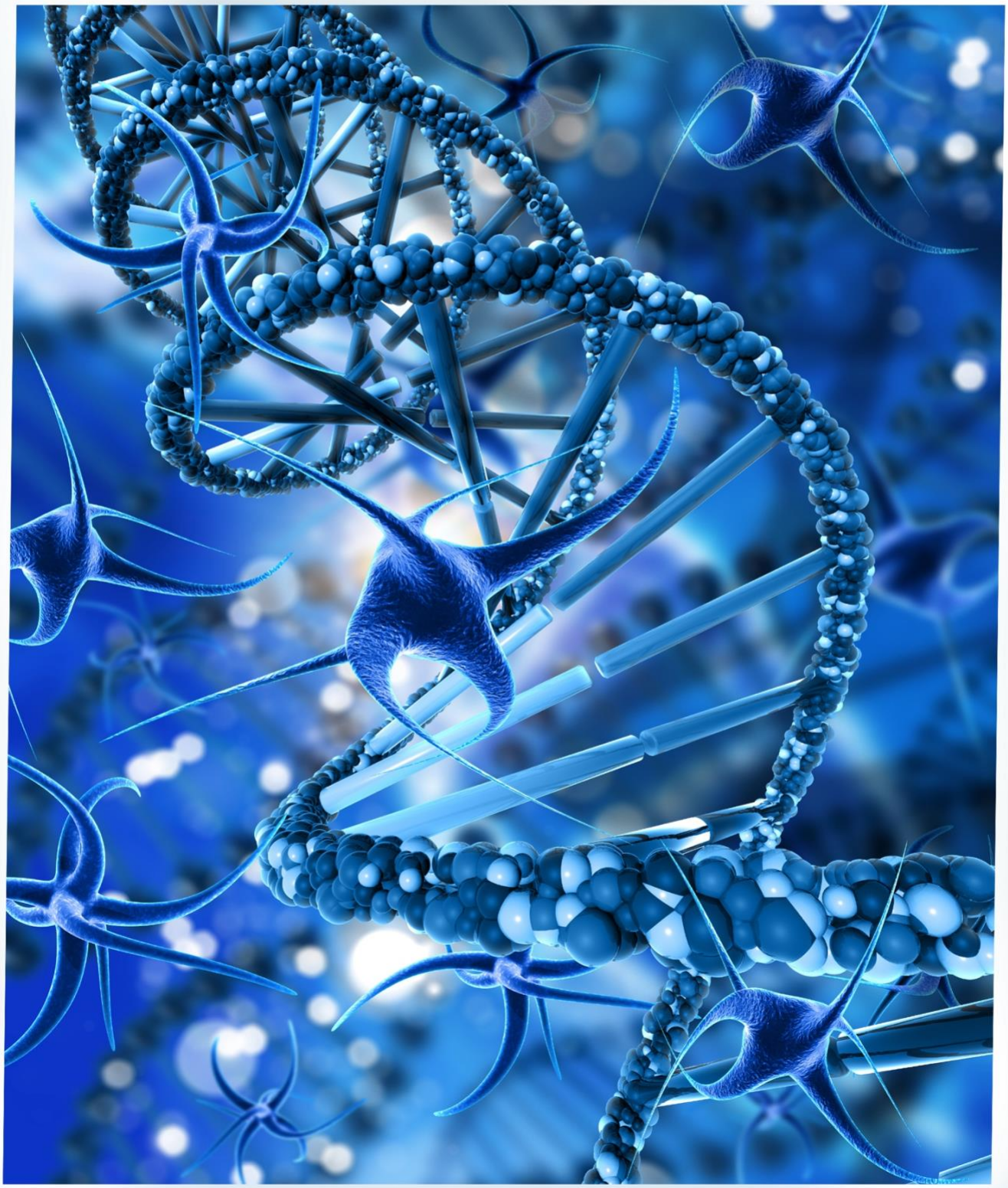
FARABİ TIP DERGİSİ
FARABI MEDICAL JOURNAL

VOLUME 3 · ISSUE 2 · June 2024

CİLT 3 · SAYI 2 · Haziran 2024



e-ISSN: 2979-9821

https://dergipark.org.tr/tr/pub/farabimedj

VOLUME 3 · ISSUE 2 · June 2024 CİLT 3 · SAYI 2 · Haziran 2024

FARABİ MEDICAL JOURNAL
FARABİ TIP DERGİSİ

OFFICIAL JOURNAL OF FACULTY OF MEDICINE OF KARADENIZ TECHNICAL UNIVERSITY
KARADENİZ TEKNİK ÜNİVERSİTESİ TIP FAKÜLTESİ RESMİ DERGİSİ

Journal Communication / *Dergi İletişim*
Karadeniz Technical University, Faculty of Medicine, Farabi Street, 61080, Trabzon, Türkiye.

e-mail: *farabimedj@ktu.edu.tr*

e-ISSN: 2979-9821

This journal is peer-reviewed and published 4 issues per year.
There is no charge for submitting and publishing articles to our journal.

Hakemli bir dergi olup yılda 4 sayı olarak yayınlanmaktadır.
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Issue Content / *Sayı İçeriği*

Research Articles */ Araştırma Makaleleri*

Mehmet Ulusahin, Ahmet Unal, Serdar Turkyilmaz

Diagnostic Value of Basic Laboratory Parameters in the Diagnosis of Complicated Appendicitis

*(Komplike Apandisitin Belirlenmesinde Temel Laboratuvar Parametrelerinin Tanısal Değeri)*__***42-49***

Zila Ozlem Kirbas, Elif Odabasi Aktas

An Ignored Fact: An Ignored Fact: Feeling of Guilt and Affecting Factors in Mothers Whose Children are Hospitalized

*(Göz Ardı Edilen Bir Gerçek: Çocuğu Hastanede Yatan Annelerde Suçluluk Duygusu ve Etkileyen Faktörler)*___***50-56***

Selim Demir, Nihal Turkmen Alemdar, Elif Ayazoglu Demir, Ahmet Mentese, Yuksel Aliyazicioglu

The Therapeutic Effect of p-Coumaric Acid on Lung Toxicity Induced by Methotrexate in Rats

*(Sıçanlarda Metotreksatın Neden Olduğu Akciğer Toksisitesi Üzerine p-Kumarik Asidin Terapötik Etkisi)*___***57-62***

Case Reports */ Olgu Sunumları*

Gozde Yilmaz, Ismail Furkan Simsek, Rukiye Aytekin, Aysegul Eylem Ozer, Necmi Baykan

Acute Abdominal Aortic Occlusion in a Paraplegic Patient: Case Report

*(Paraplejik Hastada Akut Abdominal Aort Oklüzyonu: Olgu Sunumu)*___***63-65***

Letters to the Editor / Editöre Mektuplar

Serdar Ozdemir, Abdullah Algin

Long-Term Cardiac Effects After Recovery in SARS-CoV-2 Infection

*(SARS-CoV-2 Enfeksiyonunda İyileşme Sonrası Uzun Süreli Kardiyak Etkiler)*___***66-67***

Doğancan Sönmez

Eski Bir Farmakolojik Ajan, En Yeni Antidepresan: Gepiron

*(An Old Pharmacological Agent, the Newest Antidepressant: Gepirone)*___***68-70***

Issue Reviewers / *Sayı Hakemleri*

Farabi Tıp Dergisi 3(2):42-49,2024
Farabi Medical Journal 3(2):42-49,2024
https://doi.org/10.59518/farabimedj.1392105

FARABİ TIP DERGİSİ
FARABI MEDICAL JOURNAL

Özgün Makale
Original Article

https://dergipark.org.tr/tr/pub/farabimedj

Diagnostic Value of Basic Laboratory Parameters in the Diagnosis of Complicated Appendicitis

Komplike Apandisitin Belirlenmesinde Temel Laboratuvar Parametrelerinin Tanısal Değeri

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ABSTRACT

In this investigation, we sought to examine the efficacy of laboratory parameters in predicting complicated appendicitis in patients who had surgery for acute appendicitis. 153 patients who underwent appendectomy were included and whose pathological results showed acute appendicitis. The patients were divided into two groups based on pathology findings and surgical findings: simple and complicated appendicitis groups. The patients' age, gender, preoperative leukocyte count, neutrophil count, neutrophil percentage, neutrophil–lymphocyte ratio, erythrocyte distribution width, mean platelet volume, and C-reactive protein levels were recorded. The simple and complicated appendicitis groups comprised 97 and 56 patients, respectively. Patients with complicated appendicitis were older on average than those with simple appendicitis (p=0.007). In the complicated appendicitis group, leukocyte count (p<0.001), neutrophil count (p=0.007), neutrophil percentage (p<0.001), neutrophil–lymphocyte ratio (p<0.001), and C-reactive protein levels (p<0.001) were significantly higher than in the simple appendicitis group. In terms of erythrocyte distribution width and mean platelet volume, there were no statistically significant differences between the groups. The cut-off values for age, leukocyte count, neutrophil count, neutrophil percentage, neutrophil–lymphocyte ratio, and C-reactive protein levels were 24.5/years, 12.500/µL, 9.950/µL, 78.15%, 4.98, and 0.29 mg/dL, respectively. Logistic regression analysis showed that age (OR: 1.036), neutrophil count (OR: 14.934), and C-reactive protein levels (OR: 4.225) are independent risk factors for the diagnosis of complicated appendicitis. Thus, age, neutrophil count, and C-reactive protein levels may be used as auxiliary parameters to differentiate between simple and complicated appendicitis.

Keywords: Abdominal pain, Acute appendicitis, Complicated, C-reactive protein

ÖZET

Bu çalışmanın amacı akut apandisit nedeni ile opere edilen hastalarda laboratuvar parametrelerinin komplike apandisit öngörülmesindeki etkinliğini araştırmaktır. Appendektomi uygulanmış ve patoloji sonucu akut apandisit olarak bildirilen 153 hasta çalışmaya dahil edildi. Hastalar patoloji sonuçları ve operasyon bulgularına göre basit ve komplike apandisit olarak iki gruba ayrıldı. Hastalara ait yaş, cinsiyet, operasyon öncesi lökosit sayısı, nötrofil sayısı, nötrofil yüzdesi, nötrofil-lenfosit oranı, eritrosit dağılım genişliği, ortalama trombosit hacmi ve C-reaktif protein değerleri kaydedildi. Basit apandisit grubunda 97, komplike apandisit grubunda 56 hasta mevcuttu. Her iki grupta da erkek cinsiyet ön planda idi. Komplike apandisit gubunda yaş daha ileri idi (p=0.007). Lökosit sayısı (p<0.001), nötrofil sayısı (p=0.007), nötrofil yüzdesi (p<0.001), nötrofil-lenfosit oranı (p<0.001) ve C-reaktif protein (p<0.001) komplike apandisit grubunda istatistiksel olarak anlamlı fark oluşturacak şekilde yüksek tespit edildi. Eritrosit dağılım genişliği ve ortalama trombosit hacmi için gruplar arasında anlamlı fark yoktu. Kesim değerleri yaş için 24.5/yıl, lökosit sayısı için 12500/µL, nötrofil sayısı için 9950/µL, nötrofil yüzdesi için % 78.15, nötrofil-lenfosit oranı için 4.98 ve C-reaktif protein için 0.29 mg/dl olarak hesaplandı. Lojistik regresyon analizinde yaş (OR:1.036) nötrofil sayısı (OR: 14.934) ve C-reaktif protein (OR: 4.225) komplike apandisit tanısı için bağımsız risk faktörleri olarak tespit edildi. Yaş, nötrofil sayısı ve C-reaktif protein basit-komplike apandisit ayrımında yardımcı parametreler olarak kullanılabilir.

Anahtar Kelimeler: Akut apandisit, C-reaktif protein, Karın ağrısı, Komplike

Geliş Tarihi/Received Date: 16.11.2023 | *Kabul Tarihi/Accepted Date: 23.02.2024*

INTRODUCTION

The most frequent cause of acute abdomen that necessitates surgical intervention is acute appendicitis (AA).[1] Approximately 7%–8% of the population is diagnosed with AA throughout their life.[2,3] Physical examination, laboratory values, and imaging methods such as ultrasonography (USG), and computed tomography (CT) are effective in the diagnosis of AA.[4] Although the most effective treatment is appendectomy, there are studies on the effectiveness of antibiotic therapy in specific patients.[5-7]

Imaging methods such as USG and CT are commonly used; therefore, the diagnosis of AA can usually be made more easily.[8,9] However, there are patients who have been treated for AA and found to have a normal appendix or who developed complications such as perforation and abscess due to the late diagnosis of AA.[10] In addition, there are cases wherein access to imaging methods is not always available.[11] For all such reasons, there has always been a search for cheap and practical biochemical markers that are easily accessible for the diagnosis of AA. In this regard, leukocyte count (WBC), neutrophil count, neutrophil percentage, lymphocyte count, neutrophil–lymphocyte ratio (NLR), platelet count, other platelet-related parameters, and C-reactive protein (CRP) levels, which are easily accessible by routine hemogram tests, have frequently been studied.[2,12] In this study, we sought to assess the diagnostic value of WBC, neutrophil count, neutrophil percentage, NLR, erythrocyte distribution width (RDW), mean platelet volume (MPV), and CRP levels in differentiating simple appendicitis (SA) and complicated appendicitis (CA) as well as to investigate their effectiveness in predicting CA in patients who were operated for AA.

METHODS

In this single-center retrospective study, we included patients who underwent appendectomy in the İdil State Hospital between November 6, 2018 and December 31, 2019. The patients' written consent could not be taken due to the retrospective design of the study and the anonymity of data. The patient files were scanned using the hospital information system and the demographic characteristics, laboratory values (WBC, neutrophil count, neutrophil percentage, NLR, RDW, MPV, and CRP levels), surgical findings, and pathological results were recorded. The diagnosis of AA was made based on the patient history, physical examination, laboratory values, and imaging methods. We included patients who underwent appendectomy and whose pathological results showed AA. We excluded the following patients: 1) who underwent appendectomy but were reported to have normal appendix based on the pathological results; 2) who were diagnosed with autoimmune disease, chronic inflammatory disease, hematological disease, or cancer; 3) who were pregnant and operated for AA; and 4) who received steroid and anticoagulant treatment. We finally included a total of 153 patients who were seperated into two groups based on the pathological reports and surgical findings. Patients who were reported to have severe adhesion with peripheral tissues during surgery, those who had inflammation or perforation, or whose pathological results showed gangrene, necrosis, or phlegmon were included in the CA group and the others were included in the SA group. SPSS 18.0 program was used to interpret the statistical results. Chi-square test was used for analyzing the correlation between categorical variables and outputs as well as for descriptive statistics such as median, range, and percentage. The Kolmogorov–Smirnov test was used to decide if the research data distribution was natural. The distribution of all variables was analyzed one by one. Non-parametric tests were performed because the parameters were not normally distributed. The non-normally distributed findings were interpreted using the Mann–U Whitney test. Multiple logistic regression analyses were performed to determine the effect of independent variables showing significant correlation with dependent variables in single analysis on the dependent variables. Hosmer–Lemeshow test was used for model adaptation. To evaluate diagnostic precision, the receiver operating characteristic (ROC) curve analysis was used. The cut-off values for parameters were determined with an area under the curve (AUC) of >0.600. In addition, the sensitivity and specificity values were calculated. The conditions with a type-1 error level of <5% were deemed statistically significant.

RESULTS

We included a total of 153 patients; 97 (63.4%) and 56 (36.6%) in the CA and SA groups, respectively. The proportion of male patients was higher in both the groups. The median age was 24 (17.5-33.5) years; 22 (16-30) and 29 (20.25-38.75) years in the SA and CA groups, respectively. In terms of age, there was a

significant difference between the groups (p=0.007; Table 1).

Table 1. Patients' age, gender, WBC, neutrophil count, neutrophil percentage, NLR, RDW, MPV, CRP levels, and distribution by groups

Parameters	All of the patients	Simple appendicitis	Complicated appendicitis	P value
Number of cases	153	97 (63.4%)	56 (36.6%)	-
Age †	24 (17.5-33.5)	22 (16-30)	29 (20.25-38.75)	**0.007**
Gender ‡				
Male	90 (58.8%)	53 (58.9%)	37 (41.1%)	0.166
Female	63 (41.2%)	44 (69.9%)	19 (30.1%)	
WBC*10^3/µL †	11.9 (7.9-15)	10 (7-12.9)	14 (11.9-15.8)	**<0.001**
Neutrophil count*10^3/µL†	9.4 (5.5-12.1)	7.2 (4.2-10.6)	11.3 (9.4-12.9)	**0.007**
Neutrophil percentage (%) †	77.5 (67.3-84.2)	73.2 (60.5-81.25)	81.7 (76.7-85.6)	**<0.001**
NLR †	4.83 (2.92-8.5)	3.85 (1.89-6.75)	6.51 (4.62-9.75)	**<0.001**
RDW (%) †	12.7 (12.4-13.2)	12.7 (12.3-13.2)	12.8 (12.5-13.2)	0.062
MPV (fL) †	8.1 (7.5-8.75)	8,1 (7.5-8.75)	8.05 (7.4-8.7)	0.921
CRP (mg/dL) †	0,2 (0.2-1.1)	0,2 (0.2-0.6)	0.89 (0.2-4.3)	**<0.001**

†: median (IQR), ‡: n (%); WBC: leukocyte count; NLR: neutrophil–lymphocyte ratio; RDW: erythrocyte distribution width MPV; mean platelet volume; CRP: C-reactive protein.

Table 2. ROC analysis results and cut-off values

	Cut-off value	Sensitivity (%)	Spesifity (%)	AUC	95% CI (min-max)	P value
Age (years)	24.5	57.1	57.7	0.631	0.541-0.722	**0.007**
WBC	12.5*10^3/µL	64.3	71.1	0.716	0.634-0.799	**<0.001**
Neutrophil count	9.95*10^3/µL	69.6	70.1	0.732	0.652-0.812	**<0.001**
Neutrophil percentage	78.15	62.5	62.9	0.709	0.628-0.790	**<0.001**
NLR	4.98	62.5	62.9	0.721	0.642-0.801	**<0.001**
CRP (mg/dL)	0.29	67.9	66	0.706	0.619-0.794	**<0.001**

AUC: area under the curve; CI: Confidence interval; WBC: leukocyte count; NLR: neutrophil–lymphocyte ratio; CRP: C-reactive protein.

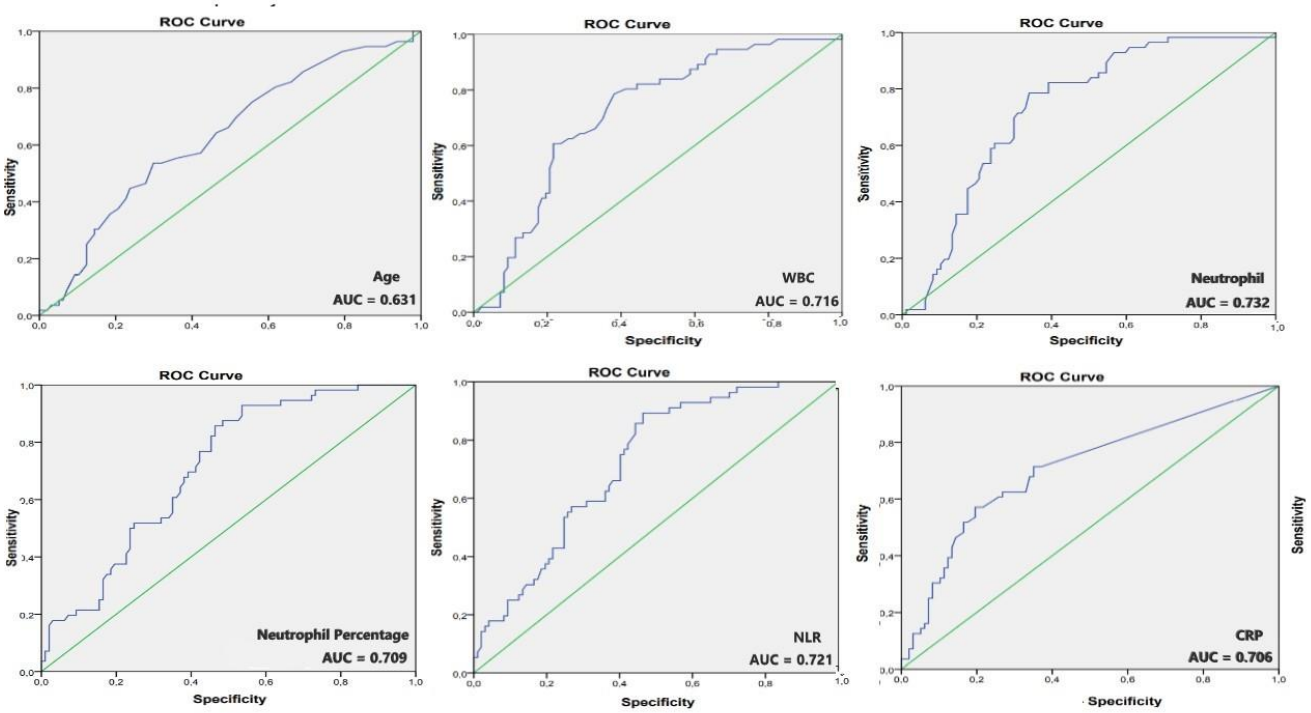

Figure 1. ROC curves for age, WBC, neutrophil count, neutrophil percentage, NLR and CRP

Table 3. Logistic regression analysis results involving age, WBC, neutrophil count, neutrophil percentage, NLR, and CRP parameters

	OR	95% CI (min-max)	P value
Age	1.036	1.002-1.072	**0.038**
WBC	0.503	0.115-2.197	0.361
Neutrophil count	14.934	2.559-87.140	**0.003**
Neutrophil percentage	1.072	0.065-17.668	0.961
NLR	0.671	0.041-11.074	0.781
CRP	4.225	1.851-9.643	**0.001**

OR: Odds ratio; CI: Confidence interval; WBC: leukocyte count; NLR: neutrophil–lymphocyte ratio; CRP: C-reactive protein.

WBC, neutrophil count, neutrophil percentage, NLR, RDW, MPV, and CRP levels are represented in Table 1. WBC ($p<0.001$), neutrophil count ($p=0.007$), neutrophil percentage ($p<0.001$), NLR ($p<0.001$), and CRP level ($p<0.001$) were significantly higher in the CA group than in the SA group. Further, RDW was higher in the CA group, but with no significant difference ($p=0.062$). In addition, the MPV values were similar in both the groups ($p=0.921$).

The ROC analysis was performed on the parameters found to be significantly different between the groups, and the parameters that were successful in predicting CA were determined. Those with an AUC of >0.6 in the ROC curve were considered to be successful. AUC values for age, WBC, neutrophil count, neutrophil percentage, NLR, and CRP levels were 0.631, 0.716, 0.732, 0.709, 0.721, and 0.706, respectively. The cut-off values for these parameters were estimated by considering the optimum sensitivity and specificity values. In the ROC analysis, the cut-off values were determined for age (24.5/year, sensitivity: 57.1%, specificity: 55.7%), WBC (12.500/µL sensitivity: 64.3%, specificity: 71.1%), neutrophil count (9.950/µL, sensitivity: 69.6%, specificity: 70.1%), neutrophil percentage (78.15%, sensitivity: 62.5%, specificity: 62.9%), NLR (4.98, sensitivity: 62.5% specificity: 62.9%), and CRP level (0.29 mg/dL, sensitivity: 67.9%, specificity: 66%). The ROC analysis results are provided in Table 2 and the ROC curves are presented in Figure 1.

Logistic regression analysis was performed for age, WBC, neutrophil count, neutrophil percentage, NLR, and CRP levels. Age (OR: 1.036, 95% CI: 1.002-1.072, p=0.038), neutrophil count (OR: 14.934; 95% CI: 2.559-87.140, p=0.003), and CRP level (OR: 4.225, 95% CI: 1.851-9.643, p=0.001) were independent risk factors for the diagnosis of CA. Additionally, WBC, neutrophil percentage, and NLR were found to be insignificant in the logistic regression analysis (Table 3). Hosmer–Lemeshow test used for model adaptation revealed that the predictive value of the model was high (p=0.635).

DISCUSSION

Acute appendicitis is a common condition encountered by surgeons.[1,13] Patients who are reported to have severe adhesion with peripheral tissues during the surgery, who have inflammation or perforation, or whose pathological results show gangrene, necrosis, or phlegmon are considered to have CA.[1,14] It is rare in patients with CA; however, complications such as abscess, peritonitis, ileus, or wound site infection may develop.[13,15,16] In the present study, we aimed to determine the basic and distinctive characteristics of SA and CA in terms of basic laboratory parameters in patients who are operated for AA.

In our study, the majority of patients in the SA and CA groups were male. In addition, the patients were significantly older in the CA group. In contrast, previous studies have reported that appendicitis generally is common in both genders, regardless of its severity, and there is no correlation between gender and appendicitis severity [14,16,17,18]; however, there are some exceptions.[4] Regarding age and severity of appendicitis, studies have reported that age is higher in CA groups.[14,15] In some studies, the correlation between advanced age and CA has also been statistically proven.[10,19,20] There are also studies reporting that age is lower in CA groups.[11]

Generally, WBC is significantly higher in CA group than in SA groups.[11,14,18,20] In some studies, WBC failed to differentiate between SA and CA.[21,22] In our study, WBC was higher in the CA group (p<0.001). Regression analysis revealed that WBC was not successful (p=0.361). The cut-off value for WBC in CA in the literature varies between 12.500 and 14.870/µL.[4,13,23] In these studies, the sensitivity and specificity values varied between 66.7%–86.1% and 41.6%–68.1%, respectively.[4,13,23] In the present study, the cut-off value was 12.500, sensitivity was 64.3% and specificity was 71.1%, which is consistent with the literature.

Neutrophil count and neutrophil percentage are generally increased in AA. There is no such consensus in the studies on CA. Ishizuka et al. reported that neutrophil count was not successful in predicting gangrenous appendicitis.[19] Another study performed to differentiate between gangrenous appendicitis and AA reported that neutrophil percentage is not significantly different between the groups.[24] In another study on the diagnosis of AA and differentiation of CA, neutrophil percentage was a significant parameter in the diagnosis of AA, and no significant difference was found between complicated and SA groups in terms of neutrophil percentage.[14] In contrast, there are studies reporting that neutrophil count [11,25] and neutrophil percentage [1,10,11] are significantly higher in CA groups. In our study, both neutrophil count and neutrophil percentage were significantly higher in the CA group. Logistic regression analysis revealed that neutrophil count is an independent risk factor for CA, but the same did not apply to neutrophil percentage. Al-gaithy et al. reported that the cut-off value for neutrophil count in differentiating between CA and inflammatory appendicitis is 7.540/µL (sensitivity: 81.2%, specificity: 65.5%).[25] In a study comparing patients with acute gangrenous appendicitis and healthy controls, the cut-off value for neutrophil percentage was 69.5% (sensitivity: 92.5%, specificity: 96.9%).[1] In another study comparing patients with pediatric SA and CA, the cut-off value for neutrophil percentage was 76% (sensitivity: 97.2%, specificity: 32.2%).[13] In our study, the cut-off value for neutrophil count was 9.950/µL (sensitivity: 70.1%, specificity: 73.2%; AUC=0.732) and neutrophil percentage was 78.15% (sensitivity: 62.5%, specificity: 62.9%). Although the sensitivity and specificity values for WBC, neutrophil count, and neutrophil percentage are high in some studies, they are so low in most of them; thus, they are not considered as excellent independent variables in differentiating between SA and CA.

In inflammatory events, neutrophil count is increased, but lymphocyte count is decreased, leading to increased NLR. NLR is a variable that can be simply calculating from the complete blood count. There are several studies have reported that NLR is a successful parameter in the diagnosis of AA and differentiation of CA.[2,18,19,26-28] The cut-off value for NLR in the diagnosis of CA varies between 5.47 and 6.94.[4,11,23,26] In these studies,

the sensitivity and specificity values varied between 61.1%–78.42% and 48.5%-70.33%.[4,11,23,26] In a study comparing patients with pediatric SA and CA, NLR was 10.4 (sensitivity: 73.2%, specificity: 61.1%).[13] In our study, NLR was significantly higher in the CA group than in the SA group, which is consistent with the literature. NLR was not significant in logistic regression analysis. The cut-off value for NLR was 4.98 (sensitivity: 62.5%, specificity: 62.9%). Despite different cut-off values in many studies, NLR is a significant parameter in differentiating between SA and CA. It should be noted that NLR may increase in many inflammatory events and its sensitivity and specificity are insufficient to differentiate between acute and CA. There are limited studies reporting the negative results for NLR. According to one study, NLR is a significant variable in the AA diagnosis; however, there was no statistically important variation in the differentiation of CA.[15] Aktimur et al. compared AA and normal appendicitis groups and reported that NLR is higher in the AA group, but statistically significant.[29] RDW is routinely studied in complete blood count, and it expresses how much the volume of circulating erythrocytes varies. RDW is an inflammatory parameter and RDW levels vary in many inflammatory events.[4,30,31] RDW was not successful in differentiating between SA and CA in three studies.[4,13,22] Gunay et el. reported that the RDW value is significantly higher in the CA group than in the appendicitis group, and it has an independent diagnostic value in CA.[11] In our study, RDW was higher in the CA group, but there was no significant difference between the groups, which is consistent with the literature. MPV is a parameter obtained from routine blood count. MPV decreases in acute inflammatory events and increases in chronic inflammatory events.[1,18,29] Literature review has also shown different results in terms of MPV in CA. In two different studies, MPV was significantly lower in CA.[1,12] Aydogan et al. reported that MPV is significantly higher in perforated appendicitis than in non-perforated appendicitis.[20] Similarly, there was no significant difference between patients with SA and CA in terms of MPV in various studies, which is consistent with our study.[11,13,15] CRP is an acute phase protein and CRP levels increase in many inflammatory events.[10] The use of CRP along with other inflammatory parameters and the physical examination findings in the diagnosis of AA and CA increase the success rates.[10]

A study comparing patients with perforated and non-perforated AA showed that WBC, CRP, and bilirubin levels are significantly higher in the perforation group and are the strongest parameters in terms of the determination of perforation.[32] In another study, although there was no statistical difference in terms of CRP levels in differentiating between AA and normal appendicitis, increased CRP level was an independent factor in predicting complications in patients with AA. The cut-off value for CRP has been found to be 25.5 mg/dL (sensitivity: 63.8%, specificity: 58.2%).[4] In another study comparing patients with CA and SA, the cut-off value for CRP was 10.5 mg/dL (sensitivity: 65.2%, specificity: 70.59%).[23] Ayrik et al. found the cut-off value for CRP to be 4.59 mg/dL (sensitivity: 66%, specificity: 69.6%).[21] Although CRP level is generally successful in differentiating CA, there are studies reporting opposite results.[15,22] In our study, CRP was significantly higher in the CA group, which is consistent with the literature. The cut-off value for the differentiation between CA and SA (0.29) was lower than that reported in the literature. However, the sensitivity and specificity values were consistent with the literature. In regression analysis, we found CRP to be an independent risk factor for CA. In logistic regression analysis, all significant variables were included in the model and all variables associated with each other, which eliminates the possibility of random significance. Logistic regression analysis performed in our study for age, WBC, neutrophil count, neutrophil percentage, NLR, and CRP levels revealed that only age, neutrophil count, and CRP levels are successful in predicting CA. Our study's key drawbacks are its retrospective existence and the small number of patients. In addition, information such as the duration of admission and the onset of symptoms are not available. However, it is considered that our study contains useful information about the diagnostic accuracy of basic laboratory parameters in terms of differentiating between CA and SA. Averaging consecutive values instead of a single value in the laboratory values may yield more beneficial results. In addition, the time of tests before operations results in change in some results; if it is possible to standardize them, more valuable results may be obtained.

CONCLUSION

Physical examination, laboratory values, and imaging methods are helpful in the diagnosis of AA and the

determination of its severity. The biochemical markers analyzed in our study can assist surgeons make more precise decisions in the following uncommon situations: 1) that imaging methods can only be accessed partially or at specific times for technical reasons; 2) patient suitability for conservative treatment for surgeons who prefer conservative treatment in AA; and 3) limited use of radiological imaging methods for pregnant, pediatric, and patients with additional problems. Presently, there is no excellent laboratory value that can be used alone in the detection of AA and the distinction of CA without the need for imaging methods. In addition, age, neutrophil count, and CRP levels may be a guide for differentiating between SA and CA.

Authorship contribution statement

Consept and desing: MU, AU, ST.

Acquisition of data: MU, AU.

Analysis and interpretation of data: MU, AU, ST.

Drafting of the manuscript: MU, ST.

Critical revision of the manuscript for important Intellectual content: MU, AU, ST.

Statistical analysis: MU, AU.

Supervision: MU, ST.

Declaration of competing interest

None of the authors have potential conflicts of interest to be disclosed.

Ethical approval

Ethics committee approval was received for this study from Ethical Committee for Clinical Studies, Karadeniz Technical University, Faculty of Medicine, 2020/163 (2020/163).

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Funding

No financial support was received for this research.

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To Cite: Ulusahin M, Unal A, Turkyilmaz S. Diagnostic value of basic laboratory parameters in the diagnosis of complicated appendicitis. Farabi Med J. 2024;3(2):42-49. doi:10.59518/farabimedj.1392105

Farabi Tıp Dergisi 3(2):50-56,2024
Farabi Medical Journal 3(2):50-56,2024
https://doi.org/10.59518/farabimedj.1449180

FARABİ TIP DERGİSİ
FARABI MEDICAL JOURNAL

Özgün Makale
Original Article

https://dergipark.org.tr/tr/pub/farabimedj

An Ignored Fact: An Ignored Fact: Feeling of Guilt and Affecting Factors in Mothers Whose Children are Hospitalized

Göz Ardı Edilen Bir Gerçek: Çocuğu Hastanede Yatan Annelerde Suçluluk Duygusu ve Etkileyen Faktörler

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ABSTRACT

This study aimed to examine the feeling of guilt experienced by mothers whose children are hospitalized and the factors affecting it. Data were collected from mothers whose children were hospitalized using a Personal Information Form and the Feeling of Guilt Scale for Mothers whose Children were Hospitalized. Analyzes were made in the SPSS 26 package program. P<0.001 and p<0.05 significance levels were used as statistical significance values. The study found a significant difference between the scale total scores and the place of residence, the husband's ability to help with child care, and the feelings of anger, helplessness, and burnout experienced by the mothers (p<0.05). It was determined that 26.4% of the variance in the dependent variable was explained by the independent variables (R^2 adjusted=0.264). The place of residence, the spouse's assistance in child care, and the feelings of anger, helplessness, and exhaustion experienced by the mother affect the guilt of mothers whose children are hospitalized. Nurses, who are the health professionals closest to the mother and family, should adopt a 'family-centered' care approach by considering the child and family together. This approach aims to assist the family by providing a supportive environment.

Keywords: Child, Guilt, Hospitalization, Mother

ÖZET

Bu araştırmada çocuğu hastanede yatan annelerin yaşadığı suçluluk duygusu ve etkileyen faktörlerin incelenmesi amaçlanmıştır. Veriler, çocuğu hastanede yatan annelerden Kişisel Bilgi Formu ve Çocuğu Hastanede Yatan Annelerde Suçluluk Duygusu Ölçeği ile toplandı. Analizler SPSS 26 paket programında yapıldı. İstatistiksel anlamlılık değeri olarak p<0.001 ve p<0.05 anlamlılık düzeyleri kullanıldı. Çalışmada ölçek toplam puanları ile yerleşim yeri, eşin çocuk bakımına yardım etme durumu, annelerin yaşadıkları öfke, çaresizlik ve tükenmişlik duyguları arasında anlamlı fark bulundu (p<0.05). Bağımlı değişkendeki varyansın %26.4'ünün bağımsız değişkenler tarafından açıklandığı (R^2 düzeltilmiş=0.264) saptandı. Çocuğu hastanede yatan annelerin suçluluk duygusunu yerleşim yeri, eşin çocuk bakımına yardımı, annenin yaşadığı öfke, çaresizlik ve tükenmişlik duyguları etkilemektedir. Anneye ve aileye en yakın sağlık profesyoneli olan hemşireler, çocuk ve aileyi bir arada ele alarak 'aile merkezli' bakım yaklaşımını benimsemelidir. Bu yaklaşım, destekleyici bir ortam sağlayarak aileye yardımcı olmayı amaçlamaktadır.

Anahtar Kelimeler: Anne, Çocuk, Hastanede yatma, Suçluluk

Geliş Tarihi/Received Date: 08.03.2024 | *Kabul Tarihi/Accepted Date: 10.05.2024*

INTRODUCTION

The separation of a child who is hospitalized for chronic diseases or acute reasons from their daily routines, home, and social environment affects not only the children but also their families negatively.[1,2] Illnesses and hospitalization can create trauma in the family by causing fear and anxiety. Hospitalization, which is a very tiring and lengthy process for the child, not only alienates the mother from her social environment when the responsibility for child care falls solely on the mother but also causes the mother to feel guilty about her child's illness.[3] Guilt is a complex emotional state that occurs when an individual feels that he or she has behaved in a way that does not comply with the moral or social norms he or she has adopted.[4] This feeling, is shaped based on the person's internal value judgments and ethical understanding. The feeling of guilt is closely related to the individual's lived experiences, cultural background and personal beliefs. Therefore, each individual's feeling of guilt and the intensity of this feeling may differ, because personal values and perspectives also vary. In this context, the feeling of guilt is a subjective experience that varies depending on the individual's relationship with his inner world and how he perceives the world around him.[5,6] It is reported in the literature that as the child's hospital stay increases, mothers' anxiety and depression levels increase, and approximately 60% of mothers experience post-traumatic stress disorder.[3,5-7] In the study conducted by Nabors et al. with mothers of children with chronic diseases, the mothers stated that the economic situation due to hospitalization stressed the family. Still, they tried to be vital for their children.[6] In the same study, it is reported that the anxiety experienced by parents disrupts family order. Gezer stated in the study results that mothers whose children were hospitalized experienced intense feelings of guilt, anger, and burnout during this period.[8] Mothers' feelings of guilt are associated with the emergence of many psychopathological symptoms.[9] It is stated that in individuals who experience feelings of guilt very frequently, interpersonal relationships may deteriorate over time, and psychological problems such as anxiety and depression may arise.[10] During this process, nurses and other health professionals should carefully listen to the issues of mothers whose children are hospitalized in an effective and safe communication environment and provide approaches that will help them cope.[1] Nurses should evaluate the patients they care for and their families and close circle with a holistic approach.[11] Pediatric nurses, who spend the most time with hospitalized children and their mothers and communicate with them most frequently, must be sensitive to the problems experienced by mothers and offer solutions.[5]

Being with a sick child in a hospital environment may cause the mother to experience different emotions such as anxiety, guilt, fear, resentment, anger and depression. The mother needs help to cope with these feelings.[7,8] Since the feeling of guilt experienced by mothers is not visible, it is not possible to prevent the negative emotions that mothers experience intensely, and treatment can be difficult and time-consuming.[11] The mother's general well-being and mental health are important during the child's development process. Therefore, it is not possible to help children without investigating the reasons for the emotions that mothers experience intensely and that negatively affect their mental health.[12] In this context, this study aimed to examine the feeling of guilt experienced by mothers whose children are hospitalized and the factors affecting it.

METHODS

Study Design

This research was conducted with a cross-sectional design with mothers whose children aged 0-18 were hospitalized in a public hospital in Türkiye between May and August 2023. Mothers who could be reached by the complete census method without using the sample selection method, whose children had been hospitalized for at least one day, who had no communication barriers, and who volunteered to participate in the study were included. The study was completed with 208 participants.

Data collection tools

Personal Information Form: The form inquired about information such as the mother's age, education level, number of children, age, gender and diagnosis of her hospitalized child.[6-8,13]

The Guilt Scale in Mothers with Hospitalized Children: The scale was developed by Gezer and Taştekin Ouyaba to measure guilt in mothers hospitalized.[13] The Feeling of Guilt Scale for Mothers with Hospitalized Children is a 5-point Likert type consisting of 18 items and five subscales. As the total score from the scale increases, it is accepted that

mothers feel more guilt. The Cronbach's alpha coefficient of the scale is 0.74. In our current study, the Cronbach Alpha value of the scale was found to be 0.78.

Collection of data

Before the interview, the patients were informed about the purpose and objectives of the study and the time allocated for the interview, and their verbal and written consent was obtained. The same researchers also collected the data. Data were collected by the researcher in clinic rooms using data collection instruments during approximately 15-20 min face-to-face interviews with the participants. Data were obtained from pediatrics, pediatric surgery and neonatal clinics.

Data analysis

The data was evaluated in the SPSS 26.0 for Windows (SPSS, Chicago, IL, USA) package program. Normal distributions of the data were reviewed by the Skewness and Kurtosis coefficients, which were in the range of (-1)- (+1).[14] Numbers, percentages, and mean and standard deviation (SD) values were used for descriptive statistics. Independent Samples and One-Way ANOVA tests were used to compare children's and parents' descriptive characteristics and scale scores. Multiple Linear Regression analysis with enter method was used to determine the relationship between dependent and independent variables. P<0.001 and p<0.05 significance levels were used as statistical significance values.

Compliance with Ethical Statement

Before the research, approval from the ethics committee of a state university (25.04.2023/ Decision no: 163/8) and institutional permission from the Provincial Health Directorate were obtained. The Declaration of Helsinki informed participants about the study, and their consent was obtained for the Informed Consent Form.

RESULTS

The average age of the mothers participating in our study was 33.70±7.03. Distribution of hospitalized children according to age groups: 0-1-year-olds were 37 (17.7%), 2-6-year-olds were 117 (56.3%), 7-12-year-olds were 26 (12.5%), and 13-18-year-olds were 28 (13.5%). The mothers' total scale score average was found to be 39.51±9.05.

Table 1 compares some characteristics of mothers and children with their total scale scores. A significant difference was found between the total scores of the scale and the place of residence of the family (p<0.05). The total scores of mothers living in villages or districts were found to be higher than those living in the city center. A significant difference was found between the total scores of the scale and the spouse's ability to help with child care (p<0.01). The total scale scores of mothers whose husbands did not help with child care were higher than those of mothers whose husbands helped with child care. A significant difference was found between the total scores of the scale and the mothers' feelings of anger while the child was in the hospital (p<0.05). The total scale scores of mothers who experienced anger were higher than those who did not. A significant difference was found between the total scores of the scale and the mothers' feeling of helplessness while the child was in the hospital (p<0.01). The total scale scores of mothers who experienced the feeling of helplessness were found to be higher than those who did not. A significant difference was found between the total scores of the scale and the mothers' feeling of burnout while the child was in the hospital (p<0.01). The total scale scores of mothers who experienced burnout were higher than those who did not. A significant difference was not found between the total scores of the scale and mother's working status and child's admission diagnosis (p>0.05). A significant difference was found between the total scores of the scale and child's age (p<0.05). As a result of the post hoc analysis made according to the child's age variable, no significant difference was found between the groups in the total scores of the scale (p>0.05, Table 1).

The relationship between some variables and the guilt scale of mothers whose children are hospitalized was examined with a multiple linear regression model (Table 2).

In the analysis of some variables belonging to the mothers, it was seen that there was a significant model in the evaluation of model goodness of fit (F/p) regression coefficients (R/R^2) (p<0.05). It was determined that the independent variables explained 26.4% of the variance in the scale-dependent variable (R^2 adjusted=0.264). It was determined that the place of residence, the mother's feeling of helplessness, the mother's feeling of burnout, and the spouse's help with child care were statistically significant negative predictors of the feeling of guilt in mothers whose children were hospitalized (p<0.05, Table 2).

Table 1. Comparison of some characteristics of mothers and children and scale total scores (n= 208)

Variables	n	(%)	Scale total score		Test value	P value
			Mean	SD		
Mother's educational status						
Primary/Middle school	55	26.4	39.69	9.39	F=0.056	0.945
High school	101	48.6	39.60	8.79		
University and above	52	25.0	39.15	9.36		
Residential area						
Village/District	57	27.4	41.82	9.65	**t=2.283**	**0.023***
City Center	151	72.6	38.64	8.69		
Mother's working status						
Working	81	38.9	38.69	9.00	t=1.047	0.296
Not working	127	61.1	40.03	9.12		
Gender of the hospitalized child						
Female	99	47,6	39.18	8.36	t=-0.504	0.615
Male	109	52,4	39.81	9.66		
Child's age						
0-1 years old	37	17.8	38.02	8.36	F=3.009	0.031
2-6 years old	117	56.3	41.07	9.09		
7-12 years old	26	12.5	36.15	8.86		
13-18 years old	28	13.5	38.07	8.98		
Child's admission diagnosis						
Respiratory system diseases	58	27.9	38.72	9.23	F=0.680	0.727
Accidents	33	15.9	40.42	7.19		
Digestive system diseases	31	14.9	41.64	9.44		
Surgical causes	16	7.7	39.06	11.10		
Childhood infectious diseases	15	7.2	39.60	10.14		
Congenital anomalies	15	7.2	37.06	10.43		
Urinary system diseases	12	5.8	36.33	7.99		
Special conditions for the newborn (prematurity, jaundice, etc.)	12	5.8	41.91	8.45		
Cardiovascular system diseases	10	4.8	40.50	8.64		
Other (Endocrine system diseases and cancers)	6	2.9	38.16	7.78		
Number of living children						
One child	66	31.7	39.27	8.46	F=0.060	0.942
2 children	76	36.6	39.78	9.31		
3 children and above	66	31.7	39.43	9.44		
How many children are hospitalized?						
First child	97	46.6	38.75	8.94	F=0.646	0.525
2nd child	70	33.7	40.11	8.90		
3rd and above child	41	19.7	40.29	9.63		
Spouse's ability to help with child care						
Yes	143	68.7	38.34	8.92	**t=2.814**	**0.005***
No	65	31.3	42.09	8.88		
Experiencing feelings of anger while the child is in the hospital						
Yes	66	31.7	41.45	8.40	**t=2.124**	**0.035***
No	142	68.3	38.61	9.23		
Feeling helpless while the child is in hospital						
Yes	122	58.7	41.57	8.93	**t=4.049**	**0.000***
No	86	41.3	36.59	8.44		
Feeling of burnout while the child is in hospital						
Yes	92	44.2	43.05	7.56	**t=5.564**	**0.000***
No	116	55.8	36.70	9.18		

*Independent T test **One-Way ANOVA

Table 2. Multiple linear regression analysis model of the scale according to some variables (n= 208)

Scale	Variables						95,0 Cl		
		B	SE	β	t	p	Lower	Upper	Model fit
Scale total score	**(Constant)**	68.424	3.586	-	19.083	**0.000**	61.353	75.494	
	Residential area	-2.960	1.193	-0.149	-2.481	**0.014**	-5.312	-0.607	
	Feeling of helplessness	-4.058	1.106	-0.227	-3.669	**0.000**	-6.239	-1.877	**Adj. R^2= 0.264 F= 19.348**
	Feeling of burnout	-6.222	1.097	-0.350	-5.674	**0.000**	-8.385	-4.060	
	Spouse's help with child care	-4.967	1.150	-0.262	-4.317	**0.000**	-7.235	-2.698	

Adj.R^2: Adjusted R square; B: Partial regression coefficient; β: Standard partial regression coefficient; 95% CI: 95% confidence interval.

DISCUSSION

The mother's mental health is of great importance in her child's healthy growth and development. For this reason, it is important to know that children cannot be genuinely helped without investigating and understanding the reasons for the negative emotions that mothers experience intensely.[12] In this context, this study aimed to examine the feeling of guilt experienced by mothers whose children are hospitalized and the factors affecting it. In the study, the sense of guilt experienced by mothers living in the village/district was higher than that of mothers living in the city center. In Gezer's study, no significant difference was found between the place of residence and the feeling of guilt experienced by the mothers.[8] In our country, there may still be problems in transportation from the periphery to the center. Mothers may have been late and felt guilty about taking their children to the hospital due to transportation problems.

Spouses' support in child care is of great importance. Our study determined that mothers who did not receive their husband's support regarding child care felt more guilty than mothers who received their husband's support. Similarly, in Gezer's study, it was determined that mothers who did not have their husbands' support in caring for the child experienced more feelings of guilt than mothers whose husbands did support them.[8] In a study conducted by Lernevall et al. with the families of children with burns, it was determined that the feeling of guilt decreased in mothers who received spousal support.[15] The study of Açıkgöz et al. four determined that mothers who did not have spousal support and were blamed by their spouses convinced themselves of this feeling of guilt over time.[5] It was also determined that these mothers had negative emotions and thoughts, such as the idea of ending their lives. For these reasons, it is stated that the mental health of mothers whose children are hospitalized is at risk.[5] The father's support of the mother during the child's hospitalization reduces the mother's guilt.[8]

The majority of mothers experience anxiety due to their child's illness and may feel guilty. It is stated in the literature that mothers of children with mental,[16] psychological, behavioral, and physical problems,[17] and multiple and severe disabilities[18] feel guilty about the child's illness or are blamed by the individuals around them. Mothers' feelings of guilt are associated with the emergence of many psychopathological symptoms.[9] It has been stated that in individuals who experience feelings of guilt very frequently, interpersonal relationships may deteriorate over time, and psychological problems such as anxiety and depression may arise.[10] Nurses who are closest to the mother and family should adopt a 'family-centered' care approach by considering the child and family together. This approach is important to help the family recognize and solve their problems. For this reason, the mental health of mothers who accompany their hospitalized children must be protected and supported. Just talking and listening to the mother whose child is hospitalized makes it easier for the mother to cope with the difficult situations she is experiencing.[19] Some of the mothers who accompany their children in pediatric clinics are affected psychologically and may experience different levels of depression, anxiety, and stress. Some risk factors, such as communication problems with healthcare professionals and sleep problems, increase the likelihood of mothers experiencing depression, anxiety, and stress. Nurses, who spend the most time with hospitalized children and their mothers, need to be sensitive to the negative emotions experienced by the mothers.[5] During this process, nurses and other healthcare professionals should consider the mother's feelings and take solution-oriented approaches to the problems.[1]

The study found that among mothers whose children were hospitalized, those who experienced feelings of anger, helplessness, and burnout felt more guilt than those who did not. In Gezer's study, it was found that mothers who experienced anger and burnout experienced more guilt than those who did not.[8] Mothers are often the primary caregivers for sick children in hospitals.[20,21] Being with a sick child in a hospital environment may cause the mother to experience different emotions such as anxiety, guilt, fear, resentment, anger and depression. The mother needs help to cope with these feelings.[22] The mother's general well-being and mental health are important during the child's development process. Therefore, it is not possible to help children without investigating the reasons for the emotions that mothers experience intensely and that negatively affect their mental health.[12]

Limitations of the Research

This study had some limitations. First, this study used self-report measurement instruments, possibly introducing some response bias. Secondly, since this study was conducted in a province in the Eastern Black Sea Region of Türkiye, the results cannot be generalized. Third, since the study was cross-sectional, causality could not be determined. Therefore, caution is recommended when interpreting the study results. Despite these limitations, the study had its strengths. This study is valuable in terms of evaluating the feelings of guilt experienced by mothers whose children are hospitalized, an exceptional group and raising awareness among mothers on this issue.

CONCLUSION

The study concluded that the place of residence, the spouse's ability to help with child care, and the mother's feelings of anger, helplessness, and burnout affect the sense of guilt of mothers whose children are hospitalized. In light of these results, it may be recommended to organize support groups where mothers can share their feelings and thoughts about their children's diseases, in addition to the guidance, consultancy and education services that nurses provide to families and children. In addition, referrals can be made to social support organizations to reduce the economic difficulties that may occur on the family due to the child's illness and thus improve family relations.

Among healthcare personnel, nurses, who are closest to mothers and families, should adopt a 'family-centered' care approach by handling the child and family together. This approach aims to assist the family by providing a supportive environment. This support provided by nurses should include helping the family identify and solve their problems, as well as preparing the family for stressful periods such as hospitalization. In this way, nurses are concerned not only with the patient's health status but also with the overall well-being and harmony of the family. This approach not only provides a more holistic perspective on the child's treatment, but also reassures and supports the family and encourages them to actively participate in the healing process.

Acknowledgement

The authors would like to thank all the participants who took part in the study.

Authorship contribution statement

Consept and desing: ZÖK.

Acquisition of data: ZÖK, EOA.

Analysis and interpretation of data: ZÖK, EOA.

Drafting of the manuscript: ZÖK, EOA.

Critical revision of the manuscript for important intellectual content: ZÖK, EOA.

Statistical analysis: ZÖK, EOA.

Supervision: ZÖK.

Declaration of competing interest

None of the authors have potential conflicts of interest to be disclosed.

Ethical approval

Before the research, approval from the ethics committee of a state university (25.04.2023/ Decision no: 163/8) and institutional permission from the Provincial Health Directorate were obtained.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Funding

No financial support was received for this research.

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To Cite: Kirbas ZO, Aktas EO. An Ignored Fact: An Ignored Fact: Feeling of Guilt and Affecting Factors in Mothers whose Children Are Hospitalized. Farabi Med J. 2024;3(2):50-56. doi:10.59518/farabimedj.1449180

Farabi Tıp Dergisi 3(2):57-62,2024
Farabi Medical Journal 3(2):57-62,2024
https://doi.org/10.59518/farabimedj.1484155

FARABİ TIP DERGİSİ
FARABI MEDICAL JOURNAL

Özgün Makale
Original Article

https://dergipark.org.tr/tr/pub/farabimedj

The Therapeutic Effect of *p*-Coumaric Acid on Lung Toxicity Induced by Methotrexate in Rats

Sıçanlarda Metotreksatın Neden Olduğu Akciğer Toksisitesi Üzerine *p*-Kumarik Asidin Terapötik Etkisi

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ABSTRACT

The use of methotrexate (MTX), a chemotherapy agent, is limited by a number of side effects, including pulmonary toxicity. Oxidative stress (OS) and inflammation are possible mechanisms of MTX-associated pulmonary toxicity. *p*-Coumaric acid (PCA) is a phenolic acid that has been demonstrated to exert a number of beneficial effects on human health, particularly in relation to antioxidant and anti-inflammatory activity. The potential effects of PCA in reducing MTX-induced pulmonary toxicity were investigated in the current study. After MTX (20 mg/kg) was administered to the rats on day 1, two different doses of PCA (2 and 4 mg/kg) were administered intraperitoneally for 3 days and the levels of OS, inflammation and apoptosis were assessed in the lung tissues collected on day 5. PCA applications largely eliminated MTX-induced OS, inflammation and apoptosis in lung tissue via enhancing the capacity of endogenous antioxidant system. The therapeutic effect of PCA against MTX-induced pulmonary toxicity should be re-evaluated in more systematic studies.

Keywords: Apoptosis, Inflammation, Methotrexate, Oxidative stress, *p*-Coumaric acid, Pulmonary toxicity

ÖZET

Bir kemoterapötik ajan olarak metotreksatın (MTX) kullanımı, akciğer toksisitesi de dahil olmak üzere bir takım yan etkiler nedeniyle sınırlıdır. Oksidatif stres (OS) ve inflamasyon, MTX ile ilişkili akciğer toksisitesinin olası mekanizmalarıdır. *p*-Kumarik asit (PCA), özellikle antioksidan ve anti-inflamatuar olmak üzere insan sağlığı üzerinde çeşitli yararlı etkileri olan bir fenolik asittir. Bu çalışmada PCA'nın MTX kaynaklı akciğer toksisitesini azaltmadaki potansiyel etkileri araştırıldı. Ratlara 1. günde MTX (20 mg/kg) enjeksiyonunu takiben 3 gün boyunca iki farklı dozda PCA (2 ve 4 mg/kg) intraperitoneal olarak uygulandıktan sonra 5.günde akciğer dokuları toplanarak OS, inflamasyon ve apoptoz düzeyleri değerlendirildi. PCA uygulamaları, endojen antioksidan sistemin kapasitesini artırarak akciğer dokusunda MTX'in neden olduğu OS, inflamasyon ve apoptozu büyük ölçüde ortadan kaldırdı. PCA'nın MTX kaynaklı akciğer toksisitesine karşı terapötik etkisinin daha sistematik çalışmalarla yeniden değerlendirilmesi gerekmektedir.

Anahtar Kelimeler: Akciğer toksisitesi, Apoptoz, İnflamasyon, Metotreksat, Oksidatif stress, *p*-Kumarik asit

Geliş Tarihi/Received Date: 14.05.2024 | *Kabul Tarihi/Accepted Date: 15.06.2024*

INTRODUCTION

Methotrexate (MTX) is a folic acid antagonist that is employed in the treatment of various types of cancer, including leukaemia, breast cancer and lung cancer.[1] The antiproliferative effect of MTX on cancer cells is attributed to its suppression of thymidylate synthesis.[2] Several reports have shown that MTX can cause a number of adverse effects, including haematological, cutaneous, gastrointestinal, neuro-, nephro- and pulmonary toxicity.[3] In particular, pulmonary toxicity is a common adverse effect that may necessitate the discontinuation of treatment.[4] The incidence of MTX-induced lung disease is estimated to be approximately 7.6%.[5] The hypothesis has been put forth that MTX-related pulmonary injury is a consequence of heightened inflammation, a process which may culminate in the emergence of fibrosis, interstitial pneumonitis, and potentially significant alveolar destruction.[2] The aetiology of tissue damage associated with the use of MTX is complex and involves multiple mechanisms, with inflammatory and oxidative stress (OS) processes playing a significant role.[6] MTX has been demonstrated to induce parenchymal lung damage by causing an increase in the amount of reactive oxygen species (ROS) and a decrease in the capacity of the antioxidant defence system.[5,7-9] MTX also results in an elevation of pro-inflammatory cytokines, including tumour necrosis factor-alpha (TNF-α).[5,10,11] This, in turn, contributes to the exacerbation of tissue damage.[12] It is therefore of the utmost importance to identify molecules that can prevent the lung injury induced by MTX.[4,13]

Phytochemicals are defined as non-nutritive secondary plant metabolites. Despite their low nutritional value, they are included in an ideal diet because of their various important biological activities, including antioxidant, antigenotoxic and anti-inflammatory properties.[14] *p*-Coumaric acid (PCA) is a member of the phenolic acid subgroup, which constitutes the most comprehensive phytochemical subgroup. It serves as an initial substrate for the production of numerous phenolic compounds in plants.[15] Particularly the antioxidant, antimicrobial and anti-inflammatory properties of PCA have increased its use in the food and cosmetic industries.[15,16] Although previous studies have demonstrated the potential of PCA to abolish cisplatin[17,18] and doxorubicin[19,20] induced tissue damage in experimental studies, no studies have evaluated the effectiveness of PCA against MTX-induced pulmonary toxicity to date. Therefore, the focus of this study was to investigate the therapeutic effect of PCA on MTX-induced pulmonary toxicity in rats through biochemical mechanisms.

METHODS

Animals and experimental design

A total of thirty female Sprague-Dawley rats (aged 8-10 weeks) were housed in an environmentally controlled room at a temperature of 21±1°C under a 12-h light/dark cycle. The animals were given free access to standard laboratory chow and water and were acclimatised for one week prior to the study. The protocol was approved by the Local Animal Ethics Committee of Karadeniz Technical University (Protocol Number: 2023/06).

The animals were randomised into 5 groups: control, only MTX administered (MTX), MTX combined with PCA (2 and 4 mg/kg) and only high-dose PCA (4 mg/kg) administered. All drug administration was performed intraperitoneally. MTX and PCA (Sigma, St. Louis, MO, USA) were prepared by dissolving in physiological saline[21-23] and 20% ethanol[17,24], respectively.

Group I (Control): On the first day, the subjects received saline. Thereafter, for a period of three days, the subjects received 20% ethanol.

Group II (MTX): On the first day, the subjects received MTX (20 mg/kg). Thereafter, for a period of three days, the subjects received 20% ethanol.

Group III (MTX+low dosage PCA): On the first day, the subjects received MTX (20 mg/kg), followed by a 3-day course of PCA (2 mg/kg).

Group IV (MTX+high dosage PCA): On the first day, the subjects received MTX (20 mg/kg), followed by a 3-day course of PCA (4 mg/kg).

Group V (only high-dose PCA): On the first day, the subjects received saline. Thereafter, the subjects were administered PCA (4 mg/kg) for 3 days.

The experimental regimen and doses of MTX[21-23] and PCA[18,25] were determined based on previous studies. The 24 h after the last treatment, the animals were euthanised by cervical dislocation under general anaesthesia and the collected lung tissues were stored for further biochemical investigations.

Biochemical analysis

The samples (10% w/v) were homogenised in phosphate buffered saline (PBS), centrifuged at 1800xg for 10 min at 4ºC, and the clear supernatant was collected. Protein levels of the supernatants were determined using a commercially available colorimetric kit according to the

bicinchoninic acid protein assay (BCA) method[26], following the manufacturer's recommendations (Pierce BCA Protein Assay Kit, Thermo Scientific, Rockford, IL). Briefly, 25 µL of serially diluted bovine serum albumin (BSA) standards and supernatants (diluted 5-fold with PBS) were pipetted into the wells of a 96-well microplate, and 200 µL of BCA working reagent was added to each well and incubated at 37°C for 30 min. After incubation, the plate was cooled to room temperature and absorbances were measured at 562 nm in a microplate reader spectrophotometer (Versamax, Molecular Devices, CA, USA). A concentration vs. absorbance graph was then plotted for the BSA standards and the protein content of the samples was determined from this graph using the absorbance values of the samples.

MDA content was assessed using the previously described method.[27] The supernatant was mixed with 3 mL of 1% phosphoric acid and 1 mL of 0.672% thiobarbituric acid. The mixture was vortexed and then incubated in a boiling water bath for 1 h. The tubes were then allowed to cool at room temperature and centrifuged at 1800xg for 10 min. Two hundred microliters of each supernatant were transferred to a 96-well plate and the absorbance was read at 532 nm using a microplate reader (Versamax, Molecular Devices, CA, USA). 1,1,3,3-tetramethoxypropane was used as a standard, and the tissue MDA levels were expressed as nmol/mg protein.

The total antioxidant status (TAS) and the total oxidant status (TOS) in lung tissue were quantified using commercially available kits (Rel Assay Kit Diagnostics, Gaziantep, Turkey) and the OS index (OSI) was calculated.[28] The levels of the antioxidant system (with the superoxide dismutase (SOD) parameter), inflammation (with the TNF-α parameter) and apoptosis (with the caspase-3 (CASP3) parameter) in lung tissue were determined using commercial ELISA kits (BT LAB, Zhejiang, China).

Statistical analysis

Statistical analysis of data was performed using SPSS (Version 23.0, NY, USA). All results were presented as mean± the standard error of the mean (SEM). The Kolmogorov-Smirnov test was used to assess the suitability of the data for normal distribution. ANOVA was used to analyse data showing normal distribution, and Tukey's post-hoc test was used for comparisons between groups. The significance level was set at $p<0.05$.

RESULTS

The effect of PCA on MTX-induced lung toxicity was evaluated in terms of OS, inflammation and apoptosis parameters and the results were presented in Table 1. MTX administration resulted in a notable elevation in the levels of lung MDA, TOS and OSI, whereas PCA treatments demonstrated a dose-dependent reduction in MDA, TOS and OSI levels.

The antioxidant capacity of lung tissue in rats treated with MTX was evaluated using(TAS and SOD parameters. The administration of MTX was found to result in a significant reduction in the levels of lung TAS and SOD. Conversely, the administration of PCA demonstrated a dose-dependent improvement in TAS and SOD levels.

The levels of inflammation and apoptosis in the lung tissue were evaluated using two distinct parameters: TNF-α and CASP3, respectively. MTX triggered a significant elevation in the levels of lung TNF-α and CASP3. Conversely, PCA treatments dose-dependently largely abolished inflammatory and apoptotic processes.

Table 1. Effect of PCA treatments on OS, inflammatory and apoptosis parameters

	Control	PCA (4 mg/kg)	MTX (20 mg/kg)	MTX+PCA (2 mg/kg)	MTX+PCA (4 mg/kg)
MDA (nmol/mg protein)	8.94±0.35	9.47±0.39	21.75±1.76***	12.09±0.52$^{\#\#\#}$	10.53±0.81$^{\#\#\#}$
TOS (µM H_2O_2 equivalent/L)	20.41±0.37	23.39±1.31	33.06±1.56**	25.79±1.98	23.98±3.38$^{\#}$
TAS (mM trolox equivalent/L)	8.47±0.09	8.11±0.28	3.72±0.40***	6.45±0.29$^{**,\#\#\#}$	7.27±0.43$^{\#\#\#}$
OSI (arbitrary unit)	0.24±0.01	0.29±0.02	0.94±0.09***	0.40±0.02$^{\#\#\#}$	0.34±0.05$^{\#\#\#}$
SOD (ng/mg protein)	0.39±0.03	0.38±0.03	0.20±0.02*	0.31±0.03	0.39±0.07$^{\#}$
TNF-α (pg/mg protein)	11.17±1.51	11.44±1.52	42.21±5.51***	24.03±3.01$^{*,\#\#}$	12.40±1.27$^{\#\#\#}$
CASP-3 (ng/mg protein)	0.27±0.02	0.21±0.01	0.71±0.08***	0.41±0.05$^{\#\#}$	0.23±0.04$^{\#\#\#}$

MTX: methotrexate, PCA: *p*-coumaric acid, MDA: malondialdehyde, TOS: total oxidant status, TAS: total antioxidant status, OSI: oxidative stress index, SOD: superoxide dismutase, TNF-α: tumor necrosis factor-alpha, CASP3: caspase-3.
P-values according to one-way ANOVA test, post-hoc Tukey test. Data were expressed as mean±SEM.
Compared with control group $^{*}p<0.05$, $^{**}p<0.01$ and $^{***}p<0.001$. Compared with MTX group $^{\#}p<0.05$, $^{\#\#}p<0.01$ and $^{\#\#\#}p<0.001$.

DISCUSSION

This study focused on elucidating the therapeutic potential of PCA in an *in vivo* model of MTX-induced pulmonary toxicity through biochemical mechanisms. Although the primary mechanism of MTX toxicity in the lungs remains to be fully elucidated, it is evident that OS, inflammation and apoptosis represent the principal mechanisms.[6,29] OS causes damage to nucleic acid, carbohydrate, lipid, protein and enzymes.[30] Lipids are biomolecules susceptible to OS, and increased ROS accelerate lipid peroxidation (LPO), resulting in the formation of various reactive aldehyde derivatives, including MDA.[20] The TOS, TAS and OSI have been employed with considerable frequency in recent years as straightforward and useful parameters for evaluating the overall OS degree in a biological sample.[31] SOD is an important cytoprotective enzyme that prevents the conversion of superoxide radicals to hydroxyl radicals.[32] Similar to previous literature[5,33,34], the findings indicated that MTX administration resulted in elevated LPO and OS levels in lung tissue and a diminished capacity of antioxidant system. Conversely, the administration of PCA following MTX has been observed to enhance the antioxidant system and to reduce LPO and OS levels dose-dependently. This observed improvement may be attributed to the potential of PCA as a phenolic acid to scavenge ROS and increase the endogenous cellular antioxidant capacity.[18,35] Similarly, the *in vivo* antioxidant activity of PCA has been previously determined in various experimental studies.[17,19,35,36]

Other mechanisms implicated in MTX-induced lung toxicity include inflammatory response and apoptosis.[5,18,37] Although inflammation is an acute adaptive response of the body to an invading attack, in the process of chronic inflammation, the sustained production of TNF-α increases tissue destruction, resulting in the activation of CASP3.[6] CASP3 activation is the main indicator that a cell has entered the irreversible apoptotic process.[29] In addition, high levels of MDA and TNF-α can induce apoptosis by activating CASP3.[5] Similar to previous literatures[5,8,13,29], findings showed that MTX administration triggered inflammatory and apoptotic processes. Conversely, the administration of PCA following MTX has been observed to suppressed these processes dose-dependently. It can be suggested that the potential antioxidant activity of PCA may be the main source of the improvement that was observed.[16,35] Similarly, the *in vivo* anti-inflammatory and anti-apoptotic activity of PCA has been previously determined in various experimental studies.[18,20,36,38]

CONCLUSION

Our findings provide new information that PCA may ameliorate MTX-associated pulmonary toxicity by suppressing OS, inflammatory, and apoptotic processes. However, this new information needs to be supported by more comprehensive analyzes in the future.

Acknowledgement

The authors wish to thank Sait Al and Ibrahim Aydin from Surgical Practice and Research Center of Karadeniz Technical University for professional assistance with the experimental studies.

Authorship contribution statement

Consept and desing: SD.

Acquisition of data: SD, NTA, EAD and AM.

Analysis and interpretation of data: SD, NTA, EAD, AM and YA.

Drafting of the manuscript: SD.

Critical revision of the manuscript for important intellectual content: YA.

Statistical analysis: AM.

Declaration of competing interest

None of the authors have potential conflicts of interest to be disclosed.

Ethical approval

This study was approved by the Local Animal Research Ethics Committee of Karadeniz Technical University (Protocol no: 2023/06) and performed according to the animal research reporting of in vivo experiments (ARRIVE) guidelines.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Funding

No financial support was received for this research.

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To Cite: Demir S, Turkmen Alemdar N, Ayazoglu Demir E, Mentese A, Aliyazicioglu Y. The Therapeutic Effect of p-Coumaric Acid on Lung Toxicity Induced by Methotrexate in Rats. Farabi Med J. 2024;3(2):57-62. doi:10.59518/farabimedj.1484155

Farabi Tıp Dergisi 3(2):63-65,2024
Farabi Medical Journal 3(2):63-65,2024
https://doi.org/10.59518/farabimedj.1419909

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Olgu Sunumu
Case Report

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Acute Abdominal Aortic Occlusion in a Paraplegic Patient: Case Report

Paraplejik Hastada Akut Abdominal Aort Oklüzyonu: Olgu Sunumu

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ABSTRACT

Acute total occlusion of the abdominal aorta is a rare and life-threatening clinical condition. Thrombus is the most common etiology. Associated morbidity and mortality remain high, with high rates of limb loss, acute kidney injury, rhabdomyolysis, and death. Diagnosis is based on the physical examination at the time of presentation. Findings include absent pulses in the lower extremities, pale and cold skin, and neurological deficits. With this case, we aimed to remind that aortic total occlusion, a rare diagnosis, can also be present in patients who present to the emergency department with paraplegia.

Keywords: Aortic occlusion, Paraplegia, Thrombosis

ÖZET

Abdominal aortada gelişen akut total oklüzyon oldukça nadir görülen ve hayatı tehdit eden klinik bir durumdur. Akut arteryel oklüzyon gelişen bir hastanın fizik muayenesinde genellikle etkilenen bölgede ağrı, soğukluk, solukluk, nabızsızlık ve parestezi tespit edilir. Bizim olgumuz daha nadir görülen bir semptom olan her iki bacakta kuvvet kaybı ile başvurdu. Genç yaşta olduğu ve ek hastalığı bulunmadığı halde kritik boyutta ve seviyede bir oklüzyonu mevcuttu. Bu olgu ile parapleji ile acil servise başvuran hastada nadir bir tanı olan aort total oklüzyonunun da olabileceğini hatırlatmayı amaçladık.

Anahtar Kelimeler: Aort oklüzyonu, Parapleji, Tromboz

Geliş Tarihi/Received Date: 15.01.2024 | *Kabul Tarihi/Accepted Date: 01.03.2024*

INTRODUCTION

Acute total occlusion of the abdominal aorta is a rare and life-threatening clinical condition.[1]Thrombus is the most common etiology. Associated morbidity and mortality remain high, with high rates of limb loss, acute kidney injury, rhabdomyolysis, and death.[2] Diagnosis is based on the physical examination at the time of presentation. Findings include absent pulses in the lower extremities, pale and cold skin, and neurological deficits. With this case, we aimed to remind that aortic total occlusion, a rare diagnosis, can also be present in patients who present to the emergency department with paraplegia.

CASE REPORT

A 41-year-old female patient applied to our emergency department with complaints of weakness and pain in both legs that started approximately 1 hour ago. The patient had no history of illness in his medical history. The patient had no clinical history of Buerger or vasculitis. She was a smoker. There was no family history of this disease. There was also no lipid metabolism disease. At the time of admission, blood pressure was measured as 142/96 mmHg, pulse 118/min, SpO2 96%, temperature 36.4 °C, and fingertip blood sugar 98 mg/dL. In the physical examination of the patient; Glasgow Coma Scale score is 15. Showed no signs of meningeal irritation, no pathological reflexes, and she was agitated and paraplegic. Pulses in both lower extremities could not be taken from the femoral to the distal end. Both legs were cold, the left leg being more pronounced.

In addition to laboratory tests, the patient was asked for thorax and abdomen computer tomography (CT) angiography and brain CT scans to rule out central events. In laboratory examinations, pH: 7.32, lactate: 8, WBC: 12.28, and other laboratory values other than these values were within normal limits. There were no acute pathological findings on the patient's brain CT. On CT angiography, the abdominal aorta appeared occluded starting from the infrarenal level (Figure-1,2,3). Pain control was achieved with narcotic analgesics. In cardiac evaluation, it was observed that there was no pathology that could be a source of embolism. The patient was consulted with cardiovascular surgery. Preoperative preparations were made and he was taken into emergency surgery by the cardiovascular surgeon. Although the diagnosis was made quite quickly, the patient's right leg was amputated from the mid-femur level.
It was thought that there was no myonephropathic metabolic syndrome. It is thought that the sole reason for amputation is recurrent thrombi due to poor vascular structure. The patient's treatment stage was evaluated together with the cardiovascular surgery consultant, and no endovascular treatment was planned for the patient. The patient, whose preoperative preparations were made, was taken to emergency embolectomy surgery by the cardiovascular surgeon in the third hour of her admission to the emergency room.

DISCUSSION

Complete occlusion of the abdominal aorta is a rare but potentially serious event.[2] The annual incidence of abdominal aortic occlusion is 2.7-5.0 cases per million people.[3] The most important etiology of abdominal aortic occlusion is atherosclerosis. Patients at highest risk for abdominal aortic occlusion include those with the same risk factors for atherosclerosis, such as smokers, those with hypertension, those with lipid metabolism disorders, and male patients.[4] On physical examination of a patient with acute arterial occlusion, pain, coldness, pallor, paralysis, pulselessness, and paresthesia are usually detected in the affected area.[5] Plegia at the time of presentation is a rarer condition. Apart from the classical symptoms, some symptoms such as abdominal pain, shortness of breath, nausea, fever and cough have also been reported in the literature.[4] It should not be forgotten in the differential diagnosis of patients whose presenting complaint is abdominal pain, flank pain, numbness in the extremities, and inability to walk. Since our case had pulselessness in the lower extremities, aortic dissection is also included in the differential diagnosis. However, chest pain or back pain was not predominant and CT angiography performed on the patient ruled out dissection. Likewise, saddle embolism was also excluded in CT angiography. The patient did not complain of abdominal pain. The reason for not having abdominal pain was interpreted as aortic occlusion starting from the distal SMA. Rapid diagnosis is important for mortality and morbidity. The mortality rate is mainly affected by the time of onset of clinical symptoms and the time until blood flow is restored.[6] In patients with suspected aortic occlusion in the preliminary diagnosis, evaluation should be done with CT angiography. After the diagnosis is made on imaging, urgent consultation with cardiac surgery is required. Treatment includes surgery, aspiration of thrombus, anticoagulant therapy, and heparinization.[7-9] The success of treatment is affected by the adequacy of collateral circulation and early intervention.

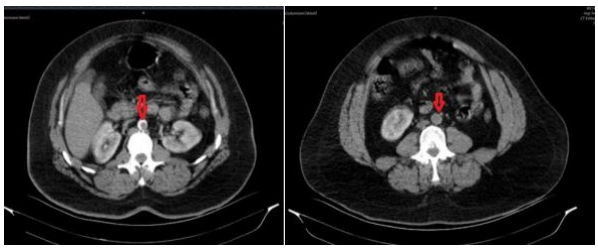

Figure 1. The abdominal aorta appears completely occluded starting from the infrarenal level

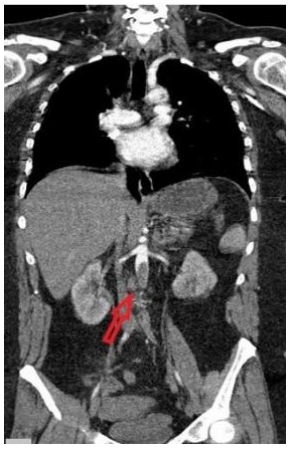

Figure 2. Coronal view of total occlusion

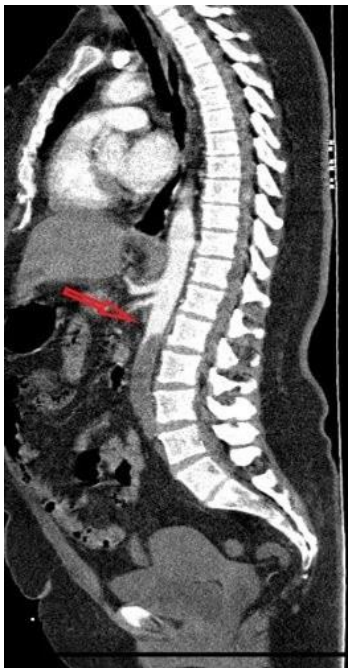

Figure 3. Sagittal view of total occlusion

CONCLUSION

As a result, it should not be thought that the patient presenting with neurological deficit may have only neurological pathology; it should also be kept in mind that there may be additional systemic pathologies.

Authorship contribution statement

Consept and desing: GY.
Acquisition of data: İFŞ, AEÖ
Analysis and interpretation of data: RA.
Drafting of the manuscript: GY, NB.
Critical revision of the manuscript for important intellectual content: NB.
Statistical analysis: NB.
Supervision: MU, ST.

Declaration of competing interest

None of the authors have potential conflicts of interest to be disclosed.

Ethical approval

Written informed consent was obtained from the patient who participated in this case.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Funding

No financial support was received for this research.

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To Cite: Yilmaz G, Simsek IF, Aytekin R, Ozer AE, Baykan N. Acute Abdominal Aorta Occlusion Presenting with Paraplegia: A Case Report. Farabi Med J. 2024;3(2):63-65. doi:10.59518/farabimedj.1419909

Farabi Tıp Dergisi 3(2):66-67,2024
Farabi Medical Journal 3(2):66-67,2024
https://doi.org/10.59518/farabimedj.1347185

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Long-Term Cardiac Effects After Recovery in SARS-CoV-2 Infection

SARS-CoV-2 Enfeksiyonunda İyileşme Sonrası Uzun Süreli Kardiyak Etkiler

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Dear editor;

SARS-CoV-2 can be transmitted from person to person through close contact with infected patients and inhalation of aerosols. Respiratory transmission has been shown to be highly lethal and the predominant way to spread the disease. Most people infected with SARS-CoV-2 are asymptomatic or show mild symptoms, most likely due to a good immune response that can control disease progression.[1,2] The rapid spread of the disease resulted in many infected patients, although it was mostly good. It resulted in an overburden on the healthcare system. It enabled the prioritization of patients according to their clinical severity and the development of triage systems.[2,3]

As SARS-CoV-2 infection is often discussed in the pulmonary context, various cardiac complications also occur in patients. Biochemical evidence of myocardial involvement elicited by high troponin has been reported in approximately 20-30% of hospitalized SARS-CoV-2 infected patients. Heart damage is mainly due to viral systemic effects, with direct viral cytotoxicity.[4] Disease severity is associated with patients' core comorbidities, including advanced age, diabetes, hypertension, obesity, and immunocompromised status. As the severity of the disease increases, the probability of cardiac injury increases, and therefore more serious cardiac complications may occur, ranging from arrhythmias to myocarditis, new-onset cardiomyopathy, myocardial infarction, and thromboembolism. These cardiac conditions, reported to have an incidence of 20-40% in patients, indicate a significantly increased morbidity and mortality when associated with SARS-CoV-2 infection.[5]

Most cardiac complications associated with acute infection complicate the clinical course of the patient and are associated with high morbidity and mortality. Patients who survive post-infection are at risk for long-term cardiac complications. A recent study evaluated the 1-year burden of cardiovascular disease in more than 150,000 SARS-CoV-2 infected patients. The observed increased incidence of arrhythmias, ischemic and non-ischemic cardiomyopathy, pericarditis, myocarditis, and thromboembolic disease suggests a significant risk of cardiovascular disease in SARS-CoV-2 infected survivors.[6] The long-term effects of the pandemic are still being reported in new clinical entities. Our knowledge of the long-term effects of coronaviruses is limited to SARS-CoV-1 infection. Because the SARS-CoV-1 virus uses the same cell entry receptors as SARS-CoV-2, cardiac complications appear like those seen with SARS-CoV-1.

Geliş Tarihi/Received Date: 21.08.2023 | *Kabul Tarihi/Accepted Date:* 27.08.2023

There are long-term follow-up studies suggesting an increased risk of cardiovascular disease, including myocardial infarction, coronary artery disease, atherosclerosis, and hyperlipidemia. In addition, an improvement in diastolic and systolic functions is observed in the follow-up of patients with arrhythmias, cardiomegaly and hypotension observed in acute infection with SARS-CoV-1. Based on SARS-CoV-1 studies, it is attempted to predict long-term cardiac complications from SARS-CoV-2. Symptoms such as cardiomyopathy may be reversible 30-90 days after infection. However, it is assumed that the risk for atherosclerosis and its complications increases markedly even years after infection.[7] A German study evaluated 100 SARS-CoV-2 infected patients who had recovered from infection at least 2 weeks after diagnosis with cMRI and showed cardiac involvement and ongoing myocardial inflammation in 78% and 60% of these patients, respectively.[8]

Long-term effects for patients with SARS-CoV-2 associated myocarditis remain to be reported. However, in the setting of viral myocarditis, it is important to consider complications such as atrial and ventricular arrhythmias and non-ischemic cardiomyopathy that do not improve despite optimal medical therapy. Case series have described autopsies of young adults who have found myocarditis to be the culprit with sudden cardiac death. Ventricular arrhythmias are implicated in sudden cardiac death and therefore high-risk patients should be closely monitored. Symptoms of prolonged SARS-CoV-2 infection include shortness of breath, palpitations, chest discomfort, fatigue, orthostatic intolerance, and a few other nonspecific symptoms. These symptoms together with orthostatic tachycardia are called postural orthostatic tachycardia syndrome (POTS) after SARS-CoV-2 infection.[9] There are several case reports describing this clinical condition. POTS is a syndrome with low awareness and familiarity in the follow-up of patients after SARS-CoV-2 infection. It also has underdiagnosis rates in patients with asymptomatic SARS-CoV-2 infection.[10] Further investigations are still ongoing to identify long-term cardiac and noncardiac sequelae.

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To Cite: Ozdemir S, Algin A. Long-Term Cardiac Effects After Recovery in SARS-CoV-2 Infection. Farabi Med J. 2024;3(2):66-67. doi:10.59518/farabimedj.1347185

Farabi Tıp Dergisi 3(2):68-70,2024
Farabi Medical Journal 3(2):68-70,2024
https://doi.org/10.59518/farabimedj.1436648

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Eski Bir Farmakolojik Ajan, En Yeni Antidepresan: Gepiron

An Old Pharmacological Agent, the Newest Antidepressant: Gepirone

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Günümüzde, depresyon gibi yaygın ruh sağlığı sorunlarına karşı etkili tedavilerin önemi giderek artmaktadır. Mevcut literatür ışığında en güncel antidepresan Gepiron ER olmuştur. Birçok antidepresan ilaç, cinsel işlev bozuklukları gibi yan etkilerle ilişkilendirilmiştir, bu da tedaviye uyumda ve hastaların yaşam kalitesinde önemli bir azalmaya neden olabilir. Bu bağlamda, Gepiron ER' nin diğer antidepresanlardan ayrılan en önemli özelliği, cinsel işlev bozukluklarına sebep olmamasıdır. Bu özellik, hastaların tedaviye uyumunu artırabilir ve yaşam kalitelerini olumlu yönde etkileyebilir. Günde bir kez uygulanabilen, oral yoldan alınan ve seçici bir 5HT-1A reseptör agonisti olan Gepiron HCL uzatılmış salınım formülü (Gepiron ER; EXXUA™), psikiyatrik bozuklukların tedavisi için Fabre-Kramer Pharmaceuticals, Inc. tarafından geliştirilmiştir. Eylül 2023'te, Gepiron ER, ABD'de yetişkinlerde majör depresif bozukluk (MDB) tedavisi için onaylanmıştır. Gepiron, 1986 yılında Bristol-Myers Squibb tarafından geliştirildi, ancak 1993'te Fabre-Kramer'e lisans verildi.[1] Gepiron ER'nin onayı, FDA'ya yaklaşık yirmi yıl süren başvuruların ardından geldi. FDA 2004, 2007 ve 2015 yıllarında ürünün başvurusunu, etkili olduğuna dair yeterli kanıt bulunmadığını düşünmeleri nedeniyle reddetmişti. Gepiron ER, iki yeni klinik araştırmadan elde edilen verilere dayanarak uzun süren bir süreç sonrasında FDA onayını aldı.[2] Gepiron MDB tedavisinde 5-HT-1A reseptörlerinde kısmi agonist etki gösteren FDA onaylı ilk ilaç olmuştur. Gepiron; Buspiron, Tandospiron ve Perospiron gibi ilaçlarla birlikte Azapiron grubunda yer alan bir psikotrop ilaçtır. Gepiron, kimyasal yapısal bir benzerlik taşıdığı Buspiron gibi, 5-HT-1A reseptörlerinde kısmi agonist olarak etki gösterir.[3] Gepiron da mirtazapin gibi benzer α2 antagonistik aktiviteye sahip olan 1-PP'ye (1-pirimidinilpiperazin) metabolize edilir. Gepiron'un metabolize olduğu birinci geçiş metaboliti 1-PP, mirtazapine'e benzer şekilde α2 antagonistik aktivite gösterir. Bu durum, Gepiron'un vücutta metabolize olduğunda, oluşan metabolitin mirtazapine gibi α2 adrenerjik reseptörleri bloke etme yeteneği olduğunu ifade eder. Bu etki, Gepiron'un terapötik etkilerini açıklamaya yardımcı olabilir, çünkü α2 antagonistik aktivite, anksiyolitik ve antidepresan etkilerin yanı sıra uyku düzenleyici etkiler de sergileyebilir. Bu nedenle, Gepiron'un etkileri üzerindeki anlaşılması gereken bir faktördür.[4] Buspiron yaygın anksiyete bozukluğu için 1986 yılında onaylanırken Gepiron MDB için 2023 yılında onaylanmıştır. Bununla birlikte, buspiron, MDB'de SSRI'ların etkinliğini arttırmaktadır. Aynı zamanda SSRI ilişkili cinsel işlev bozukluğu ve bruksizmi önlemede yardımcı olmak için başarıyla kullanılmıştır.[5]

Geliş Tarihi/Received Date: 13.02.2024 | *Kabul Tarihi/Accepted Date:* 01.04.2024

Gepiron'un diğer antidepresanlara göre kendisini ön plana çıkaran en önemli özelliği cinsel işlev bozukluğuna sebep olmamasıdır.[6] Gepiron'un etkinliliği, yetişkinlerde (18 ila 69 yaş arası) yapılan, MDB tanı kriterlerini karşılayan sekiz haftalık iki randomize, çift-kör, plasebo kontrollü, doz çalışmasının sonuçlarına dayanmaktadır. Her iki çalışmada da Gepiron' un günlük dozu kademeli olarak 72,6 mg'ye kadar titre edildi. Her iki çalışmanın birincil etkililik ölçüsü, Hamilton Depresyon Derecelendirme Ölçeği kullanılarak skorun başlangıçtan sekiz haftaya kadar değişmesiydi. Her iki çalışmada da Gepiron ER alan hastaların skorlarında plasebo alanlara kıyasla istatistiksel olarak anlamlı düzeyde daha fazla iyileşme görüldü. Gepiron ER tedavisi, ABD'de yürütülen 8 haftalık, çift kör, plasebo kontrollü, iki ayrı faz 3 çalışmasında MDB'li yetişkin hastalarda depresyon semptomlarını azaltmada etkili olmuştur. 8. haftada, Gepiron tedavisi verilen grupta Hamilton Depresyon Derecelendirme Ölçeği (HAMD-17) toplam skorunda başlangıca göre anlamlı derecede daha büyük bir iyileşme görüldü.[7,8] Avrupa'da yürütülen bir faz 3 çalışmada, Gepiron ER, 8-12 haftalık açık etiketli Gepiron ER tedavisinden sonra remisyona giren MDB'li yetişkin hastalarda nüksetmenin önlenmesinde etkili olmuştur.[9]

Klinik uygulamada MDB için Gepiron ER'nin önerilen başlangıç dozu, günde yaklaşık olarak aynı saatte yemekle birlikte günde bir kez 18,2 mg'dır. Klinik yanıt ve tolere edilebilirliğe bağlı olarak dozaj, tedavinin 4. gününde günde bir kez 36.3 mg'a yükseltilebilir, ayrıca 7. günden sonra günde bir kez 54.5 mg'a ve ilave bir hafta sonra günde bir kez 72.6 mg'a titre edilebilir. Gepiron ER' nin önerilen maksimum günlük dozu günde bir kez 72.6 mg'dır.[1] Geriatrik hastalarda, kreatinin klerensi < 50 mL/dak olanlarda ve orta derecede karaciğer yetmezliği olanlarda (Child-Pugh B), önerilen başlangıç dozu günde bir kez 18,2 mg'dır. Klinik cevaba ve tolere edilebilirliğe bağlı olarak dozaj, 7. günden sonra günde bir kez 36,3 mg'lık maksimum önerilen doza yükseltilebilir. Kreatinin klerensi ≥ 50 mL/dak olan veya hafif karaciğer yetmezliği olan (Child-Pugh A) hastalarda doz ayarlaması gerekli değildir.[1] Gepiron QT aralığını uzatır ve konjenital uzun QT sendromlu bireylerde ve başlangıçta uzamış QTc aralığı >450 milisaniye olan hastalarda kontrendikedir. Gepiron ayrıca şiddetli (Child-Pugh C) karaciğer yetmezliği olan hastalarda ve Gepiron plazma konsantrasyonlarının artması nedeniyle güçlü CYP3A4 inhibitörleri alan hastalarda kontrendikedir.[1] Tedavi sırasında QTc ≥ 450 milisaniye gelişirse Gepiron ER dozajı artırılmamalıdır. Orta dereceli CYP3A4 inhibitörleriyle birlikte uygulandığında Gepiron ER dozajı %50 azaltılmalıdır. Eş zamanlı CYP3A4 inhibitörleri veya QTc aralığını uzatan ilaçlar kullanan hastalarda, tedavi sırasında QTc≥450 milisaniye gelişen hastalarda ve torsade de pointes gelişme riski önemli olan hastalarda EKG izlemesi daha sık gereklidir. Gepiron ER tedavisine başlamadan önce elektrolit anormallikleri düzeltilmelidir. Gepiron plazma konsantrasyonlarının azalması nedeniyle güçlü CYP3A4 indükleyicileri alan hastalarda Gepiron ER'nin eş zamanlı kullanımından kaçınılmalıdır.[1] Tüm antidepresanlar gibi Gepiron da 25 yaşın altındaki kişilerde intihar düşüncesini aktive etme konusunda kara kutu uyarısına sahiptir. Serotonin sendromu riski nedeniyle MAOI'lerle kombine edilmemelidir. Gepiron bipolar duygudurum bozukluğu hastalarında manik kayma riski nedeniyle önerilmez.[7] Yapılan klinik çalışmalarda en sık görülen yan etkiler baş dönmesi, bulantı, baş ağrısı, uyku hali, uykusuzluk, ishal, üst solunum yolu enfeksiyonu, ağız kuruluğu, kusma, karın ağrısı, hazımsızlık ve iştah artışıdır. Klinik çalışmalarda Gepiron ER tedavisi, SSRI'larda yaygın olarak görülen olumsuz olaylar olan cinsel işlev bozukluğu ve kilo alımı ile ilişkili değildi.[1]

Sonuç olarak, Gepiron, uzun süren klinik çalışmalar sonrasında FDA tarafından MDB tedavisinde onay almış en yeni antidepresan özelliğini taşımaktadır. Gepiron ER, MDB tedavisinde yeni bir seçenek sunarak bu alandaki terapötik seçenekleri çeşitlendirmiş bulunuyor. Yapılan çalışmalar ve klinik deneyimler, Gepiron ER'nin etkinliğini ve güvenilirliğini desteklemekte, bu da MDB hastaları için umut verici bir gelişmedir. Ancak, tıbbi araştırmaların sürekli olarak izlenmesi ve gelişmelerin takip edilmesi gerekmektedir. Bu, hem hastaların en iyi tedaviye erişimini sağlamak hem de sağlık uzmanlarının en güncel bilgilere dayanarak tedavi seçeneklerini belirlemesine yardımcı olur.[10] Gepiron ER gibi yenilikçi ilaçlar, MDB tedavisindeki ilerlemelerin sürdürülmesinde önemli bir rol oynamaktadır. Bu nedenle, tıbbi toplumun, araştırmacıların ve klinik uzmanların bu alandaki gelişmeleri yakından takip etmesi önemlidir. Bu yeni ilaçla ilgili klinik deneyim arttıkça, literatüre daha fazla klinik veri aktarımı olacaktır. Gepiron ER' nin etkinliği ve güvenilirliği konusunda daha fazla bilgi edinildikçe, depresyon tedavisindeki rolü daha iyi anlaşılacak ve hastalar için daha etkili bir tedavi seçeneği olabilecektir.

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To Cite: Sonmez D. An Old Pharmacological Agent, The Newest Antidepressant: Gepirone. Farabi Med J. 2024;3(2):68-70. doi:10.59518/farabimedj.1436648