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Book section
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Single authored book
Akdeniz YS. Health economics: fundamentals of funds. Istanbul: Kara Tren Yayınevi; 2019.
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Cakmak F, Ipekci A, editors. Mental health care for elderly people. Istanbul: Fatih Yayınevi; 2019.
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Berberoglu D, Kocman AY, Cakmak K, Kanbakan A. Cannabinoids and pain. In: Ikızceli I, editor. Proceedings of the 10th World Congress on Emergency; 2020Aug 17-22; Istanbul, IASP Press;2020. p. 437-68.
Thesis
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U.S. Department of Health and Human Services: The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2006.
http://www.cdc.gov/tobacco/data_statistics/sgr/2006/pdfs/what-is-shs.pdf. Accessed 30 Nov 2014.

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REVIEW

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Pediyatrik Hastada Nedeni Bilinmeyen Ateş

Fever of Unknown Origin in a Pediatric Patient

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ABSTRACT

Fever is a common clinical syndrome in pediatric patients. Although fever of unknown origin has a clear definition in adults, there is no consensus on this definition in the pediatric age group. There are differences between studies, and the literature on this subject is also limited. In this study, we aimed to review the existing literature in terms of fever of unknown origin in the pediatric age group.

ÖZET

Pediyatrik hastalarda ateş sık karşılaşılan bir klinik sendromdur. Nedeni bilinmeyen ateşin ise erişkinde net tanımlaması olmasına rağmen, çocuk yaş grubunda bu tanım konusunda fikir birliği yoktur. Çalışmalar arasında farklılıklar mevcut olup, bu konudaki literatür de sınırlıdır. Biz de bu çalışmada mevcut literatürü çocuk yaş grubunda nedeni bilinmeyen ateş açısından derlemeyi amaçladık.

Keywords:
Child
Fever
Fever of unknown origin

Anahtar Kelimeler:
Çocuk
Ateş
Nedeni bilinmeyen ateş

GİRİŞ

Ateş yüksekliği kendi başına bir hastalık olmayıp, sık karşılaşılan bir semptomdur. Ateş, aslında vücudun savunma mekanizmalarındandır (1). Çocukluk çağında ateşe sık rastlanmakta; neredeyse tüm çocuklar ateşi deneyimlemektedirler (2,3). Ateş değerleri ölçülen bölgeye göre değişkenlik göstermektedir. Vücut ısısının; oral yoldan 37,8°C, aksiller yoldan 37,2°C, rektal ve timpanik yoldan 38 °C'nin üzerinde olması ateş olarak tanımlanmaktadır (4).

Ateş gerek erişkinde gerek çocukluk çağında en sık enfeksiyonlara bağlı olabileceği gibi, aşı, doku hasarı, vb gibi çeşitli nedenlerle vücut ısısını düzenleyen hipotalamustaki termoregülatör merkezdeki dengenin bozulması ile ortaya çıkan tıbbi bir durumdur (1).

Biz de bu derleme çalışmasında çocukluk çağında nedeni bilinmeyen ateş etyolojisinin literatür eşliğinde derlemeyi ve bu konuda hekimlere yol göstermeyi amaçladık.

Ateş mekanizması

Mikroorganizmalar veya bileşenleri, toksinler, ilaçlar, maligniteler, inflamasyona neden olabilecek durumlar gibi ateşe neden olabilecek etkenler ile karşılaşıldığında, hipotalamus ayar noktasını normal değerlerin üstüne çeker ve bu durum vücut ısısının artmasına neden olur (4). Vücut ısısının yükselmesinde aracılık eden moleküllere pirojen moleküller denmektedir. Bu moleküller; ekzojen ve endojen pirojenler olarak sınıflandırılır.

a. Ekzojen pirojenler: Mikroorganizmalara ait bileşenler (gram pozitif bakterilerdeki peptidoglikan tabaka veya gram negatif bakterilerdeki lipopolisakkarit yapılar), mikroorganizmalara ait toksinler (endotoksinler, enterotoksinler), aktive kompleman komponentleri, antijenantikor kompleksleri veya çeşitli ilaçlar, kimyasal toksinler gibi maddeler ekzojen pirojenlere örnektir (5).

b. Endojen pirojenler: Konakçıda ekzojen uyaranlara tepki olarak sentezlenen peptidlere endojen pirojenler denir (6). Endotoksinler ve ekzotoksinler, sitokinlerin en güçlü bakteriyel indükleyicileri arasındadır. Enfeksiyöz süreçler sırasında, tümör nekroz faktörü (TNF), interlökin1β (IL1β), gama interferon (IFNy) ve kemokinler dahil inflamatuar sitokinlerin üretimi, enfeksiyona karşı doğuştan gelen bağışıklık tepkisini düzenler (7).

Ateşin nedenleri

Erişkinlerde olduğu gibi çocuklarda da ateşin bildirilmiş en sık nedeni enfeksiyonlardır (8,9). Çocuklardaki ateş yüksekliği ebeveynleri çocuk acile getiren nedenler en sık hastalık gruplarından biridir (9,10). Günümüzde, tıp alanındaki tüm gelişmelere rağmen ateş şikâyeti ile getirilen çocuklarda sadece % 13–20'sinde ateş odağı saptanabilmektedir.

Nedeni bilinmeyen ateş

Nedeni bilinmeyen ateş (NBA), ilk olarak 1961'de Petersdorf ve Beeson tarafından, en az üç haftalık bir süre boyunca en az üç kez 38,3°C'yi aşan ve bir haftalık yatarak tedavi incelemesine rağmen tanı konmayan bir hastalık durumu olarak tanımlanmıştır. NBA prevalansı bilinmemektedir (11).

NBA etyolojisi değişken olup, en sık neden enfeksiyonlar olsa da maligniteden romatolojik hastalıklara kadar birçok etiyolojik faktör sorumlu olabilir (12). Erişkinlerde yapılan

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çalışmalarda enfeksiyonlar %50 oranla NBA'nın en sık nedeni olarak bildirilmektedir. Batı ülkelerinden yapılan çalışmalarda enfeksiyon hastalıklarının başında özellikle intraabdominal apseler, tüberküloz, endokardit ve sistemik viral infeksiyon gelmektedir (13,14). Ülkemizden yapılan 154 erişkin NBA hastasının değerlendirildiği bir çalışmada (15) en sık görülen enfeksiyoz etyolojiler tüberküloz (%13,6) ve sitomegalovirüs (CMV) enfeksiyonu (%3,2) idi. Erişkin Still hastalığı (%13,6) ve hematolojik maligniteler (%7,8) en sık görülen enfeksiyon dışı sebepler olarak bildirilmiştir.

Çocuklarda nedeni bilinmeyen ateş

Çocuklarda nedeni bilinmeyen ateş tanımı ile ilgili farklı tanımlamalar mevcuttur. Erişkindeki klasik tanım olarak, en az üç haftalık bir süre boyunca en az üç kez 38,3°C'yi aşan ve bir haftalık yatarak tedavi incelemesine rağmen tanı konmayan bir hastalık durumu olarak tanımlanan NBA, çocuklarda bazı araştırmacılar tarafından 2 haftalık ateş yüksekliği olarak tanımlanır. Fikir birliği süre bakımından net oluşmamıştır (15-19).

Erişkinlerde NBA'te altta yatan tanıların, en büyük oranını enfeksiyonlar oluşturmasına rağmen (%35), çocuklarda enfeksiyoz nedenler %50'den fazlasını oluşturmaktadır. Romatolojik hastalıklar ve maligniteler ise yetişkinlerde çocuklara göre daha sık etiyolojik nedenlerdir (16-19). Ayrıca çocuk NBA olgularının nerdeyse %25'inin tanısı konulmadan ateşi düşmektedir (17-19).

Çocuklarda ateşin nedeni iyi bir fizik muayene ve anamnezle genelde kolayca bulunabilir. Erişkinlere benzer şekilde çocuklarda da ateşin nedenleri enfeksiyonlar, kollagen doku hastalıkları, maligniteler, metabolik hastalıklar (hipertiroidizm), kardiyovasküler ve gastrointestinal sistem hastalıkları, gibi geniş bir yelpazede olabilir (20).

Çocuklarda NBA'in en yaygın nedenleri enfeksiyonlar, bağ dokusu bozuklukları ve neoplazmalardır. En sık görülen bulaşıcı hastalıklar, salmonelloz, tüberküloz, sıtma ve riketsiyal hastalıklardır. Juvenil romatizmal artrit, sıklıkla NBA ile ilişkili bağ dokusu hastalığıdır. Malignite, çocuklarda NBA etiyolojisinde sorumlu üçüncü en büyük gruptur (17-20).

2010 yılında yapılan bir meta analiz çalışmasına, 1638 çocuğu tanımlayan, dahil edilme kriterlerini karşılayan 18 çalışma incelenmiştir. Yayınlandığı tarihteki tanı 93 çocuk için (%6) malignite, 150 çocuk için (%9) kollajen vasküler hastalık, 179 çocuk için (%11) çeşitli bulaşıcı olmayan durumlar, 832 çocuk için (%51) enfeksiyoz nedenler olarak bildirilmiştir ve % 23 çocuğa ise tanı konulamamıştır. Gelişmekte olan ülkelerde bruselloz, tüberküloz ve tifo ateşi, gelişmiş ülkelerde osteomiyelit, tüberküloz ve Bartonelloz ve her ikisinde de idrar yolu enfeksiyonları ortak tanılar olarak saptanmıştır. Bakteriyel enfeksiyonlar, tüm enfeksiyoz nedenlerin %59'unu oluşturmuştu. Tanı konulmayan çocukların çoğunda hiçbir sekel kalmadan iyileşme olduğu saptanmıştı (18).

1970'lerde pediyatrik NBA ile ilgili 3 ufuk açıcı yayın, ateşin altında yatan nedenin %68-%88'inin tanımlanabileceğini ortaya koymuştur. %29-52'sinin bulaşıcı, %11-20'sinin otoimmün, %12-32'sinin teşhis konmamış ve %6-%13'sinin onkolojik nedenler olduğu bildirilmiştir (21-23). Ancak 1990'larda gerçekleştirilen daha küçük çalışmalar oldukça değişken bulgulara sahipti ve bu çalışmalar NBA'in %67'sine kadarının teşhis edilmediğini savunmuştur (24,25). Antoon ve ark. tarafından hastanede yatan çocuklarda NBA etiyolojisinin araştırıldığı 2018 yılında Amerika Birleşik Devletleri'nde (ABD) yapılan bir çalışmada, hastaların %86,4'ünde tanımlanabilir bir etiyoloji bulunmuştur. Genel olarak, tanımlanan etiyolojiler %41,2 enfeksiyoz, %27,5 otoimmün, %17,7 onkolojik ve %13,7 diğer veya tanı konulamayan nedenler olarak bildirilmiştir. Bu çalışmada NBA >7 gün süreyle 38,0°C ateş olarak tanımlamış olmasına rağmen, NBA süresi 2-3 hafta olan çalışmalarla karşılaştırıldığında NBA nedenlerinde diğer çalışmalarla kıyasla büyük bir değişiklik saptanmadığı bildirilmiştir (26). Bu çalışmada, tanılar arasında 1970'lerin yayınlarında görülmeyen tanılar arasında Kawasaki hastalığı, hemofagositik lenfohistiyositoz ve makrofaj aktivasyon sendromu, diskit, Ehrlichiosis, Metapneumovirus ve Clostridium difficile koliti gibi tanılar bildirilmiştir. Ayrıca, 1970 çalışmalarında bulunan tüberküloz ve sıtma gibi hastalıklar bu çalışmada saptanmamış olup, bunun muhtemelen nedeninin ABD'nde bu hastalıkların insidansının azalmasını ve bu hastalıkların erken teşhisinin artması olduğu sonucuna varılmıştır. Tanıların önemli bir kısmı (%24) köken olarak iyi huylu olup, ya viral ya da bilinmeyen etiyoloji kendiliğinden çözülmüştür (26).

Ülkemizden yapılan 30 çocuk NBA olgusunun değerlendirildiği bir çalışmada (27), ateş nedeni olarak 14 (%46,6) hastada enfeksiyonlar, 8 (%26,7) hastada kollajen vasküler hastalık, 5 (%16,7) hastada malign hastalık, 1 (%3,3) hastada diğer hastalık grubundan hastalık saptanmışken, 2 (%6,6) hastada ateşin nedeni belirlenememiştir. Başka bir çalışmada ise, erişkinlerde ve çocuklarda NBA ateşin etyolojisinde Leishmania, tüberküloz ve brusellozis enfeksiyon hastalıklarından en sık tespit edilen neden iken juvenil romatoid artrit ve akut lenfoblastik lösemi enfeksiyon dışı en sık nedenler olarak bildirilmiştir (28).

Kene kaynaklı hastalıklar da NBA'in önemli bir nedenidir. ABD'nde genellikle kayalık dağlar benekli ateşi, Ehrlichiosis, tularemi, Lyme hastalığı ve kene kaynaklı tekrarlayan ateşi de NBA etyolojisinde sorumlu enfeksiyoz nedenler arasında bildirilmiştir (29-31).

Çocuklarda NBA'in tanısal yaklaşımı, incelemelerle desteklenen ayrıntılı öykü ve muayeneyi içerir. Yaş, temas öyküsü, vahşi hayvanlara ve ilaçlara maruz kalma not edilmelidir. Muayene genel görünüm dışında terleme, kızarıklık, bademcik iltihabı, sinüzit ve lenf bezi büyümesi varlığını da içermelidir. Karın hassasiyeti ve hepato splenomegali gibi diğer belirtiler aranmalıdır. Kaslar ve kemikler bağ dokusu bozuklukları açısından dikkatle incelenmelidir (29-32).

Ateşli çocukların değerlendirilmesinde mevcut olan en faydalı bilgi parçalarından biri serolojik inflamatuar belirteçlerdir. Ateşli çocuklarda bu belirteçlerdeki belirgin yükselme potansiyel olarak ciddi bir inflamatuar süreci gösterir. Tam kan sayımı, mutlak nötrofil sayısı, kan hücrelerinin dağılımı, trombosit sayısı, eritrosit

sedimantasyon hızı (ESR), C-reaktif protein (CRP) ve prokalsitonin gibi inflamasyon ölçümleri tanıda yardımcı olabilir (16,33). Ancak bu testlerin hafif veya orta yükselmeleri ile ilişkili yüksek duyarlılık ve düşük özgüllük mevcuttur. NBA'te çoğu nedende inflamatuar kaskadın aktivasyonu nedeniyle bu değerlerde yükselme olabilir (26).

Ayrıca mikrobiyolojik kültürler de oldukça önemlidir. Yumuşak doku enfeksiyonları, idrar yolu enfeksiyonları ve zatürree gibi yaygın yatan pediatrik hastalıklarda kan kültürlerinin kullanılmadığına dair artan bir literatür bilgisi mevcuttur (34-36).

Radyolojik görüntüleme, NBA'in teşhisinde faydalı olabilir (29-32). Ancak, görüntüleme ve tarama prosedürlerinin vakaların <%25'inde pozitif bulgulara sahip olduğunu ve sıklıkla NBA teşhisine katkıda bulunmadığını savunan çalışmacılar da vardır (26).

Geç tanı konulan ateş etiyolojisinin, nöbetler, miyokardit, solunum yetmezliği, koma, böbrek yetmezliği ve ölüm gibi ciddi komplikasyonlara neden olabileceği göz önüne alındığında, erken teşhis önemlidir. Buna ek olarak, kesin tanı konulmayan uzun süreli ateş, sıklıkla kapsamlı bir tıbbi muayene ve tedaviye yol açar. Bu durum, istenmeyen ilaç reaksiyonu, radyasyona maruz kalma ve hastane kaynaklı enfeksiyonlar gibi riskleri artırarak hastayı daha da tehlikeye atar (29-32). Ayrıca, NBA varlığında, hastalığın teşhisini engelleyebilecekleri için antimikrobiyal ajanların denemeleri yapılmamalıdır (29-32).

Erişkinlerde NBA tanımı net yapılmasına rağmen, pediyatride NBA konusu oldukça belirsizdir ve hala zorlu bir tanı ikilemini temsil etmektedir. Mevcut verilerin çoğu, ülke çapında herhangi bir yaştaki hasta kohortlarıyla sınırlıdır. Bir tanı koymadaki en büyük zorluk, belirli bozuklukları klinik olarak tanınabilir kılan karakteristik özelliklerin yokluğu veya belirsiz olmasıdır. Gerçekte hiçbir tanı algoritması mevcut değildir ve klinisyenler tek bir hastanın çok dikkatli bir şekilde adım adım değerlendirilmesine güvenmelidir. Laboratuvar testleri veya basit görüntüleme prosedürleri NBA'in kökenini ayırt edemediğinde, invaziv tanı tekniklerine duyulan ihtiyaç yakından dikkate alınmalıdır. Makul bir açıklaması olmayan ve hiçbir lokalizasyon belirtisi olmayan ateşler, genellikle çocuklarda olağandışı veya atipik bir patern gösterme eğiliminde olan farklı yaygın hastalıkları gizler (36).

Özellikle de erişkinlerde yoğun bakım yatışları gibi artmış sağlık hizmetleri nedeniyle sağlık bakımı ilişkili enfeksiyonlar veya atipik ateş nedenleri de iyi tanımlanmıştır (37-39). Çocuklar ile ilgili benzer çalışmalara rastlanamadı.

Sonuç olarak, pediyatrik NBA arkasındaki başlıca nedenler enfeksiyonlar olmaya devam etmekte olup, bunu kollajen vasküler hastalıklar ve neoplastik bozukluklar izlemektedir, otoinflamatuar sendromlar, ilaç ateşi ve yapay ateş olasılığı da dikkate alınmalıdır. Bu konuda gözlemsel, ileriye dönük çalışmalara özellikle ülkemiz için ihtiyaç duyulmaktadır.

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ORIGINAL ARTICLE

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Evaluation of Central Venous Catheters Inserted in the Emergency Service

Acil Serviste Takılan Santral Venöz Kateterlerin Değerlendirilmesi

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ABSTRACT

Objective: *In our study, we evaluated central venous catheter procedures performed by Adnan Menderes University, Department of Emergency Medicine in the emergency room and emergency intensive care units. We planned to investigate performing central venous catheter application with ultrasound guidance and the rate of bleeding complications in patients using anticoagulants or antiplatelet.*

Material and Method: *Between 15.11.2018-15.10.2019, central venous catheter application was performed 178 cases over the age of 18 and non-pregnant were included. Research data were evaluated by using SPSS 21.0 statistics program.*

Results: *A Central venous catheter procedure was performed in 78.7% of the patients with ultrasound guidance. 36.5% of the patients had a history of anticoagulant or antiplatelet drug use. The most common complications in our patients were ventricular dysrhythmia and subcutaneous hematoma.*

Conclusion: *In conclusion, when looking at the relationship between gender, anticoagulant and/or antiplatelet drug use, preferred vein and ultrasound use during the procedure, and complication status, no statistically significant results were found.*

ÖZET

Amaç: *Çalışmamızda Adnan Menderes Üniversitesi Acil Tıp Anabilim Dalı tarafından acil servis ve acil yoğun bakım ünitelerinde yapılan santral venöz kateter işlemlerini değerlendirdik. Antikoagülan veya antiplatelet ilaç kullanan hastalarda ultrason eşliğinde santral venöz kateter uygulaması yapmayı ve kanama komplikasyon oranlarını araştırmayı planladık.*

Gereç ve Yöntem: *15.11.2018-15.10.2019 tarihleri arasında santral venöz kateter uygulaması yapılmış 18 yaş üstü ve gebe olmayan 178 olgu dahil edildi. Araştırma verileri SPSS 21.0 istatistik programı kullanılarak değerlendirilmiştir.*

Bulgular: *Hastaların %78,7'sine ultrason eşliğinde santral venöz kateter işlemi uygulandı. Hastaların %36.5'inde antikoagülan veya antitrombosit ilaç kullanım öyküsü vardı. Hastalarımızda en sık görülen komplikasyonlar ventriküler disritmi ve cilt altı hematomdu.*

Sonuç: *Sonuç olarak cinsiyet, antikoagülan ve/veya antitrombosit ilaç kullanımı, işlem sırasında tercih edilen damar ve ultrason kullanımı ile komplikasyon durumu arasındaki ilişkiye bakıldığında istatistiksel olarak anlamlı bir sonuç bulunamadı.*

Keywords:
Central Venous Catheter
Emergency Medicine
Ultrasound

Anahtar Kelimeler:
Santral Venöz Kateter
Acil Servis
Ultrason

INTRODUCTION

Central venous catheterization (CVC) is a widely used method in patients undergoing both surgical and medical treatment (1). CVC; allow for many procedures, for example, fluid maintenance, hemodynamic monitoring, intravenous drug therapy, plasmapheresis, hemodialysis and total parenteral nutrition (2). The most preferred ways of percutaneous CVC intervention are internal jugular vein (IJV), subclavian vein (SV), femoral vein (FV) or basilic vein, but can be used in other veins opening to the central circulation. Although CVC was performed by following anatomical lines without imaging for the first time, ultrasonography (USG) started in recent years (2).

As with any attempt, CVC has its complications. The most deadly of these complications were pneumothorax, hydrothorax, hemothorax and cardiac tamponade. The success and complication rates of interventions are quite different according to the experience and education levels of the practitioners (3, 4). With the visualization of subcutaneous structures in the CVC procedure performed with USG, the success rate of the procedure increases, and the complication rates are less.

In our study, we aim to evaluate the bleeding complication in catheters inserted by USG or Landmark method in patients who use anticoagulants and/or antiplatelet drugs in CVC procedure.

MATERIAL AND METHOD

This study was carried out prospectively Aydın Adnan Menderes University Hospital, Emergency Medicine Department. Our ethics committee number is given as

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Table 1: Central venous catheter ındications

Indication	n	%
Hemodialysis	97	54.5
Need for vascular access	53	29.8
Central venous pressure measurement	21	11.8
Plasmapheresis	5	2.8
Other	2	1.1

2018/1514. The study included 178 patients aged 18 years and over who applied to our emergency service between 15.11.2018 and 15.10.2019 and had CVC procedure performed by emergency physicians. Patients requiring a second CVC application were included in the study as two separate cases. The average age of the patients included in our study was 67 (18-96 years).

Research data were evaluated using the SPSS 21.0 statistical program. The compatibility of continuous variables to normal distribution was investigated using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov / Shapiro-Wilk tests). For the descriptive statistics of the study, mean and standard deviation were used for data conforming to the normal distribution, and the median, minimum and maximum for data that did not fit the normal distribution. Chi-Square Test was used to show whether there is a difference between categorical variables in the study. For statistical significance, the condition of determining the p-value less than 0.05 was sought.

RESULTS

The average age of the patients included in our study was 67 years (18-96 years). Of all patients, 79 (44.4%) were female. According to CVC indications, hemodialysis was the first reason (Table 1). Hemoglobin level, platelet count, prothrombin time (PT) and activated partial thromboplastin time (APTT) analysis of the patients are given in Table 2. When the anticoagulant or antiplatelet drugs used by the patients regularly or given during their follow-up in the emergency department or emergency intensive care are examined, 63.5% of the patients included in our study did not use any anticoagulant or antiplatelet drug. The drug use of the patients that may cause bleeding is shown in Table 3.

When the catheterization area of the patients is examined; It was observed that IJV was preferred in 90 (50.6%) patients, FV in 78 (43.8%) patients, and SV in 10 (5.6%) patients. When the catheterization procedures are examined in general, it is seen that 79.2% of the procedures are done from the right side and 20.8% from the left side.

When the complication conditions of the patients were examined during and after the CVC procedure, it was observed that complications developed in 19.1% of the patients. When the complications were examined, it was seen that the most common complication situation was bleeding (Table 4).

When it was evaluated whether CVC was performed with USG, it was seen that USG-guided CVC was implanted in 140 patients (78.7%). When the CVC procedure performed with USG and complications were compared, it was observed that the use of USG did not affect the development of complications (p=0.095) (table 5).

Considering the relationship between anticoagulant or antiplatelet drug use and complications, complications were observed in 21.5% of patients with drug use and 17.7% of patients without drug use. When the statistical analysis was performed, it was not significant (p=0.530). Analysis results are given in Table 5.

When looking at the relationship between anticoagulant or antiplatelet drug use and bleeding status, bleeding complications were observed in 7.7% of patients with drug use and 7.1% of patients without drug use. When

Table 2: Blood values analysis

	n	Mean	Median	Minimum	Maximum	SD
Hemoglobin (gr/dL)	178	10.2	9,9	2.6	17.5	2.6
Platelets (10^3/ mcrL)	178	217	193	9	612	126
APTT (sec)	168	31.84	28,30	11,00	112.70	13.96
PT (sec)	171	20.26	14,20	0.95	122.80	17.28
INR	171	1.46	1,17	0.80	6.07	0.88

PT: prothrombin time, APTT: activated partial thromboplastin time, INR: international normalized ratio, SD: standard deviation

Table 3: Drug use that may cause bleeding

Active ingredient	n	%
Acetylsalicylic acid	12	6.7
Heparin and its derivatives	30	16.9
Warfarin	10	5.6
New generation anticoagulant	6	3.4
Clopidogrel	7	3.9
Not using medication that can cause bleeding	113	63.5

Table 4: Distribution of complications by patients

Complication	n	%
Bleeding	10	5.6
Ventricular dysrhythmia	9	5.1
Catheter infection	4	2.2
Artery puncture	5	2.8
Dysrhythmia and bleeding	3	1.7
Catheter malposition	2	1.1
Other	1	0.6
No complications occurred	144	80.9

Table 5: USG usage / medication use - complication status comparison

		Complication status				p
		Yes		No		
		n	%	n	%	
USG use	Yes	30	21.4	110	78.6	0.095
	No	4	10.5	34	89.5	
Medication Use	Yes	14	21.5	51	78.5	0.530
	No	20	17.7	93	82.3	

the patients with and without bleeding were examined, no difference was found between the two patient groups in terms of anticoagulant/platelet use (p=0.549).

DISCUSSION

Our study has stated that both of anticoagulant/antiplatelet drug use and USG application are not associated with increased risk of complication in CVC placement in the emergency department.

CVC is a method widely used in patients undergoing both surgical and medical treatment. CVC; enables many procedures such as fluid maintenance, hemodynamic monitoring, intravenous drug therapy, plasmapheresis, hemodialysis and total parenteral nutrition. Although the most preferred routes are IJV, SV or FV in percutaneous CVC intervention, other veins opening to central circulation can also be used. Although CVC was performed by following anatomical lines without imaging in the first years, it started to be performed with USG in recent years (2).

In the study of Mumtaz et al. 2010 CVC procedures were applied to 1825 patients. 330 of the patients have bleeding disorders, and 4 of them have bleeding complications. As a result, it was emphasized that CVC could be safely placed in patients with underlying bleeding disorders, and care should be taken in terms of thrombocytopenia (5). A bleeding complication was observed in 6.5% of the application of 110 CVCs by Doerfler et al. to 76 patients with hemostasis disorder. It was found that there were no signs of serious bleeding in the patients. It was observed that the patients with the highest probability of bleeding were those with thrombocytopenia (6). Of 14 patients with platelet values of 50,000 / mcL or less, bleeding was observed in only 3 cases in our study. The bleeding in the patients remained in the form of subcutaneous hematoma and did not progress to a life-threatening or surgical intervention. When analyzed statistically, no meaningful result was found. When we compare our study with other studies in the literature, we think that the CVC procedure can be performed by an experienced physician in patients who use anticoagulants or antiplatelet drugs in the absence of thrombocytopenia.

In the study conducted by Balls et al., it was shown that USG was not effective in the development of complications. In the same study, it was shown that the use of USG decreases the number of punctures performed for a patient (7). In a study conducted by Milling et al. Using USG and comparing the traditional Landmark method, it was shown that the attempts performed with USG were superior in the first puncture attempt in terms of successful catheterization, the number of attempts, duration of intervention, and arterial puncture (8). In the study of Leung et al. 130 patients, CVC was implanted in half of the patients with USG and half with the traditional method. When the procedures were evaluated in terms of the number of attempts, duration of intervention and complications, it was observed that the procedures performed under USG were more successful than the procedures performed by the traditional method (9). USG was used in 37% of CVC procedures in the study of Martin et al. While the complication rate was 11% in patients using USG, it was found to be 9% in patients who were not used, and it was statistically shown that the use of USG did not affect the development of complications (10). In our study, although there were more complications in USG guided procedures, it was not found to be statistically significant. Since we are a training clinic, we think that the complication rates are high because resident doctors who have just started training perform catheter application with USG.

In conclusion; CVC can be applied to patients with coagulopathy by a physician who is knowledgeable and experienced in CVC. Although there are contradictions between USG and its complications in the literature and our study, we think that the complication rates will decrease with the increase in USG training and usage. More comprehensive studies are needed on this subject.

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Relationship of Menopausal Status with Molecular Breast Cancer Subtypes

Menopoz Durumunun Moleküler Meme Kanseri Alt Tipleri İle İlişkisi

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ABSTRACT

Objective: Breast cancer is a heterogeneous disease group that exhibits quite different biological behaviors and bear many genomic traces. Its dependence on sex hormones also determines its relationship with menopausal status. It is divided into five molecular subtypes according to receptor analysis and Ki67 level with immunohistochemical markers. This study aimed to examine the relationship between the menopausal status and these molecular subtypes to help predict our treatment strategies.

Material and Method: The database of 250 patients who were operated on for breast cancer in our Oncology Clinic between 2012 and 2020 was retrospectively analyzed. The patients were grouped by their menopausal status and clinicopathological characteristics. Statistical analysis was made at a 95% confidence interval, and a p-value lower than 0.05 was considered statistically significant.

Results: The patients were divided into 2 groups by their menopausal status as 44.8% (n = 112) as premenopausal and 65.2% (n=138) as postmenopausal. In the statistical analysis performed, the level of Ki67 was high in premenopausal women (p=0.015). Also, tumors seen in premenopausal women were associated with ER negativity (p=0.024) and high histological grade (grade3) (p=0.015). It was found that luminal subtype (luminal A, luminal B) breast cancers were observed more frequently in postmenopausal women and non-luminal subtypes (HER2+, TNBC) were observed more frequently in premenopausal women.

Conclusion: Our study confirmed the association of premenopausal patients with subtypes of aggressive nature. Clinicians should anticipate that they may need other treatment options besides hormonal therapy when determining treatment options in young patients.

ÖZET

Amaç: Meme kanseri, oldukça farklı biyolojik davranışlar sergileyen ve birçok genomik iz taşıyan heterojen bir hastalık grubudur. Cinsiyet hormonlarına bağımlılığı da menopoz durumu ile ilişkisini belirler. İmmünohistokimyasal belirteçlerle yapılan reseptör analizine ve Ki67 düzeyine göre beş moleküler alt tipe ayrılır. Bu çalışmada, tedavi stratejilerimizi öngörmemize yardımcı olması için menopoz durumu ile bu moleküler alt tipler arasındaki ilişkiyi incelemeyi amaçladık.

Gereç ve Yöntem: 2012-2020 yılları arasında Onkoloji Kliniğimizde meme kanseri nedeniyle ameliyat edilen 250 hastanın veri tabanı geriye dönük olarak incelendi. Hastalar menopoz durumlarına ve klinikopatolojik özelliklerine göre gruplandırıldı. İstatistiksel analiz %95 güven aralığında yapıldı ve 0,05'ten düşük bir p değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular: Hastalar menopoz durumlarına göre %44.8 (n=112) premenopozal ve %65.2 (n=138) postmenopozal olarak 2 gruba ayrıldı. Yapılan istatistiksel analizde premenopozal kadınlarda Ki67 düzeyi yüksekti (p=0.015). Ayrıca premenopozal kadınlarda görülen tümörler ER negatifliği (p=0.024) ve yüksek histolojik derece (grade3) (p=0.015) ile ilişkiliydi. Postmenopozal kadınlarda luminal alt tip (luminal A, luminal B) meme kanserlerinin, premenopozal kadınlarda ise luminal olmayan alt tiplerin (HER2+, TNBC) daha sık izlendiği bulundu.

Sonuç: Çalışmamız premenapozal hastaların agresif doğaya sahip subtiplerle olan ilişkisini teyit etmiştir. Klinisyenler genç hastalarda tedavi seçenekleri belirlerken hormonal tedavi dışında diğer tedavi seçeneklerinede ihtiyaç duyubileceklerini öngörmelidirler.

Keywords:
Breast cancer
Immunohistochemical analysis
Molecular subtype
Menopausal status

Anahtar Kelimeler:
Meme kanseri
İmmünohistokimyasal analiz
Moleküler alt tip
Menopoz durumu

INTRODUCTION

Breast cancer in younger women has been associated with lower survival and higher recurrence rates than elderly ones. Even though studies describe negatively affecting factors, they have not fully explained the underlying biological nature that drives these aggressive traits (1).

In the present day, the existence of 5 intrinsic breast cancer subtypes has been identified and accepted by gene expression studies and staining techniques based on immunohistochemical (IHC) markers. In clinical practice, IHC staining is grouped according to the expression levels of luminal and non-luminal subtypes, estrogen receptor-α (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER -2), and Ki67. St. The classification into five molecular subtypes has been accepted as per the recommendations of the Gallen consensus (2013) (2).

The relationship between molecular subtypes of breast

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cancer and survival has been investigated in many studies, and it was found that luminal subtypes are associated with better prognosis and less recurrent disease development than others. Recent studies also have evidence of significant differences in treatment strategies for these different subtypes (3).

It was reported that non-luminal subtypes with more aggressive features are seen more in premenopausal women, whereas menopausal women are more associated with luminal subtypes (4). In fact, in a way, there are clues about the treatment of the disease in the genomic sequence. While ER-positive patients are likely to respond to endocrine treatment and HER2-positive patients to trastuzumab treatment, the standard treatment of the Triple-negatie Breast Cancer (TNBC) group remains a mystery.

It is known that breast cancer is dependent on sex hormone levels. This study aimed to investigate the relationship between menopausal status and intrinsic breast cancer subtypes, and clinicopathological characteristics in women with breast cancer. Thereby, we hope to help with the predictability of disease relapse, overall survival, endocrine, and response to chemotherapy regimens.

MATERIAL AND METHOD

Study design

Our study was initiated by obtaining the approval of the ethics committee of Ankara University Faculty of Medicine (Decree no: İ2-119-21).

The database of 277 patients operated on for breast cancer in the Oncology Clinic of our University's Faculty of Medicine Hospital between 2012-2020 was retrospectively analyzed. Patients with surgical and medical menopause for any reason and patients who were not operated due to advanced disease were excluded from the study. İn addition, 27 patients were excluded due to missing data. Demographic and clinicopathological characteristics of the patients were recorded. From histopathological examination results, receptor status (ER, PR, and HER2), Ki67 percentage, tumor-related variables (histological type, size, grade), lymphovascular invasion (LVI) status, axillary lymph node involvement level were recorded retrospectively. The age, menopausal status, the side of the tumor, and the type of surgical procedure performed were recorded from the digital files in the database. Patients were categorized into two classes by their menopausal status.

ER and PR status were determined using immunohistochemical staining (IHC). Positive ER or PR was accepted when ≥1% of invading malignant cells exhibiting nuclear staining or immunoreactivity. Tumors were considered HER2-positive only if they showed HER2 amplification (ratio >2) using IHC staining 3+ (strong, full membrane staining in >30% of cancer cells) or fluorescent in situ hybridization (FISH). ER, PR and HER2 tests were scored as per the American College of Pathologists Guidelines (5). The cutoff rate of KI-67 was accepted as 17%.

The patients were classified according to the recommendations of the St. Gallen International Expert Consensus Report (2013) by molecular breast cancer subtypes. The patients were categorized by the receptor status of their primary tumor as follows: Luminal A (ER + and/or PR + and HER2-); luminal B HER2- (ER + and/or, PR +, HER2- and high Ki-67); luminal B HER2 + (ER +, HER2+, any Ki-67, any PR); HER2 (ER- and PR- and HER2 +) and triple-negative breast cancer (TNBC; ER- and PR- and HER2-) (2).

The status of lymph node metastasis was determined by histopathological evaluation of axillary lymph nodes obtained during mastectomy or axillary dissection. The total number of lymph nodes was determined by summing the number of non-invasive lymph nodes and metastasis-positive lymph nodes.

The patients were staged based on the American Joint Committee on Cancer (AJCC) 8th Edition according to the TNM staging system (stage 1A, 1B, 2A, 2B, 3A, 3B, 3C) (6).

Statistical Analysis

Descriptive statistical analyzes of quantitative variables were made, and all data were expressed as mean±standard deviation (SD), number, percentage, maximum and minimum values. Then, the statistical analysis was performed using SPSS (version 24). Parametric test assumptions were examined before performing the difference analysis. Normality was checked with the Kolmogorov Smirnov test, skewness, and kurtosis. In the case where the assumptions were provided, the difference analysis was performed using the one-way analysis of variance (ANOVA) and the Kruskal Wallis test when it was not provided. Paired comparisons were made using the Mann-Whitney U test. The relationship between categorical variables was analyzed using the chi-square (χ 2 test) test. Statistical analysis was made at a 95% confidence interval. A p-value lower than 0.05 was considered statistically significant.

The clinicopathological characteristics of the patients are summarized in Table 1.

RESULTS

All 250 patients included in the study were women. The patients were divided into 2 groups by their menopausal status as 44.8% (n=112) as premenopausal and 65.2% (n=138) as postmenopausal. The right breast was affected in 52.5% (n=134) of the patients, and the left breast in 48% (n=116). The mean age of the patients was 54.86±13.08 years, the mean age of premenopausal patients was 43.77±5.56 (24-53), and the mean age of postmenopausal patients was 63.86±10.2 (46-93). There was a cumulative accumulation of breast cancer in postmenopausal women between the ages of 51 and 63. The mean percentage of Ki67 was 34.88 ± 24.71 in premenopausal women and 22.02 ± 18.32 in postmenopausal women. According to the histopathological subtypes, the most common type of cases was ductal (premenopausal 33%, postmenopausal 43%), a few of them were lobular, the remaining cases were other histological types such as medullary, tubular, mucinous, metaplastic, adenoid, cystic and papillary carcinoma. In half of the patients (n=125, 50%), axillary nodal involvement was not determined. The mean pathological lymph nodes resected in the remainder was 4.8±4.7 (1-31), and the mean total lymph nodes resected were 11.9±7.2 (1-35). The distribution among the groups was almost equal by the axillary nodal involvement.

Table 1: Distribution of clinicopathological characteristics of 250 patients with breast cancer by menopausal status

Characteristics	Premenopausal (112)		Postmenopausal (138)		Total patients (250)		P-value
	Number (n)	Percentage (%)	Number (n)	Percentage (%)	Number (n)	Percentage (%)	
Type of surgery							0.550
MRM	45	18	61	24.4	106	42.4	
Mastectomy+SLNB	8	3.2	5	2	13	5.2	
BCS+SLNB	32	12.8	43	17.2	75	30	
BCS+AD	27	10.8	29	11.6	56	22.4	
Tumor histology							0.572
Ductal	83	33.2	107	42.8	191	76	
Lobular	10	4	14	5.6	24	9.6	
Other	19	7.6	17	6.8	36	14.4	
T stage							0.825
T1(<2 cm)	59	23.6	71	28.4	130	52	
T2(2-5 cm)	39	15.6	46	18.4	95	34	
T3(> 5 cm)	14	5.6	21	8.4	35	14	
T4	0	0	0	0	0	0	
LVI status							0.674
Negative	59	23.6	69	27.6	128	51.2	
Positive	53	21.2	69	27.6	132	48.8	
Node status							0.349
N0(no)	56	22.4	69	27.6	125	50	
N1(1-3)	31	12.4	49	19.6	80	32	
N2(4-10)	15	6	12	4.8	27	10.8	
N3(> 11)	10	4	8	3.2	18	7.2	

The distribution of clinicopathological characteristics by groups is presented in Table 1.

In the statistical analysis performed, no significant difference was found between the quantitative variables and the groups in terms of tumor size (p=0.609), the number of total lymph nodes resected (p=0.794), and the number of pathological lymph nodes (p=0.690). However, the Ki67 level was significantly higher in premenopausal patients than in postmenopausal patients (p=0.015).

In the chi-square analysis performed between menopausal status and categorical variables, no relationship was found between the type of surgery, histopathological subtype, axillary nodal status, LVI status, TNM stage, PR, and HER2 (p>.05).

However, a significant relationship was found between menopausal status and ER status (p=0.024), histological grade of the tumor (p=0.002), and molecular subtype of the tumor (p=0.032). When the subtypes were examined, we found that premenopausal patients were more associated with luminal A and luminal B, and postmenopausal patients were more associated with other non-luminal subtypes.

In other words, tumors seen in premenopausal women were associated with the presence of advanced histological grade (grade 3), non-luminal subtype (HER2+, TNBC), and ER negativity compared to postmenopausal women. In postmenopausal women, tumors were more closely associated with low histological grade (Grade 2-3), luminal subtype, and ER positivity.

The results are presented in Table 1, together with the distribution of variables by groups.

DISCUSSION

We examined the relationship between women with breast cancer, divided into two groups as premenopausal and postmenopausal, with clinicopathological variables and molecular subtypes. In the statistical analysis performed, the level of Ki67 was high in premenopausal women (p=0.015). Besides, premenopausal tumors were also associated with ER negativity (p=0.024) and high histological grade (grade 3) (p=0.006). We also found that breast cancer in premenopausal women was associated with non-luminal subtypes (HER2+, TNBC). On the other hand, breast cancers diagnosed in the postmenopausal period were mostly associated with luminal subtypes (luminal A, luminal B) (p=0.032).

Anders et al. found a low incidence of ER positivity in young women in their study of 784 breast cancer patients, including large-scale genomic analysis, and that HER-2 had higher expression and tumors had higher histological grade (grade 3) (7). In our study, the relationship between HER-2 expression levels and menopausal groups did not reach statistical significance.

Keegan et al. reported that non-luminal subtypes (HER2+, triple-negative) were found at a higher rate in young women and the tumors were of high histological grade (8). There is a significantly higher rate of luminal subtypes in postmenopausal women in our study. This result is probably due to the significantly low Ki67 and high ER expression in postmenopausal women.

Triple-negative breast cancer has an overall incidence of

Table 1 continuation: Distribution of clinicopathological characteristics of 250 patients with breast cancer by menopausal status

Characteristics	Premenopausal (112)		Postmenopausal (138)		Total patients (250)		P-value
	Number (n)	Percentage (%)	Number (n)	Percentage (%)	Number (n)	Percentage (%)	
Tumor grade							0.006
Grade 1	15	6	27	10.8	42	16.8	
Grade 2	32	12.8	59	23.6	91	36.4	
Grade 3	65	26	52	20.8	117	46.8	
TNM stage							0.279
1A	45	18	48	19.2	93	37.2	
1B	9	3.6	21	8.4	30	12	
2A	9	3.6	19	7.6	28	11.2	
2B	21	8.4	21	8.4	42	16.8	
3A	18	7.2	21	8.4	39	15.6	
3B	0	0	0	0	0	0	
3C	10	4	8	3.2	18	7.2	
4	0	0	0	0	0	0	
Local stage							0.455
Early-stage	84	33.6	109	43.6	193	77.2	
Locally advanced stage	28	11.2	29	11.6	57	22.8	
Receptor status							
ER							0.024
Positive	85	34	120	48	205	82	
Negative	27	10.8	18	7.2	45	18	
PR				0.157			
Positive	78	31.2	107	42.8	185	74	
Negative	34	13.6	31	12.4	65	26	
HER2							0.836
Positive	42	16.8	50	20	92	36.8	
Negative	70	28	88	35.2	158	63.2	
Molecular subtype							0.032
Luminal A	17	6.8	36	14.4	46	21.2	
Lum B (HER2-)	41	16.4	49	19.6	90	36	
Lum B (HER2+)	30	12	47	18.8	77	30.8	
HER2+	12	4.8	3	1.2	15	6	
Triple - (TNBC)	12	4.8	3	1.2	15	6	

11.2% at all ages, with a higher incidence in premenopausal women compared to postmenopausal women, regardless of race (7,9,10). However, in a national comprehensive study conducted by Lin et al. on approximately 15,000 patients, they reported that the probability of having a triple-negative subtype increased in premenopausal women compared to postmenopausal women with a high body mass index(11). Although the rate of triple-negative subtypes was low (6%) in the study, it was more associated with premenopausal women.

Even though HER-2 Neu expression was found to be higher in premenopausal women in the literature, no statistically significant relationship was found in the study(12).

In our study, the tumor size was relatively larger in premenopausal women, and although their tumors were mostly larger than 2 cm, it was not statistically significant (p=0.825). Although half of the patients had no lymphatic metastases, it was observed that most of them were postmenopausal women. On the other hand, among patients with lymphatic metastasis, although the ratio of N2 and N3 was relatively higher in premenopausal women, it was found that similarly, it did not reach statistical significance (0.349).

The majority of cases were ductal carcinomas (76%), and it was observed that these were relatively higher in postmenopausal women. Similarly, about half of the cases showed LVI, and it was observed to be more common in postmenopausal women. However, these variables could not be correlated significantly with the menopausal status in the analysis (p=0.572, p=0674).

On the other hand, approximately half (47%) of the tumors observed had high histological grade (grade 3) and were significantly more common in premenopausal women (p=0.006).

Although the results we obtained show parallelism with the studies in the literature, there are some differences.

Most studies have shown that tumors found in young and premenopausal women have more aggressive phenotypes (TNBC and HER2 positive subtypes). It was also reported that these tumors are associated with higher lymph node metastasis and higher histological grade and size (13,14,15).

Our study showed that the most appropriate clinical classification for the menopausal situation is IHC-based intrinsic subtype classification (p=0.032) rather than the classical TNM staging (p=0.279). This may be due to factors associated with particularly poor genomic character observed in premenopausal women (such as Ki67 and HER-2 elevation, ER negativity). Therefore, all these features are of vital importance in determining treatment strategies. Luminal tumors most likely respond favorably to hormonal therapies such as tamoxifen and trastuzumab treatment for HER2 overexpressing tumors. However, treatment options for TNBC are still limited and non-specific (16).

Our study showed that intrinsic subtype classification based on IHC staining is more helpful in determining treatment strategies. Accordingly, it should be predicted that premenopausal patients will need more chemotherapy due to the high Ki67 proliferation index and trastuzumab therapy due to the high HER-2. On the contrary, it can be predicted that postmenopausal patients will benefit more from hormonal treatments due to ER positivity. Thus, clinicians can predict the menopausal status and possibly the treatment options to be used at the beginning of the treatment. In their meetings with their patients, they can discuss these possible treatment strategies more informatively and openly because of their predictions.

CONCLUSION

As a result, it is known that more difficult treatment processes await these patients due to the aggressive phenotypic features seen in young patients. In this study, it was predicted that premenopausal patients would need other treatment options besides hormonal treatment. We believe this insight will help clinicians prepare their patients for treatment options.

Study Limitations

This study had limitations such as its retrospective nature and symptomatic cases. The distribution of breast cancer molecular subtypes may differ in studies involving symptomatic case series, so population-based randomized studies are needed.

In summary, it was accepted for years that breast cancer occurring in premenopausal women represents an aggressive phenotype. However, the biological parameters that direct the nature of this heterogeneous disease are still largely unknown. More randomized and prospective studies are needed to enlighten this issue.

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Anesthesia and Postoperative Outcome in Pediatric Cranial Surgery: A Retrospective Single Center Study

Pediatrik Kraniyal Cerrahide Anestezi ve Postoperatif Sonuçların Değerlendirilmesi: Retrospektif Tek Merkezli Çalışma

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ABSTRACT

Objective: *Perioperative patient monitoring and follow-up is very important to minimize morbidity and mortality in pediatric neurosurgical interventions.*
In this study, it was aimed to evaluate the perioperative anesthesia management by examining the findings of the pediatric patients who underwent cranial surgery along with to examine the effects of hemorrhagic surgical procedures, which play an active role in morbidity, both intraoperatively and postoperatively, including hospitalization in intensive care unit.

Material and Method: *Follow-up files of 303 pediatric patients between the ages of 0-18, who were taken to cranial operation, between 2015-2018 years evaluated as retrospectively.*

Results: *A total of 303 children 199 (65.7%) ≤1 year old, 104 (34.3%) >1 year old who underwent pediatric neurosurgery were included in our study. It was determined that the most frequently performed operation was shunting due to hydrocephalus and craniosynostosis. In subanalysis, in craniosynostosis operations performed frequently in infants aged ≤1, it was observed that bleeding amount was as much as subdural and epidural hematoma operations performed in children >1 year old (181ml and 196 ml, p =0.444, respectively). There was no difference between groups in intensive care unit admission.*

Conclusıons: *We think that in pediatric neurosurgery patients' perioperative anesthesia management, it is important to closely monitor the vital signs of patients, to record complications and blood transfusions in detail. We believe that due to the more aggressive duration of hypotensive processes, more attention should be paid to morbidity and mortality, especially in cases of craniosynostosis.*

ÖZET

Amaç: *Pediyatrik nöroşirurjik cerrahi girişimlerde morbidite ve mortaliteyi en aza indirgemek için perioperatif hasta monitörizasyonu oldukça önemlidir. Bu çalışmada, kraniyal cerrahi uygulanan çocuk hastaların verileri incelenerek perioperatif anestezi yönetiminin değerlendirilmesi beraberinde morbiditede etkin rol oynayan hemorajik cerrahi prosedürlerin hem intraoperatif hem de yoğun bakım ünitesinde yatış sürecini de içeren postoperatif dönemdeki etkilerinin incelenmesi amaçlandı.*

Gereç ve Yöntem: *2015-2018 yılları arasında kraniyal cerrahi nedeni ile operasyona alınmış 0-18 yaş arası, toplam 303 çocuk hastanın verileri retrospektif olarak değerlendirildi.*

Bulgular: *Çalışmamıza, pediyatrik kraniyal cerrahi geçirmiş 199'u (%65,7) ≤1 yaş, 104'ü (%34,3) >1 yaşında olmak üzere toplam 303 çocuk dahil edildi. En sık hidrosefali nedeniyle şant ve kraniyosinostoz operasyonlarının olduğu belirlendi. Alt analizde ≤1 yaş bebeklerde sık uygulanan kraniyosinostoz ameliyatlarında kanama miktarının >1 yaş çocuklarda yapılan subdural ve epidural hematom ameliyatlarında ki kadar fazla olduğu görüldü (sırasıyla 181ml ve 196ml, p=0,444). Yoğun bakıma yatışta gruplar arasında fark yoktu.*

Sonuç: *Pediyatrik beyin cerrahisi hastalarının perioperatif anestezi yönetiminde hastaların vital bulgularının yakından izlenmesi, komplikasyonların ve kan transfüzyonlarının detaylı olarak kayıt altına alınmasının önemli olduğunu düşünüyoruz. Hipotansif süreçlerin daha agresif seyir göstermesi nedeniyle, özellikle kraniyosinostoz vakalarında morbidite ve mortalitenin önlenmesi açısından daha fazla dikkat edilmesi gerektiğine inanıyoruz.*

Keywords:
Craniosynostosis
Hydrocephalus
Neurosurgery
Pediatric anesthesia
Perioperative anesthesia management

Anahtar Kelimeler:
Kraniyosinostoz
Hidrosefali
Kraniyal cerrahi
Pediyatrik anestezi
Perioperatif anestezi yönetimi

INTRODUCTION

Recent advances in pediatric neurosurgery have shown that the prognosis improves dramatically in infants and children affected by central nervous system (CNS) lesions (1). Age-related differences in surgical lesions, anatomy and physiological responses to surgery are clinically important differences between pediatric patients and adults (2). Keeping the little baby's homeostasis up to the demands of the surgery and surgeon is a difficult task for a neuroanesthesiologist (3). Perioperative management

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of pediatric patients planned for cranial surgery poses many difficulties for anesthesiologists. Anesthesiologists should be aware of the unique challenges of anesthesia management in pediatric neurosurgery patients, such as difficulty in positions during operation due to difficult airway and abnormal skull shape, sudden and massive blood loss, venous air embolism, apnea, airway obstruction, and ocular injuries (4). Hydrocephalus is defined by the increase in the volume of cerebrospinal fluid in the CNS, and > 380,000 is characterized by new cases every year. Cerebral shunt operation is the main treatment method of hydrocephalus (5). The ventriculoperitoneal shunt (VPS) is prone to complications such as mechanical failures (occlusion of the valve or catheter, catheter rupture or migration), excessive drainage and infection. Risk factors in the literature such as ethnic origin, etiology of hydrocephalus, prematurity, age under 1, male gender, spina bifida, epilepsy and degree of ventricular dilation may increase the risk of shunt revision in patients with hydrocephalus (6). The approach to children with craniosynostosis is multidisciplinary and has improved significantly over the past fifty years. Treatment is primarily surgical and anesthesia management is often further complicated by syndrome-specific problems (7). The cranial reconstruction method is a major surgical procedure and is associated with prolonged operative duration, prolonged duration of hospital stay, major blood loss, high blood transfusion rates, and the need for postoperative intensive care unit (ICU) admission after surgery (8). Another characteristic cranial surgery group is traumatic brain injury in infants and children. It remains one of the main causes of long-term disability and mortality worldwide (9). Presence of pediatric neurosurgical intensive care has reduced mortality in cases of severe pediatric traumatic brain injury (10). In addition to the follow-up in intraoperative and postoperative periods, preoperative and intraoperative evaluation together with good communication is of great importance in minimizing perioperative morbidity and mortality. Recent advances in neurosurgery, neuromonitoring, and pediatric neurology intensive care have dramatically improved the outcome in children undergoing CNS surgery (11).

This study aims to evaluate perioperative anesthesia administration by examining preoperative, intraoperative, recovery and postoperative period findings of pediatric patients undergoing cranial surgery. While examining the effects of surgical procedures performed in different age groups on perioperative anesthesia management, it is also aimed to evaluate the prognostic parameters in operations with high bleeding risk.

MATERIAL AND METHOD

The study was started after the approval of the local ethics committee (Kanuni Sultan Süleyman Training and Research Hospital / KAEK / 2018.7.08-08 / 08/2018). The follow-up files of 303 pediatric patients between the ages of 0-18, who underwent cranial surgery (hydrocephalus, craniosynostosis, collapse fractures, subdural, epidural hemorrhages, brain tumors, etc.), emergency surgery or elective surgery between 2015 and 2018, were evaluated retrospectively. The aim of this study was to retrospectively evaluate the intraoperative, postoperative data, accompanying recovery and ICU follow-up findings of pediatric cases undergoing cranial surgery under general anesthesia. Perioperative anesthesia management and mortality are planned to be examined. In a sub-analysis, it is planned to examine the factors affecting outcome in surgical procedures where massive blood loss is expected. The demographic data, American Society of Anesthesiologists (ASA) scores, intracranial pathologies, durations of surgery, intraoperative and postoperative complications (desaturation, embolism, EtCO2 reduction, bradycardia, hypertension and hypotension), amount of intraoperative bleeding, erythrocyte suspension and fresh frozen plasma replacement amounts intraoperatively and post-operatively, antagonization of the muscle relaxant in the postoperative period, the patient's need for extubation or intubated recovery or transfer to the ICU, the need for post-operative ICU admission, the duration of mechanical ventilation, length of stay in the ICU of the patients were recorded.

Statistical analysis

SPSS 25.0 (IBM Corporation, Armonk, New York, United States) and PAST 3 (Hammer, Ø., Harper, D.A.T., Ryan, P.D. 2001. Paleontological Statistics) programs were used to analyze the variables. The compatibility of univariate data to normal distribution was evaluated by the Lilliefors-corrected Kolmogorov-Smirnov test and the Shapiro-Wilk test, with variance homogeneity evaluated by the Levene test. The Mardia (Dornik and Hansen omnibus) test was used for analysis of the normal distribution of multivariate data and homogeneity of variance was evaluated by the Box's M test. The Mann-Whitney U test was used together with the Monte Carlo results in the comparison of two independent groups according to the quantitative data. The Wilcoxon signed-Rank test was used to compare two repetitive measurements of dependent quantitative variables using Monte Carlo simulation results. The Pearson Chi-Square test was used with the Fisher exact results, the Fisher-Freeman-Halton test with the exact and Monte Carlo results, with the Monte Carlo Simulation technique used in the comparison of categorical variables. Column ratios were compared with each other and expressed according to the Benjamini-Hochberg corrected p-value results. In the sub-analysis of the study, group parameters were evaluated using the Mann-Whitney U Test (age, weight, amount of intraoperative bleeding), Independent t-Test (operation time), Chi-Square Test (ICU admission, re-operation). The quantitative variables were shown as Median (Min/Max.), and categorical variables as n (%) in the tables. The variables were examined at 95% confidence level and the p-value was accepted as significant when less than 0.05.

RESULTS

A total of 303 children, 199 (65.7%) ≤1 year and 104 (34.3%) >1 year, who underwent pediatric neurosurgery, were included in the present study. Of the children, 171 were girls and 132 were boys, while there was no significant difference between the age groups in terms of gender ($p>0.05$). ASA scores were determined to be higher in children >1 year compared to children ≤1 year ($p<0.001$). (Table I). The mean duration of surgery of the patients was determined to be 60 minutes and the

Table 1: Comparison of children undergoing pediatric cranial surgery

	Total n (%)	≤1 Yaş (n=199) n (%)	>1 Yaş (n=104) n (%)	p
Gender				
Female	171 (56.4)	112 (56.3)	59 (56.7)	0.999[1a]
Male	132 (43.6)	87 (43.7)	45 (43.3)	
ASA Score				
I	45 (14.9)	14 (7.0)	31 (29.8)[A]	<0.001[1b]
II	205 (67.7)	144 (72.4)[B]	61 (58.7)	
III	53 (17.5)	41 (20.6)[B]	12 (11.5)	
Desaturation (yes)	15 (5.0)	9 (4.5)	6 (5.8)	0.781[1a]
Bradycardia (yes)	40 (13.2)	31 (15.6)	9 (8.7)	0.108[1a]
Hypertension (yes)	8 (2.6)	0 (0.0)	8 (7.7)	<0.001[2]
Hypotension (yes)	39 (12.9)	27 (13.6)	12 (11.5)	0.719[1a]
Re-operation (yes)	115 (38.0)	75 (37.7)	40 (38.5)	0.901[1a]
Postoperative FFP use	18 (5.9)	10 (5.0)	8 (7.7)	0.443[1a]
Postoperative mechanic ventilation (yes)	54 (17.8)	34 (17.1)	20 (19.2)	0.752[1a]
Reversal of neuromuscular blockade				
None	45 (14.9)	28 (14.1)	17 (16.3)	<0.001[1b]
Atropin-Neostigmin	163 (54.0)	139 (70.2) [B]	24 (23.1)	
Sugamaddex	94 (31.1)	31 (15.7)	63 (60.6) [A]	
	Median (Min. / Max)	Median (Min. / Max)	Median (Min. / Max)	
Duration of operation (min.)	60(10/ 300)	60 (10 / 300)	80 (20 / 220)	0.011[3]
Intraoperative blood loss (ml.)	20 (5 / 600)	15 (5 / 350)	80 (5 / 600)	<0.001[3]

Pearson Chi-Square Test (1a Exact, 1b Monte Carlo), Fisher Exact test (Exact); Post Hoc Test: Benjamini Hochberg correction, Mann Whitney U Test b (Monte Carlo), A ≤1 Significant according to age group, B >1 Significant according to age group, Min., Minimum; Max., Maximum; min., minutes, ASA; American Society of Anesthesiologists, FFP;Fresh Frozen Plasma

duration of surgery and intraoperative bleeding amount were higher in children >1 year (p<0.05). When the patients were evaluated in terms of their intraoperative amount of bleeding, it was seen that the mean amount of bleeding, 80 ml, in patients >1 year increased significantly compared to children ≤1 year (p<0.001) (Table I). It was determined that a maximum of 3 units of erythrocyte suspension and 2 units of fresh frozen plasma replacement were performed intraoperatively. A total of 93 children underwent postoperative erythrocyte suspension and 18 children underwent fresh frozen plasma replacement. While there was a need for the reversal of neuromuscular blockade with atropine and neostigmine combination in 163 children, it was seen that this procedure was applied more frequently in children ≤1 year than in children >1 year (p<0.001) (Table 1). However, when the children were evaluated in terms of intraoperative monitorization findings, it was seen that intraarterial tension was high in 8 children >1 year, while this was not the case in children ≤1 year. Besides, there was no significant difference between the groups in terms of intraoperative desaturation, hypotension and bradycardia (p>0.05) (Table 1). Mechanical ventilatory requirement was detected in 54 cases in total. There was no significant difference between 1 ≤ age and > 1year old children (34 and 20 respectively p = 0.752) (Table 1). It was seen that 115 of the children included in the study were re operated. There was no significant difference between the two groups in terms of the need for re operation (p>0.05) (Table I).

It was seen that the most common operations were shunting due to hydrocephalus and craniosynostosis. However, the most common re operation procedures were shunt revisions due to hydrocephalus and external ventricular drainage operations. When the etiological reasons for the operations were evaluated, it was found that 145 (48.3% reoperation) operations in children ≤1 year and 44 (59.1% reoperation) operations in children >1 year were performed due to hydrocephalus. Craniosynostosis was performed on 31 (2 re-operations) children ≤1 year and only 5 (3 re-operations) children >1 year. All operations due to epidural (13) and intracerebral hemorrhage (1) were performed on children >1 year of age. It was found that 7 of the children, who were operated for subdural hematoma were ≤1 year and 10 were >1 year-old. It was found that in children who were operated for brain tumors, 2 were performed in ≤1 year-old and 7 in children > 1 year old. In terms of postoperative ICU needs, a total of 122 pediatric cases, 2 of which were external centers, were sent to ICU. In the analysis in which craniosynostosis and subdural-epidural hematomas were evaluated mutually, the mean age was 9 months and 86 months (p<0.01), respectively, the mean weight was 8.2 kg and 27.2 kg (p<0.05), respectively,

Table 2: Comparison of children with craniosynostosis (Group: I) and Subdural-Epidural Hematoma (Group: II)

	Group I (n=36)	Group: II (n=26)	p value
Age (months)	9 ± 4.4	86 ± 72.1	<0.01
Operation time (min)	156 ± 54.2	103 ± 43.7	<0.01
Intraoperative bleeding amount (ml)	181 ± 72	196 ± 136	0.444
Intraoperative hypotension	30.6%	4.8%	0.002
Intraoperative bradycardia	9.7%	4.8%	0.722
Intraoperative hypertension	0%	6.5%	0.027
Amount of ES delivered intraoperatively (cc)	177± 103	148± 202	0.046
Postoperative intensive care need	58.8%	33.9%	0.494
Re-operation	8.1%	1.6%	0.387

Mann-Whitney U Test, Independent t- Test, Chi-Square Test, p <0.05 was evaluated at the level of significance. ES; Erythrocyte suspension, min; minute

and the operation times were 156 and 103 minutes (p<0.01) respectively. When the groups were compared in terms of the amount of intraoperative bleeding, no significant difference was observed, the mean value was 181 ml and 196 ml, respectively (p=0.444). When compared with the amount of erythrocyte suspension administered intraoperatively, 177 ml and 148 ml, respectively (p <0.046) were considered statistically significant. In terms of intraoperative hypotension frequency, the relationship between craniosynostosis (52.8%) and subdural-epidural hematoma (11.5%) groups was considered statistically significant (p=0.002). The comparison between the groups for postoperative ICU admission was 83.3% and 84.6% (p= 0.494) respectively, there was no significant difference between the groups (Table 2).

No intraoperative death was observed in the patients included in this study. Postoperative mortality occurred in 10 (3.3%) of the 303 patients. Of these patients, 5 died after hydrocephalus surgery and/or revision, 2 died after craniosynostosis surgery and the remaining 3 died after subdural and epidural hematoma surgery. In the course of mortality, craniosynostosis had early postoperative mortality with death developing in the first ninth hour after bleeding in the postoperative period. In hydrocephalus, shunt revision and hematoma cases, postoperative late mortality was encountered after intensive care conditions that could last from 1 month to 3 months.

DISCUSSION

Management of pediatric neurosurgical patients is difficult for neurosurgeons and anesthesiologists. The need for emergency procedures, severe comorbidities (such as prematurity) and communication difficulties in the age group, in addition to other complications such as sedation and intravenous access may significantly increase morbidity and mortality in these patients (12).

Surgical intervention involves the most common pediatric neurosurgical procedure ventriculoperitoneal shunting (13). In the present study, where the perioperative anesthesia management and monitoring of patients in the 0-18 age group, who underwent neurosurgical intervention in the last three years in our clinic was evaluated, it was determined that the most common surgical indications were hydrocephalus-dependent shunting and craniosynostosis. However, the most common re-operations were shunt revisions and external ventricular drainage operations due to hydrocephalus. These findings are considered to be consistent with the literature (3).

Craniosynostosis correction, hydrocephalus, and ventriculoperitoneal shunting, and brain tumor resection are the three most common surgical procedures in children with high complication rates. In the study by Drake et al., where 1082 pediatric neurosurgical procedures were evaluated, it was emphasized that the most common complications occurred after hydrocephaly-dependent shunts (38.4%) and brain tumor surgeries (17.5%) (14). In the present study, 48.3% of the children ≤1 year, who underwent hydrocephaly-dependent shunting required re-operation, while this rate increased to 59.1% in children >1 year- old. This is an inevitable surgical complication expected from perioperative anesthesia management (15). Craniosynostosis is a skull development disorder that occurs as a result of early fusion of one or more cranial sutures and occurs in approximately 1 in every 2000 live births (16). Surgical procedures for craniosynostosis are various and complex and carry a great risk for the development of significant complications in intraoperative and postoperative periods. In craniosynostosis patients, the main requirement in their operations is to cope with the inevitable and often significant blood loss that occurs during the procedures (17,18). In a study by Howe et al. conducted on 127 infants aged < 24 months, who underwent craniosynostosis surgery in Australia, it was emphasized that perioperative blood loss may exceed the total blood volume of pediatric patients (19). The difficulty in predicting blood loss due to small blood volume requires accurate timing and the appropriate amount of blood transfusion, depending on the clinician's experience. Meyer et al. reported that perioperative blood loss in 115 children undergoing craniosynostosis surgery reached 66-91% of the estimated blood volume, and that blood transfusions should be adjusted according to the extent of the surgical method. In the same study, the fact that over transfusion occurred in 32% of the children, suggested that the volume management of these patients was quite difficult (20). Kearney et al. argued that blood transfusion is almost inevitable in craniosynostosis surgery, but that blood transfusion is generally unnecessary in the postoperative period (21). In the study of Stricker et al.

in the craniofacial surgeries of infants and children, they stated that long surgical times were associated with greater blood volume losses and the possibility of at least one metabolic acidosis episode (22). Habaz et al. mentioned that besides the long-term effects of general anesthesia on neurological development in the pediatric population, significant blood loss is observed with increased exposure to anesthesia. In their study, they stated that there was an average of 18 ml/kg blood loss in their operations in the cranial vault reconstruction group and 98% blood transfusion was achieved (23). In the craniosynostosis cases of our study, similar to that of Habaz et al., we found that an average of 22 ml/kg blood loss, an average of 21.5 ml/kg erythrocyte suspension (ES) infusion and 94% blood transfusion occurred in operations lasting 156 minutes on average. We believe that the transfusion rates performed due to the hypovolemic process increase our need for ICU by causing intraoperative as well as postoperative complications. In Bonfield et al.'s retrospective study, only 6.14% of 114 cases of craniosynostosis were admitted directly to the ICU and among the reasons for admission were: preoperative increased intracranial pressure, lack of beds in the ward, older patients with large reconstruction areas, or significant medical comorbidity has existed (24). In a retrospective cohort study of 107 craniosynostosis patients by Seruya et al., they observed that only 4.7% of the patients required ICU treatment in the presence of a significantly higher incidence of comorbidities such as intraoperative blood loss and postoperative blood transfusion (25). In the review of Goobie et al., in which a total of 225 craniosynostosis cases over 10 years were examined, the need for postoperative ICU was determined as 36%, in the study, the patient's weight below 10 kg, infusion of ES over 60 ml/kg and intraoperative complications were mentioned as risk factors for the need for ICU (26). In our study, we believe that the rate of need for postoperative ICU increased due to the fact that the patient's weight was 8 kg on average, 21.5 ml/kg (177 ml) ES infusion was administered on average, and intraoperative complications such as hypotensive process at a high rate of 52.8% were encountered. While Goobie et al. reported that the length of stay in the ICU was only 1 day in 70% of the cases, the average length of stay was two days in our craniosynostosis case.

In our study, the frequency in cases of craniosynostosis under 1 year of age, the presence of comorbidity features such as intraoperative blood loss and hypotensive process, as well as the fact that our hospital is not a branch hospital in terms of neurosurgery and pediatrics, considering patient safety, we see that ICU transfer is more intense than the literature, at a rate of 83.3%. We think that the fact that the rate of intubated patients is 19.4% in the transfer to the postoperative ICU and that the higher rate of postoperative ICU transfer is detected, also plays a role in the desire to perform postoperative patient care in more reliable environments in terms of monitoring and follow-up.

Miller et al. reported that the incidence of intraoperative hypotension during emergency decompressive craniotomy in children was as high as 52%, especially in children under the age of 3 years with a higher rate, and intraoperative blood loss was the most independent risk factor in these operations (27). On the other hand Khan et al., reported that the presence of persistent intracranial hypertension is associated with mortality exceeding 80% in some series and that intraoperative blood loss exceeding 300 ml is an important predictor of poor prognosis in traumatic brain injuries (28). In Fenton et al.'s study on preventable pediatric intensive care unit (PICU) admission in 16,209 pediatric patients, most of the patients were admitted to the PICU with head trauma. More specifically, they found that 83% of the preventable admission group was head trauma, and 72% of this number was referred as an isolated injury (29).

In our study, we planned to examine two different groups which craniosynostosis and subdural-epidural hematomas as a sub-analysis among the three-year pediatric cranial surgery cases due to the high probability of intraoperative bleeding and their similarities. While the incidence of intraoperative hypotension was higher in the craniosynostosis group (52.8%), intraoperative hypertension was detected only in the subdural-epidural hematoma group with a rate of 15.4%. Contrary to Miller et al., hypotension was observed at a rate of 11.5% in the subdural-epidural hematoma group. We think that the lower rate may be affected by the fact that our age range is above 7 years on average for the group. Due to possible poor prognostic factors such as bleeding, hypotension and hypertension, the proportion of patients intubated at postoperative ICU transfer was 46.2% in the subdural-epidural hematoma group. ICU admission was found to be 84.6%, similar to the studies of Fenton et al.

In the present study, operative durations, postoperative intensive care needs, perioperative vital signs follow-up, and mechanical ventilator monitoring parameters were evaluated. It was determined that operative durations were longer in children >1 year and their vital instabilities were similar to those of infants ≤1 year during the follow-up period. Mechanical ventilator follow-up findings and postoperative blood product replacement conditions were also similar in both groups.

The present study has significant limitations. Firstly, the fact that the study was retrospective and based on files and electronic data were considered an important limitation. In addition, the fact that the age distribution in the study was wide and the number of patients included in the study was less than similar studies because this was a single-center study was considered to be another important limitation. However, it is considered that the present study has an important contribution to make in terms of facilitating the follow-up of pediatric neurosurgery interventions and evaluation of patient characteristics in our hospital. Close monitoring of patients' perioperative vital signs and detailed recording of blood products can be considered a strong aspect of the study.

CONCLUSION

Close monitoring of vital signs of pediatric neurosurgery patients and detailed recording of advanced complications and blood transfusions are thought to be important in perioperative anesthesia management. In particular, it was observed that prolonged operation time increased the amount of intraoperative bleeding. In patients with

craniosynostosis, subdural and epidural hematoma, often accompanied by massive bleeding, the need for ICU increased in the postoperative period due to frequent intraoperative hemodynamic complications.

We believe that it is necessary to be more careful in terms of morbidity and mortality, especially in cases of craniosynostosis, which are more common in children aged 1≤ years, due to massive bleeding than cranial operations in children> 1 year old, and the hypotensive process is more aggressive. It is considered that prospective and multicenter studies are needed on this subject.

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ORIGINAL ARTICLE

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Comparison of Malondialdehyde and Reduced Glutathione in Some Rat Tissues in Hypoxia and Obesity

Hipoksi ve Obezite Olgusunda Malondialdehit ve İndirgenmiş Glutatyon'un Bazı Sıçan Dokularında Karşılaştırılması

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ABSTRACT

Objective: *Obesity is an important global public health problem that is associated with many chronic diseases and is increasing day by day in our country as well as in the world. The aim of this study is to compare malondialdehyde (MDA) and reduced glutathione (GSH) in some rat tissues due to obesity and hypoxia.*

Material and Method: *In our study 24 male Sprague Dawley rats were used. Rats were divided into four groups (n:6) as standard diet/normal oxygen, standard diet/low oxygen, high-fat diet/normal oxygen, and high-fat diet/low oxygen. For the study, a special cage with low oxygen level of 17-18% in the closed system was used. Weight gain of 20-25% was achieved in obese rats. MDA and GSH levels were measured in liver, kidney and brain organ tissues of rats.*

Results: *In our study it was determined that there were significant increases in the amount of MDA and GSH. It was observed that MDA and GSH had a protective effect against hypoxia and obesity in liver and brain tissue, but not in kidney tissue.*

Conclusion: *As a result of our research we think that MDA and GSH may support the current criteria in the diagnosis and/or treatment of obesity and will contribute greatly to more comprehensive analyzes to be made in the future.*

ÖZET

Amaç: *Obezite, günümüzde birçok kronik hastalıklarla bağlantılı olup dünyada görüldüğü gibi ülkemizde de gün geçtikçe artan, önemli küresel halk sağlığı problemidir. Bu araştırmanın amacı obezite ve hipoksiye bağlı olarak malondialdehit (MDA) ve indirgenmiş glutatyon (GSH)'un bazı sıçan dokularında karşılaştırılmasıdır.*

Gereç ve Yöntem: *Çalışmamızda 24 adet Sprague Dawley cinsi erkek sıçan kullanılmıştır. Sıçanlar standart diyet/normal oksijen, standart diyet/düşük oksijen, yüksek yağlı diyet/normal oksijen ve yüksek yağlı diyet/düşük oksijen olmak üzere dört gruba (n:6) ayrıldı. Çalışma için kapalı sistemde oksijen seviyesi düşük %17-18 olan özel kafes kullanılmıştır. Obez sıçanlarda %20-25 ağırlık artışı sağlanmıştır. Sıçanların karaciğer, böbrek ve beyin organ dokularında MDA ve GSH seviyeleri ölçülmüştür.*

Bulgular: *Çalışmamızda MDA ve GSH miktarı açısından anlamlı artışların olduğu saptanmıştır. MDA ve GSH'ın karaciğer ile beyin dokusunda hipoksi ve obeziteye karşı koruyucu etkisi olurken, böbrek dokusunda olmadığı görülmüştür.*

Sonuç: *Araştırmamız sonucu MDA ve GSH'ın obezitenin tanı ve/veya tedavisinde mevcut kriterlere destek sağlayabilir olabileceği ve gelecekte yapılacak olan daha geniş kapsamlı analizlere büyük ölçüde katkı sağlayacağı düşüncesindeyiz.*

Keywords:
Hypoxia
Obesity
Malondialdehyde
Reduced Glutathione

Anahtar Kelimeler:
Hipoksiya
Obezite
Malondialdehit
İndirgenmiş Glutatyon

INTRODUCTION

Hypoxia is a condition of the body where the arterial oxygen concentration is less than normal and is caused by inflammation, sepsis, hypertension, and also causes the release of hypoxia-inducible factor 1 (HIF-1) (1, 2).

Obesity is a chronic metabolic disease that results from inequality between energy intake and expenditure. Increased fat and lipid density feature is observed in the blood. One of the most important reasons for the development of obesity is lack of physical activity (3-5). In a study it was seen that the share of physical activity insufficiency in the onset of obesity is very important (67.5%) (3). Obesity has reached epidemic proportions, contributing greatly to the global burden of some chronic diseases. Epidemiological studies have highlighted a tight link between excess fat deposition and oxidative stress (6, 7). Fat accumulation has also been recognized as a source of oxidative stress (8). Some studies suggest that oxidative stress may be a prerequisite for adipogenesis. It has been found that there is rise in the level of reactive oxygen species (ROS) during adipogenesis (9). Obesity is a very factor with syndromic and nonsyndromic variants. In 2011-2014 the prevalence of obesity was 36% among adults in the United States (10). Between 2015 and 2016, the prevalence of obesity in the United States was 39.8% among adults and 18.5% among teenagers. The

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prevalence of obesity was higher among adults aged 40-59 years than adults aged 20-39 years overall and in both men and women (11). Obesity type II diabetes, hypertension, coronary heart disease, stroke, oiled liver, dementia, obstructive sleep apnea and a risk factor for metabolic disorderliness and illness that significantly increase the risk of developing various cancer species. As a result of studies it is estimated that the average life expectancy will decrease as a result of such diseases (12-15). In general the amount of fat in the body is determined using the body mass index (BMI) and calculation is made by body weight (kg/m²) (16). There are approximately 300 million obese people all over the world and this number is increasing gradually (17).

The adipose tissue is a very active endocrine organ secreted by a series of biologically active molecules called adipokines. The dysfunction of the adipose tissue is one of the primary flaws of obesity. The bad corrupt adipose tissue function is characterized by an atherogenic adipokin structure and proinflammatory secretion (14). Oxidative stress occurs with the increase of free radicals and reactive oxygen radicals and causes severe damage to biological macromolecules and causes disorders in metabolism and physiology. Cells manage to maintain their vital functions against oxidative damage with the help of a system. This system contains glutathione peroxidase (GSHPx), superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), some trace elements and vitamins A, E, C which counter oxidative damage. Recent studies have shown that superoxide formation is enhanced in obesity related disorders and SOD is inhibited by nonenzymatic glycation and furthermore hyperlipidemia increases endothelial superoxide production. Therefore superoxides are thought to play a key role in the physiopathology of the cardiovascular and metabolic effects of obesity (18).

MDA resulting from lipid peroxidation is an indicator of oxidative stress in tissues and cells. Lipid peroxidase is a derivative enzyme of the unsaturated fatty acid that emerged as a result of dissipating complex components (19). Due to the relatively short half lives of free radicals level detection is difficult (20).

GSH is an endogenous peptide that can be synthesized in the liver without the need for genetic data, consists of glutamic acid, cysteine and glycine amino acids and is an significant water soluble antioxidant. GSH plays a vital role in cells so that enzymes and other cellular components are not kept in a reduced state. Glutathion in very loud concentrations in many cells protects biological membranes opposite lipid peroxidation. GSH is mostly synthesized in the liver and approximately 40% is excreted in bile (21-23). Free radicals react with peroxidase to defend cells against oxidative damage (24). ROS's potentially deleterious impacts are controlled by the cellular antioxidant defense system. GSH is an significant component of intracellular preventive mechanisms opposite many deleterious stimuli, including oxidative stress (25).

The aim of our study is to research the effectiveness of MDA and GSH enzyme changes in the diagnosis and treatment stages, in addition to the criteria valid in the evaluation of obesity.

MATERIAL AND METHOD

Rats Used in the Study

5 month old male Sprague Dawley rats were used in the study. Rats were housed in special lattices for 12 clock in light/dark, ventilated room temperature at 24°C. Rats other than the obesity group were given standard diet and water, and the group in which obesity was desired was given high-fat diet and water. Obese rats were fed a high fat diet for 23 weeks. Weight gain of 20-25% was achieved in obese rats. Their average weights varied between 450-534 grams (g). Animal rights are protected in line with the principles of the 'Guide for the Care and Use Guide of Laboratory Animals' (ethics committee no: 2015/86).

Table 1: Rat groups used in the study, their numbers and nutritional content

1. Group (n:6)	Standard Diet/Normal PO2 (SD/NO2)
2. Group (n:6)	Standard Diet/ Low PO2 (SD/LO2)
3. Group (n:6)	High Fat Diet/Normal PO2 (HFD/NO2)
4. Group (n:6)	High Fat Diet/Low PO2 (HFD/LO2)

Retrieval of Tissues

A mixture of 1500 µl/kg ketamine and 500 µl/kg xylazine was administered intramuscularly (i.m.) as anesthetic agent. The abdomen of the anesthetic administered rats was cut, the thorax was opened and the vena cava vessels were cut. The perfusion process was completed by injecting 5 ml of saline into the right and left ventricles of the heart.

Collection and Homogenization of Working Tissues (liver, kidney and brain)

Each rat used in the experiment was euthanized by perfusion and removing the rat's heart. All liver, kidney and brain tissue were taken. It was reperfused with physiological saline and wrapped in labeled aluminum foils. Tissues were placed in liquid nitrogen immediately after collection. After the dissection procedures were completed, the tissues were removed from liquid nitrogen and stored at -40 °C.

The homogenization process was carried out quickly and rapidly in ice. The tissues were cut with a scalpel, weighed on a precision balance (ATX224) and taken into glass tubes with buffer solution. 4500 µl of 0.2 M pH: 7.2-7.6 phosphate buffer was added to 0.5 g tissue. Tissues were sonicated on ice for 30 to 60 seconds with an ultrasonicator (BANDELIN SONOPLUS). These tissues were centrifuged (MicroCL 21 centrifuge), separated into supernatant and homogenate parts, placed in 1000 µl eppendorf tubes and stored at -40 °C.

Measurement of MDA Amount: According to the method of Uchiyama et al. it was determined by spectrophotometric measurement of the supernatant extracted from the N-butanol phase of the pink colored product formed by the reaction of MDA with thiobarbituric acid at 95 °C at 520 and 535 nm wavelengths (26).

Measurement of GSH Amount: GSH analysis was performed according to the method described by Ellman. The amount of reduced glutathione was determined by the reaction of the glutathione in the analysis tube with 5,5'-dithiobis 2-nitrobenzoic acid to give a yellow greenish color and by measuring the light intensity of this

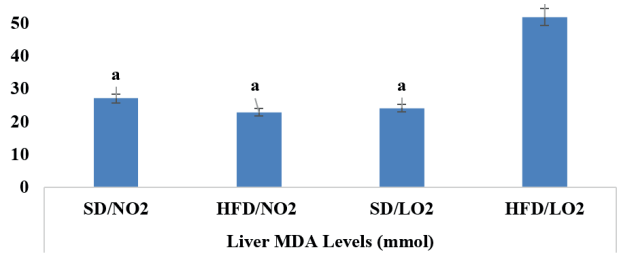

Figure 1: Amounts of MDA (mmol) in rat liver tissue. The differences between different letters in the pillars are statistically important. Results are given as ±SE.

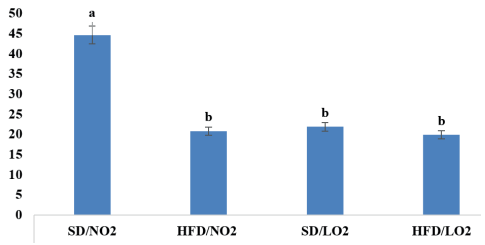

Figure 2: Amounts of MDA (mmol) in rat kidney tissue. The differences between different letters in the pillars are statistically important. Results are given as ±SE.

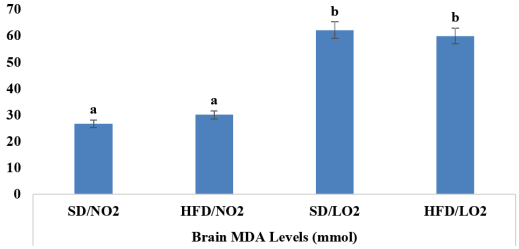

Figure 3: Amounts of MDA (mmol) in rat brain tissue. The differences between different letters in the pillars are statistically important. Results are given as ±SE.

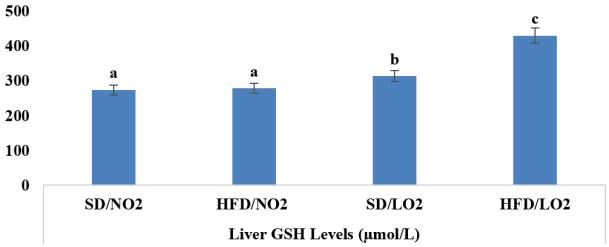

Figure 4: GSH amounts (µmol/L) in rat liver tissue. The differences between different letters in the pillars are statistically important. Results are given as ±SE.

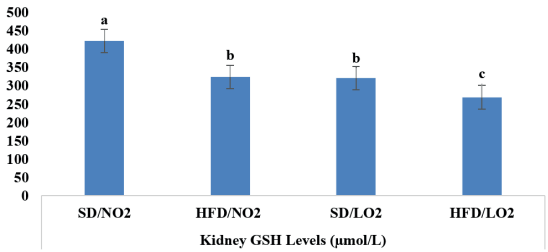

Figure 5: GSH amounts (µmol/L) in rat kidney tissue. The differences between different letters in the pillars are statistically important. Results are given as ±SE.

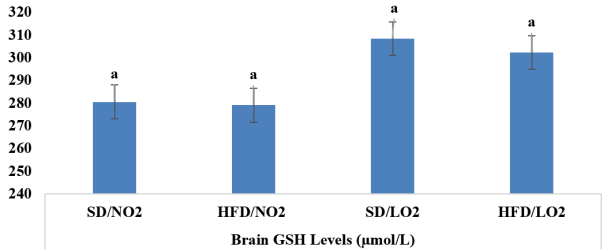

Figure 6: GSH amounts (µmol/L) in rat brain tissue. The differences between different letters in the pillars are statistically important. Results are given as ±SE.

color at a wavelength of 410 nm spectrophotometrically (27).

Statistical Analysis

Statistical evaluations were made with SPSS for Windows Version 15.0 package program. Data for measurable variables are given as mean ± standard error. The tukey test method was used to determine the differences between the groups. The value found was evaluated at the 5% significance level (95% confidence interval, $p<0.05$).

RESULTS

In all working groups; In liver, kidney and brain, MDA was determined by Uchiyama et al. and GSH analysis was performed by spectrophotometric measurement according to the method described by Ellman. Graphical representations of MDA amounts measured in tissues are given in Figure 1, Figure 2 and Figure 3, and GSH amounts are given in Figure 4, Figure 5 and Figure 6.

When all groups were examined in terms of MDA amount in rat liver it was seen that there was a important rise in HFD/LO2 ($p<0.05$). There was a significant increase in liver tissue due to obesity and hypoxia ($p<0.05$). There was no significant increase between SD/NO2, HFD/NO2 and SD/LO2 groups ($p>0.05$) (Figure 1).

When all groups were examined in terms of the amount of MDA in the rat kidney tissue it was observed that there was a significant increase in SD/NO2 ($p<0.05$). There was no important rise between HFD/NO2, SD/LO2 and HFD/LO2 groups ($p>0.05$)(Figure 2).

When the rat brains of all groups were analyzed for the amount of MDA it was seen that there was an important increase between SD/NO2-HFD/NO2 and SD/LO2-HFD/LO2 groups ($p<0.05$). There was an important rise in brain tissue due to hypoxia ($p<0.05$). While there was no important rise between SD/NO2-HFD/NO2 groups ($p>0.05$), there was no significant increase between SD/LO2-HFD/LO2 groups ($p>0.05$)(Figure 3).

When all groups were examined in terms of the amount of GSH in the rat liver it was seen that the most important rise was in HFD/LO2 and the second important rise was in SD/LO2 ($p<0.05$). There was an important rise due to hypoxia ($p<0.05$). When SD/LO2 and HFD/LO2 groups were compared it was observed that there was an important rise between these groups ($p<0.05$). There was no important rise between SD/NO2 and HFD/NO2 groups ($p>0.05$) (Figure 4).

When all groups were examined in terms of GSH amount in rat kidney it was seen that the most important rise was in SD/NO2, the second important rise was in HFD/NO2 and SD/LO2 ($p<0.05$). There was no important rise between HFD/NO2 and SD/LO2 groups ($p>0.05$). There was an

important rise between HFD/NO2-SD/LO2 and SD/NO2-HFD/LO2 groups ($p<0.05$) (Figure 5).

When all groups (SD/NO2, HFD/NO2, SD/LO2, HFD/LO2) were examined in terms of the amount of GSH in the rat brain, no significant difference was observed ($p>0.05$) (Figure 6).

DISCUSSION

In our study it was determined that the amount of MDA was rised in HFD/LO2 in the liver, SD/LO2 in the brain and in the HFD/LO2 groups compared to the other groups. It was observed that this increase was related to obesity and hypoxia. It was determined that the amount of GSH was increased in the liver and brain in the SD/LO2-HFD/LO2 groups compared to the other groups. In the kidney it was observed that the amount of MDA and GSH reduced in the other three groups compared to the control group. This makes us think that MDA and GSH play a role in maintaining body homeostasis in hypoxic conditions as well as protecting against hypoxia and obesity.

Erkasap S, Erkasap N, Aral E, et al. The protective effect of Epidermal Growth Factor (EGF) on wounds in the gastric mucosa of rats treated with ethanol was investigated. MDA, protein sulphuride groups (SH) and protein carbonyl values were measured in gastric tissue. In the ethanol+EGF group, ulcer symptoms, histamine, MDA and protein carbonyl values were decreased. When these values were compared with the values of animals without EGF they reported that EGF acted as an antioxidant as well as a protective effect on gastric mucosal injuries (28). In the presence of oxidative stress the lipid peroxidation indicator MDA level increases in various tissues and blood plasma/serum samples while the GSH and SOD enzyme activities which provide ROS elimination decrease (29, 30). In this study plasma MDA level increased and GSH and SOD enzyme activity decreased in rabbits who were injected with aglepristone for 2 consecutive days. From these results it was observed that abortion (low) and/or especially aglepristone had a negative effect on reducing antioxidant defense capacity and on oxidative stress parameters. In addition decreased antioxidant capacity was thought to play a role as a determining factor in the pathogenesis of infertility (31). Troudi et al. found a rise in MDA levels and a reduce in antioxidant enzymes such as SOD and GSH due to oxidative stress in rats in the early and late stages of pregnancy using a neurotoxic agent that triggers the formation of oxidative stress. However, no abortion occurred in either of these studies (29). In our study an increase was observed in liver tissue except kidney and brain tissue. Changes in oxidative stress parameters support our study.

It has been stated that oxidative damage accumulation in cells may play a role in the pathogenesis of some diseases due to deterioration in protein, lipid and membrane structure, as well as cell repair mechanisms (32, 33). Studies have found that there is a positive correlation between disease severity and oxidative stress markers and a negative correlation between antioxidant markers (34, 35). In our study we determined that the body tries to increase antioxidant enzyme activity against oxidant stress in order to protect itself.

In this study investigating the efficacy of free oxygen radicals in patients with head and neck malignant tumors; while the erythrocyte MDA levels and SOD activities of the patients were higher than the control group, their CAT activities decreased. It was observed that there was no statistically important difference between the GSH-Px activities in both groups. As a result of the research it was stated that erythrocyte MDA levels may play a significant role in tissue damage that leads to the development of head and neck malignant tumors and the addition of drugs with antioxidant effects may be beneficial to reduce the damage and carcinogenic effects of increased free oxygen radicals on the tissue (36). Doner et al. and Torun et al. showed that serum MDA levels were considerably increased in patients with head and neck malignant tumors compared to normal individuals. They also stated that while MDA levels increase in cancer patients, antioxidant enzyme activities may increase or decrease (37, 38). Solmaz et al. reported that CAT and SOD, enzyme activities in the tumoral tissue in head and neck epidermoid cancers gradually decrease as the stage progresses and the MDA level gradually increases (39). The increase in free oxygen radical level can cause changes to mutagenism, cytotoxicity and gene expression, it may lead to malignant tumor development and that a malignant development of this mutagenism can contribute to a malignant transformation of a malignant development (40). It has been stated that MDA which is the product of destruction by free oxygen radicals is also mutagenic and potentially carcinogenic (38).

The relationship between breast cancer and oxidative stress and the activities of some enzymes was investigated and MDA level was found to be higher in breast tumor tissue than in normal tissue. It has been thought that the increase in MDA level may be related to the formation of necrosis caused by insufficient vascularization in invasive ductal carcinoma and the increase in antioxidant enzymes may be due to the rise in enzyme expression in tumor cells (41).

Oxidative stress markers were investigated in liver, heart and kidney tissues of obese mice. The first group received HFD for 16 weeks and the second group (control group) received only SD for 16 weeks. Lipid profile measurement, tissue samples taken from the liver; blood samples were taken and checked for MDA, protein carbonyl (PCO), GSH levels and glutathione S-transferase activities (GST). Feeding with HFD has been shown to significantly rise body weight and induce dyslipidemia. In the study an important rise in MDA and PCO levels in the liver and heart tissues of obese mice and a decrease in the kidney were shown. GSH levels, reduce in kidney and liver tissues of obese animals, important rise in heart tissue were noted. A negative correlation was found between MDA-PCO levels and GSH levels in liver and kidney tissues. A positive correlation was found between GSH levels in heart tissues. It has been stated that the rise in MDA-PCO levels in obesity, being correlated with antioxidant enzyme activities and decrease in glutathione levels, accompanied by oxidative stress in liver, heart and kidney tissues, may possibly contribute to the progression of obesity-related problems (42).

In another study biochemical markers of nitric oxide (NO), MDA, GSH and the oxidative state of the follicle were

investigated to foretell the outcome of in vitro fertilization. Follicular cells were collected in the study. Biochemical analyzes of NO, MDA and GSH were performed in the collected cells. When successful and unsuccessful pregnant groups were compared in terms of NO, MDA and GSH, MDA was found to be high in follicular cells and low in the pregnant group. Correlation analysis between oxidative stress and IVF parameters revealed a weak correlation between MDA and fertilization rate. ROC curve analysis showed that MDA had a field below the 0.74 curve and could predict pregnancy with high precision. Since MDA is significantly different in pregnant and nonpregnant female and has a good sensitivity profile in predicting pregnancy it has been said that it can be considered as a marker to predict IVF success (43).

CONCLUSION

In our study it was observed that the amount of MDA increased in the liver and brain tissues, while the amount of GSH increased in the liver tissue and did not increase in the brain tissue. The most significant increase was observed in the hypoxia and obese groups of liver and brain tissues. We believe that these enzymes will have a positive effect in preventing obesity, adapting to the negative conditions that occur in hypoxia and in diagnosis and/or treatment. We think that investigating MDA and GSH enzymes in other tissues besides liver, kidney and brain tissues may yield useful results. Our research has shown that it will contribute to future comprehensive studies.

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

Ethics: This study was conducted with the Approval of Inonu University Faculty of Medicine Experimental Animals Ethics Committee (Research Protocol No: 2016/A-71)

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Animal Supply: İnönü University Experimental Animals Production and Research Center

Approval of final manuscript: All authors

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ORIGINAL ARTICLE

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Effects of Cinnamon on VEGF and NF-κB Immunoreaction in the Lung Tissue of Diabetic Rats

Tarçının Diyabetik Sıçanların Akciğer Dokusunda VEGF ve NF-κB İmmünoreaksiyonu Üzerindeki Etkileri

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ABSTRACT

Objective: *Diabetes mellitus is a metabolic disorder described as hyperglycemia induced by insulin deficiency or resistance. Increasing evidence in studies has shown that the lung is the target of diabetic complications. According to traditional medicine theories, cinnamon is considered a supportive treatment method for diabetics. The aim of this study is to investigate the effect of cinnamon on the immunohistochemical expression of VEGF and NF-κB in lung tissue of streptozotocin-induced experimental diabetic rats.*

Material and Method: *Thirty-two male rats were randomly divided into four groups: Diabetes, Diabetes + cinnamon, Cinnamon, and Control. The immunohistochemical expression of VEGF and NF-κB in the lung tissue was determined by using the streptavidin-biotin complex method.*

Results: *It was determined that while cinnamon application alone did not change VEGF expression in lung tissue, the decreased VEGF expression in the diabetes group increased with the cinnamon application. There was no significant difference in the intensity of NF-κB expression between the control and cinnamon groups. As a remarkable finding, in the diabetic group's lung tissue, there were strong positive NF-κB reactions. In addition, a weak positive NF-κB reaction was detected in the diabetes+cinnamom group.*

Conclusion: *As a result, in our study cinnamon caused reduced the increase in NF-κB expression caused by diabetes and increased the decreased VEGF expression. In conclusion, we believe that this work will be valuable in understanding possible cytokine mechanism changes that may occur in lung tissue as a result of diabetes and the development of therapeutic techniques.*

ÖZET

Amaç: *Diabetes mellitus, insülin eksikliği veya direncinin neden olduğu hiperglisemi olarak tanımlanan metabolik bir hastalıktır. Çalışmalarda artan kanıtlar, akciğerin diyabetik komplikasyonların hedefi olduğunu göstermiştir. Geleneksel tıp teorilerine göre tarçın, şeker hastaları için destekleyici bir tedavi yöntemi olarak kabul edilmektedir. Bu çalışmanın amacı, tarçının streptozotosin ile indüklenen deneysel diyabetik sıçanların akciğer dokusunda VEGF ve NF-κB'nin immünohistokimyasal ekspresyonu üzerindeki etkisini araştırmaktır.*

Gereç ve Yöntem: *Otuz iki erkek sıçan rastgele dört gruba ayrıldı: Diyabet, Diyabet + tarçın, Tarçın ve Kontrol. VEGF ve NF-κB'nin akciğer dokusunda immünohistokimyasal ekspresyonu, streptavidin-biotin kompleksi kullanılarak belirlendi.*

Bulgular: *Tarçın uygulamasının tek başına akciğer dokusunda VEGF ekspresyonunu değiştirmezken, diyabet grubunda tarçın uygulaması ile azalmış VEGF ekspresyonunun arttığı belirlendi. Kontrol ve tarçın grupları arasında NF-κB ekspresyonunun yoğunluğunda anlamlı bir fark yoktu. Dikkat çekici bir bulgu olarak, diyabetik grubun akciğer dokusunda güçlü pozitif NF-κB reaksiyonları vardı. Ayrıca diyabet+cinnamom grubunda zayıf pozitif NF-κB reaksiyonu tespit edildi.*

Sonuç: *Sonuç olarak bialışmamızda tarçın diyabetin neden olduğu NF-κB ekspresyonundaki artışın azalmasına, azalmış VEGF ekspresyonunun ise artmasına neden olmuştur. Bu bakımdan, çalışmamızda elde edilen bulguların diyabet sonucu akciğer dokusunda meydana gelebilecek olası sitokin mekanizması değişikliklerinin anlaşılmasında ve terapötik tekniklerin geliştirilmesi açısından değerli olacağı kanaatindeyiz.*

Keywords:
Cinnamon
Diabetes
Lung
NF-κB
VEGF

Anahtar Kelimeler:
Tarçın
Diyabet
Akciğer
NF-κB
VEGF

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder described as hyperglycemia induced by insulin deficiency or resistance, with long-term consequences for several organs (1). DM is a health problem associated with many serious complications. Increasing evidence in studies has shown that the lung is the target of diabetic complications (2). Predisposition to infections, pneumonia, asthma, pulmonary fibrosis, and chronic obstructive pulmonary disease are disorders induced by diabetes in the lungs (3). Today, it has been shown that alternative treatments are needed to control diabetes and reduce its complications (4). According to traditional medicine theories, cinnamon is considered a supportive treatment method for diabetics (5). Cinnamon is a spice that contains a wide range of active phytochemical compounds that have antioxidant

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properties (6). It stimulates the production of insulin-sensitive glucose transporters, which leads to lower insulin resistance (7).

Nuclear factor-kappa B (NF-κB) is a transcription factor that regulates gene expression and codes for chemokines, immune response surface receptors, cytokines, cell adhesion molecules, and inflammation (8). It also affects the signaling onset for cell differentiation and apoptosis inhibition (9). NF-κB is well known for its ability to aggregate an inflammatory response by regulating the expression of numerous inflammatory factors (10). This is accomplished by positively and negatively controlling the expression of a large number of important genes involved in the process (11).

Vascular endothelial growth factor (VEGF) is a angiogenic factor that induces the proliferation and migration of vascular endothelial cells as well as the permeability of blood vessels (12). VEGF plays a crucial role in diabetic retinopathy, inflammatory diseases, and acute lung injury. Hypoxia, different growth factors, cytokines, and other extracellular substances can all affect VEGF expression (13). It is known that there is a significant expression of VEGF in the normal lung without significant mitogenesis or angiogenesis (14). Moreover, VEGF can act as a paracrine survival factor for lung epithelial cells and endothelial cells (15).

This study's main objective is to investigate the effect of cinnamon on the immunohistochemical expression of VEGF and NF-κB, which are also expressed by many tissues and cells in the lung tissue of experimental diabetic rats induced by streptozotocin (STZ).

MATERIAL AND METHOD

Animal material

This study was approved by the Ondokuz Mayis University Animal Experiments Local Ethics Committee (dated: 11.03.2020, approval number: 68489742-604.01.03-E.6122). In this study, 32 male rats weighing 250-300 g were used. The rats were housed in a standard cage with 12 hours of light and 12 hours of darkness in a 22°C ambient temperature environment, and they were given ad libitum food and tap water.

Experiment groups

450 mg of STZ (Sigma, S0130-1G) was prepared by dissolving in 10 ml of distilled water and administered to diabetic groups (16). Thirty two rats were randomly divided into four groups. No application was made in the control group (n=8). The cinnamon group (n=8) received cinnamon extract by oral gavage at a dose of 0.5 mg/kg for 14 days (17). In the diabetes group (n=8): a single intraperitoneal injection of STZ at a dose of 45 mg/kg was used to induce experimental diabetes. Diabetes + cinnamon group (n=8): experimental diabetes was induced by a single intraperitoneal injection of STZ (45 mg/kg) and the cinnamon extract was administered to the STZ-induced diabetic rats (0.5 mg/kg for 14 days by oral gavage). Then, the rats in all groups were sacrificed, and lung tissue samples were collected for immunohistochemistry. The lung tissue samples were fixed in 10% formaldehyde solution, and the tissue sections were taken with a thickness of 5 μm from the prepared paraffin blocks.

Determination of blood glucose levels

A glucometer (PlusMED Accuro) was used to take blood from the hungry animals' tail vein 8 hours before the start of the trial to determine their blood glucose level preprandial. Animals involved in the study with a glucose level of 300 mg/dL had their preprandial blood glucose level measured for 8 hours on the 3rd day of STZ practice. From day 3 of STZ practice, cinnamon extract was administered by oral gavage for 14 days.

Immunohistochemistry

Using the Streptavidin biotin complex method, five-micrometer lung sections were stained immunohistochemically using mouse monoclonal VEGF (1/500 dilution, Santa Cruz Biotechnology, sc7269) and mouse monoclonal NF-κB (1/500 dilution, Santa Cruz Biotechnology, sc8008) primary antibodies (18). The secondary antibody was Histostain Plus (Zymed kit: 85-6743, United States). Following deparaffinization, sections were heated in a microwave oven at 700 W for antigen retrieval in a citrate buffer (pH:6) solution. The tissues were incubated in a 3% hydrogen peroxide solution to block endogenous peroxidase activity. To prevent nonspecific protein binding in sections, serum from the kit was instilled after washing with phosphate buffer solution (PBS). The primary antibody was applied, and the samples were kept at +4 0C overnight. In the negative control group, only PBS solution was used. After washing, sections were instilled with biotinylated secondary antibody and incubated at streptavidin-horseradish peroxidase complex. The final stage involved using 3,3'-diaminobenzidine (DAP) as a chromogen and covering the slides with entellan after hematoxylin counterstaining.

Immunohistochemical examination

The intensity of positive staining in immunohistochemical examination was evaluated semiquantitatively using a standard four-point scoring scale for intensity being scored as negatively (-), weakly (+), moderately (++), strongly (+++) stained (19). A Nikon digital-sight imaging system was used with a Nikon Eclipse 50i microscope to take histological pictures.

RESULTS

VEGF Expression

In alveolar epithelial cells, bronchial and bronchiole epithelial cells, smooth muscle cells, and smooth muscle cells of the median layers of large vessels, various intense reactions were observed when the VEGF immunohistochemical expression results were evaluated in general. Also, VEGF immunopositive cells were observed in the connective tissue surrounding the bronchi and bronchioles, alveolar macrophages, as well as the interalveolar areas and bronchial-associated lymphoid tissue (BALT) (Figure 1A, 1B, 1C, 1D). It was determined that while cinnamon application alone did not change VEGF expression in lung tissue, the decreased VEGF expression in the diabetes group increased with cinnamon application. The semi-quantitative analysis between groups for VEGF immunohistochemical staining are summarized in Table 1.

NF-κB Expression

In lung tissues of all groups, there were positive immunoreactions were observed in the alveolar epithelial

Table 1: Results of semi-quantitative analysis of VEGF and NF-κB immunohistochemical reactions in lung tissue.

	VEGF	NF-κB
Control group	++	++
Diabetes group	+	+++
Diabetes + cinnamom group	++	+
Cinnamon group	++	++

Semiquantitative scoring of immunostaining intensities: -, negative; +, weak; ++, moderate; +++, strong.

cells, bronchial and bronchiolar epithelial cells, and smooth muscle cells. When the immunostaining in the groups was examined no difference was observed in NF-κB immunoreaction between the control and cinnamon groups. As a remarkable finding, in the diabetic group's lung tissue, there were strong positive NF-κB reactions. In addition, a weak positive NF-κB reaction was detected in diabetes + cinnamom group (Figure 2A, 2B, 2C, 2D). The immunohistochemistry reactions and group comparisons are shown in Table 1.

DISCUSSION

Increased production of reactive oxygen species causes oxidative stress, which plays a crucial role in the pathogenesis of diabetes' late complications. NF-κB regulates the expression of most of the genes of many growth factors, including VEGF (20). Also, a study investigating the relationship between VEGF and NF-κB reported that lncRNA ANRIL, which is overexpressed in diabetes complicated with cerebral infarction, activates the NF-κB signaling pathway by upregulating VEGF (21). Hyperglycemia activates the transcription factor NF-κB, which helps control the expression of many inflammation-related genes by causing free oxygen radicals to be produced (22). NF-κB proteins can be considered regulators of cellular homeostasis because their activity is spontaneously regulated by a variety of stimuli (23). Dysregulation of NF-κB has been linked to the pathology of a variety of diseases due to its central role

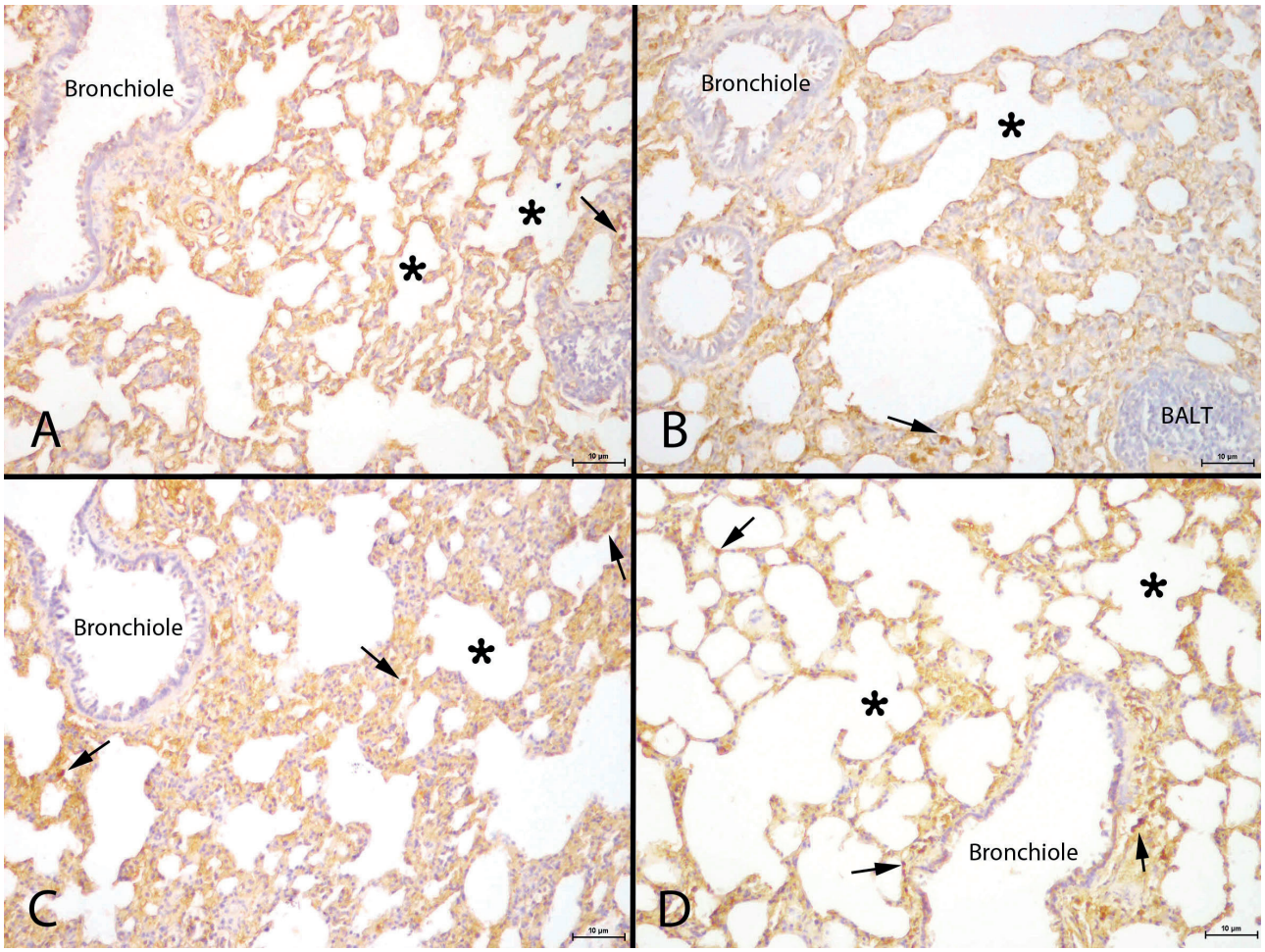

Figure 1: Representation of lung section imagings of VEGF immunohistochemical staining; A: Control group, (arrow): VEGF immun positive cell, (asterix): sacculus alveolaris. B: Diabetes group (arrow): VEGF immun positive cell, (asterix): sacculus alveolaris, (BALT): bronchus-associated lymphatic tissue. C: Diabetes + cinnamom group, (arrow): VEGF immun positive cell, (asterix): sacculus alveolaris. D: Cinnamon group (arrow): VEGF immun positive cell, (asterix): sacculus alveolaris, original magnification X20; range bar, 10 µm.

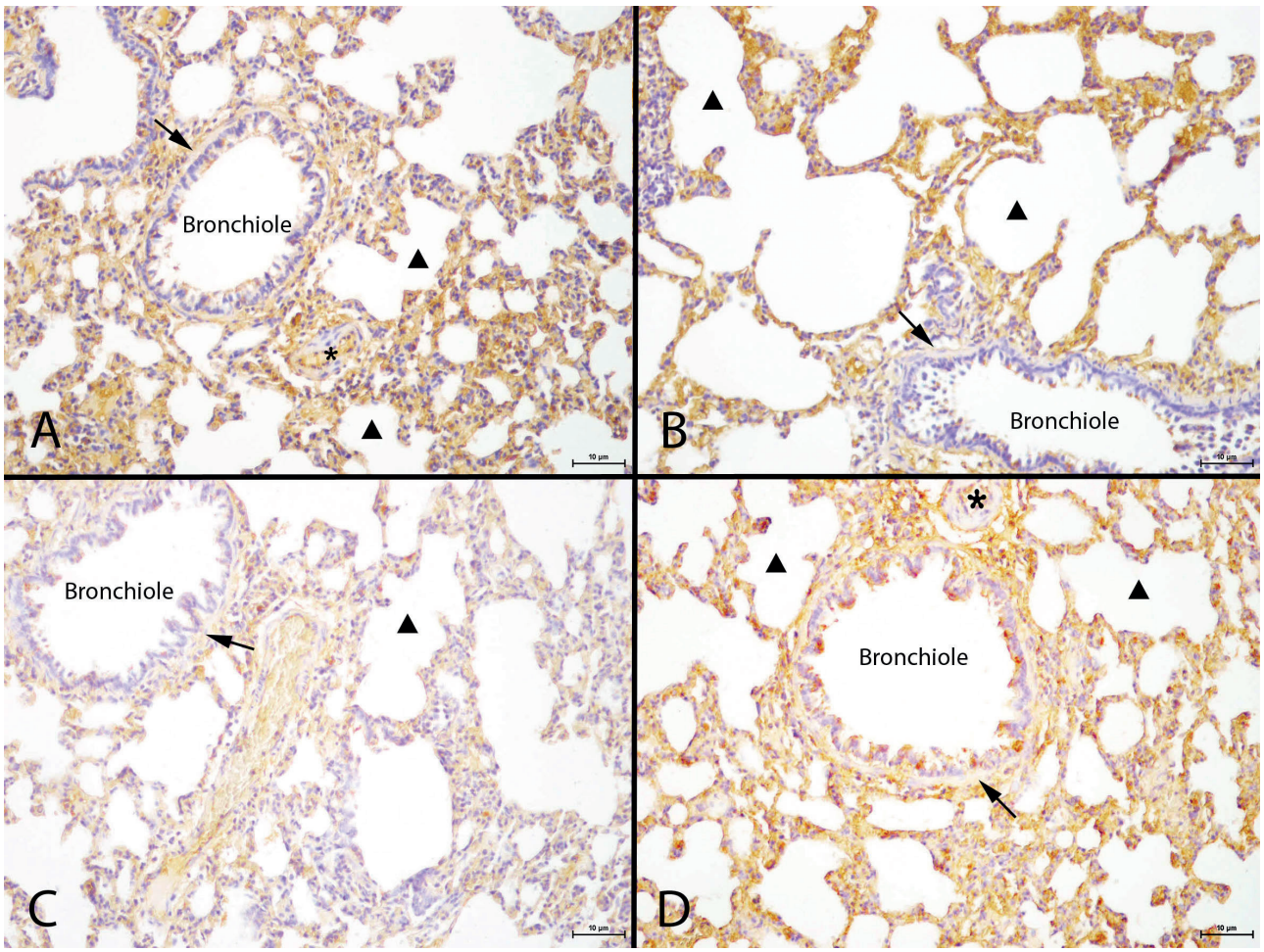

Figure 2: Representation of lung section imagings of NF-κB immunohistochemical staining; A: Control group, (arrow): bronchiolar smooth muscle, (arrowhead): sacculus alveolaris, (asterix): blood vessel. B: Diabetes group (arrow): bronchiolar smooth muscle, (arrowhead): sacculus alveolaris. C: Diabetes + cinnamom group (arrow): bronchiolar smooth muscle, (arrowhead): sacculus alveolaris. D: Cinnamon group (arrow): bronchiolar smooth muscle, (arrowhead): sacculus alveolaris, (asterix): blood vessel, original magnification X20; range bar, 10 µm.

in many cellular processes (24). It has been shown that various tissue damage pathways caused by high glucose concentration can change the expression of several genes important in the pathogenesis of diabetic complications by activating transcription factors such as NF-κB (25). According to a recent study, NF-κB can affect the insulin signaling pathway and subscribe to insulin resistance, suggesting that blocking NF-κB activity could be a novel treatment option for insulin resistance (26). A prior study has demonstrated that in the ovarian tissue of diabetic rats compared to the control group of normal rats, determined that NF-κB immunoexpression was significantly increased (27). According to a study conducted on rats, it was reported that diabetes increased the expression of NF-κB in liver tissue, and this increase decreased with ghrelin treatment (28). The study of Wang et al. indicated that dysbiosis of the gut-lung microbiota in STZ-induced diabetic mice increased the risk of pulmonary fibrotic changes by activating the NF-κB signaling pathway (29). A recent study observed that high blood sugar levels decreased after daily administration of cinnamon extract in diabetic female and male rats. In addition, the absence of any adverse effects on tissues such as kidneys and pancreas in the histochemical examination was acknowledged as positive effects of cinnamon (30). In this study, while increased NF-κB immunohistochemistry was observed in the diabetes group, it was noted that NF-κB expression decreased in the cinnamon + diabetes group. When compared to the control group, no difference was observed in the cinnamon-only group. This suggested that cinnamon may reduce the possible harmful effects that may develop due to diabetes by reducing the transmission of diabetes-related cytokines in the lung. Also, in our study, NF-κB increased immunohistochemically in rat lung tissue in the diabetes group, which may suggest that NF-κB plays an significant role in the pathogenesis of diabetes-induced lung.

The main sources of VEGF in the airways are alveolar epithelial cells, bronchial epithelial cells and smooth muscle cells, fibroblasts, and alveolar macrophages (31). Studies in animal models indicate that the absence of VEGF signaling may cause capillary and alveolar hypoplasia and decreased lung maturation and surfactant production (32, 33). Due to oxidative stress, the synthesis and secretion of VEGF in diabetic patients might deteriorate (34). According to a study on rats, it was determined that in testis tissue VEGF expression decreased in diabetic rats (35). A previous study specified that VEGF immunolocalization

was observed to decrease gradually in the lung tissue of diabetic rats 7 and 14 days after the development of diabetes, compared to the control group (36). It has also been specified that diabetes may be associated with impairments in VEGF expression and action (37). For instance, several studies suggested that both impaired angiogenesis and microcirculatory dysfunction in diabetics may be due in part to decreased expression of VEGF and its receptors (38, 39). Cinnamaldehyde, one of the cinnamon's components, has been shown to lower blood glucose levels in diabetic rats and increase plasma insulin levels. Furthermore, it has been reported that cinnamaldehyde regenerated pancreatic islets damaged by STZ through its antioxidant activity and stimulation of β-cells, which directly resembles the insulin secretagogue effect (40). Although diabetes decreased VEGF expression in our study, it was observed that cinnamon treatment reversed this effect and increased VEGF expression. However, there was no significant difference in VEGF expression between the cinnamon-treated and control groups. These data suggest that cinnamon may be contributing to the VEGF expression. Thus, it is thought that possible lung damage caused by diabetes can be prevented. But clearly, more investigations are needed to define the interaction between cinnamon and VEGF.

As a result, in our study cinnamon caused decreased the increase in NF-κB expression caused by diabetes and increased the decreased VEGF expression. In conclusion, we believe that this study will be useful in understanding possible cytokine mechanism changes that may occur in the lung tissue due to diabetes and in the development of treatment methods.

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ORIGINAL ARTICLE

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Yoğun Bakım Ünitelerinde Çalışan Hemşirelerde Koronofobinin Değerlendirilmesi

Evaluation of Coronophobia in Nurse Working in the Intensive Care Unit

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ABSTRACT

Objectictive: *To find the incidence of coronaphobia and associated risk factors of nurses who worked in a COVID-19 intensive care unit during the pandemic period.*

Material and Metod: *After obtaining approval of ethics committee (no: 2021/147), nurses were surveyed for demographic data and the Coronavirus-19 Phobia Scale (adapted to Turkish) between June 2021- January 2022 on a voluntary basis. Surveys which include incomplete answers or answers supplemented with comments were excluded.*

Results: *Data from a total of 102 participants were analyzed. The mean total score of the Coronavirus-19 Phobia scale was moderate (50.1±10.7). The sub-dimension scores were as follows: psychological score was slightly high (18.1±4.1), somatic score was slightly low (10.1±3.2), social score was moderate (13,7±3,4), economic score was low (8.2±2.7). It was found that the sub-dimensions of the scale were correlated with each other, and the strongest correlation was between the somatic and economic dimensions.*

The total scores and subdimension scores were similar among men and women, except that mean economic anxiety score in men was statistically significantly higher compared to women (9.7±3.4 vs 7.8±2.4, p=0.030).

Conclusion: *In the pandemic, exhaustion from intense work tempo, decrease in patient care quality, decrease in professional satisfaction, losses in close family and health workers due to COVID-19 increase the burden of coronaphobia even more. For a more efficient and quality health service, healthcare professionals' stakeholders should be supported with in-service training on coping methods about coronophobia, and their working hours and environments should be planned appropriately.*

ÖZET

Amaç: *Pandemi döneminde COVID-19 yoğun bakım ünitesinde çalışan hemşirelerde koronafobi sıklığını ve ilişkili risk faktörlerini saptamak.*

Gereç ve Yöntem: *Etik kurul onamını (no: 2021/147) takiben, Haziran 2021-Ocak 2022 tarihleri arasında yoğun bakım ünitelerinde hemşire statüsünde çalışan sağlık çalışanlarına gönüllülük esasına göre anket uygulandı. Demografik veriler ve Koronavirüs-19 Fobisi Ölçeğinin Türkçe'ye adapte edilmiş soruları soruldu. Eksik yanıt veya yanıt yanında yorum içeren anketler analiz edilmedi.*

Bulgular: *Toplam 102 katılımcının verileri değerlendirildi. Ortalama Koronavirüs-19 Fobisi skoru orta düzeyde (50,1±10,7) idi. Alt boyut puanları şu şekilde saptandı: psikolojik skor hafif yüksek (18,1±4,1), somatik skor hafif düşük (10,1±3,2), sosyal skor orta düzeyde (13,7±3,4), ekonomik skor hafif düşük (8,2±2,7) Alt skorların birbirleriyle korele olduğu, en kuvvetli korelasyonun somatik ve ekonomi boyutlar arasında olduğu bulundu.*

Total ve alt skorların cinsiyetler arasında benzer olduğu, ancak erkeklerde ekonomik kaygı alt skorunun kadınlara göre istatistiksel olarak anlamlı düzeyde yüksek olduğu saptandı (9,7±3,4 vs 7,8±2,4, p=0.030).

Sonuçlar: *Pandemide, yoğun iş temposundan tükenme, hasta bakım kalitesinde düşme, mesleki tatminde azalma, COVİD-19 'a bağlı yakın aile ve sağlık çalışanlarında ortaya çıkan kayıplar koronafobi yükünü daha da artırmaktadır. Daha verimli ve kaliteli bir sağlık hizmeti için sağlık çalışan paydaşlarının koronafobi konusunda başa çıkma yöntemleri ile ilgili hizmet içi eğitim ile desteklenmeli, çalışma süre ve ortamları uygun şekilde planlanmalıdır.*

Keywords:
Intensive care unit
Nurse
Coronaphobia

Anahtar Kelimeler:
Yoğun bakım ünitesi
Hemşirelik
Koronafobi

GİRİŞ

2019 yılında Çin'de başlayan ve 2020 yılında dünya sağlık örgütü tarafından ilan edilen pandemi, Türkiye ile birlikte tüm dünyayı etkisi altına alan salgın hastalık milyarlarca kişiyi etkiledi ve etkilemeye devam etmektedir. Bu süreçte sağlık çalışanları fedakarca mücadele etmektedir. Koronavirüse enfekte olan insanlar yanında, onların tedavisi ile uğraşan tüm sağlık çalışanları da sosyal, ekonomik, psikolojik açıdan etkilenmektedir.

COVID-19 pandemisiyle mücadelede ön saflarda yer alan yoğun bakım çalışanlarının koronavirüs korkusu (koronafobi) nu etkileyen faktörleri belirlemek önemlidir.

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Pandemi ile birlikte sağlık çalışanlarının iş yükünün artması yanında kendileri ve aileleri için yaşadıkları anksiyete, korku ve gelecek endişeleri onlar üzerinde negatif etkiler yaratmaktadır. Sağlık çalışanları için virüs bulaşmış hastalarla yakın mesafede ve sürekli temas halinde olmak, koronavirüs ile enfekte olma korku ve endişesi büyük bir anksiyete kaynağıdır (1–3).

Koronafobi sağlık çalışanlarında sadece kişisel problemlere değil aynı zamanda hasta bakımında olumsuz etkilere yol açabilir. COVID-19' a bağlı sağlık çalışanlarında ortaya çıkan kayıplar da tüm sağlık ekibinde endişeye neden olmuştur. Bu hastalarla yüksek oranda maruziyet gösteren birimlerde çalışan özellikle yoğun bakım ünitelerindeki hemşirelerin COVID-19' a bağlı olarak ortaya çıkan somatik, psikolojik, sosyal ve ekonomik etkilerini değerlendirmek ve olası etkenlerini ortaya çıkararak çözüme katkı sağlamak için bu çalışma planlanmıştır.

GEREÇ VE YÖNTEM

Çalışmamız Sağlık Bakanlığı Bilimsel Araştırma Kurulu ve Yerel Etik Kurulu'nun onayı (no: 2021/147) alınarak, il genelinde pandemi yoğun bakım ünitelerinde hemşire statüsünde çalışan sağlık çalışanları üzerinde gönüllülük esasına göre 1.04.2021 ile 1.1.2022 arasında gerçekleştirildi. Türk literatürüne uyarlanan, COVID-19 virüsünün etkilerine odaklanan, geçerlilik ve güvenilirliği kanıtlanmış olan Koronavirüs-19 Fobisi Ölçeği (C19-PS Ölçeği; 4) ile 102 gönüllü üzerinde yapıldı. Katılımcılardan 1 tanesi çalışma formunu doğru ve yeterli doldurmadığı için çalışma dışı bırakılmıştır (4).

Çalışma formumuz iki kısımdan oluşmaktadır. Birinci kısmı demografik verilerin sorgulandığı kısım iken ikinci kısım ise koronafobi ana başlığında 20 soruyu içermektedir. C19-PS Ölçeği, bireylerin Kovid-19 kaynaklı korku düzeylerinin ölçülmesi için Ahorsu ve arkadaşları tarafından geliştirilmiştir (5).

Ölçek maddeleri; 1 "kesinlikle katılmıyorum" ile 5 "kesinlikle katılıyorum" arasında değerlendirilen 7 maddeden oluşmaktadır. Ölçekte test yönlü madde bulunmamaktadır. Ölçeğin iç tutarlılığı 0,82 ve test tekrar test güvenirliği 0,72 olarak bulunmuştur. 1., 5., 9., 13., 17. ve 20. maddeler psikolojik alt boyutu; 2., 6., 10., 14. ve 18. maddeler somatik alt boyutu; 3., 7., 11., 15. ve 19. maddeler sosyal alt boyutu; 4., 8., 12. ve 16. maddeler ise ekonomik alt boyutu ölçmektedir. Alt boyut puanları o alt boyuta ait maddelere verilen cevapların puan toplamı ile elde edilirken; toplam puan alt boyut puanlarının toplamı ile elde edilir ve 20 ile 100 puan arasında değişir. Ölçekten alınan yüksek puan, COVID-19 korkusunun yüksek olduğunu göstermektedir. Puanların yüksekliği alt boyutlardaki ve genel koronafobideki yüksekliğe işaret eder.

Veriler SPSS 22,0 (SPSS Inc.,Şikago, IL, ABD) istatistik bilgisayar programına girilerek analiz edildi. Bulgular, sayı, yüzde ortalama ve standart sapma olarak sunuldu. Çalışmaya katılan hemşirelerin koronafobi toplam ve alt boyut puanlarının normal dağılım gösterip göstermediğini belirlemek için Shapiro-Wilk testleri yapıldı. Koronafobi düzeylerinin cinsiyet, yaş grubu, kronik hastalık öyküsü varlığı, eğitim düzeyi ve yoğun bakımda çalışma süresi değişkenlerine göre karşılaştırılmasında bağımsız örneklem t testi, Mann-Whitney U testi, tek yönlü varyans analizi (ANOVA) ve Kruskal-Wallis testleri kullanıldı. İstatistiksel önemlilik düzeyi $p<0,05$ kabul edildi.

BULGULAR

Anketi toplam 113 katılımcı cevapladı. Tüm soruları cevaplamayan (n=6) ve çoktan seçmeli cevapların yanına yorum eklendiği görülen (n=5) anketler analize katılmadı. Toplam 102 katılımcının anket verileri analiz edildi. Katılımcıların yaşları 19 ile 41 yıl arasında değişmektedir ve çoğunluğu (%73,5) 30 yaş altında, %26,2'i 30 yaşın üstündedir. Katılımcıların çoğunluğu(%78,4) kadındır. Katılımcıların çoğunluğunun eğitim seviyesi lisans düzeyindeydi. Katılımcıların çoğunluğunun (%68,6) yoğun bakımda çalışma süresi 5 yıldan az, %17,6'sının 6 ile 10 yıl arasındadır (Tablo 1).

Katılımcıların C19-PS ölçeğine göre koronafobi toplam puanı ortalaması 50,1±10,7 ile orta seviyedeydi. Alt boyut puanları psikolojik 18,1±4,1 ile orta seviyeden biraz yüksek, somatik 10,1±3,2 ile orta seviyeden biraz düşük, sosyal 13,70±3,4 ile orta seviyede ve ekonomik 8,2±2,7 ile orta seviyeden biraz düşük olarak saptandı. Ölçek alt boyutlarının birbirleriyle korelasyon gösterdiği, en kuvvetli korelasyonun Somatik ve Ekonomi boyutlar

Tablo 1: Katılımcıların demografik özelliklerinin dağılımları (n=102)

Değişkenler	Gruplar	n	%
Yaş	19-30 Yaş	75	73,5
	31-41 Yaş	27	26,5
Cinsiyet	Kadın	80	78,4
	Erkek	22	21,6
Eğitim Durumu	Ön Lisans	28	27,5
	Lisans	69	67,6
	Yüksek Lisans	5	4,9
Çalışma Süresi	0-5 Yıl	70	68,6
	6-10 Yıl	18	17,7
	11-15 Yıl	14	13,7
Kronik Hastalık	Var	9	8,8
	Yok	93	91,2

Tablo 2: Katılımcıların COVID-19 Fobisi Ölçeği puanları ve alt boyutların korelasyonları

Değişkenler	$\bar{X}$	SS	Shapiro-Wilk Testi p Değeri	1	2	3	4
Psikolojik Alt Boyut Puanı	18,10	4,111	0,060	-	0,253*	0,662**	0,270**
Somatik Alt Boyut Puanı	10,11	3,248	0,003		-	0,483**	0,687**
Sosyal Alt Boyut Puanı	13,70	3,461	<0,001			-	0,396**
Ekonomik Alt Boyut Puanı	8,23	2,746	<0,001				-
C19-PS Ölçeği Toplam Puan	50,13	10,787	0,076	-	-	-	-

*Not: C19-PS: Koronavirüs-19 Fobisi, * p<0,05, ** p<0,001*

Tablo 3: COVID-19 fobisi düzeylerinin cinsiyete göre karşılaştırılması

Değişkenler	Cinsiyet	n	$\bar{X}$	SS	SW p Değeri	Test İstatistiği ve p Değeri
Psikolojik Alt Boyut Puanı	Kadın	80	18,33	4,155	0,082	t(100) = 1,064
	Erkek	22	17,27	3,930	0,768	P = 0,290
Somatik Alt Boyut Puanı	Kadın	80	9,88	3,278	0,003	U = 673,5
	Erkek	22	10,95	3,062	0,695	p = 0,091
Sosyal Alt Boyut Puanı	Kadın	80	13,73	3,409	0,001	U = 790,0
	Erkek	22	13,59	3,725	0,033	p = 0,460
Ekonomik Alt Boyut Puanı	Kadın	80	7,81	2,419	0,009	U = 615,0
	Erkek	22	9,73	3,355	0,024	p = 0,030
C19-PS Ölçeği Toplam Puan	Kadın	80	49,74	10,602	0,109	t(100) = -0,694
	Erkek	22	51,55	11,583	0,667	p = 0,489

C19-PS: Koronavirüs-19 Fobisi, SW: Shapiro-Wilk testi

arasında olduğu bulundu (Tablo 2).

Katılımcıların COVID-19 fobisi puanlarının cinsiyetlerine göre farklılık gösterip göstermediği bağımsız örneklem t testi ve Mann-Whitney U testi ile araştırıldı. Ekonomik kaygı alt boyutunda erkeklerin kaygı puanlarının istatistiksel olarak anlamlı şekilde daha yüksek olduğu saptandı (p=0,030). Ölçeğin diğer alt boyutlarında ve koronafobi toplam puanında cinsiyetler arasında istatistiksel olarak anlamlı bir fark olmadığı saptandı (p>0,05) (Tablo 3).

Katılımcıların C19-PS puanlarının yaş gruplarına göre farklılık gösterip göstermediği bağımsız örneklem t testi ve Mann-Whitney U testi ile araştırıldı. 30 yaş altında ve 30 yaş üstünde olan katılımcıların ölçek puan ortalamaları karşılaştırıldığında, tüm alt boyutlarda ve koronafobi toplam puanında istatistiksel olarak anlamlı bir fark olmadığı saptandı (p>0,05) (Tablo 4).

Katılımcıların C19-PS puanlarının kronik hastalık öyküsü varlığına göre farklılık gösterip göstermediği bağımsız örneklem t testi ve Mann-Whitney U testi ile araştırıldı. Tüm alt boyutlarda ve koronafobi toplam puanında istatistiksel olarak anlamlı bir fark olmadığı saptandı (p>0,05) (Tablo 5).

TARTIŞMA

Katılımcıların C19-PS puanlarının eğitim düzeylerine göre farklılık gösterip göstermediği tek yönlü ANOVA ve Kruskal-Wallis testi ile araştırıldı. Tüm alt boyutlarda ve koronafobi toplam puanında istatistiksel olarak anlamlı bir fark olmadığı saptandı (p > 0,05).

Bu çalışmada pandemi döneminde COVID-19 hastası ile yüksek oranda temas halinde bulunan yoğun bakım ünitelerinde çalışan hemşirelerde ortaya çıkan koronafobinin somatik, psikolojik, sosyal ve ekonomik etkileri değerlendirildi. Katılımcıların C19-PS ölçeğine göre orta seviyede koronafobi (toplam puanı ortalaması 50,1 ± 10,7) durumuna sahip olduğu bulundu. Anket çalışmalarında çalışmanın değerlendirilmesinde, anket içeriği geçerlilik çalışmaları için örneklem büyüklüğü ile ilgi çeşitli ölçüt ve görüşler bulunmaktadır. Örneklem büyüklüğü en az 100-250 arası olması gerektiği veya ölçekteki madde sayısının 5-10 katı olması gerektiği kabul edilmektedir (6). Çalışmamız da 112 katılımcı ile yapılmış olup literatürdeki geçerliliği kanıtlanmış, yeterli olgu sayısı ile gerçekleştirilmiştir. Diğer taraftan örneklem büyüklüğünün 100 katından fazla oluşturulan çalışmalarda vardır (7).

Koronafobinin yaş, cinsiyet ve evli olup olmamaya göre olan değişimi ile ilgili farklı görüşler mevcuttur. Sakip ve ark. (8) sağlık çalışanı ve normal bireylerin dahil edildiği 3388 kişi üzerinde yaptığı bir çalışmada koronafobiye bağlı depresif yakınmaların kadınlarda daha fazla fakat evli olanlarda ve çocuk sahibi olanlarda daha az olduğu bulunmuş.

Hoşgör ve ark. (9) 244 hastane çalışanın üzerinde yaptığı çalışmada koronafobi açısından yaş grupları arasında fark olmamakla beraber tükenmişlik sendromu bakımından 50-65 yaşa göre 20-34 yaş grubunda daha fazla olduğu gösterilmiş.

Koronafobi yaşlılarda ve ek hastalığı olanlarda daha fazla olduğu savunan çalışmalar yanında, diğer taraftan koronafobi psikolojik alt boyutu kadınlarda daha fazla olduğu bildirilmektedir (8,10). Diğer bazı çalışmalarda koronafobi açısından yaş, cinsiyet, medeni durum ve mesleki unvanın fark oluşturmadığı sonucunu

Tablo 4: COVID-19 fobisi düzeylerinin yaş gruplarına göre karşılaştırılması

Değişkenler	Yaş Grubu	N	$\bar{X}$	SS	SW p Değeri	Test İstatistiği ve p Değeri
Psikolojik Alt Boyut Puanı	19-30 yaş	75	18,49	4,170	0,124	t(100) = 1,632
	31-41 yaş	27	17,00	3,803	0,210	P = 0,106
Somatik Alt Boyut Puanı	19-30 yaş	75	10,21	3,252	0,015	U = 942,5
	31-41 yaş	27	9,81	3,282	0,459	p = 0,594
Sosyal Alt Boyut Puanı	19-30 yaş	75	14,01	3,454	0,001	U = 801,0
	31-41 yaş	27	12,81	3,386	0,307	p = 0,105
Ekonomik Alt Boyut Puanı	19-30 yaş	75	8,33	2,825	0,003	U = 909,5
	31-41 yaş	27	7,93	2,541	0,015	p = 0,431
C19-PS Ölçeği Toplam Puan	19-30 yaş	75	51,05	10,749	0,235	t(100) = 1,453
	31-41 yaş	27	47,56	10,671	0,057	p = 0,149

C19-PS: Koronavirüs-19 Fobisi, SW: Shapiro-Wilk testi

Tablo 5: COVID-19 fobisi düzeylerinin kronik hastalık öyküsü varlığına göre karşılaştırılması

Değişken	Kronik Hastalık	N	$\bar{X}$	SS	SW p Değeri	Test İstatistiği ve p Değeri
Psikolojik Alt Boyut Puanı	Var	9	18,89	2,028	0,780	U = 330,5
	Yok	93	18,02	4,258	0,047	p = 0,297
Somatik Alt Boyut Puanı	Var	9	9,44	1,810	0,712	U = 371,5
	Yok	93	10,17	3,355	0,006	p = 0,557
Sosyal Alt Boyut Puanı	Var	9	13,67	1,323	0,130	U = 404,5
	Yok	93	13,70	3,605	0,002	p = 0,868
Ekonomik Alt Boyut Puanı	Var	9	8,56	1,333	0,407	U = 342,5
	Yok	93	8,19	2,849	<0,001	p = 0,366
C19-PS Ölçeği Toplam Puan	Var	9	50,56	2,128	0,609	t(67,396) = 0,343
	Yok	93	50,09	11,285	0,180	p = 0,733

C19-PS: Koronavirüs-19 Fobisi, SW: Shapiro-Wilk testi

savunulmaktadır (9,11,12).

Bizim çalışmamızda da koronafobinin yaş ve cinsiyet bakımından farklı olmadığı, sadece ekonomik kaygının erkeklerde daha fazla olduğu gösterilmiştir. Erkeklerde fazla olmasının sosyo-kültürel olarak aile geçimine katkı sağlama sorumluluğu ve kaygısının ön planda olmasından kaynaklandığını düşünmekteyiz.

Hoşgör ve ark. (9) hastane çalışanlarının üzerinde yaptığı çalışmada koronafobi düzeyi arttıkça tükenmişlik sendromu düzeyinin de arttığını bulmuşlar. Dahası koronafobi düzeyindeki bir birim artışın tükenmişlik sendromu düzeylerinde % 22,4 lük bir artışa neden olduğunu saptamışlar.

Sakip ve ark. (8) sağlık çalışanı ve normal bireylerin dahil edildiği 3388 kişi üzerinde yaptığı bir çalışmada katılımcıların %25 ten fazlasında koronafobiye bağlı depresif şikayetlerin olduğu bulmuşlar.

Dai ve ark. (13) Çin'de 4600 sağlık çalışanın katılımı ile yaptığı anket çalışmasında, katılımcıların % 39,1 inde psikolojik sıkıntı yaşadığı bildirilmiştir.

Gökmen ve ark. (12) 310 hemşirenin dahil edilerek yaptığı çalışmada koronafobide psikolojik alt boyutun 22,08 ± 6,07 ve ikinci sırada sosyal alt boyutunun 16,13 ± 5,63 olduğunu, psikolojik alt grubun istatistiksel olarak anlamlı derecede yüksek olduğunu göstermişler. Bu çalışmadaki olgular sadece YBÜ'de değil tüm hastane çalışanları dahil edildiğinden alındığından bizim çalışmamıza göre oranlar değişik ise de ilk 2 sıradaki alt gruplar (psikolojik alt boyutun 18,10 ± 4,11 ve sosyal alt boyutunun 13,70 ± 3,41) aynı idi. Fakat koronafobi alt boyutları (Psikolojik, somatik, sosyal ve ekonomik) bakımından aralarında istatistiksel anlamda fark yok idi. Bu sonucumuz literatürdeki benzer çalışmalar ile uyumludur.

Koronafobi düzeyi arttıkça ümitsizlik, tükenmişlik hissi, korku, anksiyete, psikolojik sıkıntılar, depresyon hatta intihar düşüncesinde artma gibi ruhsal sağlık sorunlara neden olabilmektedir (14).

Koronafobi farklı meslek gruplarında farklılık gösterebilmektedir. Lu ve ark. (15) Çin'de 2299 kişinin (2042 sağlık çalışanı ve 257 idare personel çalışanlarının) dahil edildiği çalışmada, YBÜ gibi enfekte hastalarla yakın olarak çalışan sağlık çalışanı olanlarda, klinik dışı idare personel çalışanlarına göre koronafobinin 1.4 kat daha fazla olduğu, anksiyete ve depresyon yatkınlığının ise 2 kat daha fazla olduğu bildirilmiştir.

Sağlık çalışanları arasındaki değerlendirmede, doktor, hemşire ve yardımcı sağlık personelini karşılaştırıldığında koronafobi açısından fark olmadığını bildirilmektedir (11). Diğer taraftan pandemi başlarında YBU'de çalışan anestezi uzmanlarındaki değerlendirmede koronafobinin

diğer hekimlere (YBÜ'de çalışmayan) göre daha yüksek olduğu gösterilmiştir (16).

Yapılan başka çalışmalarda ise koronafobinin, hemşirelerde normal topluma göre COVID-19 hastalarının tedavi edildiği YBÜ çalışanlarında servis çalışanlarına göre daha yüksek olduğu bildirilmektedir (11). Diğer taraftan önceki çalışmanın tersine Gökmen ve ark. (12) hemşireler arasında yaptığı çalışmada servis çalışanlarında YBÜ çalışanlarına göre koronafobinin psikolojik alt grubunun daha yüksek (23,49±5,83'e karşın 21,91±5,91) olduğu gösterilmiş.

COVID-19 açısından YBÜ gibi riskli konumda çalışanlarda koronafobi oranı artmaktadır. Enfekte hastalarla uzun süre temasta bulunmak, aşırı iş yükü, izole alanda uzun süre kalma, koruyucu ekipman eksikliği ve yüksek enfeksiyon oranları korku, anksiyete, depresyon ve tükenmişlik sendromu gibi psikolojik yakınmalar daha sık görülmektedir (17). Çalışma ortamındaki risk ortamı arttıkça (şüpheli hasta maruziyetinin artması, mola/dinlenme sürelerinin az olması, koruyucu ekipmana erişimin kısıtlı olması gibi) koronafobi artmaktadır (8). Lu ve ark.' nın (15) Çin'de 2042 sağlık çalışanı çalışanı üzerinde yaptığı bir çalışmada %70,6' sında koronafobi tespit etmişlerdir. Hoşgör ve ark. (9) 244 hastane çalışanın üzerinde yaptığı çalışmada orta düzeyde koronafobi olduğunu bulmuştur.

Gökmen ve ark. (12) yaptığı çalışmada 310 hemşirenin (yoğun bakım ve diğer tüm üniteler) dahil edildiği çalışmada koronafobinin % 59 olduğu gösterilmiş. Filipinlerde yapılan bir çalışmada hemşirelerde koronafobinin % 54,76 olarak bulunmuş (5). Sağlık çalışanlarından oluşan 172 kişinin katıldığı yapılan diğer bir çalışmada koronafobi % 50 olarak bulunmuştur (11). Literatürde koronafobi puanları çalışmanın yapıldığı bölge, meslek grubu, çalıştığı kurum, zaman ve katılımcı sayısı ile değişmekle beraber çalışmamız son literatür ile uyumludur.

Kronik hastalığı olanlarada COVID-19 eklenmesi komorbidite ve mortaliteyi artırmaktadır (18). Gökmen ve ark. (12) yaptığı çalışmada kronik hastalığı olanlarda koronafobinin psikolojik alt boyutunun daha yüksek (23,67±6,12'ye karşın 21,69±6,00) olduğunu bulmuşlar. Diğer taraftan Haktanır ve ark. (10) yaptığı çalışmada koronafobinin eşlik eden kronik hastalığın olup olmamasına göre fark etmediği bildirilmiş.

Bizim çalışmamızda da son çalışmayı destekler tarzda olup kronik hastalığı (spesifik hasta grubunun seçilmediği) olan ile olmayanlar arasında koronafobi açısından fark olmadığı sonucuna ulaşıldı. Bu sonucumuzda örneklem büyüklüğünde kronik hastalığı olan katılımcı sayısının az (9'a karşın 93) olması unutulmamalıdır.

Araştırmanın kısıtlılıkları:

Çalışmamızın bazı kısıtlılıkları bulunmaktadır; Çalışmamız tek merkezli ve sınırlı sayıda katılımcı ile gerçekleştirilmiştir. Bölgesel ve sosyo-demografik yapıdan dolayı kesitsel bir çalışma olarak düşünülmelidir. Pandemi döneminin ilk döneminde gerçekleştirildiği için tedavi ve aşılama gibi tedavideki değişiklikler ile kişilerin koronafobileri değişebildiği unutulmamalıdır.

SONUÇ

Pandemide, yoğun iş temposundan tükenme, hasta bakım kalitesinde düşme, mesleki tatminde azalma, işten ayrılma isteği, COVID-19 'a bağlı yakın aile ve sağlık çalışanlarında ortaya çıkan kayıplar koronafobi yükünü daha da artırmaktadır. Daha verimli ve kaliteli bir sağlık hizmeti için sağlık çalışan paydaşlarının koronafobi konusunda başa çıkma yöntemleri ile ilgili hizmet içi eğitim ile desteklenmeli, çalışma süre ve ortamları uygun şekilde planlanmalıdır.

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CASE REPORT

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Methanol Intoxication Increasing Again with COVID-19 Pandemic: Clinical Series

COVID-19 Pandemi Salgınıyla Yeniden Artan Metanol Zehirlenmeleri: Olgu Serisi

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ABSTRACT
Methanol intoxication is very rare clinical condition encountered at emergency rooms while numbers started to increase with COVID-19 pandemic. In this clinical series we mentioned about our clinical approach to methanol intoxication patient during COVID-19 pandemic.

ÖZET
Metanol intoksikasyonu çok nadir olarak karşımıza çıkmakta iken COVID-19 pandemisiyle birlikte acil servislerde daha ciddi klinik tablolarda tekrardan görülmeye başlandı. Bu olgu serimizde de pandemi ile mücadele döneminde artan sıklıkta karşılaştığımız metanol intoksikasyonu olgularına klinik yaklaşımımızı derledik.

Keywords:
Methanol Intoxication
COVID-19 Pandemic
Emergency Service

Anahtar Kelimeler:
Metanol Zehirlenmeleri
Covid-19 Pandemisi
Acil Servis

INTRODUCTION

Methanol is a clear, colorless, volatile liquid used as an industrial solvent (1). It is easily procured and illegaly used for alcohol production due to its cheap price. Although there are individual cases of intoxication, methanol intoxications with mass poisoning and deaths have also been encountered in the history. The most common reported ingestions are secondary to drinking windshield washer fluid as a suicide attempt but intentional ingestion when alcoholic beverages are diffucult to obtain is another common reason we see in our emergency service. In our case series, we presented our approach to methanol intoxication cases in the emergency service, the incidence of which increased with the lockdown during the fight against the COVID-19

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Between 19.12.2021 and 31.12.2021, there were a total of 14 applications to the emergency department resuscitation area with methanol intoxication, two of which were women. In the same period, a nationwide weekend curfew is imposed in our country due to the COVID-19 pandemic. The mean age of the patients was 24 for women and 48±2 for men. In the evaluation of the Glasgow Coma Scale (GCS) , 6 patients (42.9%) were evaluated as having GCS score of 3 at the time of admission to the emergency service. 10 patients (71.4%) were intubated during emergency follow-up. Majority of the patients (11 patients) needed intensive medical care and special treatment regimens like hemodialysis and ethanol infusion. After the first evaluation and emergency interventions, 57.1% of the patients (8 patients) were hospitalized and followed up in the intensive care unit.

Three patients requiring intensive unit care developed cardiac arrest and had cardiopulmonary resuscitation procedures applied in the emergency service. Despite intense emergency care, $NaHCO_3$ infusion, ethanol infusion and positive inotropic support, these 3 patients died in the emergency resuscitation area. One of the patients who hospitalized for methanol intoxication was infected with the COVID-19 virus and received favipavir and additionally low molecular weight heparin treatment. 11 patients were treated with loading dose of 8 mL/kg ethanol infusion followed by maintenance dose of 130 mg/kg/hour ethanol infusion in serum containing 5% dextrose in saline. Hemodialysis, which also plays an important role in the treatment of methanol intoxication was applied to 78.6 % of the patients (11 patients).

After ophthalmological examination of intoxicated patients, fixed dilated pupils were found in 2 patients, pinpoint pupils were found in 1 patient, and blurred vision and decreased visual acuity were found in 4 patients. 7 patients had normal ophthalmological examination.

Patients who died as a result of methanol intoxication had higher levels of MCV, $PaCO_2$ and blood urea compared to treated patients. In the terms of the age, avarage age of death was 62. The reason for older patients having higher mortality is thought to be chronic alcohol addiction leading to withdrawal symptoms , and difficult access

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Table: Distribution of Mean Laboratory Parameters of Methanol Intoxicated Patient (Treated Versus Exitus)

	Treated Patients	Exitus Patients
Age	39.82	62.67
MCV	93.12 fL	111.96 fL
HCO_3	14.7	5.1
Anion Gap	13.6	21.9
Serum Chloride Levels	112	114
pH	7.1	6.7
PCO_2	32 mml/l	40.7 mml/l
Htc	50	53
Blood Urea	19	26
Potassium	4.6	5.5

to ethanol during curfew causing higher consumption rates of methanol. General fetaures of patients are presented at table. Only 3 patients were discharged from emergency service without need of ethanol treatment and hemodialysis.

DISCUSSION

Half life of methanol is 14-20 hours for mild poisoning and 24 to30 hours for untreated serious poisonings. Half life of methanol can be reduced to 2.5 hours with hemodialysis treatment (2). The aim of treatment in methanol intoxication is to compete with the conversion of methanol into toxic metabolites. Ethanol is used in the treatment owing its high affinity to alcohol dehydrogenase which is responsible for the convertion of methanol to toxic metabolites (2). Ethanol treatment protocol; 100-150 mg/dl loading, 130 mg/kg/hour maintenance infusion should be continued until methanol serum levels reach zero. These treatment can sometimes last for days. Maintenace dose can be increased to 250-350 mg/kg/hour for patient undergoing hemodialysis. Hemodialysis treatment is very effective in removing methanol and toxic metabolites of methanol and can be continued until serum methanol level is zero or acidosis is over. Schwarz et al. recommends hemodialysis at serum methanol levels of 100 mg/dl and more. However, hemodialysis is also recommended regardless of methanol level in patients with severe acidosis, treatment-resistant fluid and electrolyte disturbances, ocular findings, and kidney failure (2,4). In our series, hemodialysis treatment was applied to 78.6 % of toxicated patients.

Regarding the complete blood count, Swartz et al. showed that the MCV value decreased in heavy methanol intoxication, but its mechanism could not be fully determined (4).At our series, especially for patients admitted to ICU and for patients died at emergency service, MCV levels were considerably increased (mean 111.96 fL). The reason for this was assumed to be high MCV due to chronic alcohol intake, suggesting that these patients were chronic alcohol consumers and they tended to consume methanol in the shortage of ethanol due to the curfew and their methanol consumption habits were not routine.

Due to the curfew during the pandemic period, it has been observed that different methods are used to provide alcohol and the pandemic has even led to more serious methanol intoxication cases.

Target organ in the methanol toxicity is the retina. It is known that consumption of high amounts of methanol is associated with reversible or irreversible blindness (5). Researches showed that, formic acid, a metabolite of methanol, inhibits cytochrome oxidase in the optic nevre and impairs transfer through axoplasma (6). As eye symptoms; pain, blurred vision, decreased visual field, photofobia, snowy landscape can be detected The main eye symptoms in our patients were blurred vision and narrowing of visual field. Ophthalmological examination of 7 patients was normal.

Conducted researches showed that mortality in methanol poisoning is directly proportional to the severity of acidosis. In these data, mortality was 19% in patients with PCO_2 less than 20 mmol/l despite treatment, while mortality increased up to 50% in patients with PCO_2 less than 10 mmol/l (8).

For our series mean $PaCO_2$ level was 40.7 mmol/L for patients who died, strongly different compared to other studies and thought to be associated with increased CO_2 production as a result of methanol metabolism.

As a result of the implementation of curfews during the pandemic period, it has been observed that different methods have been used to supply alcohol.The pandemic has even led to more serious methanol poisoning. As a result, it presents with a more serious toxic clinic.

CONCLUSION

In the history, rare conditions like methanol intoxication showed an inceasing trend through pandemics. Despite advanced medical technologies and medical care, methanol toxicity is still a highly mortal medical emergency. Early antidote treatment and hemodialysis are cornerstone treatment regimens applied for methanol toxicity.

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CASE REPORT

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A Diagnosis That Should be Considered in Patients Coming to The Emergency Service with Abdominal Pain: Primary Appendagitis Epiploica

Acil Servise Karın Ağrısı ile Başvuran Hastada Akla Getirilmesi Gereken Bir Tanı: Primer Epiploik Apandisit

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ABSTRACT

Primary epiploic appendagitis; occurs as a result of torsion, infarction and inflammation of epiploic appendices that serve to assist mechanical protection and peristatic movement of the colon.

Physical examination and laboratory findings may mimic various causes of abdominal pain requiring emergency surgery. However, medical treatment is often sufficient and effective in the treatment of PEA. Fast and true diagnosis is crucial in preventing unnecessary interventions. The gold standard imaging method in diagnosis is tomography. In our case presentation, a patient that has applied to our emergency room with stomachache and nausea complaints, has been diagnosed with PEA and successfully treated by means of conservative methods has been discussed.

ÖZET

Primer epiploik apandisit; kolonun mekanik koruma ve peristatik harekete yardımcı olmak ile görevli epiploik apendikslerinin torsiyonu, infarktı ve inflamasyonu sonucu ortaya çıkmaktadır. Fizik muayene ve laboratuar bulguları ile acil cerrahi müdahale gerektiren çeşitli akut karın tablolarını taklit etmekle birlikte sıklıkla medikal tedavinin yeterli ve başarılı olduğu benign seyirli bir hastalıktır. Gereksiz cerrahi müdahalelerin önlenmesi için hızlı ve doğru tanı önemlidir. Tanıda tomografi altın standarttır. Olgu sunumumuzda karın ağrısı ve bulantı ile acil servisimize başvuran PAE tanısı koyduğumuz ve konservatif yöntemler ile başarı ile tedavi ettiğimiz bir hastamız ele alınmıştır.

Keywords:
Primary appendagitis epiploica
Stomachache
Acute abdomen

Anahtar Kelimeler:
Primer epiploik apandisit
Karın ağrısı
Akut karın

INTRODUCTION

Firstly epiploic appendices that are defined by the anatomist Vesalius are the serosa-covered structures that may be present in entire area of the colon except rectum, and they are 1-2 cm in thickness, 0.5-5 cm in length and contain adipose tissue and vascular formations (1,2). Primary epiploic appendagitis (PEA) is a rare inflammatory disorder of these structures. It is frequently a kind of disorder that is self-limited and responds to medical treatment. Early and accurate diagnosis is important to prevent unnecessary surgical interventions. In our case presentation, a 44-year-old female patient who has applied to our emergency room with stomachache and nausea complaints has been diagnosed with the PEA has been discussed.

CASE

Our patient was informed about the case report and informed consent was obtained from her. 44-year- old female patient has applied to the emergency room of our hospital with extensive complaints of stomachache and nausea that have been continuing for 2 days and marked in left lower quadrant. The patient has been diagnosed with diabetes for 6 years and using metformin 1000 mg 2x1 posology since she was diagnosed. On physical examination, there was a fever of 37.6ºC, tenderness and defense in the left lower quadrant. In the laboratory examination, no features were found in neutrophil predominance except leukocytosis and high C-reactive protein (CRP) (Table). Intense colonic gas shadows were present on direct abdominal X-ray. Oral and intravenous contrast-enhanced tomography was planned. In tomography, lesions compatible with the epiploic appendagitis with contrast involvement in its periphery were observed in central adipose density in right paracolic area in distal descending colon in 1 mm successive axial contrast sections. Fatty streaks compatible with inflammation and density increasement were detected in adjacent mesenteric adipose tissue (Figure) Findings were interpreted as appendagitis epiploica. Surgical interventions were not planned for the patient. The patient was interned for medical treatment. Hydration, antibiotherapy (ceftriaxone 1-gram 2x1, metronidazole 500 mg 3x1), anti-inflammatory and antiemetic treatment were initiated. It was observed that the clinical findings of our patient improved on the 3rd day of the follow-up, and the clinical findings were completely regressed and the laboratory parameters returned to normal on the 7th

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Table: The results of blood and urine tests of the patient in the time of application

Laboratory Test	Result	Unit
ALT	20	U/L
AST	13	U/L
Urea	21	mg/dL
Creatinine	0.81	mg/dL
Amylase	31	U/L
Lipase	19	U/L
WBC	10.900	/mm³
Neutrophile	78	%
Hgb	13.1	g/dL
Plt	295	/mm³
CRP	87.5	mg/L

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, Hgb: Hemoglobin, Plt: Platelet, WBC: White blood cell, CRP: C reactive protein

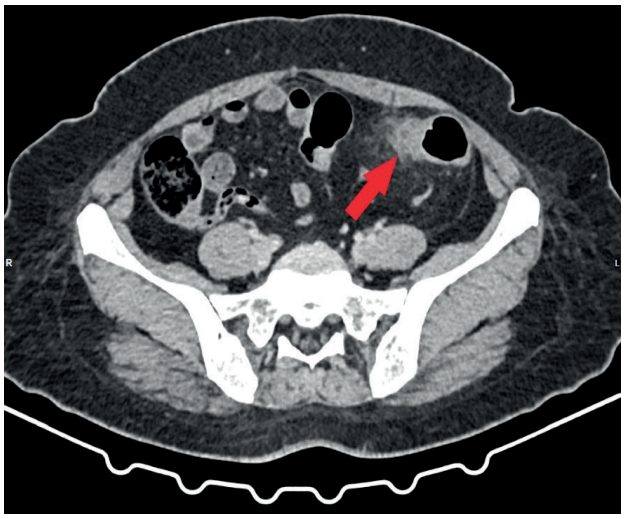

Figure: Lesions compatible with the epiploic appendagitis with contrast involvement it its periphery, central adipose density in right paracolic area in distal colon descending in axial contrast sections.

day of the follow-up.

DISCUSSION

The number of the epiploic appendix that are present throughout the colon from cecum to rectosigmoid region is about 50-100 (3). The epiploic appendix that serves to assist mechanical protection and peristaltic movement are fed by colic artery branches (4). They may be exposed to torsion and infarction as a result of their weak blood flow and pedicled formations that enable them to move freely. This case causes PAE advancement that is a rare disorder progressing with inflammation (5). If an inflammation in epiploic appendix occurs indirectly as a seconder to another intraabdominal inflammatory pathology (cholecystitis, pancreatitis, diverticulitis, appendicitis etc.), this case is called secondary epiploic appendagitis (SEA) (6).

PEA incidence is worldwide determined as 8.8/1.000.000 (7). PAE may be seen in every age and also peaks between 4th and 5th decades and men are slightly more susceptible compared to women (8, 9). Blinder et al. determined that 52.7% of the disorder was in sigmoid colon, 19% in cecum, 15% in ascending colon, 6.6% in descending colon and 6.6% in transverse colon in a literature review in which they investigated 167 patients diagnosed with PEA (10). The fact that the epiploic appendix present in sigmoid colon and cecum are more involved is probably resulted from their longer and thicker formations (11). PEA is presented by stomachache. Stomachache may be accompanied by nausea and vomiting. Pain may be seen in all quadrants in all abdomens. In a study in which 45 patients diagnosed with PEA in Marmara University have been retrospectively evaluated, it has been observed that pain has been most frequently seen in left lower quadrant with the rate of 41%, which is respectively followed by right lower quadrant (35%), right upper quadrant (0.4%) and left upper quadrant (0.02%) localizations. (3). Depending on the location in the colon, it can imitate pathologies that require urgent surgical intervention such as acute cholecystitis, diverticulitis, appendicitis. Due to the progressing process with inflammation, elevation of subfebrile fever, leukocytosis and acute phase reactants may be observed. Uncompressed mass lesions adjacent to colon may be seen in abdominal ultrasonography (12). Blood flow cannot be detected within lesion field in color doppler ultrasonography (13). The gold standard imaging method in diagnosis is tomography. Normal epiploic appendix cannot be seen in tomography. In the case of PEA, pericolonic round or oval shaped pedicled structures with fat density due to inflammation are seen on tomography (14). In the case of SEA, additional findings such as thickening of the colon wall, narrowing of the lumen and pericolic fluid accumulation may be observed. The treatment of the primary pathology that causes the inflammation in SEA is essential. As in our case, PEA is mainly a self-limited disorder that responds well to the conservative methods including appropriate antibiotic and anti-inflammatory therapy, however complications such as peritonitis, adhesion, obstruction, abscess development may rarely occur (15, 16). In such cases, immediate surgical interventions are required. Additionally, when the literature is examined, it can be seen that some authors have proposed that surgical interventions may also be advantageous for preventing early recurrences (9). In surgery, the excision of inflamed epiploic appendix with laparoscopic method is essential (17). In a histopathological study of the epiploic appendix that are surgically extracted in PEA, thrombosed blood vessels and acute infarction accompanied by fat necrosis, inflammatory cells, perivascular hemorrhage findings are seen (18).

CONCLUSION

PEA is a benign disease that can mimic various disorders that require immediate surgical intervention with physical examination and laboratory findings. It should definitely be considered in patients who apply to the emergency services with the complaint of abdominal pain. In this disorder that can be accurately diagnosed by means of tomography, surgical interventions must not be resorted immediately. Conservative methods in treatment are frequently enough and effective.

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Ethic: Informed consent was obtained from the patient.
Approval of final manuscript: All authors

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CASE REPORT

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Pandeminin Dilemması: İlaç yan etkisi mi? Ya COVID-19'sa?

The Pandemic's Dilemma: A drug side effect? What if it's COVID-19?

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ABSTRACT

The coronavirus disease 2019 (COVID-19) continues to affect our country as well as all over the world. Although the most common symptoms are fever, dry cough, and fatigue, it is seen that there are very different presentations of the disease as the number of infected patients increases. In this article, we aimed to present a difficult case of genitourinary tuberculosis (TB) who received quadruple antituberculosis treatment and whose liver enzyme elevation was attributed to COVID-19 infection, not drug side effect, and whose liver function tests completely recovered after COVID-19 treatment.

ÖZET

Koronavirüs hastalığı 2019 (COVID-19) tüm dünyada olduğu gibi ülkemizde de etkisini sürdürmektedir. En sık semptomları; ateş yüksekliği, kuru öksürük, yorgunluk gibi semptomlar olsa da enfekte hasta sayısı arttıkça hastalığın çok farklı sunumlarının da olduğu görülmektedir. Biz yazıda, genitoüriner tüberküloz (TB) nedeni ile 4'lü antitüberkuloz tedavisi alan, karaciğer enzim yüksekliği ilaç yan etkisine değil de COVID-19 enfeksiyonuna bağlanan ve COVID-19 tedavisi sonrası karaciğer fonksiyon testleri tamamen düzelen zor bir olguyu sunmayı amaçladık.

Keywords:
COVID-19
Antituberculosis treatment
Side effects
Liver enzyme elevation

Anahtar Kelimeler:
COVID-19
Antitüberkuloz tedavi
Yan etki
Karaciğer enzim yüksekliği

GİRİŞ

Koronavirüs hastalığı 2019 (COVID-19) tüm dünyada olduğu gibi ülkemizde de etkisini sürdürmektedir. En sık semptomları ateş yüksekliği, kuru öksürük, yorgunluk gibi semptomlar olsa da boğaz ağrısı, baş ağrısı, kas ağrıları, tat ve koku alma kaybı veya ishal gibi semptomlara da neden olabilir (1). COVID-19 geniş klinik spektrumuna sahip olduğundan, bazı klinik antitelerle ortak belirti-bulgular gösterebilmektedir.

Tüberküloz tedavisi ülkemizde Türkiye Cumhuriyeti Sağlık Bakanlığı Rehberi'ne göre yapılmakta olup, tedavide HRZE tedavisi (H: izoniasid, R: Rifampisin, Z: Pirazinamid, E: Etambutol, S: Streptomisin) önerilen tedavilerdendir. Bu tedavilerin yan etkileri gelişebileceğinden hastanın klinik ve laboratuvar parametrelerinin takibi önemlidir. Yan etkiler arasında; karın ağrısı, bulantı ya da iştahsızlık, döküntü, artralji, karaciğer enzim yükseklikleri gibi belirtiler ve laboratuvar bulguları olabilir (2). Minör yan etkiler tedaviyi kesmeyi gerektirmezken, majör yan etkiler geliştiğinde tedaviye ara vermek, hatta kesmek zorunda kalınabilir (3).

Genitoüriner tüberküloz (TB) nedeni ile HRZE tedavisi alan bu olgumuzu, şikayetleri öncelikle ilaç yan etkisini düşündürmekle beraber yapılan tetkikler sonucunda COVID-19 tanısı alması nedeni ile sunmayı amaçladık.

OLGU

Kırk sekiz yaşında kadın, genitoüriner TB nedeniyle 1 aydır HRZE kullanan, bilinen başka ek hastalığı olmayan hasta polikliniğimize rutin kontrol için başvurdu. Alınan anamnezinde bulantı ve hafif karın ağrısının olduğu, 7-10 gün önce başlayan ateş hissi, titreme, artralji ve halsizliğin bu yakınmalarına eşlik ettiği öğrenildi. Ateş ve artraljinin gerilediğini söyleyen hastada halsizlik, iştahsızlık devam etmekteydi. Dizüri, yan ağrısı, kusma, ishal, baş ağrısı, baş dönmesi, miyalji yoktu. Öksürük tek tük olmakla beraber boğaz ağrısı, dispne, balgam, hemoptizi olmamıştı. Anosmi-disgusi tariflemedi. Son 14 gün içinde bilinen COVID-19 tanılı kişiyle temas öyküsü yoktu. Muayenede patolojik bulguya rastlanmadı. Yakınmalarının ön planda HRZE ilaç rejimine bağlı yan etkilerle ilişkili olabileceği düşünüldü. Ancak içinde bulunduğumuz pandemi şartlarında, olası bir COVID-19 enfeksiyonu ekarte edilemedi. Hastadan hemogram, karaciğer ve böbrek fonksiyon testlerine ek olarak SARS-CoV-2 RT-PCR (Real Time Polimeraz Zincir Reaksiyonu) testi ve posterior anterior akciğer (PA AC) grafisi istendi. Beyaz küre:3300/uL, lenfosit:1280/uL, Alanin aminotransferaz (ALT):81 U/L, Aspartat Aminotransferaz (AST):105 U/L idi. Diğer biyokimyasal tetkik değerleri normaldi. PAAC grafisinde infiltrasyon yoktu. Kombine (nazofarengeal ve

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orafarengeal) sürüntü örneğinden çalışılan SARSCoV-2 RT-PCR testi pozitif olarak sonuçlandı. Transaminazlar (AST, ALT) başta olmak üzere laboratuvar takibi ve klinik gözlem amacıyla hasta izolasyon amaçlı pandemi servisine yatırıldı. Anti TB ilaçlarına ara verildi. Favipiravir tedavisi T.C. Sağlık Bakanlığı COVID-19 Tedavi Rehberi'ne (1) göre uygun şekilde başlandı. Semptomatik tedavisi düzenlendi. ALT-AST yüksekliğine sebep olabilecek başka nedenleri atlamamak için Hepatit A, B, C, HIV, EBV, CMV serolojileri istendi; patoloji saptanmadı. 5 günlük tedavi sonrası favipiravir stoplandı. Anti TB ilaçları tekrar başlandı (HRZE). Takibi süresince yakınmaları gerileyen hastanın transaminazları stabil seyretti (ALT:87 U/L, AST:66 U/L). Genel durumu iyi, vitalleri stabil olan hasta yatışının 8.gününde evde izolasyon ve izolasyon bitiminde poliklinik kontrolü önerilerek taburcu edildi. Kontrolde ALT:63 U/L, AST:46 U/L; diğer tetkikler doğaldı.

TARTIŞMA

Anti TB tedavi sırasında ilaç yan etkisi görülme sıklığı yapılan bir meta-analiz çalışmasında %8- %85 arasında bildirilmiştir. Bunlar geçici veya kalıcı yan etkiler olabilir (4). Anti TB tedavi sırasında hepatotoksiste gelişmesi için bildirilmiş risk faktörleri; ileri yaş, alkol bağımlılığı, eş zamanlı hepatotoksik ilaç kullanımı, geçmiş ya da mevcut karaciğer hastalığı olması, gebelik, postpartum dönem, damar içi ilaç kullanımı gibi nedenler olup (2,4), hastadan istenen tetkikler ve anamnez bilgilerine göre patolojik bulguya rastlanmadı. TB tedavisi alan hastalarda ilaç yan etkileri çeşitli şekillerde karşımıza çıkabilmektedir. Rifampisine bağlı flu-like semptomlar; pirazinamide bağlı artralji, tüm ilaçlara bağlı olabilen dispepsi, hepatotoksisite bunlardan bazılarıdır (2). Pandemi nedeniyle, olası COVID-19 enfeksiyonunun da transminaz yüksekliği yapabilme ihtimali ve hastanın olası vaka tanımına uyması nedeniyle istenen COVID-19 PCR sonucu ile hastaya COVID-19 tanısı kondu.

COVID-19 seyri sırasında veya tedavilere bağlı olarak transaminaz değerlerinde yükseklik saptandığı bildirilmiştir (5-7). Ülkemizden yapılan COVID-19 tedavisinde favipiravir tedavisi sonrası hepatotoksisite sıklığı %4,5 ve gastrointestinal yan etkiler %1,5 oranıında bildirilmiştir5. Hatta Ebik ve ark. çalışmasında COVID-19 enfekte 1301 hastanın %50,2 sinde tedavi sırasında ALT-AST yüksekliği gelişmesine rağmen, bu yükseklikllerin %45,3'ünün hafif ve orta düzeyde enzim artışı olduğu, çalışmaya dahil edilen olguların %4,9'unda ilaca bağlı karaciğer hasarı geliştiği bildirilmiştir (7). Favipiravir ile ilgili literatürde kısıtlı bilgi olmasına rağmen COVID-19 tedavisinde kullanılan bütün ilaçların potansiyel hepatotoksik olduğu ifade edilmiş ve bu ilaçları tek veya kombine kullanırken karaciğer hasarı yönünden dikkatli olunması gerektiği vurgulanmıştır (8). Bu nedenle sunulan hastada COVID-19 tedavisi başlanılırken, altta yatan hastalığı olan genitoüriner TB tedavisine ara verilmiş olup, favipiravir tedavisi tamamlandıktan sonra tekrar transaminaz değerleri bakılmış, değerlerde düzelme olması üzerine tedaviye tekrar başlanmıştır.

Sonuç olarak, COVID-19 semptom ve bulguları da anti TB ilaç yan etki benzeri dahil birçok hastalıkla benzerlik göstermekte olup ayırıcı tanıda akılda tutulmalıdır. Bu nedenle hastayı değerlendiren klinisyenin şüphe duyması halinde tanıya yönelik girişimde bulunması hem birey hem de toplum sağlığı açısından önemlidir.

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Etik: Hastadan bilgilendirilmiş onam formu alınmıştır.
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IMAGE PRESENTATION

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Bilateral Triquetrum Fracture with Specific Radiographic Signs

Özel Radyografi Bulgusu ile Bilateral Triquetrum Kırığı

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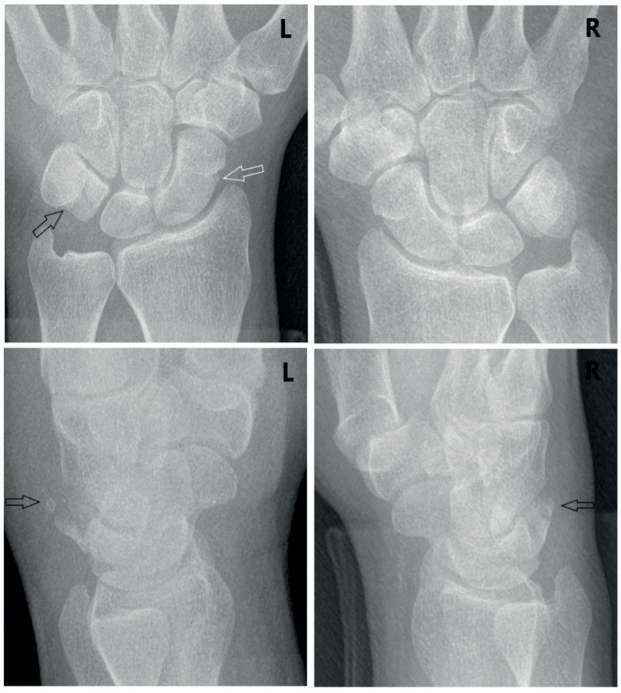

Figure 1: Bilateral triquetrum fractures on wrist radiographs, anterior-posterior and lateral view

Figure 2: "Pooping duck sign" on lateral wrist radiograph

A 44-year-old male patient presented to the emergency department with pain in both wrists because of falling. It was known that both wrists of the patient were in dorsiflexion while falling, and there was no additional injury. The Glasgow coma scale score was 15; vital values were within normal limits. The patient had bilateral wrist tenderness, pain with ulnar deviation, and edema on the dorsal side. In addition, he had pain with palpation of the left snuff box. Examinations of the ulnar and radial nerves and arteries were normal. X-rays showed a triquetrum fracture in the right hand, and a triquetrum and scaphoid fracture in the left hand. While triquetrum fractures were not apparent on anterior-posterior radiographs, they were clearly visible on both lateral radiographs (Figure 1). With a short-arm splint for the right hand and a scaphoid cast for the left hand, the patient recovered without sequelae after 6 weeks of wrist immobilization.

Triquetrum fractures are generally classified as dorsal cortex fractures and body fractures. Dorsal cortex fractures are more common and are usually seen as avulsion fractures. They occur with trauma, especially in the form of falling with wrist dorsiflexion. (1,2). Our patient also fell with the same mechanism. To diagnose triquetrum fractures, lateral and oblique radiographs should be performed in addition to anterior-posterior radiographs. In particular, dorsal cortex fractures may not be visible on the anteroposterior radiograph, while the avulsion fragment is better seen on the lateral radiograph (3). The appearance of triquetral fractures on the lateral radiograph is called the "pooping duck sign" because of the typical shape it forms with the scaphoid and lunate bone (Figure 2) (4). In our case, although both triquetrum fractures could not be clearly seen on the anterior-posterior radiograph, they were seen more clearly with typical findings on the lateral radiograph. Triquetrum fractures are typical of carpal bone fractures, which can be seen more prominently on lateral radiographs, and knowing the specific finding on the lateral radiograph may help with the diagnosis.

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LETTER TO EDITOR

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Carbon Monoxide Poisoning and Sequels of Cardiac Function

Karbon Monoksit Zehirlenmesi ve Kardiyak Fonksiyonun Sekelleri

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Dear editor,

Carbon monoxide can cause chemical anemia by binding to hemoglobin and shifts the oxyhemoglobin curve to the left, preventing oxygen from being released into the tissues (1). Elevated levels of cardiac markers such as troponin may be seen when myocardial damage occurs. Electrocardiographic or echocardiographic changes can be monitored. To explain this damage in the myocardium, the toxic effect of carbon monoxide binding to myoglobin is also mentioned in addition to the oxidative stress of carboxyhemoglobin (2). Carbon monoxide-bound myoglobin is not capable of delivering sufficient oxygen to the myocardium (2). Another plausible explanation of tissue hypoxia is binding carbon monoxide to cardiac myoglobin causes myocardial depression, hypotension, and arrhythmias. Carbon monoxide creates myocardial damage through many molecules (3) and this damage to the myocardium may be permanent. For example, within the last few years, a 21-year-old male patient was referred to our clinic with emergency medical services because of loss of consciousness. On anamnesis, it was learned that the family of a patient who had no illness story stayed in barracks and burned fire in the barracks to warm up. Glasgow Coma Score of the patient was 15 (eye 4, verbal 5, and motor 6). The vital parameters were within normal limits. Patient who was not able to protect the respiratory tract, occasionally had orotracheal intubation. There was no ischemic change on electrocardiography. Common brain edema was observed on cranial computed tomography. Troponin I level was measured at 1.937 ng/mL (normal value below 0.0262n/mL), and blood biochemical values within normal range. On the echocardiography, the left ventricle was assessed as globally hypokinetic. The troponin I observations of the patient are summarized in the figure. The patient was extubated on the fourth day after the follow-ups in our clinic. During the clinical follow-up period, the patient was given 300 mg of clopidegrel and acetylsalicylic acid 300 mg per day by nasogastric tube. After extubating consciousness and perception were evaluated as normal. On the echocardiography performed on the fifth day, ejection fraction was 45%. The patient was discharged from our clinic after total of 5 days of follow-up.

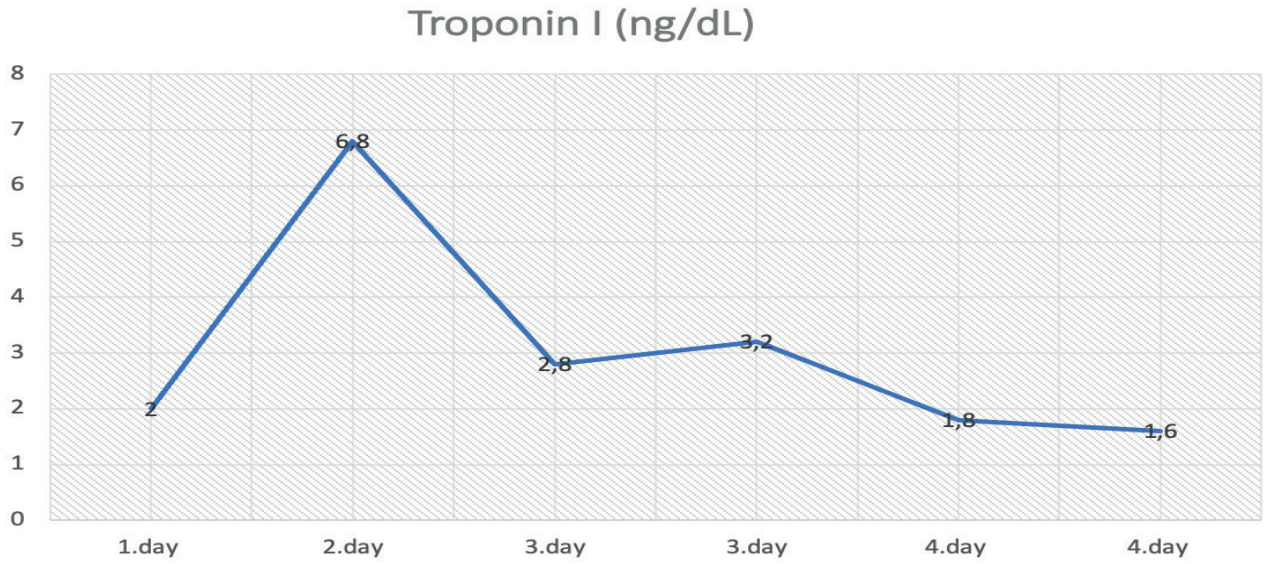

Figure: The patient's troponin I levels

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Ethic: The study does not require ethics committee approval. There is no such thing as any blood, saliva, violation of the rights of the patient, etc.
Case was presented as a poster presentation in 4th Intercontinental Emergency Medicine Congress, 4rd International Critical Care and Emergency Medicine Congress, at May 18- 21, 2017, in Antalya

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