic Surgeon, Sakarya Üniversitesi Eğitim ve Araştırma Hastanesi Adnan Menderes Caddesi Sağlık Sokak No: 195 Erenler 54100 Sakarya/ Türkiye  
Tel: +905538518523  
E-mail: dralperkurtoglu@gmail.com

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## INTRODUCTION

Distal tibial fractures with or without simple articular involvement can be difficult to treat. Realignment or fixation and stabilization of the thin, flute-shaped metaphyseal bone with a short distal fracture segment may be difficult.<sup>1</sup>

The anatomy of the distal tibia also has a limited soft tissue envelope that, when injured and operated on, can result in potentially catastrophic wound complications. Multiple modes of fixation for this type of fracture have been discussed in the literature.<sup>1,2</sup> Traditional open reduction with internal fixation using plates and screws has been linked to soft tissue complications and nonunion.<sup>2</sup> Hence, treatments aimed at minimizing soft tissue disruption have been considered; these include biology-sparing fixation techniques using plates or intramedullary nails.<sup>2</sup>

Intramedullary nailing (IMN) is widely used for the fixation of tibial shaft fractures because of its successful outcomes. IMN of distal tibial fractures avoids disturbing the soft tissue coverage and protects the vascular supply, resulting in high union rates. IMN has been reported to be effective in stabilizing the distal tibia. However, the fixation of distal tibial metaphysis fractures by IMN is associated with technical challenges due to the large cavity. Thus, IMN in patients with distal tibial fractures may lead to high rates of malunion, knee pain, and secondary procedures.<sup>3</sup>

Tibial plating provides anatomic reduction with reliable fixation, maintaining the limb alignment and allowing early rehabilitation. However, this technique is associated with a high incidence of wound complications, infections, and reoperations. With the development of minimally invasive techniques, biological plate fixation has become an attractive option for fracture treatment. Minimally invasive plate osteosynthesis (MIPO) is a valid option that results in indirect reduction, percutaneous fixation, and fewer wound complications.<sup>4</sup>

It is obvious that IMN and MIPO have their own advantages and disadvantages in treating distal tibial fractures; however, neither method is considered the gold standard. The present study aimed to compare these methods for treating extra-articular distal tibial fractures.

## MATERIALS AND METHODS

Our study was approved by the Sakarya University Ethics Committee (Date: 24.02.2021, decision no: 202). The present study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Our institutional review board approved the study protocol, and all the patients provided written informed consent prior to their inclusion in the

study.

This study was conducted from 2014 to 2017 at a tertiary care orthopedic trauma hospital. All patients aged 19–85 years who had closed extra-articular distal tibial fractures were included in the study. Patients with polytrauma, pathological fractures, compound fractures, ipsilateral or contralateral upper limb fractures, pediatric fractures, and fractures with intra-articular extension were excluded from the study. Patients who were either lost to follow-up or did not provide their consent for participating in the study were also excluded.

The patients were divided into two groups (47 patients in the IMN group and 41 patients in the MIPO group) by means of permuted randomization. In the IMN group, the patients were managed by interlocking IMN. In the MIPO group, the patients were managed using the MIPO technique. Additional fibular fixation was performed in both the groups depending on the level of simultaneous fibular fractures. All surgeries were performed by a senior surgeon in order to avoid bias. The surgeries were performed under spinal anesthesia.

A standard postoperative follow-up protocol was developed. The patients were followed up once every 3 weeks until fracture union, followed by once every 3 months for a year and twice in the subsequent year. Weight bearing was allowed when callus was seen in two cortices on an anteroposterior (AP) view or a lateral view. Although IMN is the system that allows load bearing, we did not have early weight bearing due to the fact that the fractures are very distal (distal metaphyseal area). Because we thought that there might be reduction loss with early weight bearing. At the final follow-up, clinical and radiological examinations were performed and the patients were assessed on the basis of the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale score. Coronal and sagittal alignment was assessed using AP and lateral plain radiographs. Rotation was clinically assessed on the basis of the foot–thigh angle; the difference was measured using a goniometer. Union was defined as the consolidation of three or more cortices on plain radiographs and the absence of pain during unassisted weight bearing. Malunion was defined as varus or valgus greater than 5° in the coronal plane and procurvatum or recurvatum greater than 10° in the sagittal plane (lateral x-ray) or as external or internal rotation greater than 10° (foot–thigh angle).<sup>5</sup> Any complication during the surgery and follow-up period was recorded.

In the MIPO group we used Cytronics plates (Cytronics, Bursa, Turkey) with antero-medial access. In the IMN group we used Tasarimmed nails (Tasarimmed, Istanbul, Turkey) with parapatellar



medial access.

The postoperative protocol in each group included elevation and pain management. If the patient's overall condition allowed, the postoperative protocol also included early gentle mobility with physical therapy for gait training without weight bearing on the injured leg. After the early postoperative follow-up for wound checks, suture removal, and education, the patients were followed up at 5–6-week intervals with clinical and plain radiographic examinations, which included four radiographic views of the high ankle, in which the x-ray beam was pointed in the AP, lateral, and oblique directions 5–6 cm cephalad to the ankle joint.

**Evaluation:** Patient and injury characteristics were obtained to evaluate their association with the clinical and functional outcomes.

In this study, the fractures were classified according to the Orthopaedic Trauma Association (OTA) scheme,<sup>6</sup> the union of the fracture was accepted when callus was seen in 3 cortices radiographically.<sup>7</sup> AOFAS,<sup>6</sup> Lysholm Knee Scoring Scale were used in the functional evaluation.<sup>8</sup>

**Statistical Analysis:** The SPSS 15.0 for Windows program was used for statistical analysis. Descrip-

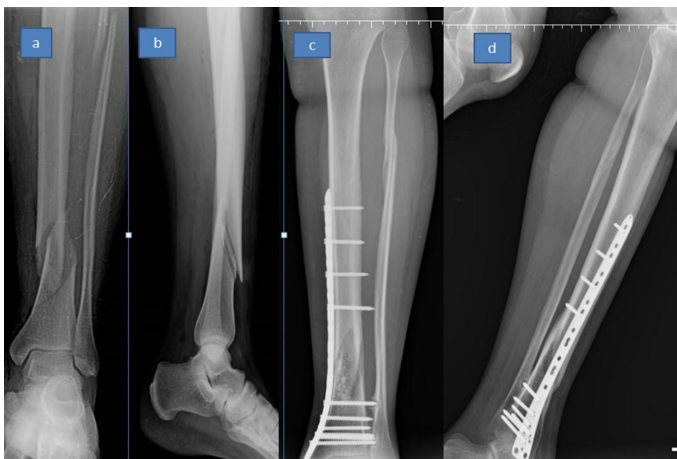
tive statistics are presented as the number and percentage for categorical variables and as the mean, standard deviation, minimum, and maximum for numerical variables. For numerical variables with a normal distribution, the comparisons between two independent groups were made using Student's t test. For numerical variables without a normal distribution, the Mann–Whitney U test was used. Spearman correlation was used to assess the relationships between the numerical variables as the parametric test conditions were not met. The determining factors were examined by linear regression analysis. A p value < 0.05 was considered statistically significant.

## RESULTS

In the present study, 88 patients who had distal tibia extraarticular fractures were included in the IMN (47 patients) (Figure 1) and MIPO (41 patients) (Figure 2) groups. In total, 59% (28/47) of the patients in the IMN group got an associated fibula fracture repaired. Moreover, fibula fractures were repaired in 44% (18/41) of the patients in the MIPO group (p>0.05).



**Figure 1:** Radiographs (a,b) before and (c,d) 10 months after intramedullary nail osteosynthesis for distal tibial fracture.



**Figure 2:** Radiographs (a,b) before and (c,d) 8 months after minimally invasive plate osteosynthesis for distal tibial fracture.

In the IMN group, the patients were evaluated at an average of 26 months after the injury (range, 19–37 months). Similarly, in the MIPO group, the patients were evaluated at an average of 26 months after the injury (range, 18–36 months). Patient demographics and injury data are provided in Table 1.

Clinical results are provided in Table 2. The mean duration between the injury and the surgery was 2.8 days (range, 1–6 days) in the IMN group and 2.4 days (range, 1–13 days) in the MIPO group; this difference was statistically significant ( $p < 0.05$ ). The mean surgery duration was 91 min (range, 75–113 min) in the IMN group and 71 min (range, 55–89 min) in the MIPO group; this difference was statistically significant as well ( $p < 0.05$ ). Moreover, the mean duration of postoperative hospitalization was 3.7 days (range, 2–6 days) in the IMN group and 4.5 days (range, 3–7 days) in the MIPO group, with the difference being statistically significant ( $p < 0.05$ ) (Table 2).

All the evaluated patients ultimately healed, with the average time to union being 21.9 weeks (range, 16–32 weeks) in the IMN group and 19.9 weeks (range, 16–33 weeks) in the MIPO group. The time to union was significantly longer in the IMN group ( $p < 0.001$ ). The complications included three (6.4%)

delayed unions in the IMN group and one (2.4%) delayed union in the MIPO group ( $p > 0.05$ ). All these patients underwent successful surgeries, including bone grafting, to achieve union. The full weight-bearing time was significantly longer in the MIPO group than in the IMN group (16.1±1.5 weeks and 11.6±1.7 weeks, respectively;  $p < 0.05$ ). In the IMN group, six (12.8%) patients had a malunion [four varus deformities (one patient 7 degree, one patient 9 degree, one patient 10 degree, one patient 12 degree), one valgus deformity (11 degree), and one sagittal plane deformity (13 degree)]. In the MIPO group, two (4.9%) patients had a malunion [ (one varus deformity (10 degree) and one valgus deformity (12 degree)]. The difference was not statistically significant ( $p > 0.05$ ). Two (4.3%) and three (7.3%) superficial infections were noted in the IMN and MIPO groups, respectively. Although the infection rate was higher in the MIPO group, the difference was not statistically significant ( $p > 0.05$ ). In the IMN group, seven patients experienced anterior knee pain (14.8%). The average AOFAS score was higher in the IMN group (87.6±7.0) than in the MIPO group (85.7±5.2) ( $p < 0.05$ ). However, the Lysholm Knee score was higher in the MIPO group (93.4±3.0) than in the IMN group (82.4±8.0) ( $p < 0.05$ ) (Table 2).

**Table 1.** Demographical characteristics of the patients.

		Group 1		Group 2		p
		n	%	n	%	
Gender	Female	23	48.9	18	43.9	0.637
	Male	24	51.1	23	56.1	
Mean age		41.7±13.8 (19-83)		43.9±18.0 (20-85)		0.514
Side	Right	22	46.8	21	51.2	0.680
	Left	25	53.2	20	48.8	
Trauma mechanism	Falling	15	31.9	10	24.4	0.720
	Sport	3	6.4	2	4.9	
	Traffic accident	29	61.7	29	70.7	
Type of fracture	Open	9	19.1	6	14.6	0.574
	Closed	38	80.9	35	85.4	
Lateral malleolus fracture		28	59.6	18	43.9	0.142
Follow up (months)		26.6±4.8 (19-37)		26.1±5.9 (18-36)		0.549
Distance to joint (mm)		81.3±8.6 (70-115)		70.3±19.3 (34-115)		<b>0.001</b>

**Table 2.** Comparison of results in the intramedullar nail and minimally invasive plate groups.

	Group 1		Group 2		p
	Mean±SD (Min-Max)		Mean±SD (Min-Max)		
Union time (week)	21.9±3.2 (16-32)		19.9±3.5 (16-33)		<b>&lt;0.001</b>
Weight bearing (week)	11.6±1.7 (9-17)		16.1±1.5 (13-19)		<b>&lt;0.001</b>
Preoperative hospitalization (day)	2.8±1.3 (1-6)		2.4±2.3 (1-13)		<b>0.011</b>
Operation time (minute)	91.0±10.2 (75-113)		70.9±10.3 (55-89)		<b>&lt;0.001</b>
Hospital time (day)	3.7±1.0 (2-6)		4.5±1.0 (3-7)		<b>&lt;0.001</b>
AOFAS Score	87.6±7.0 (74-98)		85.7±5.2 (75-97)		<b>0.031</b>
Lysholm Knee Score	82.4±8 (72-94)		93.4±3 (74-98)		<b>&lt;0.001</b>
	n	%	n	%	p
Wound problem	3	6.4	4	9.8	0.700
Malposition	6	12.8	2	4.9	0.276
Infection	2	4.3	3	7.3	0.661
Grafting	3	6.4	1	2.4	0.620

AOFAS Score: AOFAS Score: American Orthopaedic Foot and Ankle Society Score; SD: Standard deviation.



## DISCUSSION AND CONCLUSION

Several studies have compared MIPO and IMN for treating extra-articular distal tibia fractures. However, there is no definite conclusion about the superiority of one fixation method over the other.<sup>9,10</sup>

Biological plate fixation has generally been associated with low infection rates.<sup>11</sup> However, high infection rates have been reported by Lau et al. (15%)<sup>12</sup> and Collinge et al. (19%).<sup>13</sup> In 2016, Shen et al. reported wound complications to be more common in the IMN group than in the MIPO group (8.2% and 3.1%, respectively).<sup>14</sup> In their meta-analysis, Kwork et al. did not find any significant difference in the incidence of infection between the plating and IMN groups.<sup>15</sup> A recent meta-analysis on this topic concluded that the MIPO technique is associated with a longer time to union and an increased rate of wound complications.<sup>16</sup> Although wound complication and infection were found to be higher in the MIPO group than in the IMN group in the present study, the difference was not statistically significant.

In the study of Shen et al., the surgery duration was 56 min in the MIPO group and 85 min in the IMN group.<sup>14</sup> Li et al. reported a shorter surgery duration in the IMN group than in the MIPO group (87.5 min versus 114.4 min;  $p < 0.05$ ).<sup>10</sup> In the present study, the surgery duration in the MIPO group was much shorter than that in the IMN group (71 min vs. 91 min;  $p < 0.001$ ; Table 1).

Malalignment has been found to be a problem in distal tibial fractures because the small distal fragment is difficult to control. An ideal treatment should provide anatomical or at least acceptable fracture alignment to avoid posttraumatic arthritis in the ankle joint.<sup>17</sup>

Numerous studies have shown high malalignment rates when IMN or MIPO has been used to treat distal tibial fractures (8%–58% with IMN and 5%–35% with MIPO). However, the incidence certainly depends on several factors, including how malalignment has been defined.<sup>18,19</sup> Costa et al. reported no significant difference in lateral deformities ( $p=1.000$ ) and AP deformities ( $p=0.081$ ) between the IMN and plating groups. Nevertheless, they found shortening deformities ( $>10$  mm) to be associated with the IMN group ( $p = 0.028$ ).<sup>15,20</sup> Moreover, Wani et al. reported that patients treated with the IMN technique had significantly higher rotational malalignment than those treated with the plating technique. However, they did not find any significant difference in varus or valgus deformities and in the anterior/posterior angulation.<sup>21</sup> Guo et al. and Li et al. reported equal malalignment in both the groups in their studies.<sup>9,10</sup> While the incidence of union-related complications, including delayed union, nonunion, and malunion, was found to be similar between the IMN and MIPO groups in two meta-

analyses,<sup>15,22</sup> the incidence of malunion was found to be higher in the IMN group in another meta-analysis.<sup>23</sup> In the present study, the malunion rate was higher in the IMN group than in the MIPO group; however, the difference was not statistically significant.

Li et al. reported two cases of nonunion (one in the IMN group and one in the MIPO group).<sup>10</sup> In the present study, we had no case of nonunion, similar to the findings of a previous study.<sup>24</sup> Although the time to union was longer in the IMN group, the full weight-bearing time was significantly shorter in the IMN group than in the MIPO group in the present study.

Guo et al. compared MIPO with IMN in a series of 85 patients and found statistically similar AOFAS scores in both the groups.<sup>9</sup> In the present study, the AOFAS score was 87.6 in the IMN group and 85.7 in the MIPO group. We noted better functional outcomes in the IMN group.

It is known that IMN causes more anterior knee pain than MIPO. This is because no incision is made around the knee in MIPO.<sup>25</sup> Yang et al. compared the results of IMN with those of open reduction and plating of distal tibial fractures and reported anterior knee pain in half of the patients treated with IMN.<sup>26</sup> Moreover, in their retrospective series, Jansen et al. reported a significantly higher frequency of anterior knee pain during kneeling and squatting in the IMN group.<sup>27</sup> In the present study, 14.8% of the patients in the IMN group reported anterior knee pain. Moreover, the Lysholm Knee score was significantly lower in the IMN group.

The infrapatellar approach for the nail insertion has long been considered the standard procedure, however high incidence of anterior knee pain, ranging from 10 to 80%, has been reported.<sup>28</sup> For treatment of distal fractures suprapatellar tibial nailing is an alternative surgery. Suprapatellar tibial IMN may be applicable to distal tibial fractures. Providing easy anatomic reduction in the semiextended position, convenient fluoroscopic imaging, safety for the PF joint, acceptable anterior knee pain, and satisfactory functional outcomes render the SP technique more feasible.<sup>29</sup> Lu et al. found less malalignment with the suprapatellar method in distal tibia fractures.<sup>30</sup> Therefore, we preferred the suprapatellar method.

In conclusion, there are several limitations in this study. Small number of patients and relatively short follow-up periods in this study limited findings. Another limitation this study that it is a retrospective study. While MIPO is advantageous with low union time, low operating time and no damage to the knee joint, IMN allows earlier full load bearing, lower hospitalization and has better functional results.

**Ethics Committee Approval:** Our study was approved by the Sakarya University Ethics Committee (Date: 24.02.2021, decision no: 202). The present study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Our institutional review board approved the study protocol, and all the patients provided written informed consent prior to their inclusion in the study.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Author Contributions:** Concept – AK; Supervision – ES, AK, MEI; Materials – AK, OB; Data Collection and/or Processing – EO, ES; Analysis and/ or Interpretation – ID, TM, ZF; Writing – AK, ES.

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## Askorbik Asit ve Sodyum Selenitin Renal İskemi-Reperfüzyon Hasarında İnflamatuar Cevap ve Apoptoz Üzerine Etkileri

### Effects of Ascorbic Acid and Sodium Selenite on Inflammatory Response and Apoptosis in Renal Ischemia-Reperfusion Injury

<sup>1</sup>Songul DOGANAY, <sup>2</sup>Ozcan BUDAK

<sup>1</sup>Department of Physiology, Sakarya University Faculty of Medicine, Sakarya, Turkey

<sup>2</sup>Department of Histology and Embryology, Sakarya University Faculty of Medicine, Sakarya, Turkey

Songul Doganay: <https://orcid.org/0000-0002-1730-1331>

Ozcan Budak: <https://orcid.org/0000-0002-2617-3175>

#### ÖZ

**Amaç:** Bu çalışmanın amacı, renal iskemi ve reperfüzyon (IR) hasarında askorbik asit (AA) ve sodyum selenit (SS) uygulamasının anti-inflamatuar ve anti-apoptotik etkilerini araştırmaktır.

**Materyal ve Metot:** Yirmi sekiz Wistar-albino sıçan dört gruba ayrıldı. Grup I; Kontrol grubu, Grup II; IR grubu, Grup III; IR+0,25mg/kg SS ve 100mg/kg AA ve Grup IV; IR+0,50mg/kg SS ve 200mg/kg AA. Kontrol grubuna sadece cerrahi stres oluşturuldu. IR grubunda, sağ nefrektomi yapıldıktan sonra sol böbrekte 60 dk iskemi ve 24 saat reperfüzyon sağlandı. Grup III ve Grup IV'e IR grubundaki işleme ek olarak IR işleminden 5 gün önce belirlenen dozlarda SS ve AA uygulandı.

**Bulgular:** Grup I, Grup III ve Grup IV ile karşılaştırıldığında Grup II'de glomerulus ve renal tübüllerin morfolojik yapılarında şiddetli hasar olduğu görüldü ( $p<0,05$ ). Grup I, Grup III ve Grup IV ile karşılaştırıldığında Grup II'de TNF- $\alpha$ , IL-6, Kaspaz-3 ve Bcl-2 ekspresyonu ve pozitif hücre yüzdesi istatistiksel olarak arttı ( $p<0,001$ ).

**Sonuç:** Bu çalışma, askorbik asit ve sodyum selenit'in profilaktik olarak uygulanmasının akut böbrek hasarına karşı koruyucu etkiler gösterdiğini belirledi.

**Anahtar Kelimeler:** Askorbik asit, inflamasyon, renal iskemi-reperfüzyon, sodyum selenit

#### ABSTRACT

**Objective:** The aim of this study is to investigate the anti-inflammatory and anti-apoptotic effects of ascorbic acid (AA) and sodium selenite (SS) administration in renal ischemia and reperfusion (IR) injury.

**Materials and Methods:** Twenty-eight Wistar-albino rats were divided into four groups. Group I; Control group, Group II; IR group, Group III; IR+0.25mg/kg SS and 100mg/kg AA and Group IV; IR+0.50mg/kg SS and 200mg/kg AA. In the control group, only surgical stress was created. In the IR group, 60 minutes of ischemia and 24 hours of reperfusion were applied in the left kidney after right nephrectomy. SS and AA were administered to Groups III and IV at doses determined 5 days before the IR procedure.

**Results:** In comparison of Group II with Group I, Group III and Group IV; severe damage was observed in the morphological structures of the glomerulus and renal tubules in Group II ( $p<0.05$ ). Compared to Group I, Group III and Group IV the expression of TNF- $\alpha$ , IL-6, Caspase-3, and Bcl-2 and the percentage of positive cells increased statistically in Group II ( $p<0.001$ ).

**Conclusion:** This study determined that prophylactic administration of ascorbic acid and sodium selenite showed protective effects against acute kidney injury.

**Keywords:** Ascorbic acid, inflammation, renal ischemia-reperfusion, sodium selenite

#### Sorumlu Yazar / Corresponding Author:

Songul Doganay  
Department of Physiology, Sakarya University, Medical Faculty,  
Sakarya – Turkey  
Tel: +905309523295  
E-mail: [songuldoganay@sakarya.edu.tr](mailto:songuldoganay@sakarya.edu.tr)

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## INTRODUCTION

Renal ischemia is the deprivation of oxygen of the kidney due to the reduction or interruption of blood flow to the tissue. Studies have shown that restoring blood flow after ischemia can increase tissue and cell damage in hypoxic organs and limit the return of function.<sup>1</sup> Researchers are making a great effort to identify the vascular changes caused by IR injury and to identify the mechanisms underlying this pathological process.<sup>1,2</sup> Among the causes of damage to IR, primarily the increase of inflammatory cytokines (TNF- $\alpha$  and IL-6), free radicals and phagocytes are being showed.<sup>2</sup> IR damage aggravates tissue damage through the interaction of reactive oxygen metabolites, endothelium and neutrophils. By providing the tissue with oxygen support, the sudden excessive amount of oxygen entering the system causes the formation of free oxygen radicals.<sup>3</sup> Post-ischemic tissues produce numerous inflammatory mediators such as tumor necrosis factor (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ) interleukin-6 (IL-6) interleukin-10 (IL-10), which can activate or attract circulating neutrophils.<sup>4</sup> TNF- $\alpha$  is thought to have a role in the systemic inflammatory response induced by IR. In experimental studies, administration of TNF- $\alpha$  appears to cause clinical symptoms of multiple organ dysfunction syndrome (MODS).<sup>5</sup> Therefore, TNF- $\alpha$  is considered to be an inflammatory mediator that can directly initiate systemic inflammation and MODS. All the described mechanisms are interrelated and therefore it is quite difficult to provide a protective efficacy with individual mechanisms and mediators.<sup>6</sup>

Acute kidney injury (AKI), which is caused by the sudden decrease in kidney functions after IR, is a life-threatening clinical condition that causes the accumulation of waste materials in the blood.<sup>7</sup> Deterioration in renal tubule structure, hemodynamic changes, increase in oxidant substances, increased oxidative stress due to inhibition of the antioxidant system, increased inflammation with the activation of proinflammatory cytokines and immune cells are responsible for the development of AKI due to kidney IR.<sup>3,8</sup> Recent experimental studies have focused on the single or combined use of many anti-inflammatory and antioxidant agents to treat or prevent these factors.<sup>9</sup> SS and AA are immune system regulators as well as antioxidant effects.<sup>9,10</sup> The beneficial effects of using selenium and vitamin C separately or in combination with other vitamins have been shown to prevent IR damage in different organs such as the heart, lungs, intestines and kidneys.<sup>11-13</sup>

In line with this information, we aimed to investigate the pro-inflammatory and anti-apoptotic effects of the combined use of sodium selenite and ascorbic

acid against AKI caused by renal IR.

## MATERIALS AND METHODS

**Ethical Status:** Experiment protocols were carried out in accordance with international guidelines at Sakarya University Animal Laboratory (SUDATEM), after approval from Sakarya University Animal Care and Use Ethics Committee (Date: 04.11.2020, decision no: 61).

**Animals:** All rats were kept in wire cages under standard laboratory conditions with a 12-hour light/dark light cycle, a temperature of  $22 \pm 2^\circ\text{C}$  and a humidity of 50-60%. Before the study, all rats were fed with standard pellet chow and tap water. For anesthesia, 30 mg/kg ketamine and 10 mg/kg xylazine were administered intraperitoneally (i.p.). Sodium selenite (SS) (Sigma Chemical East ellsworth rd. item no; N0636, USA) and ascorbic acid (AA) (Sigma Chemical 3050 Spruce Street. item no; 255564, USA) i.p. were given.

**Experiment Protocol and Experimental Groups:** In our study, 28 Wistar-albino male rats weighing approximately 280-300 g (12-14 weeks old) were used. The animals were randomly divided into 4 groups with 7 rats in each group. All surgical procedures were performed while the rats were under anesthesia. SS and AA doses were determined according to previous studies.<sup>14</sup>

**Group I (Control, n=7):** After the abdominal areas of the rats in this group were shaved and cleaned, both sides of the dorsal retroperitoneal regions were opened and closed without any procedure.

**Group II (IR group, n=7):** As in Group I, after right nephrectomy was performed on rats after surgical preparation; the left kidney artery, vein and ureter were clamped with a nontraumatic microvascular surgical clamp, preventing blood flow for 1 hour and ischemia was created, and then 24-hour reperfusion was achieved.

**Group III (IR+0.25mg/kg SS and 100mg/kg AA, n=7):** The low prophylactic dose of 0.25mg/kg SS and 100mg/kg AA is given i.p. for five days before performing the IR procedure. Then, the IR procedure was applied as in Group II.

**Group IV (IR+ 0.50mg/kg SS and 200mg/kg AA, n=7):** This group was i.p given a single high dose of 0.50mg/kg SS and 200mg/kg AA as a prophylactic for five days before applying the IR procedure. Then, the IR procedure was applied as in Group II. After the experimental period, the animals were sacrificed and the kidney tissues were taken into 10% formaldehyde for histological examinations.

**Histopathological Examination:** Tissue samples were kept in 10% buffered formalin solution for 2 days, then they were dehydrated, cleared and embedded in paraffin blocks. For histopathological exami-

nation, sections of 4 microns were taken from each block, stained with hematoxylin-eosin (H&E) and examined using a Light microscope (Olympus CX31 -Japan).

Kidney tissue sections were evaluated using the scale degree of kidney damage (tubular cell necrosis, cytoplasmic vacuolization, hemorrhage, and tubular dilatation), which was previously designed for semi-quantitative evaluation.<sup>15</sup> Specifically, a single deep coronal section was examined under the microscope, depending on the extent of kidney involvement and the degree of damage. The scores were formed such as (0) is normal kidney; (1) is minimal damage (0-5% turnout); (2) is mild damage (5-25% involvement); (3) is moderate damage (25-75% involvement) and 4 is severe damage (75-100% involvement).<sup>15</sup>

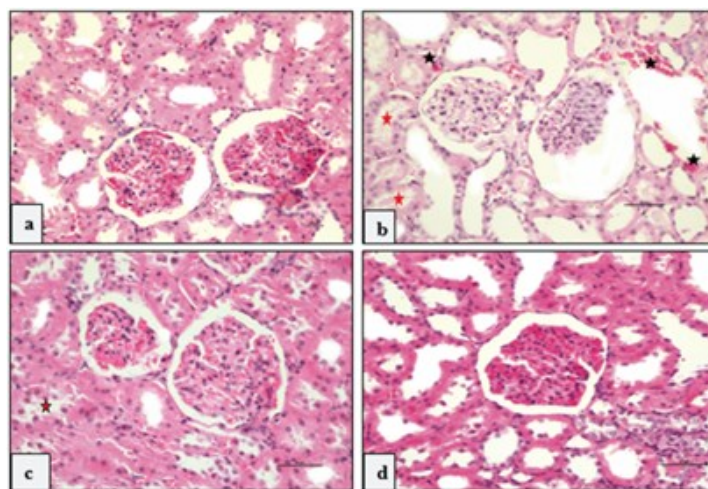
**Immunohistochemical Examination:** Sections of 4 or 5  $\mu\text{m}$  thickness from tissues embedded in paraffin blocks were taken on a slide with "Poly-L-Lysine" and after deparaffinization, immunohistochemical (IHC) staining was performed using the EnVision Flex detection kit (Agilent Technologies, California, USA) in accordance with the manufacturer's recommendations. Antigen unmasking was done by microwave incubation of the slides in a solution of citrate buffer (pH 6) for 40 min. Primary antibody diluted 1/300 (TNF- $\alpha$ : sc-52746, Santa Cruz-USA; IL-6:sc-32296, Santa Cruz-USA; Bcl-2: sc-7382, Santa Cruz-USA; Caspase -3:sc-56053, Santa Cruz-USA) was dripped and incubated overnight at +4°C in a humid environment. Diaminobenzidine (DAB) was used to make the dye visible. After staining with hematoxylin and eosin, the immunopositivity of the samples was evaluated by giving a semiquantitative H score. To evaluate the IHC staining results, both the inten-

sity of the image reaction (weak-1, intense-2) and the density of positive cells in percent (%0 - (0); 50-1% - (1); 51-75% - (2); 76-100% - (3)) scoring scale was used. The IHC image score calculation was calculated for each image by multiplying the image density reaction by the positive cell density.<sup>16</sup>

**Statistical Analyzes:** Statistical analyzes were performed using the SPSS 24.0 package program (SPSS Inc. and Lead Tech. Inc. Chicago. USA). Kolmogorov-Smirnov test was used to evaluate the normal distribution of the data. In the comparison of more than two variables, one-way ANOVA was used for data showing normal distribution, and Kruskal Wallis one-way analysis of variance test was used for data not showing normal distribution. In order to determine which group was different from the others, TUKEY HSD was used for homogeneous variances and Mann-Whitney U test was used for non-parametric tests. Results are given as mean $\pm$ standard deviation (SD) and median-interquartile range (IQR). Statistical evaluation was considered significant if  $P < 0.05$ .

## RESULTS

It was observed in the histopathological evaluations of the tissue samples that there were differences in the morphological structures of the glomerulus and renal tubules. Interstitial space, Bowman's capsule, structure of glomeruli, distal and proximal tubular epithelium were in regular morphological structure in Group I and Group IV groups. Severe damage was observed in the morphological structures of the glomerulus and renal tubules in Group II, which was the IR group that did not receive treatment, compared to the other groups (Figure 1).



**Figure 1.** Microscopic images of kidney samples of control, untreated and treated IR groups after hematoxylin and eosin (H&E) staining. Kidney morphology was normal in Group I (a) and nearly normal in Group IV (d); Group II (b) showed high-intensity hemorrhage areas (black star), occasional tubular cell necrosis (red star) and cytoplasmic vacuolization. Group III (c) showed minimal cellular debris in rare areas, with no hemor-



The comparison of the histopathological scores of the experimental groups in terms of tubular necrosis, cytoplasmic vacuolization, hemorrhage and tubular dilatation of kidney damage is shown in Table 1. Statistically significant degeneration was observed in Group II, which is the IR group, compared to Group I, Group III, Group IV ( $p < 0.001$ ). In comparisons made between Group I, Group III and Group IV, kidney morphology was preserved close to normal, especially in Group IV. There was no statistically significant difference between these groups ( $p > 0.05$ ) (Table 1).

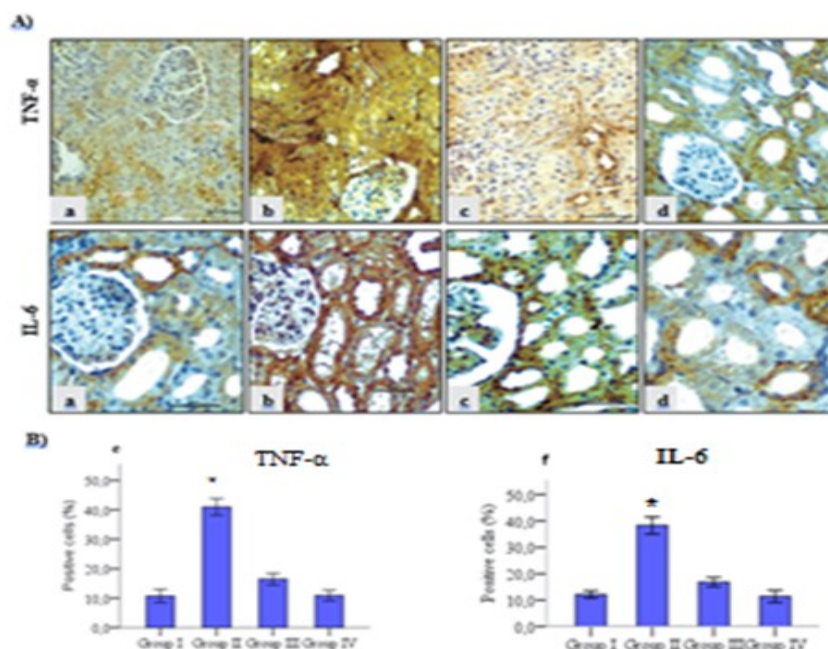
In the immunohistochemical examination of the kidney tissue, normal levels of TNF- $\alpha$ , IL-6, Caspase-3,

and Bcl-2 expression were observed in Group I. In Group II, TNF- $\alpha$ , IL-6, caspase-3, and Bcl-2 expressions were significantly higher than Group I, Group III, Group IV (Figure 2A-3A), and the percentage of positive cells increased statistically significantly. ( $p = 0.000$  for all) (Figure 2B-3B). Comparing with Group II, the immunopositivity decreased in Group III and Group IV (especially Group IV), close to Group I, and this decrease was statistically significant ( $p = 0.000$ ) (Figure 2B-3B). There was no statistical difference in the evaluations made between Group III and Group IV ( $p > 0.05$ ).

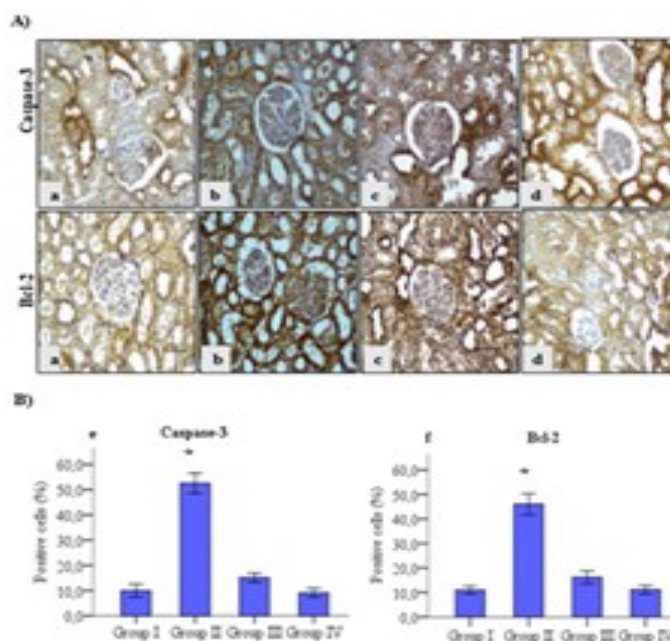
**Table 1.** Comparison of histopathological scores of kidney injury between experimental groups.

Group (Each group n=7)	Tubular Necrosis Median (IQR)	Cytoplasmic Vacuolization Median (IQR)	Hemorrhage and Tubular Dilatation Median (IQR)
Group I	0 (1)	0 (0)	0 (0)
Group II	3 (1)	2 (1)	2 (1)
Group III	0 (1)	1 (1)	1 (1)
Group IV	0 (0)	0 (1)	0 (0)
P value (Kruskal Wallis)	0.000	0.001	0.000
P value (Mann-Whitney U)	0.001; I-II, III, IV	0.001; I-II 0.003; II-IV 0.007; II-III	0.001; I-II, III, IV

Values are presented as median (interquartile range); n: numbers.



**Figure 2.** TNF- $\alpha$  and IL-6 positive staining percentage and expression were normal in the control and treatment groups (a, c, d); it is most intense in Group II (b). Extremely high TNF- $\alpha$  and IL-6 expression increased percentage of positive cells (e, f) in damaged areas in Group II. Decreased expression and percentage of positive cells in treated Group III and Group IV (e, f). \* $p < 0.001$  when compared to Group I, Group III and Group IV. H&E, 200X.



**Figure 3.** Caspase-3 and Bcl-2 positive staining percentage and expression were normal in the control and treatment groups (a, c, d); It is seen that it is most intense in Group II (b). Extremely high expression of Caspase-3 and Bcl-2 in damaged areas in Group II, increased percentage of positive cells (e, f). Decreased expression and percentage of positive cells in treated Group III and Group IV (e, f). \* $p < 0.001$  when compared to Group I, Group III and Group IV. H&E, 200X.

## DISCUSSION AND CONCLUSION

After the decrease or complete cessation of renal blood flow, acute renal failure (ARF) is triggered with various degrees of damage to the tissue with reperfusion.<sup>17</sup> ARF is a life-threatening disease with a high mortality rate. Oxidative stress and inflammatory response play an important role in the progression of ARF. Products and phytochemical compounds with strong inhibitory effects on these mechanisms can be a useful treatment for ARF.<sup>18</sup> Therefore, in this study, the anti-inflammatory and anti-apoptotic effects of using ascorbic acid and sodium selenite together in different doses against renal ischemia-reperfusion injury were investigated.

Studies in the literature have shown an increase in cytoplasmic vacuolization, vascular hemorrhage, and tubular dilatation in tissues after IR.<sup>19</sup> It was observed that the co-administration of high and low doses of ascorbic acid and sodium selenate to the treatment groups in order to alleviate the damage after IR, this damage was significantly reduced, especially in the high dose group. Positive effects of ascorbic acid and selenium administration on IR damage to reduce or treat renal IR damage have also been demonstrated in previous studies.<sup>20,21</sup> As a result of a study in which different doses of AA were applied before and after ischemia to prevent hepatic ischemia-reperfusion injury. It even produces antioxidant activity, and that it has pre-oxidant effects in high-dose application.<sup>22</sup> Hasanvand et al.,<sup>23</sup> and Ostrońska-Cieślak et al.<sup>24</sup> reported that the application of

selenium against kidney IR injury reduces kidney damage.

Kidney damage after IR causes the production of inflammatory mediators such as various cytokines and chemokines from tubular and endothelial cells. This results in the infiltration of inflammatory cells into the renal interstitium. Inflammatory cells in the kidney produce pro-inflammatory cytokines.<sup>25</sup> In ischemic ARF, the levels of proinflammatory cytokines/chemokines such as interferon gamma (IFN- $\gamma$ ), interleukin-2 (IL-2), interleukin (IL-10), tumor graft factor beta (TGF- $\beta$ ), IL-6, macrophage inflammatory protein 2 (MIP-2), and monocyte chemoattractant protein 1 (MCP-1) increase in the kidney.<sup>26</sup> In the current study, we observed that TNF- $\alpha$ , IL-6 expression and the percentage of positive cells increased in the IR group compared to the control and treatment groups as a result of the IHC evaluation. It has been shown that the application of high and low doses of ascorbic acid and sodium selenite reduces TNF- $\alpha$  and IL-6 expression and the percentage of positive cells; especially high-dose application gives results close to the control group.

Apoptosis is mainly initiated by the extrinsic pathway that is triggered extracellularly (presence of TNF- $\alpha$  or absence of growth factor) or the intrinsic pathway triggered from intracellular DNA damage, endoplasmic reticulum stress, or mitochondria. It eliminates abnormal or dead cells to maintain homeostasis. In IR injury, cells die from apoptosis in the first 24 hours of reperfusion.<sup>27</sup> Once the caspases



involved in apoptosis are activated, they induce a series of reactions that lead to the initiation of effector caspase cell death. Caspase-3 is an important marker in the initiation of apoptosis-inducing cascades. Oxidative stress and severe inflammation trigger the activation of caspase-3, which leads to cell apoptosis.<sup>28</sup> In our study, caspase-3 and Bcl-2 expression and the percentage of positive cells were increased in the IR group compared to the control and treatment groups. The expression and the percentage of positive cells decreased in high and low doses of AA and SS treatment groups, and especially high dose administration gave results close to the control group.

Many factors contribute to apoptosis. But key elements are categorized into two major protein families, including caspase enzymes and the Bcl-2 family. The Bcl-2 family is a set of cytoplasmic proteins that regulate apoptosis. The two main groups of this family, the Bcl-2 and Bax proteins, are functionally opposite: Bcl-2 and Bcl-xL inhibit apoptosis, while Bax counteracts this effect. Caspases, particularly caspase-3, are known to play a key role in the Bax/Bcl-2 ratio in driving apoptosis.<sup>29</sup> Recent evidence indicates that Bcl-2 is also a downstream death substrate of caspases and can thus inactivate the Bcl-2 anti-apoptotic function of caspase enzymes. Although there is a feedback loop between Bcl-2 and caspase, Bcl-2 cannot always prevent apoptosis.<sup>30</sup> The results of our study concluded that Bcl-2 expression increased with caspase-3 in the IR group. It has been shown that the application of AA and SS did not increase the expression of Bcl-2. These results suggest that AA and SS can not trigger the anti-apoptotic effect of Bcl-2.

In conclusion, prophylactic administration of AA and SS significantly improved kidney morphology in renal IR injury and promoted cell survival by targeting inflammatory cytokines and apoptosis.

**Ethics Committee Approval:** The study was approved by the Sakarya University Animal Experiments Local Ethics Committee (Date: 04.11.2020, decision no: 61).

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Author Contributions:** Concept – SD; Supervision – SD, OB; Materials – SD, OB; Data Collection and Processing – SD, OB; Analysis and Interpretation – SD, OB; Writing – SD.

**Peer-review:** Externally peer-reviewed.

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## Total Diz Artroplastisi Sonrası Ağrı Yönetimi: Kısa-Orta Dönem Sonuçlarımız

### Pain Management after Total Knee Arthroplasty: Our Short-Medium Term Results

<sup>1</sup>Zafer ŞEN, <sup>2</sup>Alper KURTOĞLU

<sup>1</sup> Türk Kızılay Ticaret Borsası Konya Hastanesi Ortopedi ve Travmatoloji, Konya, Türkiye

<sup>2</sup> Sakarya İl Sağlık Müdürlüğü Sakarya Üniversitesi Eğitim ve Araştırma Hastanesi Ortopedi ve Travmatoloji, Sakarya, Türkiye

Zafer Şen: <https://orcid.org/0000-0003-0807-6715>

Alper Kurtoğlu: <https://orcid.org/0000-0001-9890-1330>

#### ÖZ

**Amaç:** Total diz artroplastisi sonrası diz ağrısı ciddi morbidite oluşturduğu için ağrı yönetiminde farklı teknikler uygulanmaktadır. Bu çalışmada intraoperatif uyguladığımız Ranawat kokteyli ile hastaların klinik olarak opioid ihtiyaçları, fonksiyonel sonuçları ve hasta memnuniyetinin değerlendirilmesi amaçlanmıştır.

**Materyal ve Metot:** Çalışmaya total diz artroplastisi uygulanan 310 hasta dahil edildi. Tüm hastalara derin ve yüzeysel olmak üzere iki kısım içeren Ranawat kokteyl enjeksiyonu uygulandı. Hastaların VAS skorları (preoperatif, postoperatif 12, 24, 48. saat), opioid ihtiyaçları ve hasta memnuniyet ölççeği ile memnuniyet değerlendirildi.

**Bulgular:** Ortalama yaş 64,4±16,4 olarak bulundu. Preoperatif preop VAS değer ortalaması 7,1±1,9, postoperatif 12. saatteki ortalaması 5,2±2,8, postoperatif 24. saatteki ortalaması 3,7±2,3 ve postoperatif 48. saatteki ortalaması 2,4±1,4 olarak bulundu. Olguların %68,3'ü (212 hasta) çok memnun, %31,62'si (98 hasta) az memnun idi. Ameliyat sonrası opioid ihtiyacı %23,5 olarak bulundu.

**Sonuç:** Multi odak kokteyl enjeksiyonu total diz artroplastisi uygulanmış olan hastalarda rehabilitasyonu kolaylaştırmak açısından basit, güvenli ve etkili bir postoperatif analjezi kontrol disiplini.

**Anahtar Kelimeler:** Periartiküler enjeksiyon, ranawat kokteyl, total diz artroplastisi

#### ABSTRACT

**Objective:** Since knee pain causes serious morbidity after total knee arthroplasty, different techniques are applied in pain management. In this study, it was aimed to evaluate the clinical opioid needs, functional results and patient satisfaction of the patients with the Ranawat cocktail that we applied intraoperatively.

**Materials and Methods:** 310 patients who underwent total knee arthroplasty were included in the study. Ranawat cocktail injection containing two parts, deep and superficial, was applied to all patients. The patients' VAS scores (preoperative, postoperative 12, 24, 48th hours), opioid needs, and patient satisfaction scale were evaluated for satisfaction.

**Results:** The mean age was found to be 64.4±16.4 years. The mean preoperative VAS value was 7.1±1.9 the mean at the postoperative 12th hour was 5.2±2.8 the mean at the postoperative 24th hour was 3.7±2.3 and the mean at the postoperative 48th hour was 2.4±1.4. 68.3% (212 patients) of the cases were very satisfied, 31.62% (98 patients) were less satisfied. The postoperative opioid requirement was found to be 23.5%.

**Conclusion:** Multifocal cocktail injection is a simple, safe and effective postoperative analgesia control discipline to facilitate rehabilitation in patients who have undergone total knee arthroplasty.

**Keywords:** Periarticular injection, ranawat cocktail, total knee arthroplasty

#### Sorumlu Yazar / Corresponding Author:

Zafer Şen

Adres: Şükran Mahallesi, Taş Kapu Medrese Sokak, No:15, 42200,

Konya Kızılay Hastanesi, Karatay/Konya

Tel: +90505 462 88 25

E-mail: senzaferesen@hotmail.com

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## GİRİŞ

Total diz artroplastisi diz eklemlerinde oluşan ileri derecede eklem hasarına bağlı ağrıyı azaltmak, fonksiyonelliği ve yaşam kalitesini artırmak için sıklıkla uygulanan cerrahi bir yaklaşımdır.<sup>1</sup> Bu cerrahi genellikle artrit (osteoartrit, romatoid artrit, diğer) sonucu oluşan ağrı, deformite veya sınırlı fonksiyondan kaynaklanan ciddi işlev kaybı durumlarında uygulanmaktadır. Osteoartrit bu uygulamanın en temel sebeplerinden biri olarak görülmektedir.<sup>2</sup> Bununla beraber, total diz artroplastisi sonrasında postoperatif ağrı yönetimi bugün bile sorun olmaya devam etmektedir ve total diz artroplastisi olacak olan hastaların ana endişelerinden biridir.<sup>3</sup> Ameliyattan sonra hastalarda oluşan şiddetli ağrı, mobilizasyon ve erken hareketlerin geç başlanmasına, böylece derin ven trombozu riskinin artmasına neden olur. Sonuçta, hastane enfeksiyonunun artmasına, hastanede kalış süresinin artmasına neden olmaktadır.<sup>4</sup>

## MATERYAL VE METOT

**Etik Komite Onayı:** Çalışmamız Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi İlaç ve Tıbbi Cihaz Dışı Araştırmalar Etik Kurul Başkanlığı tarafından onaylanmıştır (Tarih: 17.04.2020, karar no: 2020/2426). Çalışma uluslararası 1964 Helsinki Deklerasyonuna ve daha sonraki değişikliklerde belirtilen etik standartlara uygun olarak yürütülmüştür. Kurumsal inceleme kurumumuz çalışma protokolünü onayladı ve tüm hastalar çalışmaya dahil edilmeden önce yazılı bilgilendirilmiş onam verdi. Çalışmamıza Ocak 2018 ile Haziran 2019 yılları arasında Sağlık Bilimleri Üniversitesi Konya Eğitim Araştırma Hastanesinde total diz artroplastisi uyguladığımız 310 hastayı dahil ettik. Cerrahi işlemlerin hepsi spinal anestezi altında gerçekleştirilmiştir.

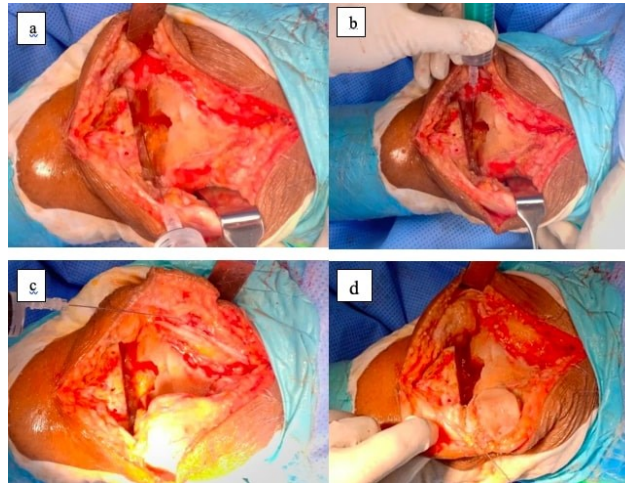
Hastalarımızın hepsi 45 yaş ve üzeri ve Kellgren-

Lavrence sınıflamasına göre grade 3-4 artrozları olan hastalar idi.<sup>10</sup> Fakat, sekonder artrozu olan hastaları, 45 yaş altında olan hastaları, yumuşak doku hasarı olan hastaları, ek hastalıklarından dolayı elektif cerrahiye uygun olmayan hastaları, revizyon gereken hastaları, lokal multi odak enjeksiyon içeriğinin herhangi birine alerjik durumu olan hastaları, aynı zamanda 6 aylıktan az takibi olan hastaları çalışmamıza dahil etmedik.

Total diz artroplastisi cerrahisi uygulanan tüm hastalar, 350 mmhg (milimetre civa) basınçlı turnike altında tek cerrah tarafından opere edilmiştir. Hastalarımızın %15,48'i erkek (48 hasta), %84,52'si (263 hasta) bayan idi. Olgularımızın hepsine, midline insizyon medial parapatellar approach ile cerrahi yaklaşım uygulanmıştır. Olgularımızın hiç birine patellar implant konmamıştır.<sup>11</sup>

Ranawat kokteyl karışımı derin ve yüzeysel olmak üzere iki kısımdan oluşmaktaydı. Derin kısmının içeriğinde 24 cc (200-400 mg) bupivakain, 0,8 cc (8 mg) morfin sülfat, 1 cc (40 mg) metil prednizolon asetat, 10 cc (750 mg) sefuroksim aksetil, 0,3 cc (300 mcg) epinefrin, 22 cc %0,9'luk sodyum klorür içerirken yüzeysel kısmın içeriğinde ise 20 cc (200-400 mg) bupivakain, 20 cc %0,9'luk sodyum klorür bulunmaktaydı.

Femoral, tibial kesiler yapıldı, patella hazırlandıktan sonra cerrahi alan steril olarak yıkandı ve kurulama işlemi yapıldı. Bu işlemden sonra hazırlanan Ranawat kokteyl enjeksiyon, cerrahi alandaki yedi bölgeye 3-5 cc olacak şekilde enjekte edildi. Biz ayrı iki 50 cc'lik enjektör ve 22 gauge (pembe uç) enjektör ucu kullandık. Enjeksiyonlar, orijinal implantları ve kemik çimentosunu koymadan önce yapıldı. Enjeksiyon aşamasına gelince ilk önce derin enjeksiyon için hazırlanmış olan enjektör kullanıldı. Her bölgeye 3-5 cc olacak şekilde enjekte edildi. Öncelikle medial menisküs kapsül bölgesine enjekte edildi (Şekil 1).



**Şekil 1.** Enjeksiyonun anatomik yerleri. Medial kapsül (a), lateral kapsül (b), medial ve lateral retinaküler (c), quadriseps tendonu ve patella çevresine (d), Ranawat kokteyl enjeksiyonu.

Sonrasında alt ekstremité uzatıldı ve lateral menisküs kapsüleri bölgesine 3-5 cc olacak şekilde Ranawat kokteyl enjekte edildi. Arkasından cerrahi alan, eklem bölgesinden fleksiyona getirildi. Posteriora doğru, tibial kemikten asistanlar yardımı ile itme uygulanarak posterior kapsül açığa çıkartıldı. Derin enjeksiyon için hazırlanmış Ranawat kokteyl enjeksiyonu (RKE), posteromedial kapsüle 3-5 cc olacak şekilde enjekte edildi. Aynı işlem sırasında, posterolateral kapsüleri bölgeye 3-5 cc olacak şekilde enjeksiyon uygulandı. Ardından, cerrahi alan diz eklemi bölgesinden asistanlar yardımı ile ekstansiyona getirildi. Derin enjeksiyon için hazırlanmış olan enjektörden medial ve lateral retinaküler bölgeye 3-5 cc olacak şekilde enjekte edildi. Sonrasında yüzeysel enjeksiyon için hazırlanmış enjektöre geçildi. İlk önce suprapatellar poşa enjeksiyon uygulandı. Yüzeysel enjeksiyon için hazırlanmış enjeksiyonda kalan ilaçlar, quadriseps tendonuna ve patella çevresine enjekte edildi.

Bu işlemlerin ardından kurulama yapıldı. Daha önceden denemesi yapıp ebatı belirlenen orijinal implantlar çimento yardımı ile yerleştirildi. Kanama kontrolünün ardından, dren yerleştirildi. Kapsül, cilt altı doku ve cilt kapatıldı. Pansumanı yapıldıktan sonra, pamuk ve elastik bandaj ile sarıldı. Dren, ameliyattan 3 saat sonraya kadar açılmamasına dikkat edildi.

Hastalarımıza postop analjezi için, rutin olarak intravenöz form olarak 2 gram parasetamol verildi. Hastalar ağrıyı tolere edemediklerinde ise, tramadol 50 mg (günde en fazla iki kez olmak üzere) verildi. Hastalara diğer bacağı anti embolik çorap giydirildi. Spinal anestezinin etkisi geçtikten sonra pasif hareketlere hemen başlandı. Cerrahi bölgeye soğuk uygulaması yapıldı.<sup>12</sup>

Aktif hareketlere ise postoperatif 1.gün başlandı.

Aktif diz hareketleri gonyometre yardımı ile kayıt edildi, hastaların tolere edebildiği kadar yürüteç ile yürütüldü. Hastaların analjezi kontrolü için ağrı durumları ameliyat sonrasında 12, 24 ve 48. saatlerde VAS skalası ile ölçüldü. VAS skalası, hastanın ağrı durumunu 0 ile 10 değerleri arasında belirten sayısal bir skaladır.<sup>13</sup> Hastanın hareket açıklıkları ise postop 12, 24 ve 48. saatlerde ölçülerek kayıt edildi.

**İstatistiksel Analiz:** Veri Veri İstatistiksel analizde Statistical Package for Social Sciences (SPSS) for Windows 23,0 programı kullanılmıştır. Hastaların demografik değişkenlere ait verileri değerlendirirken tanımlayıcı istatistiksel analizler (ortalama, standart sapma, yüzde, minimum, maksimum) kullanıldı. Elde edilmiş olan VAS değerleri Wilcoxon testi ile analiz edildi.  $p < 0,005$  olacak şekilde anlamlı kabul edildi.

## BULGULAR

Çalışmamıza 310 hasta dahil edildi ve ortalama yaş 64,4 olarak bulundu (Tablo 1).

Hastalarımızda %6,8 oranında diyabetes mellitus tanısı mevcut idi. Hastalarımızın %29,5'inde 5 yıldan daha az, %31,8'inde 6-10 yıl, %15,3'ünde 11-15 yıl, %23,4'ünde 15 yıldan daha fazla kronik diz ağrısı mevcut idi (Tablo 2).

Çalışmaya dahil olan olgularımızın preoperatif VAS değeri ortalaması  $7,1 \pm 1,9$ , postoperatif 12. saatteki ortalaması  $5,2 \pm 2,8$ , postoperatif 24. saatteki ortalaması  $3,7 \pm 2,3$  ve postoperatif 48. saatteki ortalaması  $2,4 \pm 1,4$  olarak bulundu (Tablo 3). Hastaların preoperatif ve postoperatif 12, 24, 48. saatlerdeki VAS değerleri Wilcoxon testi ile değerlendirildi. Hastaların ağrılarının kademeli olarak azaldığı ve bu azalmanın istatistiki olarak anlamlı olduğu bulundu ( $p < 0,001$ ) (Tablo 3).

**Tablo 1.** Olguların demografik özellikleri.

Cinsiyet	Hasta Sayısı	Ort±SD	% (Yüzde)
E	48	67,4±12,6	15,48
K	262	63,9±16,1	84,52
<b>Toplam</b>	310	64,4±16,4	100

Ort: Ortalama; SD: Standart deviasyon.

**Tablo 2.** Kronik diz ağrısının yıllara göre dağılımı.

Kronik Diz Ağrısı	Ağrı süresi	%
	5 yıldan daha az	29,5
6-10 yıl	31,8	
11-15 yıl	15,3	
15 yıldan daha fazla	23,4	

**Tablo 3.** VAS değerleri ortalaması.

VAS	Preoperatif	Postoperatif 12.saat	Postoperatif 24.saat	Postoperatif 48.saat	p
<b>Ort±SD</b>	7,1±1,9	5,2±2,8	3,7±2,3	2,4±1,4	<0,001

Ort: Ortalama; SD: Standart deviasyon.

Hastalarımızın, yaş, cinsiyet, DM (diyabetes mellitus) tanısının olması ve VAS değerleri arasında anlamlı bir ilişki kurulamamıştır ( $p>0,05$ ) (Tablo 4).

### TARTIŞMA VE SONUÇ

Total diz artroplastisi son evre osteoartritin en etkin tedavisidir ve bu tedavinin amacı hastaların ağrısız bir yaşam sürmelerini ve hayat konforunu arttırmaktır.<sup>14</sup>

Cerrahi sonrası erken hareket iyileşmeyi hızlandırmakta ve komplikasyon oranlarını azaltmakla birlikte postoperatif ağrı gelişmesi ve ağrıdan dolayı hareketlere başlamada gecikme ve zorluk yaşanması cerrahlarda yapılacak olan işleme dair endişe uyardırmaktadır.<sup>15</sup> Postoperatif ağrının fazla olması egzersizlere uyumu bozmakta, hastanede kalış süresini arttırmakta ve cerrahiden memnuniyet oranını azaltmaktadır.<sup>16,17</sup> Aynı zamanda ağrıdan dolayı, hastalarda stresin arttığı, uyku bozuklukların olduğu da bildirilmiştir.<sup>18</sup> Yeterli ağrı kontrolün sağlanması ile erken rehabilitasyon sağlanabilmekte ve cerrahinin başarısı artırılmaktadır.<sup>19</sup>

Cerrahi sonrası ağrının giderimi için çoğu kez opioidler reçete edilmektedir.<sup>20</sup> Ancak, opioidler baş ağrısı, baş dönmesi, bulantı, kusma, ilaç bağımlılığı gibi yan etkilere neden olabilmektedirler.<sup>21</sup>

Eklem artroplastisinde ağrı kontrolü için femoral sinir bloğu, addüktör kanal bloğu ve siyatik sinir bloğunu içeren sinir blokları uygulanabilmektedir.<sup>22</sup> Bununla birlikte, bu yöntemler sinir hasarı, azalan kas kontrolü, kanama ve enfeksiyon ile ilişkilendirilmiştir.<sup>23</sup>

Sinir bloğu yapılmadığı için bizim hastalarımızın hiçbirinde kanama, azalmış kas kontrolü, sinir hasarı gibi komplikasyon görülmedi.

Meier yapmış olduğu çalışmada, lokal postoperatif intra-artiküler infiltrasyon analjezisinin etkin olduğunu bildirmiştir.<sup>24</sup> Ancak bu yöntemin ameliyattan sonra kateter yerleştirme gerekliliği gibi dezavantajı da bulunmaktadır.<sup>25</sup>

İntraoperatif olarak eklem çevresi multiodak çoklu ilaç kombinasyonlarının ağrı azaltılmasında etkin olduğu gösterilmiştir.<sup>26,27</sup>

Multiodak kokteyl enjeksiyonunun uygulanması sonucunda, daha iyi hasta memnuniyeti, azalmış

opioid kullanımı, ameliyat komplikasyonlarında azalma olduğu bildirilmiştir.<sup>28</sup>

Bu nedenlerden dolayı yeterli ve etkili postoperatif analjezi için, kokteyl karışım enjeksiyonu etkin tedavi olarak uygulanabilmektedir.<sup>5,9</sup> Bizde çalışmamızda multiodak kokteyl enjeksiyonu ile postoperatif ağrı gelişimini azaltarak hastaların cerrahi memnuniyetlerini yüksek olarak bulduk.

Multiodak periartiküler kokteyl enjeksiyon, kusma, bulantı, kaşıntı, solunum depresyonu, baş ağrısı, ortostatik hipotasyon gibi sistemik yan etkileri olan epidural analjeziden ve opioidlerden üstündür.<sup>29</sup>

Aynı şekilde, kas güçsüzlükleri yapan ve mobilizasyonda gecikmeyle derin ven trombozuna neden olabilen periferik femoral blok analjeziden de üstünlüğü gösterilmiştir.<sup>5</sup> Bizim bu çalışmamızdaki hiçbir hastada derin ven trombozu gelişmedi.

Kokteyl içinde olan epinefrin, analjezi süresini artırdığı ve konforlu bir süreç geçirdiği, kan damarlarında vazokonstriksiyon ile kanamanın da azaldığı gözlenmiştir. Tramadol, opioid reseptörlerine etki ederek ağrı sinyal iletimine etki eder, sefuroksimin ise postoperatif enfeksiyon oranını azaltması hedeflenmiştir.<sup>5</sup> Metilprednizolon, prostaglandinlerin vazodilatör etkisini inhibe ederek proinflatuar tepkiyi inhibe eder.<sup>30</sup> Multiodak kokteyl enjeksiyon içeriklerinden olan bupivakainin ise, uzun etkili olmasından da dolayı, opioid kullanımını azalttığı ve sürecin daha konforlu olduğu görülmüştür. Multiodak kokteyl karışımının, bu etkilerinden dolayı, hastanede kalış sürelerinde azalma, postop ağrıda azalma, hastane enfeksiyon oranında azalma, yeterli mobilizasyon olduğu görülmüştür.<sup>28</sup>

Postoperatif analjezi yönetimi, yeterli ve erken mobilizasyona izin veren konforlu bir süreç geçirmesini sağlayan bir sistematik içinde olmalıdır. Taburculuk esnasında, yürüme mesafesini artırıcı telkinlerde bulunmak önemlidir.<sup>18</sup> Bizde uyguladığımız multiodak enjeksiyon ile postoperatif erken rehabilitasyonu daha az ağrı ile gerçekleştirebildik.

Kısa takip süresi ve sonuçları karşılaştırmak için kontrol grubunun olmaması bu çalışmanın eksik yönleridir. Uzun vadeli sonuçların değerlendirilmesi, bileşenlerin ayrı ayrı analiz edilmesi ve bunların faydalarının ve komplikasyonlarının daha detaylı

**Tablo 4.** Yaş, cinsiyet ve diyabetes mellitus ile VAS değerleri arasındaki ilişki.

		24. saatteki VAS	p
Yaş	>65	2,6±1,4	0,692
	<65	2,4±1,6	
Cinsiyet	Kadın	2,5±1,5	0,543
	Erkek	2,2±1,8	
Diyabetes Mellitus	Var	2,4±1,6	0,714
	Yok	2,3±1,7	

Ort: Ortalama; SD: Standart deviasyon

analiz edilmesi gereklidir. Sonuç olarak multidok kokteyl enjeksiyonu opioid kullanım ihtiyacını azalttığı için opioide bağlı komplikasyonları azaltır, sinir bloklarındaki gelişebilecek olan sinir hasarı, kas kontrolü azalması, kanama gibi komplikasyonları ortadan kaldırır. Ayrıca postoperatif lokal intra-artiküler infiltrasyon analjezide uygulanan ek katater uygulama işlemine gerek duyulmaması avantaj sunar. Basit bir şekilde uygulanabilmesi, güvenli olması, postoperatif kanama miktarını azaltması, erken dönemdeki rehabilitasyonu kolaylaştırması, cerrahi işlemin komplikasyonlarını azaltması, hasta memnuniyetini artırması, postoperatif ağrının gideriminde etkin olması, mortalite ve morbidite oranlarını azaltması özelliği nedeni ile etkili analjezi kontrol disiplini olarak düşünülmektedir.

**Etik Komite Onayı:** Çalışmamız Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi İlaç ve Tıbbi Cihaz Dışı Araştırmalar Etik Kurul Başkanlığı tarafından onaylanmıştır (Tarih: 17.04.2020, karar no: 2020/2426). Çalışma uluslararası Helsinki Deklerasyonuna uygun yürütülmüştür.

**Çıkar Çatışması:** Yazarlar çıkar çatışması bildirmemişlerdir.

**Yazar Katkıları:** Fikir/Tasarım: ZŞ, AK; Veri Toplama/İşleme: ZŞ; Analiz/Yorum: ZŞ, AK; Yazıyı Yazma: ZŞ, AK; Eleştirel İnceleme/Revizyon: ZŞ, AK.

**Hakem Değerlendirmesi:** Dış bağımsız.

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## Sıçanlarda Amiodaronun Sebep Olduğu Akciğer Hasarında Beyaz Lahana Ekstraktının Koruyucu Rolü

### Protective Role of White Cabbage Extract Against Amiodarone-Induced Lung Damage in Rats

<sup>1</sup>Esin AK, <sup>2</sup>İsmet Burcu TURKYILMAZ, <sup>3</sup>Aleyna MUHAN, <sup>2</sup>Refiye YANARDAG

<sup>1</sup> Department of Basic Medical Sciences, Faculty of Dentistry, Marmara University, Istanbul, Turkey

<sup>2</sup> Department of Chemistry, Faculty of Engineering, Istanbul University-Cerrahpaşa, Istanbul, Turkey

<sup>3</sup> Department of Basic Medical Sciences, Institute of Health Sciences, Marmara University Istanbul, Turkey

Esin Ak: <https://orcid.org/0000-0002-3467-7808>

İsmet Burcu Turkyılmaz: <https://orcid.org/0000-0003-2789-5943>

Aleyna Muhan: <https://orcid.org/0000-0002-1958-4814>

Refiye Yanardag: <https://orcid.org/0000-0003-4185-4363>

#### ÖZ

**Amaç:** Bu çalışmada amiodaron'un sebep olduğu akciğer hasarında beyaz lahananın koruyucu etkileri araştırılmıştır.

**Materyal ve Metot:** Bu çalışmada, sıçanlar 4 gruba ayrılmıştır. Kontrol grup: dokunulmamış sıçanlar, WCAE grup, sıçanlara 7 gün 500 mg/kg beyaz lahana ekstraktı verildi; AMD grup, sıçanlara 7 gün 100 mg/kg amiodaron (AMD) verildi; AMD+WCAE grup, sıçanlara aynı dozlarda beyaz lahana ekstraktı ve AMD verildi.

**Bulgular:** AMD+WCAE grubunda, beyaz lahana ekstraktı tedavisi interstisyel ödem ve konjesyonun azalmasına, alveolar yapılar da iyileşme ve bunun yanı sıra parankimdeki enflamatuvar hücre infiltrasyonunun gerilemesine sebep olmuştur. Ek olarak, AMD+WCAE grubunda parankimde kollajen liflerinin birikmesinde önemli derecede bir azalma görülmüştür. Akciğerdeki glutatyon seviyesi, total antioksidan kapasitesi ve glutatyon-S-transferaz, paraoksonaz and karbonik anhidraz aktiviteleri azalırken, lipid peroksidasyon, ileri okside protein ürünleri, total oksidan durumu, reaktif oksijen türleri, oksidatif stres indeksi, nitrik oksit ve hidroksiprolin seviyeleri, katalaz, süperoksit dismutaz, glutatyon peroksidaz, glutatyon redüktaz, laktat dehidrogenaz and ksantin oksidaz aktiviteleri AMD grubunda artmıştır. Beyaz lahana ekstraktı tedavisi AMD'un neden olduğu bu seviyeleri ve aktiviteleri tersine çevirmiştir.

**Sonuç:** Beyaz lahana ekstraktının amiodaron'un sebep olduğu akciğer hasarını azaltabileceği sonucuna varabiliriz.

**Anahtar Kelimeler:** Akciğer, amiodaron, beyaz lahana ekstraktı, oksidatif stres

#### ABSTRACT

**Objective:** It was intended to study the protective roles of white cabbage on amiodarone induced lung damage.

**Materials and Methods:** Rats were distributed into 4 groups, Control group, intact animals; WCAE group, animals given white cabbage extract (WCAE, 500 mg/kg) for 7 days; AMD group, animals administered amiodarone (AMD, 100 mg/kg) for 7 days; AMD+WCAE group, animals given white cabbage extract and amiodarone at the same dose.

**Results:** White cabbage extract treatment in AMD+WCAE group showed reduced interstitial edema and congestion, an improvement in alveolar structures besides regression of inflammatory cell infiltration in lung parenchyma. Moreover, a prominent reduction in the amount of collagen fibers deposition in the parenchyma was seen in AMD+WCAE group. Lung levels of glutathione and total antioxidant capacity and activities of glutathione-S-transferase, paraoxonase and carbonic anhydrase were decreased while the activities of lipid peroxidation, advanced oxidized protein products, total oxidant status, reactive oxygen species, oxidative stress index, nitric oxide and hydroxy proline levels, catalase, superoxide dismutase, glutathione peroxidase, glutathione reductase, lactate dehydrogenase and xanthine oxidase were increased in AMD group. Administration of white cabbage extract reversed these levels and activities in AMD group.

**Conclusion:** In conclusion, white cabbage extract can ameliorate amiodarone induced lung damage.

**Keywords:** Amiodarone, lung, oxidative stress, white cabbage extract

#### Sorumlu Yazar / Corresponding Author:

Esin Ak, Marmara University, Faculty of Dentistry, Department of Basic Medical Sciences, Istanbul, Turkey.  
Tel: +90506 599 07 81  
E-mail: esinbir@yahoo.com

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## INTRODUCTION

Amiodarone (AMD) is a class III antiarrhythmic drug and due to its iodine containing structure, AMD has a tendency to accumulate in lungs and thyroid gland, leading to the dysfunction of the involved organs.<sup>1</sup>

Clinically, amiodarone related lung damage is a well-known cause of severe pulmonary fibrosis in the long term, causing a significant mortality and morbidity. It was shown that AMD treatment results in thickening of alveolar septa with fibrosis, inflammatory cellular infiltration and disruption of the alveolar epithelium. AMD related lung damage is shown to be secondary to multifunctional etiologies like hypersensitivity, direct toxic action and increased oxidative stress.<sup>2</sup>

Limiting the oxidative stress related to AMD exposure in the lung tissue via antioxidant agents could be a reasonable approach for preventing the lung damage. For this purpose, substances with proven the antioxidant action like fish oil, L-carnitine and alpha lipoic acid and so forth have been shown to limit the tissue damage related to AMD.<sup>3-5</sup>

Brassica vegetables (including cabbage, cauliflower and broccoli) are reported to have a high concentration of antioxidant compounds, such as phenols and flavonoids.<sup>6</sup> The use of white cabbage was shown to tackle the oxidative damage and induces a protective action against endothelial, cardiac, hepatic and renal injury in several studies.<sup>7</sup>

Herein, we aimed to investigate the alterations in biochemical markers of oxidative stress and morphology related to AMD treatment in lungs and to study the effect of white cabbage extract (WCAE) on AMD related lung damage in rats.

## MATERIALS AND METHODS

**Ethics Committee Approval:** In this study, female Sprague Dawley rats (8-12 weeks old, 300-350 g) were obtained from the Marmara University Faculty of Medicine Animal Laboratory. All procedures were performed according to the Guide for the Care and Use of Laboratory Animals. Experimental protocols were approved by the Institutional Animal Care and Use Committee of the University (Date: 26.11.2014, decision no:71.2014mar) and followed the Institutional Animal Care and Use Committee of Marmara University.

**Experimental Design:** Animals were distributed into 4 groups, each group consists of 5 animals. Control group, intact animals; WCAE group, animals given WCAE (500 mg/kg) for 7 days; AMD group, animals administered AMD (100 mg/kg) for 7 days, AMD+WCAE group, animals given WCAE and AMD at the same dose. In all groups, WCAE and AMD were given by gavage technique. In

AMD+WCAE group, WCAE was applied one hour prior to AMD. After sacrifice on day 8, the lung tissues were taken for both histological and biochemical analysis.

**Preparation of White Cabbage Aqueous Extract (WCAE):** The white cabbage leaves were obtained from local markets of Istanbul, Turkey. The leaves were washed carefully with distilled water and then dried at room temperature. After they were dried, the leaves (100 g) were extracted by adding distilled water (1000 mL) and boiled for 8 hours. At the end of the process, the extract filtered and lyophilized. The lyophilized extract was freshly dissolved in distilled water and the applied to the animals for 7 days.

**Biochemical Analyses:** Lung tissues were homogenized by using 0.9% NaCl to make up (10%, w/v) homogenates. The preparates were centrifuged at +4 °C and 10000 x g for 10 minutes. The supernatants were collected for determining biochemical parameters as described previously in our study<sup>8-10</sup>; reduced glutathione (GSH), lipid peroxidation (LPO), advanced oxidized protein products (AOPP), hydroxy proline (HP), catalase (CAT), carbonic anhydrase (CA), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-S-transferase (GST), total antioxidant capacity (TAC), total oxidant status (TOS), reactive oxygen species (ROS), oxidative stress index (OSI), nitric oxide (NO), xanthine oxidase (XO), lactate dehydrogenase (LDH) superoxide dismutase (SOD), paraoxonase (PON) and lung protein levels were determined.

**Histological Analyses:** For light microscopic investigations, after fixing in 10% neutral buffered formaldehyde, lung samples were processed routinely before embedding in paraffin. Paraffin sections (5-µm-thick) were stained with hematoxylin and eosin (HE) for morphologic evaluation and Masson's trichrome for detection of collagen fibers. Sections were investigated by a photomicroscope (Olympus BX51, Tokyo, Japan) and photographed with a camera (Olympus DP72, Tokyo, Japan). Histopathological damage scoring was done at least five microscopic areas for each sample on the basis of following criteria: vascular congestion, interstitial edema, inflammatory cell infiltration and alveolar structural disturbance. Each criterion was semiquantitatively scored as 0: normal, 1: mild, 2: moderate and 3: severe damage. The maximum score was 12. To calculate the percentage of the mean area of collagen fiber deposition, 5 images from 5 non-overlapping areas in each lung sample were used and quantitation was done by image analysis software (Image J, v.2.1, NIH, USA).

**Statistical Analyses:** All analysis was done via GraphPad Prism 6.0 (GraphPad Software, San Die-

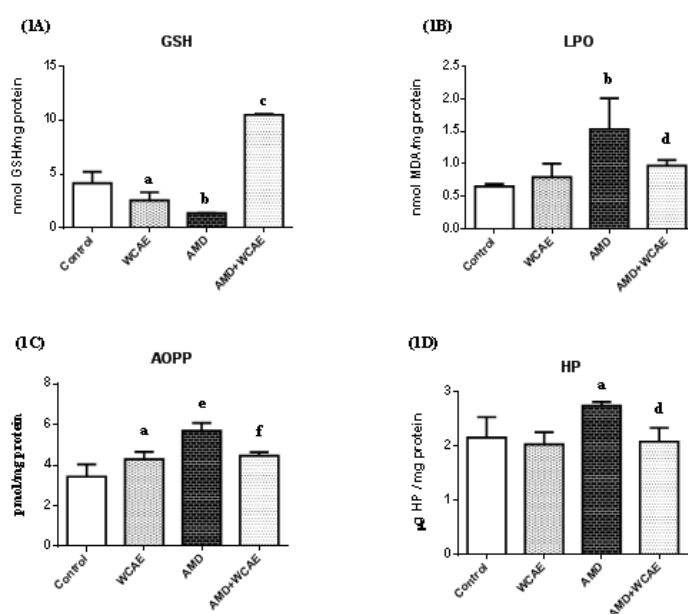
go, California, USA). The values were given as means ± standard deviation (SD). The data were evaluated using an unpaired t-test and analysis of variance (ANOVA) followed by Tukey's multiple comparison tests. A P value less than 0.05 was regarded statistically significant.

**RESULTS**

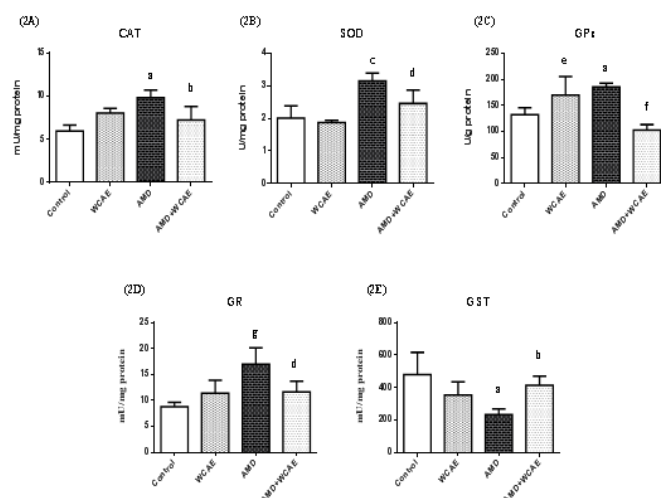
Administration of WCAE significantly decreased GSH levels and increased AOPP levels in control group ( $p < 0.05$ , Figure 1). Administration of AMD significantly decreased GSH levels ( $p < 0.001$ , Figure 1) and increased LPO, AOPP and HP levels in control group in a significant manner, respectively

( $p < 0.001$ ;  $p < 0.0001$ ;  $p < 0.05$ , Figure 1). WCAE reversed these levels in AMD group as statistically significant, respectively ( $p < 0.0001$ ;  $p < 0.05$ ;  $p < 0.001$ , Figure 1).

WCAE increased GPx activity in control group significantly ( $p < 0.05$ , Figure 2). CAT, SOD, GPx and GR activities were increased, and GST activity was decreased after AMD administration in control group in a significant manner, respectively ( $p < 0.01$ ;  $p < 0.001$ ;  $p < 0.0001$ , Figure 2). In AMD+WCAE group, all the activities given in this figure were reversed significantly when we compared to AMD group, respectively ( $p < 0.05$ ;  $p < 0.01$ ;  $p < 0.0001$ , Figure 2).



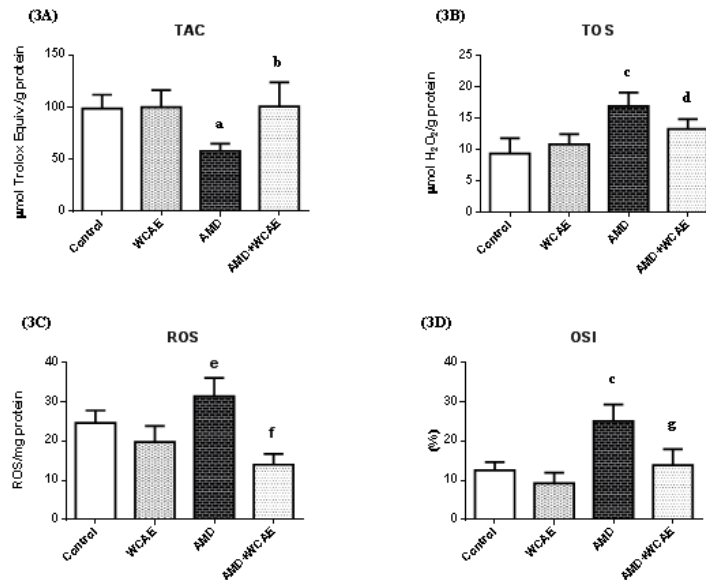
**Figure 1.** Comparison of biochemical markers in experimental groups. The lung GSH (1A), LPO (1B), AOPP (1C) and HP (1D) levels of experimental groups; <sup>a</sup>:  $P < 0.05$  vs control group; <sup>b</sup>:  $P < 0.001$  vs control group; <sup>c</sup>:  $P < 0.0001$  vs AMD group; <sup>d</sup>:  $P < 0.05$  vs AMD group; <sup>e</sup>:  $P < 0.0001$  vs control group; <sup>f</sup>:  $P < 0.001$  vs AMD group.



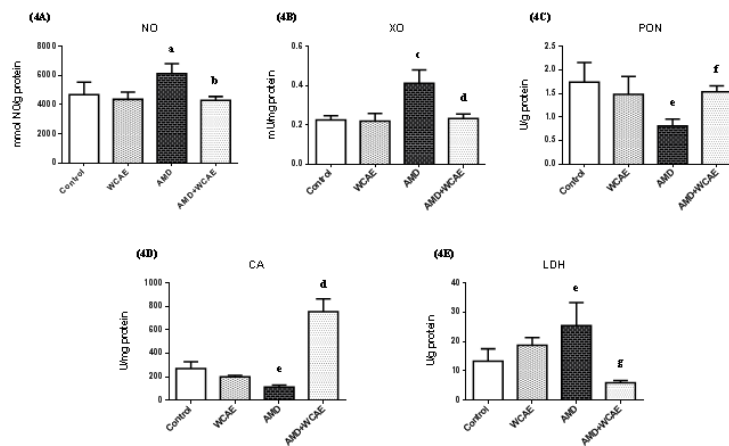
**Figure 2.** Comparison of biochemical markers in experimental groups. The lung CAT (2A), SOD (2B), GPx (2C), GR (2D) and GST (2E) activities of experimental groups; <sup>a</sup>:  $P < 0.01$  vs control group; <sup>b</sup>:  $P < 0.05$  vs AMD group; <sup>c</sup>:  $P < 0.001$  vs control group; <sup>d</sup>:  $P < 0.01$  vs AMD group; <sup>e</sup>:  $P < 0.05$  vs control group; <sup>f</sup>:  $P < 0.0001$  vs AMD group; <sup>g</sup>:  $P < 0.0001$  vs control group.

Diminished TAC and elevated TOS, ROS and OSI levels were determined in AMD group as compared to control group and the alterations in these levels were in a significant manner, respectively ( $p < 0.01$ ;  $p < 0.0001$ ;  $p < 0.05$ , Figure 3). Administration of WCAE to AMD group significantly reversed these levels, respectively ( $p < 0.01$ ;  $p < 0.05$ ;  $p < 0.0001$ ,  $p < 0.001$ , Figure 3).

AMD treatment increased NO levels, XO and LDH activities but decreased PON and CA activities in control group as statistically significant, respectively ( $p < 0.05$ ;  $p < 0.0001$ ;  $p < 0.01$ , Figure 4). WCAE significantly reversed all the parameters in AMD group which were mentioned in Figure 4, respectively ( $p < 0.01$ ;  $p < 0.0001$ ;  $p < 0.05$ ;  $p < 0.001$ ).



**Figure 3.** Comparison of biochemical markers in experimental groups. The lung TAC (3A), TOS (3B); ROS (3C) and OSI (3D) levels of experimental groups; <sup>a</sup>:  $P < 0.01$  vs control group; <sup>b</sup>:  $P < 0.01$  vs AMD group; <sup>c</sup>:  $P < 0.0001$  vs control group; <sup>d</sup>:  $P < 0.05$  vs AMD group; <sup>e</sup>:  $P < 0.05$  vs control group; <sup>f</sup>:  $P < 0.0001$  vs AMD group; <sup>g</sup>:  $P < 0.001$  vs AMD group.



**Figure 4.** Comparison of biochemical markers in experimental groups. The lung NO levels (4A), XO (4B), PON (4C), CA (4D) and LDH (4E) activities of experimental groups; <sup>a</sup>:  $P < 0.05$  vs control; <sup>b</sup>:  $P < 0.01$  vs AMD group; <sup>c</sup>:  $P < 0.0001$  vs control group; <sup>d</sup>:  $P < 0.0001$  vs AMD group; <sup>e</sup>:  $P < 0.01$  vs control group; <sup>f</sup>:  $P < 0.05$  vs AMD group; <sup>g</sup>:  $P < 0.001$  vs AMD group.

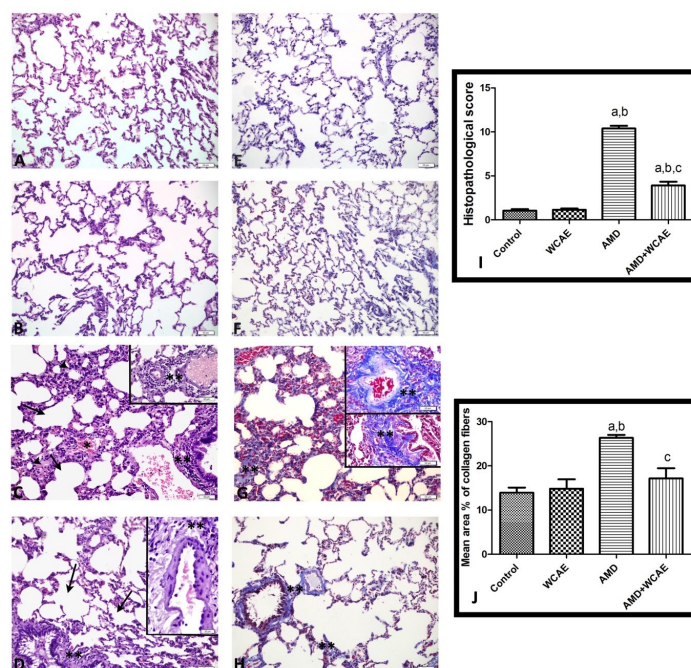
Lung tissues of control and WCAE groups showed a regular parenchyma morphology including alveoli and interstitium, whereas AMD treatment caused severe interstitial edema with vascular congestion, degenerated alveolar structures and moderate inflammatory cells infiltration mainly lymphocytes in the lung parenchyma. AMD+WCAE group showed reduced interstitial edema and congestion, an improvement in alveolar structures besides regression of inflammatory cell infiltration in lung parenchyma. Higher histopathological damage score of lung tissue in AMD group were significantly reduced by treatment with WCAE ( $p < 0.001$ ; Fig. 5).

In control and WCAE groups, collagen fibers were regularly distributed in lung parenchyma, however prominently increased collagen fiber accumulation was detected in the inter-alveolar septa, around bronchioles and blood vessels in AMD group. AMD+WCAE group showed a reversal of the increased amount of collagen fiber accumulation seen in AMD group. The increased percentage of the mean area of collagen fiber accumulation in AMD group was significantly reduced by treatment with WCAE ( $p < 0.01$ ; Figure 5).

## DISCUSSION AND CONCLUSION

Amiodarone is described as having amphiphilic character with its benzofuran ring and N-diethylamino side chain part.<sup>11</sup> Although these parts lead to AMD to be physiologically more active, AMD starts an unwanted accumulation by using these parts for both the entrance into cell and exodus throughout the cell. The accumulated AMD inhibits phospholipid metabolism by blocking lysosomal phospholipase.<sup>12</sup>

Lung GSH status has been declared as an indicator for an effective pulmonary response<sup>2</sup> and besides, AMD has been reported as being transformed to quinone reactives which are tended to bind GSH.<sup>13</sup> Taylor et al.<sup>14</sup> emphasizes the possibility of oxidant sourced damage of AMD by triggering the formation of malondialdehyde products associated with LPO levels. AOPP is a marker for non-enzymatic protein oxidation especially due to increased reactive oxygen species (ROS) levels.<sup>15</sup> Elevations at these altered levels may not be alone enough to describe ROS-related AMD toxicity, but also HP. Because the alterations in cellular protein levels may affect lung collagen deposition which can be measured for evaluation of HP.<sup>4</sup> Al-Shammari et al.<sup>2</sup> re-



**Figure 5:** Histological findings of lung tissue in experimental groups. Representative photomicrographs of lung tissue (A-H): Regular lung parenchyma morphology in control (A) and WCAE (B) groups; Severe interstitial edema with vascular congestion (\*) which causes the decrease in alveolar space (arrowheads), distended alveolar walls (arrows) and moderate perivascular and peribronchiolar lymphocyte infiltration (\*\*-inset) in AMD group (C); Regression of inflammatory cell infiltration (\*\*-inset) and regular alveolar morphology (arrows) in AMD+WCAE group (D); Regular distribution of collagen fibers in control (E) and WCAE (F) groups; A prominent increase in the collagen fibers accumulation in the inter-alveolar septa, around bronchioles and blood vessels (\*\*-inset) in AMD group (G); A marked reduction in the collagen fiber accumulation in the inter-alveolar septa, around bronchioles and blood vessels (\*\*-inset) in AMD+WCAE group (H); HE stain (A-D) and Masson's trichrome stain (E-H); The graph of histopathologic damage score (I) and the percentage of the mean area of collagen fiber deposition (J) of lung tissue; \*:  $P < 0.001$  vs control; <sup>a</sup>:  $P < 0.001$  vs WCAE group; <sup>b</sup>:  $P < 0.01$  vs AMD group (I). <sup>a</sup>:  $P < 0.001$  vs control; <sup>b</sup>:  $P < 0.01$  vs WCAE group; <sup>c</sup>:  $P < 0.01$  vs AMD group (J).

ported an elevation of HP levels of AMD induced lung injury in rats. Our results for GSH, LPO and HP are in accordance with other publications.<sup>2,4,14,16</sup> Turkyilmaz and Yanardag<sup>17</sup> reported that AMD induced hepatotoxicity resulted an elevation of carbonylated protein product and we observed an elevation in AOPP levels of AMD treated rats with the same logic. In our study, we determined diminished GSH and increased levels of LPO, AOPP and HP in lung tissue of AMD administered rats. The sulfur-containing compounds are very effective on Brassica species and they are known as having organic poly sulfur compounds which contain highly reactive sulfur atoms while they are in a reduced position. This property explains their antioxidant ability.<sup>18</sup> Moreover, one of the other Brassica species, red cabbage, has been declared as having preventive effect on LPO and protein structure alteration on chemical induced damage.<sup>19</sup> Ibrahim Fouad and Mousa<sup>4</sup> indicated the importance of alpha lipoic acid as having sulfur moiety in its structure and protective effect on AMD-induced pulmonary fibrosis. Based on these approaches and information, we can say that WCAE increased GSH levels and decreased LPO, AOPP and HP levels probably by its sulfur ingredients and antioxidant activity.

AMD disrupts the membrane structure by activating protein C and triggering this molecule as related oxygen radicals.<sup>14</sup> In the present study, we got increased activities of SOD, CAT, GPx and GR in AMD treated lung tissues. This elevation is an indicator for the deleterious effect on mitochondrial process of AMD. Besides, GST activity was found to be decreased as a conclusion of diminished GSH levels, a substrate for its detoxification activity. We also approached from another angle as determining decreased TAC and increased TOS, ROS and OSI levels produced by AMD. Nicolescu et al.<sup>20</sup> showed that AMD has increased ROS levels in human peripheral lung epithelial cells. WCAE reversed these enzymatic alterations and disruption of antioxidant system. Cabbage includes many vitamins, phenolic compounds and glucosinolates. These substances are the main characters which construct the antioxidant property of this plant.<sup>21</sup>

Although NO has many stimulating effects in organism, its excess production leads to react many molecules like superoxide anion and the further products will be more dangerous by attacking many macromolecules.<sup>22</sup> XO, a key enzyme for purine catabolism, plays an important role for the formation of uric acid. However uric acid has been reported as inflammation elevator effect which further causes cell death.<sup>23</sup> We determined increased NO levels and XO activities in AMD treated lung tissues. PON is one of the important antioxidant enzymes and it is vulnerable under oxidative circumstances. In addi-

tion, in lung diseases like chronic obstructive pulmonary disease and related chronic oxidative stress, PON has been declared as being observed with its lowered activity.<sup>24</sup> AMD decreased PON activity probably by the reason of its oxidant stimulator activity which we mentioned above by explaining the alterations in antioxidant parameters. Hazineci et al.<sup>25</sup> mentioned the ROS-triggering effect of AMD on heart tissue, and they prevented its ROS triggering effect on heart tissue by using white cabbage as considering and proving its antioxidant potential. Based on this approach, we may assume that the alteration of NO levels, XO and PON activities as positively may have been related to the powerful antioxidant capacity of WCAE.

In this study, AMD inhibited CA in lung tissue. Kılınç et al.<sup>26</sup> showed that some cardiovascular therapeutics have inhibited CA isoenzymes. When we consider the susceptibility of CA to pH alterations, we may put forward for the inhibitory effect of AMD on CA by its elevator effect on hydrogen ion concentration by the rapid entry-exit cycle of AMD which was explained by Stravitz and Sanyal.<sup>27</sup> AMD also causes an elevation in LDH activities of lung tissues. According to one approach by Kim et al.<sup>28</sup> the glucose elevator effect of AMD has been mentioned and this situation has also been related to its disrupting effect on mitochondrial dysfunction which could explain the reason of LDH elevation by AMD. According to the study of Turkyilmaz and Yanardag<sup>17</sup> on AMD induced hepatotoxicity, vitamin U have diminished LDH activity by scavenging the radicals produced by AMD. So, we may assume that WCAE may have reversed the CA and LDH activities by its antioxidant composition.

Al-Shammari et al.<sup>2</sup> revealed that AMD induced lung damage becomes histologically evident as early as one week after exposure with vascular congestion, interstitial capillary dilation with lymphocyte infiltration. They also found that the severity of lung damage is correlated to the duration of exposure. In an experimental study by Gado et al.<sup>5</sup>, lung damage was established via a 10 day course of AMD application and they showed that L-carnitine could ameliorate lung dysfunction related to AMD via a mechanism which involves the production of NO rather than lipid peroxidation. Similar to these results, we observed severe interstitial edema with vascular congestion, degenerated alveolar structures and moderate inflammatory cells infiltration mainly lymphocytes in the lung parenchyma after 1 week of AMD application. Concurrent treatment with WCAE prevented the lung damage in rats exposed to AMD, probably through its antioxidant potential. Another important issue with AMD treatment is collagen deposition in the lung tissue, eventually leading the development of pulmonary fibrosis. In a study by



Fouad and Mousa<sup>4</sup>, administration of AMD causes significant increases in the lung HP and collagen contents. In the same study, they showed that the use of an antioxidant agent, alpha lipoic acid, could reverse the oxidative stress, fibrosis, and inflammation parameters. In accordance with their results, we found that treatment with WCAE ameliorated the collagen deposition and increased HP content induced by AMD application.

In conclusion, AMD induced lung damage continues to be an important health issue in patients exposed to the agent. Due to its powerful antioxidant capacity, WCAE might have a protective role in amelioration of AMD induced lung damage.

**Ethics Committee Approval:** Our study was approved by the Institutional Animal Care and Use Committee of the University (Date: 26.11.2014, decision no:71.2014mar) and followed the Institutional Animal Care and Use Committee of Marmara University.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Author Contributions:** Concept –RY, EA; Supervision –RY, IBT, EA; Materials –RY, IBT, EA; Data Collection and/or Processing – RY, IBT, EA; AM; Analysis and/ or Interpretation – RY, IBT, EA, AM; Writing –RY, IBT, EA.

**Peer-review:** Externally peer-reviewed.

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## Covid-19'un Nadir Bir Komplikasyonu Olan Pnömomediastinum

### Pneumomediastinum, A Rare Complication of Covid-19

<sup>1</sup>Canatan TAŞDEMİR, <sup>1</sup>Yusuf AYDEMİR, <sup>1</sup>Hasan DÜZENLİ

<sup>1</sup> Sakarya Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Kliniği, Sakarya, Türkiye

Canatan Taşdemir: <https://orcid.org/0000-0003-1856-9660>

Yusuf Aydemir: <https://orcid.org/0000-0003-2479-2949>

Hasan Düzenli: <https://orcid.org/0000-0003-3850-2367>

#### ÖZ

Yeni Koronavirüs Hastalığı'nın (COVID-19) çok çeşitli komplikasyonları olmakla birlikte, bunlardan en az görülenlerden biri de pnömomediastinumdur. Mediastinumda serbest hava bulunması olarak tanımlanan pnömomediastinumda, klinik olarak nefes darlığı, göğüs ağrısı ve cilt altı amfizemi izlenir. Biz burada hiçbir risk faktörü olmadığı halde COVID-19 ile enfekte bir hastada gelişen spontan pnömomediastinum vakasını sunuyoruz.

**Anahtar Kelimeler:** Cilt altı amfizemi, corona virüs, pnömomediastinum

#### ABSTRACT

Although the new coronavirus disease (COVID-19) has a wide variety of complications, one of the least common of these is pneumomediastinum. In pneumomediastinum, which is defined as the presence of free air in the mediastinum, clinically dyspnea, chest pain and subcutaneous emphysema are observed. Here, we present a case of spontaneous pneumomediastinum in a patient infected with COVID-19 without any risk factors.

**Keywords:** Corona virus, pneumomediastinum, subcutaneous emphysema

#### Sorumlu Yazar / Corresponding Author:

Canatan Taşdemir

Sakarya Eğitim ve Araştırma Hastanesi Göğüs Hastalıkları Kliniği,  
Sakarya

Tel: 0532 483 22 80

E-mail: [canatan64@hotmail.com](mailto:canatan64@hotmail.com)

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#### GİRİŞ

Yeni koronavirüs hastalığı (COVID-19), şiddetli akut solunum yolu sendromu koronavirüsü 2 (SARS-CoV-2) adı verilen yeni bir virüsün neden olduğu hastalıktır. COVID-19'un en yaygın semptomları; ateş, kuru öksürük, tat ve koku kaybı, burun tıkanıklığı, boğaz ağrısı, baş ağrısı, kas veya eklem ağrısı ve yorgunluktur.<sup>1</sup> Hastaların %80'i hastanede tedaviye ihtiyaç duymadan iyileşir, yaklaşık %15'i ciddi bir şekilde hastalanır ve hastane yatışı gerektirir, %5 kadarı ise yoğun bakıma ihtiyaç duyar. Ölümüne yol açan komplikasyonlar arasında, ağır akciğer tutulumuna bağlı solunum yetmezliği, tromboembolizm ve çoklu organ yetmezliği yer alır. 60 yaş üstü kişiler ve yüksek tansiyon, kalp ve akciğer sorunları, diyabet, obezite, kanser gibi altta yatan tıbbi sorunları

olanların, ciddi hastalığa yakalanma riski daha yüksektir.<sup>1</sup> Bununla birlikte, hangi yaşta olursa olsun herkes COVID-19'a yakalanıp ciddi bir şekilde hastalanabilir.

Pnömomediastinum, mediasten de serbest hava bulunmasıdır.<sup>2</sup> Pnömomediastinumun etiyolojisinde birçok faktör rol oynamakla birlikte oluşum tipine göre primer ve sekonder olmak üzere iki gruba ayrılır. Pnömomediastinum genellikle solunum veya sindirim sistemi organ perforasyonuna bağlıdır. Primer spontan mediastinum ise periferik alveol rüptürünün sebep olduğu nadir görülen benign bir hastalıktır.<sup>2</sup>

Pnömomediastinumun tanısında, nefes darlığı, göğüs ağrısı ve cilt altı amfizem semptomlarının üçünün olması önemlidir.<sup>3</sup> En sık bulgusu cilt altı amfizemi

iken, tipik bulgusu ise göğüs ön kısmında oskültasyon anında kalp tepe atımıyla eş zamanlı olarak duyulan çıtırtı sesidir.<sup>4,5</sup>

### OLGU SUNUMU

**Etik Komite Onayı:** Çalışmamız olgu sunumu olduğu için etik kurul onayı gerekmemektedir. Hastaya bilgilendirilmiş gönüllü olur/onam formu imzalatılmıştır.

40 yaşında, daha önceden hiçbir hastalığı olmayan erkek hasta, 3 gündür başlayan öksürük, halsizlik, ateş ve son 1 gündür başlayan nefes darlığı şikâyetiyle müracaat etti. Hastanın ateşi 36°C, Nabızı 99/dk, solunum sayısı 26/dk, tansiyon arteriyeli 110/70 mmHg, oksijen saturasyonu %88 (oda havasında) ve %93 (2lt/dk oksijen alırken) olarak ölçüldü.

Fizik muayenesinde; genel durumu orta, şuur açık koopere ve oryente, dispneik ve takipneik görünümdeydi. Dinlemekle solunum sesleri kabaydı.

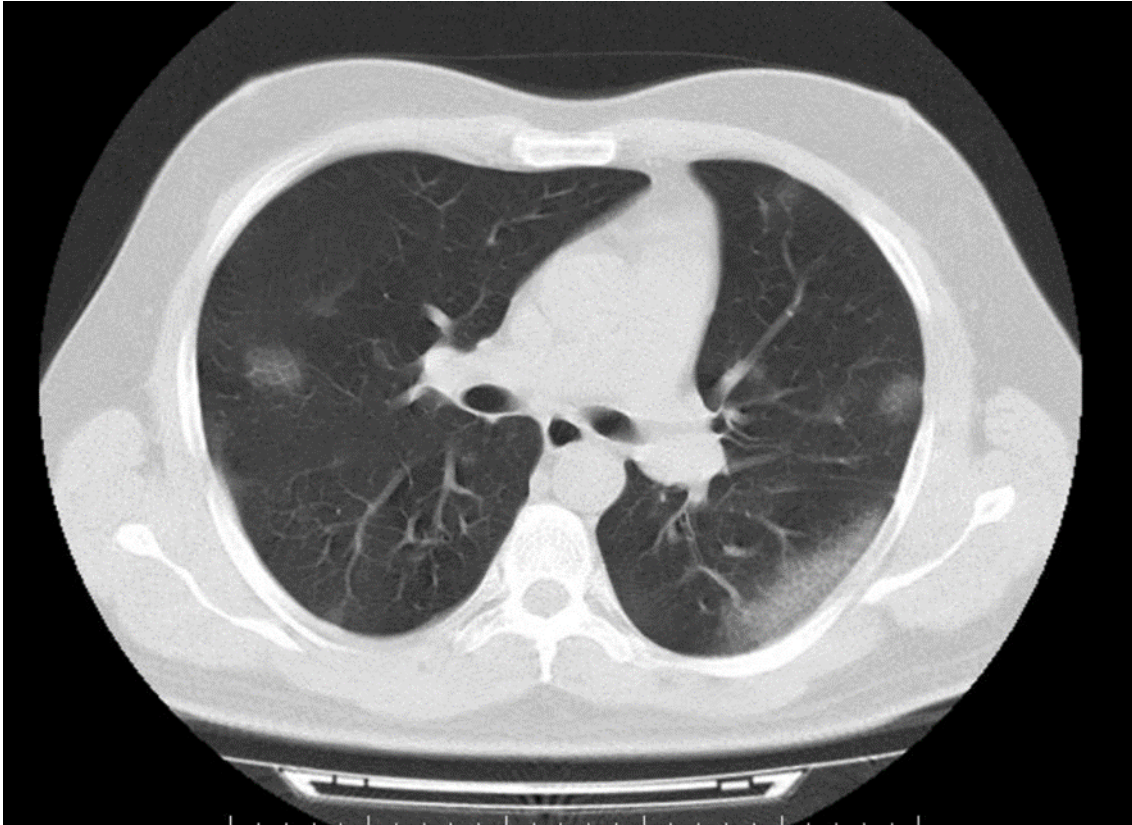
Laboratuvar incelemelerinde; hemoglobin: 14.1 g/dL, hematokrit: %42.6, lökosit: 12700 K/uL, lenfosit: 634 (%4.98), C reaktif protein: 114 mg/L, prokalsi-

tonin: 0.319 ng/ml, interlökin-6: 15.08 pg/ml, laktat dehidrogenaz: 694 U/L, ferritin: 2190 µg/L, D-dimer: 502 ugFEU/L olarak ölçüldü.

Hastanın çekilen toraks bilgisayarlı tomografisinde (BT), bilateral parankimal yamasal buzlu cam alanları mevcuttu (Şekil 1). Hastada viral pnömoni düşünüülerek COVID-19 PCR testi istendi ve kliniğimize yatırılarak tedavisi başlandı.

Hastada tedavinin dördüncü gününde aniden göğüs ağrısı ve nefes darlığında artma şikâyeti başladı. Fizik muayenesinde daha önceden olmayan, boyun ve göğüs ön kısmında palpasyonla krepatasyon tespit edildi. Dinlemekle göğüs ön kısmında, kalp tepe atımıyla eş zamanlı çıtırtı sesi vardı. Çekilen akciğer grafisinde, boyunda ve supraklaviküler bölgede cilt altı amfizemine bağlı hava gölgeleri gözlemlendi (Şekil 2).

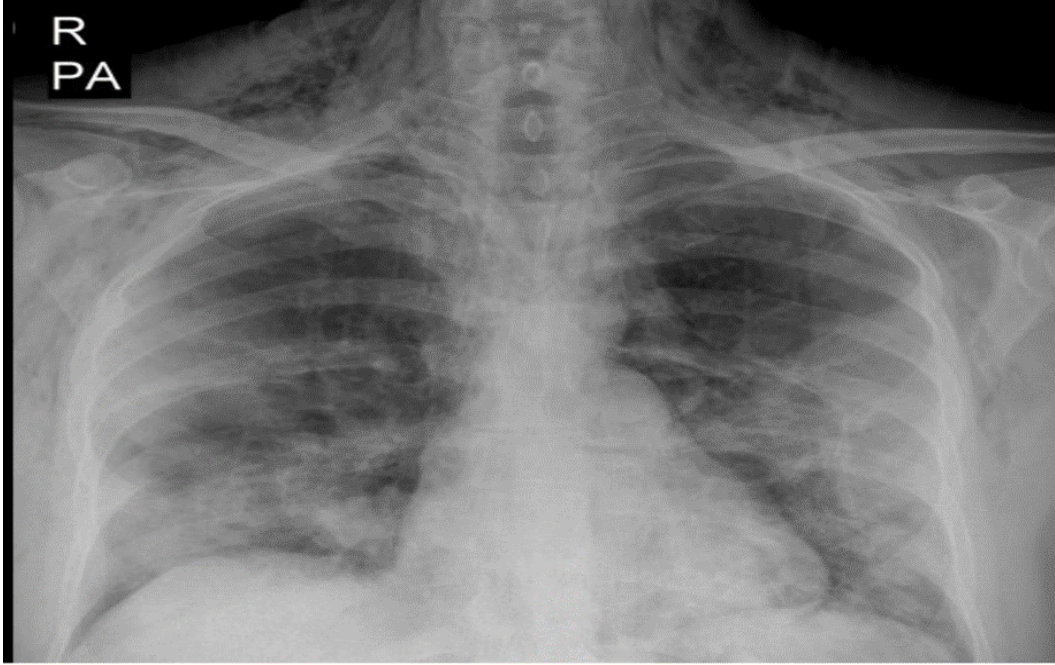
Hastanın yeni toraks BT görüntüleri alındı. Göğüs duvarını çevreleyen yaygın gaz koleksiyonları (cilt altı amfizemi) ve pnömomediastinum izlendi (Şekil 3).



Şekil 1. Toraks BT'de bilateral yamasal buzlu cam alanları.

COVID-19 PCR testi pozitif sonuçlanan hastaya, Favipravir tedavisi 5 gün, Enoksaparin Sodyum 2x4000 IU 10 gün, Deksetazon 16 mg 10 gün, Famotidin 10 gün, Moxifloxasin İV 5 gün, Anakinra 1.gün 4x100 mg, 2.gün 3x100 mg, 3. gün 2x100 mg ve izleyen 4 gün 1x100 mg olacak şekilde toplam 7 gün süreyle verildi. Ayrıca hastaya rezervuarlı mas-

ke ile oksijen tedavisi uygulandı. Yüksek akımlı oksijen ihtiyacı olmadı. Hastanın günlük PA akciğer grafisi ile takibi yapıldı, tedavinin onuncu gününde cilt altı amfizemine bağlı krepatasyonlar tamamen kayboldu. Çekilen akciğer grafisinde cilt altı amfizemine bağlı hava imajları kaybolmuştu (Şekil 4). Has-



**Şekil 2.** Akciğer grafisinde boyun ve supraklaviküler bölgelerde cilt altı amfizemi ile uyumlu hava dansiteleri.



**Şekil 3.** Toraks BT'de mediastinal ve cilt altı hava gölgeleri.

tanın saturasyonu 2 lt/dk oksijen alırken %95, oksijensiz ve hafif efor sonrası ise % 92 idi. Genel durumu düzelen hasta oksijensiz olarak taburcu edildi.

### TARTIŞMA VE SONUÇ

COVID-19 ‘un çeşitli komplikasyonları arasında nadir de olsa pnömotoraks ve pnömomediastinum yer almaktadır. COVID-19 da spontan pnömomediastinumun bildiren çok az sayıda rapor vardır. Üçpınar ve ark. başvurusunda spontan pneumotoraks ve pneumomediastinumun birlikte olduğu bir COVID-19 vakası bildirmişlerdir.<sup>6</sup> Shan ve ark. başvurusunda cilt altı amfizemi, pnömotoraks ve pnömomediastinumun birlikte olduğu bir COVID-19 vakası bildirmişlerdir.<sup>7</sup> Yapılan çok merkezli retrospektif bir vaka serisinde 16 merkezden 71 COVID-19 isbatlanmış hastanın, 54’ünde pnömotoraks, 6’sında pnömotoraks ve pnömomediastinum birlikteliği, 11’inde pnömomediastinum bildirilmiştir.<sup>8</sup> Pnömotoraks ve pnömomediastinum, spontan olarak COVID-19 hastalarında nadiren görülebilmekle birlikte, daha sık olarak invaziv pozitif basınçlı ventilasyonun bir komplikasyonu olarak görülebilmektedir.<sup>9</sup> Pnömomediastinum tanısında radyolojik inceleme önemli yere sahiptir. Genellikle PA Akciğer grafisi ve Toraks BT’de cilt altı amfizemi ayırt edilebilir. Bu nedenle ani klinik kötüleşme olan hastalarda kontrol akciğer grafisi çekilmelidir.

Pnömomediastinumun oluşum mekanizması henüz tam olarak bilinmemektedir. Olası bir açıklama, şiddetli pnömoninin yaygın alveoler hasara ve yırtılmaya neden olarak, mediastinal boşluğa ve subkutan amfizeme ilerleyebilen interstisyel amfizeme yol açıyor olmasıdır. Ciddi solunum ve dolaşım bozukluğuna yol açma potansiyeline sahip bir durum olsa da, genellikle kendi kendini sınırlayan bir hastalıktır. Buna rağmen, özellikle mekanik ventilatör altındaki hastalarda tedavi yönetimine değişiklikler (volütravmayı önlemek için yüksek ekspiratuar basınçlardan kaçınmak gibi) gerektirir. İlaveten orta ağır akciğer tutulumuna bağlı sınırlı solunum fonksiyonları olan hastalarda ölümcül bir komplikasyon olabilmektedir.<sup>10</sup>

Sonuç olarak pnömomediastinum COVID-19’un bir komplikasyonu olarak görülebilir. Ani olarak saturasyon düşüklüğünün, nefes darlığının, göğüs ağrısının başladığı COVID-19 hastalarında, cilt altı amfizemi varlığına da bakılmalı, palpasyonla krepatasyon olması pnömomediastinumunu düşündürmelidir. Böyle hastalarda invaziv basınçlı ventilasyon öncesi toraks görüntülemesi tekrarlanarak tanı doğrulanmalıdır.

**Etik Komite Onayı:** Çalışmamız olgu sunumu olduğu için etik kurul onayı gerekmemektedir. Hastaya bilgilendirilmiş gönüllü olur/onam formu imzalanmıştır.

**Çıkar Çatışması:** Yazarlar çıkar çatışması bildirme-



Şekil 4. Tedavi sonrası çekilen Akciğer grafisi.



mişlerdir.

**Yazar Katkıları:** Vaka izlemi-CT, YA, HD; Veri toplanması ve işlenmesi-CT; Yazıyı yazan-CT.

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## Kapsam Belirleme İncelemesi: Malezya'daki Aborjinler Arasındaki Parazit Kontrol Uygulamaları Hakkında Sağlık Okuryazarlığı Açıklıkları

### Scoping Review: Health Literacy Gaps about Parasites Control Practices among Aborigines in Malaysia

<sup>1,2</sup>Normalina ALIAS, <sup>1,2</sup>Mohamad Helmy JAAFAR, <sup>1,2</sup>Muhammad Lokman MD. ISA

<sup>1</sup>Department Basic Medical Sciences, Kulliyah of Nursing, International Islamic University Malaysia, Jln Sultan Ahmad Shah, Bandar Indera Mahkota, 25200 Kuantan, Pahang, Malaysia

<sup>2</sup>IUM Human Molecular and Cellular Biology Research Cluster (iMoleC), International Islamic University Malaysia, Jln Sultan Ahmad Shah, Bandar Indera Mahkota, 25200 Kuantan, Pahang, Malaysia.

Normalina Alias: <https://orcid.org/0000-0001-8697-505X>  
Mohamad Helmy Jaafar: <https://orcid.org/0000-0002-9368-5170>  
Muhammad Lokman Md. Isa: <https://orcid.org/0000-0001-8063-3526>

#### ÖZ

Malezya'da aborjinler arasında en sık görülen hastalık parazit enfeksiyonudur. Bu olay, aborjinler arasında düşük sağlık okuryazarlığı ile ilişkilidir. Bununla birlikte, Malezya'daki aborjinler arasında sağlık okuryazarlığı açıklıkları ile ilgili az sayıda çalışma bulunmaktadır. Bu çalışmada, Arksey ve O'Malley beş aşamalı çerçeve kullanılarak bir kapsam incelemesi kullanılmıştır. 2010'dan 2019'a kadar ilgili çalışmaları bulmak için üç çevrimiçi veritabanı SCOPUS, SCIENCE DIRECT VE PUBMED kullanıldı. Arama stratejisi taranan 481 çalışma belirlendi ve yalnızca 13 uygun tam metin çalışma seçildi. Mevcut inceleme, Malezya'daki aborjinler arasındaki sağlık okuryazarlığı açıklıklarına kapsamlı bir genel bakış sunmaktadır. Aborjinler arasındaki dört sağlık okuryazarlığı açıklığı, listelenen 13 çalışmadan tespit edilmiştir: hijyen, tesis, eğitim ve uygulama. İnceleme, kontrol önleminin yeniden değerlendirilmesini ve uygun eğitim yoluyla sağlığın teşviği, iyileştirilmiş tesisler, yoksulluğu azaltma programları ve kitlesel ölçekte kurtları yok etme uygulaması gibi uzun vadeli müdahaleler önermektedir. **Anahtar Kelimeler:** Aborjinler, sağlık okuryazarlığı, sağlık eğitimi

#### ABSTRACT

Parasitic infection is the most common disease among aborigine in Malaysia. This incident is associated with low health literacy among aborigine. However, there are few studies that are related to health literacy gaps among aborigine in Malaysia. A scoping review was used in this study by using five stage framework Arksey and O'Malley. Three online database SCOPUS, SCIENCE DIRECT AND PUBMED were used to find relevant studies from 2010 until 2019. The search strategy identified 481 screened studies and only 13 eligible full text studies were chosen. The current review provides an extensive overview of health literacy gaps among aborigine in Malaysia. The four health literacy gaps among aborigine have been identified from 13 listed studies: hygiene, facility, education and practice. The review recommends reassessment of control measure and long term intervention such as health promotion through proper education, improved facilities, poverty reduction programs, and implementing mass-scale deworming.

**Keywords:** Aborigine, health education, health literacy

#### Sorumlu Yazar / Corresponding Author:

Muhammad Lokman Md Isa  
Department Basic Medical Sciences, Kulliyah of Nursing, IUM Human Molecular and Cellular Biology Research Cluster (iMoleC), International Islamic University Malaysia, Jln Sultan Ahmad Shah, Malaysia.  
Tel: +60 12-964 5581  
Email: [lokman@ium.edu.my](mailto:lokman@ium.edu.my)

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#### INTRODUCTION

Health literacy is the primary determinant of a person's health and well-being.<sup>1</sup> It is a component of various literacies listed in health and education, such as cultural literacy, technology literacy, media literacy, and scientific literacy. Health literacy has three levels, which are basic or practical (skills of reading and writing in daily life), communicative or interactional (skills of psychological, cognitive and learning), and vital (skills of information use and circumstances handling) according to past research studies.<sup>2</sup> Health literacy studies will produce new recommendations and new information for health care

providers to share with their client.

Few studies provide evidences that parasitic infections are health recurrent issue among aborigine.<sup>3</sup> According to reports, the total prevalence of STH (Soil Transmitted Helminths) in Malaysia is 72.7 %, with the dominant infection being *T. trichiura* being 58.4 %, followed by *A.lumbricoides* being 45.5 % and the least infection being 23.1 % hookworm.<sup>4</sup> Strategies of control of parasitic infection may vary based on locality or suitability either chemical approaches such as drugs,<sup>5</sup> non-chemical approaches such as hygiene practices,<sup>6</sup> or biological – bio control.<sup>7</sup>

The success of the parasitic control depends on the management of parasitic control programs and cooperation given by aborigine.<sup>8</sup>

Aborigine or indigenous peoples are individuals with special cultures, systems of understanding and beliefs. Indigenous peoples also have much in common with other marginalized segments of society, such as lack of political representation and participation, economic marginalization and deprivation, lack of access to social services and discrimination.<sup>9</sup> Several studies have shown that chronic disease prevalence among indigenous peoples throughout the world is disturbingly high.<sup>10</sup> The aborigine in Peninsular Malaysia has a lower health ranking than the general population in terms of wellbeing.<sup>9</sup>

Poor hygiene is one of the factors contributing to the parasite or bacterial infection. It is vital to avoid environmental-personal hygiene from infection. Infections with parasites can be prevented by improving supply systems, sanitation, hygiene, especially among aborigine.<sup>11</sup> Infections with parasites can be infected by a variety of sources. One of the primary sources of infection is faecal-oral transmission.<sup>12</sup> There are two forms of direct and indirect transmission. Direct transmission is the transmission of faecal-oral or from human to human or animal to human. Transmission through contaminated food causes infection indirectly. Poor hygiene, lack of clean water sources, and no hand washing, bathing, or hair washing exacerbate the situation. This problem can lead to parasitic infections such as head lice infections.

Another issue that will lead to parasite infection is a lack of knowledge among aborigines. Some aborigines are unaware of the infection that is afflicting them. The most parasitic infection affecting aborigines is soil-borne helminth (STH) infections consisting of *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm infections.<sup>13</sup> Poor aborigine health education and awareness make them neglect their polluted world and their safety.

Based on the author knowledge, there are fewer studies related to health literacy among aborigine conducted in Malaysia.

The scoping review aims to identify the health literacy gaps in developing guidelines related to health literacy towards parasites control among aborigines throughout the published article. Besides that, the objective is also to recognize recommendation practices in order to control parasitic infection.

## MATERIALS AND METHODS

The paper was Editor invited review. Ethics committee approval is not required.

The scoping review has been used in this study to identify health literacy gaps among aborigine from 2010 until 2019 publishing papers.

According to Craig et al.<sup>14</sup> stated that there are seven benefits through scoping review which are (i) provide indicator of topics for subsequent systemic review; (ii) to examine a broad area of knowledge, and identify the gaps in the research knowledge/base; (iii) to clarify and map key concept/definition underpinning a research area; (iv) to clarify working definition and/or the conceptual boundaries of topics; (v) to report on the types of evidence that are published in a certain field; (vi) to examine emerging evidence when it still unclear what other, more specific questions can be posed and valuably addressed; (vii) to examine the conduct of research on a certain topic (to inform the design of future research studies).

The methodological framework by Arksey and O'Malley has been use as guidance for this study. The components of the framework are (i) identify research question, (ii) identify relevant studies, (iii) studies selection, (iv) charting the data (v) collating, summarizing and reporting the results.<sup>15</sup>

### **Identifying Research Question to be Addressed:**

The study's research questions were;

- i. What are the health literacy gaps about parasite control practices among aborigine?
- ii. What are the recommended practices towards parasitic control among aborigine?

### **Identifying Relevant Studies Related to Research Question:**

This study search strategy used electronic database searching of published paper from 2010 until 2019 in SCOPUS, SCIENCE DIRECT AND PUBMED related to health literacy among aborigine keywords. All search starts in January 2020 until March 2020. The studies selections are completed over 3 months.

**Search Strategy:** Health literacy\* OR Health education\* AND Aborigine OR Aborigine\* AND Malaysia.

**Studies Selection to Include in the Review:** The process of study selection was followed Preferred Reporting of Items for Systematic Reviews and Meta-analyses (PRISMA). Studies found using keywords will be screened by title. Any inclusion or exclusion criteria that do not meet will be rejected. The abstract was read in order to categorize the studies as relevant, not relevant, or potentially relevant.

Established keywords were used based on previous research and expert review. Two duplicated articles were removed at this stage after careful screening.

We will contact the article's correspondence via e-mail if there is any confusion or require more clarification to ensure that the article is correctly chosen for review.

**Inclusion Criteria:** The type of article that is included in this study is assessed based on study period from 2010 until 2019. Only articles from SCOPUS, SCIENCE DIRECT AND PUBMED to be used. Keywords that used are based on research titles

which were health literacy, health education, and aborigine. The type of research of the article must be in quantitative, qualitative or mixed-method study only. The article chosen must be in the English language only. The location study was in Malaysia.

**Exclusion criteria:** Unrelated to abstract, health literacy, and non-aborigine and not in Malaysia region.

**Charting the Data of Including Studies:** All the data of the relevant studies are extracted by authors, including the year of publication, location, study design or sample size, and outcomes with brief limitation.

**Collating, Summarizing and Reporting the Results:** As the study is scoping review, narrative analyses undertake to summarize the report findings.

**Data Abstraction and Analysis:** The 13 studies were reviewed by two trained reviewers independently. Papers were only considered for review if all of the reviewers agreed on them. If there was a disagreement, the paper was evaluated by a third reviewer.<sup>16</sup> The findings will be compared, and any discrepan-

cies will be forwarded and discussed with the third reviewer before finalization.

**RESULTS**

In the discovery process all papers were found using three online database searches: SCOPUS, PUBMED AND SCIENCE DIRECT. A total of 481 papers were found. However, after through screening, 14 articles were selected for this study review. (Figure 1: Process of Literature Search). The study list was tabulated in Table 1. All articles are considered good quality after a thorough assessment.

Throughout thorough discussion among the team, four health literacy gaps among aborigines have been identified from 14 listed articles: hygiene, facility, education and practice.

In the study list, health gaps on education obtained in thirteen studies, health gaps in facilities obtained in seven studies, health gaps in hygiene obtained in twelve studies and health gaps in practice obtained in ten studies.

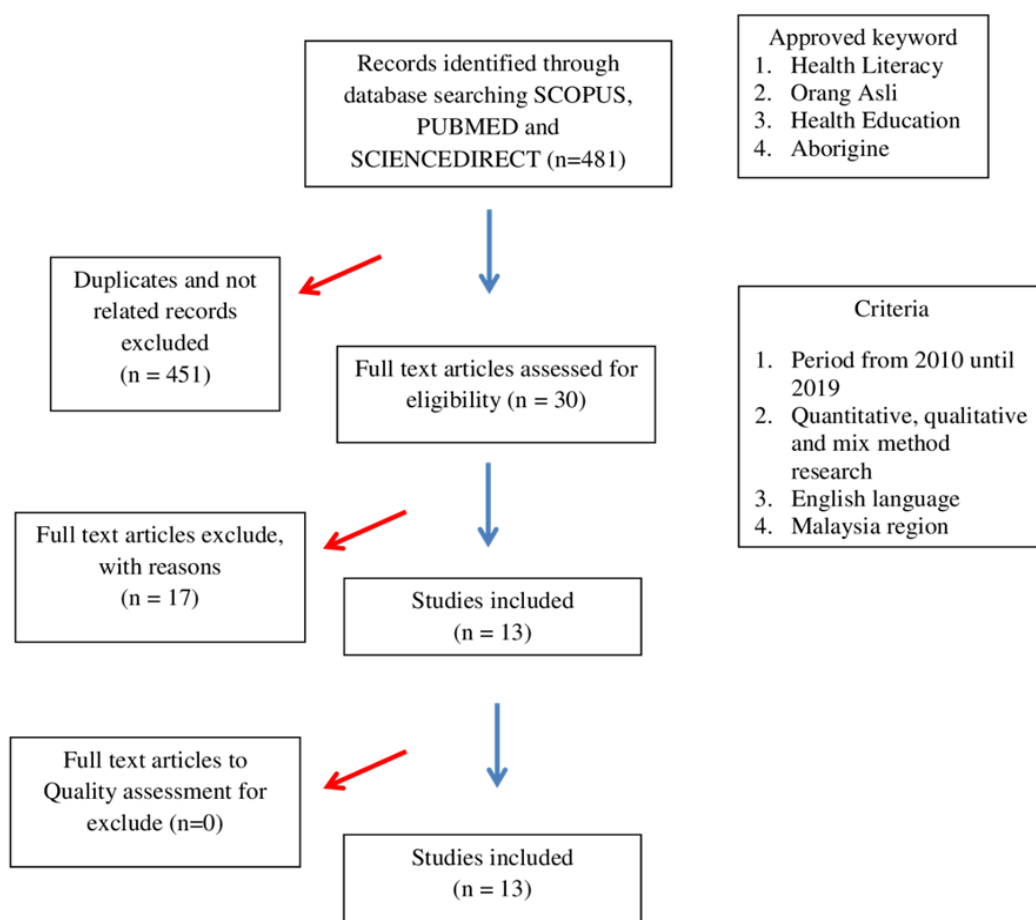


Figure 1. Process of literature search.



**Table 1.** List of the research literature.

No	Author	Title	Location	Sample/ Type of Re- search	Findings	Health issue	Contribution Factor - Gap	Outcomes & Recommendation
2	Al-Mekhlafi HM et al. 2014 (13)	Does vitamin A supplementation protect schoolchildren from acquiring soil-transmitted helminthiasis? A randomized controlled trial	Malaysia	n = 250 RCT Experimental study	98.6% children infected at least one STH species. Prevalence ascariasis, trichuriasis and hook worm infection was 67.8%, 95.5% and 13.4%.	Reinfection of parasites. Vitamin A supplementation showed no protective effect against STH reinfection due to high endemicity.	Education Hygiene	Vitamin A deficiency (VAD) and iron deficiency anaemia (IDA) that can have community-level effects on adult work and productivity, and on children's development, learning and school performance. Long term interventions to reduce poverty will help significantly in reducing this STH infection.
3	Huat LB et al. 2012 (17)	Prevalence and risk factors of intestinal helminth infection among rural Malay Children	Malaysia	n = 79 . Cross sectional study	Multivariate analysis on predictors helminths infection were Poor education of mother (p=0.015), eating raw salad (p=0.03) .	Less trained mothers were possibly also unaware of proper hygienic practises and health-seeking behaviours.	Education Hygiene Practice	Focus on the efficacy of education mother in preventing intestinal helminth infections among their children shall establish.
4	Ngui R et al. 2015 (19)	Patterns and Risk Factors of Soil-Transmitted Helminthiasis among Orang Asli Subgroups in Peninsular Malaysia	Malaysia	n = 634 cross sectional study	Multivariate analysis confirmed that low family income(p=0.005) House hold with no toilet facility (p=0.018) , walking barefoot (p=0.018) and close contact with animal (p=0.002) more likely to have STH infection.	Poor environmental sanitation, personal and sanitary behaviour including defecation practices, lack of footwear, not washing hands before eating significant risk factors for various infection diseases including parasitic infection.	Education Hygiene Facilities Practice	Integrated effective control program such as poverty reduction program, implementing mass scale deworming and health promotion campaign need to be established to control the infections.

Table 1. List of the research literature (Continue).

5	Tang & Kamei 2019 (21)	Soil-Transmitted Helminthiasis among Orang Asli (Aborigine) Schoolchildren at RPS Banun, Gerik, Perak, Malaysia.	Malaysia	n = 116 cross sectional study	81.9% of school children were found to be infected with at least one STH species	Observed that aborigine's children tended to not wash hands before and after eating and eat raw foods without washing and defecate at the site of river. Poor water supply and sanitation observed.	Education Hygiene Facility Practice	Integrated approaches towards STH control such as environmental sanitation, health education about personal and food hygiene and enhancement of nutritional status shall be implemented.
6	Al-Delaimy et al. 2014 (23)	Epidemiology of Intestinal Polyparasitism among Orang Asli School Children in Rural Malaysia	Malaysia	n = 498 cross sectional study	Multivariate analysis - Unsafe water (p=0.003), absence of toilet in house (p=0.014), presence of infected family member (p=0.026), not cutting nails periodically (p=0.010) and not washing vegetables before eating (p=0.001) significant risk factor for polyparasitism.	Using unsafe water supply, presence of other family members infected with intestinal parasitic infection, not washing vegetable before consumption, absence of a toilet in the house, not wearing shoes when outside, not cutting nails periodically, and not washing hands before eating	Education Hygiene Facility Practice	Effective and sustainable control measures, proper health education on hygiene practices, proper sanitation, and safe drinking water supply to be implemented to reduce STH infection.
7	Ahmed A et al. 2011 (24)	The burden of moderate-to-heavy solid transmitted helminth infections among rural Malaysian aborigines: an urgent need for an integrated control programme	Malaysia	n = 254 cross sectional study	Univariate analysis revealed using untreated water supply (p=0.013), absence in house toilet (p=0.027) and having domestic animals (p=0.044) had significantly risk factor moderate to heavy STH infections. Logistic regression confirmed using untreated water for drinking (p=0.001) and absence in house toilet (p=0.003) significant risk factor moderate to heavy infection.	Poor personal hygiene including no hand washing before and after eating with poor facilities caused no end issue.	Education Hygiene Facility Practice	Serious attention required to overcome the issues. More poverty alleviation schemes, proper sanitation, provision of clean and safe drinking water, health education and deworming school based programmes to be conducted.
8	Wong WK et al. 2016 (25)	Helminthic Infection and Nutritional Studies among Orang Asli Children in Sekolah Kebangsaan Pos Legap, Perak	Malaysia	n = 33 , mixed method	Anthropometry analysis showed 78% children were malnourished and 33% were stunted.	Consistent with high STH infection and low nutritional status	Education Hygiene Facility Practice	To improve socioeconomic status, educational standard and health facilities. Effective medication to be administered and nutritional programs to be embarked.

Table 1. List of the research literature (Continue).

9	Rajoo Y et al. 2017 (26)	Neglected Intestinal Parasites, Malnutrition and Associated Key Factors: A Population Based Cross-Sectional Study among Indigenous Communities in Sarawak, Malaysia	Malaysia	n = 341 cross sectional study	Multivariate analysis indicated absence of toilets (p=0.002), close contact with animals (p=0.027) significant predictors for Intestinal Parasitic Infections. Low parental education attainment (p=0.006) significant indicator for anaemia. Meanwhile, low house income predictor for stunting (p=0.0001) and underweight (p=0.037)	Study highlighted that intestinal parasitic infections, anaemia and malnutrition still prevalent among rural indigenous community.	Education Hygiene Practice	Improving socioeconomic status , periodic mass deworming, iron supplementation and health education to include public health intervention programs.
10	Nantha & Mohamed (2019) (27)	Soil-Transmitted Helminthiasis amongst the Orang Asli (aboriginal) School Children at Sungai Raba Village Gerik, Perak, Malaysia.	Malaysia	n = 139 cross sectional study	Prevalence STH was 74.1%.Highest infection rate between children aged between 10 - 11 years (83%/0).	Low health standard - careless on personal hygiene	Education Hygiene Practice	Improving socioeconomic status including enhanced access to quality health care and adequate sanitation potential significant reduced the STH infection.
11	Nasr NA et al.2013 (28)	Towards an effective control programme of soil-transmitted helminth infections among Orang Asli in rural Malaysia. Part I: Prevalence and associated key factors	Malaysia	n = 215 cross sectional study	78.1% of children were found to be infected with one or more STH species	Using unsafe water supply, absence of proper sanitation, hygiene practices associated with STH infections.	Education Hygiene Facility Practice	Urgent de-worming programmes and providing proper sanitation, clean water supply, proper health education regarding personal hygiene practice should be established.
12	Chin YT et al. 2016 (29)	Prevalence and risk factors of intestinal parasitism among two indigenous sub-ethnic groups in Peninsular Malaysia	Malaysia	n = 186 cross sectional studies	Multivariate analysis risk factors Untreated water source (p:0.007); Not wearing shoes outside at home (p:0.014);Not washing hands after defecation (p:0.009);family size (p:0.012);not boiling water before consumption (p:0.023) „unemployed (p:0.020)	Variations in living habits such as personal hygiene practices may predispose different groups to different parasitic infection.	Education Hygiene Facilities Practice	Imperative to implement sound intervention strategies such as periodic preventive chemotherapy with health education in order to eradicate STH infection.
13	Al-Delaimy AK et al. 2014 (30)	Developing and evaluating health education learning package (HELP) to control soil-transmitted helminth infections among Orang Asli children in Malaysia	Malaysia	n = 317 controlled intervention	Health education learning package (HELP) provides significant impact compared those in control school (p<0.05).	To access impact HELP to improve knowledge of aborigine's Community	Education	HELP Health education learning package displayed significant impact and improved knowledge about parasitic infection. Incidence rates of hookworm infection significant lower compared to control.

## DISCUSSION AND CONCLUSION

According to the World Health Organization,<sup>1</sup> health education is any mix of learning opportunities intended to help individuals and societies enhance their health by improving awareness or changing attitudes. Health education is a significant component of health promotion activities. Health literacy is the product of good health education, improving the capacity of individuals to access and use health knowledge to make informed health choices and preserve essential health. Education is critical for these studies because it raises aborigine awareness about anti-parasitic packages. Based on previous research, too little is known about the effect of vitamin A supplements on STH infections.<sup>13</sup> Vitamin A deficiency and iron deficiency anemia can have a community-wide impact on adult work and productivity, as well as children's development, learning, and academic performance. Less educated mothers were more likely to be unaware of good hygienic practices and health-seeking behaviours.<sup>17</sup> This demonstrates that if the level of mothers on hygiene knowledge is low, the entire family suffers. This is because parents will set a good example for their children. Proper education will provide aborigine with the necessary information about parasite infection. Families will learn by share basic knowledge and practice good hygiene internally. Simultaneously, the proportion of aborigine infected with parasites would decrease.

Seven studies shared the same idea that lacking proper facilities contributes to the health issues among aborigine in Malaysia.<sup>4,19,21,23,25,28-29</sup> Facilities are places, amenities, or pieces of equipment that are available for a specific purpose. The Department of Orang Asli Development (Malay : *Jabatan Kemajuan Orang Asli*) abbreviated JAKOA in Malaysia has already provided many facilities for the aborigine population, such as project toilets and clean water. However, according to previous research, some Aborigine villages continue to be underserved in terms of facilities.<sup>18</sup> Ngui et al.<sup>19</sup> stated that the household-based toilet facilities among these groups were almost non-existent. Due to poor maintenance, some aborigines did not use this facility. They have clear sources of subterranean water-flow pollution.<sup>19</sup> Review showed that poor environmental sanitation and poor clean water supply are associated with recurrent STH infection.

Practice refers to the ways in which they demonstrate their knowledge and attitude through action.<sup>20</sup> Ten studies noted on health gaps about proper practice that contributes to the recurrent infection of STH among aborigine.<sup>17,19,21,23-29</sup> Children of aborigine tended not to wash their hands before and after feeding. They ate raw foods such as fruit without washing.<sup>21</sup> Walking outside without slippers or

shoes is another bad habit that needs to be broken. The shoes are crucial to protect parasitic infection. It is necessary to change the habitual practice accordingly. In order to prevent parasitic infections, health care providers must constantly advise parents to monitor children regularly.

Hygiene is a series of health-care practices performed. Hygiene refers to conditions and activities that help preserve health and prevent the spread of diseases.<sup>22</sup> Personal hygiene refers to keeping the body clean. Many people are equal to hygienic 'cleanliness,' but hygiene is a broad term. This involves options such as how much to take a bath or shower, wash hands, cut fingernails and wash clothing. This also requires a commitment to maintaining surfaces at home and work, including facilities for safe and pathogen-free baths. It is frequently stated that aborigine's children have poor personal hygiene.<sup>23</sup> As we all know, introducing something foreign into the body can endanger our safety. Parasitic infections are common in children because some of them do not wash their hands after playing with sand, and some even eat sand as a result of their play activities. They are now vulnerable to parasites as a result of their already weakened systemic immune system. The review showed that aborigines have a low standard of proper hygiene. Perhaps due to habitual life style caused hygiene concern is not their priority.

Based on the findings, the four elements shall not be ignored in developing protocol or guidelines in anti-parasitic infection among aborigines. The four elements must be integrated and work in synergy to ensure that the program's outcomes are as efficient as possible. The review recommends reassessment of control measure<sup>4</sup> and long term intervention<sup>13</sup> to control parasitic infection. The poverty reduction program to improve socioeconomic status among aborigine was a part of long term intervention to overcome the STH infection.<sup>4,13,19,24-27</sup> Besides that, improving proper facilities such as improving sanitation areas and providing clean and safe water also contributes to the proper strategies of managing parasitic infection.<sup>21,23,26-28</sup>

The establishment of a health promotion campaign and the implementation of mass-scale deworming will accelerate the parasitic control programme.<sup>4,19,25,27-29</sup> The relevant thirteen studies also recommend proper health education to aborigines.<sup>4,13,17,19,21,23-30</sup> Huat<sup>17</sup> encourages educating aborigine mother to prevent parasitic infection towards the children. The review supports health education on hygiene and daily practices to ensure continuity of proper and healthy lifestyle.

This scoping review has numerous strengths from this research. The intensity of this research can be established by the using several databases using

SCOPUS, PUBMED and SCIENCEDIRECT to find studies related to health literacy related to the aborigine. Some researches, including study emphasis outside of Malaysia and not focused on aborigine were omitted. All forms of studies such as quantitative, qualitative and mixed-method were included to skip small related studies.

In conclusion, identifying the contributing critical health gap element in the development of new health literacy guidelines is crucial to slow the increase in the percentage of parasitic infections among aborigines. Education, facilities, practice, and hygiene are just a few critical elements that must be prioritized.

There is a limitation of this review which is that sources are restricted. There is only a range of research papers that are relevant and applicable to this report.

Future research should use these elements to develop basic guidelines for aborigines that are approachable and self-explanatory. This will raise their awareness of parasite infection by providing proper guidance and aborigine health education. Furthermore, higher authorities must ensure that these aborigines live a healthy lifestyle and avoid activities that may result in parasite infection.

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