e-ISSN:2149-7869

Cilt: 25 Sayı: 4 / Ekim 2024

Kocatepe TIP DERGİSİ

Kocatepe Medical Journal

KOCATEPE TIP DERGİSİ

KOCATEPE MEDICAL JOURNAL

Yayımlayan / *Published by*

Afyonkarahisar Sağlık Bilimleri Üniversitesi

Afyonkarahisar Health Sciences University

Afyonkarahisar Sağlık Bilimleri Üniversitesi Adına Sahibi
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Cilt / *Volume*: 25 Sayı / *Number*: 4 / Ekim 2024 Sayısı /*October 2024*

Üç ayda bir yayınlanır / Published per three months

KOCATEPE TIP DERGİSİ

KOCATEPE MEDICAL JOURNAL

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Yayın Sekreteri: Ayşe SÜRÜÇ

ISSN 1302-4612
e-ISSN 2149-7869

Cilt / *Volume* 25 Sayı / *Number* 4 / *Ekim* / *October* 2024

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ARAŞTIRMA YAZISI / RESEARCH ARTICLE

MADDE KULLANIM BOZUKLUĞU TANILI HASTALARDA ALEKSİTİMİ VE ALGILANAN STRES İLİŞKİSİNİN ARAŞTIRILMASI

INVESTIGATION OF THE RELATIONSHIP BETWEEN ALEXITHYMIA AND PERCEIVED STRESS IN PATIENTS DIAGNOSED WITH SUBSTANCE USE DISORDER

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ÖZET

AMAÇ: Çalışmamızda, madde kullanım bozukluğu tanılı hastalarda, duyguları tanıma, ifade etme, dışa dönük düşünme ve hayal gücünde kısıtlılıkla karakterize bir kişilik özelliği olarak tanımlanan aleksitimi ile algılanan stres arasında ilişkinin araştırılması amaçlanmıştır.

GEREÇ VE YÖNTEM: Hastanemiz alkol ve Madde Bağımlılığı Tedavi Merkezi'ne (AMATEM) başvuran 52 madde kullanım bozukluğu tanılı hasta ve benzer sosyokültürel özelliklere sahip ancak madde kullanım bozukluğu ve ek psikiyatrik rahatsızlığı olmayan 50 sağlıklı kontrol dahil edilmiştir. Katılımcılar sosyodemografik veri formu ile Toronto Aleksitimi Ölçeği-20 (TAÖ-20), Algılanan Stres Ölçeği (ASÖ) ölçeklerini doldurmuştur.

BULGULAR: Hasta grubunda ASÖ ile TAÖ-20'nin duyguları tanımada güçlük (r=0,685) ve duyguları söze dökmede güçlük (r=0,515) alt boyutları arasında anlamlı bir korelasyon saptanmıştır (p<0,01). Kontrol grubunda ise ASÖ ile TAÖ-20'nin tüm alt boyutları arasında daha düşük fakat anlamlı korelasyon belirlenmiştir (r=0,318-0,394, p<0,05). Gruplar arası bağımsız T-testi sonuçlarına bakıldığında ise TAÖ-20 alt boyutları (duyguları tanımada güçlük, duyguları sözde dökmede güçlük, dışa dönük düşünme) açısından hasta grubu lehine anlamlı farklılıklar olduğu görülmüştür (p<0,05).

SONUÇ: Aleksitimi madde kullanım bozukluğu olan kişilerde daha yüksek seviyelerde karşımıza çıkmakta ve algılanan stres seviyeleriyle kontrol grubuna göre daha güçlü ilişkiler kurmaktadır.

ANAHTAR KELİMELER: Aleksitimi, Alkol tüketimi, Madde kullanımına bağlı bozukluklar, Opiyat bağımlılığı.

ABSTRACT

OBJECTIVE: In our study, it is aimed to investigate the relationship between perceived stress and alexithymia, which is defined as a personality trait characterized by a limited ability to recognize and express emotions, externally-oriented thinking, and imagination, in patients diagnosed with substance use disorder.

MATERIAL AND METHODS: 52 patients diagnosed with substance use disorder who applied to our hospital's Alcohol and Drug Treatment Center (ADTC) and 50 healthy controls with similar sociocultural characteristics but without substance use disorder and additional psychiatric disorders were included. Participants filled out the sociodemographic data form and the Toronto Alexithymia Scale-20 (TAS-20) and Perceived Stress Scale (PSS) scales.

RESULTS: In the patient group, a significant correlation was found between the PSS and difficulty identifying feelings (r=0,685) and difficulty describing feelings (r=0,515) subscales of TAS-20 (p<0,01). In the control group, it was observed that lower but significant correlations were established between ASQ and all subscales of TAS-20 (r=0,318-0.394, p<0,05). When the independent T-test results between the groups were examined, it was seen that there were significant differences in favor of the patient group in terms of TAS-20 subscales (difficulty identifying feelings, difficulty describing feelings, externally-oriented thinking) (p<0,05).

CONCLUSIONS: Alexithymia occurs at higher levels in people with substance use disorder and has stronger relationships with perceived stress levels than in the control group.

KEYWORDS: Alexithymia, Alcohol consumption, Substance related disorders, Opioid addiction.

Geliş Tarihi / Received:19.12.2023
Kabul Tarihi / Accepted: 20.03.2024
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Etik Kurul / Ethical Committee: Sağlık Bilimleri Üniversitesi Ankara Eğitim ve Araştırma Hastanesi Etik Kurulu (26.07.2023-E-23/1320).

GİRİŞ

Madde kullanım bozukluğu, tüm dünyada özellikle gençler arasında artan bir hızla ilerleyerek önemli bir sağlık sorunu haline gelmiştir. Literatürde alkol kullanım bozukluğu ve madde kullanım bozukluğu prevalansını sırasıyla %8 ve %2-3 arasında saptayan epidemiyolojik çalışmalar bulunmaktadır (1, 2). Madde kullanım bozukluğu tanı ve tedavi sürecini olumsuz yönde etkileyebilecek faktörlerin araştırılması önem arz etmektedir.

Aleksitimi, süreklilik gösteren, somatoform bozukluk, depresyon, kaygı bozuklukları (özellikle travma sonrası stres bozukluğu ve obsesif kompulsif bozukluk) gibi patolojilerde sıklıkla karşımıza çıkmakla birlikte sağlıklı örneklemde de görülebilen bir kişilik özelliğidir (3 - 5). Aleksitimi, duyguları tanıma, ifade etme, dışa dönük düşünme ve hayal gücünde kısıtlılıkla karakterize bir kişilik özelliği olarak tanımlanabilir (6, 7). Madde kullanım bozukluğu tanısında da çalışılmış olan bu kavram, toplum örneklemiyle karşılaştırıldığında alkol kullanan bireylerde daha sık saptanmıştır (8 - 10). Aleksitimi hastalıklara, alkol-madde kullanımına sekonder olarak ortaya çıkabilen bir durum fenomeni de olabilir (11). Freyberger, sekonder aleksitiminin tıbbi hastalıklara veya psikolojik rahatsızlıklara bağlı ortaya çıkabileceğini savunmuştur (12). Messina ve ark. ikincil aleksitiminin psikolojik bir travma ya da tıbbi bir hastalığın yarattığı psikolojik sıkıntı sonrası ortaya çıkabileceğini belirtmiştir (13). Fakat literatürde ikincil ortaya çıkan alekstimi ile ilgili sonuçlar tutarsızdır (14). Literatüre bakıldığında opiyat kullanım bozukluğu olan kişilerde aleksitimi çalışmalarının kısıtlı olduğu saptanmıştır.

Stres ve madde kullanım bozukluğu ilişkisi literatürde sıklıkla çalışılmış olmasına karşın bu kavramı aleksitimi ile birleştiren çalışma sayısı kısıtlıdır (15 - 17). Stres-aleksitimi hipotezine göre azalmış duygusal farkındalık, baş etmede problemlere yol açarak kişinin daha fazla stres altında kalmasına ve ruhsal problemlere yol açabilir (18). Aleksitimi ve madde kullanım bozukluğu ilişkisi çeşitli çalışmalarla ortaya konmuştur ancak halen yeni çalışmalara ihtiyaç duyulmaktadır (19). Bu çalışmada amacımız stresin önemli bir presipitan faktör olduğu kanıtlanmış madde kullanım bozukluğu tanılı örneklemde aleksitimi şiddetini araştırmaktır. Kendi duygularını, bedensel durumlarını ve karşısındaki bireyin duygularını okumakta güçlük çeken aleksitimi şiddeti yüksek bireylerde algılanan stres düzeyi saptanacaktır. Ayrıca bu parametreler kontrol grubuyla karşılaştırılacaktır.

Hipotezlerimiz;

• Hasta grubunda aleksitimi total ve alt grupların puanları algılanan stres puanı ile pozitif yönde ilişkilidir.
• Aleksitimi şiddeti hasta grubunda kontrol grubuna göre anlamlı şekilde yüksektir.

GEREÇ VE YÖNTEM

Örneklem

Çalışmaya Ankara Eğitim ve Araştırma Hastanesi Madde Bağımlılığı Tedavi Merkezi'ne AMATEM Kliniği'ne başvuran 52 madde kullanım bozukluğu tanılı hasta ve benzer sosyokültürel özelliklere sahip ancak madde kullanım bozukluğu ve ek psikiyatrik rahatsızlığı olmayan 50 sağlıklı kontrol dahil edilmiştir. Örneklem sayısı G*power'da α=0.05 hata payı, 1-β=0.80 (power), f^2=0.05 etki büyüklüğü kriterlerine göre bağımsız gruplar t testi analizi için hesaplanarak her grup için n=51 olmak üzere toplam örneklem sayısı 102 olarak bulunmuştur. Araştırmanın dışlama kriterleri epilepsi, demans, deliryum benzeri organik bir durumun varlığı, anlıksal yetiyitimi varlığı, son 6 ay içinde elektrokonvülsif tedavi (EKT) almış olmak, psikoz ve bipolar afektif bozukluk tanılarının olması olarak belirlenmiştir. Dışlama kriterleri ya da başka bir sebeple çalışmaya dahil edilmeyen birey olmamıştır. Çalışmanın konusu ve amacı anlatıldıktan sonra çalışmaya katılmayı kabul eden katılımcılarda aydınlatılmış onam formu alınmıştır. Katılımcılar sosyodemografik veri formu ile Toronto Aleksitimi Ölçeği-20 (TAÖ-20), Algılanan Stres Ölçeği (ASÖ) ölçeklerini doldurmuştur.

Kullanılan Ölçekler

Sosyodemografik veri formu: Araştırmacılar tarafından oluşturulan bu form, katılımcıların yaş, cinsiyet, medeni durum gibi sosyodemografik verilerini ayrıca kullanılan maddenin adı, kullanım yolu, ilk madde kullanım yaşı gibi klinik verileri saptamayı amaçlamaktadır.

Toronto Aleksitimi Ölçeği-20: Bagby, Parker ve Taylor tarafından geliştirilmiş ve Güleç ve ark. tarafından Türkçeye uyarlanmıştır (20 - 22). 5'li

likert tipi (1=kesinlikle katılmıyorum, 5=kesinlikle katılıyorum), 20 maddeden oluşan bir kendini değerlendirme ölçeğidir. Duygularını Tanımada Güçlük (TAÖ-1), Duyguları Söze Dökmede Güçlük (TAÖ-2), Dışa-Dönük Düşünme (TAÖ-3) alt-ölçekleri vardır. Yüksek puanlar yüksek aleksitimik seviyeyi gösterir.

Algılanan Stres Ölçeği: Cohen, Kamarck ve Mermelstein (1983) tarafından geliştirilmiştir (23). Toplam 14 maddeden oluşan ASÖ kişinin hayatındaki birtakım durumların ne derece stresli algılandığını ölçmek için tasarlanmıştır. Katılımcılar her maddeyi "Hiçbir zaman (0)" ilâ "Çok sık (4)" arasında değişen 5'li Likert tipi ölçek üzerinde değerlendirmektedir. Maddelerden olumlu ifade içeren 7'si tersten puanlanmaktadır. ASÖ-14'ün puanları 0 ile 56 arasında değişmektedir. Yüksek puan kişinin stres algısının fazlalığına işaret etmektedir. Ölçeğin Türkçe geçerlilik ve güvenilirliği Eskin ve ark. tarafından yapılmıştır (24).

Etik Kurul

Çalışma için Ankara Eğitim ve Araştırma Hastanesi etik kurulundan onay alınmıştır (26.07.2023/E-23/1320).

İstatistiksel Analiz

Veriler SPSS (Statistical Package For The Social Sciences) 22.0 programı ile değerlendirilmiştir. Verilerin normal dağılıma uygunluğu basıklık çarpıklık değerleri ile değerlendirilmiş; ayrıca kategorik (nitel) değişkenler için frekans (n) ve yüzde (%), standart sapma (ss) istatistikleri verilmiştir. Çalışmada veriler, bağımsız gruplar T-testi, Pearson korelasyon testi ile analize tabi tutulmuş; p<0,05 anlamlı kabul edilmiştir.

BULGULAR

Sosyodemografik Veriler

Hasta grubunda ortalama yaş 33,87±9,06, kontrol grubunda 35,28±7,03 olarak saptanmıştır. Hasta grubunun %92,3'ünün (n=48), kontrol grubunun %80'inin (n=40) erkek olduğu görülmüştür. Hasta grubunda ilk madde kullanım yaşı 18,98±4,77 saptanırken halihazırda %69,2'si opiyat (n=36), %21,2'si alkol (n=11), %9,6'sı ise pregabalin (n=5) kullanıyordu. Sosyodemografik ve klinik veriler **Tablo 1**'de sunulmuştur.

Tablo 1: Grupların sosyodemografik özellikleri

	Hasta (n=52)	Kontrol (n=50)
Yaş	33,87±9,06	35,28±7,03
Cinsiyet		
Erkek	48 (%92,3)	40 (%80)
Kadın	4 (%7,7)	10 (%20)
Medeni durum		
Evli	20 (%38,5)	38 (%76)
Bekar/boşanmış	32 (%61,5)	12 (%24)
Eğitim yılı	9,90±2,57	15,44±5,28
İlk madde kullanım yaşı	18,98±4,77	
Damar içi madde kullanım öyküsü		
Evet	13 (%25)	
Hayır	39 (%75)	
Madde çeşitleri		
Eroin	36 (%69,2)	
Alkol	11 (%21,2)	
Pregabalin	5 (%9,6)	

Korelasyon Verileri

Hasta grubunda ASÖ ile TAÖ-20'nin duyguları tanımada güçlük (r=0,685) ve duyguları sözde dökmede güçlük (r=0,515) alt boyutları arasında anlamlı bir korelasyon saptanmıştır (p<0,01). Kontrol grubunda ise ASÖ ile TAÖ-20'nin tüm alt boyutları arasında daha düşük fakat anlamlı korelasyon ilişkilerinin kurulduğu görülmüştür (r=0,318-0,394, p<0,05). Korelasyon verileri **Tablo 2**'de sunulmuştur.

Tablo 2: Korelasyon tablosu (Hasta ve Kontrol Grubu)

Hasta	**1**	**2**	**3**	**4**
1. ASÖ	-			
2.TAÖ-1	,685**	-		
3.TAÖ-2	,515**	,757**	-	
4.TAÖ-3	,226	,434**	,307*	-
Kontrol				
1. ASÖ	-			
2.TAÖ-1	,358**	-		
3.TAÖ-2	,394**	,767**	-	
4.TAÖ-3	,318*	,235	,447**	-

Not: *p<0,05, **p<0,01, TAÖ-1= Duyguları tanımada güçlük,

TAÖ-2=Duyguları söze dökmede güçlük,

TAÖ-3=Dışa dönük düşünme,

Hasta ve Kontrol Grubunun Karşılaştırılması

Gruplar arası bağımsız T-testi sonuçlarına bakıldığında ise TAÖ-20 alt boyutları (duyguları tanımada güçlük, duyguları sözde dökmede güçlük, dışa dönük düşünme) açısından gruplar arasında anlamlı farklılıklar olduğu görülmüştür (sırasıyla p=0,001, p=0,08 ve p=0,036). Veriler **Tablo 3'**de sunulmuştur.

Tablo 3: Korelasyon tablosu (Hasta ve Kontrol Grubu)

Değişkenler	**Gruplar**	**N**	$\bar{x}$	**SD**	**t**	***p***	***df***
TAÖ-1	Hasta	52	18,80	7,79	3,458	,001**	100
	Kontrol	50	14,36	4,92			
TAÖ-2	Hasta	52	14,32	4,63	2,715	,008*	100
	Kontrol	50	12,14	3,42			
TAÖ-3	Hasta	52	23,38	4,21	2,125	,036*	100
	Kontrol	50	21,74	3,59			
ASÖ	Hasta	52	27,17	8,86	0,056	,956	100
	Kontrol	50	27,08	7,96			

Not: *p<0,05, **p<0,01, N = örneklem büyüklüğü, $\bar{x}$ = ortalama, SD = Standart sapma, TAÖ-1= Duyguları tanımada güçlük, TAÖ-2=Duyguları söze dökmede güçlük, TAÖ-3=Dışa dönük düşünme, ASÖ=Algılanan Stres Ölçeği

TARTIŞMA

Çalışmamızda madde kullanım bozukluğu tanılı hastaların aleksitimi ve algılanan stres düzeylerinin kontrol grubuyla karşılaştırılması; ayrıca algılanan stres ve aleksitimi arasındaki ilişkinin saptanması hedeflenmiştir. Hem hasta hem kontrol grubunda algılanan stres ve aleksitimi arasında anlamlı ilişkiler saptanmıştır. Aleksitimi alt boyutlarının hasta grubunda anlamlı olarak daha yüksek olduğu görülmüştür. Literatüre bakıldığında madde kullanım bozukluğu hasta grubunda çalışmaların sıkıntı toleransı düzeylerine daha fazla odaklandığı görülmektedir. Henschel ve ark.'larının reçeteli opioid kullanım bozukluğu olan bireylerde yaptığı çalışmada aleksitimi ile sıkıntı toleransı arasında negatif ilişki saptanmıştır (25). Winward ve ark.'larının alkol kullanım bozukluğu tanılı hastalarda yaptığı bir başka çalışmada ise ağır-epizodik alkol tüketiminin daha düşük sıkıntı toleransı ile ilişkili olduğunu saptamıştır (16). Semcho ve ark.'larının tedavi arayışında olan esrar kullanan bireylerde yaptığı çalışmada ise sıkıntı toleransının baş etme becerilerini yordadığı görülmüştür (17).

Madde kullanım bozukluğu tanılı hastalarda sıkıntı toleransı ve aleksitimi ilişkisini incelemek bağımlılık tedavisinde önemli bir hedef olabilir (25). Aleksitimisi olan bireyler kişilerarası stres yaratan durumlarla başa çıkabilmek için opiyat ya da diğer maddeleri kullanmaya yönelebilir (9). Madde kullanan bireylerin stresi nasıl algıladıklarını değerlendirmek önem arz etmektedir.

Çalışmamızda algılanan stres düzeylerinin gruplar arasında benzer olması çalışmamızı gerçekleştirdiğimiz sosyokültürel ve sosyoekonomik çevre ile açıklanabilir. Düşük sosyoekonomik seviyeye sahip olan bireylerin stres düzeylerinin daha yüksek olduğu bilinmektedir (26). Opioid kullanan kadın hastaları kontrol grubuyla karşılaştıran bir çalışmada hasta grubunda duyguları tanımada güçlük, duyguları söze dökmede güçlük ve dışa dönük düşünmede anlamlı zorluk saptanmıştır. (27). Çalışmamızda erkek hastaların da dahil edilmesi çalışmamızın genellenebilirliğini artırmaktadır. Alkol kullanım bozukluğu ile yapılan çalışmalar aleksitiminin hem bağımlılık gelişiminde hem de tedavi sonuçlarını etkilemede rolü olduğunu göstermektedir (28). Çalışmamızda hasta grubunun aleksitimi düzeylerinin kontrol grubuna göre anlamlı şekilde yüksek oluşu bu açıdan literatürle uyumlu görünmektedir. Literatürde özellikle alkol kullanım bozukluğu olan bireylerde aleksitimi ve aleksitiminin kişilik, depresyon, anksiyete, benlik saygısı ile ilişkisine bakılmıştır (29 - 32). 2019 yılında yapılan ve aleksitimi ile kişilik arasındaki ilişkiyi araştıran bir çalışmada alkol hastalarının yanında madde kullanan hastalar da dahil edilmiş ancak madde kullanan hastaların kullandığı maddeler belirtilmemiştir (31).

Çalışmamızın bazı kısıtlılıkları bulunmaktadır. Çalışmamızın tek merkezli olması, ölçeklerin hastalar tarafından doldurulуyor olması, birincil/ikincil aleksitimi ayrımı yapmıyor olması, ağırlıklı olarak erkek hastalardan oluşması ve kullanılan madde çeşitleri ile aleksitimi-algılanan stres ilişkisinin incelenmemesi çalışmanın kısıtlılıkları arasında sayılabilir.

Çalışmamız, AMATEM kliniğimizde madde kullanım bozukluğu tanılı hastaları kontrol grubuyla karşılaştırarak aleksitimi ve algılanan stres ilişkisini inceleyen ilk çalışmadır. Reçetesiz madde kullanım bozukluğu olan kadın ve erkek bireyleri dahil etmesi açısından çalışmamız önem arz etmektedir.

Çalışmamız sonucunda aleksitimi madde kullanım bozukluğu olan kişilerde daha yüksek seviyelerde karşımıza çıkmakta ve algılanan stres seviyeleriyle kontrol grubuna göre daha güçlü ilişkiler kurmaktadır. Madde kullanım bozukluğu tanılı kişilerde aleksitimi atlanmaması gereken bir kişilik özelliğidir.

Çalışmamız kısıtlılıklarına rağmen AMATEM kliniğimizde takipli hastaların aleksitimi ve algılanan stres verilerini sunan ilk çalışma olması açısından kıymetlidir. Çalışmamızda birincil aleksitimi ile madde kullanımına bağlı gelişen ikincil aleksitimi farkı incelenmemiştir. Gelecek çalışmalarda aleksitimi kavramının madde alt gruplarında ve daha geniş örneklemlerde araştırılması ile birincil/ikincil aleksitimi kavramının incelenmesi önerilmektedir.

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Kocatepe Tıp Dergisi
Kocatepe Medical Journal
25:413-419/Ekim 2024 Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

SERUM ANJİYOPOİETİN BENZERİ PROTEİN 8 DÜZEYLERİ İLE HİPERTANSİYON EVRELERİ ARASINDAKİ İLİŞKİ

THE RELATIONSHIP BETWEEN SERUM ANGIOPOIETIN-LIKE PROTEIN 8 LEVELS AND HYPERTENSION STAGES

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ÖZET

AMAÇ: Hipertansiyon ciddi komplikasyonlara yol açabilen ciddi bir durumdur. Günümüzde, hipertansiyon tanısı koymak ve hastalığı evrelemek için klinik uygulamada kullanılan standart bir biyobelirteç yoktur. Bu çalışmanın amacı, anjiyopoietin benzeri protein 8'in (sANGPTL8) serum düzeylerinin hipertansiyon hastalarında ve hipertansiyonun ileri evrelerinde değişip değişmediğini araştırmaktır.

GEREÇ VE YÖNTEM: Çalışmamız, prospektif gözlemsel bir çalışmadır. Kardiyoloji polikliniğimizde, 42 hipertansif ve 41 hipertansif olmayan sağlıklı hastada, sANGPTL8 düzeylerini ölçmek için bir ELISA kiti kullandık ve gruplar arasındaki istatistiksel farklılıkları değerlendirdik. Two-tailed p< 0.05 değerini istatistiksel olarak anlamlı kabul ettik.

BULGULAR: Evre 2 hipertansiyon grubundaki ortalama sANGPTL8 düzeyleri, evre 1 ve hipertansif olmayan gruba göre istatistiksel olarak anlamlı derecede yüksek olarak tespit edildi (sırasıyla, 813 pg/ml, 524.89 pg/ml ve 518.07 pg/ml) (p= 0.001).

SONUÇ: Çalışmamız, evre 2 hipertansif hastalarda ortalama sANGPTL8 düzeylerinin, evre 1 hipertansif ve normotansif bireylerden daha yüksek olduğunu göstermiştir (p= 0.001). ANGPTL8 ile birlikte kullanılabilecek ek biyobelirteçler ve ANGPTL8 üzerine yapılacak daha fazla araştırma, bu adipokinin ileri evre hipertansiyon tanısında etkili bir biyobelirteç olarak kullanılmasını sağlayabilir.

ANAHTAR KELİMELER: Hipertansiyon, Anjiyopoietin benzeri protein 8, Kan basıncı, Son organ hasarı.

ABSTRACT

OBJECTIVE: Hypertension is a serious condition that can lead to serious complications. Currently, there is no standard biomarker used in clinical practice to diagnose hypertension and stage the disease. The aim of this study was to investigate whether serum levels of angiopoietin-like protein 8 (sANGPTL8) change in hypertensive patients and advanced stages of hypertension.

MATERIAL AND METHODS: Our study is a prospective observational study. We used an ELISA kit to measure sANGPTL8 levels in 42 hypertensive patients and 41 healthy non-hypertensive patients at our cardiology clinic and evaluated statistical differences between the groups. A two-tailed p< 0.05 was considered statistically significant.

RESULTS: The mean sANGPTL8 levels in the stage 2 hypertension group are statistically significantly higher than in the stage 1 and non-hypertensive group (813 pg/ml vs 524.89 pg/ml and 518.07 pg/ml respectively) (p= 0.001).

CONCLUSIONS: According to our study, mean sANGPTL8 levels were higher in stage 2 hypertensive patients compared to stage 1 hypertensive and normotensive individuals (p=0.001). Additional biomarkers that can be used in combination with ANGPTL8 and further research on ANGPTL8 may enable this adipokine to be used as an effective biomarker in diagnosing advanced hypertension.

KEYWORDS: Hypertension, Angiopoietin-Like Protein 8, Blood Pressure, End-organ damage.

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Kabul Tarihi / Accepted: 08.04.2024
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INTRODUCTION

Hypertension is a major risk factor for cardiovascular disease, contributing significantly to morbidity and mortality worldwide. High systolic blood pressure is a primary cause of death and disability, according to the 2017 Burden of Disease Study (1). The relationship between blood pressure and increased cardiovascular disease risk is gradual and continuous from 115/75, considered the normotensive range (2).

In April 2013, Yi and colleagues discovered a hormone called ANGPTL8, which they named "betatrophin" due to its significant role in promoting pancreatic b-cell proliferation (3). ANGPLT8 is mainly synthesized in the liver and adipose tissues. It is a circulating adipokine that affects glucose and lipid metabolism (4).ANGPTL8 has been identified as a critical marker regulating serum glucose and lipid metabolism, controlling cardio-metabolic disease risk (5, 6). The ANGPTL8 gene expression is regulated by the inflammatory state, and its levels are decreased by tumor necrosis factor-a (TNF-a) under inflammation (7). Circulating ANGPTL8 is related to inflammatory disease, metabolic parameters, and oxidative stress (8).

Studies over the past 15 years have determined that inflammation plays a vital role in developing essential hypertension (9 - 12). A recent study consisting of 14 prospective cohort studies, 2 retrospective cohort studies, 5 nested case-control studies, and a systematic overview has shown that individuals with high levels of inflammation markers in their bloodstream are at a heightened risk of developing hypertension (13).

Our team posited that advanced hypertensive patients may have elevated sANGPTL8 levels, given the known involvement of inflammatory processes in the development of hypertension. Our hypothesis further suggested that there is a positive correlation between ANGPTL8 levels and the stage of hypertension. There is no previous study comparing sANGPTL8 levels in hypertension stages. In light of the knowledge that the probability of fatal end-organ damage increases as the hypertension stage progresses, early diagnosis, treatment and staging of hypertension are crucial. The purpose of this study is to investigate the potential of serum levels of sANGPTL8 to serve as a diagnostic marker for hypertension and its progression to advanced stages.

MATERIALS AND METHODS

The Study Population

Our study is a prospective observational study. We enrolled hypertensive patients and healthy individuals who applied to our cardiology outpatient clinic between June and July 2017. We divided hypertensive individuals into stage 1 and stage 2 hypertension patients. We excluded stage 3 hypertensive patients (2 patients), which we first included in the study because we determined that they would not gain statistical significance in comparison due to their small number. We excluded hypertensive patients with secondary hypertension, antihypertensive medication, diabetes, heart failure, coronary artery disease, peripheral artery disease, cerebrovascular disease, chronic renal failure, obesity, cancer, inflammatory and infectious diseases, and pregnancy.

Laboratory Measurements

The diagnosis of hypertension was confirmed with a 24-hour ambulatory blood pressure measuring device (Contec brand, ABPM50 model, made in China). We described hypertension stages according to the 2018 European Guidelines On The Management of Hypertension as stage 1; systolic blood pressure (SBP) 140-159 mmHg or diastolic blood pressure (DBP) 90-99 mmHg, and stage 2, SBP 160-179 mmHg or DBP 100-109 mmHg (14). The body mass index is calculated as weight in kilograms divided by the square of the height in meters, expressed as kg/m^2. To measure waist and hip circumference, a tape measure is used. The waist-hip ratio is then calculated by dividing the waist circumference in centimeters by the hip circumference in centimeters. sANGPTL8 levels were obtained venously after 8-10 hours of fasting and placed in vacuum blood collection tubes containing gel and clot activator. Serum was obtained by rotating these tubes at 1600 rpm for 10 minutes in a centrifuge device. Collected samples were stored in the refrigerator at -20 degrees Celsius. sANGPTL8 levels were measured

with the commercially available enzyme-linked immunosorbent assay kit (Catalogue no. E11644h; Wuhan EIAab Science, Wuhan, China).

Ethical Committee

Our study was approved by the Malatya Clinical Research Ethics Committee with protocol number 2017/24 and the research was conducted under the Declaration of Helsinki. Written and signed consent was obtained from each participant.

Statistical Analysis

The data were analyzed using SPSS software (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY, USA, IBM Corp.). We expressed categorical variables as frequencies and percentages and continuous variables as mean and standard deviation for normally distributed data or median values and interquartile ranges for non-normally distributed data. We conducted the Kolmogorov-Smirnov test to determine if the variables followed a normal distribution. Taking George et al.'s study as a reference, it was determined that the variables were normally distributed since their skewness and kurtosis values were within ±2 (15). Parametric tests were applied: Independent-Samples T test for variables with two subgroups and One-way ANOVA test for variables with more than two subgroups. Two-tailed p-values < 0.05 were considered statistically significant. Upon detection of non-homogeneity of variances, Tamhane's T2 post hoc test performed a pairwise comparison between groups. The categorical variables were analyzed using the appropriate chi-square test and expressed as percentages (%) and absolute numbers. In contrast, we expressed continuous variables as means and standard deviations or medians for normally distributed data. Since the variables were normally distributed, the correlation between the continuous variables was evaluated using the Pearson correlation test. The relationship between sANGPTL8 levels and the hypertension stages was analyzed through a linear regression model. The effect size in the three-group variables was measured using the formula $(\eta^2 = \frac{SS_{ef}}{SS_t})$ (16,17). Receiver Operating Characteristic (ROC) curve analysis was used to predict stage 2 hypertension using sANGPTL8 levels.

RESULTS

We conducted a prospective observational study with 83 participants, 41 healthy and 42 hypertensive. The mean age of the study population is 39.73 with ±14.09 standard deviation. The study population consisted of 37 males and 46 females. There were no statistically significant differences between hypertension subgroups regarding age, gender, and waist-hip ratio classes. A statistically significant difference was determined between the three groups regarding sANGPTL8 levels and body mass index values (p=0.001, and p=0.002 respectively) **(Table 1)**.

Table 1: Demographic and clinical data of the study population

Characteristics	Normotensive (n=41)	Stage 1 HT (n=19)	Stage 2 HT (n=23)	*p*
Age (years)	33.49 ± 10.28	44.47 ± 13.13	46.96 ± 16.12	.3
Male n (%)	18 (43.9)	9 (47.4)	10 (43.5)	.1
WHR (0.8- 1.0) n (%)	31 (47)	16 (24.2)	19 (28.8)	.7
BMI (kg/m²)	24.60 ± 4.65	28.01 ± 2.51	27.57 ± 4.12	**.002***
SBP (mmHg)	-	146.84 ± 6.71	163.04 ± 7.8	**.002***
DBP (mmHg)	-	90.53 ± 8.48	98.3 ± 6.53	**.002***
MAP (mmHg)	-	109.32 ± 4.89	119.83 ± 4.82	**.003***
sANGPTL 8 levels (pg/ml)	518.07 ± 211.76	524.89 ± 184.61	813 ± 351.11	**.001***

*Age and BMS values are presented as mean ± standard deviation. All other data expressed as mean ± standard deviation or n (%). Differences between groups were analyzed by the χ² test or One- Way Anova Test. Abbreviations: BMI= Body mass index. sANGPTL8= Serum angiopoietin-like protein 8. WHR= Waist-hip ratio. SBP= Systolic blood pressure. DBP= Diastolic blood pressure. MAP= Mean arterial pressure. *p < .01*

The mean sANGPTL8 level of stage 2 hypertensive individuals (813 ± 351.11 pg/ml) was higher than the normotensive (518.07 ± 211.76 pg/ml) and stage 1 hypertensive individuals (524.89 ± 184.61 pg/ml) **(Figure 1)**.

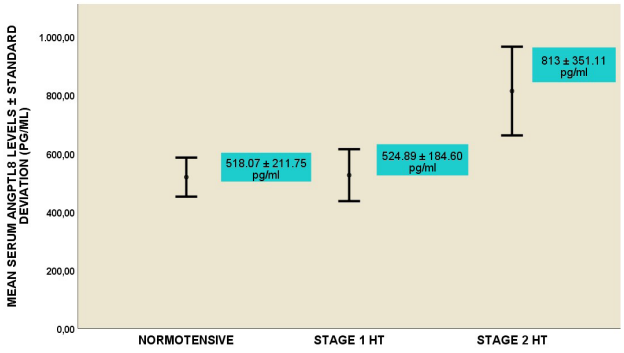

Figure 1: Serum ANGPTL8 levels (pg/ml) at different stages of hypertension. Data expressed as mean ± standard deviation. The One way ANOVA test was performed. p< .01. ANGPTL8: Angiopoietin-like protein 8. HT: Hypertension

Based on post-hoc tests, it has been determined that patients with stage 2 hypertension exhibit notably elevated sANGPTL8 levels compared to those with stage 1 hypertension and those who are normotensive (with p-values of 0.005 and 0.003, respectively). Conversely, no significant disparity was detected between those with stage 1 hypertension and normotensive individuals (p= 0.99) **(Table 2)**.

Table 2: Comparison of hypertension stages according to sANGPTL 8 levels

Hypertension Stage	n	Mean	Std. Dev.	F	*p*	Sig. dif.	η^2 (Eta^2)
Normotensive	41	518.07	211.75	11.140	**.001**	3>1	.22
Stage 1 HT	19	524.89	184.60			3>2	
Stage 2 HT	23	813	351.11				

**p< .01 One Way Anova Test. η^2 (Eta^2)= .22 means that the effect size is large. Abbreviations: HT= Hypertension. sANGPTL8= Serum angiopoietin-like protein 8. Std Dev.= Standard deviation. Sig. dif. : Significant difference 1= Normotensive Group. 2= Stage 1 Hypertensive Group. 3= Stage 2 Hypertensive Group.*

When age, systolic, diastolic, body mass index, and sANGPTL8 levels were evaluated using one-tailed Pearson correlation analysis, a statistically significant, low-level positive relationship was found between sANGPTL8 levels and systolic blood pressure (r= 0.286, p= 0.03) **(Table 3)**.

Table 3: Pearson's correlation test to determine the relationship between sANGPTL 8 levels and age, systolic and diastolic blood pressures and BMI

Variables	N	*r*	*p*
Age (years)	83	.062	.289
BMI (kg/m^2)	83	.159	.076
SBP (mmHg)	42	.286	**.033***
DBP (mmHg)	42	.128	.209

*Abbreviations: BMI= Body mass index. sANGPTL8= Serum angiopoietin-like protein 8. SBP= Systolic blood pressure. DBP= Diastolic blood pressure. *p< .01, r= Pearson correlation.*

However, no statistically significant correlation was found between diastolic blood pressures and sANGPTL8 levels (p= 0.2). Linear regression analysis was performed to predict sANGPTL 8 levels. The levels of sANGPTL8 were significantly predicted by systolic blood pressure and BMI (F=2.866, p=0.35, and 0.37 respectively). Systolic blood pressure and BMI accounted for approximately 18% of the variation in sANGPTL8 levels. When the body mass index and systolic blood pressure increase by one unit each, the levels of sANGPTL8 increase by 29,656 and 9,432 units respectively **(Table 4)**.

Table 4: Linear regression analysis to predict sANGPTL 8 levels

Variables	R	R^2	F	*p*	B	t	*p*
Age (years)	.430	.184	2.866	**.049**	.325	.101	.920
BMI (kg/m^2)					29.656	2.157	**.037**
SBP (mmHg)					9,432	2.181	**.035**

*Abbreviations: BMI= Body mass index. SBP= Systolic blood pressure. sANGPTL8= Serum angiopoietin-like protein 8. *p< .05*

We measured the η2 (Eta2) value as .22 for three groups. The study's effect size is large according to Cohen's guidelines Table 2 (18). In the ROC curve analysis, the sANGPTL8 cut-off point for predicting stage 2 hypertension was 530.5 pg/ml. Sensitivity and specificity by this cut-off point for sANGPTL8 in predicting stage 2 hypertension are 69.6% and 70%, respectively **(Table 5)**. The AUC (Area under the ROC curve) for ANGPTL8 was 0.769 **(Figure 2)**.

Table 5: Sensitivity And Specificity By The Optimized Cut-off Points For Serum ANGPTL8 Levels In Predicting Hypertension

Risk Factor	AUC (95%)	Cutt off	*p*	Sensitivity (%)	Specificity (%)
serum ANGPTL8	0.769 (0.653-0.886)	530.5 pg/ml	**.001***	69.6	70

*Abbreviations: ANGPTL8= Angiopoietin-like protein 8. AUC= Area Under the ROC (*Receiver Operating Characteristic*) Curve. *p< .01*

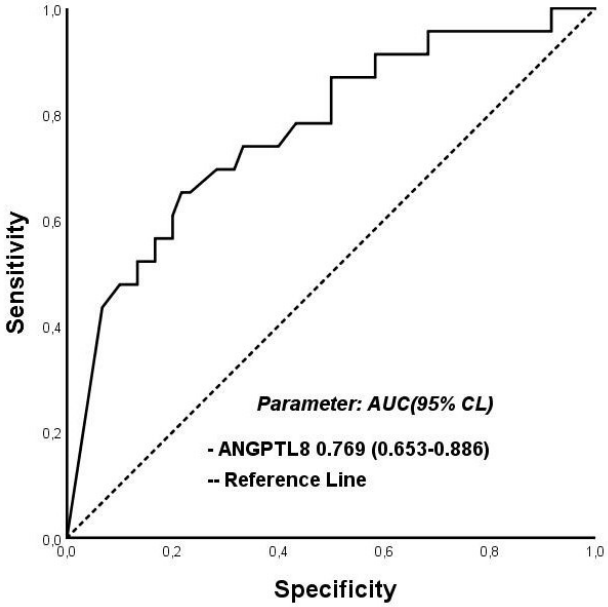

Figure 2: ROC curve analysis of Angiopoietin-like protein 8 in predicting hypertension. CI: Confidence interval. AUC: Area Under the ROC Curve. ANGPTL8: Angiopoietin-like protein 8.

DISCUSSION

Our research has delved into the correlation between sANGPTL8 level and hypertension stage. Notably, our study is the first to have explored this association. Previous studies have indicated that sANGPTL8 levels tend to be higher in individuals with hypertension. Our team's study has revealed a notable difference in sANGPTL8 levels between hypertensive patients classified as stage 1 versus those classified as stage 2 and normotensive individuals. Specifically, the sANGPTL8 levels of patients with stage 2 hypertension were found to be significantly higher than those with stage 1 hypertension and normotensive individuals (**Figure 3)**.

Previous studies consistently demonstrate that high systolic blood pressure is a leading risk factor for morbidity and mortality (1). It is known that the duration of the disease and the blood pressure elevation are linked to life-threatening complications like congestive heart failure, end-stage renal disease, and stroke (19). Therefore, early hypertension diagnosis, staging, and treatment are crucial.

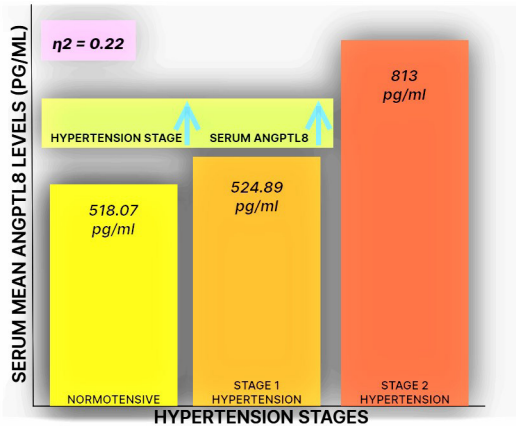

Figure 3: As the stage of hypertension advances, the levels of ANGPTL 8 serum increase. η2 (Eta2): effect size symbol. ANGPTL8: Angiopoietin-like protein 8.

In 2013, a hormone by the name of ANGPTL8 was identified by Yi and a team of colleagues (3). This hormone regulates glucose and lipid metabolism and is involved in metabolic diseases such as obesity and diabetes (20 - 22). Circulating ANGPTL8 is related to inflammatory disease. Zhang Y et al. showed that ANGPTL8 has an intracellular location associated with regulating inflammation (8). As a result of a study, it was determined that plasma ANGPTL8 levels were high in patients with severe infection. Furthermore, a strong correlation between circulating ANGPTL8 and lipopolysaccharide-induced acute inflammatory response was reported in animal models (23). However, the role of ANGPTL8 in the inflammation and inflammation-related signalling pathway is unknown.

Many studies showed that inflammation plays a vital role in developing essential hypertension, and high circulating inflammation markers were significantly related to the risk of developing hypertension (9 - 13). There are various ways in which inflammation and blood pressure can be linked. One possible mechanism is that high blood pressure can trigger the development of atherosclerosis by altering the biomechanical stimuli exerted by pulsating blood flow, such as increased hydrostatic pressure or cyclic strain, which can affect the genes and function of endothelial cells (24).

Our study indicated a positive correlation between systolic blood pressure and sANGPTL8 levels, but there was no correlation between diastolic blood pressure and sANGPTL8 levels. Maurer L et al. (25) also found similar correlation results between ANGPTL8 and blood pressure in their study. In a recent study, Chae et al. (26) noted that increased blood pressure may stimulate inflammation, a possible mechanism underlying hypertension. They found a positive correlation between increased blood pressure and inflammatory markers measured in their study. They also reported that serum levels of the inflammatory marker Intercellular adhesion molecule-1 (sICAM-1) positively correlated with systolic blood pressure but no diastolic blood pressure. It is unknown why some inflammatory marker's serum levels correlate with systolic blood pressure but not diastolic blood pressure. More comprehensive studies are needed in the future to elucidate this situation.

Many studies have reported that sANGPTL8, which is increased in inflammatory conditions, is also increased in hypertensive patients (25, 27, 28). Based on the knowledge that inflammatory processes are involved in the development of hypertension, we aimed to determine the relationship between sANGPTL8 levels and the presence and stage of hypertension. According to the results of our study, sANGPTL8 levels increased in stage 2 hypertensive patients. The results of our study are partially different from those of Abu-Farha et al. (27) and Hu, Lin et al. (28). As a result of these two studies, sANGPTL8 levels were found to be higher in hypertensive patients than in normotensive individuals. However, these two studies did not evaluate the relationship between hypertension stages and sANGPTL8 levels. In a recent animal experiment, Jiao et al. (29) found that ANGPTL8 expression was increased in hypertensive mice, rats and patients. They also found that VSMC (Vascular smooth muscle cell) -specific deletion of ANGPTL8 attenuated AngII-induced hypertension and hypertensive cardiovascular remodelling. Based on the findings of our study, sANGPTL8 levels exhibit an increase with a rise in systolic blood pressure but not with an increase in diastolic blood pressure. Additionally, these levels tend to increase in patients with stage 2 hypertension but not necessarily in all hypertensive patients. ROC analysis suggests that ANGPTL8 adipokinin is not a potent biomarker for predicting stage 2 hypertension (sensitivity 69.6%, specificity 70%). However, additional

biomarkers that can be used with ANGPTL8 and further research on ANGPTL8 may enable ANGPTL8 to be used as an effective biomarker in the diagnosis of advanced hypertension. Our research has several limitations. We conducted our study at a single center with a relatively small sample size due to the high cost of the sANGPTL8 ELISA kit, which was constrained by our budget. The group of stage 3 hypertensive patients was excluded from the evaluation due to the small number of such patients initially included in the study. Another area for improvement of the study is its design, which did not allow us to establish the causality and role that sANGPTL8 may play in hypertension development. The study's division into normotensive and hypertensive subgroups instead of observing patients with similar clinical characteristics suggests a high standard deviation of sANGPTL8 levels between the two groups. Furthermore, although we controlled for potential confounders that elevate sANGPTL8 levels, such as diabetes, hypercholesterolemia, and obesity, it is always possible that unrecognized confounding variables exist.

In conclusion, ANGPTL8 along with other biomarkers, could potentially be used as an effective tool to diagnose advanced hypertension. In selected hypertensive patients who do not have underlying conditions that may cause an increase in sANGPTL8 levels, such as diabetes, coronary artery disease, chronic inflammatory disease, or acute infection, those with elevated sANGPTL8 levels may be at a higher risk of advanced hypertension. Also, with future studies comparing sANGPTL8 levels measured before and after antihypertensive treatment in patients with hypertension, it will be possible to determine whether this adipokine is an appropriate biomarker to measure the success of antihypertensive treatment and blood pressure regulation in routine clinical use.

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Kocatepe Tıp Dergisi
Kocatepe Medical Journal
25:420-/428 Ekim 2024 Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

DU145 PROSTAT KANSERİ HÜCRE HATTINDA DOSETAKSEL ve AMİGDALİN TEDAVİSİNİN HÜCRE ÖLÜMÜ, İNTEGRİN-α ve İNTEGRİN-β EKSPRESYONLARI ÜZERİNDEN ETKİLERİNİN KARŞILAŞTIRILMASI

COMPARISON OF THE EFFECTS OF DOCETAXEL and AMYGDALIN TREATMENT ON CELL DEATH, INTEGRIN-α and INTEGRIN-β EXPRESSIONS IN DU145 PROSTATE CANCER CELL LINE

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ÖZET

AMAÇ: Prostat kanseri (PK) erkeklerde kansere bağlı ölümler arasında ikinci sırada yer almaktadır ve ölümlerin çoğu metastaz kaynaklıdır. Kanser metastazında hücre yüzey reseptörleri olan integrinler önemli rol oynarlar. İntegrin alfa2beta1'in metastatik prostat kanserlerinde kollajen I'e bağlanmayı artırarak hücre adezyon, migrasyon ve invazyonunda etkili olduğu gösterilmiştir. Prostat kanserinde Dosetaksel kemoterapisi kullanılmakta fakat ileri evrelerde bu tedavi etkisiz kalmaktadır. Amigdalin meyve tohumlarında yaygın olarak bulunan siyanojenik bir glikozittir ve kanser tedavisinde kullanımı konusunda literatürde çelişkiler bulunmaktadır. Çalışmamızda Amigdalin ve Dosetaksel tedavilerinin DU145 prostat kanseri hücre hattına olan etkilerini *integrinalfa2 (ITGA2)* ve *integrinbeta1 (ITGB1)* ekspresyonları, ayrıca hücre ölümü üzerine olan etkilerini Caspase-3 ve Beclin-1 üzerinden karşılaştırmayı amaçladık.

GEREÇ VE YÖNTEM: DU145 hücreleri çoğaltılarak dört gruba ayrıldı. Birinci gruba Amygdalin, ikinci gruba Dosetaksel, üçüncü gruba Amygdalin ve Dosetaksel birlikte verilerek 24 saat boyunca aktif maddelere maruz bırakıldı. Dördüncü gruba (Kontrol) herhangi bir madde verilmedi. *ITGA2 ve ITGB1* genlerinin mRNA düzeyleri Real-Time PCR yöntemiyle belirlendi. Hücre ölümünü değerlendirmek için immünositokimyasal olarak Caspase-3 ve Beclin-1 boyamaları yapıldı.

BULGULAR: Amigdalin, Dosetaksel uygulanan gruplarda *ITGA2* ve *ITGB*1 ekspresyonlarında artış görüldü (P<0.05). Amigdalin+Dosetaksel verilen grupta *ITGB1* ekspresyonundaki azalma anlamlıydı (P<0,001). Caspase-3 (P<0.05) ve Beclin-1 (P<0.05) immünoreaktivitelerinin her üç grupta kontrol grubuna kıyasla arttığı gözlendi.

SONUÇ: DU145 PK hücrelerinde Dosetaksel'in hücre ölümünü Amigdaline göre daha çok artırdığı, Amigdalin ve dosetakselin birlikte kullanıldığında *ITGA2* ve *ITGB1* ekspresyonlarını önemli şekilde azalttığı gözlemlenmiştir. Sonuçlarımız Amigdalin ve dosetakselin ikili tedavisinin prostat kanseri metastazlarının önüne geçebileceğini düşündürmektedir.

ANAHTAR KELİMELER: Amigdalin, Dosetaksel, Prostat kanseri, *İntegrin alfa2beta1*.

ABSTRACT

OBJECTIVE: Prostate cancer (PC) ranks second among cancer-related deaths in men, and most deaths are caused by metastasis. Integrins, which are cell surface receptors, play an important role in cancer metastasis. It has been shown that integrin alpha2beta1 expression is effective in cell adhesion, migration, and invasion by increasing binding to collagen I in metastatic PCs. Docetaxel chemotherapy is used in PC, but it is ineffective in advanced stages. Amygdalin is a cyanogenic glycoside commonly found in fruit seeds, there is conflict in the literature regarding its effectiveness in cancer treatment. We aimed to compare the effects of Amygdalin and Docetaxel treatments on the DU145 prostate cancer cell line on *integrinalfa2 (ITGA2)* and *integrinbeta1 (ITGB1)* expressions, as well as their effects on cell death, Caspase-3, and Beclin-1.

MATERIAL AND METHODS: Propagated DU145 cells were divided into four groups. Amygdalin was given to the first group, Docetaxel was given to the second group, and Amygdalin and-Docetaxel were given together to the third group. They were exposed to the active substances for 24 hours. The fourth group (Control) was not given any substance. mRNA levels of *ITGA2* and *ITGB1* genes were determined by the Real-time PCR method. Caspase-3 and Beclin-1 staining were performed immunocytochemically to evaluate cell death.

RESULTS: There was an increase in *ITGA2* and *ITGB1* expressions in the groups administered by Amygdalin and by Docetaxel (P<0.05). The decrease in *ITGB1* expression was significant in the group given Amygdalin+Docetaxel (P<0.001). Caspase-3 (P<0.05) and Beclin-1 (P<0.05) immunoreactivities were observed to increase in all three groups compared to the control group.

CONCLUSIONS: It was observed that Docetaxel increased cell death more than Amygdalin in DU145 PC cells, and when Amygdalin and Docetaxel were used together, *ITGA2* and *ITGB1* expressions were significantly reduced. Our results suggest that dual treatment of Amygdalin and Docetaxel may prevent prostate cancer metastases.

KEYWORDS: Amygdalin, Docetaxel, Prostate cancer, *Integrin alpha2beta1*.

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Kabul Tarihi / Accepted: 20.04.2024
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INTRODUCTION

Prostate Cancer (PC) is the second most common cause of morbidity and mortality in men after lung cancer due to its high potential for metastasis (1). PC is a type of invasive carcinoma characterized by the expansion of organ volume and the transformation of normal glandular structure into preneoplastic lesions as a result of disruption of the balance between cell proliferation and cell death as a result of genetic and epigenetic changes in the prostate gland (2 - 4). It is known that PC-related deaths are largely due to metastasis (3 - 5). The clinically significant form of this disease, which can occur in highly heterogeneous forms, is locally advanced PC. Surgical intervention is the basic approach in the treatment of locally advanced PC with metastatic potential. In addition to surgery, endocrine therapy (chemical castration approaches) is applied with the use of anti-androgenic agents (6 - 8). Although current treatment has very effective results at the beginning, an aggressive phenotype defined as castration-resistant PC (CRPC), which occurs as androgen insensitivity, is encountered in 80-90% of patients after approximately 18-24 months. In CRPC, for which effective treatment is not currently possible, the average life expectancy is limited to a few months with the most effective chemotherapeutic agents as well as anti-androgenic drugs (9). DU145 is a cell line widely used in in vivo experiments to model CRPC and aggressive PC (10).

Docetaxel (Doce) shows its effect by inhibiting the polymerization of microtubules and nuclear translation of androgen receptors during the metaphase stage of mitosis (11). While Doce-based therapies are increasingly successful in treating PC following early diagnosis, they remain inadequate in patients with advanced and metastatic PC. Both the rapid occurrence of drug resistance and the high rate of toxicity have led researchers to develop new treatment protocols and search for agents that reduce these effects of Doce (such as Doce + angiogenesis inhibitors, + apoptotic agents, + antimetabolites, + proteasome inhibitors, etc.) (12 - 15). Amygdalin is a cyanogenic glycoside found in fruit seeds in nature. It is an agent that is being tested for use in alternative medicine for the treatment of anemia, asthma, high blood pressure, atherosclerosis, diabetes, migraine, and cancer (16 - 18). In human PC cell lines, Amygdalin is effective by increasing apoptosis through *B-cell lymphoma-2 Associated X protein (Bax) and B-cell lymphoma-2 (Bcl-2)* genes (19), and it has been shown to stop the growth of prostate cancer cells by delaying cell cycle progression (20). In these studies, it was determined that Amygdalin showed significant anti-tumor activity on PC cells, and therefore, it was stated that more studies were needed on its use for therapeutic purposes.

Integrins are a large family of proteins that form transmembrane heterodimers on the cell surface and mediate cell-matrix and cell-cell interactions (21). It affects the growth and spread of cancer cells by affecting cell migration, invasion, matrix degradation, and angiogenesis in cancer cells. Integrins also play important roles in the extracellular matrix composition and organization of the tumor stroma, cancer development, metastasis, and treatment resistance (22, 23). There are 24 known members of integrins, and the expression of these members, especially *ITGA2* and *ITGB1*, has been shown to increase in metastatic prostate cancers (24). After the expressions of *ITGA2* and *ITGB1* in many PC cell lines were presented, it was stated that all three of them, together with Integrin α-6, could be studied as PC stem cell markers (25). In another study, it was stated that the use of agents that reduce *ITGA2* expression would be the most appropriate approach in the treatment of this type of cancer (26).

Based on this information, the present study aims to evaluate the effects of the combined use of Doce and Amygdalin in the DU145 PC cell line on metastasis through *ITGA2* and *ITGB1* expressions and on cell death through Beclin-1 and Caspase-3 immunocytochemistry staining.

MATERIALS AND METHODS

Cell Passage

The DU145 prostate cancer cell line used in our study was obtained from the American Type Culture Collection. In an atmosphere of 37°C, 5% CO2, and 95%, cells were incubated in DMEM medium (Gibco, 11594486) containing 10% (v/v) fetal bovine serum (FBS, Sigma Aldrich, Germany, F9665), 5 mM glutamine (Capricorn Scientific, Germany, Cat. No: GLN-B), 100 U/ml

penicillin, 100 µg/ml streptomycin (Capricorn Scientific, Germany, Cat. No: PS-B). Cells were planted in a culture dish containing the medium in the bottles and incubated for 48 hours (27).

Removal And Preparation of The Cells

After achieving 80% confluency in the cells, 0.25% trypsin (Capricorn Scientific, Germany, Cat. No: TRY-3B) was added and removed. Trypsin is inactivated by adding a medium to the removed cells. The mixture was placed in a 15 ml falcon and then centrifuged at 400g for 5 minutes. After that 2400 µl of fresh medium was added to the pellet and mixed with a pipette. 10 µl of trypan blue was added to the 10 µl cell suspension taken here and mixed. Cell counting was performed by taking 10 µl of the resulting mixture. The total cell count was 6.08 x 10^5 cells/ml and the number of viable cells was 5.87 x 10^5 cells/ml. Cells were seeded from this suspension into a 12-well culture dish, with 200 µl per well. The wells were divided into Doce (100 nM, 24h) (Sigma-Aldrich, USA, Cat. No: 01885), Amygdalin (10 mg/ml, 24h) (Sigma, USA, Cat. No: 10050), Doce (100 nM) +Amygdalin (10 mg/ml) and Control groups, and drug applications were made at the specified doses (20, 28).

Real-time PCR Analysis

Total RNA was extracted from DU145 cells by using the PureZole reagent according to the manufacturer's protocol. (Biorad, USA, Cat. No: 732-6890). RNA amount and RNA purity were quantified by Nanodrop ND-1000 spectrophotometer V3.7 (Thermo Fisher Scientific, Waltham, Massachusetts, USA). RNA samples were stored at -80°C until use. All the RNA samples were reverse transcribed into cDNA by iScript Reverse Transcription Supermix (Biorad, USA, Cat. No: 1708841) under the following conditions: One cycle at 25°C for 5 minutes, 46°C for 20 minutes, and 95°C for 1 minute. Real-time polymerase chain reaction (PCR) was performed after reverse transcription. *ITGA2* and *ITGB1* gene expression analysis was performed using Rotor-Gene Q (QIAGEN GmbH, Hilden, Germany). cDNAs that belong to each application group were added to iTaq Universal SYBR Green Supermix (Biorad, USA, Cat. No: 1725122) according to the manufacturer's protocol. Oligonucleotide primers were designed by Oligomere Biotechnology (Ankara, Türkiye) based on the following primer sequences **(Table 1)**.

Table 1: Primer sequences

Gene	Primer sequences 5→3'
ITGA2-F	TGTGGTGAGGACGGACTTTG
ITGA2-R	CATCAACCGGCAGGGAGAAT
ITGB1-F	GCGCGGAAAAGATGAATTTACA
ITGB1-R	ACATCGTGCAGAAGTAGGCA
GAPDH-F	CATTGCCCTCAACGACCACTTT
GAPDH-R	GGTGGTCCAGGGGTCTTACTCC

We used the following RT-PCR protocol for *ITGA2* and *ITGB1* gene mRNA analysis: 95°C for 30 seconds of initial denaturation followed by 40 cycles of 95°C for 5 seconds and 60°C for 30 seconds. Melting curve analysis was performed for confirmation of single-product amplification at the end of the PCR. 65-95°C, 0.5°C increments at 5 sec/step. Each run has been performed in triplicate (**Figure 1)**.

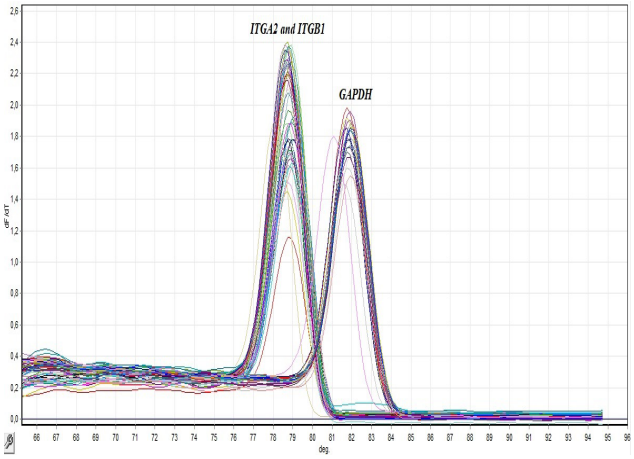

Figure 1: Example of *ITGA2*, *ITGB1* and *GAPDH* melting curve

REST 2009 Software is an independent instrument designed for the examination of gene expression data derived from quantitative, real-time PCR experiments. The evaluation or quantification of relative gene expression entails the utilization of reference genes' expression as a means to standardize the expression levels of genes of interest across diverse samples (29).

Immunocytochemistry

Cells forming treated with Amygdalin, Doce, Doce+Amygdalin groups, and the Control group were cultured in the 12-well chamber slide (Ibidi cells in focus, 81201). At the end of the 24th hour, the medium was removed. Cells were fixed with paraformaldehyde. After washing with phosphate-buffered saline (PBS). 0.1% Triton-X100 (Bio Basic Inc.) solution was added and kept on ice for 15 minutes. Then, it was incubated with 3% H_2O_2 (Emprove, 7722-

84-1) and washed three times with PBS. The blocking solution was then applied for 10 minutes. Cells were incubated with primary antibodies Caspase-3 (1/200, sc-56053, Santa Cruz Biotechnology) and Beclin-1 (1/200, sc-1142, Santa Cruz Biotechnology)) for 1 night at +4 ^{0}C. The next day, it was washed 3 times with PBS. After treatment with a secondary antibody (Large Volume Anti-polyvalent HRP, Thermo Scientific), AEC chromogen (Thermo Scientific) was applied. Mayer's hematoxylin (Sigma Aldrich) was used for counterstaining, and the preparation was covered with a water-based sealer. Experiments were performed in three repetitions. Cells in the preparations were counted under a light microscope using the Image Analysis Program (NIS Elements, Japan). The evaluation was made by counting 500 different cells at X20 objective magnification. Scoring was done with an H-score, a semi-quantitative method. Stained cells were evaluated in terms of percentage and staining intensity was taken as a second criterion (30).

Ethical Committee

This study was approved by the Afyonkarahisar Health Sciences University Clinical Ethics Committee with decision number 162 dated 01.06.2018.

Statistical Analysis

For immunocytochemistry evaluation, all data is represented as mean ± standard error of the mean (SEM) throughout the study. Statistical comparisons were performed using one-way ANOVA followed by an appropriate post-hoc test (Tukey). Comparisons giving P values less than 0.05 were accepted as statistically significant. For PCR evaluation, All the data analyses were performed using REST 2009 V2.0.13 and SPSS v.19 Software (Qiagen, Hilden, Germany) using Pair Wise Fixed Reallocation Randomizasyon test (29) where P<0.05 is deemed to represent a statistically significant result.

RESULTS

ITGA2 and *ITGB1* Genes Expression Levels

ITGA2 and *ITGB1* gene expression levels in the DU145 cell line exposed to 10 mg/ml Amygdalin, 100 nM Doce, and 10 mg/ml Amygdalin +100 nM Doce for 24h were analyzed by Real-time PCR method using Rotor Gene-Q (Qiagen). *ITGA2* and *ITGB1* genes' mRNA levels for each group were determined according to the mRNA levels of *ITGA2* and *ITGB1* genes expressed in the control group. The *GAPDH* gene was used as a reference gene for normalization. *ITGA2* and *ITGB1* gene expressions were upregulated in 10 mg/ml Amygdalin application (1.473; 1.057, fold change, respectively). Upregulation of the *ITGA2* gene was statistically significant (P<0.05). *ITGA2* and *ITGB1* gene expressions were upregulated in 100 nM Doce application (1.233; 1.186, fold change, respectively). However, these upregulations were not statistically significant (P>0.05). *ITGA2* and *ITGB1* gene expressions were downregulated in 10 mg/ml Amygdalin+100nM Doce application (0.810, 0.710-fold change; respectively). Downregulation of the *ITGB1* gene is statistically significant (P<0.001) **(Figure 2)**.

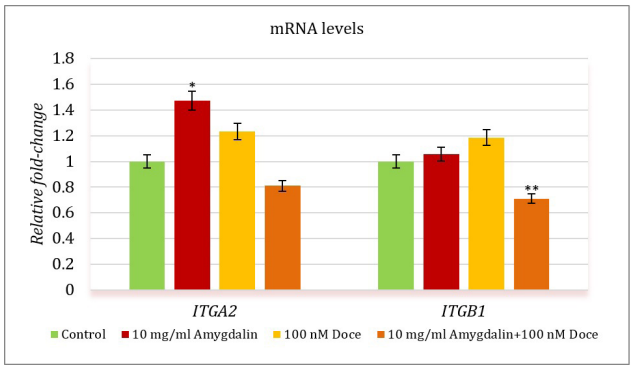

Figure 2: Relative mRNA expression of *ITGA2* and *ITGB1* in DU145 cells exposed to 10 mg/ml Amygdalin, 100 nM Doce and 10 mg/ml Amygdalin+100 nM Doce were given as fold regulation levels. *GAPDH* is reference gene for normalization.
*Represents the significance of P<0.05 **Represents the significance of P<0.001

Immunocytochemistry Results

In the H-score evaluation made by immunocytochemical staining, the intensity of caspase-3 staining was increased in the amygdalin-administered group compared to the control group (P=0.0037). The increase in caspase-3 staining was highest in the Doce group. While the intensity of staining increased in the Amygdalin+Doce group compared to the Control and Amygdalin groups (P<0.001, P<0.001 respectively), its intensity was found to decrease compared to the group given only the Doce group, but it was not found to be statistically significant (P=0076). Beclin-1 staining intensity is parallel to caspase-3 staining intensity. The intensity of staining was seen to be highest in the Doce group. The

intensity of staining in the Amygdalin-administered group increased compared to the Control group (P=0.003). Although the staining intensity was found to be increased in the Amygdalin + Doce group compared to the control and Amygdalin groups (P<0.001, P=0.027 respectively), it was seen to decrease compared to the Doce group (P=0.003) **(Figure 3, 4)**.

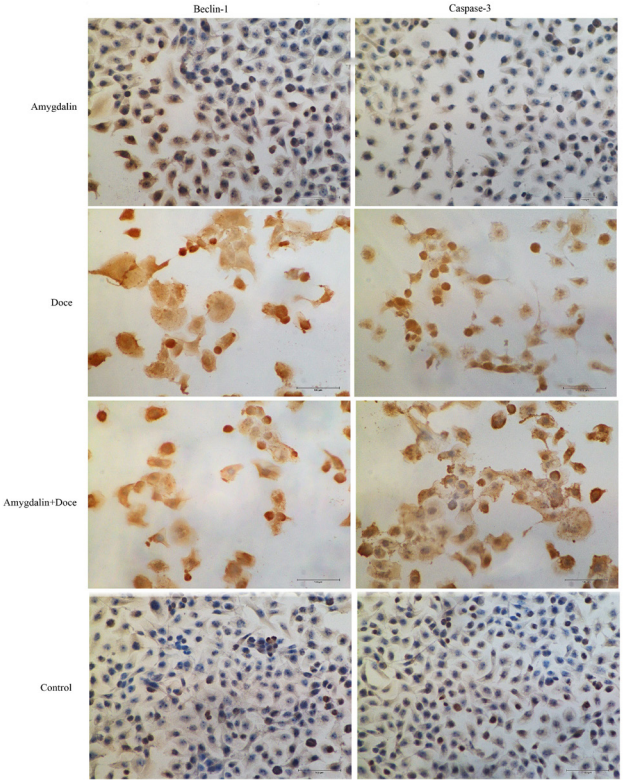

Figure 3: Beclin-1 and Caspase-3 immunocytochemical staining in all group. 20X magnification, scale bar 100 µm

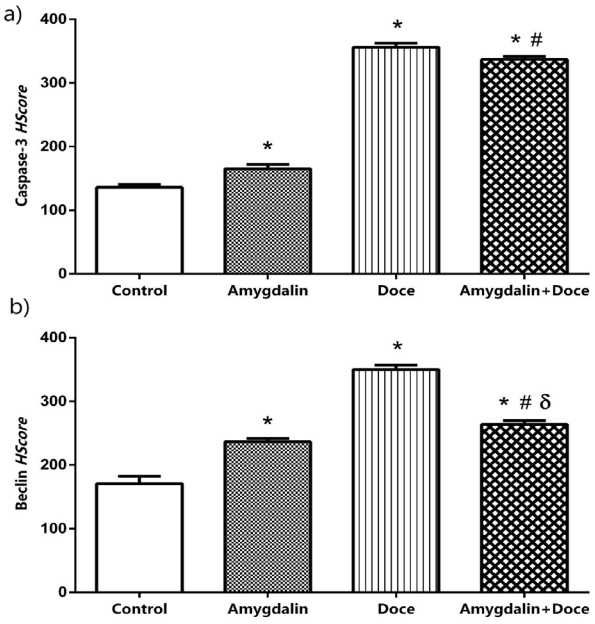

Figure 4: a) Graph showing H-score results caspase-3 **b)** Graph showing H-score results beclin-1, *significance compared to control, #significance according to amygdalin, #significance according to Doce* # Represents the significance of P<0.05

DISCUSSION

PC, the most common solid tissue cancer among men in developed countries, is a serious, life-threatening health problem. While radical prostatectomy and/or radiotherapy are sufficient in the localized type of PC in which tumor cells are limited to the prostate gland, current treatments are not curative in locally advanced, metastatic PC and CRPC (31). PC-related deaths are largely due to metastasis and castration resistance (5). Therefore, new treatment approaches are needed. Preventing metastasis in cancer treatment is an important step in the treatment. The increased expressions of *ITGA2* and *ITGB1* in PC metastases are presented as evidence that these molecules are effective in metastasis (32, 33). Salemi et al. emphasized that the use of ITGA2 and ITGB1 inhibitor BTT-3033 in PC cell lines is an agent that can be used in the treatment of PC by reducing cell viability, proliferation, epithelial-mesenchymal transition, and increasing apoptosis (27). Accordingly, reducing the expressions of *ITGA2* and *ITGB1* is an important step in preventing the spread of cancer cells and in cancer treatment. Our study investigated the effects of Doce, used in the PC treatment, and Amygdalin, whose efficacy in cancer treatment is still under investigation, on *ITGA2* and *ITGB1* expression in DU145 PC cells.

Doce is an agent that is still used effectively in the PC treatment protocol today (12). Studies in PC cell lines have also shown that Doce is cytotoxic to these cells. Cristofani et al. reported that 100 nM doses of Doce reduced cell viability with maximal effect in PC3, DU145, and LNCaP PC cell lines (28). Liu et al. emphasised that it increased apoptosis in PC3 and DU145 PC cells, more so in LNCaP PC cells (34). In the study by Budman et al, Doce was combined with 18 different agents and applied to DU145, LnCaP and PC3 PC cell lines and its synergistic effect with different agents was evaluated. This study emphasised that Doce is the basic agent to be used effectively in PC treatment and that its efficacy can be enhanced with other agents (35). In our study, 100 nM was used for Doce, which is the maximum effective dose in Du145 PC cells in the literature, and it was found that it effectively increased cell death by observing a significant increase in caspase-3 and beclin-1 staining intensities in the Doce-treated groups.

Amygdalin is a compound belonging to the cyanogenic glycoside family. Its use in traditional medicine dates back hundreds of years. It is known that it was used as an expectorant agent in the 1800s (36). Amygdalin regained popularity in the 1970s and 1980s and was seen as a promising agent that could be used in cancer treatment. At this time, Cyanide was thought to be the active cancer-killing component in Amygdalin. It is assumed that Cyanide is released when amygdalin is broken down by enzymes in the cancerous tissue and kills the cancer cell, and that the enzyme called Rhodanese, which can detoxify Cyanide, is present in normal tissues but is missing in cancer cells. Thus, it was thought that cancer cells were selectively eliminated by Cyanide, while normal cells were not damaged (37). On the other hand, there are studies stating that cancer patients treated with high doses of Amygdalin show symptoms of cyanide poisoning, that blood Cyanide levels should be monitored throughout the treatment, and that Amygdalin does not have a therapeutic effect (38). Thereupon, the American Food and Drug Administration (FDA) declared Amygdalin as a toxic product that cannot be used as a medicine, and it was banned in the USA in 1979 (39). In recent years, with the search for supportive agents in cancer treatments, Amygdalin has come to the fore again and the need to investigate its anticancer activities has been emphasized (40). Treatment of metastatic PC is still a matter of research, and the effects of Amygdalin on this type of cancer have been studied in various ways. Makerevic et al. stated that Amygdalin has antitumor effects in PC cell lines by reducing tumor cell growth and suppressing colony formation, depending on the dose (20). Chang et al., in their study, found that the expression of the pro-apoptotic protein Bax increased, the expression of the anti-apoptotic protein Bcl-2 decreased, and the caspase-3 enzyme activity increased in the group treated with Amygdalin, thus showing that Amygdalin increased apoptosis in DU145 and LNCaP cell lines (19). In the present study, a dose of 10 mg/ml of Amygdalin was used, and it was observed that Caspase-3 and Beclin-1 staining intensities increased in the Amygdalin-applied group compared to the Control group, and therefore, Amygdalin increased apoptotic and autophagic cell death. However, this effect was found to be significantly lower than in the group given Doce alone. Again, the fact that cell death was less in the group in which the Amygdalin+Doce combination was applied compared to the group in which only Doce was applied, shows that the cytotoxic effect of Doce is greater than in the Amygdalin and combination treatment groups.

Integrins are structures that regulate intercellular and cell connection with the matrix, so they play important roles in cell migration and adhesion. In the study conducted by Mani et al., it was found that Amygdalin significantly reduced chemotactic activity, cell migration, and adhesion in DU-145 cells (41). In this study, it was found that Amygdalin application increased *ITGA2* and *ITGB1* and decreased *ITGA6* in DU-145 cell lines. Additionally, in this study, it was stated that the increase in *ITGA6* is an important indicator in chemotaxis, that the increase in *ITGA2* and *ITGB1* in the Amygdalin application shows a negative correlation for the DU145 line, and that the decrease in *ITGA6* for this cell line is more effective on metastasis. In another study, Tsaur et al. emphasized that amygdalin moderately increased *ITGβ1* in Taxan-resistant PC cell lines; therefore, its roles in PC are unclear and need to be investigated (42). Additionally, in our study, an increase in *ITGB1* expression, especially in *ITGA2*, was observed in the group to which we applied Amygdalin. These increases suggested that *ITGA6* expression should be supported with other agents, as in the study by Mani et al. (41). Our findings support the literature in this respect. The main target of metastatic PC cells is bone. Bone cells can produce proteins that facilitate the migration and metastasis potential of PC cells. Although it is known that there are increases in the expression levels of *ITGA2, ITGB1*, and *ITGA3* in this process (43, 44), there are still studies in the literature reporting that the effects of *ITGA2* and *ITGB1* on PC cells are not clear (45). It has also been reported that *ITGA2* and *ITGB1* expressions are downregulated in advanced PC (46, 47) In studies on the adhesion of prostate epithelial cells or human prostate carcinoma cells to type I collagen and the stroma of human bone marrow, the majority of studies report that the interactions are predominantly through *ITGA2* and *ITGB1* (48,

49). For this reason, it was thought that agents that treat PC would reduce *ITGA2* and *ITGB1*. Ojalill et al. found that *ITGA2* and *ITGB1* expressions increased in DU145 cells treated with 50 nM Doce. In their study, they attributed the increase in *ITGA2* and *ITGB1* to the increase in resistance in living DU145 cells. Similarly, they noted that surviving cells expressed more CD44 (stem cell marker), and cells with stem cell markers may be more drug-resistant (33). In the present study, there was an increase in *ITGA2* and *ITGB1* expressions in cells administered 100 nM Doce, but this increase was not found to be significant. We think that the fact that more cells die at the 100 nM dose explains this situation. Additionally, a decrease in *ITGA2* and *ITGB1* expressions was observed when 100 nM Doce and 10 mg/ml Amygdalin were administered to DU145 cells together. It shows that the treatment resistance observed when Amygdalin and Doce are administered separately is reversed when the two agents are administered together. The decrease in *ITGA2* and *ITGB1* expressions in combination treatment indicates a decrease in the metastasis ability of DU145 PC cells.

The most important limitation of our study is that the cytotoxicity test could not be performed because our project budget was limited. The cytotoxic effect of Doce was found to be high in accordance with the literature, but the cytotoxic effect of Amygdalin was less than in the literature. If a more optimum dose had been determined by the cytotoxicity test and this dose had been used, we would have been able to observe the optimum cytotoxic effect of Amygdalin and combined treatment. However, even at this dose, the reduction of *ITGA2* and *ITGB1* in combination therapy shows that it may be effective in the treatment by reducing the metastasis of DU145 cells. We mainly looked for clues to the possible synergistic effects of the Doce+Amygdalin combination, in recent studies. The findings of our study need to be supported by three-dimensional cell culture and experimental animal models.

In conclusion, the Amygdalin and Doce combination treatment reduced *ITGA2* and *ITGB1* expressions in the DU145 cell line. Therefore, it is thought that the application of Amygdalin in addition to Doce treatment may prevent metastases in addition, Amygdalin reduces the cytotoxicity of Doce, suggesting that their combined use may reduce the negative effects of Doce in non-cancerous cells, indicating that combination therapy is promising. In this context, more comprehensive studies in vitro and in vivo are needed.

ACKNOWLEDGMENTS

Afyonkarahisar Health Sciences University Scientific Research Projects Commission with project number 19.TIP.013. This study was presented as an oral abstract at the II. International Congress of Science and Innovation, 25-27 July 2021, TURKEY.

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Kocatepe Tıp Dergisi
Kocatepe Medical Journal
25:429-437/Ekim 2024 Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

KRONİK HASTALIĞI OLAN YETİŞKİN BİREYLERİN 6 ŞUBAT 2023 KAHRAMANMARAŞ MERKEZLİ DEPREMLER SONRASI HASTALIK YÖNETİMİNE İLİŞKİN DENEYİMLERİ: NİTEL BİR ARAŞTIRMA

EXPERIENCES OF ADULTS WITH CHRONIC ILLNESSES IN DISEASE MANAGEMENT FOLLOWING THE KAHRAMANMARAŞ-CENTERED EARTHQUAKES ON FEBRUARY 6, 2023: A QUALITATIVE STUDY

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ÖZET

AMAÇ: Bu araştırmada 6 Şubat 2023 Kahramanmaraş merkezli depremler sonrasında kronik hastalığı olan yetişkin bireylerin ilk 72 saatteki hastalık yönetimine ilişkin deneyimlerinin incelenmesi amaçlandı.

GEREÇ VE YÖNTEM: Bu araştırma nitel bir yöntemle, Nisan - Mayıs 2023 tarihleri arasında, Malatya'da yaşayan ve dâhil edilme kriterlerini karşılayan 16 depremzede ile yürütüldü. Araştırmanın verileri bireysel bilgi formu ve yarı yapılandırılmış görüşme formu ile toplandı. Yarı yapılandırılmış görüşme formundan elde edilen veriler nitel içerik analizi yaklaşımı kullanılarak analiz edildi.

BULGULAR: Araştırmanın ana temaları; (1) kalınan yerin hastalık sürecine etkisi, (2) hastalık yönetiminde karşılaşılan sorunların nedeni, (3) optimal hastalık yönetimini sürdürme çabaları ve (4) hastalık yönetimine ilişkin depremin öğrettikleri olarak belirlendi.Deprem sonrasında hastalık yönetimini olumsuz etkileyen durumlar ilaç eksikliği, bilgi eksikliği, utanma ve önceliklerin değişmesi olarak belirlendi. Hastalık yönetimini sürdürebilmek için bazı katılımcılar daha güvenli şehirlere gitmek, ilaçlarını reçetesiz olarak temin etmek ve yakınlarından destek almak gibi çabalar gösterdi.

SONUÇ: Deprem öncesi hazırlıklar planlanırken kronik hastalığı olan bireyler için bireysel deprem hazırlığını içeren çalışmalar yapılmalıdır. Deprem sonrası dönemde ise sağlıklı haberleşmenin devamlılığı sağlanmalı, reçetesiz ilaç kullanımına bağlı gelişebilecek olumsuzluklar göz önünde bulundurulmalı.

ANAHTAR KELİMELER: Deneyim, Depremler, Hastalık yönetimi, Kronik hastalık.

ABSTRACT

OBJECTIVE: This research aims to examine the experiences of adult individuals with chronic illnesses in managing their disease during the first 72 hours following the earthquakes centered in Kahramanmaraş on February 6, 2023.

MATERIAL AND METHODS: This research was conducted using a qualitative method with 16 earthquake survivors living in Malatya between April and May 2023 who met the inclusion criteria. Data for the research were collected through an individual information form and a semi-structured interview form. The data obtained from the semi-structured interview form were analyzed using a qualitative content analysis approach.

RESULTS: The main themes of the study were determined as (1) the impact of the living conditions on the disease process, (2) the reasons for the problems encountered in disease management, (3) efforts to sustain optimal disease management, and (4) lessons learned from the earthquake regarding disease management. Situations negatively affecting disease management after earthquakes were identified as medication shortages, lack of information, shame, and changes in priorities. To maintain disease management, some participants made efforts such as moving to safer cities, obtaining medications without prescriptions, and getting support from their relatives.

CONCLUSIONS: While planning pre-earthquake preparations, studies that include personalized earthquake preparation for individuals with chronic diseases should be carried out. In the post-earthquake period, the continuity of healthy communication should be ensured, and the negativities that may arise due to the use of non-prescription drugs should be taken into consideration.

KEYWORDS: Earthquakes, Experience, Disease management, Chronic illness.

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GİRİŞ

Kronik hastalığa sahip yetişkinlerin sayısı her geçen gün artmaktadır. Bu hastalıklar, neden olduğu mortalite ve morbidite nedeniyle hem hastalara hem de topluma ciddi yükler getirmektedir (1). Dünya Sağlık Örgütü verilerine göre 2019 yılında dünyadaki ölümlerin yaklaşık %74'ü kronik hastalıklarla ilişkilidir (2). Bu hastalıkların bakım ve tedavisi için 2010 - 2030 yılları arasında yapılacak harcamaların 47 trilyon dolara ulaşacağı öngörülmektedir (3).

Kronik hastalığa sahip bireylerin yaşam süresindeki artışa bağlı olarak ilaç kullanım süresi, bakım süresi ve hastalık yönetim süresi uzamaktadır. Kronik hastalıkların uygun şekilde yönetilmemesi sağlık durumu ve semptomlarda kötüleşmeye ve hastane yatışlarında artışa neden olabilir (4). Dinamik bir süreç olan kronik hastalıkların kendi kendine yönetimi; hastalıkla ilgili bilgi düzeyi, psikolojik durum, yakınları tarafından verilen desteğin düzeyi ve sağlık hizmetlerinin kullanılabilirliği gibi birçok faktörden etkilenebilir (5). Hastalığı kendi kendine yönetebilme düzeyi iyi olan hastalar değişen koşullardaki çeşitli sorunlarla daha kolay baş edebilirler (6).

Uzamış hastalık yönetiminin başarıyla sürdürülmesi için hastaların sağlık bakım sistemlerine kesintisiz bir şekilde ulaşabilmeleri oldukça önemlidir. Bireysel ve toplumsal düzeyde yaşanan pek çok doğal afet hastaların sağlık bakım sisteminden kesintisiz olarak faydalanmasını engellemektedir (7). Hastaların kesintisiz bakım hizmeti almalarını engelleyen doğal afetlerden biri de depremlerdir. Özellikle yıkıcı depremler sonrasında şehirlerin hatta ülkelerin alt yapılarında, ulaşım hatlarında, iletişim kanallarında ve sağlık hizmeti sunumlarında ciddi aksamalar görülmektedir. Büyük Doğu Japonya depremi sonrasında sağlık bakım hizmetlerindeki kesintiden dolayı kronik hastalığı olan birçok yetişkin semptom alevlenmesi yaşamış veya ölmüştür (1).

Türkiye'nin Kahramanmaraş ilinde 6 Şubat 2023'de meydana gelen 7.7 ve 7.6 moment büyüklüğünde (mW) iki büyük deprem sonucunda toplamda 11 şehir ciddi şekilde etkilenmiş, 50.000'de fazla insan hayatını kaybetmiş, 301.000 konut yıkılmış veya ağır hasar almıştır. İlk depremden Hatay ikinci depremden ise Malatya şehirleri en büyük hasarı almıştır. Deprem sonrası 11 şehirde hayat durma noktasına gelmiş ve hükümet tarafından uluslararası yardım talebinde bulunulmuştur (8). Yapılan çalışmalarda deprem sonrası dönemde sağlık hizmetlerine talepte ciddi bir yoğunluk oluşmuştur.

Özellikle deprem bölgesindeki sağlık kuruluşlarında daha çok yaralı hastaların bakım ve tedavileri öncelikli olmuştur (9). Her türlü yardımın bölgeye ulaştırılmasında aksamalar olduğundan özellikle ilk 72 saat boyunca kronik hastalığı olan depremzedeler kendi çabalarıyla hastalıklarını yönetmek durumunda kalmışlardır (10).

Türkiye sınırlarında önemli fay hatları bulunmasına rağmen, literatürde kronik hastalığa sahip bireylerin deprem sonrası hastalık yönetimi ile ilgili deneyimlerinin incelendiği çalışmaların yetersiz olduğu görülmektedir. Bu çalışmada 6 Şubat 2023 Kahramanmaraş depremleri sonrasında kronik hastalığı olan yetişkin bireylerin ilk 72 saatteki hastalık yönetimine ilişkin deneyimlerinin incelenmesi amaçlandı.

GEREÇ VE YÖNTEM

Araştırmanın Tasarımı

Nitel içerik analizi yöntemleri kullanılan bu araştırma 6 Şubat 2023 Kahramanmaraş merkezli depremlerden en fazla etkilenen illerden biri olan Malatya'da yaşayan bireylerle yürütüldü. Yarı yapılandırılmış görüşme formundan elde edilen veriler nitel analiz yöntemi kullanılarak incelendi. Verilerin raporlanmasında COREQ (Consolidated Criteria for Reporting-Nitel Çalışmalar) kontrol listesi kullanıldı.

Araştırmanın Evren ve Örneklemi

Araştırmanın örneklemini Nisan - Mayıs 2023 tarihleri arasında dâhil edilme kriterlerini karşılayan 16 depremzede oluşturdu. Görüşülen kişilerin hiçbiri araştırmaya katılmayı reddetmedi veya araştırmadan çekilmedi. Dâhil edilme kriterleri; araştırmaya katılmaya gönüllü olmak, depremlerin ilk 72 saatinde Malatya ilinde ikamet ediyor olmak, sürekli tedavi ve bakım almasını gerektiren kronik hastalığa sahip olmak, anlama ve kendini ifade etmede sorun olmaması ve 18 yaş ve üzerinde olmaktı. Bu kriterleri karşılamayan depremzedeler araştırmaya dâhil edilmedi. Örneklem belir-

lenirken kartopu örnekleme yöntemi tercih edildi. Pilot uygulamaya katılanlar araştırmacıların depremzede olan yakınlarıydı. Pilot uygulamayı tamamlayan her depremzededen araştırmanın dâhil edilme kriterlerini taşıyan bir tanıdıklarını önermesi istendi. Böylece örnekleme ulaşılması hedeflendi. İçerik analizi çalışmalarında belirli bir örneklem büyüklüğü kullanılmaz. Bu araştırmada da örneklem büyüklüğünün belirlenmesinde veri doygunluğu kavramı kullanıldı. Bu kavrama göre, tekrarlı yanıtların başlaması yeterli örnekleme ulaşıldığının bir göstergesi olarak kabul edilmektedir (11).

Verilerin Toplanması

Araştırmanın verileri bireysel bilgi formu ve yarı yapılandırılmış görüşme formu ile toplandı. Veri toplama formları araştırmacılar tarafından ilgili literatür taranarak hazırlanan sorulardan oluşturuldu (12 – 15). Görüşme formundaki sorular nitel araştırma tecrübesi de olan, konunun uzmanı 3 farklı araştırmacı tarafından değerlendirildi. Görüşme formunun geçerlik ve güvenirliğini test etmek amacıyla 5 depremzede ile görüşme yapılarak pilot uygulama yapıldı. Pilot uygulama sonrasında görüşme formunda herhangi bir düzeltme yapılmasına gerek olmadığı belirlendi. Pilot uygulama sırasında elde edilen veriler analize dâhil edilmedi. Tüm görüşmeler katılımcıların belirlediği yerlerde (ev, iş yeri gibi) yüz yüze gerçekleştirildi. Katılımcılara gerekli açıklamaların yapılması yaklaşık 5 dakika sürdü. Bu açıklamalarda araştırmanın amacı, kapsamı, etik yönleri ve olası yararları hakkında bilgilendirmeler yapıldı. Araştırmadaki katılımcılarla bireysel bilgi formu ve yarı-yapılandırılmış görüşme formu dolduruldu. Görüşmeler kimsenin olmadığı bir odada yaklaşık 15-20 dakika sürdü. Ek olarak katılımcılara kişisel bilgilerinin ve ses kayıtlarının gizli tutulacağı ve isimlerinin hiçbir yerde açıklanmayacağı ifade edildi. Tüm görüşmeler daha önce nitel araştırma deneyimi olan birinci yazar (doktora mezunu, akademisyen, hemşire, erkek) ve nitel araştırma konusunda bilgilendirilen ikinci yazar (doktora mezunu, klinisyen, hemşire, erkek) tarafından yapıldı. Katılımcı ifadelerinin daha sonra dinleyip yazılı hale getirilebilmesi için tüm görüşmeler ses kayıt cihazı kullanılarak kaydedildi. Katılımcılara deneyimlerini, duygu ve düşüncelerini samimi bir şekilde ifade etme fırsatı verildi. Araştırma sonrasında katılımcılara, açıklamalarına ilişkin herhangi bir geri dönüş yapılmadı.

Bireysel Bilgi Formu

Bireysel bilgi formu katılımcıların bireysel özelliklerini içeren toplam 7 sorudan oluşuyordu. Bu sorular yaş, cinsiyet, meslek, gelir durumu, mevcut kronik hastalıklar ve deprem sonrası konutun durumuydu.

Yarı-Yapılandırılmış Görüşme Formu

Kronik hastalığı olan depremzedelerin deprem sonrası ilk 72 saatteki deneyimlerini içeren veriler yarı-yapılandırılmış görüşme formu kullanılarak toplandı. Yarı-yapılandırılmış görüşme formu katılımcıların bu süreçteki deneyimlerine ilişkin 9 sorudan oluşmaktaydı **(Tablo 1)**.

Tablo 1: Yarı-yapılandırılmış görüşme formu soruları

Depremden sonra bulunduğunuz konuttan nasıl çıktığınızı anlatır mısınız?
Deprem sonrası ilk 72 saatte yanınızda kimler vardı? Bu kişiler tıbbi tedavi ve bakım sürecinde size ne gibi destekler sağladı?
Deprem sonrası ilk 72 saatte nerede kaldınız? Kaldığınız bu yer tıbbi tedavi ve bakım süresinde size ne gibi deneyimler yaşattı?
Depremden sonra bulunduğunuz konuttan çıkarken yanınıza tıbbi tedavi bakım süreçlerinde kullandığınız hangi ekipmanlarınızı/ilaçlarınızı alabildiniz?
Deprem sonrası dışarıda kaldığınız ilk 72 saatte hangi ilaç/tıbbi ekipmanın eksikliğini yaşadınız? Bu eksikliği telafi etmek için ne gibi çabalarınız oldu?
Deprem sonrası dışarıda kaldığınız ilk 72 saatte ne gibi sağlık problemleri yaşadınız? Bu problemleri çözmek için ne gibi girişimlerde bulundunuz?
Yaşadığınız bu deprem olayı tıbbi tedavi ve bakım süreciniz ile ilgili size ne öğretti?

Verilerin Analizi

Katılımcıların bireysel özellikleri frekans, yüzde, ortalama veya standart sapma gibi tanımlayıcı istatistikler kullanılmadan **Tablo 2**'de gösterildi. Yarı yapılandırılmış görüşme formundan elde edilen veriler nitel içerik analizi yaklaşımı kullanılarak analiz edildi (16). İçerik analizi dört aşamada gerçekleştirildi. Öncelikle görüşmelerin ses kayıtları, tüm önemli noktalar ve özel ifadeler dâhil olmak üzere aynen yazıya aktarıldı. İkinci aşamada, metin içeriği ve anlam ilişkileri hakkında genel bir anlayış sağlamak ve görüşmelerin ilk kodlarını belirlemek amacıyla yazılı metin tekrar gözden geçirildi. Üçüncü aşamada, benzerlik ve farklılıkların keşfedilmesi amacıyla sürekli karşılaştırmalı analize dayalı olarak kodlar alt kategorilere (küçük alt başlıklara) ayrıldı (17). Dördüncü aşamada, alt kategoriler kategorilere (daha kapsamlı ortak başlıklar) ayrıldı. Kategoriler anlamlarına göre isimlendirildi ve deneyimi anlatan temalar belirlendi.

Güvenilirlik

İçerik analizi şeklinde yürütülen çalışmaların güvenirliğini artırmak için çeşitli yöntemler kullanılabilir (18). Bu araştırmada, ikinci yazarın nitel araştırma analizi konusunda deneyimi olmadığından kodlama, tema oluşturma, veri analizinin doğruluğu ve geçerliliğinin sağlanması aşamaları birinci yazar tarafından yürütüldü. Daha sonra oluşturulan tema ve alt temalar nitel araştırma deneyimi olan ancak araştırma ekibinde bulunmayan bağımsız bir araştırmacı (doktora mezunu, akademisyen, hemşire, kadın) tarafından kontrol edildi. Yapılan son düzeltmelerin ardından üzerinde mutabık kalınan temalar ve alt temalar oluşturuldu.

Etik Kurul

Araştırmaya başlamadan önce Kilis 7 Aralık Üniversitesi'nin Bilimsel Etik Kurulundan onay (Tarih: 11.04.2023, No: 2023/08) alındı. Tüm katılımcılar bu araştırmaya katılmadan önce yazılı ve sözlü bilgilendirilmiş onam verdi. Tüm işlemler Helsinki Dünya Tıbbi Deklarasyonuna uygun olarak gerçekleştirildi.

BULGULAR

Araştırmaya katılan depremzedelerin bireysel ve deprem deneyimine ilişkin bazı özellikleri Tablo 2'de verildi.

Tablo 2: Katılımcıların bireysel özellikleri

Katılımcı	Yaş	Cinsiyet	Meslek	Gelir durumu	Mevcut kronik hastalık	Deprem sonrası konutun durumu
1	53	Erkek	Polis	Gelir gidere eşit	Tip 2 Diyabet, Kolesterol, Hipertansiyon	Ağır hasarlı
2	38	Kadın	Hemşire	Gelir gidere eşit	Tip 2 Diyabet	Az hasarlı
3	60	Erkek	Emekli	Gelir gidere eşit	Tip 2 Diyabet	Orta hasarlı
4	37	Kadın	Hemşire	Gelir gidere eşit	Ankilozan spondilit, Haşimoto tiroidi	Az hasarlı
5	63	Kadın	Ev hanımı	Gelir giderden fazla	Tip 2 Diyabet	Az hasarlı
6	63	Kadın	Ev hanımı	Gelir gidere eşit	Tip 2 Diyabet, Kolesterol	Az hasarlı
7	57	Kadın	Ev hanımı	Gelir giderden az	Hipertansiyon	Hasarsız
8	62	Erkek	Emekli	Gelir giderden az	Hipertansiyon	Az hasarlı
9	66	Erkek	Marangoz	Gelir gidere eşit	Kronik obstrüktif akciğer hastalığı	Az hasarlı
10	63	Kadın	Ev hanımı	Gelir gidere eşit	Romatoid artrit	Ağır hasarlı
11	44	Kadın	Öğretmen	Gelir gidere eşit	Romatoid artrit, Haşimoto tiroidi	Az hasarlı
12	58	Kadın	Ev hanımı	Gelir giderden az	Tip 2 Diyabet, Hipertansiyon	Az hasarlı
13	67	Kadın	Ev hanımı	Gelir gidere eşit	Tip 2 Diyabet	Hasarsız
14	66	Kadın	Ev hanımı	Gelir giderden az	Ritim bozukluğu, Hipertansiyon	Az hasarlı
15	49	Kadın	Ev hanımı	Gelir gidere eşit	Romatoid artrit	Ağır hasarlı
16	68	Erkek	Emekli	Gelir gidere eşit	Kalp yetmezliği, Tip 2 Diyabet	Ağır hasarlı

Kronik hastalığı olan yetişkin depremzedelerin depremlerin ilk 72 saatindeki hastalık yönetimine ilişkin ifadeleri incelendiğinde dört ana tema ve bu temalarla ilişkili on bir alt tema oluşturuldu. Oluşturulan ana temalar:

- Kalınan yerin hastalık sürecine etkisi,
- Hastalık yönetiminde karşılaşılan sorunların nedeni,
- Optimal hastalık yönetimini sürdürme çabaları ve
- Hastalık yönetimine ilişkin depremlerin öğrettikleridir.

Tema 1: Kalınan Yerin Hastalık Sürecine Etkisi

Katılımcıların depremlerin ilk 72 saatinde kaldıkları yerlerin hastalık sürecine etkisi ile ilgili deneyimleri incelendiğinde iki alt tema oluşturuldu.

Alt tema 1: Hastalığı yönetememe korkusu

İnsülin kullanmak zorunda olan diyabetli bir depremzede; havanın ısınmasının, insülininin bozulmasına neden olabileceği endişesi yaşadığını ve insülini olmadan etkili bir şekilde hastalığını yönetemeyeceğini şu sözlerle ifade etti:

"İnsülinlerimi yanıma almıştım ama hava biraz daha sıcak olsaydı ilaçlarım bozulur diye endişelendim. İnsülinim olmadan şekerimi düşüremem" (Katılımcı 16, Erkek).

Alt tema 2: Semptom alevlenmesi

Bazı katılımcılar deprem sonrasında kaldıkları yerlerin hastalık yönetiminde olumsuzluklara neden olduğunu ve bu durumla ilişkili çeşitli semptomlar yaşadıklarını ifade ettiler. Kronik obstrüktif akciğer hastalığı (KOAH) nedeniyle tedavi almakta olan bir katılımcının deneyimi şöyleydi:

"Belediyenin nikâh salonunda kaldık. 3000 civarında insanla bir arada kaldığımız için kötü koku oluyordu. Soğukta üşüttüm. Öksürük oldu. (…) havasız ortamda balgam çıkarmakta zorlandım" (Katılımcı 9, Erkek).

Tema 2: Hastalık Yönetiminde Karşılaşılan Sorunların Nedeni

Deprem sonrası evlerinden uzaklaşan katılımcıların ilk 72 saatte hastalık yönetiminde karşılaştıkları sorunların nedeni incelendi. Katılımcıların ifadelerinden dört alt tema oluşturuldu.

Alt tema 1: İlaç eksikliği

Katılımcıların çoğunluğu panik ve korku halinde evlerinden dışarı kaçtıkları için sürekli kullanmak zorunda oldukları ilaçlarını yanlarına almamıştı.

Bir katılımcı ilaçlarını kullanamadığı için yaşadıklarını şöyle ifade etti:

"Benim için olmazsa olmazlardan insülinin eksikliğini yaşadım. Çünkü insülin yapmadığım için yemek bile yiyemiyordum. Yesem şekerim çok yükseliyordu. Bunun eksikliğini çok yaşadım. Yemek dağıtılırken insülin aklıma geldi. (…) Yemeği insülin yapmadan yedim. Sonrasında şekerim yükseldi. Bunu fark ettim. Nabzımın yükselmesi, ağzımın kuruması, sık idrara çıkmam gibi şeyler yaşadım ama insülin olmadığı için yapabileceğim bir şey yoktu" (Katılımcı 2, Kadın).

Alt tema 2: Bilgi eksikliği

Deprem sonrasında iletişimde yaşanan aksaklıklar nedeniyle bazı katılımcılar ilaçlarını temininde zorluklar yaşadığı ifade ettiler. Bir katılımcı ilaçlarını temin edebilmek için bulunduğu şehri terk etmek durumunda kaldığını şu şekilde ifade etti:

"Tiroid ilacım bitmek üzere olduğu için şehir değiştirmek zorunda kaldık. Daha sonra bazı eczanelerin açık olduğu, hatta reçetesiz ilaç verdiklerini öğrendim" (Katılımcı 11, Kadın).

Alt tema 3: Utanma

Bazı katılımcılar hastalığını etkin yönetebilmek için ihtiyacı olan ekipmanları istemeye utandığından zorluk yaşadığını söylediler. Ankilozan spondilit tanılı bir katılımcı bu deneyimini şu şekilde ifade etti:

"Ortopedik yatağımın eksikliğini hissettim ama bunu istemeye yüzüm tutmadı. (...) dört yatağa 40 kişi sığışmak zorunda kaldık. Kızım küçük, sürekli kucağımdaydı, ona sarılır vaziyetteydim. Tutuk bir haldeydim. İnsanlar normal yatak bulmakta bile zorluk çekiyorlardı. Diğer insanlardan biraz daha konfor ve rahatlık istemeye utandım. Çünkü insanlar benimle aynı durumdaydı" (Katılımcı 4, Kadın).

Alt tema 4: Önceliklerin değişmesi

Deprem anının oluşturduğu korku ve olumsuz hava şartlarından dolayı bazı katılımcılar hastalık yönetimini düşünemediklerini belirttiler. Bu durum tedavi uyumlarında azalmaya neden oldu. Hatta bir katılımcı depremlerin akut dönemi bittikten sonra bile tedavi uyumunu sağlamakta zorlandığını ifade etti:

"O dönemde hastalıkla ilgili hiçbir şey düşünemedim. O gün ısınma derdim oluyordu. Sıcaklık -20'lere ulaşmıştı. Bir de karın doyurma… Başka bir şey düşünemedik" (Katılımcı 8, Erkek). "O kadar korkmuştum ki ilaçlarımı kullanmayı unutuyordum. Depremden sonra 1-2 ay ilaçlarımı kullanmadım" (Katılımcı 12, Kadın).

Tema 3: Optimal Hastalık Yönetimini Sürdürme Çabaları

Yaşadıkları tüm sorunlara rağmen bazı katılımcılar optimal düzeyde de olsa hastalık yönetimini sürdürmeye devam ettiler. Bu süredeki deneyimlerinde 3 alt tema elde edildi.

Alt tema 1: Güvenli bölgelere tahliye

Depremlerin ilk günlerinde herhangi bir ilaç tedavisine erişemediği için bir süre ilaçlarını kullanamayan bazı katılımcılar, depremden etkilenmeyen başka bir şehre giderek tedavisine devam edebildi. Bir katılımcının ifadesi şöyleydi:

"(…) herkes ilk planda can derdine düşmüştü. (…) 15 gün boyunca tıbbi yardım alamadım. Daha sonra Ankara'ya gittik. Raporlu ilaçlarımı orada temin edebildim" (Katılımcı 9, Erkek).

Alt tema 2: Reçetesiz alınan ilaçları kullanma

İlaçlarını yanına almadan evden dışarı çıkan bazı katılımcılar, daha önce rapor verilen ilaçlarını eczanelerden reçetesiz olarak temin edip kullanmayı sürdürdüler. Romatoid artrit tanısı olan bir katılımcı bu durumu şöyle ifade etti:

"Romatizma hastası olduğum için kaslarım çok ağrıyordu. (…) hastaneler çok kalabalıktı. Ama devletimiz sağ olsun bize, doktora gitmek zorunda kalmadan, reçetesiz ilaç alma hakkı verdi. İlaçları oradan temin edip kullanmaya başladık" (Katılımcı 15, Kadın).

Alt tema 3: Yakınlardan alınan destek

Katılımcıların çoğunluğu deprem sonrası ilk 72 saat boyunca optimal hastalık yönetimini sürdürebilmek için yakınlarından destek aldılar. Diyabet tanılı bir katılımcı aldığı desteği şu şekilde ifade etti:

"*Korktuğum için eve girip ilaçlarımı alamadım. Eşim ne olacaksa olsun deyip içeri girip ilacımı ve şeker ölçüm cihazımı aldı"* (Katılımcı 5, Kadın).

Tema 4: Hastalık Yönetimine İlişkin Depremin Öğrettikleri

Yaşanılan büyük deprem sonrasında evlerinden çıkmak durumunda kalan katılımcılar hastalık

yönetimi ile ilgili çeşitli sorunlar yaşadılar. Deprem sonrası yaşadıkları bu olumsuz durumlardan öğrendikleri sorgulandığında iki alt tema elde edildi.

Alt tema 1: Kesintisiz bakımın önemi

Deprem sonrasında hastalık yönetimi ile ilgili deneyimleri incelendiğinde kronik hastalığı olan katılımcıların çoğunluğu kesintisiz bakımın önemini anladıklarını belirtti. Katılımcılar sıklıkla ilaçlarının her an ulaşılabilir olmasının önemine vurgu yaptılar. Bir katılımcı bu durumu şu şekilde anlattı:

"Deprem bana çok şey öğretti. İlaçlarım, elbiselerim bir valizde, girişte hazır bekliyor. Acil durumda ben alamazsam bile sonrasında birileri gidip alıp gelebiliyor" (Katılımcı 6, Kadın).

Alt tema 2: Sağlığını önemseme

Yaşanan depremler sonrasında bazı katılımcılar çevrelerindeki insanlara faydalı olabilmeleri için öncelikle kendilerinin sağlıklı olması gerektiğini vurguladı. Aynı zamanda hemşire olan bir katılımcı deprem sonrası dönemde bile çalışmaya devam ettiğini belirtti. Bu süreçte hastalarına faydalı olabilmesi için kendisinin sağlığının iyi olması gerektiğini şu şekilde ifade etti.

"(…) büyük bir felaketti. Çalışma arkadaşlarımla birlikte acil serviste büyük bir özveri ile çalıştık. Uçaklarda oksijen maskesini öncelikle kendinize daha sonra çocuklarınıza takın derler. Dolayısıyla önce kendi ilaçlarımı almalıyım. Çünkü ben iyi olmazsam hastalarım, arkadaşlarım, ailem kimse iyi olmaz. Bunun farkındayım" (Katılımcı 2, Kadın)

TARTIŞMA

Kahramanmaraş merkezli olarak meydan gelen iki büyük deprem sonrasında milyonlarca insan evini terk etmek zorunda kalmıştır. Bu dönemde evini terk etmek zorunda kalan depremzedeler yaşamlarını devam ettirebilmek için yeme, içme, barınma gibi temel ihtiyaçlarını karşılama gayreti içine girmişlerdir. Kronik hastalığı olan bireyler ise tüm bunlara ilaveten hastalıklarının yönetimi ile ilgili zorluluklarla da mücadele etmek zorunda kalmışlardır. Bu çalışmada 6 Şubat 2023'de meydana gelen iki büyük deprem sonrasında kronik hastalığı olan yetişkinlerin hastalık yönetimine ilişkin deneyimleri incelendi. Araştırmaya katılan depremzedelerin çoğunluğu deprem sonrası ilk 72 saat boyunca barınma sorunları yaşadılar. Bu sürede kaldıkları yerler hastalık süreci ile ilgili çeşitli sorunlar yaşamalarına neden oldu. Kaldığı yerde, yanındaki insülin kartuşunu soğuk tutacak ekipmanı olmayan bir hasta insülin ilacının bozulması ile ilgili endişelendi. İnsülin kartuşlarının bozulmadan saklanabilmesi için 2-8^{o}C'de muhafaza edilmelidir. 6 Şubat'ta gerçekleşen bu deprem sırasında Türkiye'de kış mevsimi yaşanmaktaydı. Bundan dolayı insülin kartuşlarının muhafazasında ciddi sorunlar yaşanmamış olabilir. Ancak sıcak mevsimlerde gerçekleşen depremlerde insülin soğuk zincirinin sürdürülmesi ile ilgili sorunlar yaşandığı bilinmektedir (19). Depremlerin ne zaman olacağı tahmin edilemediğinden deprem hazırlıkları yapılırken her türlü mevsimsel şartların göz önünde bulundurulması gerekmektedir. KOAH'lı bir başka katılımcı ise kalabalık ve iyi havalandırılamayan bir yerde kaldığından öksürük ve balgam semptomlarında artış olduğunu ifade etti. Önceki deprem deneyimleri göstermektedir ki kalabalık barınma alanlarında bulunan ve solunum sistemi hastalığı olan bireylerde pnömoni dâhil ciddi problemler ortaya çıkmaktadır (20). Deprem sonrası barınma alanları belirlenirken yeterli ısınma ve havalandırma koşulları sağlanmalıdır. Ayrıca insülin vb. soğuk zincirde muhafaza edilmesi gereken tıbbi malzemeler için gerekli soğutucu ekipmanların da hazır bulundurulması gerekmektedir.

2011 yılında gerçekleşen büyük doğu Japonya depremi sonrasında bazı kronik hastalığı olan bireylerin ilaç temini ile ilgili sıkıntı yaşadığı bilinmektedir (21). Ülkemizde gerçekleşen 6 Şubat Kahramanmaraş depremi sonrasında da kronik hastalığı olan depremzedeler çeşitli ilaçlara erişimde sorun yaşamıştır. İlaç teminindeki sorunların hızlıca çözülebilmesi için, depremden iki gün sonra afet bölgesindeki sağlık raporu bulunan kişilerin ilaçlarını bir defaya mahsus olarak reçetesiz olarak temin edebileceği duyuruldu (22). Bu duyuru ile ilgili bilgisi olmayan bir katılımcı ilaç bulamadığı için başka bir şehre gitmek zorunda kaldığından bahsetti. Deprem bölgesindeki iletişim ve haberleşme sisteminde yaşanan aksaklıklar bu durum üzerinde etkili olmuş olabilir. Deprem sonrası dönemde sağlıklı haberleşmenin devamlılığının sağlanması gerekmektedir.

Katılımcılarımızdan biri yaşadığı fiziksel sıkıntıların nedeninin, hastalık yönetimi için ihtiyacı olan ortopedik yatağı istemeye utanması olduğunu söyledi. Deprem gibi doğal afetlerden sonra görülebilecek olumsuz durumlardan biri de utanma duygusudur. Deprem sonrası oluşan utanma ve suçluluk gibi olumsuz duyguların post-travmatik stres bozukluğu ile ilişkili olduğu bilinmektedir (23). İlerleyen dönemlerde, iki büyük depremi aynı günde yaşamış olan, deprem sonrasında günlerce yıkıntıların içinde bulunmak zorunda kalan, yakınlarını veya evlerini kaybeden depremzedelerin mutlaka psikolojik açıdan değerlendirilmesi gerekmektedir.

Deprem sonrası sağ kalanlar sıklıkla çeşitli barınma merkezlerinde toplanırlar. Bu kişiler sağlıklı kalmaktan çok hayatta kalmaya öncelik verirler. Bu nedenle deprem sonrası uzun süre barınma merkezlerinde kalan depremzedelerde kilo alımı, sağlıksız beslenme ve yetersiz fiziksel aktivite gibi sorunlar görülebilir (24). Araştırmamızdaki katılımcılardan bazıları deprem sonrası ilk 72 saat boyunca barınma ve beslenme ihtiyacından dolayı hastalık yönetimini önemsemediğini ifade etti. Deprem sonrasında sağlıkları ile ilgili öncelikleri değişen depremzedelerin en kısa sürede etkili hastalık yönetimi konusunda harekete geçirilmesi gerekmektedir.

Depremin oluşturduğu kaotik ortamda bile bazı katılımcılar optimal düzeyde de olsa hastalık yönetimini sürdürmeye çalıştı. Bazı katılımcılar bulundukları şehirlerde etkili hastalık yönetimi sağlayamayacağını düşündüğünden daha güvenli şehirlere gittiğini ifade etti. Bazıları ise hükümetin onlar için sağladığı hakkı kullanarak ilaçlarını reçetesiz olarak temin ettiğini belirtti. Deprem gibi afetlerden sonra ilaçların ücretsiz ve reçetesiz olarak sunulması geçmişten beri uygulanan çözüm odaklı bir yöntemdir (25). Ancak bu yöntemin bazı sakıncaları olabilir. Bir hekim tarafından takip edilemeyen reçetesiz ilaçlar hatalı doz alımları, ilaç etkileşimleri ve yan etki gibi olaylara neden olabilir (26). Bu nedenle deprem gibi olağanüstü durumlarda reçetesiz ilaç verilmesi gibi yöntemler yerine çevrimiçi olarak hasta-hekim iletişimini arttıracak daha etkili yöntemlerin benimsenmesi reçetesiz ilaç kullanımına bağlı gelişebilecek olumsuzlukları engelleyebilir. Bazı katılımcılar deprem sonrası dönemde yakınlarından destek alma eğilimindeydi. Kronik hastalıkların etkili yönetilmesinde aile desteğinin önemli olduğu bilinmektedir (27). Deprem öncesi yapılacak hazırlıklarda hasta yakınlarının güçlendirilmesini sağlayacak programlar hazırlanarak hastaların afet durumlarında karşılaşabileceği sorunlarla daha kolay baş etmesi sağlanabilir.

Kahramanmaraş merkezli olarak 6 Şubat 2023'de yaşanan iki büyük deprem sonrasında kronik hastalığı olan bireyler hastalık yönetimi ile ilgili bazı konularda yetersizliklerinin olduğunu ifade etti. Araştırmamıza katılan bireylerin bu dönemde hastalık yönetimine ilişkin öğrendikleri sorgulandığında kesintisiz bakımın önemini ve kendi sağlığının önemsemesi gerektiğini daha iyi anladıkları belirlendi. Kesintisiz bakıma vurgu yapan katılımcıların en sık tekrar ettiği konu ilaçlarını sürekli yanlarında bulundurma gerekliliğiydi. Deprem öncesi hazırlık yapılırken özellikle kronik hastalığı olan bireylerin kesinlikle sürekli kullandığı ilaçları ve bakım ekipmanlarını içeren bir deprem çantası hazırlamaları önerilmektedir (28). Ülkemizde yapılan bir çalışmada katılımcıların sadece %33'ünün bir afet çantası hazırladığı belirlenmiştir (29). Kronik hastalığı olan bireylerin deprem sonrası etkili hastalık yönetimini sağlayabilmeleri için mutlaka bireysel deprem hazırlığını da içeren çalışmalar yapılmalıdır.

Araştırmamıza katılan depremzedelerin çoğunluğu deprem sonrası ilk 72 saat boyunca barınma sorunları yaşadılar. Bu sürede kaldıkları yerler hastalık süreci ile ilgili çeşitli sorunlar yaşamalarına neden oldu. Deprem sonrasında hastalık yönetimini olumsuz etkileyen diğer durumlar ilaç eksikliği, bilgi eksikliği, utanma ve önceliklerin değişmesi olarak belirlendi. Hastalık yönetimini sürdürebilmek için bazı katılımcılar daha güvenli şehirlere gitmek, ilaçlarını reçetesiz olarak temin etmek ve yakınlarından destek almak gibi çabalar gösterdi. Kesintisiz bakımın önemine vurgu yapan katılımcıların en sık tekrar ettiği konu ilaçlarını sürekli yanlarında bulundurma gerekliliğiydi.

Deprem öncesi hazırlıklar planlanırken her türlü mevsimsel şartlar göz önünde bulundurulmalı, barınma alanlarının yeterli ısınma ve havalandırma koşulları sağlanmalı, kronik hastalığı olan bireyler için mutlaka bireysel deprem hazırlığını da içeren çalışmalar ya-

pılmalıdır. Deprem sonrası dönemde ise sağlıklı haberleşmenin devamlılığı sağlanmalı, reçetesiz ilaç kullanımına bağlı gelişebilecek olumsuzluklar göz önünde bulundurulmalı, depremzedeler en kısa sürede etkili hastalık yönetimi konusunda harekete geçirilmeli ve mutlaka psikolojik açıdan değerlendirilmelidir.

Araştırmamızın en önemli sınırlılığı, sadece depremin ilk 72 saatinde Malatya'da bulunan depremzedelerle yürütülmesidir. Bu nedenle elde edilen veriler tüm depremzedeler için genellenemez.

TEŞEKKÜR

Çalışmaya katılan tüm depremzedelere samimi ve içten yanıtları için teşekkür ederiz.

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Kocatepe Tıp Dergisi
Kocatepe Medical Journal
25:438-442/Ekim 2024 Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

ARTIK ELİMİZDE DAHA FAZLA KANIT VAR; ULTRASONOGRAFİ KABURGA KIRIKLARININ GÖSTERİLMESİNDE GÜVENİLİR BİR ARAÇTIR

WE HAVE MORE EVIDENCE THAN BEFORE; ULTRASONOGRAPHY IS A RELIABLE TOOL TO SHOW RIB FRACTURES

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ÖZET

AMAÇ: Bu çalışmanın amacı künt göğüs travmasında şüpheli kosta kırıklarının ultrasonografi (US) değerlendirmesinde gözlemciler arası güvenilirliği ölçerek US'un tanısal değerini belirlemektir.

GEREÇ VE YÖNTEM: Künt göğüs travması nedeniyle acil servise başvuran ve kosta kırığı şüphesi olan, yaş ortalaması 48 olan (18 ila 95 yaş) toplam 52 hasta (32 erkek, 20 kadın) çalışmaya dahil edildi. Tüm hastaların direk akciğer grafileri ve US incelemeleri iki radyolog (20 yıllık US deneyimi olan bir kıdemli radyolog hekim ve bir yıllık US deneyimi olan bir asistan hekim) tarafından bağımsız şekilde değerlendirildi.

BULGULAR: Akciğer grafisinde sadece iki kosta kırığı tespit edildi. Her iki radyolog tarafından yapılan US incelemede 19 hastada 22 kırık tespit edildi. Sadece bir kosta kırığı kıdemli radyolog hekim tarafından fark edildi, asistan hekim tarafından fark edilmedi. US ile kosta kırığı tespitinde gözlemciler arası uyum çok iyiydi (Kappa: 0.917) ve bu uyum istatistiksel olarak anlamlıydı (p=0.002). Tüm kırıklar kostanın kemik kısmında yer almaktaydı ve kostal kıkırdak veya kostokondral bileşkede kırık saptanmadı.

SONUÇ: Bu çalışma ile kosta kırığı tanısında US incelemenin, gözlemciler arası değişkenliğinin çok düşük olduğunu ve yüksek oranda tekrarlanabilir bir tanı aracı olduğunu gösterdik.

ANAHTAR KELİMELER: Gözlemciler arası değişkenlik, Kosta kırığı, Radyografi, Ultrasonografi.

ABSTRACT

OBJECTIVE: The aim of this study is to assess the value of ultrasonography (US) by determining the inter-observer reliability on US evaluation of suspected rib fractures in blunt chest trauma.

MATERIAL AND METHODS: A total of 52 patients (32 males, 20 females) with a mean age of 48 years (18-95 years) who presented to the emergency department with blunt chest trauma and suspected rib fracture were included in the study. All patients were assessed with US by two radiologists (a senior radiologist with 20 years of US experience and a resident with one year of US experience) independently and chest x-rays were also evaluated.

RESULTS: Only two rib fractures were detected on chest x-rays. 22 fractures were detected from 19 patients with US by both radiologists. One rib fracture was noted only by the senior radiologist and not by the resident. Interobserver agreement was very good (kappa: 0.917) and statistically significant (p=0.002). All fractures were located at the bony portion of the rib and no fracture was found at the costal cartilage or costochondral junction.

CONCLUSIONS: We demonstrated that US is a highly reproducible diagnostic tool for rib fractures with very low inter-observer variability.

KEYWORDS: Interobserver variability, Rib fractures, Radiography, Ultrasonography.

Geliş Tarihi / Received: 22.11.2023
Kabul Tarihi / Accepted: 09.05.2024
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INTRODUCTION

Rib fractures constitute an important portion of admissions to emergency department (ER) and patients are usually present with a blunt thoracic trauma (1 - 4). Typical clinical history and chest pain are the main symptoms. Although conventional chest x-ray (CXR) has lower sensitivity, it is almost always used as a first line modality for detection of rib fractures (1, 5, 6). Sensitivity of CXR could show variability according to pulmonary parenchymal changes, age or bone mineral density. As reported by studies in the literature, sensitivity of CXR changes between 13.5% to 61.3% (7, 8). Whereas ultrasonography (US) is a widely used, cheap, safe and readily found in almost every ER, it can be used for a diagnosis of rib fracture (9). Thus, it remains to be determined whether it could be used for assessing rib fractures in routine clinical practice. There were studies reporting superiority of US over plain films for rib fractures (2, 5, 10). However, in order to put a diagnostic tool into routine usage as a robust technique, first of all, the results of it must be reproducible and reliable.

The aim of the current study is to assess the inter-observer agreement of US on suspected rib fractures in blunt chest trauma.

MATERIALS AND METHODS

Study Population

Within one-year period, patients who admitted to the ER, present with blunt chest trauma and localized chest pain were included. Multi-system trauma, patients having comorbidities or clinically unstable patients were excluded.

Chest X-ray and Ultrasound Evaluation

All patients assessed by two radiologists independently and they were blinded to each other's findings (first radiologist with a 20 years experience in body radiology and second radiologist with one year experience in US).

All patients underwent posteroanterior chest x-ray. Firstly, CXRs were examined on a high resolution diagnostic monitor. The presence and number of rib fractures were noted. Then, patients were evaluated consecutively with an approximately 30 minutes intervals by using 7.5-12 MHz transducers. Patients were both at the supine and lateral decubitis position and the tranducer was placed parallel to the axis of the costal surface (8). On the suspected hemithorax, whole ribs and also the site of tenderness were evaluated carefully. Every US examination took approximately 20-30 minutes. Normal US findings of the costal bone is a continuous echogenic line deep to the muscle and superficial to the pleural surface **(Figure 1)**.

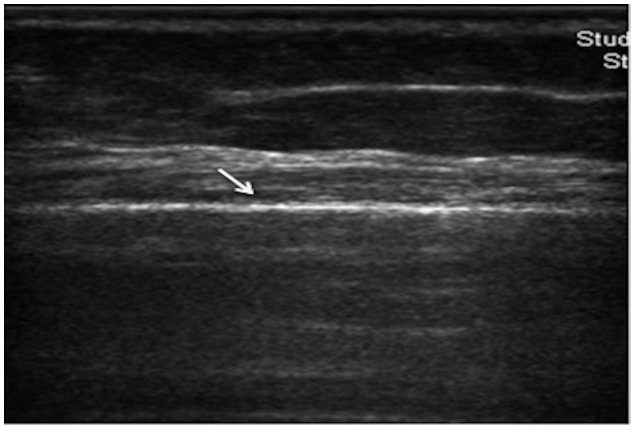

Figure 1: Continuity of costal surface in a normal patient.

Four US findings were recorded; cortical deformity, defined as separation of the fracture edges **(Figure 2)**; posterior acoustic shadowing at the fracture edges Figure 2; step-off deformity, defined as displacement or overlap of the fracture edges **(Figure 3)**; and localised haematoma at subperiostal area **(Figure 4)**. In order to make sure that the cortical irregularity area is not a nutrient vessel, the presence of sensitivity with probe pressure was noted and power Doppler US findings were evaluated. Computed tomography (CT) was not performed to avoid radiation in patients with minor trauma who were included in the study.

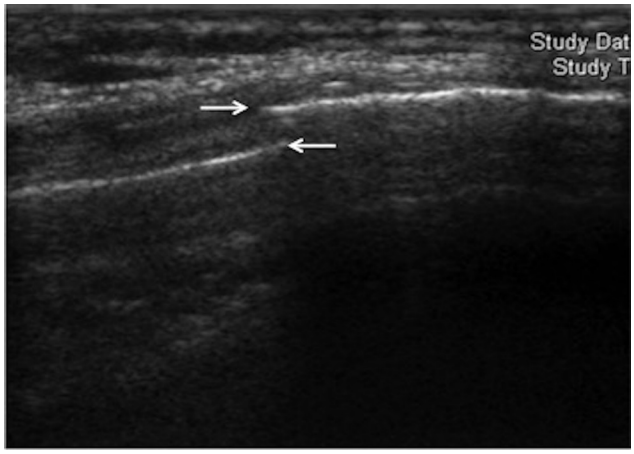

Figure 2: Cortical dehiscence at the costal surface (arrow) and posterior acoustic shadowing at the fracture ends (asterisk).

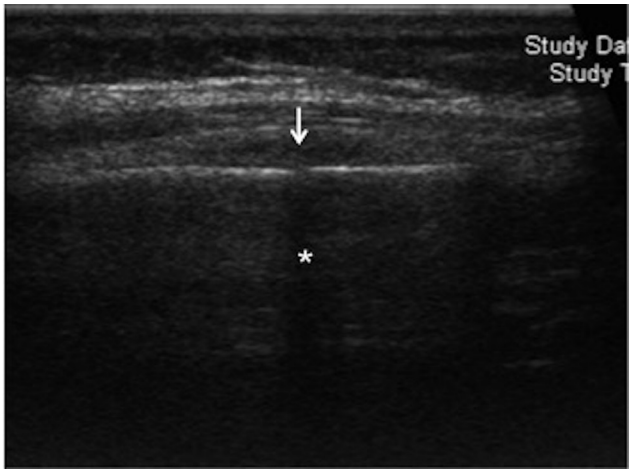

Figure 3: Displacement of the fracture edges at the costal fracture site (arrow).

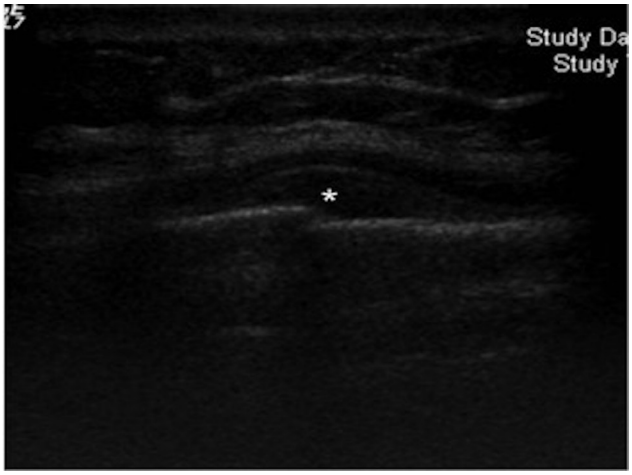

Figure 4: Local haematoma associated with step-off deformity of the fracture edges (asterisk).

Ethical Committee

The current study based on the retrospective analysis of the prospectively gathered data and Ufuk University ethics committee approved this single center study, dated 13.12.2022 and numbered 12024861-89. Written informed consent was obtained from all patients before the US examination. This study was made in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Mean, standard deviation, and range were evaluated for all the demographic data. Inter-observer agreement was assessed by kappa statistics and Cohen's kappa value was calculated. All statistical analyses were made by using a commercially available software (version 20.0, IBM SPSS Statistics, IBM Corp.)

RESULTS

A total of 52 patients (32 males, 20 females) with a mean age of 48 years (range between 18 and 95 years) were enrolled, in this study. Dyspnea and chest pain increasing with inspiration were the most frequent complaints. All patients were evaluated within 0.5 to 6 hours after admitting to ER. On CXRs, only two rib fractures were detected. In 19 cases (36.5%), 22 fractures were found via US by both radiologists. The inter-observer agreement was remarkably high for US with a Cohen's kappa value of 0.917 **(Table 1)**. One rib fracture was noted only by the senior radiologist and not by the resident. 21 of 22 fractures were detected on the lateral aspect of the 5th to 10th ribs. All fractures were located at the bony part of the rib and no fracture was found at the costal cartilage or costochondral junction.

Table 1: Inter-observer agreement for US and chest X-ray in detection of rib fractures.

	Fracture (+) (n=19/52)	Senior radiologist	Junior radiologist	Kappa
Sonography (+)	19	19	18	0.917
Radiography (+)	2	2	2	1

DISCUSSION

Rib fracture is a relatively common finding in blunt chest trauma and accompanies approximately 35-40% of thoracic injuries (2). From 4th to 10th ribs are mostly and contiguously affected. Because of fragility, osseous parts affected more than chondral regions. In cases where clinical complaints and findings suggest rib fracture, imaging modalities are used to detect the fracture and associated injuries (11). In our study, out of 52 patients with suspected rib fracture, just 19 patients had a fracture. Prevalence of rib fractures relatively low in our study when compared to similar studies in the literature (4, 5). This might be due to the inclusion of only the outpatients without multi-system trauma, in this series. Furthermore, lower pre-diagnosis accuracy of the referring emergency medicine specialist regarding rib fractures in our study, might have caused diminished prevalence.

In order to make a definitive diagnosis, the clinician must use imaging modalities. There are several imaging modalities for the assessment of rib fractures including CXR, CT, US, nuclear medicine and magnetic resonance imaging (MRI) (12). CXR is the first-line imaging tool on traumatic injury at emergency department. It is specific but not sensitive and misses more than

50% of rib fractures (13). CT enables evaluation along the entire axis of the ribs with multi-planar imaging technique and has a high sensitivity in detecting rib fractures. CT is the recommended method for diagnosing rib fractures because it is highly sensitive and can reveal other underlying trauma pathologies (12, 14). Bone scintigraphy has sensitivity but not specificity for rib fractures (15). It can be accepted as "gold standard" method for rib fractures, but it is not cost-effective to perform bone scintigraphy for rib fractures in emergency departments and clinical practice. MRI is highly influenced by respiratory movements and therefore has the lowest diagnostic value in detection of rib fractures (1). Meanwhile, Capelastegui et al. (16) showed that MRI detected rib and/or sternum fractures in 86% of patients with work-related trauma and interobserver agreement was excellent. With the advanced techniques within MRI technology, it is possible that in equivocal cases, MRI findings could be useful. On the other hand, US enables the evaluation of ribs parallel to its long axis and also gives the opportunity of assessing costal cartilage and bony rib, simultaneously. When a suspected rib fracture was not detected with CXR, after waiting for two weeks, CXR was repeated for revealing callus formation. However, with the use of US, immediate diagnosis could be possible without radiation exposure. In the current study, we have found a high inter-observer agreement indicating that US is a reliable and reproducible imaging modality for the detection of rib fractures that we could use confidently (Table 1).

There are also disadvantages of the US. First of all, the examination time is long (1, 2, 9, 17). It takes approximately 10-15 minutes according to user experience and daily work load of the radiology department. In addition, duration of the examination depends on how cooperative the patient is. Secondly, pain resulting from the applied pressure on the fracture, during an US examination leads to patient discomfort. Thirdly, obesity and large breast tissue can limit the sonographic sensitivity and finally retro-scapular ribs and infraclavicular segment of the first rib cannot be assessed by the US (1, 8).

False positives must also be considered during sonographic assessment. If the transducer is not placed parallel to the long axis of the rib, pseudo-fracture appearance cannot be avoided (18, 19). The costochondral junction and the pleural echogenic surface are the main reasons causing that pitfall. The anterior surface of the costochondral junction is not regular as the bony costal surface and it can easily be mistaken as the angled rib edges. Pleura is similar with the anterior costal surface, both of which have bright linear appearance (8). In order to overcome this pitfall, the gliding sign of the pleura and the absence of posterior acoustic shadowing of the broken rib edge can be used (1). Just like the pleural echogenic surface, the costochondral junction has not the posterior acoustic shadowing that is seen in rib fractures.

Our results demonstrated that the US is an useful and reproducible imaging modality for assessing rib fractures and much more sensitive than the CXR. Griffith et al (1) and Hurley et al (2) showed that US is a more sensitive imaging modality than radiography for determining rib fractures. Turk et al (18) also found that US is more sensitive than X-ray by detecting 26 rib fractures in 18 patients who have normal CXRs. We found similar results as only 2 fractures were detected by CXR and 22 fractures were detected by US, in this series. In a systematic review and meta-analysis study, Gilbertson et al (6) showed that ultrasonography has high sensitivity (89.3%) and specificity (98.4%) for the diagnosis of any rib fracture. We already know that the sensitivity for detecting rib fractures was higher with CT (62.4%) than with X-ray, and that rib fractures were more likely to be detected at all sites with CT. Furthermore, if a rib fracture is suspected in a patient with minor trauma and no additional injury is expected, the US may be useful in establishing the diagnosis because of its superiority on rib fracture detection when compared to radiography. It is also useful in cases where ionising radiation should be avoided.

There are several limitations in the current study. First of all, there was no gold standard technique used for confirming rib fractures and assessing false positive and false negative results. Secondly, because US is an operator dependent technique, training and performance of the operator might hamper the quality (9). Finally, the small sample size and lack of

randomization were the other drawbacks. In conclusion, we have demonstrated that the US is a reproducible diagnostic tool for rib fractures with very low inter-observer variability. The widespread use of the US will contribute to the diagnosis and treatment of rib fractures.

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Kocatepe Tıp Dergisi
Kocatepe Medical Journal
25:443-447/Ekim 2024 Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

DİSTAL ÜRETER TAŞI OLAN HASTALARDA MEDİKAL EKSPULSİF TEDAVİNİN BAŞARISINI ETKİLEYEN ÖNGÖRÜCÜ FAKTÖRLER

PREDICTIVE FACTORS AFFECTING THE SUCCESS OF MEDICAL EXPULSIVE THERAPY IN PATIENTS WITH DISTAL URETERAL STONE

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ÖZET

AMAÇ: Bu çalışmada distal üreter taşı nedeniyle medikal ekspulsif tedavi başlanan hastalarda spontan taş düşürmeyi etkileyen faktörleri araştırmayı amaçladık.

GEREÇ VE YÖNTEM: Eylül 2022 ve Ekim 2023 tarihleri arasında 4-10 mm boyutlarında distal üreter taşı olan toplam 148 hasta dahil edildi. Hastalara medikal ekspülsif tedavi olarak silodosin 4 mg başlandı ve en fazla dört hafta takip edildi. Spontan taş düşürmeyi etkileyen hasta ve taşa bağlı değişkenler değerlendirildi.

BULGULAR: Katılımcıların yaş ortalaması 42,92±12,78 yıldı. Taş düşürme oranı %64,2 idi. Taş boyutu, taş yükü, üreter duvar kalınlığı, taşın üreterovezikal bileşkeye olan uzaklığı, nötrofil lenfosit oranı ve hidronefroz derecesi daha düşük olan hastalarda spontan taş düşürme oranı anlamlı olarak daha yüksekti (hepsi için $p<0.05$). Çok değişkenli analizde, taşın üreterovezikal bileşkeye olan mesafesi, üreter duvar kalınlığı ve nötrofil-lenfosit oranı spontan pasajın bağımsız belirleyicileriydi (sırasıyla p:0.036, p:0.001, p:0.001).

SONUÇ: Taşın üreterovezikal bileşkeye olan mesafesi, üreter duvar kalınlığı ve nötrofil-lenfosit oranı, spontan taş düşürmeyi tahmin etmede yararlı parametreler olabilir. Bu faktörler distal üreter taşlarının tedavisine yönelik karar verme sürecinde önemli bir rol oynamaktadır.

ANAHTAR KELİMELER: Üreter taşları, Ürolitiyaz, Medikal ekspulsif tedavi.

ABSTRACT

OBJECTIVE: In this study, we aimed to investigate the factors affecting spontaneous stone passing in patients who received medical expulsive therapy due to distal ureteral stones.

MATERIAL AND METHODS: From September 2022 to October 2023, a total of 148 patients with distal ureteral stones sized 4-10 mm were included. Patients received silodosin 4 mg as medical expulsive therapy and were followed up for a maximum of four weeks. The patient- and stone-related variables affecting spontaneous stone passage were evaluated.

RESULTS: The mean age of the participants was 42.92±12.78 years. The stone expulsion rate was 64.2%. The rate of spontaneous stone passage was significantly higher in patients with lower stone size, stone burden, ureteral wall thickness, distance of the stone to the ureterovesical junction, neutrophil-lymphocyte ratio and hydronephrosis grade. (all, $p<0.05$). The distance of the stone to the ureterovesical junction, ureteral wall thickness, and neutrophil-to-lymphocyte ratio were independent predictors of spontaneous passage (p:0.036, p:0.001, p:0.001, respectively).

CONCLUSIONS: The distance of stone to the ureterovesical junction, ureteral wall thickness, and neutrophil-to-lymphocyte ratio can be useful parameters to estimate spontaneous stone expulsion. These factors play important roles in decision-making for the management of distal ureteral stones.

KEYWORDS: Ureteral Calculi, Urolithiasis, Medical expulsive therapy.

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INTRODUCTION

Urolithiasis is a common disease worldwide, with an incidence of up to 20% (1). Twenty percent of urinary system stones are located at the ureter, and 70% of ureteral stones are distal ureteral stones (2). Although there are treatment methods such as extracorporeal shock wave lithotripsy (ESWL), endoscopic lithotripsy (EL) and surgical stone removal in the management of ureter stones, medical expulsive therapy (MET) is proposed for distal ureter stones smaller than 1 cm in the European Association of Urology guidelines (3). The success rate of spontaneous expulsion has been reported up to 70% with MET. Therefore, MET should be offered first to patients with uncomplicated distal ureter stones <1 cm to avoid the need for surgical intervention (4). The content of MET consists of plenty of fluid intake, pain palliation and medical treatment (alpha-adrenergic blocker, corticosteroid, phosphodiesterase type 5 inhibitor, antispasmotic or calcium channel blocker) for 4 weeks (5).

Studies investigating the success of MET have mostly focused on which medical treatment is more effective (6 - 8). However, the success of MET is also affected by patient and stone-related factors. The number of studies conducted on this subject is insufficient. The present study aimed to evaluate the factors affecting the success of spontaneous stone passage in adult patients with uncomplicated 4-10 mm sized distal ureter stones and in whom MET was initiated.

MATERIALS AND METHODS

The data of patients who applied with renal colic and were diagnosed as ureteral stones between 4-10 mm in the distal ureter at Department of Urology, Kemer State Hospital, and subsequently treated with MET between September 2022 and October 2023 were retrospectively examined. Exclusion criteria are listed below:

•Patients with urinary tract infection, fever>38°C or other focal infection
•Patients with bilateral or multiple ureter stones
•Patients with anamnesis of solitary kidney
•Patients with hematological, inflammatory disease or malignancy
•Patients who needed instant intervention due to renal impairment
•Patients with a history of using drugs that may change blood cell ratios (corticosteroids, oral contraceptives, etc.)

All patients were assessed by physical examination, complete blood tests, kidney function tests, urinalysis, urine culture, urinary ultrasonography (USG), and X-ray kidney, ureter, and bladder (KUB). Computed tomography (CT) was performed for all patients to confirm the diagnosis. All of the participants received silodosin 4 mg once a day as MET. Besides, 50 mg/day diclofenac sodium tablets were prescribed for episodes of renal colic. All of the patients were advised to remain active, drink 3 L of water daily, and strain their urine to search for stones. They were told to report the time they saw stones in the filtered urine. Patient follow-up was done once a week for 4 weeks with kidney function tests, urinalysis, X-ray KUB. Drugs were continued until stone expulsion or for a maximum four weeks. CT was reapplied in patients with suspicious or unsuccessful expulsions of stone at the end of the fourth week. Patients with no stone expulsion at the end of 4 weeks were advised to undergo an interventional treatment.

Demographic data of included participants (age, gender, body mass index [BMI], and neutrophil-to-lymphocyte ratio [NLR]) were noted. Stone-related parameters including stone size, stone burden, ureteral wall thickness (UWT), distance to the ureterovesical junction (UVJ), and hydronephrosis grade were also recorded using CT. The stone size was determined by calculating the widest diameter of the stone. The stone burden was calculated from CT scans and recorded in square millimeters. NLR was calculated by dividing neutrophil count by lymphocyte count before starting treatments.

Ethical Committee

Ethics committee approval was received from Antalya Training and Research Hospital. (Approval number: 2023-14/8).

Statistical Analysis

Data are presented as number (%) or mean±standard deviation for continuous variables, and frequency (%) for categorical data. Normality assumption was evaluated with the Shapiro Wilk test. Student's t-test was used for normal-

ly distributed continuous variables; otherwise, the Mann– Whitney U test was used. Pearson chi-square or Fisher's exact test was performed for categorical variables. All potential variables in the descriptive analysis were included in the initial univariable analysis and then only variables that were determined as significant ($p<0.200$) were included in the final presented multivariate logistic regression models. Statistical analysis was performed by using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp.). A p-value <0.05 was accepted as statistically significant.

RESULTS

148 patients finished the study. The mean age of the cohort was 42.92±12.78 years. Most of the patients were men (83.1%). The number of patients who experienced spontaneous stone expulsion was 95 (64.2%). The average expulsion interval was 9.35±4.89 days in patients who spontaneously passed the stone. The characteristic features of the patients and the comparison of patients who passed stones and those who failed to pass the stone are summarized in **(Table 1)**. The factors affecting the spontaneous expulsion were examined by univariate and multivariate analyses. The distance of the stone to UVJ, UWT, and NLR were independent predictors of spontaneous passage **(Table 2)**.

Table 1: Demographic data and comparison of characteristics according to stone passage status

Variables	Total n=148	SP+ n=95	SP- n=53	p value
Age, years, mean±SD	42.92±12.78	42.26±13.24	44.11±11.93	0.400
Gender, n,%				0.983
Male	123 (83.1)	79 (83.2)	44 (83)	
Female	25 (16.9)	16 (16.8)	9 (17)	
BMI, kg/m^2, mean±SD	25.45±2.79	25.26±2.66	25.81±3.01	0.250
Stone size, mm, mean±SD	6.51±1.87	5.94±1.78	7.52±1.57	**<0.001**
Stone burden, mm^2, mean±SD	33.84±21.68	26.95±18.92	46.18±20.97	**<0.001**
UWT, mm, mean±SD	1.74±0.82	1.41±0.55	2.32±0.91	**<0.001**
Distance to UVJ, mm, mean±SD	14.15±10.26	12.03±8.76	17.96±11.65	**0.002**
NLR, mean±SD	1.85±0.73	1.59±0.58	2.32±0.76	**<0.001**
Hydronephrosis Grade Group, n,%				**<0.001**
Grade 0,1	62 (41.9)	54 (56.8)	8 (15.1)	
Grade 2,3	86 (58.1)	41 (43.2)	45 (84.9)	

SP;spontaneous passage, BMI;body mass index, UWT;ureteral wall thickness, UVJ;ureterovesical junction, NLR; neutrophil-to-lymphocyte ratio

Table 2: Predictive factors for spontaneous distal ureteral stone passage

Variables	B	S.E.	P value	Odds ratio	95% C.I.for EXP(B)	
					Lower	Upper
Stone Size	-.221	.463	.633	.801	.323	1.987
Stone Burden	.038	.039	.336	1.039	.961	1.122
Distance to UVJ	.047	.022	**.036**	1.048	1.003	1.095
Ureteral Wall Thickness	1.314	.386	**.001**	3.720	1.745	7.931
NLR	1.229	.379	**.001**	3.416	1.625	7.183
Hydronephrosis Grade Group	.912	.544	.094	2.489	.856	7.236

UVJ; ureterovesical junction, NLR; neutrophil-to-lymphocyte ratio

DISCUSSION

Studies questioning the effectiveness of MET have mostly focused on which drug is more successful. A recent meta-analysis showed that alpha blockers ensure prominent advantages over placebo in the management of distal ureter stones (9). Furthermore, in a meta-analysis study comparing the effectiveness of the three most commonly used alpha-adrenergic blockers as MET, silodosin was shown to be the most effective molecule (10). In a randomized prospective study, the authors concluded that silodosin 4 mg facilitated the expulsion of distal ureteral stones (11). However, patient- and stone-related factors can also affect treatment success in addition to the treatment option. So, we investigated the patient- and stone-related factors affecting spontaneous stone passing in patients who used silodosin as MET. The present concludes that the distance of stone to the UVJ, UWT, and NLR are independent predictive factors for spontaneous stone expulsion.

The NLR is a biomarker of inflammation. It is commonly used in the prognosis of cancer patients (12). It has been shown that the stone causes ureteral mucosal edema and inflammation during its passage through the ureter (13). Excessive inflammation may reduce spontaneous stone passing by increasing mucosal impaction of the stone. For this reason, some researchers have investigated the significance of inflammation as a predictor of spontaneous stone passage. In the study by Heidar et al. (14), higher NLR was useful for predicting failure of spontaneous passage. Similarly, NLR was inversely associated with spontaneous stone expulsion (15,16). Previous studies on this topic also suggested that C-reactive protein which is another inflammation marker was correlated with the failure of MET (17,18). Our study showed that NLR independently affected the spontaneous stone passage on multivariate analysis.

Stone-related factors including stone size, stone burden, Hounsfield unit (HU), UWT, Framingham score, and presence of hydronephrosis have been investigated as predictive factors for stone passage. The results of studies on stone size and stone burden, which are the most evaluated factors, are controversial. Several investigators found that stone size and stone burden were significantly correlated with spontaneous passage on multivariate analysis (16-19). Conversely, some authors failed to identify this correlation (20-22). Bokka and Jain concluded that HU cannot be used as a

predictor of outcome (23). Nevertheless, Sahin et al. found a significant correlation between HU and spontaneous passage (24). On multivariate analysis, UWT was an independent predictor of stone passing in the majority of studies (16, 19, 20, 22). Mucosal edema and inflammation induced by the stone in the ureteral mucosa may be an important indicator of failure of spontaneous passage. UWT and inflammation markers such as NLR and CRP that show the mucosal edema and inflammation of the ureter could be promising to predict treatment success. Our data suggest that stone size, stone burden, and the degree of hydronephrosis were statistically significant predictors in the univariate analysis. However, this was not confirmed by the multivariate analysis. The distance of stone to the UVJ and UWT were significant predictors of successful passage.

There is a variety of options including conservative therapy, ESWL, or EL to treat the distal ureter stones. MET is an inexpensive and non-invasive treatment given the fact that most ureteral stones pass spontaneously. However, MET has also the risk of complications including infections, colic episodes, and renal function loss. Therefore, it becomes essential to predict situations in which MET may fail and early intervention is needed. For this purpose, a nomogram that contains ureteral mucosal edema and inflammation markers is needed to estimate spontaneous stone passage in the decision-making process.

This study had some limitations. First, it was conducted retrospectively with few patients. Second, we measured the NLR at the beginning of the treatment. Measurements taken during follow-up may be more instructive in the success of MET. Further prospective studies that evaluate patient- and stone-related factors in detail are needed to overcome these limitations. In conclusion, the distance of stone to the UVJ, UWT, and NLR can be useful parameters for spontaneous stone expulsion. These factors play a considerable role in decision-making for the management of distal ureteral stones.

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Kocatepe Tıp Dergisi
Kocatepe Medical Journal
25:448-453/Ekim 2024 Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

OTİZM SPEKTRUM BOZUKLUĞU TANILI VE TİPİK GELİŞİM GÖSTEREN KÜÇÜK ÇOCUKLARIN BESLENME DAVRANIŞLARININ, UYKU SORUNLARININ, EBEVEYN KAYGI VE DEPRESYON DÜZEYLERİNİN DEĞERLENDİRİLMESİ

EVALUATION OF EATING BEHAVIOR, SLEEP PROBLEMS, PARENTAL ANXIETY AND DEPRESSION LEVELS OF YOUNG CHILDREN DIAGNOSED WITH AUTISM SPECTRUM DISORDER AND TYPICALLY DEVELOPING

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ÖZET

AMAÇ: Bu çalışmada, otizm spektrum bozukluğu (OSB) olan küçük çocukların beslenme davranışı ve uyku sorunlarının, ebeveynlerinin depresyon ve kaygı düzeylerinin sağlıklı kontrollerle karşılaştırılması ve OSB semptom şiddeti, ebeveyn kaygı ve depresyon düzeyleri ile çocukların beslenme davranışı ve uyku sorunlarına yönelik ilişkinin değerlendirilmesi amaçlanmaktadır.

GEREÇ VE YÖNTEM: Araştırmanın örneklemi, 18 ay ile 60 ay arasında OSB tanısı alan 81 hasta ve 60 sağlıklı çocuk ile oluşturmuştur. OSB tanısı Ruhsal Bozuklukların Tanısal ve İstatistiksel El Kitabı-5 (Diagnostic and Statistical Manual of Mental Disorders [DSM])'e göre çocuk ve ergen psikiyatri uzmanı tarafından konulmuştur. Hasta grubundaki küçük yaş çocukların OSB semptom şiddeti, klinisyen tarafından Çocukluk Otizmi Derecelendirme Ölçeği (ÇODÖ) uygulanarak değerlendirilmiştir. Çocuklarda Beslenme Davranışı Anketi (ÇBDA), Çocuk Uyku Alışkanlıkları Anketi (ÇUAA) ve Beck Depresyon Ölçeği (BDÖ), Beck Anksiyete Ölçeği (BAÖ) çalışmaya alınan çocukların ebeveynleri tarafından doldurulmuştur.

BULGULAR: OSB grubunda ÇBDA içme tutkusu alt ölçeği ($z = -2.87$, $p = 0.004$), ÇUAA toplam puanı ($z = -3.013$, $p = 0.003$), ebeveyn BDÖ ($z = -5.213$, $p < 0.001$), ve ebeveyn BAÖ ($z = 4.474$, $p < 0.001$) toplam puanları sağlıklı kontrollere göre istatistiksel olarak anlamlı düzeyde daha yüksek olduğu saptanmıştır. OSB ve sağlıklı kontroller arasında ÇBDA diğer alt ölçek puanlarının istatistiksel olarak anlamlı bir farklılık göstermediği saptanmıştır. Hasta grubunda, otizm belirti şiddeti ile ÇBDA alt ölçek puanları, ÇUAA, ebeveyn BDÖ ve BAÖ toplam puanları arasında bir ilişki bulunmamıştır.

SONUÇ: OSB olan küçük çocukların sağlıklı çocuklara göre daha çok uyku problemi yaşantıladıkları, içeceklere yönelimlerinin daha çok olduğu ve ebeveynlerinin depresyon ve anksiyete düzeylerinin daha yüksek olduğu belirlenmiştir. Bu çalışma OSB tanısı ile küçük çocukların uyku sorunları, içeceklere olan yönelimleri ve ebeveynlerinin ruh sağlığı arasında anlamlı bir ilişki olduğunu göstermektedir.

ANAHTAR KELİMELER: Çocuk psikiyatrisi, Beslenme davranışı, Uyku, Otizm spektrum bozukluğu, Depresyon

ABSTRACT

OBJECTIVE: This study aimed to compare the feeding behavior and sleep problems of young children with autism spectrum disorder (ASD), to compare depression and anxiety levels of their parents with healthy controls, and to evaluate the relationship between ASD symptom severity, parental anxiety and depression levels, and children's feeding behavior and sleep problems.

MATERIAL AND METHODS: The sample of the study consisted of 81 patients diagnosed with ASD and 60 healthy children between 18 months and 60 months. The diagnosis of ASD was made by a child and adolescent psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM). The Childhood Autism Rating Scale (CARS) was used to assess the severity of young children ASD symptoms in the patient group. The Children's Eating Behavior Questionnaire (CEBQ), the Children's Sleep Habits Questionnaire (CSHQ), and the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) were filled out by the parents of the children included in the study.

RESULTS: In the ASD group, it was found that the subscale scores of the CEBQ desire to drink ($z = -2.87$, $p = 0.004$), the total score of the CSHQ ($z = -3.013$, $p = 0.003$), parental BDI ($z = -5.213$, $p < 0.001$), and parental BAI ($z = 4.474$, $p < 0.001$) were statistically significantly higher than healthy controls. No statistically significant difference was detected between the ASD and control groups in terms of other subscale scores of CEBQ. In the patient group, no relationship was found between ASD symptom level and CEBQ subscale scores, CSHQ, parent BDI and BAI total scores.

CONCLUSIONS: It was determined that young children with ASD had more sleep problems, more tendency towards beverages and their parents had higher levels of depression and anxiety than healthy children. This study shows that there is a significant relationship between ASD diagnosis and young children's sleep problems, their orientation towards beverages and their parents' mental health.

KEYWORDS: Child Psychiatry, Feeding behavior, Sleep, Autism spectrum disorder, Depression.

Geliş Tarihi / Received: 01.03.2024
Kabul Tarihi / Accepted: 17.05.2024
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GİRİŞ

Otizm spektrum bozukluğu (OSB), sosyal iletişim eksiklikleri ve sınırlı tekrarlayan davranış veya ilgi kalıpları ile karakterize olan nörogelişimsel bir bozukluktur (1). Son yirmi yılda elde edilen veriler ışığında çocuklardaki OSB yaygınlık oranlarının 2000 yılında 1/150, 2014 yılında 1/68 iken, 2018'de 1/44'e yükselerek belirgin bir artış gösterdiği belirlenmiştir (2,3). Otizmin etiyolojisi hala bilinmemektedir ancak genetik faktörlerin yanı sıra çevresel faktörlerin de etiyolojisinde önemli rol oynadığı düşünülmektedir (3).

Beslenme ve yeme problemleri, her yaştan ve bilişsel beceriden otizmli bireyleri etkileyen önemli sorunlar arasındadır (4). Beslenme ve yeme problemleri tüm çocukların %10-20'sinde görülmekle birlikte, bu sorunun OSB tanılı çocukların en az %70'inde olduğu belirtilmektedir (3). 2019 yılında yapılan bir çalışmada, atipik yeme davranışlarının (örneğin, sınırlı besin tercihi ve markaya özgü tercihler) OSB tanılı çocuklarda (%70,4) normal gelişim gösteren çocuklara (4.8 %) ve diğer bozuklukları olan çocuklara (13.1%) kıyasla daha sık görüldüğü belirtilmiştir (5). Bununla birlikte, küçük yaş grubundaki çocuklarda gelişen beslenme problemlerinin otizmin erken bir belirtisi olabileceğini öne süren araştırmacılar da bulunmaktadır (6). OSB tanılı çocukların, uyku sorunları açısından yüksek risk altında olduğu düşünülmektedir (7). OSB tanılı çocuklarda uyku sorunlarının yaşam boyu yaygın olduğu ve bu tanıya sahip çocukların yaklaşık %80'inde uyku sorunlarının görüldüğü bildirilmektedir (8). OSB tanılı çocukların insomnia, toplam uyku süresinde azalma, uykuya başlamada gecikme ve gece uyanmalarında artış gibi çeşitli uyku sorunlarını yaşantıladıkları bildirilmektedir (9).

OSB tanılı çocukların belirtilerinin, bu tanıya sahip çocukların ebeveynleri için çocuğa bakım verme zorluklarını ve ebeveynlik stresini arttırdığı bildirilmektedir (10). OSB tanılı gençlerin ebeveynlerinin, genel popülasyondaki yetişkinlere göre daha yüksek depresyon riskine sahip olduğu belirtilmektedir (11). Yapılan bazı çalışmalarda, OSB'li çocukların ebeveynlerinde, hem normal gelişim gösteren çocukların ebeveynlerine hem de diğer gelişimsel bozuklukları olan çocukların ebeveynlerine kıyasla ebeveyn kaygısı ve ebeveyn depresyonunun yüksek düzeyde olduğu tespit edilmiştir (12, 13). Yukarıda belirtildiği gibi, OSB tanısı ile çocukta beslenme davranışları, uyku sorunları ve ebeveynlerinin kaygı, depresyon düzeyleri etkileşim içindedir. Bununla birlikte, bildiğimiz kadarıyla, önceki çalışmaların hiçbirinde OSB tanısı konulan erken yaş dönemindeki çocukların beslenme davranışlarını, uyku sorunlarını, ebeveynlerinin kaygı ve depresyon düzeylerini birlikte değerlendirerek sağlıklı kontrol grubuyla karşılaştıran bir çalışma bulunmamaktadır.

Bu çalışmanın amacı, çocuklarda beslenme davranışlarının, uyku sorunlarının, ebeveynlerinin anksiyete ve depresyon düzeylerinin OSB grubu ile sağlıklı kontrol gruplarında karşılaştırılması ve birbirleri ile olan ilişkisinin incelenmesidir.

Çalışmanın hipotezleri şunlardır:

- OSB tanılı çocuklarda uyku sorunlarının sağlıklı gruba göre daha yüksek olacağı;
- OSB tanılı çocuklarla sağlıklı grup arasında beslenme davranışları arasında farklılık olacağı;
- OSB tanılı çocukların ebeveynlerinde anksiyete ve depresyon düzeylerinin sağlıklı grubun ebeveynlerine göre daha yüksek olacağı;
- OSB hasta grubunda otizm semptom şiddeti ile çocuğun beslenme davranışı, uyku sorunları, ebeveyn anksiyete ve depresyon düzeyleri arasında anlamlı bir ilişkinin olacağı varsayılmıştır.

GEREÇ VE YÖNTEM

Bu çalışma, çok merkezli, kesitsel bir çalışma olarak tasarlanmıştır. Çalışma Ekim 2023 - Şubat 2024 tarihleri arasında Afyonkarahisar Sağlık Bilimleri Üniversitesi Tıp Fakültesi Çocuk ve Ergen Psikiyatrisi Polikliniği, Meram Tıp Fakültesi Çocuk ve Ergen Ruh Sağlığı ve Hastalıkları Polikliniği, Sağlık Bilimleri Üniversitesi, İzmir Tepecik Eğitim ve Araştırma Hastanesi Çocuk ve Ergen Psikiyatrisi Polikliniği'nde gerçekleştirilmiştir. Ruhsal Bozuklukların Tanısal ve İstatistiksel El Kitabı-5 (Diagnostic and Statistical Manual of Mental Disorders [DSM]) tanı kriterlerine göre çocuk ve ergen psikiyatri uzmanı tarafından OSB tanısı konan, psikotrop ilaç kullanımı olmayan 18-60 ay arasındaki çocuklar ve ebeveynleri çalışmaya alınmıştır. Çocukluk Otizmi Derecelendirme Ölçeği (ÇODÖ) klinisyen tarafından çocuklara uygulamıştır. Kontrol grubunu ise çocuk ve ergen psikiyatrisi polikliniklerine çeşitli şikayetlerle başvuran (rutin kontrol veya yaş dönemine yönelik sorunlar hakkında danış-

manlık alan), 18-60 ay arası zihinsel, bedensel gelişimsel gecikmesi olmayan, OSB tanısı olmayan çocuklardan ve çocukların ebeveynlerinden oluşturulmuştur. Yapılan değerlendirme sonucunda ebeveynler çalışma hakkında bilgilendirilmiş, tüm katılımcılara yazılı aydınlatılmış onam formu verilmiş ve çalışmaya sadece gönüllü olan katılımcılar dâhil edilmiştir. Hasta ve sağlıklı kontrol grubunda çalışmayı kabul eden ebeveynler çocukları için Çocuklarda Beslenme Davranışı Anketi (ÇBDA)'ni Çocuk Uyku Alışkanlıkları Anketi (ÇUAA)'ni ve kendilerine yönelik Beck Depresyon Ölçeği (BDÖ)'ni, Beck Anksiyete Ölçeği (BAÖ)'ni doldurmuşlardır.

Veri Toplama Araçları

Sosyodemografik Veri Formu: Hastaların ve ebeveyninin cinsiyet, yaş gibi sosyodemografik özelliklerini içeren sorulardan oluşmaktadır.

Çocukluk Otizmi Derecelendirme Ölçeği (ÇODÖ): Ölçek otizm şüphesi varlığında, bu çocukların değerlendirilmesinde ve otistik bozukluğu olan çocuğun diğer gelişimsel bozukluğu olan çocuklardan ayrılmasında oldukça sık olarak kullanılmaktadır (14). Bu ölçek 15 maddeden oluşmakta ve ölçek puanlaması 15 ile 60 arasında değişmektedir. Bu ölçeğin Türkçe geçerlilik ve güvenilirliği yapılmıştır (15, 16).

Çocuklarda Beslenme Davranışı Anketi (ÇBDA): Ölçek 35 maddeden oluşmaktadır. Likert tipi anket olup, 5 puan üzerinden değerlendirilmektedir. Alt ölçekleri gıda heveslisi, duygusal aşırı yeme, gıdadan keyif alma, içme tutkusu, tokluk heveslisi, yavaş yeme, duygusal az yeme ve yemek seçiciliği'dir. Bu alt ölçekler çocuğun iştahını belirlemeyi amaçlamıştır (17). Ölçeğin Türkçe geçerlilik ve güvenilirliği yapılmıştır (18).

Çocuk Uyku Alışkanlıkları Anketi (ÇUAA): Ölçek çocukların uyku alışkanlıklarını ve uyku ile ilişkili sorunlarını değerlendirmeye yönelik geliştirilmiştir (19). Ölçeğin kesim noktası 41 puan olarak belirlenmiştir ve 41 puanın üzerindeki değerler klinik olarak anlamlı uyku sorunlarını göstermektedir. Ülkemizde Türkçe geçerlilik ve güvenilirliği yapılmıştır (20).

Beck Depresyon Ölçeği (BDÖ): 21 maddeden oluşan bir öz değerlendirme ölçeğidir (21, 22). Ölçek puanlaması 0 ile 63 puan arasında değişmekte ve puan arttıkça depresyonun şiddeti artmaktadır. Ölçeğin kesme puanı 17 'dir. Ölçeğin belirlenen Cronbach Alfa katsayısı 0.80'dir (21).

Beck Anksiyete Ölçeği (BAÖ): Ölçek 21 madde içermektedir. Bu ölçeğin puan aralığı 0-63'dür. Ölçekten alının puan arttıkça anksiyete şiddeti de artmaktadır. Ölçeğin Türkçe geçerlilik ve güvenirliliği yapılmıştır (23).

Etik Kurul

Çalışma prosedürleri Helsinki Deklarasyonuna uygun olarak gerçekleştirildi. Çalışma Afyonkarahisar Sağlık Bilimleri Üniversitesi Tıp Fakültesi etik kurulundan etik onayı almıştır (tarih:10.10.2023, etik kurul no. 2023/453).

İstatistiksel Analiz

Araştırmada elde edilen verilerin istatistiksel analizinde SPSS 26.0 programından yararlanılmıştır. Örneklemin demografik özellikleri tanımlayıcı istatistikler kullanılarak analiz edilmiştir. Tüm değişkenlerin normal olup olmadığını belirlemek için Shapiro–Wilk ve Kolmogorov–Smirnov testleri kullanıldı. İki grup arasında sayısal değişkenler karşılaştırmak için Student T testi veya Mann Whitney U testi kullanılmıştır. Değişkenler arasındaki korelasyonu belirlemek için parametrik değerler için Pearson korelasyon, parametrik olmayan veriler için Spearman korelasyon testi kullanıldı. İstatistiksel önemlilik düzeyi $p<0.05$ olarak kabul edilmiştir.

BULGULAR

Araştırmaya hasta sayısı 81, sağlıklı kontrol sayısı 60 olmak üzere toplamda 141 olgu alınmıştır. Yaş ortalamaları (p=0.973), cinsiyet dağılımı (p=0.076) ve anne-baba eğitim düzeyi (sırası ile p=0.087, p=0.117) açısından gruplar arasında anlamlı farklılık saptanmamıştır **(Tablo 1)**.

Tablo 1: Grupların Yaş, Cinsiyet, Anne-Babanın Eğitim Düzeyine Göre Değerlendirilmesi

		OSB (n=81)		Kontrol (n=60)		p
		Sayı	%	Sayı	%	
Cinsiyet	Kız	21	25.9	24	40.0	0.076
	Erkek	60	74.1	36	60.0	
Anne eğitim	İlkokul	13	15.9	6	10.0	0.087
	Ortaokul	14	17.1	5	8.3	
	Lise	27	32.9	17	28.3	
	Üniversite	27	32.9	32	53.3	
Baba Eğitim	İlkokul	8	9.8	4	6.7	0.117
	Ortaokul	14	17.1	6	10.0	
	Lise	27	32.9	14	23.3	
	Üniversite	32	39.0	36	60.0	
Yaş		40.43±1.39		40.26±1.88		0.973

n:olgu sayısı

ÇBDA içme tutkusu alt ölçeği (z = -2.87, p = 0.004), ÇUAA toplam puanı (z = -3.013, p = 0.003), ebeveyn BDÖ (z = -5.213, p < 0.001), ebeveyn BAÖ (z = 4.474, p < 0.001) toplam puanları hasta grubunda sağlıklı gruba göre istatiksel olarak anlamlı yüksek bulunmuştur. Hasta ve sağlıklı kontrol grubu arasında ÇBDA gıda heveslisi (z = -1.092, p = 0.272), ÇBDA duygusal aşırı yeme (z = -1.541b, p = 0.123), ÇBDA gıdadan keyif alma (t = -1.127, p = 0.262), ÇBDA tokluk heveslisi (t = -1.043, p = 0.299), ÇBDA yavaş yeme (z = -1.263, p = 0.207), ÇBDA duygusal az yeme (z = -1.82, p = 0.065), ÇBDA yemek seçiciliği (z = -2.038, p = 0.101) alt ölçeklerinin istatiksel olarak farklılık göstermediği bulunmuştur **(Tablo 2)**.

Tablo 2: OSB ve Kontrol Grubu Çocukların ÇBDA alt ölçek, ÇUAA, Ebeveyn BDÖ, Ebeveyn BAÖ Toplam Puanlarının Dağılımı

	OSB (n:81)		Kontrol (n:60)		t/z	p
	Ortalama	SS	Ortalama	SS		
ÇBDA gıda heveslisi	10.02	0.42	9.13	0.35	-1.092[b]	0.272
ÇBDA duygusal aşırı yeme	6.82	0.29	6.033	0.24	-1.541[b]	0.123
ÇBDA gıdadan keyif alma	15.92	0.55	16.78	0.46	-1.127[a]	0.262
ÇBDA içme tutkusu	9.2	0.78	6.93	0.35	-2.87[b]	0.004
ÇBDA tokluk heveslisi	20.01	0.56	20.85	0.53	-1.043[a]	0.299
ÇBDA yavaş yeme	10.19	0.42	9.4	0.51	-1.263[b]	0.207
ÇBDA duygusal az yeme	10.83	0.381	11.76	0.47	-1.82[b]	0.065
ÇBDA yemek seçiciliği	7.901	0.304	8.60	0.30	-2.038[b]	0.101
ÇUAA	51.43	0.9	47.06	0.93	-3.013[b]	0.003
Ebeveyn BDÖ	13.59	1.192	5.55	0.68	-5.213[b]	<0.001
Ebeveyn BAÖ	9.96	1.2	3.316	0.502	-4.474[b]	<0.001

SS: Standart Sapma, [a]Bağımsız Örneklem T Test, [b]Mann-Whitney U Test

ÇBDA: Çocuklarda Beslenme Davranışı Anketi, ÇUAA: Çocuklarda Uyku Alışkanlıkları Anketi, BDÖ: Beck Depresyon Ölçeği, BAÖ: Beck Anksiyete Ölçeği

Spearman korelasyon analizinde ebeveyn BDÖ toplam puanı ile ÇBDA duygusal aşırı yeme alt ölçek puanı (p=0.004), ebeveyn BDÖ toplam puanı ile ebeveyn BAÖ toplam puanı (p<0.001) arasında istatiksel olarak pozitif korelasyonlar elde edilmiştir **(Tablo 3)**.

Tablo 3: OSB Olan Çocukların ÇBDA Alt Ölçeği, ÇUAA toplam Puanlarının ÇODÖ, Ebeveyn BDÖ, Ebeveyn BAÖ Toplam Puanlarıyla Olan İlişkisinin Araştırılması

	ÇBDA gıda heveslisi		ÇBDA duygusal aşırı yeme		ÇBDA gıdadan keyif alma		ÇBDA içme tutkusu		ÇBDA tokluk heveslisi		ÇBDA yavaş yeme		ÇBDA duygusal az yeme		ÇBDA yemek seçiciliği		ÇUAA		Ebeveyn BDÖ		Ebeveyn BAÖ	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
ÇODÖ Toplam Puan	0.008	0.94	-0.04	0.68	-0.4	0.71	0.18	0.09	0.11	0.301	0.05	0.6	0.13	0.24	-0.005	0.96	0.10	0.34	-0.001	0.99	0.01	0.87
Ebeveyn BDÖ	0.17	0.12	0.22	0.04	0.17	0.11	0.06	0.59	-0.03	0.776	0.11	0.2	-0.14	0.19	-0.05	0.62	0.01	0.88		-	0.5	<0.001
Ebeveyn BAÖ	0.08	0.47	0.13	0.24	0.20	0.06	0.10	0.34	-0.003	0.98	-0.05	0.6	-0.05	0.64	-0.02	0.8	0.01	0.87	0.5	<0.001		-

ÇBDA: Çocuklarda Beslenme Davranışı Anketi, ÇUAA: Çocuklarda Uyku Alışkanlıkları Anketi, BDÖ: Beck Depresyon Ölçeği, BAÖ: Beck Anksiyete Ölçeği, ÇODÖ: Çocukluk Otizmi Derecelendirme Ölçeği

TARTIŞMA

Bu çalışmada, 18-60 ay arasındaki OSB tanısı alan çocuklarda ve sağlıklı kontrollerde beslenme davranışı, uyku sorunları, ebeveyn depresyon ve anksiyete düzeyleri arasındaki ilişki araştırılmıştır. Çalışmamızda, OSB tanılı çocuklarda kontrol grubuna göre uyku sorunlarının, içeceklere olan yönelimlerinin, ebeveyn depresyon ve anksiyete düzeylerinin anlamlı ölçüde yüksek olduğu saptanmıştır.

Bu çalışmada, OSB tanılı çocuklarda yapılan bazı çalışmalarla (24 - 26) benzer şekilde, OSB tanısı olan küçük çocuklarda uyku sorunlarını kontrol grubuna göre anlamlı düzeyde yüksek olduğu bulunmuştur. OSB tanılı çocukların ebeveynleri genellikle çocuklarının gece yatma saatine direndiklerini, uykuyu başlatmakta zorlandıklarını ve erken uyandıklarını ifade etmektedirler (24). Uyku bozukluklarının bireyin günlük işlevlerini olumsuz etkilenmesine ve bakım verenlere ek bir yük getirerek bireye karşı olumsuz tutumların gerçekleşmesine neden olabileceği öne sürülmektedir. Ayrıca davranış sorunlarının, iletişim sorunlarının ve stereotipik davranışlarının artışına neden olabileceği bildirilmektedir (7). Çalışmamız literature benzer şekilde OSB'de uyku sorunlarının erken çocukluk döneminde normal gelişim gösteren çocuklardan daha sık gözlemlendiğini göstermektedir. Bu bilgiler, uykunun OSB tanılı çocukların semptomlarının ortaya çıkışı, prognozu ve ebeveynleri ile olan etkileşimi açısından önemli olabileceği göz önüne alındığında, OSB tanılı çocuklarda uyku sorunlarını iyileştirmeye yönelik etkili stratejilerin bulunmasının önemli olabileceğini düşündürtmektedir.

Çalışmamızda ebeveyn depresyon ve anksiyete düzeyi OSB grubunda kontrol grubuna göre anlamlı olarak yüksek bulunmuştur. OSB'li çocuklarda uyku sorunlarının ebeveynler için oldukça zorlayıcı olduğu ve bu durum artan ebeveyn stresi, ebeveyn uyku bozukluğu ve ebeveynlerin kötü yaşam kalitesi ile ilişkilendirilmektedir (27). Bununla birlikte çalışmamızda OSB tanılı çocuklarda otizm şiddeti ile ebeveyn depresyon ve anksiyete düzeyleri arasında anlamlı bir ilişki bulunamamıştır. Bu durumun nedeni ebeveynin uyku sırasında çocuğunun uyku davranış-

larından tam olarak farkında olamayabileceği ve çocuğun uyku sorunlarını yanlış değerlendirmesinden kaynaklı olabileceği düşünülebilir (24, 28). Aynı zamanda çalışmamızda kullandığımız ölçüm araçları, çalışmaya dahil ettiğimiz yaş grupları ve ebeveyn psikopatolojisi çocuğun durumunu objektif değerlendirmesine engel oluşturmuş olabilir. Çalışmamızın sonucuyla uyumlu olarak bazı çalışmalar OSB tanılı çocukların ebeveynlerinin anksiyete ve depresyon düzeylerinin daha fazla olduğunu göstermektedir (12, 13). Yukarıdaki bilgiler ışığında, çalışmamız OSB tanılı ebeveynlerin ruh sağlığına yönelik önlemlerinin alınmasının gerekli ve önemli olabileceğini düşündürtmektedir.

Çalışmamızın kesitsel doğasının olması ve örneklem büyüklüğünün küçük olması çalışmamızın sınırlılığını oluşturmaktadır. Bu nedenle, bu çalışmanın daha büyük örneklemlerle yapılarak çoğaltılması gerektiği düşünülmektedir. Ayrıca çalışmamızın bir diğer kısıtlılığı da ölçeklerinin çocukların beslenme davranışlarını, uyku sorunlarını, ebeveynlerinin depresyon ve anksiyete düzeylerini ölçmek için kullanılmasıdır. Çalışmamızın güçlü yönü hasta ve kontrol grubunun çocuk psikiyatri hekimi tarafından muayene edilmesi, psikotrop ilaç kullanımı olmayan OSB tanılı hasta grubu ile çalışmanın oluşturulması ve komorbid durumların dışlanması sayılabilir.

Çalışmamızın bulguları, OSB tanılı küçük çocuklarda sağlıklı kontrollere göre uyku sorunlarının, içeceklere olan yönelimlerinin, ebeveyn depresyon ve anksiyete düzeylerinin daha yaygın olduğunu göstermektedir. Bu sonuçlar, OSB'li çocuklarda uyku sorunlarının iyileştirilmesine yönelik girişimlerin ve OSB'li çocukların ebeveynlerinin psikiyatrik sıkıntılarını hafifletmek için kullanılabilecek etkili strateji ve müdahale yöntemlerin geliştirilmesinin önemli olabileceğini düşündürtmektedir.

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Kocatepe Tıp Dergisi
Kocatepe Medical Journal
25:454-459/Ekim 2024 Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

GÖĞÜS CERRAHİSİNDE MULTİDİSİPLİNER YAKLAŞIM: 10 YILLIK ÇALIŞMA

MULTIDISCIPLINARY APPROACH IN THORACIC SURGERY: A 10 - YEAR STUDY

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ÖZET

AMAÇ: Multidisipliner yaklaşım her tıbbi bölümde olduğu gibi göğüs cerrahisi bölümünde de son derece önemlidir. Bu çalışmanın amacı, göğüs cerrahisi bölümünün multidisipliner yaklaşımdaki yerini ve diğer bölümlerle olan ilişkilerini konsültasyon kayıtları üzerinden ortaya koymaktır.

GEREÇ VE YÖNTEM: 01.01.2013 - 31.12.2022 tarihleri arasında (10 yıllık bir dönemde) Göğüs Cerrahisi Anabilim Dalı'ndan istenen konsültasyonlar ve Göğüs Cerrahisi Anabilim Dalı'nın istediği konsültasyonlar hastane bilgi yönetim sisteminden elde edilmiş ve tanımlayıcı istatistiksel yöntemlerle analiz edilmiştir.

BULGULAR: 01.01.2013 - 31.12.2022 tarihleri arasında göğüs cerrahlarından en çok konsültasyon talep eden bölüm 2793 (%38,78) konsültasyon ile acil servis olmuştur. Bu dönemde göğüs cerrahisi en çok anesteziyoloji ve enfeksiyon hastalıkları bölümlerinden konsültasyon talep etmiştir (n = 1638 (%29,97) ve 1104 (%17,42), sırasıyla).

SONUÇ: Göğüs cerrahisi travma ekibinin bir parçasıdır ve aynı zamanda akciğerin cerrahi hastalıklarını tedavi eden bölümdür. Bu nedenle özellikle acil servisler ve göğüs hastalıkları bölümleri tarafından göğüs cerrahisi konsültasyonu talep edilmektedir. Göğüs cerrahisi bölümü anesteziyoloji, göğüs hastalıkları ve kardiyoloji bölümleri ile yakın temas halindedir ve özellikle ameliyat öncesi değerlendirme için bu bölümlerden çok sık konsültasyon istenmektedir. COVID-19 ile bu preoperatif ekibe enfeksiyon hastalıkları da eklenmiştir.

ANAHTAR KELİMELER: Multidisipliner yaklaşım, Multidisipliner ekip, Göğüs cerrahisi, Konsultasyon.

ABSTRACT

OBJECTIVE: The multidisciplinary approach is extremely important in the thoracic surgery department, as it is in every medical department. The aim of this study was to reveal the place of the department of thoracic surgery in the multidisciplinary approach and its relations with other departments through consultation records.

MATERIAL AND METHODS: Consultations requested from the other departments (inbound) and by the thoracic surgery department (outbound) in a period of 10 years (January 1, 2013 and December 31, 2022) were obtained from the hospital information management system and analyzed by descriptive statistical methods.

RESULTS: In the 10-year period, the department that requested the most consultations from thoracic surgeons was the emergency department, with 2793 (38.78%) consultations. In this period, thoracic surgery mostly requested consultation from the anesthesiology and infectious diseases departments (n = 1638 (29.97%) and 1104 (17.42%), respectively).

CONCLUSIONS: Thoracic surgery is a part of the trauma team and is also the department that treats surgical diseases of the lung. Therefore, thoracic surgery consultation is requested especially by emergency services and chest diseases departments. The thoracic surgery department is in close contact with the anesthesiology, pulmonology, and cardiology departments and frequently requests consultation from these departments, especially for preoperative evaluation. With COVID-19, infectious diseases were also added to this preoperative team.

KEYWORDS: Multidisciplinary approach, Multidisciplinary team, Thoracic surgery, Consultation.

Geliş Tarihi / Received:12.02.2024
Kabul Tarihi / Accepted: 03.06.2024
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INTRODUCTION

A multidisciplinary approach refers to an integrated approach by medical and allied healthcare professionals to provide individualized treatment plans for patients. It involves the collaboration and coordination of multiple healthcare disciplines to improve patient outcomes and satisfaction (1). One of the best indicators of the relationship between medical departments, namely the multidisciplinary approach, is consultations. Consultation refers to the process in which the primary physician, who assumes the role of diagnosing and treating patients, seeks advice from physicians specializing in relevant fields regarding a specific matter pertaining to the patient. Through this process, the primary physician obtains additional knowledge and technical support (2).

Although there are many publications in the literature examining consultations in the departments of chest diseases (3, 4), emergency department (5, 6), general surgery (7), internal medicine (2), dermatology (8, 9), ophthalmology (10), plastic surgery (11), anesthesiology (12), physical medicine and rehabilitation (13, 14) and psychiatry (15), there are not many publications examining consultations in the field of thoracic surgery (16).

The objective of this study is to examine the role of the thoracic surgery department within a multidisciplinary framework and its interactions with other departments. Analyzing the consultations that the thoracic surgery department has requested and provided will help achieve this.

MATERIAL AND METHODS

Study Design

The records of the consultations made between January 1, 2013, and December 31, 2022 (10 years) from thoracic surgery to other departments and to the thoracic surgery department were retrieved as "bulk data" from the hospital information management system database used in our university hospital. Erroneous and incomplete records, cancelled records, and duplicate records were removed from the dataset and manually checked in the hospital information management system. Afterwards, the records obtained were divided into two groups; consultations from other departments to thoracic surgery (inbound consultations) and consultations from thoracic surgery to other departments (outbound consultations). The patient's age, gender, date, and department information were taken into consideration.

Ethical Committee

The study was approved by the local ethics committee (Code: 2011-KAEK-2, Meeting: 2023/2, No: 96).

Statistical Analysis

The data were collected with Microsoft Excel for Mac (Microsoft Corp., USA). Data analysis and figures were made using Python 3.9.13 with Pandas 1.4.4 and Seaborn 0.12.2 libraries. The results obtained from the study were presented using descriptive statistical methods (frequency, percentage, mean, and standard deviation).

RESULTS

After removing inappropriate consultation records, a total of 12667 consultation records were identified. It was determined that 7202 consultations were requested from the thoracic surgery department (inbound) and 5464 consultations were requested from the other departments (outbound) in about a 10-year period between January 1, 2013, and December 31, 2022. Annual inbound and outbound consultation distributions are shown in **(Figures 1)**.

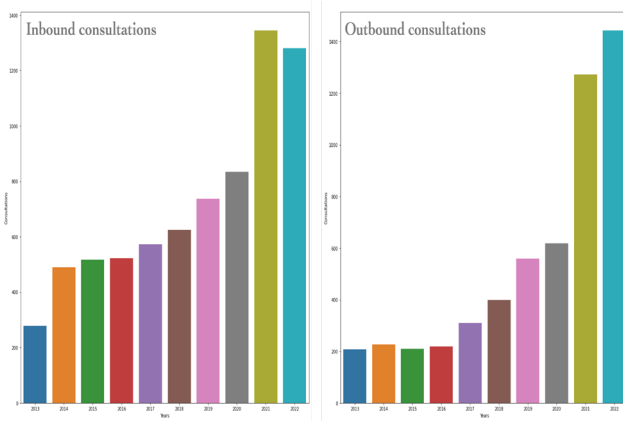

Figure 1: Annual inbound and outbound consultations

Of a total of 7202 inbound consultations, 68.12% were male and 31.88% were female patients (n = 4906 and 2296, respectively).

The mean age of the consulted patients was 52.97 ±19.51. For 5464 outbound consultations, 66.01% were male and 33.99% were female (n = 3607 and 1857, respectively). Detailed demographic information on inbound and outbound consultations was given in **Table 1**.

Table 1: Demographics of consultations

	Inbound		Outbound		Total	
	n	Age*	n	Age*	n	Age*
Male	4906 (68.12%)	52.24 ±19.52	3607 (66.01%)	56.20 ±17.95	8514 (67.21%)	53.92 ±18.97
Female	2296 (31.88%)	54.53 ±19.42	1857 (33.99%)	54.15 ±17.61	4153 (32.79%)	54.36 ±18.63
All	7202 (56.86%)	52.97 ±19.51	5464 (43.14%)	55.51 ±17.86	12667	54.06 ±18.86

* Mean and standart deviation

In the 10-year period, the department that requested the most consultations from thoracic surgeons was the emergency department, with 2793 (38.78%) consultations **(Table 2)**.

Table 2: Top 10 departments

Inbound	Outbound
Emergency Medicine (38.7%)	Anesthesiology (29.9%)
Pulmonology (15.3%)	Infectious Disease (17.4%)
Oncology (7.9%)	Cardiology (12.4%)
Anesthesiology (6.8%)	Pulmonology (11.4%)
General Surgery (5.5%)	Internal Medicine (3.4%)
Neurosurgery (5.0%)	Oncology (3.2%)
Orthopedics (3.7%)	General Surgery (3.1%)
Internal Medicine (3.0%)	Neurology (2.5%)
Hematology (1.4%)	Endocrinology (2.4%)
Cardiology (1.3%)	Neurosurgery (1.7%)
Others (11.4%)	Others (12.6%)

In the same period, thoracic surgery mostly requested consultation from the Anesthesiology and Infectious Diseases departments (n = 1638 (29.97%) and 1104 (17.42%), respectively). The distribution of the inbound and outbound consultations according to the departments is given in **(Figure 2)**.

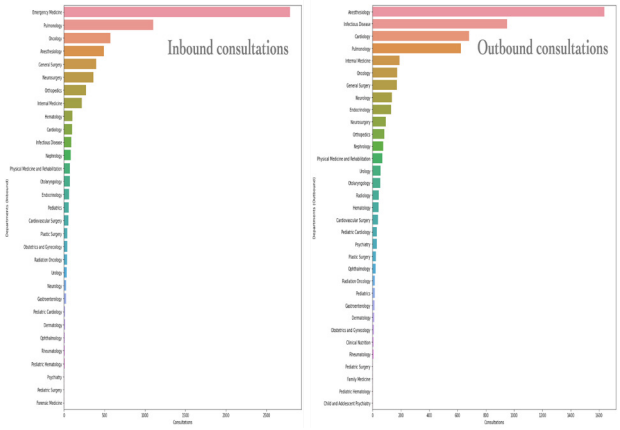

Figure 2: Distrubution of inbound and outbound consultations

The distribution of the first 5 departments with the highest number of consultations by years is shown in **(Figure 3)**.

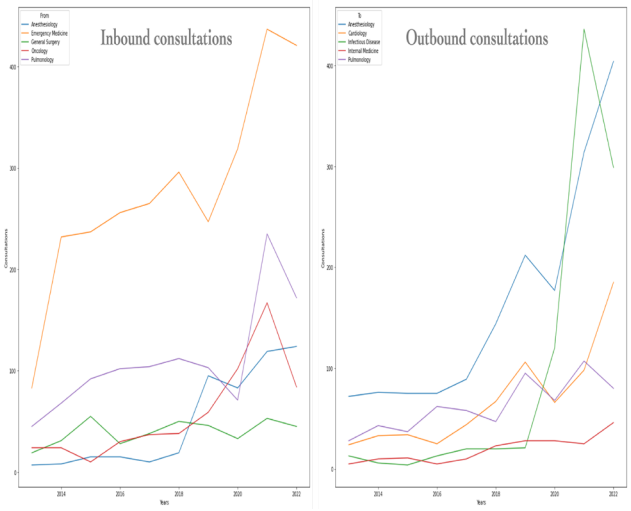

Figure 3: Annual distrubution of top 5 departments

DISCUSSION

The thoracic surgery department, which deals with the surgical treatment of respiratory diseases and anatomical structures in the thorax, often works in a multidisciplinary manner like other departments in medicine (17). Consultations are an important parameter in determining the relationships between medical departments. Therefore, consultations with thoracic surgery (inbound consultations) help us understand the place of thoracic surgery in the multidisciplinary team, and outgoing consultations help us show which medical departments thoracic surgery may need in the treatment of patients.

In the last 10 years, a total of 7202 consultation requests have been received from other departments for the thoracic surgery department in our university hospital. During the same period, the number of consultations requested by thoracic surgery from other departments was 5464.

The role of thoracic surgery in a multidisciplinary approach: inbound consultations

The thoracic surgery department is an important part of the multidisciplinary team in the treatment of surgical diseases of the respiratory system and in the evaluation of patients with thoracic trauma. In a study conducted by Çobanoğlu on 388 patients, the department that requested the most consultation from thoracic

surgery was the emergency department, with 50.5 percent (16). In the same study, pulmonology among internal departments (14.43%) and general surgery among surgical departments (7.98%) required thoracic surgery support in the treatment of patients (16). In a similar study published by Gedik et al. and covering the years 2014 - 2020, it was noted that the consultation request from the emergency service was almost as much as the sum of all other departments (512 vs 666, respectively) and 79.6% of the consultations were requested due to trauma (18).

Similarly, in our study, we found that the department that requests the most consultation from thoracic surgery is the emergency department, followed by the chest diseases department (38.8% and 15.3%, respectively). The sum of these two departments was more than half of all consultations requested.

The fact that trauma and thoracic emergencies are the areas where thoracic surgery is most needed explains the high demand from the emergency department. From the perspective of thorax trauma, although surgical intervention may be required in specific circumstances, conservative therapy, oxygen treatment, pain control, and monitoring are more commonly used (19). A study analyzing patients with emergency thoracic trauma found that non-surgical treatments were required in 72.3% of blunt traumas and 22.4% of penetrating traumas (20). Based on the findings of another study, tube thoracostomy emerged as the predominant approach for the management of chest injuries, with a substantial majority of patients (80.5%) undergoing this particular intervention (21). Since the available data did not include surgical procedures and medical treatments performed on patients in the emergency department, we could not draw a conclusion in this direction.

Furthermore, whether surgical or non-surgical, patients with lung conditions are first referred to pulmonology and then to thoracic surgery, which makes it reasonable for the pulmonology department to be in second place.

The oncology department ranked third with 7.9%. Patients with lung cancer may require thoracic surgery for both surgical restaging and pleural effusion. In addition, thoracic surgery support is important in the evaluation of thoracic masses in cancer patients.

In our university hospital, the majority of patients in need of intensive care are hospitalized in the anesthesia and reanimation department. A thoracic surgery evaluation may be required, especially for patients hospitalized in intensive care after cancer or trauma. Therefore, anesthesiology was the 4th most consulted department with 6.8%.

In our study, general surgery, neurosurgery, and orthopedics were the 5th, 6th, and 7th departments that requested thoracic surgery consultations (5.5%, 5.0%, and 3.7%, respectively). This is due to the fact that patients with thoracic trauma often have concurrent head trauma, abdominal trauma, and extremity trauma.

As a result, thoracic surgery is part of trauma-related departments such as the emergency department, anesthesia, general surgery, neurosurgery, and orthopedics. Thoracic surgery also collaborates with oncology and pulmonology in the evaluation of lung diseases and cancer patients. Thoracic surgery may also be frequently required in the treatment of trauma and cancer patients hospitalized in intensive care units in anesthesiology, pulmonology, oncology, general surgery, and neurosurgery departments.

Areas where thoracic surgery needs help: outbound consultations

Due to the difficulties in categorizing consultation reports, the purpose of outbound consultations could not be revealed in our study. However, since thoracic surgery is a surgical branch, most consultations were requested from anesthesia, pulmonology, and cardiology departments, probably for the preoperative evaluation of patients (29.9%, 12.4%, and 11.4%, respectively). Preoperative evaluation is essential to estimating postoperative outcome, optimizing medical therapy, and identifying the best perioperative strategy for the patient undergoing lung surgery (22). The preoperative evaluation and perioperative management of patients undergoing thoracic surgery require a multidisciplinary approach to assess the relative risks and benefits of surgery, optimize perioperative conditions, and plan the treatment regimen (23). The main

task of preoperative evaluation of surgical patients is undertaken by the anesthesiologist. However, many specialists (surgeon, pulmonologist, cardiologist, oncologist) are an important part of the multidisciplinary team in the risk assessment process (22). Similarly, in our study, anesthesiology, cardiology, and pulmonology were important departments in the preoperative evaluation.

The COVID-19 pandemic has had a significant impact on surgical procedures in thoracic surgery. Preoperative COVID-19 screening is crucial to ensure patient safety, reduce complications, and prevent transmission of the virus to healthcare workers and other patients (24). During the COVID-19 pandemic, preoperative COVID-19 screenings were performed by the infectious diseases department in our hospital. Therefore, the infectious diseases department has become a part of the preoperative team. Requesting an infectious diseases consultation from all patients to be operated on regardless of their medical condition, age, or medical status has made the infectious diseases department the second most requested consultation. The number of consultations (possibly due to preoperative consultations) has increased in recent years, corresponding to the increase in surgical procedures conducted in our department. However, it is clearly seen in Figure 4 that infectious disease consultations have increased much more due to the COVID-19 pandemic.

It should also be noted that, in addition to medical requirements, legal obligations and health strategies may also necessitate the consultation of another department. Even if there is no medical necessity, consultation can be requested from the thoracic surgery department just for legal procedures. Therefore, evaluating the medical relations between the departments based solely on the number of consultations may produce inaccurate results.

Similar to the literature (25), our study results show that the thoracic surgery department is a part of the trauma team. Thoracic surgeries are often needed in the emergency medicine and pulmonology departments. Moreover, the thoracic surgery department, which is a surgical department, is in close relationship with the anesthesiology, pulmonology, cardiology, and oncology departments and frequently requests consultation from these departments, especially in terms of preoperative evaluation. It is also obvious that infectious diseases have also joined this team with the COVID-19 pandemic. Therefore, although thoracic surgery seems like an isolated surgical department, it is part of the multidisciplinary team in patient treatment. We believe that these types of studies will also contribute to the planning of health services, but studies that include detailed data for the entire nation or are at least multi-centered will yield more accurate results.

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Kocatepe Tıp Dergisi
Kocatepe Medical Journal
25:460-465/Ekim 2024 Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

GÖĞÜS AĞRISI OLAN ÇOCUKLARDA AĞRI SKALASI KULLANIMI: KARDİYAK KÖKEN AÇISINDAN BİR GÖZLEM

USE OF PAIN SCALE IN CHILDREN WITH CHEST PAIN: AN OBSERVATION IN TERMS OF CARDIAC ORIGIN

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ÖZET

AMAÇ: Çocuk ve ergenlerde göğüs ağrısı genellikle kalp dışı nedenlere bağlıdır. Etiyolojinin ayırt edilmesinde temel varsayım kardiyolojik değerlendirmedir. Ağrının şiddeti ile kardiyolojik etiyolojisi arasındaki ilişki daha önce araştırılmamıştır. Bu çalışmada, çocuk kardiyolojisi polikliniğine göğüs ağrısı şikayeti ile başvuran çocuklarda ağrıyı daha iyi tanımlayabilmek için ağrı skalası, demografik-laboratuvar verileri, elektrokardiyografi ve ekokardiyografi bulguları, kardiyak orijinli göğüs ağrısı ile ağrı şiddeti arasındaki ilişki olduğu hipotezinden hareketle değerlendirmeyi amaçladık.

GEREÇ VE YÖNTEM: Bu çalışma üçüncü basamak çocuk hastanesi çocuk kardiyoloji polikliniğine başvuran 131 hasta ile gerçekleştirildi. Göğüs ağrısını sorgulamak için Wong-Baker Yüz Ağrısı Ölçeği kullanıldı.

BULGULAR: Çalışmaya 80 kız ve 51 erkek dahil edildi. Olguların yaş ortalaması 13,4±2,9 idi. Ekokardiyografik bulgular: %87,8'i normal, %12,2'si patolojik bulguya sahipti. En sık görülen kardiyak patoloji mitral kapak yetersizliğiydi (%4,6). Wong-Baker Faces ağrı skalasına göre hastalar en çok 4 puan (%29) ve 6 puan (%47,3) mimik gösterdi.

SONUÇ: Göğüs ağrısı olan çocuklarda ekokardiyografi sınırlı tanısal güce sahiptir. Bu çalışma ağrı ölçeği ile kardiyak patoloji arasında anlamlı bir ilişki tespit edemedi. Wong-Baker Yüz Ağrısı Ölçeği ile yapılan değerlendirme yetersiz olarak değerlendirildi.

ANAHTAR KELİMELER: Göğüs ağrısı, Kalp, Ekokardiyografi.

ABSTRACT

OBJECTIVE: Chest pain in children and adolescents is usually due to non-cardiac causes. The basic assumption in distinguishing the etiology is the cardiologic evaluation. The relationship between the severity of pain and its cardiologic etiology has not been investigated before. This study aimed to evaluate the pain scale, demographic-laboratory data, electrocardiographic and echocardiographic findings in order to better define pain in children who were admitted to the pediatric cardiology outpatient clinic with chest pain, based on the hypothesis that there is a correlation between chest pain with cardiac origin and pain severity.

MATERIAL AND METHODS: This study was carried out with 131 patients in the pediatric cardiology outpatient clinic of the tertiary pediatric hospital. The Wong-Baker Faces Pain Scale was used to inquire about chest pain.

RESULTS: 80 girls and 51 boys were included in the study. The mean age of the cases was 13.4±2.9 years. Echocardiographic findings: 87.8% were normal, 12.2% had pathological findings. The most common cardiac pathology was mitral valve regurgitation (4.6%). According to the Wong-Baker Faces pain scale, patients mostly showed 4 points (29%) and 6 points (47.3%) mimics.

CONCLUSIONS: Echocardiography has limited diagnostic power in children with chest pain. This study failed to detect any significant relationship between pain scale and cardiac pathology. The evaluation with the Wong-Baker Faces Pain Scale was assessed to be insufficient.

KEYWORDS: Chest pain, Heart, Echocardiography.

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Kabul Tarihi / Accepted: 03.06.2024
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INTRODUCTION

Chest pain in childhood is among the most common reasons for referral to pediatric emergency and pediatric cardiology outpatient clinics. Unlike adults, the probability of chest pain being cardiac in children is very low (1). When the causes of chest pain are examined, idiopathic (12-85%), followed by the musculoskeletal system (15-31%) and respiratory system (12-21%), while cardiologic causes are seen among (4-6%) (2). Although cardiologic causes are rare, the differential diagnosis should be made carefully, as the risk of morbidity and death is high, which worries the family a lot (3).

Pain has been defined as an unpleasant sensory and emotional experience or tissue damage that occurs in relation to actual or potential tissue damage (4). The general definition of pain also includes the evaluation of various parameters such as the severity, duration, and repetitive nature of the pain. While making the differential diagnosis of chest pain, the severity of the pain is usually not questioned. The relationship between pain severity and demographic findings and true heart-related pain has not been studied in the literature. There are many behavioral observational pain scales. The Wong-Baker Faces Pain Scale (WBFPRS) includes six hand-drawn facial expressions in the horizontal plane that can be used for children aged 3-18.

Patients try to indicate the pain they feel by looking at these statements. It symbolizes the phrase “no pain” with a smiley face on the far left. Pain intensity increases from left to right. On the far right, there is a face expression that represents the expression "unbearable pain", crying with tears (5). This study we aimed to evaluate the pain scale, demographic-laboratory data, electrocardiography (ECG) and echocardiography (ECHO) findings in order to better define pain in children who were admitted to the pediatric cardiology outpatient clinic with chest pain, based on the hypothesis that there is a correlation between chest pain with cardiac origin and pain severity.

MATERIALS AND METHODS

Study Protocol

This study was carried out in the pediatric cardiology outpatient clinic of the tertiary pediatric hospital between June 2020 and April 2021. All patients participating in our study detailed information was given and informed consent was requested. WBFPRS was used as an observational pain scale in this study. Demographic parameters such as age, gender, height, weight, and ECG, ECHO findings, and WBFPRS responses were obtained by filling in the "chest pain inquiry and evaluation form" together with the archive file records of 131 patients were admitted with chest of chest pain. Age, gender, height, weight, body mass index (BMI), percentile distribution of body mass index, seasonal distribution by time of hospital admission, character and duration of chest pain, recurrent pain, history of upper respiratory tract infection (URTI), relationship of pain with exercise, cessation of pain, presence of fainting, presence of palpitations, family history of heart disease at an early age were recorded as demographic data. Creatine kinase (CK-MB) and troponin I parameters, which indicate cardiac injury, were collected within the laboratory examinations.

Pain Scale

WBFPRS was used to question the chest pain **(Figure 1)**. The pain scale from left to right was shown to the patients in ascending order. Patients over 7 years of age were questioned to participate in the study regardless of gender. At the time of chest pain, they were asked to express the severity of the pain felt between 0-10 points on the scale.

Figure 1: The Wong-Baker Faces Pain Scale

Age Group

Patients were grouped according to their ability to express their age group was limited. Two groups were constituted with the expectation that chest pain would become more evident and their ability to express themselves would improve at the age of 12 and beyond. The first group was formed between the ages of 7-11, and the second group was between the ages of 12-18.

Cardiologic Evaluation

Electrocardiography recordings were performed using Nihon Kohden Cardiofax S device at 25 mm/sec and 10 mm/mV with 12 leads. All echocardiography measurements were made by a single physician with the Vivid 5S (General Electric Medical Systems) device.

Ethical Committee

The study protocol was approved by the local ethics committee (Adıyaman University Non-Interventional Clinical Research Ethics Committee. No. 2022/04-10, dated 20.04.2022).

Statistical Analysis

Statistical analysis were made with the Statistical Package for Social Sciences (SPSS Statistics for Windows, Version 24.0; IBM Corp., Armonk, NY, USA). Parametric numerical values were expressed as mean ± standard deviation. Student`s t-test was used to compare variables. Chi-square test was used for categorical variables. P value <0.05 was considered statistically significant. Pearson bivariate correlation analysis was performed for correlation between WBFPRS and other parameters. Kruskal-Wallis nonparametric analysis of variance was performed for ordinal variables.

RESULTS

A total of 131 cases, including 80 girls (61%) and 51 boys (39%), participated in this study. Fifty eight girls (44%) were 12 years and older. The mean age of the cases was 13.4±2.9 years. The patients were admitted to hospital most frequently in the autumn (42%) and summer (40.5%) months **(Table 1)**.

No statistically significant difference was detected in the comparison of WHPRS scores between age groups (p=0.95). Seven patients (5.3%) had weight below 3rd percentile and 9 patients (6.9%) had weight above 97th percentile. Two patients (1.5%) had height below 3rd percentile and 3 patients (2.3%) above 97th percentile **(Table 2)**.

Table 1: Characteristics of children with chest pain according to history and physical examination and distribution of pain scale scores

Parameter	WBFPRS score / Variants (%)	2	4	6	8	10	Total frequency N	P value
Gender	Male (39)	2	15	24	10	0	51	0.39
	Female (61)	2	16	39	19	4	80	
Season	Winter (14.5)	0	10	4	5	0	19	0.66
	Spring (3.1)	0	0	4	0	0	4	
	Summer (40.5)	1	14	25	10	3	53	
	Autumn (42)	3	13	24	14	1	55	
Pain Type	Squeezing (45)	2	15	30	10	2	59	0.93
	Sinking (41.2)	2	12	24	14	2	54	
	Combustion (13.8)	0	4	9	5	0	18	
URTI Presence	Yes (5.3)	0	3	4	0	0	7	0.49
	No (94.7)	4	28	59	29	4	124	
Pain Recurrency	Yes (89.5)	4	29	56	23	4	116	0.37
	No (11.5)	0	2	7	6	0	15	
Exercise Relation	Yes (25)	0	12	15	4	1	32	0.16
	No (75)	4	19	48	25	3	99	
Faint	Yes (2,3)	0	1	1	0	1	3	**0.036**
	No (97.7)	4	30	62	29	3	128	
Palpitation	Yes (49)	1	14	30	16	3	64	0.61
	No (51)	3	17	33	13	1	67	
Cardiological Pathology	Yes (12.2)	1	6	6	2	1	16	0.42
	No (87.8)	3	25	57	27	3	115	
ECHO Finding	Normal (87.8)	3	25	57	27	3	115	0.15
	AI (2.3)	0	1	2	0	0	3	
	MR (4.6)	1	1	2	1	1	6	
	MVP (3,8)	0	4	1	0	0	5	
	MVP-MR (1.5)	0	0	2	0	0	2	
Family history	Yes (13.1)	1	2	6	1	0	10	0.53
	No (86.9)	3	29	57	28	4	121	
ECG Finding	Normal (55.7)	1	22	32	15	2	73	0.44
	1st degree AV block (3.1)	0	0	2	2	0	4	
	RBBB (6.9)	1	1	5	2	0	9	
	Sinus bradycardia (2.3)	0	2	1	0	0	3	
	Sinus arrhythmia (13)	2	2	6	7	0	17	
	Long QT (1.5)	0	0	2	0	0	2	

Abbreviations in the Table 1: Mitral valve prolapse (MVP), aortic insufficiency (AI), mitral regurgitation (MR), mitral valve prolapse and mitral regurgitation (MVP+MR), Upper respiratory tract infection (URTI), echocardiography (ECHO), Right bundle branch block (RBBB).

Table 2: Distribution of age group, height and weight by age, BMİ, chest pain duration by pain scale scores.

	WBFPRS score / Variants (%)	2	4	6	8	10	Total frequency N	P value
Age Group	7-11 ages (23)	3	6	16	4	1	30	0.95
	12-18 ages (77)	1	25	47	25	3	101	
Height by Age	<3p (1.5)	0	0	1	1	0	2	0.36
	3-10p (9.2)	1	3	5	2	1	12	
	10-25p (7.6)	0	0	5	4	1	10	
	25-97p (74.8)	3	27	47	19	2	98	
	>97p (2.3)	0	1	1	1	0	3	
Weight by Age	<3p (5.3)	0	1	2	2	2	7	0.22
	3-10p (11.5)	0	6	4	5	0	15	
	10-25p (14.5)	2	1	11	4	1	19	
	25-97p (57.3)	2	21	38	13	1	75	
	>97p (6.9)	0	2	4	3	0	9	
BMI	Underweight (4.6)	0	2	2	2	0	6	0.98
	Normal weight (80.2)	4	24	51	22	4	105	
	Overweight (5.3)	0	5	2	0	0	7	
	Obese (5.3)	0	0	4	3	0	7	
Duration of Pain	<1 min (16)	1	6	9	4	1	21	0.2
	1-5 min (54.2)	3	20	34	13	1	71	
	5-10 min (14.5)	0	3	9	7	0	19	
	10-60 min (10.7)	0	2	11	0	1	13	
	>60 min (4.6)	0	0	0	5	1	6	

Based on BMI, 6 patients (4.6%) were underweight, 105 patients (80.2%) had normal weight, 7 patients (5.3%) were overweight, and 7 patients (5.3%) were obese. There was no statistical relationship between BMI and WBFPRS values (p=0.98). Fifty-nine patients (45%) described stinging pain and 54 (41.2%) patients described burning pain. About 16% of patients had chest pain for less than 1 minute and 54.2% of the

patients highlighted the duration of chest pain as 1-5 minutes. While 14.5% of patients had chest pain for 5-10 minutes, 4.6% of patients expressed chest pain for 60 minutes at least.

Only 5.3% of the cases had Upper respiratory tract infection (URTI). Although 116 patients (88.5%) stated that the pain recurred, 15 patients (11.5%) noted that they had pain for the first time. About 25% of the patients associated chest pain with exercise. While 49% of the patients felt palpitations during chest pain and 2% of the patients experienced fainting.

ECHO findings were abnormal in 12.2% of the patients. About 35% of the patients had a previous ECHO examination. Seven percent of the participants had a family history of heart disease before the age of 35. The ECG samples were normal in 55% of the patients whereas 2 patients had QT intervals longer than normal. According to the WBFPRS, 29% of the patients showed facial expression 4 and 47.3% of the patients demonstrated facial expression 6 (Table 1).

There was a statistically significant difference between the presence of fainting and the pain scale (p=0.03). No correlation was indicated between pain duration and scale (p=0.2), (Tables 1 and 2).

DISCUSSION

Although chest pain is a common disorder in children and adolescents, it is less associated with heart diseases in children, unlike adults (2). In a comprehensive study that lasted for about 10 years and was conducted with 3700 patients, the causes of chest pain were idiopathic in 52%, musculoskeletal system in 36%, while cardiovascular system disease was found in only 1% of patients (6). Similar studies have found similar rates (1-7%) (2, 3). In our study, 87.8% of the patients with chest pain and ECHO were evaluated as normal and 12.2% as pathological. The most common cardiac pathology was mitral regurgitation (MR) (4.6%) and mitral valve prolapse (MVP) (3.8%). Other cardiac pathologies were aortic regurgitation (AR) (2.6%) and MVP+ MR (1.6%).

This study reported that cardiac causes in the etiology of chest pain were proportionally higher than in recent studies (2, 3, 6). This finding might be attributed to the initial application of the patients to the pediatric emergency services, and the patients are referred to the pediatric cardiology outpatient clinic for further examination after the general evaluation and cardiac examinations are performed. That is, the patients who had their cardiac enzymes measured at the emergency department and found within normal range might not have admitted to outpatient clinics of pediatric cardiology.

The use of ECHO in the evaluation of cardiac causes of chest pain in children has little diagnostic value. It causes unnecessary cost to the parent and the healthcare system. A poorly selected caseload can cause physical and psychological wear and tear for all healthcare professionals. Gibbons et al. showed that there is was no need for ECHO examination in patients with chest pain due to its low detection rate (7).

Güvenç et al. reported that the population presenting with chest pain consisted mostly of adolescents aged 12-14 years (8). In this study, the mean age of the population was similar. Moreover, In this study, it was observed that chest pain was more common in girls (61%) than boys (39%). However, this finding was not statistically significant. There were similar male-female ratios in other Turkish studies (9, 10). However, literature indicates significantly higher frequency of chest pain in boys than girls (11). Similar to literature, 77% of the patients in this study were adolescents. It has been reported that especially psychogenic chest pain is more common in adolescent girls (12).

Recent studies have indicated that the frequency of chest pain is increased in obese children (13). In this study, 5.3% of the patients were overweight and 5.3% of them were obese. In addition, there was no significant relationship between obesity and either duration or severity of chest pain. This finding can be due to the insufficient presentation of obese patients within the cohort.

The most common form of chest pain in children is squeezing pain. In this study, 45% of the patients described squeezing pain, 41.2% of them had stinging pain, and 13.8% of the patients revealed burning pain. On the contrary,

Tiryaki et al. reported that nearly 71% of the pediatric patients had stabbing-stinging pain (14).

In this study, admission to the outpatient clinic of pediatric cardiology was the most frequent in autumn and summer seasons and the least common in winter season. COVID-19 pandemic is the probable underlying reason for this finding. Measures such as curfew and home isolation due to the pandemic in the last spring and winter months may have prevented the emergence of the patients with non-cardiac chest pain, especially infectious ones. According to previous studies, the admission rate of the patients with chest pain changes by seasons and non-specific infectious chest pain is more frequent than expected. In pediatric studies, the duration of chest pain is generally addressed as 0-5 minutes. As for the present study, 54.2% of the patients felt pain for 1-5 minutes. Aygun et al. found that 26.7% of the patients had chest pain up to 1 minute and 47.3% of the patients had chest pain for 1-10 minutes (15). Çağdaş et al. designated that 85.8% of the patients experienced chest pain for 0-5 minutes (16).

In case of chest pain with cardiac etiology, short-term pain was observed to be at the forefront, as in the noncardiac pain group (mostly 1-5 minutes). The length of time also did not appear to be useful in distinguishing cardiac origin.

URTI is involved in the etiology of chest pain in children. In other words, URTI was accompanied by chest pain in 5.3% of the patients. It can be expected that patients admitting to outpatient clinics of pediatric cardiology complain about the recurrence of pain. While 88.5% of the patients stated that the pain recurred, Exercise-related chest pain, which is considered more significant for chest pain of cardiac origin, constitutes approximately one-fourth of the applications in childhood and adolescence. Similarly, 25% of the patient in our study had chest pain associated with exercise. While 49% of the patients had palpitations during chest pain, 2% of them experienced fainting. Çağdaş et al. found the frequency of URTI as 16.7%, palpitations as 28.3%, and syncope/presyncope as 13.3% (16). Nevertheless, Aygun et al. specified exercise-related chest pain in 5.5% of the pediatric patients (15). The most accurate explanation of pain is possible with the person's self-expression. Unlike adults, children do not have sufficient communication and expression skills for describing the characteristics of the pain they feel. That's why, methods that do not require communication skills are recommended to allow the expression of pain by children. WBFPRS is one of the pain scales that have been adopted to determine the severity of both acute and chronic pain between the ages of 3 and 18 (5).

Young children tend to exaggerate the scale because of the crying visual. Therefore, the majority of the cohort in this study has been made up by adolescents and statistical analysis has been performed on the basis of age groups. The findings with respect to age complied with a previously published study (17).

As a result, the number of patients referred to the outpatient clinic of pediatric cardiology due to chest pain, both by emergency and pediatricians, continues to make up the majority of the applications. However, Ertürk et al. concluded that the incidence of chest pain was 2.4% among the patients admitted to the outpatient clinic of pediatric cardiology (18). Although cardiac pathologies constitute the minority for the causes of chest pain, this is a mostly disturbing and distressing symptom for both the patients and their parents. Pediatric patients who have acute onset chest pain which is unrelated with exercise, fainting, family history of heart disease should not be referred to a pediatric cardiologist if there are no pathological findings in physical examination and ECG samples. Otherwise, there would be financial burden and unnecessary anxiety in the patients and their families. WBFPRS was assessed to be insufficient for the evaluation of chest pain in children and adolescents.

Limitations of the study, the power of the present study is limited by relatively small cohort size, absence of other pain scales as well as heterogeneity in demographic and clinical characteristics. Another limitation is the conductance of this study during seasons which coincide with COVID-19 pandemic.

ACKNOWLEDGEMENTS

We would like to thank all the nurses who informed us about the use of the pain scale and provided an infrastructure for our study.

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Kocatepe Tıp Dergisi
Kocatepe Medical Journal
25:466-475/Ekim 2024 Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

ARI EKMEĞİNİN ALZHEİMER SIÇAN MODELİNDE KARACİĞER 5HT2B ARACILI GLUKOZ DÜZENLEMESİ ÜZERİNE ETKİSİ

EFFECT OF BEE BREAD ON LIVER 5HT2B-MEDIATED GLUCOSE REGULATION IN ALZHEIMER'S RAT MODEL

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ÖZET

AMAÇ: Bu çalışmada Alzheimer hastalığının (AH) sıçan modelinde arı ekmeğinin insülin, serotonin (5-hidroksitriptamin, 5-HT) ve leptin hormonlarında meydana getireceği değişimin glukoz regülasyonu ve kilo değişimi üzerindeki etkisinin incelenmesi amaçlanmıştır.

GEREÇ VE YÖNTEM: Alzheimer hastalığı sıçan modeli, lateral ventriküllere intraserebroventriküler (i.c.v.) Streptozotosin (STZ) enjeksiyonu yoluyla oluşturuldu. Arı ekmeği uygulaması, STZ enjeksiyonundan sonra 3 hafta boyunca oral gavaj ile gerçekleştirildi. Plazmada leptin, insülin, 5-HT düzeyleri ile karaciğer dokusunda leptin, insülin, 5-HT, 5HT reseptör 2B (5HT2B), glukoz taşıyıcı 2 (GLUT2), glukoz 6-fosfataz (G6paz) düzeyleri Elisa kit ile ölçüldü. Açlık kan glukoz düzeyleri glukometre kullanılarak ölçüldü ve İnsülin Direnci İçin Homeostatik Model Değerlendirmesi (HOMA-IR) düzeyleri formül kullanılarak hesaplandı. Her bir sıçanın ağırlık değişimi, başlangıç ağırlıklarının son ağırlıklarından çıkarılmasıyla hesaplandı.

BULGULAR: AH grubunda bulunan sıçanların açlık kan glukoz, plazma insülin ve HOMA-IR düzeyleri ile karaciğer 5-HT, plazma 5-HT ve leptin düzeylerinin azaldığı, karaciğer 5-HT2B ve GLUT-2 düzeyleri ile kilo kaybının arttığı görüldü. Arı ekmeği tedavisinin bu hayvanlarda karaciğer 5-HT2B, G6paz düzeyleri ve plazma leptin düzeylerini önemli ölçüde artırdığı, ayrıca plazma 5-HT, karaciğer 5-HT ve GLUT-2 düzeyleri ile kilo kaybını belirgin şekilde artırdığı görüldü. Ayrıca arı ekmeğinin plazma insülin düzeyini etkilemeden açlık kan glukoz düzeylerini azalttığı saptandı.

SONUÇ: Bu sonuçlar, AH grubundaki sıçanların karaciğer dokusunda glukoz metabolizmasının anti-diyabetik savunma sistemi oluşturacak şekilde modüle edildiğini gösterdi. Arı ekmeği uygulamasının Alzheimer oluşturulmuş sıçanlarda leptin aracılı insülin duyarlılığını artırarak açlık kan glukoz düzeylerini azalttığı saptandı.

ANAHTAR KELİMELER: Alzheimer hastalığı, Karaciğer, Arı Ekmeği, 5-HT2B, Leptin.

ABSTRACT

OBJECTIVE: This study aimed to examine the effect of bee bread on glucose regulation and weight change through the change of insulin, serotonin (5-hydroxytryptamine, 5-HT), and leptin hormones in the rat model of Alzheimer's disease (AD).

MATERIAL AND METHODS: Alzheimer's disease rat model created via intracerebroventricular (i.c.v.) Streptozotocin (STZ) injection into the lateral ventricles. Beebread administration was performed with daily gavage for three weeks after the STZ injection. Leptin, İnsulin, 5-HT levels in plasma and leptin, insulin, 5-HT, 5HT receptor 2B (5HT2B), glucose transporter 2 (GLUT2), glucose 6-phosphatase (G6pase) levels in liver tissue were measured with Elisa kit. Fasting blood glucose levels were measured using a glucometer, and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) levels were calculated using the formula. Each rat's weight change was calculated by subtracting their initial weight from their final weight.

RESULTS: In the AD-created rats, ıt was observed that blood glucose, plasma insulin, and HOMA-IR levels, liver 5-HT, plasma 5-HT, and leptin levels decreased, liver 5-HT2B and GLUT-2, and weight loss increased. In the AD-created rats, bee bread treatment significantly increased liver 5-HT2B, liver G6pase levels, and plasma leptin levels, also markedly increased plasma 5-HT, liver 5-HT, GLUT-2, and weight loss levels, and decreased fasting blood glucose levels without affecting plasma insülin levels in the AD group.

CONCLUSIONS: These results showed that glucose metabolism was modulated to generate an anti-diabetic defense system in the liver tissue of AD-created rats. Beebread administration reduced fasting blood glucose levels by increasing leptin-mediated insulin sensitivity in the AD-created rats.

KEYWORDS: Alzheimer's disease, Liver, Bee Bread, 5-HT2B, Leptin.

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Kabul Tarihi / Accepted: 03.06.2024
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Etik Kurul / Ethical Committee: Akdeniz Üniversitesi Kurumsal Hayvan Bakımı ve Kullanım Komisyonu (ID:1619/2023.08.005).

INTRODUCTION

Alzheimer's disease (AD) is characterized by accumulations of extracellular amyloid β-peptides (Aβ) and intracellular hyperphosphorylated tau (phospho-tau) proteins (1, 2). Aβ production is a physiological process, and the imbalance between Aβ production and clearance is essential in AD development. Recent evidence showed that most of the brain Aβ in the brain can be transported to the periphery (3), and most Aβ is cleared in the liver. Therefore, the first organ affected by AD pathology is the liver. The liver is the primary organ for maintaining peripheral glucose metabolism (4). Disruption of peripheral glucose metabolism leads to glucose metabolism disruption in the central nervous system and increased Aβ toxicity, Tau hyperphosphorylation, oxidative stress, neuroinflammation, and neurodegeneration (5). Therefore, well-coordinated hepatic glucose metabolism is crucial for health. Control of hepatic glucose metabolism is achieved by a complex integration of hormones produced in various tissues (6).

Serotonin (5-hydroxytryptamine or 5-HT) is derived from tryptophan. There are two separate 5-HT pools in the body, both central and peripheral (7). Peripheral 5-HT has complex effects on peripheral glucose regulation (8). Peripheral 5-HT encourages gluconeogenesis by fructose 1,6-bisphosphatase (FBPase) and glucose 6-phosphatase (G6pase), which are rate-limiting enzymes in gluconeogenesis through HTR2B during fasting in hepatocytes. In addition, 5HTR2B signaling promotes the degradation of glucose transporter 2 (GLUT2) in hepatocytes and prevents glucose uptake (9). Additionally, increased food intake increases peripheral 5-HT production, resulting in insulin secretion and leptin release. Leptin both increases insulin sensitivity in skeletal muscle and increases glucose uptake, glucose oxidation, and glycogen synthesis with insulin-like effects (10). It also acts as a key regulator of body weight and fat stores by modulating food intake and metabolism (11). However, Muck-Seler D et al. show that low platelet 5-HT concentration in the late stage of AD may indicate the severity and/or clinical progression of AD (12). Thus, modulation of the 5HT network may be an approach to ensuring peripheral and central glucose regulation in Alzheimer's disease.

Bee bread (Perga) is a fermented form of pollen collected by the honey bee and stored in the honeycomb (13). A recent study found that bee bread affected glycemic conditions, lipid profile, and hepatic functions in diabetic rats (14). It is thought that the rich nutrient content and positive health effects of bee bread, which is a functional food (13), will have an important impact on AD. In this study, we propose to explore the effects of 5-HT-5HT2B on body weight and hepatic glucose metabolism in the AD rat model. We also investigate whether bee bread can impact these changes.

MATERIALS AND METHODS

Animals and Treatment

Male albino Wistar rats aged three months were used throughout all experiments. During all experimental processes, animals were housed in steel cages under standard conditions and given standard rat chow and tap water ad libitum (humidity 50 ± 5% and 23 ± 1 °C) with 12:12 h light-dark cycles at all times. Streptozotosin (STZ, (2-deoxy-2(([methyl(nitroso)amino]carbonyl)amino)-(α and β)-D-glucopyranose) was purchased from Santa Cruz Biotechnology (catalog number: sc-200719). STZ solutions used in our study were prepared depending on previous studies. First, the body weight of animals was measured and noted. Then, the amount of STZ required for each rat was weighed individually in microcentrifuge tubes according to body mass. For example, 1.05 mg of STZ should be weighed and then diluted in 6 µl citrate buffer (0,05M) for a 350 g rat. This prepared solution corresponds to a dose of 2 mg/kg (15). Bee bread was purchased from Nutral Therapy (Nutral Therapy, Kayseri, Türkiye). The bee bread solution used in our study was prepared using capsules containing 800 mg of bee bread. Bee bread capsules are water-soluble. A bee bread capsule was dissolved in 20 ml of tap water to obtain a bee bread solution at a concentration of 40 mg/ml. The weight of each rat was determined, and the bee bread solution was administered by oral gava-

ge. Bee bread solutions used in our study were prepared based on previous studies (13, 16, 17).

Experimental Procedure

The animals were randomly divided into four groups (n = 6 for each group). Sham group (SH) received 2 µl citrate buffer (2µl/ventricle) via intracerebroventricularly (i.c.v) injection. On the 7th day, tap water was given by oral gavage for 21 days; (2) Bee bread (SHP) group received 2 µl citrate buffer (2µl/ventricle) via i.c.v. Injection. On the 7th day, bee bread solution was given by oral gavage for 21 days; (3) Alzheimer's disease (AD) group received two µl of STZ (STZ; 2mg/kg, 2µl/ventricle) via i.c.v. Injection and on the 7th day, tap water was given by oral gavage for 21 days; (4) Bee bread (perga) + AD group (ADP) received two µl of STZ (2mg/kg, 2µl/ventricle) via i.c.v. Injection. On the 7th day, bee bread solution by oral gavage for 21 days. The weight of the animals was recorded at the beginning and end of the experimental processes. To calculate weight gain, we subtracted the initial weight measurement from the final weight measurement of each rat. On the last day, feeding to the animals was stopped 12 hours before to measure fasting blood sugar.

Surgery Protocol

The animal model for Alzheimer's Disease (AD) was created according to a previously published protocol (15). Rats were anesthetized using intraperitoneal injections of ketamine (80 mg/kg) and xylazine (5 mg/kg). Afterward, the skulls were placed in a stereotaxic apparatus for skull surgery. Fasting blood glucose levels are measured with blood taken from the tail vein by glucometer (plusMED Blood GlucoseMeter, Accuro, pM1-300, Bionime Corporation, Taiwan) (5). Standard procedures were followed to sterilize a middle sagittal incision in the scalp. A dental drill was used to create bilateral holes in the skull over the lateral ventricles (AP: −0.8 mm, ML: ±1.4 mm, DV: −3.6 mm). Rats in the AD and ADP groups were given an i.c.v. Injection of 2 µl STZ (1 µl/min) and the SH and SHP groups were given an injection of 2 µl citrate buffer into the ventricle. The surgery had come to an end; the wound on the scalp was stitched up, and sulfamethoxazole was applied to prevent any infections. Additionally, penicillin (40,000 U) was applied to the gluteus muscle once a day for three days. After a week, the administration of substances through oral gavage began. The SH and AD groups were given tap water by oral gavage for 21 days, while the SHP and ADP groups were given bee bread solution (200 mg/kg/day) by oral gavage for 21 days (13, 17).

Tissue Collection and Biochemical Analysis

At the end of the experimental period, rats were anesthetized with ketamine (80 mg/kg, i.p.) and xylazine (5 mg/kg, i.p.). The blood samples were collected from their veins into tubes containing ethylenediaminetetraacetic acid (EDTA). The liver tissues were excised, flash-frozen in liquid nitrogen, and stored at -80°C for biochemical analysis. Tissue samples were homogenized in cold phosphate-buffered saline (PBS), centrifuged at 10,000×g for 5 minutes, and the resulting supernatants were stored at -80 °C for protein assays. Plasma was obtained by centrifuging the blood samples at 3000 rpm for 15 minutes at 2-8°C within 30 minutes after collection. 5-HT, 5HT2BR, Leptin, G6Pase, GLUT2 and insülin levels in the samples were measured with ELISA Kits (Sunred Biological Technologies Rat 5-HT ELISA Kit, Catalog No: 201-11-1683; Rat 5HT2BR ELISA Kit, Catalog: SRB-T-84698; Rat G6Pase ELISA Kit, Catalog No: SRB-T-84846; Rat GLUT2 ELISA Kit, Catalog No: 201-11-5377; Rat Insulin ELISA Kit, Catalog No: 201-11-0708; Rat Leptin ELISA Kit, Catalog No: 201-11-0261, China). Standard curves were created with the absorbance values of known amounts of standards. The results were expressed as pg/mg tissue protein for leptin levels, ng/mg tissue protein for 5-HT, GLUT2 and G6Pase, ng/g tissue protein for 5-HT2BR, and mIU/L for insulin levels. The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) evaluation was calculated using the following formula: insulin (mIU/L) multiplied by fasting blood glucose (mM) divided by 22.5 (18).

Protein measurements: Protein concentrations were quantified by modified Bradford assay (19).

Ethical Committee

Experimental procedures were performed following the guidelines established by the Institutional Animal Care and Use Committee at Akdeniz University (approval ID:1619/2023.08.005).

Statistical Analysis

The data obtained was analyzed using SPSS 23.0 (SPSS, Chicago, IL, USA) software for Windows. For normally distributed variables, a one-way ANOVA followed by Tukey's Post Hoc Test was used to analyze the biochemical parameters. For non-normally distributed variables, Kruskal-Wallis followed the Mann-Whitney U test was used.

RESULTS

Fasting Glucose Levels

Statistical analysis revealed a significant difference in the fasting glucose levels among the various groups, $X^2(3) = 8.405$, $p = 0.038$ **(Figure 1)**.

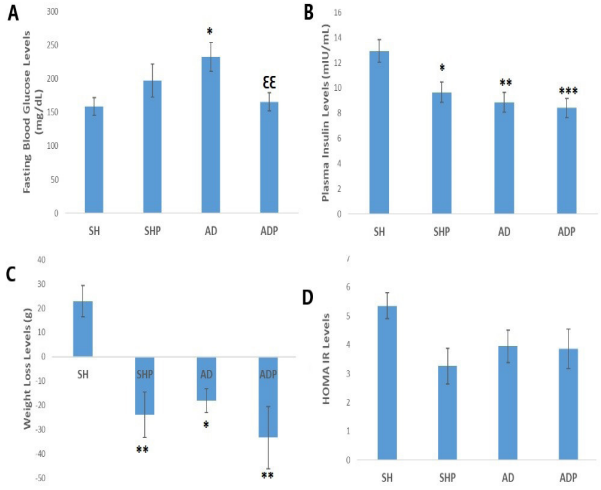

Figure 1: Plasma fasting blood glucose levels in SH and experimental groups. Statistical analysis was by Kruskal Wallis One Way Analysis of Variance on Ranks and all pairwise multiple comparison procedures were done by Mann-Whitney U test. B: Serum insulin levels in SH and experimental groups. C: Weight loss levels in SH and experimental groups. D: HOMA-IR levels in SH and experimental groups. Statistical analysis was by one-way analysis of variance (ANOVA) followed by Tukey's Post Hoc Test. All values are mean ± SEM and n=6 for each group. *, p<0,05 vs sham; **, p<0,01 vs sham; ***, p<0,001 vs sham; εε p<0,01 vs AD.

Fasting glucose levels are shown in **Table 1**. The AD group had significantly higher plasma glucose levels compared to the SH group (U:3, p=0.016). The administration of bee bread resulted in a marked increase in plasma fasting glucose levels of the SHP group as compared to the SH group, but the observed trend was not statistically significant (U:11.5, p=0.296). Additionally, the administration of bee bread significantly decreased plasma glucose levels of the ADP group in comparison with the AD group (U:1.50, p=0.008).

Table 1: Biochemical analysis results of the groups.

Parameters/Groups	AD Group	ADP Group	SH Group	SHP Group
Fasting Glucose Levels	232,50±21,662*	165,67±13,363$^{\varepsilon\varepsilon}$	158,67±13,152	197,33±24,41
Plasma Insulin Levels	8,866±0,796**	8,408±0,749***	12,934±0,8752	9,654±0,81*
Analysis of Weight Loss Levels	-18,00 ±4,926*	-33,33±12,80**	22,83 ± 6,405	-23,83 ± 9,38**
HOMA-IR Levels	3,947±0,566	3,853±0,690	5,352±0,4531	3,259±0,61
Liver 5-HT Levels	1,199±0.075**	1,700±0.164	1,950 ± 0.213	1,149±0.08**
Plasma 5-HT Levels	35,015±1,903**	42,476±4,894	44,142±1,034	39,539±1,23*
Liver 5-HT2BR Levels	16,489±1,67*	34,250±6,32**#$^{\varepsilon}$	9,569±2,150	17,561±2,63*
Liver GLUT-2 Levels	0.440±0.038*	0.503±0.034**	0.250±0.029	0.445±0.065*
Liver Glucose 6 Phosphatase Levels	0,296±0,033#	0,895±0,091***#$^{\varepsilon\varepsilon\varepsilon}$	0,289 ± 0,040	0,583±0,091*
Plasma Leptin Levels	198,61± 14,73***	267,59±11,52#$^{\varepsilon}$	294,07±19,92	199,16 ± 12,80***

All values are mean ± SEM and n=6 for each group. *, p<0,05 vs sham; **, p<0,01 vs sham; ***, p<0,001 vs sham; #, p<0,05vs. SHZ; ε, p<0,05 vs AD; εε, p<0,01 vs AD; εεε, p<0,001 vs AD. 5-HT, 5 hydroxytryptamine; 5-HT2BR, 5-hydroxytryptamine receptor 2 B; GLUT2, glucose transporter 2.

Plasma Insulin Levels

Statistical analysis revealed a significant difference in the levels of plasma insulin between various groups, F (3.20) = 6.378, p =0.003 Figure 1. Plasma insülin levels are shown in Table 1. The AD group had significantly lower plasma insulin levels when compared to the SH group (p=0.010). The administration of bee bread showed a significant reduction in plasma insulin levels in the SHP group when compared to the SH group (p=0.044). Additionally, the administration of bee bread slightly decreased the plasma insulin levels of the ADP group in comparison with the AD group(p=0.978).

Analysis of Weight Loss Levels

According to statistical analysis, there was a significant difference in the levels of weight loss across the various groups, F (3.20) = 7.734, p =0.001 Figure 1. The body weight levels are shown in Table 1. The body weight levels of the AD group were significantly reduced compared to the SH group (p=0.020). The administration of bee bread significantly decreased the body weight levels of the SHP group when compared to the SH group (p=0.044). Additionally, the administration of bee bread markedly decreased the body weight levels of the ADP group in comparison to the AD group (p=0.644). However, this decreasing trend did not reach the level of significance.

Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) Levels

There was no significant difference in the levels of HOMA-IR observed in the different groups, F (3.20) = 2.273, p =0.111 (Figure 1D). The HOMA-IR levels are shown in Table 1. The AD group

showed lower levels of HOMA-IR as compared to the SH group. Administration of bee bread showed a marked decrease in HOMA-IR levels of the SHP group as compared to the SH group. However, this decreasing trend did not reach a significant level. The administration of bee bread did not affect HOMA-IR levels in the ADP group as compared to the AD group.

Liver 5-HT Levels

Statistical analysis revealed a significant difference in the levels of liver 5-HT between various groups, F (3.20) = 7.050, p =0.002 **(Figure 2)**. Liver 5-HT levels are shown in Table 1. The liver 5-HT levels were found to be significantly lower in the AD group as compared to the SH group (p=0.009). The use of bee bread in the SHP group significantly reduced liver 5-HT levels in comparison with the SH group (p=0.005). On the other hand, the administration of bee bread markedly increased liver 5-HT levels in the ADP group compared to the AD group, although the trend did not reach the level of significance (p=0.107).

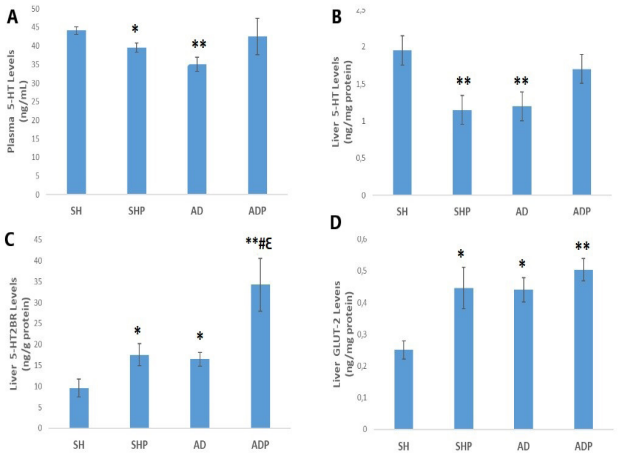

Figure 2: Livers 5-HT levels in SH and experimental groups. Statistical analysis was by one-way analysis of variance (ANOVA) followed by Tukey's Post Hoc Test. B: Plasma 5-HT levels in SH and experimental groups, and C: Livers 5-HT2B levels in SH and experimental groups. Statistical analysis was by Kruskal Wallis One Way Analysis of Variance on Ranks and all pairwise multiple comparison procedures were done by Mann-Whitney U test. D: Livers GLUT-2 levels in SH and experimental groups. Statistical analysis was by one-way analysis of variance (ANOVA) followed by Tukey's Post Hoc. All values are mean ± SεM and n=6 for each group. *, p<0,05 vs sham; **, p<0,01 vs sham; ***, p<0,001 vs sham; #, p<0,05 vs. SHZ; ,εp<0,05 vs AD; εεp<0,01 vs AD; εεε, p<0,001 vs AD.

Plasma 5-HT Levels

Statistical analysis revealed a significant difference in the levels of plasma 5-HT between various groups $X^2(3) = 9.817$, p = 0.020 Figure 2. Plasma 5-HT levels are shown in Table 1. The study found that plasma 5-HT levels were significantly lower in the AD group than in the SH group (U:2, p=0.010). When bee bread was administered, it significantly reduced plasma 5-HT levels in the SHP group compared to the SH group (U:5, p=0.036). However, there was no significant difference in plasma 5-HT levels between the ADP and AD groups after bee bread administration (U:8.50, p=0.128).

Liver 5-HT2BR Levels

There was a notable difference in the levels of 5-HT2BR among the various groups, $X^2(3) = 12.927$, p = 0.005 Figure 2. Liver 5-HT2BR levels are shown in Table 1. The liver 5-HT2BR levels in the AD group were significantly higher than those in the SH group (U:4, p=0.025). The administration of bee bread resulted in a significant increase in the liver 5-HT2BR levels in the SHP group compared to the SH group (U:4, p=0.025). Additionally, the administration of bee bread resulted in a significant increase in the plasma 5-HT2BR levels of the ADP group compared to the AD group (U:5.00, p=0.037). Furthermore, the liver 5-HT2BR levels in the ADP group were significantly higher than those in the SH group (U:1, p=0.006) and the SHP group (U:5, p=0.037).

Liver GLUT-2 Levels

Statistical analysis revealed a significant difference in the levels of liver GLUT-2 between various groups, F (3.20) = 6.206, p =0.004 Figure 2. Liver GLUT2 levels are shown in Table 1. The liver GLUT-2 levels were significantly higher in the AD group compared to the SH group (P=0.031). The administration of bee bread significantly increased liver GLUT-2 levels in the SHP group when compared with the SH group (P=0.026). Additionally, the administration of bee bread increased liver GLUT-2 levels in the ADP group compared to the AD group, but the increase was not statistically significant (P=0.743).

Liver Glucose 6 Phosphatase Levels

Statistical analysis revealed a significant difference in the levels of liver G6P between various groups, F (3.20) = 16.817, p =0.000 **(Figure 3)**.

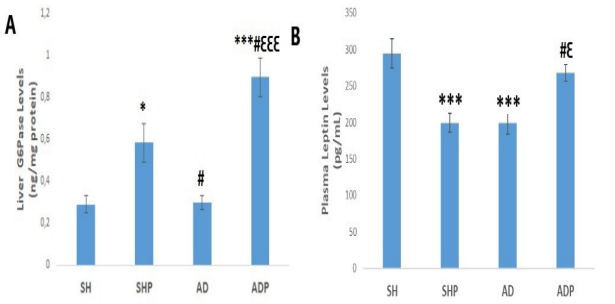

Figure 3: Livers G6Pase levels in SH and experimental groups. B: Plasma Leptin levels in SH and experimental groups. Statistical analysis was by one-way analysis of variance (ANOVA) followed by Tukey's Post Hoc Test. All values are mean ± SEM and n=6 for each group. *, p<0,05 vs sham; **, p<0,01 vs sham; ***, p<0,001 vs sham; #, p<0,05 vs. SHZ; ε, p<0,05 vs AD; εε, p<0,01 vs AD; εεε, p<0,001 vs AD.

Liver G6Pase levels are shown in Table 1. The liver G6P levels were not changed in the AD group compared to the SH group (p=1.00). Administration of bee bread significantly increased liver G6P levels of the SHP group in comparison with the SH group (p=0.036). Furthermore, the administration of bee bread increased liver G6P levels of the ADP group in comparison with the AD group (p=0.000).

Plasma Leptin Levels

There was a statistically significant difference in plasma leptin levels between groups, F (3.20) = 10.339, p =0.000 Figure 3. Plasma leptin levels are shown in Table 1. The plasma leptin levels were significantly decreased in the AD group compared to the SH group (p=0.001). Administration of bee bread significantly decreased plasma leptin levels of the SHP group in comparison with the SH group (p=0.001). Furthermore, the administration of bee bread increased plasma leptin levels of the ADP group in comparison with the AD group (p=0.020).

DISCUSSION

The effect of bee bread supplementation on liver glucose metabolism was evaluated in an experimental AD model created via i.c.v. STZ injection. The STZ and bee bread doses used in our study were determined by reference to previous studies. The injection of STZ into the brain causes insulin resistance and other changes that are similar to those seen in Alzheimer's Disease. Therefore, this injection technique is useful for studying the metabolic changes that occur in Alzheimer's Disease and for developing new treatment approaches (15).

Previous reports have shown that patients with Alzheimer's disease (AD) and mouse models of AD often display impaired glucose-insulin homeostasis and body weight loss prior to the onset of AD symptoms (5, 20). Our study investigated various markers related to peripheral glucose metabolism, including fasting blood glucose, serum insulin levels, and HOMA-IR levels. We found that plasma insülin levels significantly decreased while fasting blood glucose levels significantly increased in the AD group. Insulin is a hormone produced by pancreatic β-cells. It enhances glucose uptake in tissues such as muscle and fat. Thus, it has a primary function of maintaining peripheral glucose homeostasis (21). Epidemiological data indicate that both hyper- and hypoinsulinemia increase the risk of developing AD (22). Moreover, Rivera et al. showed that the levels of insulin and IGF-I polypeptide genes and their corresponding receptors are significantly reduced in advanced AD compared to aged control brains (23). Impairment of insulin secretion by β cells of the pancreatic islets (β cell dysfunction) leads to hypoinsulinemia and hyperglycemia that characterize Type 2 Diabetes Mellitus (T2DM) (24). Diabetes is a disease that often has no symptoms and typically occurs in later life. Insulin resistance can occur years before DM and its complications (25, 26). However, Bondar et al. showed that patients with reduced function of β cells had lower indices of insulin resistance and were characterized by a more prolonged duration of diabetes and high fasting glycemia (27). Consistent with this information, we observed a significant reduction in HOMA-IR levels in the AD group compared to the SH group. In conclusion, the information obtained indicates that the findings obtained from our study reflect the findings of T2DM in the AD group (28).

It is known that the control of glucose homeostasis is achieved by the complex integration of hormones produced in various tissues. Emerging evidence suggests that 5-HT in the periphery impacts liver glucose metabolism depending on physiological conditions. We investigated how 5-HT affects hepatic glucose homeostasis through HTR2B. In our study, it was

observed that the 5-HT levels were significantly reduced in both the serum and liver tissue of AD group rats. Also, our results showed that the 5HT2B levels increased in the liver of AD rats. Similarly, a study by Paulose et al. showed that there was a decreased 5-HT increase in 5-HT receptors in the brains of pyridoxine-deficient young rats (29). In this respect, our results were found to be compatible with studies showing a negative correlation between 5-HT receptor level and 5-HT concentration (30). Furthermore, in our study, it was observed that GLUT2 levels increased in parallel with the increase in 5HT2B levels in the liver of AD rats, but G6Pase levels did not change. GLUT2 is the main member of the GLUT family in hepatocytes. It plays a crucial role in controlling the uptake of glucose in the liver cells, which is dependent on the levels of glucose in the bloodstream. After entering the cell, glucose is quickly transformed into glucose-6-phosphate by the enzyme glucokinase. It is then either metabolized by glycolysis or stored as glycogen (31). Therefore, our findings revealed that 5 HT2BR promoted glucose entry into hepatocytes by increasing GLUT2 levels in the liver of AD rats. Our results are based on previous findings showing the effect of 5-HT2B receptor activation on glycogen synthesis in astrocytic cells (32). Moreover, when the results were evaluated together, it is possible to say that as an adaptation mechanism, hepatic GLUT2 level was increased by 5HT2BR in the AD. To the best of our knowledge, our study is the first to demonstrate that 5-HT2BR may regulate glucose metabolism as an adaptation mechanism in Alzheimer's disease by increasing glucose entry in the liver. Additionally, our findings are from previous studies showing the reduction of peripheral 5-HT in AD (33).

The effect of beef bread supplementation on hepatic glucose metabolism in an AD model created via STZ injection was evaluated in this study, with a focus on 5-HT2B-mediated effects. We found that bee bread administration caused a marked increase in 5-HT levels in plasma and liver tissue and also significantly increased 5HT2B levels in the liver of the ADP group. It is known that the presence of the tryptophan (Trp) substrate is critical in serotonin synthesis, and dietary Trp increases 5-HT synthesis (7, 34). Bee bread is known to contain more than 300 compounds, such as free amino acids, sugars, fatty acids, minerals, organic acids, polyphenols, and vitamins. Additionally, Bayram et al. showed that bee bread contains many amino acids, including tryptophan (17). This information suggests that the tryptophan content of bee bread increases peripheral 5HT synthesis in the ADP group. Additionally, our research indicates that when there is an increase in 5H levels, hepatic 5HT2B levels may also increase. We found that administering bee bread significantly increased G6Pase levels while slightly increasing GLUT2 levels in the livers of rats in the ADP group. This suggests that glucose output from the liver tissue of ADP group rats increased significantly. However, contradictory results have been produced by studies examining the impact of 5-HT on hepatic gluconeogenesis, glycogen storage, glucose uptake, and glycolysis (35). Studies performed in rodents reported that the injection of 5-HT or 5-HT receptor agonists results in hyperglycemia (36). Another study demonstrated that the neurotransmitter 5-HT plays a role in regulating brain glycogen levels in rainbow trout. This results in a breakdown of glycogen when the fish are in a normoglycemic or hypoglycemic state but not in a hyperglycemic state (37). Lee et al. have shown that 5-HT elicited hyperglycemic responses in Procambarus clarkii in a dose-dependent manner (38). In this respect, our results are consistent with studies showing that the effect of 5-HT on glucose metabolism may vary depending on the physiological state. Therefore, we concluded that bee bread administration promotes gluconeogenesis by increasing the level of G6Pase through the 5-HT-HTR2B pathway in the ADP group. However, interestingly, it was observed that bee bread administration reduced the fasting glucose levels of ADP group rats. As far as we know, our study is the first to demonstrate that bee bread administration reduced the fasting glucose levels of Alzheimer's rats created by i.c.v. STZ injection. Moreover, we found that bee bread administration slightly reduced plasma insulin levels without affecting HOMA-IR levels. Therefore, we examined the effect of leptin levels on peripheral glucose levels. Leptin can independently reduce blood gluco-

se levels, especially in hyperglycemic models of leptin or insulin deficiency. Although leptin does not increase insulin levels, it has been shown to strongly increase insulin sensitivity in Type1 Diabetes (T1D) models (39, 40). Bee bread administration increased leptin levels in the plasma of the ADP group. Moreover, bee bread administration reduced glucose levels in the plasma of the ADP group without affecting insulin levels. Doğanyigit Z. et al. showed that the administration of bee bread increased the leptin immunoreactivity in the gastric tissue of obese rats (13). In this respect, our findings are consistent with previous studies. When these data are evaluated together, it can be said that the net effect of bee bread administration in experimental Alzheimer's model rats is to reduce plasma glucose levels by increasing leptin levels in the plasma. Moreover, previous findings show the circulating levels of leptin are significantly lower in patients with AD than in controls (41). Supporting this information, in our study, leptin levels decreased in the plasma of AD group rats.

In both human patients with Alzheimer's disease and Tg2576 mice, which are a special type of mouse that has been genetically modified to produce extra amyloid precursor protein (APP), there is an early reduction in body weight and plasma leptin levels. This occurs even before the formation of amyloid plaques or cognitive dysfunction. This weight loss was associated with the inhibition of hypothalamic neuropeptide Y (NPY) neurons by Aβ (42). In this respect, the findings obtained from our study were consistent with other studies showing that early weight loss occurs in AD disease. Additionally, in our study, the weight loss of ADP group rats increased due to bee bread administration, which is consistent with studies showing that Leptin can impact body weight by affecting hypothalamic neurons (11). Leptin treatment has consistently been shown to decrease Aβ levels by targeting all aspects of Aβ metabolism (43-45). Based on these results, we propose that the decreased levels of leptin in the blood may play a role in the deterioration of cognitive function and the worsening of Alzheimer's disease. Considering the peripheral and central effects of leptin on AD pathogenesis, it can be said that bee bread may reduce AD pathology. For example, propolis, a honey bee product, has been used in traditional medicine for many years (46). Recently, the effect of natural bee products on the pathogenesis of AD has been demonstrated. (47, 48). Nisa et al. suggested that phytoligand molecules obtained from honey bee products could be novel β-site APP-cleaving enzyme 1 (BACE-1) inhibitors for Alzheimer's disease. (47). "As far as we know," our study is the first to show the effect of bee bread on the hormones that regulate glucose in the pathogenesis of AD.

Nevertheless, administration of bee bread slightly increased the fasting glucose levels and significantly decreased the insülin levels in the plasma of healthy rats. Also, HOMA-IR levels markedly decreased in the SHP group. These results indicate that administering bee bread may cause hyperglycemia by disrupting insulin secretion in the pancreas. In addition, bee bread administration significantly increased the 5-HT2BR, GLUT2, and G6Pase levels in the liver of the SHP group. It is suggested that bee bread affects 5-HT2B-mediated glucose metabolism in the liver of SHP rats. However, interestingly, it was observed that bee bread administration significantly decreased the 5-HT levels in the plasma and liver tissue of SHP group rats. Moreover, our study observed that the administration of bee bread significantly decreased the leptin levels in the plasma of SHP group rats and increased weight loss. It is known that both Leptin and central 5-HT play a role in the regulation of nutritional signals and energy metabolism (7). According to the results obtained, it is seen that bee bread affects energy metabolism.

In particular, increased plasma Trp/large neutral amino acids (LNAA) ratio enhances brain Trp uptake and 5-HT synthesis (7). İmportantly, central 5-HT is known to play a role in regulating nutritional signals and energy metabolism. Disruption of central serotonin signaling via 5-HT2C receptors induces hyperphagia in mice, leading to obesity, insulin resistance, and impaired glucose tolerance independent of leptin (7). The amount of leptin released into the bloodstream is directly proportional to the amount of fat stored in the body. The circulating leptin levels also decrease as the body loses weight and fat stores decrease. Reduced leptin levels

signal the brain to increase food intake and decrease energy expenditure to restore body weight (11). In light of this information, our results suggest that bee bread may increase brain 5-HT levels, leading to weight loss and decreased leptin release from adipocytes. When these data are evaluated together, it is thought that the bee bread agent has an increasing effect on plasma glucose levels by reducing the leptin and insulin levels in the plasma of SHP rats, similar to the AD group. It also affects 5-HT2B-mediated glucose metabolism in the liver of SHP rats. In addition, the findings suggest that it is necessary to investigate the effects of healthy-oriented natural bee products on brain tissue.

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Kocatepe Tıp Dergisi
Kocatepe Medical Journal
25:476-483/Ekim 2024 Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

MRSA'YA KARŞI BİTKİSEL ÇAY ÖRNEKLERİNİN SİPROFLOKSASİN İLE SİNERJİK ETKİSİ VE ANTİOKSİDAN AKTİVİTELERİ

SYNERGISTIC EFFECT OF HERBAL TEA SAMPLES WITH CIPROFLOXACIN AGAINST MRSA AND THEIR ANTIOXIDANT ACTIVITIES

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ÖZET

AMAÇ: *Sambucus nigra L*. (mürver), *Salvia sclarea L*. (adaçayı), *Rosmarinus officinalis L*. (biberiye) ve *Coriandrum sativum L*. (kişniş) bitkileri gıdalarda tatlandırıcı ajan olarak kullanılmakta ve dünyada çeşitli hastalıkların tedavisinde halk hekimliğinde iyi bilinmektedir. Bu bitkiler ayrıca, enfeksiyonlarda özellikle öksürük, ateş ve soğuk algınlığı semptomlarını hafifletmek amacıyla yaygın olarak kullanılırlar. Bu çalışma, Türkiye'de *S. nigra*, *S. sclarea, R. officinalis* ve *C. sativum* 'un ticari örneğinden elde edilen üç farklı ekstrenin toplam fenol içeriğini ve antioksidan aktivite potansiyelini taramayı ve karşılaştırmayı amaçlamaktadır. Ayrıca, *Staphylococcus aureus* ATCC 29213 (metisiline duyarlı- MSSA) ve *Staphylococcus aureus* ATCC 43300'e (metisiline dirençli- MRSA) karşı Minimum İnhibitör Konsantrasyonu (MİK) değerlerini ve bir antibiyotik olan siprofloksasin ile sinerjistik aktivite gösterip göstermediği araştırılmıştır.

GEREÇ VE YÖNTEM: *S. nigra* ve *C. sativum*'un meyveleri, *S. sclarea*'nın toprak üstü kısımları ve *R. officinalis*'in yaprakları Türkiye'de bitki çayı pazarlayan bir ticari şirketten satın alınmıştır. Bu örneklerden elde edilen ekstrelerin toplam fenolik içeriği ve antioksidan potansiyeli araştırılmıştır. Ayrıca bitki örneklerinin metisiline dirençli *Staphylococcus aureus* 'a (MRSA) karşı siprofloksasin ile sinerjik etkisi belirlenmiştir.

BULGULAR: *R. officinalis* (biberiye) ve *S.sclarea* (misk adaçayı) ekstreleri yüksek fenolik içerik ve antioksidan aktivite gösterirken, *C. sativum* (kişniş) ve *S.nigra* (mürver) ekstreleri daha düşük fenolik madde içerdiği ve daha zayıf antioksidan aktivite gösterdiği tespit edilmiştir. Ayrıca, *S. sclarea*'nın etanol ekstresi ile birlikte siprofloksasinin, *S. aureus* ATCC 43300'e karşı additif antibakteriyel aktivite gösterdiği bulunmuştur.

SONUÇ: *R. officinalis* (biberiye) ve *S.sclarea* (misk adaçayı) ticari örneklerinden hazırlanan bitki çaylarının yüksek fenolik içeriğiyle antioksidan aktiviteyi destekleyebileceği ve siprofloksasinin misk adaçayının etanol ekstresi ile birlikte metisiline dirençli *S. aureus* ATCC 43300'e karşı additif antibakteriyel aktivite gösterdiği bulunmuştur. Söz konusu etkiye ait mekanizmanın ayrıntılı olarak anlaşılması için daha ileri çalışmalara ihtiyaç vardır.

ANAHTAR KELİMELER: Antioksidanlar, İlaç sinerjisi, Bitki preparatları.

ABSTRACT

OBJECTIVE: *Sambucus nigra L*. (elderberry), *Salvia sclarea L*. (clary sage), *Rosmarinus officinalis L*. (rosemary), and *Coriandrum sativum L*. (coriander) are all consumed as flavoring agents for food and are well-known in traditional medicine for the treating various diseases worldwide. These herbs are also commonly used for microbial infections, especially to relieve cough, fever, and cold symptoms. This study aims to screen and compare the content of total phenols and antioxidant activity potential of three different extracts from each commercial sample of S. nigra, *S. sclarea, R. officinalis* and *C. sativum* from Türkiye. We also investigated the (Minimum Inhibitory Concentration (MIC) values against *Staphylococcus aureus* ATCC 29213 (methicillin-susceptible, MSSA) and *Staphylococcus aureus* ATCC 43300 (methicillin-resistant, MRSA) and the synergistic activity with an antibiotic, ciprofloxacin, by checkerboard assay.

MATERIAL AND METHODS: The fruits of *S. nigra* and *C. sativum*, the aerial parts of *S. sclarea,* and the leaves of *R. officinalis* were purchased from a trading company that marketed them as herbal tea in Türkiye. This study investigated the total phenolic content and antioxidant potential of extracts from commercial samples. We also determined the synergistic effect of herbal tea samples with ciprofloxacin against methicillin-resistant *Staphylococcus aureus* (MRSA).

RESULTS: *R. officinalis* (rosemary) and *Salvia sclarea* (clary sage) extracts showed high phenolic content and antioxidant activity, whereas it was determined that *C.sativum* (coriander) and *S. nigra* (elderberry) extracts exhibited lower antioxidant activity and low phenolic compounds. Moreover, ciprofloxacin in combination with the ethanolic extract of *S. sclarea* showed additive antibacterial activity against *S. aureus* ATCC 43300.

CONCLUSIONS: We conclude that herbal tea prepared from commercial *R. officinalis* (rosemary) and *S.sclarea* (clary sage) samples can support the antioxidant activity with high phenolic content and that ciprofloxacin combined with the ethanolic extract of clary sage showed additive antibacterial activity against methicillin-resistant *S. aureus* ATCC 43300. Further studies are needed to understand the mechanism of additive action in detail.

KEYWORDS: Antioxidants, Drug synergism, Plant preparations.

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Kabul Tarihi / Accepted:12.06.2024
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INTRODUCTION

Staphylococcus aureus is a pathogen responsible for a wide spectrum of infections. Methicillin-resistant *S. aureus* (MRSA), an opportunistic bacterium that is resistant to various medicines, has been identified as one of the causes of hospital and outpatient infections. Aside from that, MRSA-related illnesses have been more common over the past years (1, 2).

Antimicrobial resistance is reported as significant public health issue both in our country and in the world. The World Health Organization (WHO) 2014 report states that antimicrobial resistance seriously threatens the prevention of various infectious diseases caused by bacteria, parasites, viruses, and fungi, and the success of treatment of these diseases. Although it is reported that antibiotic resistance can occur naturally, it has been stated that the overuse and misuse of antibiotics in humans accelerate the process. It has been remarked that antimicrobial resistance causes a decrease in the effectiveness of antibacterial, antiparasitic, antiviral, and antifungal drugs and makes treatment difficult, costly, and even impossible. For this reason, it is known that there is a need for new compounds that will increase the efficacy of antibiotics or that can be used alone or in combination with treatment protocols (3, 4).

Sambucus nigra L. (elderberry), *Salvia sclarea L.* (clary sage), *Rosmarinus officinalis L.* (rosemary) and *Coriandrum sativum L.* (coriander) are all consumed as flavoring agents for food and very well known plants as traditional remedies of various ailments worldwide. They have also a common use for microbial infectious especially relieving cough, fever, and cold symptoms related to RTI (Respiratory Tract Infection) (5 - 13). Previous phytochemical studies stated that these plants are rich sources of different polyphenols which could be linked to their biological activities depending on antioxidant properties (11, 14 - 16).

In light of all these findings, this study was designed to search for potential candidates that have synergistic effects with ciprofloxacin against infections triggered by methicillin-resistant *Staphylococcus aureus* (MRSA). This study aims to screen and compare the content of total phenols and antioxidant activity potential of three different extracts from each commercial sample of *S. nigra, S. sclarea, R. officinalis* and *C. sativum* from Türkiye. We also investigated the minimum inhibitory concentration (MIC) values against *S. aureus* ATCC 29213 (methicillin-susceptible, MSSA) and *S. aureus* ATCC 43300 (methicillin-resistant, MRSA) and the synergistic activity with an antibiotic, ciprofloxacin, by checkerboard assay.

MATERIALS AND METHODS

Plant Material

The fruits of *S. nigra* and *C. sativum*, the aerial parts of *S. sclarea*, and the leaves of *R. officinalis* were supplied by a trading company that purchased them as herbal tea in Türkiye.

Preparation of Extracts

3 different extraction methods were used and a total of 12 extracts were prepared. The names of the samples and their codes are listed **(Table 1)**.

Table 1: The names and codes of extracts

	Extraction procedure		
Plant name	Infusion	Ultrasound extraction with water	Ultrasound extraction with EtOH 70%
Sambucus nigra, fruit	1a	1b	1c
Salvia sclarea, aerial part	2a	2b	2c
Rosmarinus officinalis, leaves	3a	3b	3c
Coriandrum sativum, fructus	4a	4b	4c

a. Extraction based on the label information: The infusions were prepared from 5 g of each powdered sample by adding 100 mL of boiling water and waiting for 10 minutes, and then filtered. The aqueous extracts were lyophilized.

b. Extraction in an ultrasonic bath with water: 5 g of each powdered sample went through extraction with 100 mL of water in an ultrasonic bath with 35 kHz frequency (Bandelin Sonorex) for 1 hour and then filtered. The aqueous extracts were lyophilized

c. Extraction in an ultrasonic bath with ethanol: 5 g of each powdered sample was extracted with 100 mL of 70% ethanol in an ultrasonic bath with 35 kHz frequency (Bandelin Sonorex) for 1 hour and then filtered. The extracts obtained with ethanol were evaporated to dryness.

Total Phenolic Content

With a few minor adjustments, the Folin-Ciocalteu technique was employed to figure out

the total amount of phenolics present in the extracts. Briefly, plant extract samples (1 mg/mL) were prepared and reacted with 10% Folin-Ciocalteau's reagent. The tubes were then filled with 7.5% Na_2CO_3, and they were subjected to incubation at 45°C for 15 minutes. The absorbance value of the samples was obtained at 765 nm. The experiments were done in triplicate. The same procedure was performed with gallic acid and the outcomes were stated as mg of gallic acid equivalent (GAE) per g of crude extract for each sample (17).

Total Flavonoid Content

The aluminum chloride method was performed to determine the total quantity of flavonoids present in the extracts with slight modifications. Briefly, plant extract samples (1 mg/mL) were prepared and 20% $NaNO_2$ was added to each tube. Following 5 minutes of incubation, 10% AlCl3 was added. 1 M NaOH was added 6 min later and the mixture was diluted with distilled water to a total volume of 1 mL. At 510 nm, the absorbance was recorded. The tests were carried out in triplicate. The same procedure was performed with quercetin and the outcomes were stated as mg of quercetin equivalent (QE) per g of crude extract for each sample (18).

Total Antioxidant Capacity

The total antioxidant capacity of the extracts were measured by using phosphomolybdate assay. 0.6 M sulfuric acid, 28 mM sodium phosphate, and 4 mM ammonium molybdate were reacted to get working solution. Different concentrations of plant extract samples (0.1-1mg/mL) were added to this working solution in a ratio of 1:10. Then incubation was performed at 95°C for 90 min. The tubes were cooled following the end of the incubation. The absorbance value of the samples was recorded at a wavelength of 765 nm. The tests were carried out in triplicate. Total antioxidant capacities were determined as mg ascorbic acid (AAE) per gram crude extract for each sample (19).

Ferric Ion Reducing Antioxidant Power (FRAP) Assay

The antioxidant capacity of the plant extracts were investigated by measuring their ferric-reducing antioxidant potential. The method is operated on the conversion of [Fe(III)-TPTZ] complex, which is formed as a result of the reaction of iron (III) with Tripyridyltriazine (TPTZ), to [Fe(II)-TPTZ]. 10 mM TPZT, 20 mM FeCl3 $6H_2O$, and 300 mM sodium acetate buffer (pH= 3.6) was reacted to prepare the FRAP reagent. This reagent was applied to the prepared plant extracts which was then left to incubate at 37°C for 30 min. The absorbance value of the samples was measured at 593 nm. The experiments were performed in triplicate. The findings were presented as Trolox (Vitamin E) equivalent per gram crude extract for each sample (20).

(2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)) (ABTS) Free Radical Scavenging Assay

The antioxidant capacity of the extracts was assessed by testing their ability to scavenge ABTS free radicals. 2.45 mM potassium persulfate was added to a 7 mM ABTS aqueous solution to get ABTS working solution. Overnight, the reaction mixture was allowed to rest at room temperature in the dark. As a result of diluting ABTS radical cation with ethanol, the final absorbance at 734 nm(pH=7.4) was 0.700±0.02. Serial dilutions of samples (0.01-1 mg/mL) were prepared and mixed with ABTS working solution in a ratio of 1:10. The mixture was incubated at ambient temperature for 6 minutes. The absorbance value of the samples was measured at 734 nm. Three duplicates of each experiment were run. The outcomes were represented as Trolox (Vitamin E) equivalent per gram crude extract for each sample (21).

Antibacterial Activity Test

S. aureus ATCC (American Type Culture Collection) 29213 (methicillin-susceptible, MSSA) and *S. aureus* ATCC 43300 (methicillin-resistant, MRSA) were employed as test bacteria in the antibacterial activity test. The broth microdilution method was utilized to calculate the minimum inhibitory concentration (MIC) values. A series of two-fold dilutions were produced using Mueller Hinton Broth (Difco, Difco Laboratories, Detroit, MI, USA), with concentrations between 512 g/mL to 4 g/mL. The inoculums were prepared from subcultures for 24 hr. The final setting for the bacterial count was 5 $x10^5$ CFU/mL. The microplates were subjected to incubation at 35 °C for 18 to 24 hours. The final well where observable microbial growth was completely sup-

pressed was recorded to estimate the minimum inhibitory concentration (MIC, g/mL). Alcohol was used to dissolve the test substances. utilized as the negative control. Ciprofloxacin (Sigma, USA) and gentamicin (Sigma, USA) were employed as reference drugs (22, 23).

Broth Microdilution Checkerboard Method

The broth microdilution method, as previously reported, was used to test checkerboard synergy. The extract which has the lowest MIC value was chosen for the checkerboard test between samples. Ciprofloxacin (Sigma, USA) concentrations ranging from 0.03 to 16 g/ mL were examined. Ciprofloxacin was mixed with ethanolic extract of *S.sclarea* at concentrations between 16 and 512 µg/mL against *S. aureus* ATCC 43300 (MRSA) (24). The microtiter plate was subjected to incubation at 37°C for 24 h. FICIwas calculated using the first non-turbid well in each column and row of a 96-well U-bottom microplate (25). The formula that comes next was used to get the ΣFIC (Fractional Inhibition Concentration) for the resulting mixture of agent A (ciprofloxacin) and agent B (ethanolic extract of *Salvia sclarea*). ΣFICI(Fractional Inhibition Concentration Index) = FICA (MIC Value of Substance A In the Combination) + FICB (MIC Value of Substance B In the Combination) , where FICA = MICA (in combination with B) /MICA (alone), and FICB = MICB (in combination with A) /MICB (alone) (26). The following was the interpretation of the combination test results using the FIC index: FICI ≤ 0.5 is considered synergistic;>0.5 to <4 additive /indifference, and ≥ 4 antagonistic (27).

Ethical Committee

This research does not require ethical approval.

Statistical Analysis

IBM SPSS 25 was performed to analyze the data statistically. Three separate runs of each experimental test were operated. The findings were displayed as mean±standard deviation (SD). The post-hoc Tukey test was followed by a one-way analysis of variance. A p-value less than 0.05 was used to indicate statistical significance.

RESULTS

Yields of The Extracts

In this study, the synergistic activity of the extracts from the fruits of S. nigra and C. sativum, the aerial parts of *S. sclarea*, and the leaves of *R. officinalis* obtained by three different methods were evaluated and compared, and the content of phenolic compounds and antioxidant activities of the extracts were determined. In the first method, the extracts were prepared as an infusion based on the label information. In the second method, the extraction was performed with water for one hour in an ultrasonic bath, and in the last method, the extraction was also performed for one hour in an ultrasonic bath with an extraction solvent of 70% ethanol (EtOH). The yields of extracts according to the codes are as follows: (1) *S. nigra*, fruit 1a-27.44%; 1b-35.24%;1c-42.73%. (2) *S. sclarea*, herba; 2a-5.95%; 2b-28.90%; 2c-32.88%. (3) *R. officinalis,* leaves 3a-6.45%; 3b-12.97%; 3c-21.74%. (4) *C. sativum*, fruit 4a-11.76%; 4b-14.28%; 4c-22.36%. According to the results, the highest yields are obtained by ultrasonic extraction with EtOH 70%.

Total Phenolic Content

The total phenolic content of the extracts were derived from the calibration curve of gallic acid (y=0.005x+0.0965, R^2=0.9953) and reported in GAE per gram dry extract **(Table 2)**.

Table 2: Total phenolic and flavonoid contents of plant extracts

Plant extract	Total phenolic content mg GAE / g crude extract		Total flavonoid content mg QE / g crude extract	
	Mean	SD	Mean	SD
1a	55,4400	1,5974	45,0000	3,2222
1b	60,8800	0,3904	44,0741	1,7368
1c	57,8000	2,8703	51,4444	1,2522
2a	73,6300	0,6930	139,0000	5,5076
2b	61,8600	2,8402	83,0000	3,9487
2c	86,6733	1,0633	138,0370	0,7883
3a	90,9667	0,7798	145,6667	3,6124
3b	82,3667	1,4342	128,9630	2,1839
3c	87,9600	1,0182	149,7778	0,4714
4a	22,8733	0,3630	53,0741	3,4647
4b	21,4533	0,0808	40,1111	2,9856
4c	16,4400	0,9606	56,4074	1,0082

mg GAE / g crude extract: mg of gallic acid equivalent per g of crude extract; **mg QE / g crude extract:** mg of quercetin equivalent per g of crude extract

Rosmarinus officinalis contains the highest amount of phenolics among all plants. The infusion of 3a extract with 90.9667± 0.7798 mg GAE/g crude extract yielded the highest concentration of phenolics which was significantly greater than the other extracts (p=0.0001). 3a was followed by 3c, 2c, 3b, and 2a, in that order.

Total Flavonoid Content

The total flavonoid content of the extracts were derived from the calibration curve of quercetin (y=0.0009x+0.0271, R^2 = 0.9955) and expressed

in QE per gram dry extract (Table 2). The lowest level of flavonoids was found in "b" extracts which were prepared by extraction in an ultrasonic bath with water. When methods "a" and "c" were used, a significantly higher amount of flavonoids was found compared to method "b" in *Salvia sclarea*, *Rosmarinus officinalis*, and Coriandrum sativum extracts (p=0.001). However, there was no significant difference between the flavonoid contents of the extracts obtained by method "a" and "c" in S*ambucus nigra, Salvia sclarea*, *Rosmarinus officinalis* and *Coriandrum sativum* (p=0.230, 1.000 0.927, 0.965, respectively). In general, *Rosmarinus offcinalis* contains higher amount of flavonoids than the others. The greatest amount of flavonoids was observed in 3c with a level of 149.7778±0.4714 mg QE/g crude extract. Total flavonoid concent of 3c was significantly higher than other extracts except 3a (p=0.008 for 2a, p=0.003 for 2c, and p=0.0001 for the other samples). No significant difference was observed in 3a and 3c based on flavonoid amounts (p=0.927). The second highest flavonoid content was determined in 3a followed by 2a, 2c, and 3b, respectively.

Total Antioxidant Capacity

The total antioxidant capacity of the extracts were calculated from the calibration curve of ascorbic acid (y=0.0099x+0.0268, R^2= 0.9961) and expressed in AAE per gram dry crude extract **(Table 3)**.

Table 3: Total antioxidant capacity of plant extracts

Plant extract	mg AAE / g crude extract		FRAP value		TEAC value (µM TE/g crude extract)	
	Mean	SD	Mean	SD	Mean	SD
1a	250,6809	39,9648	17,3113	0,4261	38,0079	1,884051
1b	224,8822	5,0871	19,1207	0,4359	45,1625	2,246536
1c	226,3636	3,7415	18,4080	0,1225	40,3023	2,616737
2a	251,7172	7,0729	50,5980	1,5502	65,0965	0,418678
2b	217,3079	79,5735	30,3300	0,6212	42,5227	0,732686
2c	262,5589	5,8971	49,0760	0,7828	58,2874	0,628017
3a	312,7273	2,8641	56,8353	0,2065	85,3266	2,539538
3b	287,0707	2,3667	48,7960	0,6416	63,6903	1,570042
3c	290,7071	3,4742	47,4947	0,7123	76,7905	1,046695
4a	126,1953	0,7581	12,0753	0,5054	"-"	-
4b	127,3737	2,2153	10,6813	0,4486	"-"	-
4c	110,8081	4,7140	8,9030	0,3352	"-"	-

mg AAE / g crude extract: ascorbic acid equivalents (AAE) in milligrams per gram of crude extract; **FRAP:** Ferric ion reducing antioxidant power assay; **TEAC:** Trolox equivalent antioxidant capacity; **µM TE/g extract:** µM Trolox equivalent per gr crude extract; **"-":** no activity

The total antioxidant capacity of all extracts was at significant levels compared to solvent control (p=0.0001). "c" and "a" extracts were found to have higher total antioxidant capacity than "b" extracts. *Rosmarinus officinalis* was the most potent antioxidant among all samples. 3a had the greatest total antioxidant capacity (312.7273±2.8641 mg AAE/g crude extract), which was significantly higher than the others (p=0.0001). The second was 3c followed by 3b, 2c, and 2a, respectively.

Ferric Ion Reducing Antioxidant Power Assay

The ferric ion-reducing antioxidant power of the extracts were calculated from the calibration curve of trolox (y=0.05x+0.2073, R^2= 0.9982). The results were expressed (Table 3). The antioxidant power of all extracts were significantly higher than the control (p=0.0001). *Rosmarinus officinalis* and *Salvia sclarea* was found more effective than the other plants in this assay. However, applied extraction techniques had no specific discernible impact on the antioxidant capacity of the extracts. 3a had the greatest ferric ion reducing power which was significantly higher than the other extracts (p=0.0001). The second active one was 2a followed by 2c, 3b, and 3c, respectively.

ABTS Free Radical Scavenging Assay

ABTS free radical scavenging potential of the extracts were calculated from the calibration curve of Trolox and the results were expressed as µM Trolox equivalent per gr dry extract. The results were shown in (Table 3). Except plant 4, the other extracts possessed statistically significant activity than solvent control (p=0.0001). *Rosmarinus officinalis* was the most potent one. 3a had the greatest ABTS free radical scavenging potential which was significantly higher than the other extracts (p=0.017 for 3c and p=0.0001 for the other extracts). The second active one was 3c followed by 2a and 3b, respectively. The ability of the extracts to scavenge this free radical was not significantly impacted by the extraction technique.

Antibacterial Activity

MIC values (µg/mL) of the extracts are given **(Table 4)**.

Table 4: . Minimum inhibitory concentration values (µg/mL) of the extracts

Plant extract	Gram-positive bacteria	
	S. aureus ATCC 29213(MSSA)	*S.aureus* ATCC 43300 (MRSA)
1a	-	-
1b	-	-
1c	-	-
2a	-	-
2b	-	-
2c	256	128
3a	-	-
3b	-	-
3c	256	256
4a	-	-
4b	-	-
4c	-	512
%70 ethanol	-	-
Ciprofloxacin	<0.25	0.5
Gentamicin	0.5	<0.25

"-": No activity

Broth Microdilution Checkerboard Method

Checkerboard Assay was used to evaluate the synergistic effect of ciprofloxacin with the ethanolic extract of *S.sclarea* which showed the lowest MIC value against *S. aureus* ATCC 43300. Ciprofloxacin in combination with the ethanolic extract of *S.sclarea* exhibited additive antibacterial activity against *S. aureus* ATCC 43300. FICA was 0,24 while FICB was 0,5. The ΣFIC value was 0,74 for *S. aureus* ATCC 43300 thus indicating an additive interaction between ciprofloxacin and the ethanolic extract of clary sage.

DISCUSSION

It is well known that the extraction procedures strongly influence the yield and chemical composition of the extracts. Therefore, it is not surprising that in this study, the yield of all extracts was increased by longer extraction time and sonication in the ultrasonic bath. In addition, aqueous ethanol as an extraction solvent has a positive effect on the yield. According to our results, extract 3a from *R. officinalis* had the lowest extraction yield but the highest total phenolic content and antioxidant potential. Our results are in agreement of previous reports. In fact, the extract of rosemary is accepted as a natural antioxidant attributed to phenolic acids (such as rosmarinic acid), flavonoids and diterpenoids mainly, carnosol and carnosic acid (11, 28, 29).

Both rosemary and clary sage are popular in the food, cosmetic, and medicinal industries for their antioxidant constituents such as phenolic acids, flavonoids, and diterpenoids. Rosmarinic acid, carnasol, and carnosic acid are also found in the genus Salvia. Cuvelier et al. (30) reported the relationship between antioxidant activity potential and the presence of rosmarinic acid, carnosic acid, and carnosol as major constituents. In this study, rosemary and clary sage extracts were found to have high phenolic content and antioxidant activity, while coriander and elderberry had lower antioxidant activity with low phenolic content.

Based on the results of the checkerboard assay, the ethanolic extract of clary sage could be used safely in combination with ciprofloxacin in the treatment of MRSA infections. Polyphenols are compounds with different structural properties and different functional groups. They are naturally present in plants and have a wide variety of applications in the medical field in regards to having antioxidant, and anti-inflammatory actions, such as; allergic diseases, diabetes, cardiovascular and neurodegenerative diseases. Besides, polyphenol-rich plant extracts were reported as having the potential to inhibit bacterial and fungal growth. Earlier reports mentioned that plant extracts with high levels of polyphenols have the ability to block the development of pathogenic bacteria and fungi. They could have potential in clinical settings. Ultrasonication could be a useful tool to increase the yield of the extract, but on the other hand, continuous cavitation could cause the degradation of some polyphenolic compounds depending on the extraction parameters (temperature, solvent, time, frequency, drog-solvent ratio, etc.). In this study, the highest yields are obtained by ultrasonic extraction with EtOH 70% (31-33).

We conclude that herbal tea prepared from commercial rosemary and clary sage samples can support the antioxidant activity with high phenolic content and that ciprofloxacin combined with the ethanolic extract of clary sage showed additive antibacterial activity against methicillin-resistant *S. aureus* ATCC 43300. Further studies are needed to understand the mechanism of additive action in detail.

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Kocatepe Tıp Dergisi
Kocatepe Medical Journal
25:484-489/Ekim 2024 Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

DİFERANSİYE TİROİD KANSERLİ HASTALARDA TİROTROPİN SUPRESYON DÜZEYİNİN DİYASTOLİK KALP FONKSİYONLARI ÜZERİNE ETKİSİ

EFFECT OF THYROTROPIN SUPPRESSION LEVEL ON DIASTOLIC HEART FUNCTIONS IN PATIENTS WITH DIFFERENTIATED THYROID CANCER

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ÖZET

AMAÇ: Bu çalışmanın amacı opere diferansiye tiroid kanserli (DTK) hastalarda tiroid-stimüle edici hormon (TSH) supresyon düzeylerine göre kardiyak yapı ve diyastolik fonksiyonlardaki değişikliklerin araştırılmasıdır.

GEREÇ VE YÖNTEM: Kesitsel olarak dizayn edilen bu araştırmaya hastanemiz endokrinoloji polikliniğinde takipli, tiroid cerrahisi sonrası bir yıldan uzun süredir tiroid hormon replasmanı ve TSH supresyon tedavisi alan 125 DTK'lı hasta dahil edildi. Çalışmamızda olgular American Thyroid Association (ATA) 2015 kılavuzu risk değerlendirmelerine uygun olarak gruplara ayrılmıştır. Buna göre hastalar birinci grup TSH seviyesi <0,1 mIU/L olanlar (n:30), ikinci grup TSH düzeyi 0,1-0,5 mIU/L arasında olanlar (n:56) ve üçüncü grup ise TSH düzeyi 0,5-2 mIU/L arasında olanlar (n:39) şeklinde üç gruba kategorize edilmiştir. İlk iki grup supresyon, 3. grup ise replasman (kontrol) grubu olarak belirlenmiştir. Tüm hastalara M-mode ve pulse-vave doku dopler ekokardiyografi yapılmıştır.

BULGULAR: Sol ventrikül diyastol sonu çapı (EDD), TSH aralığı <0,1 mIU/L olan grupta, replasman grubuna göre anlamlı olarak daha uzun bulunmuştur (45,35±3,54 ve 42,74±6,08; p=0,016). Yine erken diastolik dolumda mitral kapak velositesini gösteren E velocity grup 1 de, replasman grubuna göre anlamlı olarak daha düşük bulunmuştur (0,7(0,6-0,8) ve 0,84(0,7-0,98); p=0,010). A, E' velositeleri ve E/A oranı gruplar arasında farklılık göstermemiştir.

SONUÇ: Diferansiye tiroid kanseri nedeniyle TSH supresyon tedavisi alan hastalarda, klinik semptom olmamasına rağmen, farklı TSH supresyon düzeylerinde, miyokard yapı ve fonksiyonlarında değişiklikler farklı olabilmektedir. Diyastolik disfonksiyonun erken saptanması açısından özellikle yüksek riskli DTK grubunda kardiyak değerlendirmelerin yapılması önemlidir. TSH supresyonu yapılan hastaların takiplerinin aksatılmaması ve supresyon seviyelerinin bireysel olarak uyarlanması gereklidir.

ANAHTAR KELİMELER: Diferansiye tiroid kanseri, TSH supresyon düzeyi, Diyastolik disfonksiyon.

ABSTRACT

OBJECTIVE: The aim of this study was to investigate the changes in cardiac structure and diastolic functions according to thyroid-stimulating hormone (TSH) suppression treatment degree in patients with differentiated thyroid cancer (DTC).

MATERIAL AND METHODS: This cross-sectional study included 125 patients with DTC who were being followed in the endocrinology clinic of our hospital and had been receiving thyroid hormone replacement and TSH suppression therapy for more than one year following thyroid surgery. In our study, patients were divided into groups based on the American Thyroid Association (ATA) 2015 guideline risk assessments. The patients were divided into three groups: first group patients with TSH levels <0.1 mIU/L (n=30), second group those with TSH levels between 0.1-0.5 mIU/L (n=56), and third group those with TSH levels between 0.5-2 mIU/L (n=39). The first two groups were classified as suppression groups, and the third as replacement (control) group. All patients underwent M-mode and pulse-vave tissue doppler echocardiography.

RESULTS: The group 1 with TSH interval <0.1 mIU/L had significantly longer left ventricular end-diastolic diameter (EDD) than the replacement group (45.35±3.54 vs. 42.74±6.08; p=0.016). E velocity, which measures mitral valve velocity at early diastolic filling, was found to be significantly lower in group 1 than in the replacement group (0.7(0.6-0.8) and 0.84(0.7-0.98); p=0.010). The groups did not differ in terms of A, E' velocities, or E/A ratio.

CONCLUSIONS: In patients receiving TSH suppression therapy for differentiated thyroid cancer, changes in myocardial structure and function may vary depending on the level of TSH suppression, even if clinical symptoms are absent. Cardiac evaluations are critical for early detection of diastolic dysfunction, particularly in the high-risk DTK group. Follow-up of patients receiving TSH suppression should not be interrupted, and suppression levels should be adjusted individually.

KEYWORDS: Differentiated thyroid cancer, TSH suppression level , Diastolic disfunctions.

Geliş Tarihi / Received: 11.03.2024
Kabul Tarihi / Accepted:01.07.2024
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Etik Kurul /Ethical Committee: Uşak Üniversitesi Etik Kurulu (30.06.2021/134-12).

GİRİŞ

Tiroid bezinin en sık görülen kanserleri diferansiye tiroid kanserleri (DTK) dir. Diferansiye tiroid kanserlerinde en yaygın görülen tip, papiller tiroid karsinomu (PTK) olup bunu foliküler tiroid karsinomu takip eder. Görüntüleme yöntemlerinin yaygın kullanımı nedeniyle PTK insidansı son yıllarda hızla artmakla birlikte prognozu oldukça iyidir. Çoğu kansere göre daha erken yaşlarda tanı konulmakta, insidansı kadınlarda erkeklerden yaklaşık 3 kat fazladır (1). DTK'de tiroidektomi sonrası hipotiroidizmi ve potansiyel tümör büyümesini önlemek için levotiroksin (L-T4) ile uzun süreli tirotropin (tiroid-stimulan hormon, TSH) supresyon tedavisi uygulanmaktadır (2). Son kılavuzlar hastalığın rekürrens ihtimaline göre belirlenen risk stratifikasyonuyla birlikte tedavi yan etkilerini de değerlendirerek altta yatan ko-morbiditelere göre bireyselleştirilmiş TSH supresyon seviyelerini önermektedir. Amerikan Tiroid Cemiyeti (American Thyroid Association; ATA) kılavuzunda düşük riskli hastalar için TSH seviyelerinin 0,5-2 mU/L, orta riskli hastalar için 0,1- 0,5 mU/L arasında ve yüksek riskli hastalar için <0,1 mU/L tutulması önerilmektedir (3).

Tiroid hormonları miyokartta direkt inotrop etki göstermekte, periferik vasküler direnci azaltmakta, kalp hızı ve atım hacmini artırmaktadır (4, 5). TSH supresyon tedavisi (TSHST) alan DTK'lı hastalarda subklinik hipertiroidizm ya da ekzojen olarak indüklenmiş olan ılımlı tirotoksikoz görülebilmektedir. Subklinik hipertiroidizm sistolik ve diastolik kardiyak fonksiyonlarda bozukluk yapabileceği gösterilmiştir (6). TSH supresyon tedavi süresinin kardiyak fonksiyonları olumsuz etkilediği bazı çalışmalarda gösterilmiş olmakla beraber, diğer çalışmalarda anlamlı fark saptanmamıştır (7 - 11). Sonuç olarak DTK'li hastalarda TSHST'nin uzun dönemde kalp fonksiyonlarına etkilerini değerlendiren araştırmalar sınırlıdır ve sonuçları çelişkilidir. Ayrıca bu durum TSH supresyon derecelerine göre incelenmemiştir. Bu çalışmanın amacı DTK'lı hastalarda farklı TSH supresyon düzeyine göre kardiyak yapı ve diyastolik fonksiyonlardaki değişikliklerin araştırılmasıdır.

GEREÇ VE YÖNTEM

Hasta Seçimi

Kesitsel olarak dizayn edilen bu araştırmaya hastanemiz Endokrinoloji polikliniğinde takipli, tiroid cerrahisi sonrası bir yıldan uzun süredir tiroid hormon replasmanı ve TSH supresyon tedavisi alan 125 DTK'lı hasta dahil edildi. Bilinen kardiyovasküler hastalık, başka bir organda malignite, diabetes mellitus, hipertansiyon, kronik böbrek hastalığı veya kronik karaciğer hastalığı öyküsü olan, herhangi bir elektrolit bozukluğu olan, aritmojenik yan etkisi olan bir ilaç kullanan ve TSH değeri 2 mU/L'den yüksek bulunan hastalar çalışma dışı tutuldu. Çalışmaya dâhil edilen hastaların demografik bilgileri [cinsiyet, yaş, boy, vücut ağırlığı, beden kitle indeksi (BKI)], tiroid kanseri tipi ve ATA kılavuzuna göre risk stratifikasyonu, Levotiroksin (LT4) tedavi süresi ve dozu kaydedildi. Çalışmamızda olgular ATA kılavuzuna risk değerlendirmelerine uygun olarak gruplara ayrıldı. Birinci grup TSH seviyesi <0,1 mIU/L olan hastalar (n:30), ikinci grup TSH düzeyi 0,1-0,5 mIU/L arasında olanlar (n:56) ve üçüncü grup ise TSH düzeyi 0,5-2 mIU/L arasında olanlar (n:39) şeklinde üç gruba kategorize edildi. İlk iki grup, supresyon, 3. grup ise replasman (kontrol) grubu olarak belirlenmiştir. Tüm hastaların tiroid fonksiyonları (TSH, (serbest T4- ST4), glukoz, lipid ölçümleri, böbrek fonksiyon testleri, elektrolit ölçümleri yapılmış, dahil edilme kriterlerine uymayan sonuçları olan vakalar çalışma dışı tutulmuştur. Olguların kan basıncı, hasta otururken 10 dakika dinlendikten sonra civalı tansiyon aleti kullanılarak ölçülmüştür.

Ekokardiografi Analizleri

Tüm hastaların sol lateral dekübitus pozisyonunda iken, transtorasik olarak, ACUSON SC2000 Ultrason Sistemi ve 1,5-4,6 MHz transdüser ile ekokardiyografi değerlendirmeleri yapılmıştır. Ekokardiyografi parametreleri ardışık 3 ölçümün ortalaması olarak alınarak değerlendirildi. M-mode ekokardiyografi incelemeleri Amerikan Ekokardiyografi Derneği (ASE) klavuzuna göre yapılmıştır (12). Diyastol sonunda sol ventrikül çapı (EDD), sistol sonunda sol ventrikül çapı (ESD), sol ventrikülün kitlesi (LVM), sol ventrikülün kitle indeksi (LVMI), interventriküler septumun kalınlığı (IVST), sol ventrikülün posterior duvar kalınlığı (LVPWT) ve sol atriyumun çapı (LAD) ve Teichholtz yöntemiyle Ejeksiyon fraksiyonu (EF), ölçüldü. Pulsed wave doku doppler ekokardiyografi değerlendirmeleri de ASE klavuzu önerilerine uygun olarak yapılmıştır (12). Diyastolik fonksiyonların değerlendirilmesinde; E, erken diyastol dolumu sırasında mitral kapak velositesini, A; geç diyastol dolumu sırasında

mitral kapak velositesini, E'; erken diyastolde mitral annulus velositesini, A', geç diyastolde mitral annular velositeyi değerlendirmektedir. Pulse dopler kayıtları, örnek volümü annüler çizginin 1 cm üzerindeki mitral kapak uçlarına denk gelen noktaya koyarak alınmıştır. E/A oranı, mitral kapağın E ve A akım hızlarının maksimum ölçümlerine göre hesaplandı. Erken (E') ve geç (A') diyastolik hızlar ve bunların oranları (E'/A'), septal ve lateral duvarlardan ölçüldü, E' ve A' velositelerinin artış ve azalma zamanları hesaplandı.

Etik Kurul

Bu araştırma "Helsinki Bildirgesi"nde belirtilen etik kurallara göre yürütülmüş ve Uşak Üniversitesi Tıp Fakültesi Yerel Etik Kurulunca onaylanmıştır (30.06.2021 referans numarası/Protokol no: 134–12). Katılımcılara çalışmanın amacı ve protokolü ayrıntılı olarak anlatılarak yazılı onamları alınmıştır.

İstatistiksel Analiz

Verilerin analizinde SPSS Statistics 18 kullanılmıştır. Shapiro-Wilk testi ile sürekli değişkenlerin normal dağılıma uygunluğu incelenmiştir. Kategorik değişkenler frekans (n) ve yüzdeyle (%), sürekli değişkenler ortalama±standart sapma (SS), medyan (IQR: 25-75) ile ifade edilmiştir. Pearson Ki-kare, Yates düzeltmesi, Fisher-Exact Test, Monte Carlo test ve Bonferroni düzeltmesi kategorik değişkenlerin analizinde kullanılmıştır. İkiden fazla bağımsız grup karşılaştırıldığında parametrik test varsayımları sağlanıyorsa One Way ANOVA ve post hoc LSD testi, sağlanmıyorsa Kruskal Wallis testi ve post hoc Bonferroni düzeltmesi yapılmıştır. Pearson korelasyon testi ile sürekli değişkenler arasındaki ilişki değerlendirilmiştir. İstatistiki anlamlılık seviyesi 0,05 olarak alınmıştır.

BULGULAR

Klinik, Demografik Veriler ve Tiroid Fonksiyonları

Çalışmaya toplam 125 hasta dâhil edilmiş olup vakaların 113'ü (%90,4) kadın, 12'si (%9,6) erkeklerden oluşmaktadır. Yaş ve BKI ortalamaları sırasıyla 42±6 yıl ve 29,55±6,46 kg/m^2 bulunmuştur. Tiroid kanseri alt türü, tiroid kanseri risk stratifikasyonu, LT4 tedavi süresi ve doz aralığı **Tablo 1** de gösterilmektedir. Hastaların %39,2'si ≥ 150 mcg, %20'si ≤100mcg ve 40,8'i 100-150 mcg arasında LT4 replasman tedavisi alıyordu. Hastaların 120'sinde (%96) papiller tiroid karsinomu ve 5'inde (%4,0) foliküler tiroid karsinomu mevcuttu. Vakaların %42,4'ünde 5 yıldan uzun süredir ve %16'sın da 10 yıldan uzun LT4 maruziyeti tespit edilmiştir (Tablo 1). Levotiroksin kullanım süresi açısından 3 grup arasında istatistiksel farklılık izlenmemiştir.

Tablo 1: Hastaların Bazal Klinik Özellikleri

Hasta Sayısı (n=125)	Sayı (n)	Yüzde (%)
LT4 Dozu (mcg/gün)		
≤100	25	20,0
100-150	51	40,8
≥150	49	39,2
LT4 tedavi süresi (yıl)		
1-5	52	41,6
6-9	53	42,4
>10	20	16,0
Histolojik tip		
Papiller	120	96
Foliküler	5	4,0
RAI		
Yok	59	47,2
Var	66	52,8
ATA risk stratification		
Düşük risk	100	80,0
Orta risk	18	14,4
Yüksek risk	7	5,6

LT4: Levotiroksin, RAI: Radyoaktif iyot tedavisi, ATA: American Thyroid Association

Grupların karşılaştırmalı analizlerinde demografik verilerinde (BKI, yaş, cinsiyet) ve kan basınçlarında anlamlı bir farklılık gözlemlenmemiştir. Birinci grubun %85,2'si, 2. grubun %90,9'u ve 3. grubun %93'ü kadınlardan oluşmaktadır. Her 3 grupta serbest-T4 (sT4) değerleri birbirinden farklı olup, 1. grupta ST4 düzeyleri, sırasıyla 2. ve 3. gruba (replasman grubu) göre (p:0,014 ve p<0,001), 2. grupta sT4 değerleri ise replasman grubuna (3. grup) göre daha yüksek olarak tespit edilmiştir (P:0.002) **(Tablo 2)**. Ancak tüm gruplarda ST4 normal sınırlar içerisindedir.

Tablo 2: TSH Düzeylerine Göre Demografik Özellikler, Kan Basıncı Ölçümleri ve Tiroid Fonksiyon Testleri

TSH Aralığı(mIU/L)	<0,1 (n=27) Grup-1	0,1-0,5 (n=55) Grup-2	0,5-2 (n=43) Grup-3	p	p^{1-2}	p^{1-3}	p^{2-3}
Yaş (yıl)	44(38-47)	41(38-46)	44(38-47)	0,551ᶞ			
Boy (cm)	162(157-167)	163(158-165)	160(155-165)	0,415ᶞ			
Kilo (kg)	74±17	77±15	80±15	0,297ᶠ			
BKI (kg/m^2)	27,5(23,3-32,5)	28,3(24-33,1)	29,6(25-35)	0,240ᶞ			
Cinsiyet				0,627*			
Kadın	23(85,2)	50(90,9)	40(93)				
Erkek	4(14,8)	5(9,1)	3(7)				
Kan Basıncı				pᶞ			
SKB (mmHg)	120(110-120)	120(120-125)	120(120-120)	0,575			
DKB (mmHg)	70(70-70)	70(70-80)	70(70-80)	0,387			
TFT							
ST4	1,51±0,16	1,4±0,18	1,29±0,19	<0,001ᶠ	0,014	<0,001	0,002
TSH	0,04(0,01-0,06)	0,25(0,17-0,40)	0,87(0,65-1,15)	<0,001ᶞ	<0,001	<0,001	<0,001

ᶞ Kruskal WallisH test, *med(IQR)* ᶠOneway Anova testi, *ort±SS* *Pearson ki-kare testi, Fisher exact test, *n (%)*
BKI: Beden kitle indeksi, DKB: diastolik kan basıncı, SKB: sistolik kan basıncı,

TFT: Tiroid fonksiyon testleri, ST4: serbest T4

Ekokardiografi Sonuçları

Tüm hastalara M-mode ekokardiyografi yapılmıştır. Sol ventrikülün diyastol sonu çapı (EDD), TSH aralığı <0,1 mIU/L olan 1. supresyon grubunda, 0,5-2 mIU/L aralığında olanlara yani replasman grubundaki hastalardan anlamlı olarak daha uzundur (45,35±3,54 ve 42,74±6,08; p=0,016). İkinci supresyon grubunda, 3. gruba (replasman grubu) göre EDD daha uzun olmakla beraber istatistiksel öneme ulaşmamıştır.

Teichholtz yöntemi ile bakılan EF da ve M-mode EKO ile bakılan diğer sistolik ve diastolik parametrelerde gruplar arası fark saptanmamıştır **(Tablo 3)**.

Tablo 3: TSH Supresyon Derecesine Göre Ekokardiyografik Parametreler

TSH Aralığı (mIU/L)	<0,1 (n=27) Grup-1	0,1-0,5 (n=55) Grup-2	0,5-2(n=43) Grup-3	P	p1-2	P1-3	p2-3
IVST (mm)	9(8-10)	9(8-10)	9(8-10)	0,701[k]	-	-	-
LVPWT (mm)	8(8-10)	8(7-9)	9(8-10)	0,078[k]	-	-	-
LVM(g)	114,13(101,3-140,47)	118,67(97,34-147,83)	132,74(108,79-152,95)	0,284[k]	-	-	-
LVMI (g/m^2)	65,78(58,41-76,04)	66,34(54,59-78,8)	68,3(55,93-78,23)	0,604[k]	-	-	-
EDD (mm)	45,35±3,54	44,73±3,9	42,74±6,08	0,049[f]	0,054	0,016	0,484
ESD (mm)	29(27-32)	30(28-32)	30(28-32)	0,699[k]	-	-	-
LAD (mm)	30,33±4,86	30,55±3,85	31,79±3,36	0,206[f]	-	-	-
E (m/s)	0,7(0,6-0,8)	0,7(0,6-0,9)	0,84(0,7-0,98)	0,011[k]	0,999	0,010	0,157
A (m/s)	0,74(0,6-0,8)	0,73(0,61-0,85)	0,75(0,6-0,82)	0,773[k]	-	-	-
E' (cm/s)	9,95±3,34	10,96±3,68	10,76±3,5	0,360[f]	-	-	-
E/A (oran)	1(0,8-1,3)	1(0,8-1,3)	1,2(0,9-1,4)	0,210[k]	-	-	-
E/E' (oran)	7,5(5,7-9,7)	6,9(5,6-8,8)	8,2(6,7-10)	0,330[k]	-	-	-
EF (%)	65(60-65)	65(60-65)	65(60-65)	0,363[k]	-	-	-

[k]Kruskal WallisH test, Post Hoc Bonferroni düzeltmesi, *med(IQR)* [f]Oneway Anova testi, Post Hoc LSD test, *ort±SS.*

IVST: İntraventriküler septum kalınlığı, LVPWT: Sol ventrikül arka duvar kalınlığı, LVM: Sol ventrikül kütlesi, LVMI: Sol ventrikül kütle indeksi, EDD: Diastol sonu çap, ESD: Sistol sonu çap, LAD: Sol atrium çapı, E: erken diyastolik dolumda mitral kapak velositesi, A: geç diyastolik dolumda mitral kapak velositesi, E': erken diyastolik mitral annular velosite, EF: ejeksiyon fraksiyonu

Pulsed wave doku doppler ekokardiyografide erken diastolik doluş sırasındaki mitral kapak velositesini gösteren E, grup 1 de, 3. gruba (replasman) göre daha düşük bulunmuştur (0,7(0,6-0,8) ve 0,84(0,7-0,98); p=0,010). Diğer doku dopler değerleri olan A, E' velositeleri ve E/A oranı her 3 grup arasında farklılık göstermemiştir (Tablo 3). Hastaların ST4 düzeyleri ile EDD ve E velositesi arasında yapılan korelasyon analizinde ST4 ile E arasında negatif korelasyon tespit edilmiştir (r=-0,204; p=0,023)**(Tablo 4)**.

Tablo 4: EDD ve E Parametreleri ile ST4 Arasındaki Korelasyon İlişkisi

		EDD	E
ST4(ng/dL)	**R**	0,028	**-0,204**
	P	0,756	**0,023**

EDD: Diastol sonu çap, E: erken diyastolik dolumda mitral kapak velositesi

ST4: serbest T4 Spearman Rho Korelasyon Analizi

TARTIŞMA

Bu çalışmanın ana sonucu, hiçbir klinik semptom olmamasına rağmen, TSHST alan hastalarda TSH supresyon derecesine göre replasman grubu ile karşılaştırıldığında diyastolik fonksiyonlarda farklılık olabileceğinin gösterilmiş olmasıdır. Yakın zamanda yapılmış büyük vaka sayısına sahip iki retrospektif kohort çalışmasında DTK'lı hastalarda sırasıyla koroner kalp hastalığı, iskemik inme ve atrial fibrilasyon (AF) insidansının sağlıklı popülasyona göre arttığı gösterilmiştir (13, 14). Bu durumun TSH supresyon süresine mi yoksa supresyon derecesine mi bağlı olduğu hala tam olarak belirlenebilmiş değildir. Bundan dolayı farklı derecelerde TSH baskılanmasının kardiyovasküler morbidite ve mortalite üzerindeki etkilerinin açıklığa kavuşturulması gerekmektedir. Subklinik tiroid disfonksiyonu durumlarında, dolaşımdaki tiroid hormonu seviyelerindeki minimal ancak kalıcı değişiklikler kardiovasküler sistemde bozulmalara neden olabilmektedir. Tiroid hormonlarının miyokardiyal kontraktiliteyi ve kalp atım hızını artırarak ve sistemik vasküler direnci azaltarak kardiyak debiyi artırdığı bilinmektedir. Subklinik hipertiroidizmin, kalp hızı artışı, atriyal aritmiler, sol ventrikül kitlesinde artış, ventriküler relaksasyonda bozulma, egzersiz kapasitesinde bozulma ve kardiyovasküler mortalite riskiyle ilişkisini gösteren çalışmalar mevcuttur (4, 5). Bilindiği üzere DTK'de LT4 ile TSHST alan, hastalar eksojen subklinik hipertiroidizm veya farklı düzylerde tirotoksikozla karşılaşabilmektedir. Son kılavuzlar hastalığın rekürrens ihtimaline göre oluşturulan risk sınıflamasıyla birlikte tedavinin yan etkilerini de gözeterek olası ko-morbiditelere göre bireyselleştirilmiş TSH supresyon seviyelerini önermektedir (3). Bu çalışmayla DTK'lı hastalarda, farklı derecelerdeki TSH supresyonunun kardiyovasküler fonksiyonlar üzerindeki etkilerinin açıklığa kavuşturulması amaçlanmıştır.

Çalışmamızda TSH <0,1 mIU/L olan belirgin supresyon grubundaki hastaların sol ventrikül (LV) EDD ölçümleri replasman (3. grup) grubundan daha uzun olarak saptanmıştır (45,35±3,54 ve 42,74±6,08; p=0,016). Yani TSH supresyon derecesinin sol ventrikül diastolik fonksiyonlarını etkileyebileceği gösterilmiştir. Bildiğimiz kadarıyla daha önce DTK'lı hastalarda TSH supresyon derecelerine göre ekokardiyografik olarak diastolik parametreleri değerlendiren çalışma bulunmamaktadır. Bir çalışmada TSH supresyon süresi 5-9 yıl arasındaki DTK'li hasta ve kontrol grubu ekokardiyografileri yapılarak değerlendirilmiş ve uzun süreli TSHST'nin kardiyak yapı ve fonksiyonlar açısından güvenilir olduğu düşünülmüştür. Ancak bu çalışmada vaka sayısı kısıtlı olup TSH supresyon derecesine göre analiz yapılmamıştır (10).

Uzun süreli LT4 tedavisinin, kontrollere kıyasla sol ventrikül kitle indeksinde ve kalp hızında artış, kardiyak rezerv ve egzersiz toleransında azalmayla birlikte olduğu Biondi ve ark. tarafından yapılan birkaç çalışmayla gösterilmiştir.

Bu çalışmaların çoğu heterojen gruplarda veya semptomatik vakalarda yapılmış olup genellikle küçük gruplarda gerçekleştirilmiştir (15, 16). Bizim çalışmamızda hastaların tümü asemptomatik, kardiyovasküler hastalığı ve ko-morbiditeleri olmayan 50 yaş altı DTK'lı homojen bir gruptan oluşmakta olup, belirgin supresyon yapılan 1. grupta EDD değerleri replasman grubuna göre uzun bulunmuştur. Bilindiği gibi E velositesi erken diyastolik dolumda mitral kapak velositesini göstermektedir. Çalışmamızda E velositesi 1. grupta (yüksek riskli), replasman grubuna kıyasla anlamlı olarak düşük saptanmıştır. Aynı şekilde E velositesi 2. grupta da replasman grubuna göre düşük tespit edilse de istatiksel anlam göstermemiştir. Çeşitli araştırmalarda E, A, E' velositeleri değerlendirilmiş olup fark bulunmadığı tespit edilse de E velositesinin çalışmamızda olduğu diğer bazı çalışmalarda da düşük olduğu tespit edilmiştir (8, 10, 11, 17).

Diyastolik disfonksiyonun erken evresinde, sol ventriküler relaksasyonunda bozulma ve hızlı doluş peryodunda sol ventriküler basınçda düşme sonucu diyastolik dolum azalır. Bundan dolayı ekokardiyogramda E dalgası amplitüdünde düşme görülür. Hızlı dolma sırasında sol atriyumda bulunan kan uygun miktarda sol ventriküle iletilemediği için geç diyastolik sol atrium volümü yüksek kalır. Dolayısıyla atriyumun kasılması artarak ve kompansatuvar doluş görülür. Bu durum ekokardiyografiye A dalgası amplitüdünde artma olarak yansır ve E/A 1'in altına düşer (18). Çalışmamızda E velositesi belirgin supresyon grubunda replasman grubuna göre azalmıştı. Bu durum TSH supresyon düzeyi arttıkça kardiyak etkilenmenin değişebileceğini göstermektedir. Diyastolik disfonksiyonun erken saptanması açısından özellikle yüksek riskli DTK grubunda kardiyak değerlendirmelerin yapılması önemlidir.

Bir çalışmada DTK hastalarında LT4 ile TSH supresyon tedavisinin sol ventrikül kitlesini artırdığı ve diyastolik disfonksiyona sebep olduğu bildirilmiştir. Yazarlar semptomatik olan vakalara beta bloker uyguladıklarında semptom ve bulguların düzeldiğini göstermişler ve çalışmamızdakine benzer şekilde E velositesini kontrol grubuna göre düşük bulmuşlardır. Araştırıcılar TSH baskılayıcı tedavi alan hastalarda artan kalp işinin de diyastolik fonksiyon bozukluğunun bir nedeni olduğu vurgulamışlardır (19). Uzun süreli olarak sabit dozda LT4 ile TSHST alan hastaların değerlendirildiği bir diğer araştırma da sol ventrikül EDD'de anlamlı bir artış olduğu saptanmıştır (20). Çalışmamız bu çalışmayı destekler niteliktedir. Çalışmamız ve bu çalışmalar, uzun dönem TSHST alan hastaların kardiyak açıdan değerlendirilmesinin günümüzde halen önemli olduğunu göstermektedir. Bizim çalışmamamızın diğerlerinden farkı, farklı supresyon düzeylerinde izlenen DTK vakalarında kardiyak etkilenmenin farklı olabileceğinin gösterilmiş olmasıdır. Supresyon derecesi arttıkça kardiak etkilenme artabilmektedir. Bu nedenle DTK hastaların risk durumlarına göre sınıflanması ve ATA klavuzunda önerildiği gibi devam eden risk stratifikasyonu yapılarak risk grubunun tekrar değerlendirilmesi ve buna göre gerekirse supresyon düzeyinin gevşetilmesi önemlidir.

Çalışmamızın güçlü yanları tümü DTK'lı homojen bir gruptan oluşması, hastaların risk gruplarına ayrılarak karşılaştırılması, LT4 maruziyetinin 1 yıl ve daha üzerinde olması, kalp hastalığı ve/veya semptomatik olanların çalışmaya dahil edilmemesi ve bakılan tüm parametrelerin alanında etkin bir kardiyoloji uzmanı tarafından kör olarak değerlendirilmesidir.

Çalışmamızın sınırlı yanlarıysa, nispeten vaka sayısının az olması, sağlıklı kontrol grubunun olmaması, hastaların LT4 maruziyet süresine göre kardiyak parametreler açsından karşılaştırılmaması ve çalışmanın tek merkezli olmasıdır.

Sonuç olarak, bu çalışmada DTK'lı hastalarda farklı TSH supresyon düzeylerinde, miyokard yapısında diyastolik fonksiyonlarda değişiklikler olabileceği gösterilmiştir. Çalışma grubumuzun asemptomatik ve kardiovasküler hastalığı olmayan bireylerden oluştuğu düşünüldüğünde bu durum dikkate değer görünmektedir. Zira kardiyovasküler hastalığı ya da ek komorbiditesi olanlarda kardiyak değerlendirme ve TSHST düzeyine dikkat etmek daha da önemli olacaktır. Diyastolik disfonksiyonun erken saptanması açısından özellikle yüksek riskli DTK grubunda kardiyak değerlendirmelerin yapılması önemlidir. Ayrıca düşük risk kategorisindeki hastalarda daha düşük derecede TSH baskılanması gerekliliği klinik pratikte gözden kaçırılmamalıdır.

Son olarak, TSH supresyonu yapılan hastaların takiplerinin aksatılmaması ve supresyon seviyelerinin bireysel olarak uyarlanması mantıklı görünmektedir.

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Kocatepe Tıp Dergisi
Kocatepe Medical Journal
25:490-495/Ekim 2024 Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

YAŞLI HASTALARDA ERCP SONRASI KOLESİSTEKTOMİ SONUÇLARI

RESULTS OF CHOLECYSTECTOMY AFTER ERCP IN ELDERLY PATIENTS

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ÖZET

AMAÇ: Bu çalışma ile endoskopik retrograd kolanjiopankreatikografi (ERCP) sonrası yapılan kolesistektomi operasyonlarında ileri yaşın laparaskopik kolesistektomi için bir risk faktörü olup olmadığının değerlendirilmesi amaçlanmıştır.

GEREÇ VE YÖNTEM: 01.01.2021 – 01.05.2023 tarihleri arasında Afyonkarahisar Sağlık Bilimleri Üniversitesi Tıp Fakültesi Genel Cerrahi kliniğinde ERCP yapılan ve ERCP işlemi sonrasında ERCP'ye bağlı komplikasyon görülmeyen kolesistektomi yapılmış olan 246 hasta çalışmaya dahil edilmiştir. Hastaların sosyodemografik özellikleri, ameliyat sonrası hastanede kalış süreleri, ameliyat sonrası komplikasyon durumları, laparoskopiden açık ameliyata geçme durumları ve ASA (American Society Anesthesiologists) skorları karşılaştırılmıştır.

BULGULAR: Yaşlara göre ayrılan hasta grupları incelendiğinde postoperatif komplikasyon açısından istatistiksel anlamda fark olmadığı tespit edildi (p=0,433). Her iki grubun ameliyat sonrası hastanede kalış günleri karşılaştırıldığında 75 yaş ve üzeri hastaların, 75 yaş altı hastalara göre daha uzun süre hastanede kaldıkları görülmüştür (p<0,001). Açık ameliyata geçme oranları arasında ise herhangi bir istatistiksel fark olmadığı görülmüştür (p=0,539).

SONUÇ: Mevcut çalışma sonuçları bizlere semptomatik safra kesesi ve safra yolları taşı olan hastalarda yaşa bağlı olmaksızın hastaların tamamlayıcı tedavilerinin yapılması gerektiğini göstermektedir. Yaşlılık, ERCP sonrası laparoskopik kolesistektomi yapılması için bir risk faktörü değildir.

ANAHTAR KELİMELER: ERCP, Kolesistektomi, Komplikasyonlar, Yaşlı.

ABSTRACT

OBJECTIVE: The purpose of this study was to determine if being older increases the risk of laparoscopic cholecystectomy in cholecystectomy operations performed after endoscopic retrograde cholangiopancreatography (ERCP).

MATERIAL AND METHODS: 246 patients who underwent ERCP at the General Surgery Clinic of Afyonkarahisar Health Sciences University between 01.01.2021 and 01.05.2023 and who underwent cholecystectomy without any ERCP-related complications after the ERCP procedure were included in the study. The sociodemographic characteristics of the patients, postoperative hospital stay, postoperative complications, converting from laparoscopy to open surgery, and ASA (American Society Anesthesiologists) scores were compared.

RESULTS: Upon analyzing the patient groups based on age, it was found that there was no significant variation in terms of postoperative complications (p = 0.433). Patients 75 years of age and older stayed in the hospital longer than patients under 75 years of age (p<0.001), according to a comparison of the postoperative hospital stay days of the two groups. It was observed that there was no statistical difference between the rates of converting to open surgery (p = 0.539).

CONCLUSIONS: The current study results show us that complementary treatments should be applied to patients with symptomatic gallbladder and biliary stones, regardless of age. Old age is not a risk factor for laparoscopic cholecystectomy after ERCP.

KEYWORDS: ERCP, Cholecystectomy, Complications, Elderly.

Geliş Tarihi / Received: 07.03.2024
Kabul Tarihi / Accepted: 01.07.2024
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Etik Kurul /Ethical Committee: Afyonkarahisar Sağlık Bilimleri Üniversitesi Etik Kurulu (07.07.2023/2023/298).

GİRİŞ

Günümüzde tıp alanındaki gelişmeler sayesinde hastalıkların tanısı kolaylaşmış, tedavi süreleri kısalmış ve hastaların beklenen yaşam sürelerinin arttığı görülmüştür. Kolelitiazis hastalığının görülme sıklığının yaşla birlikte arttığı bilinmektedir. Bu gelişmeler doğrultusunda cerrahi müdahale ihtiyacı olan kolelitiazisli yaşlı hasta sayısı artmış ve tıp alanındaki gelişmelere bağlı olarak ileri yaş hastalara uygulanan cerrahi işlemlerin başarı oranı da yükselmiştir (1). Laparoskopik kolesistektomi, semptomatik kolelitiazisin tedavisinde uzun yıllardır altın standart olarak kabul edilmiş yöntemdir (2). Ancak ileri yaştaki hastalara uygulanacak cerrahi işlemlerde yaşın getirdiği yandaş hastalıklar, intraoperatif ve post operatif komplikasyon riskinin artması gibi sebepler cerrahı kaygılandıran unsurlardır (3). Semptomatik kolelitiazis etkin olarak tedavi edilmediği takdirde akut kolesistit, akut kolesistite bağlı peritonit ve safra kesesi perforasyonu gibi morbiditesi yüksek hastalıklara yol açabileceği unutulmamalıdır (4).

Kolelitiazisin önemli komplikasyonlarından biri koledokolelitiyazistir (5). Koledokolelitiyaz primer olarak veya safra kesesindeki taşların koledok lümenine düşmesi ile oluşur. Kolelitiazis ve koledokolelitiyazis birlikte görülme sıklığı yaşlı popülasyonda, genç popülasyona göre 4 kat daha fazla olduğu bilinmektedir (6). Koledok taşları pankreatit ve kolanjit gibi ciddi komplikasyonlarla ilişkilidir. Bu sebepten dolayı koledok taşları asemptomatik olsalar bile çıkarılmaları gerekmektedir (7). Endoskopik retrograd kolanjiopankreatikografi (ERCP) koledokolelitiyazisin tanısında altın standarttır. Ayrıca diğer noninvaziv görüntüleme yöntemlerine göre terapötik üstünlüğü olduğu için koledokolelitiyazisin tedavisinde cerrahinin yerini almıştır (8).

ERCP: Ampulla Vateri' den duodenoskop yardımıyla kontrast madde verilerek, karaciğer, pankreas, safra kesesi ve pankreası drene eden kanalların X-ray yardımıyla görüntüleme işlemidir (9). ERCP işlemi sedo-analjezi veya genel anestezi verilerek hastalara uygulanabilmektedir. Bundan dolayı bu işlemin ileri yaş hastalarda uygulanabilirliği hem anestezi hem de cerrahi açıdan zorlaşmaktadır. Yapılan çalışmalarda hem tanı hem de tedavi için uygulanan ERCP işleminin yaşlı popülasyonda etkinliği gösterilmiştir (10 - 11). Mevcut çalışma ile büyük risk olarak görülen ileri yaşın ERCP sonrası yapılan laparaskopik kolesistektomilerde bir risk faktörü olup olmadığının değerlendirilmesi amaçlanmıştır. Çalışma sonucunda elde edilen verilerin ileri yaş hastalara uygulanacak cerrahi prosedürlerin seçiminde yol göstermesi beklenmektedir.

GEREÇ VE YÖNTEM

Çalışmanın onayı alındıktan sonra 01.01.2021 – 01.05.2023 tarihleri arasında Afyonkarahisar Sağlık Bilimleri Üniversitesi Genel Cerrahi kliniğinde ERCP yapılan ve ERCP işlemi sonrasında ERCP'ye bağlı komplikasyon görülmeyen kolesistektomi yapılmış olan 269 hastanın dosyası retrospektif olarak incelendi. 2 hastanın gebe olması, 4 hastanın safra kesesi patolojisinin sonucunun malign olması, 4 hastanın postoperatif dönemde yoğun bakımda kardiyo-pulmoner nedenlerden dolayı ex olması, 8 hastanın üst batın cerrahisi öyküsü nedeniyle direkt olarak açık kolesistektomi ile ameliyatına alınması, 5 hastanın da ameliyat sonrası başka bölümlere devir edilmesi sebebiyle çalışmaya dahil edilmedi ve mevcut çalışma 246 hasta ile tamamlandı.

Hastaların hastaneye başvuru sebepleri karın ağrısı ve sarılık şikayetleriydi. Hastaların tamamında radyolojik yöntemlerle (MR Kolanjiografi, Bilgisayarlı Tomografi ve Ultrasonografi) hem koledok taşının hem de safra kesesi taşının olduğu gösterilmiş olup, laboratuvar değerlerinde yüksek kolestaz enzim değerleri saptanmıştır. ERCP ile kolesistektomi arasında geçen süre hiçbir hastada 6 haftadan daha uzun değildi.

Çalışmamızda ERCP sonrası laparoskopik kolesistektomi yapılan hastalar Dünya Sağlık Örgütü (DSÖ) yaşlılık için kronolojik tanımlaması dikkate alınarak "75 yaş altı" ve "75 yaş ve üzeri" olarak ikiye ayrılmıştır. 75 yaş ve üzeri Grup 1, 75 yaş altı Grup 2 olarak belirlendi. Grup 1 toplamda 74 hastadan, Grup 2 de 172 hastan oluştu. Hastaların sosyodemografik özellikleri, ameliyat sonrası hastanede kalış süreleri, ameliyat sonrası komplikasyon durumları, laparoskopiden açık ameliyata geçme durumları ve ASA (American Society Anesthesiologists) skorları karşılaştırılmıştır. Ameliyat tekniği; Genel anestezi altında toplam 4 porttan Amerikan tekniği ile yazarlar tarafından yapıldı. Tüm hastalara batın içi dren yerleştirildi. Tüm hastalara 1 gram sefalosporin ile cerrahi profilaksi uygulandı.

Etik Kurul

Araştırma için Afyonkarahisar Sağlık Bilimleri Üniversitesi Tıp Fakültesi Etik Komitesi'nin 07.07.2023 tarih ve 2023/298 sayılı kararı ile etik kurul onayı alınmıştır.

İstatistiksel Analiz

Verilerin normallik varsayımları Kolmogorov Smirnov testi ile incelendi. Normal dağılım özelliği göstermeyen sürekli değişkenlerin tanımlayıcı istatistiklerinde medyan ile çeyrekler arası aralık (IQR Inter quartile range) değerleri, kategorik değişkenlerin tanımlayıcı istatistiklerinde ise frekans (n) ve yüzde (%) değerleri verildi. Gruplar arası karşılaştırmalarda sürekli değişkenler için Mann Whitney U Test' i, kategorik değişkenler için ise Ki kare analizi/Fisher's Exact testi kullanıldı. Analizlerde IBM SPSS.25 programı kullanılmış ve anlamlılık düzeyi olarak p<0.05 değeri kabul edildi.

BULGULAR

Çalışmaya 74 (% 30,1) Grup 1, 172 (% 69,9) Grup 2'den olmak üzere toplam 246 hasta dahil edildi. Grup 1 de 39 (% 52,7) kadın hasta, 35 (% 47,3) erkek hasta oldu görüldü. Grup 2 de 94 (% 54,7) kadın hasta, 78 (% 45,3) erkek hasta olduğu görüldü. Her iki grupta kadın ve erkek hasta sayısında istatistiksel olarak anlamlı değişiklik bulunmadı (p=0,779). Grup 1 de en genç hasta 75 yaşında bulundu ve yaş ortalaması ve standart sapması 81.93 ± 3,25 olarak bulundu. Grup 2 de ise en genç hasta 18 yaşında ve yaş ortalaması 52.21 ± 25.65 bulundu. Beklenildiği üzere her iki grubun yaşları anlamlı derecede birbirinden farklıydı (p<0,001).

Her iki grubun ameliyat sonrası hastanede kalış günleri karşılaştırıldığında Grup 1 de 2.11 ± 0,73 gün, Grup 2 de 1.39 ± 0,61 gün olarak bulundu. Grup 1 hastalarının postoperatif hastanede kalış sürelerinin istatistiksel olarak da daha uzun sürede olduğu görüldü (p<0,001).

Her iki grupta da en sık görülen ASA değeri 2 dir. Grup 1 de 49 (%66,2) Grup 2 de 130 (%75,6) hastada ASA 2 değeri bulunmuştur. Toplam hastaların ASA skorlaması tabloda gösterilmiştir **(Tablo 1)**.

Grup 1 de toplamda 3 hastada postoperatif komplikasyon görüldü. 2 hastada postoperatif kanama görülmüş olup kan transfüzyonu yapıldı. Diğer hastada postoperatif 1.ve 2. günde safra fistülü gelişmiş ve sonraki takiplerinde fistül kesilmiştir. Grup 2 de ise toplam 4 hastada postoperatif dönemde kanama gelişti. 3 hastada kanama için kan transfüzyonu yapıldı ve 1 hastanın epigastrik trokar yerinden kanaması olduğu tespit edilmiş ve tekrar ameliyata alınıp hemostazı sağlanmıştır. Hastaların komplikasyon durumları tabloda gösterilmiştir (Tablo 1). Orantısal olarak Grup 1 de % 4,1 Grup 2 de % 2,3 oranında ameliyat sonrası komplikasyon görülmesine rağmen, istatistiksel olarak farklılık saptanmamıştır (p=0,433).

Açığa geçme kriteri olarak yeterli diseksiyonun yapılamamış olması ve Callot Üçgeni'nin tam olarak ortaya konulamaması belirlenmiştir. Toplam çalışmaya dahil edilen hastalardan 13 tanesinin kolesistektomisi laparoskopik olarak tamamlanılamayıp açık cerrahi yöntemle yapılabilmiştir. Bunlardan 5 tanesi Grup 1 hastası iken, 8 tanesi Grup 2 de bulunmaktaydı. Orantısal olarak Grup 1 % 6,8, Grup 2 % 4,7 olarak bulunmuştur. İstatistiksel olarak her iki grup arasında açığa geçme durumu arasında anlamlı farklılık bulunamamıştır (p=0,539).

Tablo 1: Grup 1 ve Grup 2'nin sosyodemografik verilerinin ve muayene bulguların karşılaştırılması

	Grup 2		Grup 1		p
	Medyan (IQR)		Medyan (IQR)		
Yaş	55.00 (41.25 – 65.00)		82.00 (80.00 – 84.00)		<.001
Hastanede kalış süresi	1.00 (1.00 – 2.00)		2.00 (2.00 – 2.00)		<.001
	n	%	n	%	
Cinsiyet					.779
Kadın	94	54.7	39	52.7	
Erkek	78	45.3	35	47.3	
ASA skoru[a]					-
1	25	14.5	0	0.0	
2	130	75.6	49	66.2	
3	17	9.9	23	31.1	
4	0	0.0	2	2.7	
Post-operatif komplikasyon					.433
Yok	168	97.7	71	95.9	
Var	4	2.3	3	4.1	
Açığa geçme					.539
Yok	164	95.3	69	93.2	
Var	8	4.7	5	6.8	

[a]Ki kare analizinin varsayımları karşılanmadığı için p değeri verilememiştir.

TARTIŞMA

Yaşlılığın standart bir tanımı olmamakla beraber fizyolojik, biyolojik, ekonomik veya sosyolojik olmak üzere pek çok alanda tanımı vardır. Dünya Sağlık Örgütü (DSÖ) yaşlılık için kronolojik tanımlamayı dikkate almıştır ve 74-84 yaş arasını yaşlı olarak ve 84 yaş üzerini de en yaşlı olarak tanımlamıştır. Çeşitli kılavuzlarda yaşlılığın sınıflanmasını kronolojik olarak 65 yaş veya 75 yaş olarak belirtilmektedir (12). Bizde bu çalışmada DSÖ'nün kronolojik sınıflamasına

göre hastaları 75 yaş üzeri ve 75 yaş altı olarak sınıfladık. Yaşla birlikte hipertansiyon, akciğer hastalıkları gibi rahatsızlıklarda artış olup bu da bu gruba yapılan cerrahi müdahalelerin sonucunu olumsuz olarak etkilemektedir ve cerrahi komplikasyonlar yaşla birlikte artmaktadır (13). Diğer yandan tıp alanında ki gelişmelere bağlı olarak ortalama yaşam süresinin artması ve safra kesesi ,safra yolları taşının yaşla birlikte görülme sıklığının artmasına bağlı olarak daha fazla sayıda yaşlı nüfusta semptomatik safra kesesi taşı ve safra yolu taşına bağlı olarak cerrahi işlem gereksinimi artmıştır (14). Yapılan ayrı ayrı çalışmalarda yaşlı popülasyonda hem ERCP'nin hem de laparoskopik kolesistektominin güvenle uygulanabileceği gösterilmiştir (15 - 17). Schreurs ve arkadaşlarının çalışmasında ERCP sonrası kolesistektomi yapılmadan takip edilen hastalar ile kolesistektomi yapılarak takip edilen hastalar arasında takip sürecinde tekrarlayan koledok taşı gelişimi ve kolanjit gelişimi açısından anlamlı bir fark bulunmamıştır (18). Güncel cerrahi text kitaplarında koledokolelitiazis semptomatik safra taşları başlığı altında değerlendirilmektedir. Tedavi olarak ERCP ile sfinkterotomi yapılarak koledok taşının temizlenmesinin ardından rutin laparoskopik kolesistektomi önerilmektedir (19). Bizde bu çalışmamızda 75 yaş üzeri ERCP yapılan ve sonrasında kolsistektomi yapılan hastaların sonuçlarını 75 yaş altı hastaların sonuçları ile karşılaştırdık.

Çalışmaya dahil edilen hastaların 133 (%54,06) kadın iken 113 (%45,94) erkek hasta olarak bulunmuştur. Aynı şekilde gruplarda da kadın hasta sayısının daha fazla olduğu görülmüştür. Safra taşları kadınlarda daha sık görüldüğü bilinmektedir ve çalışmamız literatür ile uyumludur (20). Grup1'de yaş ortalaması 81,93 olarak bulunmuş grup 2'de ise 52,21 dir. Köklü ve arkadaşlarının yaptığı yaşlı hastalarda ERCP ile ilgili çalışmada yaşlı grubun yaş ortalaması 74,93 genç grubun ortalaması 49,83 olarak bulunmuştur ve istatistiksel olarak anlamlıdır (10). Yine yaşlı hastalarda laparoskopik kolesistektominin risk faktörlerinin araştırıldığı bir diğer çalışmada yaşlı grubun ortalama yaşı 68,82 olarak bulunmuşken genç grubun yaş ortalaması 77,73 bulunmuştur (21). Bizim çalışmamızda gruplar arası yaş ortalaması istatiksel olarak da anlamlı bulunmuştur. Her iki grupta da en çok ASA2 değeri bulunmuştur. Laparoskopik cerrahinin, ameliyat sonrası hissedilen ağrı ve günlük hayata dönüş açısından açık cerrahiye göre daha üstün olduğu bilinmektedir (22). Yaşlı hastalarda açık ve laparoskopik kolesistektominin karşılaştırıldığı bir çalışmada laparoskopik kolesistektomi sonrası morbiditenin daha az olduğu ve bu yaş grubunda kontrendikasyon olmadığı sürece laparoskopik yaklaşımın uygulanması gerektiği belirtilmiştir (23). Bizde çalışmamızda laparoskopik yöntemle kolesistektomi yapılan hastaları dahil ettik. Laparoskopik elektif kolesistektomilerde açığa geçme oranı % 1,2 olarak bildiren çalışmalar mevcuttur (24). Akut kolesistit durumlarında açığa geçme oranının daha da arttığı bilinmektedir (25). Yaşlı hastalarda yapılan laparoskopik kolesistektomi sonuçları ile ilgili çalışmada 65-80 yaş arası grupta % 13 oranında açığa geçiş mevcutken 80 yaş ve üzeri grubunda bu oran %11 olarak belirtilmiştir (26). Yapılan geniş çaplı meta analizlerde de yaşlı popülasyonda laparoskopik ameliyattan açığa dönüş oranı % 7-39 aralığında gösterilmiştir (27). Bizim çalışmamızda bu oran yaşlı popülasyonda % 6,8, 75 yaş altı grupta % 4,7 olarak bulunmuştur. Bizim çalışmamızda bu oranın düşük olmasının sebebi geçirilmiş üst batın cerrahisi olan hastaların çalışmaya dahil edilmemiş olması ve diğer çalışmalarda açık cerrahiye dönüşüm sebebi olan koledok taşlarının çalışma grubumuzda olmamasından kaynaklanmaktadır. Orantısal olarak yaşlı grubun açık cerrahiye dönüşümü 75 yaş altı gruba göre daha fazladır. Bunun sebebi yaşlı hastalarda kardiyo-pulmoner yan etkileri sebebiyle laparoskopik cerrahide fazla ısrarcı davranamamak olabilir. İstatistiksel olarak her iki grupta arasında anlamlı bir farklılık yoktur.

Grup1'de 3 (%4,1) grup 2'de 4 (%2,3) olmak üzere toplamda 7 hastada (%2.84) postoperatif komplikasyon görülmüştür. Her iki grup arasında komplikasyon durumu bakımından istatistiksel anlam yoktur. Grup 2 'deki 1 hasta kanama sebebiyle tekrar ameliyata alınmıştır Bhandari ve ark. yaptığı bir çalışmada laparoskopik kolesistektomiye bağlı komplikasyon oranları genç ve yaşlı hastalarda sırası ile %14,6 ve %17,9 olarak bildirilmiş ve istatistiksel olarak anlamlı bulunmamıştır (28). Bizim çalışmamızda da istatistiksel olarak iki grup arasında fark yoktur. Oran olarak düşük bulunması

açığa geçiş oranımızın daha düşük olması ve açık cerrahide laparoskopik kolesistektomiye göre komplikasyon oranının daha düşük olmasından kaynaklandığını düşünüyoruz.

60 yaş altı ve 60 yaş üstü laparoskopik kolesistektomi yapılan hastalarla ile ilgili yapılan çalışmada hastanede kalış süreleri sırasıyla 1.08±1.14 ve 1.13±0.99 bulunmuştur (29). Bizim çalışmamızda genç grupta bu süre 75 yaş altında 1.39±0.61 ve 75 ve üzeri hastalarda 2.11±0.73 olarak anlamlı bulunmuştur. Bunun sebebinin yaptığımız çalışmada yaşlı grubun yaş ortalaması daha yüksek olduğu için ameliyat sonrası taburculuğun daha uzun sürmesinden kaynaklı olduğunu düşünüyoruz. Yapılan başka bir çalışmada ise yaşlı grubun ameliyat sonrası hastanede kalış süresinin daha uzun olduğu gösterilmiş ve bizim bulgularımıza benzerdir (3).

Mevcut çalışma sonuçları bizlere semptomatik safra kesesi ve safra yolları taşı olan hastalarda yaşa bağlı olmaksızın hastaların tamamlayıcı tedavilerinin yapılması gerektiğini göstermektedir. Yaşlılık ERCP sonrası kolesistektomi yapılması için bir risk faktörü değildir. Ancak yaşlı popülasyonun ameliyat sonrası normal yaşamlarına en erken dönemde dönebilmeleri ve ameliyat öncesi risk faktörlerinin tam olarak ortaya konulabilmesi için multidisipliner yaklaşım gerekmektedir.

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Kocatepe Tıp Dergisi
Kocatepe Medical Journal
25:496-501/Ekim 2024 Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

PROSTAT KANSERİ HÜCRE HATTINDA (PC-3) DL-FENİLALANİN VE DL-ALANİN'İN HEDGEHOG YOLU İLE İLİŞKİSİNİN ARAŞTIRILMASI

INVESTIGATION OF THE RELATIONSHIP OF DL-PHENYLALANINE AND DL-ALANINE WİTH THE HEDGEHOG PATHWAY IN THE PROSTATE CANCER CELL LINE (PC-3)

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ÖZET

AMAÇ: Bu çalışmada, DL-Fenilalanin ve DL-Alanin'nin PC-3 prostat kanser hücre hattında Hedgehog sinyal yolağı üzerinden etkisinin araştırılması amaçlanmıştır.

GEREÇ VE YÖNTEM: DL-Fenilalanin ve DL-Alaninin PC-3 kanser hücrelerinde hücre canlılığına etkisi MTT yöntemi ile belirlemiştir. DL-Fenilalanin için belirlenen IC50 değeri PC-3 ve HEK-293 hücrelerine uygulandı. Total RNA izolasyonu ve cDNA sentezi yapıldı. Hedgehog yolağı ile ilişki anahtar genlerin (*SHH, PTCH, SMO, GLI-1*) gen ifadesi qPCR (Kantitatif PCR) ile belirlendi.

BULGULAR: PC-3 hücreleri üzerinde DL-Alanin sitotoksik etki göstermedi. DL-Fenilalanin hücre canlılığını zamana ve doza bağlı olarak azalttı. DL-Fenilalanin için IC50 değeri 48.saatte 500 µg/mL olarak belirlendi. PC-3 hücrelerinde DL-Fenilalanin uygulamasından sonra tüm genlerin ekspresyonunda aşağı regülasyon, HEK-293 hücrelerinde ise yukarı regülasyon tespit edildi ($p<0.05$).

SONUÇ: DL-Fenilalanin prostat kanseri hücrelerinde Hedgehog yolağını inhibe etmiştir. Bu inhibisyon kontrol grubu HEK-293 hücrelerinde gözlenmemiştir. DL-Fenilalanin prostat kanseri tedavisi için terapötik bir aday olabilir ancak, DL-Alanin'nin böyle bir etkisi bulunmamıştır.

ANAHTAR KELİMELER: PC-3, DL-Fenilalanin, DL-Alanin, Hedgehog.

ABSTRACT

OBJECTIVE: In this study, it was aimed to investigate the effect of DL-Phenylalanine and DL-Alanine on the Hedgehog signaling pathway on the PC-3 prostate cancer cell line.

MATERIAL AND METHODS: The effects of DL-Phenylalanine and DL-Alanine on cell viability in PC-3 cancer cells were determined by the MTT method. The IC50 value determined for DL-Phenylalanine was applied to PC-3 and HEK-293 cells. Total RNA isolation and cDNA synthesis were performed. Gene expression of key genes related to the Hedgehog pathway (*SHH, PTCH, SMO, GLI-1*) was determined by qPCR (Quantitative PCR).

RESULTS: DL-Alanine showed no cytotoxic effect on PC-3 cells. DL-Phenylalanine decreased cell viability in a time- and dose-dependent manner. The IC50 value for DL-Phenylalanine was determined to be 500 µg/mL at 48 hours. After DL-Phenylalanine application in PC-3 cells, down-regulation in the expression of all genes was detected, while up-regulation was detected in HEK-293 cells ($p<0.05$).

CONCLUSIONS: DL-Phenylalanine inhibited the Hedgehog pathway in prostate cancer cells. This inhibition was not observed in the control group HEK-293 cells. While DL-Phenylalanine may be a therapeutic candidate for the treatment of prostate cancer, DL-Alanine was not found to have such an effect.

KEYWORDS: PC-3, DL-Phenylalanine, DL-Alanine, Hedgehog.

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Kabul Tarihi / Accepted: 06.07.2024
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INTRODUCTION

According to World Health Organization (WHO) GLOBOCAN data for 2022, prostate cancer is the 2nd most common type of cancer globally in terms of incidence and mortality rate (1). Well-known risk factors for prostate cancer include: age, ethnicity, family history and mutations, obesity, tobacco consumption, metabolic syndromes (2). Heterogeneous prostate cancers can remain silent for a long time or behave very aggressively. For this reason, it is important to determine tumor behavior as well as making the diagnosis (3). The best known prognostic factors regarding the tumor are preoperative PSA score, Gleason score (histological grade), tumor volume, surgical margin status and pathological stage (4).

Besides DNA copy number changes, some genetic changes occur in prostate cancer, including inactivation of tumor suppressor genes, loss of specific genomic sequences, and gain of other genes associated with the activation of oncogenes (5, 6). Although the heterogeneity and changes in analytical and post-analytical data observed in prostate cancer create obstacles to the development of appropriate models for treatment; the clinical use of biological, genetic, and molecular pathological data that benefit cancer prevention, and survival continues to become increasingly important day by day (7).

The Hedgehog signaling pathway, which is important in embryonic development, and tissue regeneration, is linked to many biological processes. It also regulates the activity of stem cells in vertebrate, and invertebrate organisms, as well as maintaining homeostasis in various tissues, and organs (8). Three Hedgehog proteins, Sonic Hh (Shh), Indian Hh (Ihh), and Desert Hh (Dhh), are found in mammals (9). The main target genes of the Hh signaling pathway are PTCH1, PTCH2, and GLI1 (10). Abnormal postnatal Hedgehog signaling has been linked to many malignancies, including basal cell (11, 12, 13). In other tumors such as stomach, and prostate, activation of Hh signaling is associated with tissue invasion, and increased metastatic potential. Hh inhibition reduces tumor cell proliferation in prostate, and stomach cancer (14).

In recent years, L-Alanine amino acid polymorphism has attracted great attention due to its use in drug production (15). DL-Alanine, a non-essential amino acid consisting of amino ,and carboxyl groups, is a racemic mixture of D- , and L- form, ,and is an important source of energy for muscles ,and the central nervous system (16). Phenylalanine is an important component of body proteins, and is an important precursor of many aromatic compounds that make up more than half of the Aspartame molecule, and are necessary for normal body function (17). Phenylalanine, an essential amino acid, is converted into tyrosine by the phenylalanine hydroxylase enzyme (PAH) in the liver with the help of the tetrahydrobiopterin cofactor in the first step of the catabolic pathway. Decreased or absent activity of the PAH enzyme causes blood phenylalanine levels to increase, and phenylalanine to have a toxic effect on the brain (18). Additionally, cytotoxic, and anticancer effects of phenylalanine have been reported in various cancer cells (19, 20). In this study, it was aimed to investigate the cytotoxic effects of DL-Alanine, and phenylalanine on prostate cancer cells, and their relationship with the Hedgehog pathway.

MATERIALS AND METHODS

Cell Culture

PC-3 (CRL-1435™) grade IV prostatic adenocarcinoma cells, and HEK293 control cell line were obtained from ATCC. Cells were incubated with 10% filtered fetal bovine serum (FBS), 1% Penicillin/streptomycin solution, and DMEM (Dulbecco's Modified Eagle's Medium) fresh medium by keeping them in a humidified environment at 37°C with 95% free air, and 5% CO_2. According to the manufacturer's instructions, a sufficient number of passages were frozen with medium containing 10% DMSO (dimethyl sulfoxide), and stored in a sterile cryotube.

MTT Cytotoxicity Test

The MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide) test was applied as mentioned previously (21). The dose range was prepared as 1,5,50,100,125,250,350,500,1000 µg/mL for DL-Alanine and DL-Phenylalanine (24h, 48h, 72h). MTT dye was treated with cells cultured approximately overnight in a 96-well cell culture plate. Crystal structures were dissolved with DMSO, and spectrophotometric absorbance measurement was taken at 570 nm.

RNA Isolation

After the IC_{50} (Half maximal inhibitory concentration) value determined in the MTT test was applied to the cells, the cells were removed with Trypsin-EDTA. Experimental groups were created for quantitative PCR (qPCR) by applying the DL-Phenylalanine IC_{50} value to both PC-3 cells and HEK293 cells. The cells, precipitated by centrifugation at 1500 g for 5 minutes, were lysed by applying TRIzol. After applying chloroform, and isoamyl alcohol respectively, RNA was precipitated with 75% ethanol, and cleaned of residues. After the alcohol was evaporated at room temperature, the RNA pellet was gently dissolved in different volumes of 75-100 µl.

cDNA Synthesis

The reverse transcriptase enzyme catalyzed the cDNA synthesis reaction of total RNA samples. In this reaction, the Revertaid First Strand cDNA synthesis kit (Thermo Fisher Scientific) was used. Appropriate primers, dNTP, reverse transcriptase, buffer, and RNase inhibitor were mixed with RNA (1000 ng). Reaction steps were followed according to the kit's instructions.

Real Time PCR

All primers used in this step were designed using the IDT Primer Quest Tool. These designed primers **(Table 1)** were mixed with iTaq universal SYBRGreen supermix, and nuclease-free water. The mixture was added to the fast optical 96-well plate, and covered with a cohesive seal. Amplification was performed using the Quantstudio 3 qPCR (Quantitative polymerase chain reaction) system (Thermofisher Scientific). The qPCR reaction (SYBRGreen Master Mix, cDNA, nuclease-free water) was set up (Five minute 95 °C denaturation step followed by 40 cycles of 5 s at 95 °C and 30 s at 57-58°C).

Table 1: The nucleotide sequences of the primer pairs

Gene	Oligonucleotide sequence (5′-3′)	Amplicon size
SHH	F-CCGAGCGATTTAAGGAACTCA R-ATCACCGAGATGGCCAAAG	133
PTCH	F-GGGTGGCACAGTCAAGAACAG R-TACCCCTTGAAGTGCTCGTACA	108
SMO	F-ATCGCTACCCTGCTGTTATTC R-GGGCACCATCCATGAACT	90
GLI-1	F-GAGCTGGACATGCTGGTT R-ATTCAGGCTCACGCTTCTC	148
GAPDH	F-GGAGCGAGATCCCTCCAAAAT R-GGCTGTTGTCATACTTCTCAT	197

Ethical Committee

The study protocol was approved by the ethics board of Karatay University Drug and Non-Medical Device Research Ethics Committee (2023/025).

Statistical Analysis

Gene expression levels were evaluated through Ct (threshold cycle) values. Differences in gene expression level between control and dose groups were calculated according to Livak's $2^{-\Delta\Delta CT}$ (2(-Delta Delta C(T)) method (22) and normalized using the GAPDH housekeeping gene. Observed differences in gene expression between groups were calculated as fold increases and evaluated with student's t-test. Statistically $p<0.05$ significance level was accepted.

RESULTS

MTT Assay Results

The cytotoxic effect on PC-3 cells was investigated in the dose range of 1-1000 µg/mL for DL-Alanine, and DL-Phenylalanine. While no cytotoxic effect was observed for DL-Alanine in the specified dose range, the IC_{50} value for DL-Phenylalanine was determined as 500 µg/mL at the 48th hour. It was determined that phenylalanine suppressed cell viability depending on concentration, and time **(Figure 1)**.

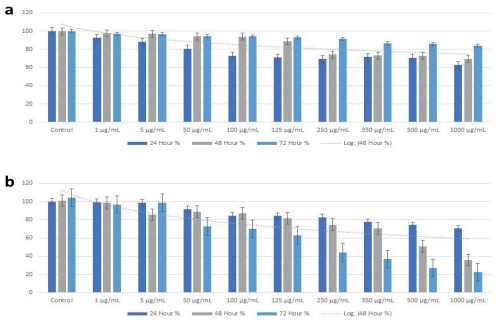

Figure1: MTT cell viability graph at different doses. a. DL-Phenylalanine treatment results, b. DL-alanine treatment results

After applying the determined IC_{50} value to PC-3 cells (control, phenylalanine, and alanine applied), they were examined under an inverted microscope. A decrease in cell number was detected in the DL-Phenylalanine applied group compared to control PC-3 cells. Additionally, no significant change was detected in the morphology of the cells **(Figure 2)**.

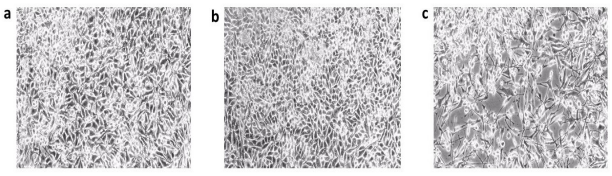

Figure 2: Invert microscope cell morphology images. a. PC-3 control cells, b. PC-3 cells after application of 1000 µg/mL 72 h DL-alanine c. PC-3 cells after application of 500 µg/mL 48 h (IC50) DL-phenylalanine

Real Time PCR Results

After applying the IC_{50} value of DL-Phenylalanine to PC-3 cells, down-regulation was detected in all Hedgehog-related genes (Table 1). Among these gene expression changes, the greatest change was observed in the *PTCH* gene. The order of gene expression changes from largest to smallest is as follows; *PTCH* (fold=2.24, p=0.002), *SMO* (fold=2.19, p=0.013), *SHH* (fold=1.98, p=0.003), *GLI-1* (fold=0.28, p=0.001), respectively **(Figure 3)**.

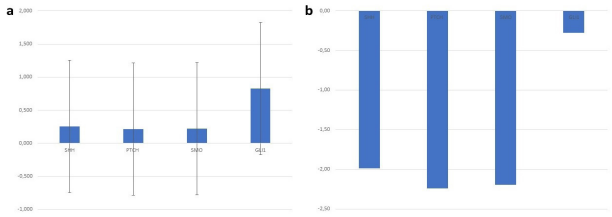

Figure 3: . PC-3 cells qPCR results. a.Relative gene expression fold change $2^{-\Delta\Delta Ct}$ graph b. Fold change log 2 graph.

On the contrary, after applying the IC_{50} value of DL-Phenylalanine to HEK-293 cells, up-regulation of the relevant genes was detected. Among these expression changes, the most changes were detected in the *GLI-1* gene. The order of gene expression changes from largest to smallest is as follows; *GLI-1* (fold=1.52, p=0.002), *PTCH* (fold=1.25, p=0.001), SMO (fold=0.86, p=0.013), *SHH* (fold=0.32, p=0.017), respectively **(Figure4)**.

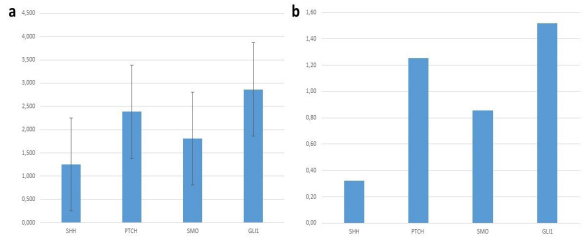

Figure 4: HEK-293 cells qPCR results. a.Relative gene expression fold change $2^{-\Delta\Delta Ct}$ graph b. Fold change log 2 graph

When all these results are evaluated together, gene expression changes on HEK-293 cells are minimal, but significant gene expression changes were detected on prostate cancer cells.

DISCUSSION

Prostate cancer is one of the common types of cancer that is very difficult to diagnose, and treat. Due to the difficulty of treatment in prostate cancer tumors associated with poor prognosis, various alternative treatment methods are needed (3). Especially in functional medicine applications, supplementation of essential, and organic molecules has recently been preferred in cancer treatment (23). Because while many chemotherapeutic drugs inhibit cancer cells, they can also negatively affect many healthy cells (24). Innovative approaches in medicine support cancer therapy with smart drug technology, and functional medicine.

Alanine, and phenylalanine are essential amino acids encoded in the cell genome, and low phenylalanine can cause genetic/metabolic syndromes such as phenylketonuria (25). Thanks to different derivatives, and modifications of L-Alanine, its use in cancer treatment is predicted (26, 27). In addition, the effect of β-alanine, one of the different alanine forms, on cervix, and renal tumors in particular, has been demonstrated (28). However, in our study, Alanine did not show a cytotoxic effect on prostate cancer cells within the given dose range. This may be related to the overaggressive, and poor prognosis of the grade IV PC-3 prostate cancer cell line used in our study.

The role of extracellular alanine in cell metabolism is not yet fully understood. Recent have reported that pancreatic cancer cells use extracellular alanine as a carbon source to regulate the TCA (tricarboxylic acid) cycle in a GPT2 (glutamate-pyruvate transaminase 2)-dependent manner (29). It was also discovered that extracellular alanine activates T cells (30). No change in alanine levels was detected in extracellular alanine catabolism before, and after the threatment of CB839 in resistant non-small cell lung cancers (31). Another study predicted that alanine was secreted at higher levels in prostate cancer cells compared to normal prostate cells, and could be a potential biomarker (32). This suggests that prostate cancer cells secrete alanine extracellularly, and do not contain it intracellularly. In the MTT test, externally administered DL-Alanine was not used within the framework of the cell's needs, and could not show any effect. Perhaps, in overdoses, alanine could have a toxic effect. In contrast, DL-Phenylalanine showed a cytotoxic effect on prostate cancer cells. These results are consistent with the fact that phenylalanine is a biologically active molecule, and phenyl rings can also have anticancer effects

(33, 34). In addition, studies conducted in recent years have revealed that the use of phenylalanine in metal complexes such as boron, poly-phenylalanine structures or dipeptides is important in the fight against cancer (20, 35).

Matijin-Su (MTS) is a phenylalanine dipeptide monomer compound with various biological activities (36, 37), and MTS derivatives exhibit various pharmaceutical activities (38). These pharmaceutical activities include antitumor ability, and anti-inflammatory activities (36, 39, 40). Additionally, MTS derivatives significantly inhibited proliferation, and prevented metastasis in HepG2 hepatocellular carcinoma cells. Additionally, MTS derivatives exhibited low toxicity in normal hepatocyte cells (38). In our study, it is not surprising that DL-Phenylalanine did not have a toxic effect on HEK-293 normal embryonic kidney cells, and did not inhibit the Hedgehog pathway, one of the self-renewal pathways, but it is compatible with the literature. DL-Phenylalanine has an inhibitory effect on PC-3 prostate cancer through the Hedgehog pathway. This effect can be evidenced by the down-regulation of *SMO*, and *GLI-1* following down-regulation of the *SHH* ligand. Additionally, in our study, it was observed that PTCH receptor gene expression was parallel to the decrease in *SHH* gene expression level.

Investigating whether many biocompatible molecules such as phenylalanine are effective in cancer therapies is very important for anticancer therapies. In the future, *in vitro*, and *in vivo* studies on the modification of different biological molecules, and their use in the fight against cancer should be expanded. In particular, understanding the relationship of cancer-related proliferative, apoptotic, and self-renewal signaling pathways with biological molecules will play a key role in targeted therapies.

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Kocatepe Tıp Dergisi
Kocatepe Medical Journal
25:502-509/Ekim 2024 Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

KOAH'TA QUADRİCEPS FEMORİS VE GASTROCNEMİUS KAS EĞİTİMİNİN GÜNLÜK YAŞAM AKTİVİTELERİNE ETKİSİNİN KARŞILAŞTIRILMASI

COMPARISON OF THE EFFECTS OF QUADRICEPS AND GASTROCNEMIUS MUSCLE TRAINING ON ACTIVITIES OF DAILY LIVING IN COPD

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ÖZET

AMAÇ: Kronik Obstrüktif Akciğer Hastalığı (KOAH), egzersiz toleransında bozulma ve yaşam kalitesinde azalma gibi semptomlara sahiptir. Bu çalışmada stabil KOAH hastalarında quadriseps femoris (QF) ve gastrocnemius (GC) kasları nöromüsküler elektriksel stimülasyon (NMES) ile güçlendirildiğinde KOAH hastalarında egzersiz performansı ve yaşam kalitesi üzerine etkileri karşılaştırıldı.

GEREÇ VE YÖNTEM: KOAH'lı 45 hasta kontrol, gastrocnemius kas (GC Grubu) ve quadriseps femoris kas (QF Grubu) olmak üzere rastgele üç gruba ayrıldı. Kontrol grubuna sadece pulmoner rehabilitasyon, GC grubuna pulmoner rehabilitasyona ek olarak GC kasına NMES ve QF grubuna pulmoner rehabilitasyona ek olarak QF kasına NMES uygulandı. Hastalar tedavi öncesi ve sonrasında Görsel Analog Skala (VAS), Altı Dakika Yürüme Testi, St. George's Respiratory Questionnaire anketi (SGRQ), Kısa Form-36 (SF-36) ve Beck Depresyon Envanteri ile değerlendirilmiştir. İstatistiksel analiz IBM SPSS 23.0 programında yapıldı ve $p<0.05$ anlamlı kabul edildi.

BULGULAR: VAS, fiziksel fonksiyon, Beck Depresyon, altı dakika yürüme ve yorgunluk test verilerinde tedavi öncesi ve sonrası arasında kontrol grubunda fark bulunmazken ($p>0,05$), GC ve QF gruplarında ise istatistiksel olarak anlamlı fark tespit edildi ($p<0,05$). Tüm testlerin tedavi öncesi ve sonrası değerlerinde gruplar arasında anlamlı fark yoktu ($p>0,05$).

SONUÇ: KOAH'lı hastalarda QF veya GC kaslarının güçlendirilmesinin egzersiz performansını ve yaşam kalitesine katkı sağladığı görünmektedir. Ancak KOAH'ta QF ve GC kas eğitiminin yaşam kalitesine etkisi bakımında birbirine üstünlüğü yoktu.

ANAHTAR KELİMELER: Pulmoner Hastalık, Transkütanöz Elektriksel Sinir Stimulasyonu, Kuadriseps Kası, Gastroknemius Kası, Egzersiz.

ABSTRACT

OBJECTIVE: Chronic Obstructive Pulmonary Disease (COPD) has symptoms such as impaired exercise tolerance and decreased quality of life. In this study, the effects on exercise performance and quality of life in COPD patients were compared when the quadriceps femoris (QF) and gastrocnemius (GC) muscles were strengthened by neuromuscular electrical stimulation (NMES) in stable COPD patients.

MATERIAL AND METHODS: Forty-five patients with COPD were randomly divided into three groups as control, gastrocnemius muscle (GC Group) and quadriceps femoris muscle (QF Group). The control group received pulmonary rehabilitation only, the GC group received NMES to the GC muscle in addition to pulmonary rehabilitation, and the QF group received NMES to the QF muscle in addition to pulmonary rehabilitation. Patients were evaluated with Visual Analog Scale (VAS), Six Minute Walk Test, St. George's Respiratory Questionnaire (SGRQ), Short Form-36 (SF-36) and Beck Depression Inventory before and after treatment. Statistical analysis was performed in IBM SPSS 23.0 program and $p<0.05$ was considered significant.

RESULTS: While there was no difference in VAS, physical function, Beck Depression, six-minute walk and fatigue test data before and after treatment in the control group ($p>0.05$), a statistically significant difference was found in the GC and QF groups ($p<0.05$). There was no significant difference between the groups in the pre and posttreatment values of all tests ($p>0.05$).

CONCLUSIONS: Strengthening the QF or GC muscles seems to improve exercise performance and quality of life in patients with COPD. However, QF and GC muscle training in COPD were not superior to each other in terms of their effect on quality of life.

KEYWORDS: Pulmonary Disease, Transcutaneous Electric Nerve Stimulation, Quadriceps Muscle, Gastrocnemius Muscle, Exercise.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar damage, usually caused by significant exposure to harmful particles or gases (1). Due to chronic inflammatory response and recurrent infections in the airways; fibrosis, gas exchange abnormalities, air trapping and an increase in the amount of mucus are observed in the small airways (2). Systemic inflammation, hypoxemia and hypercapnia, myopathy due to steroids used, and malnutrition cause peripheral muscle weakness in patients with COPD (3,4). The weakness in peripheral muscles seen in COPD is explained by type 2 fiber, metabolic enzyme, decrease in mitochondrial activations and impaired capillaryization (5). In COPD, it has been reported that loss of strength in lower extremity muscle groups as well as pulmonary dysfunction are effective in decreasing exercise and walking capacity (6). Walking activity, which affects functional activity, is closely related to lower extremity muscle strength (7). Although there are multiple muscles involved in walking activity, the most important ones are the quadriceps femoris and gastrocnemius muscles (7, 8). The quadriceps femoris muscle (QF) is one of the postural muscles and plays an important role in various phases of standing and walking. The gastrocnemius muscle (GC) makes significant contributions to walking activity during heel lift activity at the end of the stepping phase (9, 10).

Neuromuscular electrical stimulation (NMES) is the use of low-level electrical currents to create muscle contraction. It creates contraction by stimulating the nerve fibers in a healthy muscle and directly muscle fibers in a denervated muscle by electrical currents. NMES is a method that has been used successfully to increase the muscle performance as a localized exercise method for weak muscles (11). It is known that quadriceps muscle strengthening with NMES has positive effects on exercise capacity and dyspnea during daily activities in severely decompensated COPD patients (12). In order to increase functional activity in COPD patients, it is important to strengthen the lower extremity muscles as well as pulmonary rehabilitation. However, strengthening all lower extremity muscles individually can be both time-consuming and tiring for a COPD patient. In this study, the possible effects of training the QF and GC muscles, which play an important role in walking activity, on the functional activity levels of stable COPD patients were investigated.

MATERIALS AND METHODS

Study Design

This study was designed as a single blind randomized controlled trial. Patients consecutively admitted to the chest diseases department outpatient clinic of Hitit University Erol Olçok Training and Research Hospital in Çorum and followed according to the "Global Initiative for Chronic Obstructive Lung Disease" (GOLD) classification were randomly (gender and age matched randomization method) divided into three groups of 15 patients each. Only the pulmonary rehabilitation program (Control Group) was applied to the patients in the first group (n=15). In the second group (GC Group), in addition to the pulmonary rehabilitation, 20 minutes of NMES was applied to the GC muscle. In the third group (QF Group), in addition to the pulmonary rehabilitation, 20 minutes of NMES was applied to the QF muscle. This treatment protocol was applied to all patients by physiotherapists in 20 sessions for 4 weeks, with each treatment session for 45 minutes, 5 times a week in total. All assessments before and after treatment were evaluated by a researcher who was blinded to the groups.

Participants

A total of 45 stable COPD patients were included in the study. Inclusion criteria for the study; being between the ages of 18-75, diagnosed as group B stable COPD according to GOLD criteria by one pulmonologist, PaO_2 >55 mm Hg, $PaCO_2$ <45 mmHg in room air (13). Exclusion criteria from the study were; exacerbation, cor pulmonale or respiratory muscle fatigue (abdominal paradox breathing), cardiac instability (with acute MI, congestive heart failure or uncontrollable arrhythmia), musculoskeletal disorder (conditions affecting the exercise ability), and presence of difficulty in communicating.

The study began after obtaining approval from the local ethics committee. The patients were informed about the content, purpose and app-

lication of the study and their consent was obtained. Age, gender, educational status, occupation, marital status, date of the COPD diagnosis, time until the start of treatment and additional diseases of every patient were recorded. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Outcome Measures

Visual Analog Scale: The Visual Analog Scale (VAS) was first used as a pain rating scale by Hayes and Patterson (14) in 1921. It is often used in epidemiological and clinical research to measure pain intensity or frequency. It categorizes pain as mild, moderate and severe (15).

6 Minute Walk Test (6 MWT): The patients were administered to a 6 MWT in accordance with the walking protocol of McGavin et al. (16). In a marked area in the closed hospital corridor, patients were asked to walk the longest distance they could walk for 6 minutes, and heart rate, blood pressure, respiratory rate, finger oxygen saturation, and walking distance at the end of walking were recorded at the beginning and at the end of walking.

St. George's Respiratory Questionnaire (SGRQ): The SGRQ questionnaire was used to evaluate the health-related quality of life of the patients. This questionnaire was developed specifically to determine the severity of the disease in COPD and asthma. Effects of the disease on quality of life are examined in 3 parts: symptoms, activity and daily life. Symptoms; cough, sputum, wheezing and shortness of breath. Physical functions, household chores, and hobbies are questioned to determine activity status. These activities are activities that are limited by shortness of breath. The total score of the questionnaire varies between 0-100. A score of zero indicates normal and a score of 100 indicates maximum disability (17).

Beck Depression Inventory (BDI): BDI (Beck et al.) was developed in 1961 to measure the behavioral manifestations of depression in adolescents and adults. Depression levels according to BDI scores are: 0-13 points, no depression; 14-19 points low; 20-28 points moderate and 29-63 points are classified as high depression. The highest score that can be obtained from the scale is 63. A high total score indicates a high level or severity of depression (18).

Short Form-36 (Short Form 36 – SF 36): SF-36 was used to evaluate the quality of life of the patients. SF-36 is a scale that was developed by Ware in 1987 to be used in examining the health status and quality of life of individuals. The scale, which includes thirty-six statements, is in the form of a multi-title scale that evaluates two main headings (physical and mental dimensions) and eight concepts (physical function, physical role difficulty, emotional role difficulty, energy/vitality/vitality, mental health, social functionality, pain, general health perception). The scores of each sub-dimension and two main dimensions in the scale range from 0-100. The SF-36 with a positive score was scored in such a way that the higher the score of each health area, the higher the health-related quality of life (19).

Treatment Programs

Pulmonary Rehabilitation Program: During the treatment, all patient groups participating in the study were performed pursed-lip breathing in order to control dyspnea, improve ventilation and oxygenation, segmental breathing exercises to prevent accumulation of secretions, reduce paradoxical breathing and improve chest mobility, accompanied by a physiotherapist in the hospital. In addition, six different relaxation positions (high side lying, high lying on the back, leaning forward, loose sitting, leaning on the back, loose sitting, loosely sitting on the back, to reduce respiratory distress during diaphragmatic breathing and dyspnea attack) standing) was taught. Coughing and huffing, forced expiration technique and postural drainage positions that the patient will do at home were shown to the patients for easy removal of secretions. In addition, each patient was advised to perform 10 repetitions per hour with an intensive spirometer. In addition, the patients were trained to regularly perform the described physiotherapy methods twice a day (20).

Neuromuscular Electrical Stimulation (NMES): In addition to the pulmonary rehabilitation program, a total of 20 sessions of NMES were applied to the QF and GC muscle groups of the patients in the stimulation group 5 times a week for 20 minutes a day for 4 weeks. NMES application was performed by physiotherapists using the Cefar Compex Theta 500 device. In NMES application to the QF muscle, the negative electrode (5x7.5 cm) was placed 5-7 cm proximal to the

patella, and the positive electrode (5x7.5 cm) 10-12 cm distal from the inguinal region (21, 22). For the GC muscle, the negative electrode (5x7.5 cm) was placed proximal to the insertion of the Achilles tendon, and the positive electrode (5x7.5 cm) was placed approximately 3 cm below the popliteal fossa. Although there are limited studies in the literature, 100-200 µs transition time, 60 Hz and above frequencies were accepted as effective in amplification, so the frequency was 100 Hz and the transition time 200 µsec in this study (22, 23). In all NMES applications, patients were asked not to make voluntary contractions during the stimulation by taking the maximal tolerance as a criterion for increasing the flow intensity. In general, the flow intensity was increased at a rate that would cause contraction in the QF and GC muscle groups, but not cause discomfort in the patient.

Randomization and blinding

A randomization procedure was performed for 48 COPD patients. According to GOLD criteria, participants with stable COPD in group B were randomly divided into three groups as control, GC, and QF using randomization according to their age and gender. At baseline and after the treatment period of 4 weeks (20 sessions), all assessments were evaluated by the investigator (H.Ç), who was blinded to the groups throughout the study.

Ethical Committee

The study proposal was approved by the Research Ethics Board of Hitit University Faculty of Medicine (number: 2016-23), (ClinicalTrials.gov Identifier: NCT05501457).

Statistical Analysis

In this study, analysis of the normal distribution was performed using 5 parameters (Skewness-Kurtosis, Shapiro Wilk Test, P-P plots, Standard deviation/Mean and Histogram). Data that were considered to be normally distributed were considered parametric, and those that were not normally distributed were considered nonparametric. Parametric data were presented as Mean±Standard Deviation (Mean±SD). While the One Way ANOVA test was applied in multi-independent group analysis of parametric data, the tukey test was applied because the variances were homogeneous in posthoc comparisons (p>0.05). Related Samples T Test was applied for comparison of two dependent groups of parametric data. Non-parametric data were shown as Median (Minimum-Maximum). In the independent multi-group comparisons of nonparametric data, Kruskal Wallis H Test was used, and in post hoc comparisons, Bonferroni correction was made and Mann Whitney U test was applied. Wil-Coxon Sign Test was used for the comparison of two dependent groups of nonparametric data.

RESULTS

Of the 56 COPD patients admitted to the clinic, 48 (21 female, 27 male) met the inclusion criteria. After randomization, the study was started with 16 individuals with COPD in each group. However, one participant in each group could not continue the study due to disease exacerbation. The flow chart of the study is shown in **(Figure 1)**.

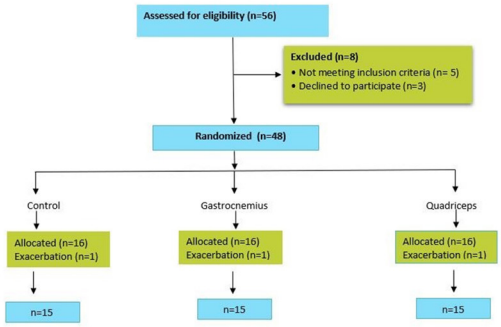

Figure 1: Flow diagram of the study

The mean age of the patients was 58.80±5.30 years in the GC group, 57.65±5.57 years in the QF group and 59.40±5.02 years in the control group. There was no statistically significant difference between the groups(p=0.499).The groups had similar sex ratios, body mass indexes and duration of COPD. While there was no significant difference in VAS values before and after treatment in the control group (p=0.669), there was a statistically significant difference in the GC and QF groups (p=0.007), (p=0.006). There was no significant difference between before and after treatment in all sub-parameter values of SGRQ tests in all groups (p=0.576, p=0.651, p=0.055). There was a significant difference between SF-36 score before and after treatment only in physical function sub-parameters in GC and QF groups (p=0.047). There was no

significant difference between before and after treatment in all other sub-parameter values of the SF-36 scale (p=0.043). While there was no difference between the control group (p=0.589) in the Beck Depression, six-minute walking and fatigue test before and after the treatment, there was a statistically significant difference in the GC and QF groups (p=0.048, p=0.030). There was no significant difference between the groups in the pre- and post-treatment values of all tests (p=0.682, p=0.888, p=0.217), **(Table 1)**.

Table 1: Comparison of COPD patients according to groups and within-group before and after treatment (*p<0.05. **p<0.01. ***p<0.001)

	Control Group (min-max)	GC Group (min-max)	QF Group (min-max)	Sig (p2)
Age (years)	59.40±5.02	58.80±5.30	57.65±5.57	0.499
Pre-treatment VAS	6 (2.50-8.50)	4.50 (3-8)	4 (2-8)	0.299
Post-treatment VAS	5.50 (1.50-10)	3 (2-7)a*	3 (1.50-6)a*	0.028
Sig. (p1)	0.669	0.007**	0.006**	
Pre-treatment SGRQ (Symptom)	350 (150-650)	550 (200-725)	475 (150-800)	0.104
Post-treatment SGRQ (Symptom)	375 (75-675)	550 (200-700)	375 (100-675)	0.136
Sig. (p1)	0.576	0.651	0.055	
Pre-treatment SGRQ (Activity)	900 (200-1500)	1100 (375-1500)	750 (375-1400)	0.427
Post-Treatment SGRQ (Activity)	825 (0-1750	1100 (400-1575)	650 (300-1750)	0.299
Sig. (p1)	0.754	0.753	0.043*	
Pre-Treatment SGRQ (Effect of Disease)	1550 (400-2600)	1800 (770-3600)	1500 (100-2650)	0.431
Post-treatment SGRQ (Effect of Disease)	1525 (100-2475)	1750 (750-3640)	1420 (150-2300)	0.248
Sig. (p1)	0.932	0.683	0.268	
Pre-Treatment SGRQ (Total)	2950 (275-4675)	3300 (1370-5400)	2950 (750-4850)	0.287
Post-treatment SGRQ (Total)	2625 (875-4650)	3225 (1325-5425)	2550 (650-4625)	0.168
Sig. (p1)	0.955	0.900	0.096	
Pre-Treatment SF-36 (Physical Function)	40 (0-100)	25 (5-75)	45 (0-100)	0.165
Post-Treatment SF-36 (Physical Function)	45 (5-100)	32 (10-75)	50 (20-90)	0.127
Sig. (p1)	0.479	0.047*	0.070	
Pre-Treatment SF-36 (Physical Role Difficulty)	50 (0-100)	30 (0-100)	50 (0-100)	0.281
Post-treatment SF-36 (Physical Role Difficulty)	50 (0-100)	40 (0-100)	60 (0-100)	0.166
Sig. (p1)	0.857	0.602	0.246	
Pre-Treatment SF-36 (Emotional Role Difficulty)	33 (0-100)	33 (0-66.60)	45 (0-120)	0.509
Post-Treatment SF-36 (Emotional Role Difficulty)	33.30 (0-100)	33.30 (0-100)	66.60 (0-100)	0.103
Sig. (p1)	0.655	0.859	0.074	
Pre-Treatment SF-36 (Energy / Vitality / Vitality)	45 (10-95)	40 (0-85)	45 (10-85)	0.604
Post-Treatment SF-36 (Energy/Vivacity/Vitality)	50 (10-100)	45 (10-85)	50 (30-100)	0.459
Sig. (p1)	0.694	0.717	0.276	
Pre-Treatment SF-36 (Spiritual Health)	60 (28-100)	52 (0-100)	56 (40-100)	0.623
Post-Treatment SF-36 (Spiritual Health)	60(16-92)	55 (15-110)	60 (32-92)	0.369
Sig. (p1)	0.244	0.148	0.285	
Pre-Treatment SF-36 (Social Functioning)	50 (0-100)	40 (0-100)	50 (0-100)	0.365
Post-Treatment SF-36 (Social Functioning)	42.50 (9-100)	40 (15-100)	60 (9-112)	0.321
Sig. (p1)	0.345	0.858	0.505	
Pre-Treatment SF-36 (Pain)	37.50 (22.5-100)	37.50 (0-100)	45 (0-100)	0.846
Post Treatment SF-36 (Pain)	45 (9-100)	40(10-100)	45 (10-120)	0.694
Sig. (p1)	1.000	0.330	0.169	
Pre-Treatment SF-36 (General Health Perception)	45 (20-90)	42 (15-110)	45 (0-100)	0.544
Post-Treatment SF-36 (General Health Perception)	55 (10-100)	45 (0-100)	60 (20-75)	0.483
Sig. (p1)	0.682	0.888	0.217	
Pre-Treatment Beck Depression Inventory	13 (2-61)	19 (3-43)	19 (2-32)	0.294
Post-Treatment Beck Depression Inventory	13 (3-42)	15 (7-35)	15 (6-25)	0.469
Sig. (p1)	0.589	0.048*	0.030*	
Pre-Treatment 6 Minutes Walk Test (Meter)	385 (250-465)	350 (230-550)	350 (100-465)	0.921
Post-Treatment 6 Minutes Walk Test (Meter)	375 (280-435)	375 (395-600)	380 (200-480)	0.735
Sig. (p1)	0.098	0.037*	0.020*	
Pre-Treatment Fatigue	4 (1-10)	4 (1-10)	4 (1-9)	0.802
Post-Treatment Fatigue	4 (0-10)	3 (0-7)	3 (0-8)	0.946
Sig. (p1)	0.476	0.049*	0.008*	

**Sig. (p1): Statistical value between in-group pre- and post-treatment data.*
**Sig. (p2): Statistical value of pre-treatment and post-treatment data between groups*
** VAS: Visual Analogue Scale*
** SGRQ: St. George's Respiratory Questionnaire*
** SF-36: Short Form 36*

DISCUSSION

In the present study, the effects of GC and QF muscles strengthened by NMES application on exercise performance and quality of life of COPD patients were evaluated. In patients with COPD, in GC and QF groups where GC and QF muscles were strengthened together with pulmonary rehabilitation; VAS, physical function, Beck depression, six-minute walking distance and post-exercise fatigue were improved compared to the pulmonary rehabilitation group. However, GC and QF groups were not superior to each other. We think that it is important to strengthen the QF and GC muscles separately or together with pulmonary rehabilitation for exercise performance and quality of life in individuals with COPD.

Although QF is the sole muscle that undertakes the extensor mechanism of the knee, it also contributes to the stability of the patella. It has a large cross-sectional surface area and can shorten by about 8 cm when contracted (9). The QF muscle has an important role in static and dynamic aspects. Its static role is to prevent knee flexion while standing. Its dynamic role is to provide strong knee extension as in jumping and running exercises (24). Adequate lower extremity muscle strength is needed to perform many daily living activities such as sitting, standing, walking and climbing stairs. QF weakness is associated with decreased activities of daily living and risk of falling (25). In the present study, it was observed that COPD patients whose QF muscle was strengthened with the NMES method increased in their daily living activities. These results show how important the QF muscle is in the activities of daily living and the lower extremity muscle that should be the first focus in the treatment of COPD patients is the QF.

Kamiya et al. (24) measured QF muscle strength with a hand dynamometer and exercise capacity as MET with the treadmill exercise test in their study on 621 coronary artery disease patients. As a result of their study, maximum QF muscle strength was found to be associated with exercise capacity in patients with coronary artery disease. QF muscle strength was found to be a strong predictor of exercise capacity. In the study, it was observed that physical function and walking distance increased, and the level of fatigue after exercise decreased in COPD patients whose QF muscle was strengthened. The study findings were found to be compatible with the literature.

The GC muscle plays an important role in actions such as walking and running by pushing the surface. In this way, it is directly related to the individual's gait and overall performance (10). The GC muscle is one of the most important locomotor muscles of the body, which has two parts, bipennate, biarticular, medial and la-

teral, which are effective in both the knee and ankle joints (26). Lamontagne et al. reported that there is a negative correlation between gastrocnemius muscle spasticity severity and walking speed in stroke individuals (27). The gastrocnemius muscle is a biarticular muscle. One of the advantages of biarticular muscles is the transfer of power from the proximal to the distal joints (28). For this reason, it is suggested that the effects of biarticular muscles on the body should be considered as a whole, not only on the joints they spread (29). In the study, it was observed that COPD patients whose GC muscle was strengthened with pulmonary rehabilitation had improvements in VAS, walking distance and fatigue levels compared to COPD patients who received only pulmonary rehabilitation. From these results, we can say that the weakness of the GC muscle in patients with COPD impairs the pushing phase of walking, then walking and finally exercise performance. In the study, it was observed that COPD patients whose GC muscle was strengthened with pulmonary rehabilitation had improvements in VAS, walking distance and fatigue levels compared to COPD patients who received only pulmonary rehabilitation. With these results, we can say that the GC muscle is weak in patients with COPD, and that walking at first disrupts the pushing phase, then walking and finally exercise performance. We believe that the GC muscle is one of the muscles that should be considered in the treatment of COPD.

In a randomized controlled double-blind study, Bourjeily-Habr et al., found significant improvement in the maximum strength of the quadriceps and hamstring muscles and a distance increase in the progressively increased shuttle walking test in stable outpatients with poor baseline exercise tolerance, low respiratory reserve, and severe COPD who were trated with NMES versus the placebo-treated group. In that study NMES was applied to the quadriceps, hamstring, and gastro-soleus muscles. But did not report any significant changes in lung function, peak workload, or peak oxygen consumption in either group (30). In the present study, physical function and walking distance increased in the GC and QF groups compared to the control group. It was observed that the level of pain and fatigue felt by the COPD patients in the GC and QF groups decreased even more than in the control group. All these results suggest that exercise performance in COPD patients is affected by weakness in the lower extremity muscles as well as lung dysfunction, and strengthening the GC and QF muscles in COPD improves exercise performance and quality of life.

In the study of Neder et al. in COPD patients with severe respiratory distres; the treatment group that recieved NMES to the QF muscles for 6 weeks, maximum isokinetic strength of the QF muscle was significantly improved, muscle fatigue was decreased, and exercise-related dyspnea was improved compared to the control group. It has been shown that it causes an increase in the exercise capacity together with daily life activity (31). Another study revealed that patients with malnourished COPD and patients with low endurance following hospitalization due to COPD showed greater improvement in QF muscle strength and dyspnoea during daily activities after 4 weeks of NMES treatment applied to the QF muscle compared to the control group (12). Again, in a double-blind placebo-controlled study involving NMES treatment applied to the QF muscle of patients with advanced COPD, it was shown that NMES increased the functional exercise capacity of patients by strengthening the QF muscle (32). In their study, Vieira et al. divided 20 COPD patients into two groups, they reported that there were significant improvements in pulmonary function tests, borg scale and quality of life in the group in which NMES was applied to both quadriceps muscles (33). Our study is the first to compare lower extremity muscles in COPD using NMES. There were significant improvements in VAS, physical function, Beck depression scale, six-minute walking test, and post-exercise fatigue in the group in which NMES was applied to the QF muscle. Similar results were obtained in the group in which NMES was applied to the GC muscle as well as the group that was applied NMES to the QF muscle. Although the literature shows the importance of the QF muscle in increasing the exercise capacity, the study shows that the GC muscle is as important for the exercise capacity and quality of life as the QF muscle.

The limitations of our study are the lack of long-term follow-up of COPD patients. In addition, unlike the literature, the fact that it was performed in patients with stable early stage COPD is among our limitations.

In conclusion, strengthening of the QF or GC muscle together with pulmonary rehabilitation has a positive effect on treatment in individuals with stable COPD. However, no superiority was observed between these two groups. Strengthening the QF or GC muscle together with pulmonary rehabilitation or both muscle groups together with pulmonary rehabilitation can be added to the treatment. It may be a useful method for maintaining or improving the conditioning of peripheral muscles during acute exacerbations of COPD or any disease that may interfere with regular exercise training in this population. Considering all these data, we can say that strengthening the QF or GC muscle with pulmonary rehabilitation in COPD increases exercise performance and quality of life more.

This study was supported by Hitit University Scientific Research Projects Unit with the project code SMYO19002.16.0.

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Kocatepe Tıp Dergisi
Kocatepe Medical Journal
25:510-518/Ekim 2024 Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

YENİDOĞANLARDA AKUT BÖBREK HASARI MORBİDİTE VE MORTALİTESİNİ ETKİLEYEN FAKTÖRLER

FACTORS AFFECTING MORBIDITY AND MORTALITY OF ACUTE KIDNEY INJURY IN NEWBORNS

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ÖZET

AMAÇ: Akut böbrek hasarı, yenidoğan yoğun bakım ünitelerinin ciddi sorunlarından biridir. Çalışmamızda yenidoğan yoğun bakım ünitelerinde akut böbrek hasarının sıklığı, risk faktörleri, primer tanıları, tedavileri ile erken dönem prognozları ve mortalitesinin değerlendirilmesi amaçlandı.

GEREÇ VE YÖNTEM: Çalışmamıza 1 Ocak 2013 - 31 Aralık 2016 tarihleri arasında hastanemiz yenidoğan yoğun bakım ünitesinde yatan ve akut böbrek hasarı geliştiği belirlenen yenidoğanlar akut böbrek hasarı grubu, her hasta için, aynı zamanda yatmış, akut böbrek hasarı tanısı almamış ikişer hasta kontrol grubu olarak alındı. Akut böbrek hasarı tanısı serum kreatinin >1,5mg/dl ve/veya ölçümleri arasında iki kat artışı ile konuldu.

BULGULAR: Çalışma süresince yenidoğan yoğun bakım ünitesinde yatan 7418 hastadan 201'inde (%2,7) akut böbrek hasarı saptandı. Bunların %42,3'ü preterm, %57,7'ü termdi. Hastaların %92,5'inde (186) prerenal akut böbrek hasarı saptandı. Akut böbrek hasarı olan hastaların %57,5'i oligo-anürikti ve 109 (%54,2) hasta kaybedildi. Renal replasman tedavisi 49'unda (%24,5) gerekti. Kritik konjenital kalp hastalığı (65; %32,3), hipoksik iskemik ensefalopati (36; %17,9), prematürite (23; %11,4), sepsis (21; %10,4), dehidratasyon (17; %8,5) en sık primer akut böbrek hasarı nedenleriydi. Akut böbrek hasarı gelişmesinde karaciğer fonksiyon testi bozukluğu, amfoterisin-B, vankomisin, aminoglikozid kullanımı, nöbet geçirme, proteinüri varlığı ve prematürite; akut böbrek hasarı mortalitesinde ise dopamin kullanımı ve renal replasman tedavi alması bağımsız risk faktörleri olarak belirlendi.

SONUÇ: Yenidoğanlarda akut böbrek hasarı çoğunlukla prerenal nedenliydi. İlk üç nedeni Kritik konjenital kalp hastalığı, hipoksik iskemik ensefalopati ve prematüriteydi. Yoğun bakım gerektiren yenidoğanların izleminde akut böbrek hasarı gelişebileceği unutulmamalı, riskler dikkatle değerlendirilmeli, yakından izlenmeli, nefrotoksik ilaçlar dikkatli kullanılmalı, akut böbrek hasarı belirlendiğinde uygun tedavi gecikmeden başlanmalıdır.

ANAHTAR KELİMELER: Bebek, Yenidoğan, Akut böbrek hasarı, Risk faktörleri, Prognoz.

ABSTRACT

OBJECTIVE: Acute kidney injury is one of the serious problems in Neonatal Intensive Care Units. Our study was aimed to evaluate the incidence, risk factors, primary diagnoses, treatments with early prognosis, and mortality of acute kidney injury in the neonatal intensive care units.

MATERIAL AND METHODS: Hospitalized newborns who had been diagnosed with acute kidney injury in neonatal intensive care units between January 1, 2013, and December 31, 2016, were included in the study as the acute kidney injury group. Two hospitalized newborns without acute kidney injury for each acute kidney injury patient were included in the study as a control group. The diagnosis of acute kidney injury was made with serum creatinine >1.5mg/dl and/or a two-fold increase between measurements.

RESULTS: Acute kidney injury was detected in 201 (2.7%) of 7418 patients hospitalized in the neonatal intensive care units during the study. Of these, 42.3% were preterm. Prerenal acute kidney injury was detected in 92.5% (186). Of these, 57.5% were oligo-anuric, and 109 (54.2%) patients died. Renal replacement therapy was required in 49 (24.5%) patients. Critical congenital heart disease (65;32.3%), hypoxic ischemic encephalopathy (36;17.9%), prematurity (23;11.4%), sepsis (21;10.4%) and dehydration (17;8.5%) were the most common causes of acute kidney injury. Liver function test abnormality, amphotericin-B, vancomycin, aminoglycoside use, seizures, presence of proteinuria, and prematurity were the independent risk factors in the development of acute kidney injury. Dopamine use and renal replacement therapy were determined as independent risk factors in acute kidney injury mortality.

CONCLUSIONS: Acute kidney injury in newborns was mostly prerenal. It should not be forgotten that acute kidney injury may develop during the follow-up of newborns requiring intensive care, and the risks should be carefully evaluated, closely monitored, nephrotoxic drugs should be used carefully, and when acute kidney injury is detected, appropriate treatment should be started without delay.

KEYWORDS: Infant, Newborn, Acute kidney injury, Risk factors, Prognosis.

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Kabul Tarihi / Accepted: 06.07.2024
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GİRİŞ

Akut böbrek hasarı (ABH), glomerüler filtrasyon hızında (GFH) hızlı bir düşüşle oluşan, böbrek fonksiyonunda ani bir azalma olarak tanımlanır (1). Yenidoğanlarda diğer yaş gruplarından daha sık görülür (2). Kesin bir sınıflama sistemi olmadığından tanı koymak zor olmasına rağmen hastalığın erken dönemde saptanması ve tedavisi önemlidir. Literatürde yenidoğanlardaki ABH insidansı hakkında fikir birliği yoktur. İnsidansı %8-24, mortalite oranları %10-61 gibi geniş bir aralıkta bildirilmiştir (2). Yenidoğanlarda ABH multifaktöriyeldir (3). En sık perinatal asfiksi ve sepsis olmakla beraber prematürite, konjestif kalp yetmezliği, terapötik girişimler ve bazı nefrotoksik ilaçlar gibi çok sayıda predispozan faktör vardır ve merkezlere göre farklılık göstermektedir (2 - 3). Prognoz altta yatan hastalığa, derecesine ve reversibilitesine bağlıdır. Mortalite oranının yüksekliği ve kronik böbrek yetmezliği gelişiminin sık olması nedeniyle ABH hala önemini korumaktadır (1). Bu çalışmanın amacı; üçüncü düzey referans merkezindeki yenidoğan kliniğinde ABH tanısı alan hastaların sıklığını, etiyolojiyi, predispozan risk faktörlerini, kullanılan tedavileri, erken dönem prognozlarını ve mortalitesini belirlemektir.

GEREÇ VE YÖNTEM

Ocak 2013 - Aralık 2016 tarihlerinde hastanemiz Yenidoğan Yoğun Bakım Ünitesinde (YYBÜ) yatan tüm hastaların elektronik dosyaları geriye dönük incelendi ve ABH tanısı alan olgular ABH grubu (ABH-G) olarak çalışmaya alındı. Postnatal ilk 28 günündeki term ve düzeltilmiş yaşı ≤28 gün olan preterm yenidoğanlar, postnatal 0-28. günlerde bakılan serum kreatin değerinin >1,5 mg/dL veya iki ölçüm arasında iki kat artış olması durumunda ABH tanısı aldı (4). Demografik ve antropometrik benzerliğine bakılmaksızın ABH saptanan hastanın öncesinde ve sonrasında servise yatan ancak ABH tanısı almamış ikişer hasta kontrol grubu (K-G) olarak çalışmaya alındı. Akut böbrek hasarı geliştiği sırada postnatal 28 günden büyük term veya düzeltilmiş yaşı 28 günden büyük preterm yenidoğanlar ve postnatal 0-28. günleri arasında olmasına rağmen serum kreatin değerinin <1,5 mg/dL olan veya iki ölçüm arasında iki kat artış olmayan hastalar çalışma dışı bırakıldı. Hastaların klinik, laboratuvar ve görüntüleme yöntemi ile prerenal, renal, postrenal ABH ayrımları yapıldı. İntravenöz sıvı tedavisine rağmen serum kreatinin yüksekliği devam eden ve ultrasonografide (USG) primer böbrek patolojisi saptanan hastalar renal ABH olarak tanımlandı. İntravenöz sıvı tedavisi ile serum kreatinin düzeyi hızla düzelen hastalar prerenal ABH olarak tanımlandı. Postrenal ABH olan hastalar ise USG ile tanı aldı (5). Böbrek hasarının etiyolojisi altta yatan hastalık ile belirlendi. Böbrek hasarına yol açan birden fazla etiyolojik faktörün olduğu durumlarda klinik ile belirlenen ana hastalık primer etiyolojik neden olarak kabul edildi (6). Tüm hastalarda belirlenen tanılar ile ABH gelişim sıklığı ve mortalite oranları araştırıldı. Tüm hastalar türk bebeklerinde belirlenen normogram/eğriler kullanılarak gebelik yaşlarına ve doğum ağırlıklarına göre sınıflandırıldı (7). Günlük idrar miktarının >5,5 ml/kg/saat olması poliüri, <1 ml/kg/saat olması oligüri, idrar çıkışının hiç olmaması anüri olarak tanımlanıp ABH oligürik ve non-oligürik olarak sınıflandırıldı (8). Gebelik yaşı 41-37 hafta arası term, ≥42 hafta postterm, <37 hafta preterm, gebelik yaşına göre doğum ağırlığı <10 persantil SGA; 10-89 persantil arası AGA ve ≥90 persantil LGA kabul edildi.<2500 gr düşük doğum ağırlığı (DDA) olarak tanımlandı (7). Kritik konjenital kalp hastalığı (K-KKH), yaşamın ilk yılında ameliyat veya kateterle müdahale gerektiren hastalık olarak tanımlandı (9). Perinatal asfiksi tanısında Türk Neonatoloji Derneği (TND) Neonatal Ensefalopati Tanı ve Tedavi Rehberi (2017) kullanıldı. Beşinci dakika Apgar skoru 5'in altında olanlar, doğumdan sonra ilk saatlerde kan gazında metabolik asidozu olan veya baz açığı -12 ve üzerinde olanlar perinatal asfiksi olarak kabul edildi (10). Sepsis tanısı Töllner skorlamasına göre koyuldu. Skoru 5-10 olanlar "Şüpheli sepsis", >10 bulunanlar "Sepsis", kan kültüründe üreme olanlar "Kültür pozitif sepsis" olarak kabul edildi. Sepsis risk faktörü olup kan kültüründe üreme olmayan, laboratuvar bulguları ile enfeksiyonu dışlanamayan bebeklere klinik sepsis kabul edildi. Sepsis için risk faktörleri olarak korioamnionit, Erken Membran Rüptürü (EMR), annede enfeksiyon/kolonizasyon varlığı; mekonyumlu doğum, doğumda resüsitasyon gereksinimi ve prematürite kabul edildi (11). Ultrasonografik değerlendirme ile primer olarak böbrek, üreter, mesaneyi ilgilendirdiği belirlenen hastalıklar

üriner patoloji olarak tanımlandı. Major malformasyonlar ciddi tıbbi, cerrahi ya da kozmetik sonuçları olan; yarık damak, yarık dudak, santral sinir sistemi anomalileri (meningomyelosel, spina bifida, anensefali gibi), kalp ve dolaşım sistemi anomalileri, omfalosel, gastroşisiz, anal atreziyi içeren hastalıklar olarak tanımlanmaktadır (12). Ancak kalp ve dolaşım sistemi anomalilerinden K-KKH hastalığı sıklığı fazla olduğundan ayrı bir grup olarak alınmıştır. Kanama; İKK, pulmoner kanama, gastrointestinal sistem kanaması ve minör kanamalar olarak sınıflandırıldı. Karaciğer fonksiyon testi (KCFT) bozukluğu alanin aminotransferaz (ALT) ve aspartat transaminaz (AST) enzimleri için postnatal yaş (gün) ve cinsiyetlerine göre referans sınırının üzerinde olması olarak tanımlandı. Referans sınırları; ALT için ≤7gün 6-40 ünite/litre (Ü/L), 8-30 gün arasında olan erkek bebekte 10-40 Ü/L, kızlarda 8-32 Ü/L iken AST'de≤7 gün erkek 30-150 Ü/L, kız 24-150 Ü/L, 8 gün arasında 9-80 Ü/L olarak belirlendi (13). Çalışmaya alınan hastaların demografik özellikleri, ABH olduğu dönemdeki klinik ve laboratuvar bilgileri, tedavileri, erken dönem prognoz ve mortaliteleri hasta elektronik dosyalarından taranıp kaydedildi. Akut böbrek hasarı grubu hastalarının ABH nedeni (prerenal, renal, postrenal), ABH tanısı olduğu süre boyunca en düşük idrar çıkış hızı (İÇH), ABH'ye neden olan primer etiyolojik tanıları, renal replasman tedavisi (RRT) gereksinimleri ve RRT ile mortalite ilişkisi kaydedildi. Primer etiyolojik nedenlerin gebelik yaşına, doğum ağırlığına, ABH gelişme zamanına göre dağılımı ve tanılarına göre mortalitesi belirlendi. Ayrıca ABH-G ve K-G'ler olası risk faktörleri açısından karşılaştırıldı.

Etik Kurul

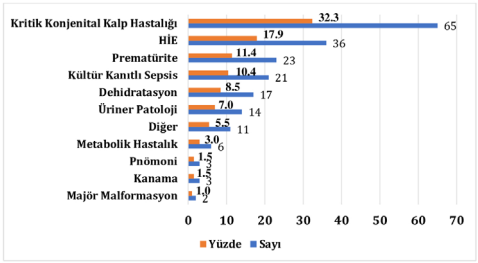
Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji Onkoloji Eğitim Araştırma Hastanesi Klinik Araştırmalar Etik Kurulundan etik kurul onayı alındı (Tarih: 16.04.2019 Sayı: 2019-081).

İstatistiksel Analiz

Sayısal değişkenler ortalama ± standart sapma, medyan [minimum-maksimum] değerler ile özetlendi. Sayısal değişkenler için iki grup Mann Whitney U testi ile karşılaştırıldı. Risk faktörlerinin denetlenmesi için Odds Ratio Oranı (OR) ve güven aralıkları hesaplandı. Korelasyonlar Spearman ve Pearson korelasyon katsayıları ile değerlendirildi. Anlamlılık düzeyi p<0.05 olarak alındı.

BULGULAR

Çalışma döneminde YYBÜ'de %32,3'ü (2396) preterm, %67,7'si term toplam 7418 yenidoğan yatırılarak izlenmişti. Bu hastaların 201 (%2,7)'i ABH tanısı aldı. Gebelik yaşları bilinen ABH-G için 194 hasta üzerinden gebelik süreleri için projeksiyon yapıldı. Akut böbrek hasarı grubunda hastaların %42,3'ü (82/194) preterm, %57,7'si (112/194) termdi. Pretermlerde ABH sıklığı (%3,42), term bebeklerden (%2,23) daha yüksekti (p<0,002). Hastaların %92,5'inde (186) prerenal, %6,5'inde (13) renal, %1'inde (2) postrenal sebeplerden kaynaklanan ABH saptandı. Akut böbrek hasarı olup İÇH bilgisine ulaşılabilen hastaların (113, %56,2) İÇH ortalaması 1,02±1,29 ml/kg/saat bulundu. Bu hastaların %41,6'sında (47/113) İÇH normal sınırdayken, %16,8 (19/113) oligürik, %40,7 (46/113) anürik ve %0,9'u (1/113) poliürik bulundu. Genel olarak hastaların % 57,5'i oligo-anürik, % 42,5'i non-oligürikti. Primer etiyolojik nedenler sıklık sırasıyla **Şekil 1**'de, en sık görülen primer etiyolojik nedenlerin gebelik yaşına ve doğum ağırlığına göre dağılımı **Tablo 1**'de gösterilmiştir.



Şekil 1: Akut Böbrek Hasarının Primer Etiyolojik Nedenlerinin Dağılımı

Tablo 1: En Sık Görülen Primer Etiyolojik Nedenlerin Gebelik Yaşı ve Doğum Ağırlığına Göre Dağılımı.

Gebelik Yaşı (hafta)	n (%)	Primer Etiyolojik Neden	Doğum Ağırlığı (gr)	n (%)	Primer Etiyolojik Neden
<32 6/7	17 (53,1)	Prematürite	<1000 gr	11(50)	Prematürite
	15 (46,9)	Kültür kanıtlı sepsis		9 (40,9)	Kültür kanıtlı sepsis
33-34 6/7	4 (30,8)	K-KKH	1000-1499	5 (35,7)	Prematürite
	3 (23,1)	Prematürite		4 (28,6)	Kültür kanıtlı sepsis
35-36 6/7	7 (30,4)	K-KKH	1500-2499	11(27,5)	K-KKH
	5 (21,7)	Üriner patoloji		6 (15)	HİE
> 37	48 (42,9)	K-KKH	> 2500	52 (42,3)	K-KKH
	30 (27)	HİE		28 (22,8)	HİE

Akut böbrek hasarı çoğunlukla (%61,2) yaşamın ilk haftası içinde gelişmişti ve ilk 7 gününde en sık ABH nedenleri K-KKH (%26), doğum asfiksisi (%24,4), prematürite (%16,2) idi. Yedinci günden sonra ise en sık nedenler sırasıyla K-KKH (%50), dehidratasyon (%12,5) ve sepsis (%12,5) olarak belirlendi. Prematürite ve Hipoksik İskemik Ensefalopatide (HİE) ilk 7 günde ABH gelişme riski daha yüksekti (sırasıyla %87, p=0,001; %86,1, p=0,001). Kritik konjenital kalp hastalı-

ğında ilk 7 günde ABH gelişme riski açısından anlamlı fark yoktu (%50,8, p=0,923). Akut böbrek hasarı grubuyla (82 kız: %40,8; 119: %59,2 erkek), K-G 169 kız: %42; 233 erkek: %58) arasında cinsiyet açısından fark saptanmadı (p= 0,770). Akut böbrek hasarı grubunda K-G'ye göre sezaryen (C/S) doğum oranı daha fazlaydı (sırasıyla %65,4-%47,5, p<0,001). Akut böbrek hasarı grubunda (82 preterm: %42,3; 112 term: %57,7); K-G'ye (114 preterm: %28,8; 282term: %71,2) göre preterm oranı yüksek bulundu (p=0,001). Akut böbrek hasarı grubunda HİE tanılı hastalar (36; %18), K-G'ye (9; %2,3) göre daha fazlaydı (p<0,001). Yine K-KKH hastalar ABH-G'de (65; %32,3), K-G'ye (30; %7,5) göre daha fazlaydı (p<0,001). Klinik özelliklerine göre nicel ve kategorik değişkenlerin gruplar arası dağılımı ve mortalite ile ilişkisi **Tablo 2, 3**'te gösterilmiştir.

Tablo 2: Klinik Özelliklere Göre Nicel Değişkenlerin Gruplar Arası Dağılımı ve Mortalite Karşılaştırması

Klinik Özellikler	ABH-G	K-G	p1	p2
	Ort±SS; ortanca	Ort±SS; ortanca	Dağılım	Mortalite
APGAR skoru 1. dakika	4,69±2,75	7,42±2,09	**<0,001**	0,318
APGAR skoru 5. dakika	4,87±2,27	8,86±1,66	**<0,001**	0,587
TPN aldığı süre (gün)	10,6±16,51 ; 4	3±9,1 ; 0	**<0,001**	0,496
Mekanik ventilatör süresi (gün)	11,77±16,51 ; 6	2,92±19,21; 0	**<0,001**	**<0,001**
Hastanede kalış süresi (gün)	26,22±29,5 ; 19	13,99±25,1 ; 7	**<0,001**	**<0,001**

TPN: total parenteral nütrisyon; p1: klinik özelliklerin gruplar arası karşılaştırması; p2: klinik özelliklerin mortalite ile ilişkisi

Tablo 3: Klinik Özelliklere Göre Kategorik Değişkenlerin Gruplar Arası Dağılımı ve Mortalite Karşılaştırması

Klinik Özellikler	ABH-G		K-G		p1	p2
	Sayı	%	Sayı	%	Dağılım	Mortalite
Yatış yaşı (0-7 gün)	125	62,2	247	61,4	0,859	0,091
Çoğul gebelik	14	7	24	6	0,55	0,367
Pozitif basınçlı ventilasyon	76	37,8	40	10	**<0,001**	0,432
SGA	18	9	15	3,7	**0,006**	0,712
LGA	20	10	50	12,4	0,426	0,713
AGA	159	79,1	330	82,1	0,63	0,270
Fetal distres	45	22,4	21	5,2	**<0,001**	0,057
Annede risk faktörü	64	31,8	132	32,8	0,36	0,532
HİE	36	17,9	9	2,2	**<0,001**	**0,038**
Hipotermi tedavisi	34	16,9	8	2	**<0,001**	**0,040**
Nöbet öyküsü	51	25,4	17	4,2	**<0,001**	**0,013**
Kanama	55	27,4	33	8,2	**<0,001**	**0,002**
Göbek kateteri	93	46,3	52	12,9	**<0,001**	0,094
Nekrotizan enterokolit (NEK)	11	5,5	10	2,5	0,059	0,519
Amfoterisin B kullanımı	38	18,9	11	2,7	**<0,001**	0,220
Aminoglikozid kullanımı	139	69,2	221	55	**0,001**	0,673
Furosemid kullanımı	83	41,3	25	6,2	**<0,001**	0,085
Vankomisin kullanımı	96	47,8	55	13,7	**<0,001**	0,405
Dopamin kullanımı	134	66,7	43	10,7	**<0,001**	**<0,001**
Dobutamin kullanımı	111	55,2	24	6	**<0,001**	**<0,001**
ACE inhibitörü kullanımı	39	19,4	8	2	**<0,001**	0,260
Aldaktazid® kullanımı	31	15,4	13	3,2	**<0,001**	0,746
Transfüzyon (herhangi bir veya birden fazla kan ürünü) alımı	168	83,6	69	17,2	**<0,001**	**<0,001**
Trombosit süspansiyon alımı	97	48,3	17	4,2	**<0,001**	**<0,001**
Eritrosit süspansiyon alımı	137	68,2	61	15,2	**<0,001**	**<0,001**
Taze donmuş plazma alımı	158	78,6	44	10,9	**<0,001**	**<0,001**
TPN alımı	118	58,7	86	21,4	**<0,001**	0,865
Mekanik ventilatör kulanım öyküsü	165	82,1	65	16,2	**<0,001**	**<0,001**

TPN: Total parenteral nütrisyon p1: klinik özelliklerin gruplar arası karşılaştırması; p2: klinik özelliklerin mortalite ile ilişkisi

Tablolardaki p1 değeri klinik özelliklerin ABH-G ile K-G arasındaki karşılaştırmasını, p2 değeri ise klinik özelliklerin mortalite ile ilişkisini göstermektedir. Laboratuvar özelliklerine göre nicel ve kategorik değişkenlerin gruplar arası dağılımı ve mortalite ile ilişkisi **Tablo 4 ve 5'**te gösterilmiştir.

Tablo 4: Laboratuvar Özelliklerine Göre Nicel Değişkenlerin Gruplar Arası Dağılımı ve Mortalite Karşılaştırması

Laboratuvar Özellikleri	ABH-G	K-G	p1	p2
	Ortalama±SS	Ortalama±SS	Dağılım	Mortalite
SNAPPE II	40,7±31,8	25,06±23,06	**0,036**	0,152
En yüksek kreatinin(mg/dl)	2,34±1,04	0,6±0,28	**<0,001**	**0,005**
En yüksek BUN (mg/dl)	53,13±37,91	14,18±13,06	**<0,001**	**0,014**
En düşük kalsiyum (mg/dl)	7±1,24	8,89±1,27	**<0,001**	**0,001**
En yüksek potasyum(mg/dl)	6,31±1,27	5,15±0,72	**<0,001**	0,907
C-Reaktif protein (mg/dL)	49,24±58,96	16,07±37,38	**<0,001**	0,891
İdrar dansite	1008,21±4,69	1006,89±5,14	**0,008**	0,814
En yüksek beyaz küre (x 10^3/µL)	23,58±12,94	13,46±7,35	**<0,001**	**0,003**
En düşük hematokrit (%)	30,05±9,26	42,08±11,12	**<0,001**	0,241
En düşük trombosit(x 10^3/µL)	99,56±98,02	264,7±127,21	**<0,001**	**<0,001**
En düşük İÇH	1,02±1,29	3,02±1,63	**<0,001**	**0,001**

SNAPPE: Score for neonatal acute physiology and perinatal extension; İÇH: idrar çıkış hızı

p1: klinik özelliklerin gruplar arası karşılaştırması; p2: klinik özelliklerin mortalite ile ilişkisi

Tablo 5: Laboratuvar Özelliklerine Göre Kategorik Değişkenlerin Gruplar Arası Dağılımı ve Mortalite Karşılaştırması

Laboratuvar Özellikleri	ABH-G		K-G		p1	p2
	Sayı	%	Sayı	%	Dağılım	Mortalite
Kültür (+) enfeksiyon	65	%32,3	74	%18,4	**<0,001**	0,198
Kan ve/veya BOS kültür (+)	48	%23,9	30	%7,5	**<0,001**	0,314
İdrar kültürü (+)	16	%8	23	%5,7	0,292	**0,003**
Diğer kültür (+)	15	%7,5	31	%7,7	0,907	0,942
KCFT bozukluğu	112	%55,7	25	%6,2	**<0,001**	0,171
Hematüri	55	%27,4	25	%6,2	**<0,001**	0,489
Proteinüri	46	%22,9	24	%6	**<0,001**	0,545

BOS: beyin omurilik sıvısı; KCFT: karaciğer fonksiyon testi

p1: klinik özelliklerin gruplar arası karşılaştırması; p2: klinik özelliklerin mortalite ile ilişkisi

Kontrol grubundaki hastaların 97'si (%24,1) indirek hiperbilirubinemi, 51'i (%12,7) pnömoni, 30'u (%7,5) K-KKH, 29'u (%7,2) prematürite, 25'i (%6,2) dehidratasyon, 21'i (%5,2) klinik sepsis, 18'i (%4,2) yenidoğan geçici takipnesi (YDGT), 17'si (%4,2) omfalit, 17'si (%4,2) idrar yolu enfeksiyonu (İYE), 13'ü (%3,2) kültür kanıtlı sepsis,9'u (%2,2) HİE nedeniyle yatırılmıştı. Prematüriteye bağlı ABH'de %73,9 (17/23), K-KKH'de %66,2 (43/65), kültür kanıtlı sepsiste %61,9 (13/21), üriner patolojide %42,9 (6/14), HİE'de %38,9 (14/36), metabolik hastalıkta %33,3 (2/6) ve dehidratasyonda %17,6 (3/17) oranında bulundu. Hastaların 49'una (%24,5) RRT gerekmiş ve 46'sına (%93,8) periton diyalizi (PD), ikisine (%4) renal üriner patoloji nedeniyle PD ve Continuous veno-venous hemodialysis (CCV-HD), birine (%2) metabolik hastalık nedeniyle hemodiyafiltrasyon yapılmıştı. Periton diyalizi yapılan hastaların 22'si (%47,8) K-KKH tanılı hastalardı. Mortalite ABH-G'de (109; %54,2), K-G hastalardan(14; %3,5) belirgin yüksekti (p<0,001). RRT alanların %81,6'sı (40/49), almayanların %45'i (68/151) kaybedildi ve RRT alanlarda mortalite belirgin yüksekti (p<0,001). Mono varyant analizde ABH geliştirme riski anlamlı olan parametreler (gebelik yaşı, doğum ağırlığı, doğumda canlandırma/Pozitif Basınçlı Ventilasyon (PBV) gereksinimi, SGA doğum, fetal distres, HİE, nöbet öyküsü, kanama, kültür pozitif enfeksiyon, kan ve/veya BOS kültürü, göbek kateteri, nefrotoksik ilaç kullanı-

mı, herhangi bir kan ürünü transfüzyonu, TPN alımı, KCFT bozukluğu, hematüri ve proteinüri olması, MV öyküsü) ile ABH'de mortalite riski anlamlı çıkan parametreler (preterm olma, DDA, HİE, nöbet öyküsü, kanama, idrar kültürü, dopamin ve dobutamin kullanımı, herhangi bir transfüzyon alımı, MV öyküsü, RRT gereksinimi, hastanede kalış süresi) lojistik regresyon analizine alındı. Bu değerlendirmede preterm olmanın term olmaya göre ABH tanısı alma riskini 1,8 kat arttırdığı bulundu [OR: 1,81 %95 GA: (1,266-2,592, P=0.015)]. Ayrıca ABH gelişim riskinin KCFT bozukluğu olanlarda 18,7, amfoterisin B kullananlarda 8,28, nöbet öyküsü olanlarda 7,7, vankomisin kullananlarda 5,7, proteinüri olmasının 3,2 ve aminoglikozid kullanımı 1,8 kat fazla olduğu bulundu **(Tablo 6)**.

Tablo 6: Lojistik Regresyon Analizi ile ABH Gelişimi ile İlişkili Faktörler

	OR	%95 Güven Aralığı			p
KCFT Bozukluğu	**18,744**	11,453	-	30,676	**0,005**
Amfoterisin B Kullanımı	**8,287**	4,134	-	16,612	**0,017**
Nöbet öyküsü	**7,700**	4,309	-	13,758	**0,007**
Vankomisin Kullanımı	**5,768**	3,879	-	8,579	**0,031**
Proteinüri	**3,207**	1,747	-	5,887	**0,028**
Aminoglikozid Kullanımı	**1,836**	1,284	-	2,627	**0,023**
Preterm doğum	**1,811**	1,266	-	2,592	**0,015**

KCFT: karaciğer fonksiyon testi

Kaybedilen hastalarda en önemli risk faktörleri dopamin kullanımı ve RRT gereksinimi idi. Hastalarda kaybedilme oranının dopamin kullananlarda 13,8 kat (p=0,002), RRT gerekenlerde 5,4 kat (p=0,003) arttığı bulundu **(Tablo 7)**.

Tablo 7: Lojistik Regresyon Analizi ile Mortalite İle İlişkili Risk Faktörleri

Dopamin Kullanımı	**13,859**	**6,541**	-	**29,363**	**0,002**
RRT Gereksinimi	**5,425**	2,460	-	11,965	**0,003**

RRT: renal replasman tedavisi

TARTIŞMA

Çalışmamızda YYBÜ'de yatan 7418 hastadan 201'inde (%2,7) ABH saptandı. Bunların yarısından fazlası termdi. Yenidoğanlarda ABH'nın çoğunlukla prerenal nedenli olduğu bulundu. Primer etiyolojik nedenlerden ilk üçü K-KKH, HİE ve prematürite idi. Bunların %57,5'i oligo-anürikti ve 109 (%54,2) hasta kaybedildi. Renal replasman tedavisi 49 hastada (%24,5) gerekli oldu. Akut böbrek hasarı gelişmesinde karaciğer fonksiyon testi bozukluğu, amfoterisin-B, vankomisin, aminoglikozid kullanımı, nöbet geçirme, proteinüri varlığı ve prematürite bağımsız risk faktörleri olarak belirlendi. Akut böbrek hasarı mortalitesinde ise dopamin kullanımı ve RRT alması bağımsız risk faktörleri olarak saptandı. Günümüze kadar ABH için çok sayıda tanımlamalar yapılmış olmakla birlikte yenidoğanlar için henüz belirli bir tanımı yoktur. Yenidoğanlarda ABH tanısı için idrar çıkışı, serum kreatinin (S-Kr) düzeyi, GFH ve kreatinin klirensi değerlerinin değişik kombinasyonlarda kullanımını öneren çalışmalar vardır (14,15). Sadece S-Kr düzeyini temel alan çalışmalar da olmakla birlikte fikir birliği sağlanan tek bir S-Kr değeri yoktur (16). Bir çalışmada S-Kr >2 mg/dl (6), diğerinde S-Kr>1,5 mg/dl (17) olmasını ABH olarak kabul etmişlerdir. Çalışmamızda S-Kr>1,5 mg/dL olması veya iki ölçüm arasında iki kat artış olması ABH olarak kabul edildi (1).

Yenidoğanda ABH tanı kriterleri tam oturmadığından tam sıklığı da bilinmemektedir. Yenidoğanlarda non-oligürik böbrek yetmezliği de görüldüğünden bildirilenlerden daha yüksek bir sıklığı olduğu düşünülmektedir (2). Tanıdaki zorluklar nedeniyle literatürde ABH sıklığı (%1-31) ve mortalite oranı (%19-83) çok geniş aralıklarda verilmektedir (18). Bir derlemede kritik hastalıklı yenidoğanlarda (S-Kr >1,5 mg/dL sınır değer olarak alan tek merkezli çalışmada) ABH sıklığının %8-24 arasında, mortalitesinin %10-61 arasında olduğu bildirilmektedir (4). Hastanemiz YYBÜ'de 4 yıllık çalışma döneminde ABH sıklığı %2,7 bulundu. Ülkemizde 2004 yılında yapılan bir çalışma YYBÜ'deki ABH sıklığını %3,4 olarak bildirmişlerdir (17). Bu oran, bizim hastalarımızdaki ABH sıklığı ile benzerdir ve tanımlanan geniş aralıkların içerisinde yer almaktadır. Ancak çalışmamızın geriye dönük olması, hastalarımızın İÇH kayıtlarında eksiklik nedeniyle bazı hastalarda ABH tanısı konamamış olabilir.

Günümüzde preterm bebek doğumları giderek artmakla birlikte yeni hizmete giren üst düzey YYBÜ'ler sayesinde pretermlerin yaşam şansları artmıştır. Birçok hastalık pretermlerde daha sık görülmekte, daha hızlı ilerlemekte ve daha yüksek oranda komplikasyon ve mortaliteye neden olmaktadır (19). ABH insidansını yalnızca pretermleri kapsayan bir çalışmada %18 (20), diğer çalışmada ise termlerde %3,4, pretermlerde %31 olarak bildirmişlerdir (17). Çalışmamızda pretermlerde ABH sıklığı %3,42, termlerde %2,23 bulundu ve ABH görülme sıklığı term hastalarda literatürle uyumlu iken, preterm hastalarda daha düşüktü. Yatan hastalarımızda çok küçük preterm bebeklerin daha az olması yanı sıra İÇH değerlerine tüm hastalarda

ulaşılamamış olmasıyla kısmen açıklanabilir. Yenidoğan döneminde ABH'nin en sık prerenal sebeplerden dolayı ortaya çıktığı bildirilmektedir (3). Ottonello ve ark. (21), neonatal ABH hastalarının %85'inde, Youssef ve ark. (3) %96,3'ünde prerenal azotemi saptamışlardır. Verilerimiz de benzer şekilde prerenal azoteminin daha sık olduğunu desteklemektedir. Yetersiz böbrek perfüzyonunun bir sonucu olarak ortaya çıkan prerenal azotemi hızlı tedaviyle sıklıkla geri dönebilen bir durumdur (1). Erken tanı ve tedavi ile geri dönüşlü olabilmesi ve kalıcı hasarın önlenebilmesi nedeniyle YYBÜ'de yatan tüm bebeklerin prerenal azotemi açısından yakın izlemleri önemlidir.

Primer etiyolojik nedenlere bakıldığında bir çalışmada ABH'nin en sık nedeni asfiksi iken, daha sonra sepsis/metabolik hastalık ve konjenital böbrek veya kardiyak sorunlar olarak bildirilmiştir (17). Diğer bir çalışmada perinatal asfiksi ABH ile ilişkili en sık sebep iken geri kalan hastaların tanıları sepsis, respiratuar distres sendromlu prematürite ve doğuştan kalp malformasyonları olarak gösterilmiştir (1). Başka çalışmada ise en sık neden sepsis olarak bildirilmiştir (6). Literatürde HİE primer etiyolojik neden olarak öne çıkarken, çalışmamızda K-KKH'nin ön plana çıktığı ve hemen arkasından HİE geldiği daha sonra ise prematürite ve sepsis geldiği görülmektedir. Asfiktik yenidoğanlarda ABH görülme sıklığı %41,7 (22), 5.dakika APGAR skorları 6 ve altında olan hastalarda ABH insidansı %54 olarak belirtilmiş ve ABH gelişen yenidoğanlarda en sık etiyolojik nedenin HİE olduğunu bildirmişlerdir (23). Akut böbrek hasarlı yenidoğanlarda primer etiyolojik neden olarak HİE'nin sıklığı çok geniş aralık tanımlanmakla birlikte tüm çalışmalarda ABH açısından önemi vurgulanmakta, nörolojik hasarın ciddiyeti ile ilişkili olarak böbrek tutulumunun HİE'li bebeklerde sık görüldüğü bildirilmektedir. Çalışmamızda da HİE sıklığı kontrol grubuna göre yaklaşık 9 kat fazla bulundu. Ayrıca nöbet öyküsü olan hastalarda ABH oranının daha yüksek olduğu ve ABH riskini bağımsız olarak 7 kat arttırdığı belirlendi. Bu durumun nöbet geçiren hastada en sık etiyolojik nedenin HİE olmasından (24) ve ABH-G'de ikinci en sık nedenin HİE olmasından kaynaklanabileceği düşünüldü. Kalp hastalığı olan yenidoğanlarda ABH sıklığı bir çalışmada %21,2 (25), diğer çalışmada %5-20 arasında (26) bildirilmiştir. Çalışmamızda K-KKH, ABH etiyolojisinde yaklaşık üçte bir oranda en sık primer etiyolojik neden olarak saptanırken, kontrol grubuna göre 5 kat fazla bulundu. Bu durum hastanemizin KKH merkezi olmasına, ikinci sırada HİE'nin olması ise ülkemizdeki en çok hasta kabul eden hipotermi merkezlerinden biri olmasına bağlı olabilir.

Yenidoğanda ABH tanı yaşına göre de primer nedenin değişebileceği bildirilmektedir. Bir çalışmada ABH olan yenidoğanların %66'sında ABH'nin yaşamın ilk haftasında geliştiğini, en sık nedenlerin sırasıyla sepsis, hipovolemi, doğum asfiksisi, genitoüriner sistem anomalileri iken 7 günden sonra ilk sırayı sepsis sonrasında konjestif kalp yetmezliğinin aldığını bildirmiştir (6). Bizim çalışmamızda da benzer şekilde hastaların çoğunda ABH'nin yaşamın ilk haftası içinde geliştiği gösterilmiştir.

Pretermlerde yapılan bir çalışmada ABH olan yenidoğanlarda, vankomisin (%22,5) ve dopamin (%31,5) kullanım oranının daha yüksek olduğu ve lojistik regresyon analizinde de bağımsız risk faktörü olduğu bildirilmiştir (27). Çalışmamızda da benzer şekilde ABH olan yenidoğanlarda vankomisin (%47,8) ve dopamin (%66,7) kullanım oranı yüksekti ve ABH gelişimi ile ilişkili bağımsız risk faktörü olduğu bulundu. Bu durum bu tedavileri alan hastaların klinik olarak daha ağır seyirli olması ve ikinci bir organ disfonksiyonu olup inotrop ihtiyacı olması ile açıklanabilir. Bu yüzden YYBÜ'de yatan yenidoğanlar ABH açısından çok yakın izlenmeli, ilaç kullanımında dozlar çok iyi ayarlanmalıdır.

Yenidoğan ABH'de diyaliz ihtiyacı bir çalışmada %30,3 (%93,3 periton diyalizi) (28), diğerinde %22,2 (17) olarak bildirilmiştir. Bu diyaliz gereken hastalarda en sık sepsis/metabolik hastalık tanısı saptanmıştır. Çalışmamızda da benzer şekilde ABH olan hastaların %24,5'inde RRT gereksinimi oldu ve %93,8'ine periton diyalizi yapıldı. Periton diyalizi yapılan hastalarımızda ilk üç primer etiyolojik nedenler sırasıyla K-KKH, HİE, üriner patoloji olarak belirlendi. Bu farklılığın nedeninin kliniklerin hasta popülasyonlarının farklılığından olduğu düşünüldü.

Yenidoğanda ABH olan hastalarda oligüri sıklığı %8-82 gibi geniş bir aralıkta bildirilmektedir (29). Bir çalışmada %50'sinden fazlasının (22), bir diğerinde %44'ünün (1), bir

diğerinde ise %70,4'ünün (3) non-oligürik olduğu bildirilmiştir. Verilerimiz ABH'nin daha çok oligürik seyrettiği serileri destekler nitelikteydi. Çalışmamızda oligürik olan hastaların daha fazla olmasının sebebinin çalışmamızın retrospektif olmasından, bazı hastaların İÇH kayıtlarına ulaşılamamış olunmasından, non-oligürik hastaların idrar çıkışının normal olması sebebiyle özellikli olarak görülmeyip kayıtlara girilmemesinden kaynaklanabileceği düşünüldü.

Akut böbrek hasarı olan hastalarda MV tedavisinin daha sık uygulandığını ve hastanede kalış süresinin daha uzun olduğu bildirilmektedir. MV gereksiniminin ABH olanlarda %49, olmayanlarda %20,2 olduğunu ve bu değerlerin ABH gelişmemiş hastalara göre önemli ölçüde yüksek olduğunu bildirmişlerdir (14). Çalışmamızda MV'ye bağlanma oranı ABH olanlarda kontrol grubuna göre yüksekti ancak bağımsız risk faktörü olarak bulunmadı. Bu durum kısmen ABH gelişenlerdeki preterm oranının daha fazla olması ve prematüriteye bağlı solunum sıkıntısı yaratan hastalıkların daha fazla olması ile açıklanabilir.

Literatürde yenidoğanlarda ABH ve KCFT bozukluğu arasındaki ilişkiyi inceleyen yayın bulunamadı. Ancak erişkinlerde böbrek yetmezliği ve karaciğer enzim yüksekliği ile ilgili bildirilmiş birkaç olgu sunumu vardır. Bu olgu sunumlarında böbrek ve karaciğer yetmezliğinin eş zamanlı gelişmesi durumunda şoktan şüphelenilmesi gerektiğini ve şokun daha nadir görülen formlarının araştırılmasını gerektiğini bildirmişlerdir.Ayrıca kompansatuar mekanizmalar nedeniyle uç organ fonksiyon bozukluğu belirtilerini düşünerek hemodinamik şoktan önce gelebileceği konusundaki farkındalığı arttırıp hızlıca altta yatan nedenin tedavisinin yapılması gerekliliğini vurgulamışlardır (30). Çalışmamızda KCFT bozukluğu ABH olan yenidoğanlarda %55,7 oranındaydı ve ABH gelişimi açısından bağımsız risk faktörü olarak belirlendi. Bu durum bu hastaların klinik durumunun ağır olmasına, hasta grubunda hipoksiye bağlı multisistemik tutulum gösterme olasılığı yüksek olan HİE hastalarının önemli bir yer tutmasına ve ABH yanısıra ikinci bir sistem tutulumunun tabloyu ağırlaştırmasına bağlı olabilir. Gerek KCFT bozukluğu gerekse ABH saptanan hastalarda diğer sistemlerin de yakın monitorizasyonu önemli görülmektedir. Karaciğerin fonksiyonunu değerlendiren birçok parametre olmakla birlikte çalışmamızda sadece iki enzimin yüksekliğine bakılabilmişti. Daha spesifik çalışmalar gerekebilir. Akut böbrek hasarı ve proteinüri ilişkisini inceleyen az sayıda olmakla beraber kalp ameliyatı geçiren çocuklarda ameliyat öncesi ve sonrası idrar albümin/kreatinin oranlarının ABH'yi öngörüp öngörmediği araştırılan bir çalışmada postoperatif idrar albümin/kreatinin oranının, ABH için erken bir tanı testi olduğunu belirtmişlerdir (31). Çalışmamızda ABH olanlarda proteinüri oranı (%22,9) kontrol grubundan yüksekti ve ABH gelişimi için bağımsız risk faktörleri arasındaydı. Verilerimiz YYBÜ'de yatan hastalarda öncelikle noninvaziv bir test olan idrar analizinin yapılması gerektiğini ve proteinüri saptanan hastalarda ABH açısından izlemin gerekliliğini vurgular niteliktedir.

Akut böbrek hasarlı hastalarda mortalite altta yatan morbiditelere göre değişmektedir (6). Mortalite bir çalışmada %24,4 (17), başka çalışmada %38,8 (6), diğerinde ise %41,8 (28) olarak bildirilmiştir. Çalışmamızda ABH olan yenidoğanlarda mortalite %54,2 idi ve literatürden yüksekti. Bu yükseklik K-KKH, HİE gibi mortalitesi yüksek hastalıkların daha sıklıkta olmasından, hastaların genel durumlarının RRT gerektirecek ve inotrop kullanımına ihtiyaç duyacak ağırlıkta olmalarından kaynaklanabileceği düşünüldü.

Pretermlerde birçok komplikasyon ile birlikte mortalitenin de artabileceği bilinmektedir. Bir çalışmada preterm (%40) ve term (%45) yenidoğanlarda ABH mortalitesi benzerken (32) çalışmamızdaki preterm mortalitesi (%67,1) daha yüksekti. Çalışmamızda prematürite ABH gelişimi için bağımsız risk faktörü olarakda bulundu. Pretermlerde ABH riski daha fazla olduğu gibi komplikasyonların daha sık olduğunu ve mortaliteye daha yatkın olduğunu düşündürmektedir. Bu nedenle tüm preterm bebekler YYBÜ yatışları esnasında ABH açısından yakın izlenmelidirler. Renal replasman tedavisi alan hastalarda mortalite oranı bir çalışmada %55,5 (14), başka çalışmada %50 (17) olarak bildirilmiştir. Çalışmamızda RRT alan hastaların %81,6'sı kaybedildi ve mortalite yüksek bulundu. Bu farklılığın serimizde K-KKH oranının daha fazla olmasından kaynaklandığı düşünüldü. Mortalite ilişkili lojistik regresyon analizi ile değerlendirildiğinde RRT gereksiniminin bağımsız risk faktörü olduğu görüldü.

Çalışmamızda yenidoğanlarda ABH gelişimi açısından KCFT bozukluğu olması, amfoterisin

B, vankomisin, aminoglikozid kullanımı, nöbet öyküsü olması, proteinüri olması, prematüritenin olması bağımsız risk faktörleri olarak belirlendi. Literatürde ise ABH olan yenidoğanlarda en sık görülen predispozan faktörlerin sepsis, RDS ve MV olduğu bildirilmiştir (3).

Yenidoğanlarda ABH mortalite ile ilişkili olarak en önemli risk faktörlerinin dopamin kullanımı ve RRT gereksinimi olduğu bulundu. Literatür mortalitede önemli risk faktörlerinin sepsis ve MV olduğu bildirmiştir (3). Diğer bir çalışmada primer hastalık etiyolojisi mortalite için tek bağımsız risk faktörü olarak bulunmuş ve sepsis kaynaklı ABH hastaların hipovolemi kaynaklı ABH hastalarına kıyasla ölüm riskinin yaklaşık 14 kat fazla olduğu belirtilmiştir. Gebelik yaşı, doğum ağırlığı, cinsiyet, maksimum S-Kr düzeyi ve tanı yaşı bizim çalışmamıza benzer şekilde mortalite açısından anlamlı bulunmamıştır (6).

Çalışmanın geriye dönük olması, idrar çıkış hızının kayıtlarda eksik olması çalışmamızın kısıtlı yönleriydi. İdrar çıkış hızı kayıtlarının eksikliği nedeniyle bazı ABH olan hastalar gözden kaçırılmış olabilir. Çalışmamızın 4 yılı kapsayacak şekilde olması, 4 yıl boyunca ABH saptanan hasta sayısının çok olması ve her olguya karşılık aynı süre içinde yatmış iki hasta alınarak kontrol grubunun oluşturulması çalışmanın kuvvetli yönleriydi.

Sonuç olarak YYBÜ'lerde izlenen başta K-KKH, HİE, prematürite, sepsis ve dehidratasyon tanılı hastalar olmak üzere tüm hastaların ABH riski taşıyabileceği hep göz önüne alınmalıdır. Maternal ve perinatal risk faktörlerinin olup olmadığı dikkatle değerlendirilmeli, klinik ve laboratuvar izlemleri yakından yapılmalı, idrar çıkış hızları, kreatinin ve idrar analiz değerleri özellikle proteinüri izlenmeli, nefrotoksik ilaçlar çok dikkatli kullanılmalıdır. Akut böbrek hasarı saptanan hastalarda uygun tedavi gecikmeden başlanmalı, inotrop ihtiyacının olması ve RRT gereksiniminin mortaliteyi arttırabileceği unutulmamalıdır.

Akut böbrek hasarı risk faktörlerinin daha hassas belirlenmesi için, idrar çıkış hızının da günlük olarak takip edilebileceği prospektif planlanmış geniş çalışmalar gerekmektedir.

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Kocatepe Tıp Dergisi
Kocatepe Medical Journal
25:519-524/Ekim 2024 Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

DİŞ HEKİMLİĞİ HASTALARININ KÖK KANAL TEDAVİSİ KONUSUNDA BİLGİ SEVİYELERİ VE BAKIŞ AÇILARI

DENTISTRY PATIENTS' KNOWLEDGE LEVELS AND PERSPECTIVES ON ROOT CANAL TREATMENT

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ÖZET

AMAÇ: Hastaların kök kanalı tedavisi konusunda bilgi düzeyleri, bilgi kaynakları ve bakış açıları konularının demografik veriler eşliğinde değerlendirilmesidir.

GEREÇ VE YÖNTEM: Diş hekimliği fakültesine genel dental muayene için gelen hastalardan gönüllü 500 katılımcıya önceden yapılandırılmış kapalı uçlu sorulardan oluşan anket formu doldurmaları için dağıtıldı. Anket demografik verilere yönelik sorular ile hastaların kök kanal tedavisine yönelik bilgi, farkındalık ve tutumlarını değerlendirmeye yönelik 12 adet çoktan seçmeli soruyu içermekteydi. Tamamlanan anketle, katılımcıların kök kanal tedavisi hakkındaki bilgi ve görüşleri demografik veriler eşliğinde analiz edildi. Tanımlayıcı istatistikler ve regresyon modeli istatistiksel analiz için kullanıldı.

BULGULAR: Hastaların 335'inin (%67) kök kanal tedavisi konsunda bilgi sahibi olduğu bulunmuştur. Bilgi kaynağının ise %77,6 oranında diş hekimi olduğu anlaşılmıştır. Cinsiyetin kök kanal tedavisi bilgi düzeyi ve tutumunda etkili olmadığı görülmüştür (p=0,926). Yaş düzeyi arttıkça, kök kanal tedavisi bilgi düzeyi düşmektedir (p=0,044). Eğitim ve gelir düzeyi arttıkça, kök kanal tedavisi bilgi düzeyi de artmaktadır (p=0,000).

SONUÇ: Hastaların kök kanal tedavisi konusunda bilgi ve farkındalık düzeylerinin yaş, eğitim ve gelir seviyesinden etkilendiği görülmüştür. Sosyal medya ve çevre, bu konuda hastaların bilgi ve farkındalığını etkilese de diş hekimlerinin temel etmen olduğu anlaşılmaktadır.

ANAHTAR KELİMELER: Kök kanal tedavisi, Sağlık anketleri, Diş hekimliği, Bilgi.

ABSTRACT

OBJECTIVE: To evaluate the level of knowledge, sources of information, and perspectives of patients about root canal treatment with demographic data.

MATERIAL AND METHODS: A questionnaire consisting of pre-structured closed-ended questions was distributed to 500 volunteer participants from patients who came to the dental school for general dental examination. The questionnaire included questions on demographic data and 12 multiple-choice questions to assess patients' knowledge, awareness and attitudes towards root canal treatment. With the completed questionnaire, participants' knowledge and opinions about root canal treatment were analyzed with demographic data. Descriptive statistics and regression model were used for statistical analysis.

RESULTS: It was found that 335 (67%) of the patients had information about root canal treatment. The source of information was found to be the dentist by 77.6%. Gender was not found to have an effect on the level of knowledge and attitude towards root canal treatment (p=0.926). As the age level increases, the level of knowledge about root canal treatment decreases (p=0.044). As the level of education and income increases, the level of knowledge about root canal treatment increases (p=0.000).

CONCLUSIONS: Patients' knowledge and awareness levels were found to be affected by age, education and income level. Although social media and the environment affect patients' knowledge and awareness, it is understood that dentists are the main factor.

KEYWORDS: Root canal therapy, Health surveys, Dentistry, Knowledge.

Geliş Tarihi / Received: 05.08.2023
Kabul Tarihi / Accepted: 06.07.2024
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INTRODUCTION

Parallel to the developments in medical science, there have been developments in dentistry practices all over the world. Along with scientific developments, specialization and specialization on certain subjects in the field of dentistry have become compulsory. In 1942, some dentists came together in Chicago to establish an organization to support laboratory and clinical research on root canal treatment (RCT), and the American Association of Endodontics was established at this meeting. Endodontics was one of the 8 different specialties accepted with the omnibus law published in the Official Gazette in 2011 in Türkiye (1).

Toothache is quite common in society and patients seek treatment to relieve this pain. The most common treatment to relieve toothache is RCT and tooth extraction (2). In these cases, endodontic treatment is an option to protect the tooth. Endodontic treatment or RCT is a procedure in which the infected pulp is cleaned to stop or prevent pulpal or periapical pathologies (3). RCT involves removing the diseased tissue, disinfecting the root canal and filling it with an inert material (4). With RCT, many teeth with pulp and periradicular infections that need to be extracted can be retained in the mouth for long periods of time (5).

If tooth extraction is performed instead of RCT, it can lead to many undesirable conditions such as tooth displacement, disruption of occlusion and aesthetic problems (6). In addition, tooth loss is associated with many problems such as being an indicator of functional aging, increased risk of dementia, psychological problems and deterioration of health due to decreased quality of life (7, 8). Rehabilitation of the extracted tooth area with prosthetic applications, including implant applications, has disadvantages such as high cost and the need for additional operations in addition to the loss of the natural tooth.

As mentioned above, RCT has many importance and advantages, but it draws attention to the level of knowledge and awareness of patients on this subject. Many sources play a role in patients' knowledge and awareness of RCT, including past experiences, dentists, social environment, social media, communication tools and family members (6, 9). Doumani et al. (10) concluded that knowledge and awareness about RCT differed between various races and populations. Habib et al. (11) showed in their study that knowledge and awareness about RCT may influence the patient's final choice and decision. Therefore, the aim of the present study was to investigate the level of knowledge and awareness of patients applying to the faculty of dentistry in a specific population in Türkiye.

MATERIALS AND METHODS

A self-administered questionnaire was prepared and delivered to 500 voluntary participants from patients who came to Afyonkarahisar Health Sciences University Faculty of Dentistry for routine dental examination. The survey was prepared inspired by previous studies (6, 10, 12). In the questionnaire, sociodemographic data on age, gender, education level and income level of the participants were obtained (Table 1). The survey contained 12 multiple-choice questions to assess participants' knowledge, awareness, and attitudes (experiences, expectations, and concerns) towards RCT (Table 2). The inclusion criteria for the study were male or female patients between the ages of 15-70. Exclusion criteria were mentally disabled patients, pediatric patients, and patients over 70 years of age.

Ethical Committee

Approval numbered 2021/5-277 was obtained from Afyonkarahisar Health Sciences University Clinical Research Ethics Committee. Participants consent was received.

Statistical Analysis

A three-stage analysis was performed to determine the level of knowledge about RCT. First, the demographic characteristics of the patients participating in the study were analyzed with descriptive statistics. Then, the questions asked to determine the level of knowledge of the participants about RCT were analyzed with descriptive statistics. In the last analysis step, regression modeling was used to determine whether demographic characteristics create any difference in the level of knowledge about RCT.

RESULTS

In order to determine the demographic characteristics of these 500 patients who participated in the survey, the results obtained according to gender, age, educational status, and income le-

vel are given in Table 1. When Table 1 is examined, a homogeneous distribution is observed according to gender. Of the 500 patients who participated in the survey, 247 were female and 253 were male. In order to determine the age of the participants, this part of the questionnaire was asked open-endedly and then scaled. It is determined from the questionnaire forms obtained that a significant portion of the participants are relatively middle-aged. In particular, the fact that 324 out of 500 participants are in the 31-50 age group is proof of this judgment. While the number of participants under the age of 18 is 9, the number of participants over the age of 61 is only 18 **(Table 1)**.

Table 1: Analysis of Demographic Variables

Demography		Frequency	Percentage
Gender	Female	247	49.4
	Male	253	50.6
Age	18 and below	9	1.8
	19-30	74	14.8
	31-40	153	30.6
	41-50	171	34.2
	51-60	75	15.0
	61 and above	18	3.6
Education Level	Primary School	70	14.0
	Middle School	15	3.0
	High School	158	31.6
	University	252	50.4
	Postgraduate	5	1.0
Income Level	Below Minimum Wage	15	3.0
	Minimum Wage	181	36.2
	3600-5000	209	41.8
	5001-6500	75	15.0
	8650 and above	20	4.0

As a result of the answers given to the question posed to determine the educational level of the participants, it is seen that more than 80% of the participants have high school and higher education. In particular, the fact that 50.4% of the participants, in other words, more than half of the participants, have a bachelor's degree reveals that the participant profile is an educated segment. When the question regarding income level is asked, it is evidenced that more than half of the participants have an income above the minimum wage. It can be said that the group declaring income below the minimum wage stems from the unemployed group under the age of 18 and the middle-aged group consisting of retirees (Table 1).

After determining the demographic characteristics, questions related to this field were asked to the participants in order to determine the level of knowledge about RCT **(Table 2).** In addition, if the participant had a history of treatment related to RCT, their experiences and preferences were asked. In this section, if the patient had no previous experience and treatment history related to RCT, they were asked to leave the question blank. The responses to the questions in this group, which consisted of a total of 12 questions, were reported using the frequency analysis method (Table 2).

Table 2: Knowledge Level of Root Canal Treatment

Question	Presented Option	Frequency
Do you have any information about root canal treatment?	Yes, I have sufficient information.	110
	I have partial information.	225
	No, I do not have any information.	165
How did you get the information you have about root canal treatment?	From friends and/or acquaintances.	42
	By researching on the internet and/or social media.	34
	From my dentist	264
What do you think is the name of the department that deals with root canal treatment?	Endodontics	150
	I don't know	350
How many years do you think a root canal treatment will be valid?	1-5 Years	88
	6-10 Years	133
	11-20 Years	44
	Lifetime	70
If a tooth that has undergone root canal treatment hurts, why/who do you think it is caused by?	My Dentist	104
	Poor Oral Hygiene	153
	I consider such a situation normal and I don't blame anyone.	78
Do you think root canal treatment is a difficult procedure?	Yes, I see it as a difficult process.	200
	No, I do not see it as a difficult process.	120
	I don't have any information.	180
Have you had root canal treatment before?	Yes	290
	No.	184
If you have had root canal treatment before, how would you describe the experience?	Good.	134
	Normal	36
	Bad	120
Where did you have your root canal treatment?	Private Examination/Private Clinic	180
	Ministry of Health Affiliated Hospital/Mouth and Dental Health Center	40
	University Hospital/Dental Hospital	70
Do you know the title of the physician who performed your root canal treatment?	Dentist	110
	Endodontics Specialist	44
	Intern	26
	I don't know	110
Would you choose root canal treatment or one of the alternative treatments listed below?	Root Canal Treatment	304
	Tooth Extraction	10
	Tooth Extraction + Implant	1
	I don't have any idea	185
If you prefer extraction instead of root canal treatment, what is the reason?	Root canal treatment is not a successful treatment	6
	A previous bad treatment experience	4
	The implant is a healthier procedure after extraction	1

In the last stage, regression model was used. The main purpose of the regression model is to determine which one(s) of the demographic characteristics have a statistical effect on the level of knowledge of RCT. For this purpose, 12 questions measuring the knowledge level of the participants were included in the analysis as dependent variables, and the gender, education level, age, and income level of the participants were included as independent variables. As a result of the analysis performed by establishing a Least Squares regression model, the R^2 (74.71%) and adjusted R^2 (50.40%) figures, which measure the model significance, show that the model is significant.

Then, as a result of the analysis conducted with the help of the E-views program, it was determined that three of the four variables (age, education level and income level), which were determined as independent variables, statistically affected the level of RCT knowledge at 5% significance level **(Table 3)**.

Table 3: Results of the Regression Model

VARIABLE	Coefficient	Std. Error	T-statistic	Probability (P Value)
C	3.189	0.195	16.361	0.000
Gender	-.006	.063	-.093	.926
Age	-.063	.031	-2.021	.044
Education Level	.147	.036	-4.127	.000
Income Level	.130	.036	-3.652	.000

R-squared	0.747166	Mean dependent exists	9.032326
Adjusted R-squared	0.504039	S.D. dependent exists	0.859375
S.E. of regression	0.605211	Akaike info criterion	1.933808
Sum squared resid	15.38376	Schwarz criterion	2.130632
Log likelihood	-40.44448	Hannan-Quinn criter.	2.007874
F-statistic	12.68732	Durbin-Watson stat	2.208878
Prob(F-statistic)	0.000001		

According to the results of the regression model in Table 3, the gender status of the participants does not statistically affect the level of RCT knowledge at 5% significance level (p=0.926). On the other hand, all other independent variables (age, education level and income level) affect the dependent variable RCT since the p value is lower than 5% significance level. The p-values and model coefficient values show that RCT knowledge decreases with age, but increases with income and education level (Table 3).

DISCUSSION

Endodontics is a specialty that has been constantly evolving over the last fifty years, incorporating a variety of modern tools that help to preserve the patient's natural teeth, thus helping to ensure the patient's normal function and aesthetics. The knowledge of patients planning to undergo endodontic treatment can be influenced by different information they receive from friends, family members, media, or visits to dental clinics. The aim of this study was to examine the level of knowledge and attitudes of dental school patients toward RCT.

The first question that comes to mind when assessing patients' knowledge and awareness of RCT is whether patients have knowledge about RCT. In studies that have examined this question, it was found that the proportion of patients who stated that they had no idea about RCT to the relevant question varied between 24% and 72% (9, 11, 13 - 15). The fact that this range is wide suggests that it depends on the population studied. Similarly, 33% of the patients in the current study reported that they did not have any information about RCT. Even in patients who come to the dental school for routine dental examination, the fact that a significant proportion of patients responded that they did not have any information draws attention to the necessity of informing patients. In previous studies, the proportion of those who reported receiving information about RCT from dentists ranged from 13.5% to 64.9% (6, 16, 17).

According to the results of the current study, 77.6% of those who answered the question of where they obtained information about RCT from stated that they obtained it from their dentist. While the patients' main source of information about RCT was dentists (77.6%), there was no significant difference between obtaining information from social media or the internet (10%) and from friends (12.4%). The source of information obtained from the internet can be of varying quality, ranging from professional reviews by colleagues to personal opinions and anecdotes of patients. As a result, information obtained from the internet may lead to misinformation, stress, and increased tendency to self-diagnosis or self-treatment (18). In the current study, although the rate of information acquisition from the internet or social media was not very high, it was still found to be effective. It is very likely that the effectiveness of these sources will increase over time. However, although these sources have the advantage of easy accessibility, it should not be ignored that their reliability is questionable.

Taşsöker et al. (1) asked about the specialty where RCT was performed and 27.6% of the participants answered that it was the endodontic department. In the current study, 30% of the patients answered the similar question as an endodontic department.

RCT is a successful treatment method when performed by both dentists and endodontists, with a retention rate of 98% in the first year and 86% in the 10th year (19 - 21). Among those who answered the question of how many years the RCT would be valid, 34% said up to 10 years, and 66% said more than 10 years. It is understood that the majority of the participants expect a long life expectancy from the RCT.

A question similar to the question of why/whom it is caused by in case of pain in a tooth that has undergone RCT was not seen in similar studies

we examined (9 - 10, 12, 17). When asked who or why they would blame for the pain in a tooth with RCT, 31% said the dentist, 45.7% said poor oral hygiene, and 23.3% said they would not blame anyone. Informing the patients before and after the application of RCT may reduce the 31% who may blame the dentist.

In the current questionnaire, when asked if RCT was a difficult procedure, 40% responded that it was a difficult procedure, 24% that it was not a difficult procedure and 36% had no idea. Jancezarek et al. (22) asked about the experience of RCT and 34% answered that the experience was poor. Iyer et al. (6) reported that 43.75% reported anxiety during the RCT experience. Although these studies were conducted in different countries and by different physicians, similar results were obtained. As a result of the current study, in accordance with the literature, the necessity of studies aimed at relieving anxiety in patients and the need for advanced training in RCT is evident.

Iyer et al. (6) reported that 51.69% of middle-aged people preferred private clinics over public hospitals. The reasons for this were that private clinics were cleaner and appointments could be made in a shorter time. According to Al Johara's study (23), the factors that determine patients' approach when choosing an institution are the level of knowledge of the physician, communication, convenience, cost, and clinical facilities. According to the results of the study by Iqbal et al. (24) it was stated that professional experience, staff courtesy and sincere behavior were effective in patients' choice of institution. In the current study, the majority of the participants preferred private clinics in line with the literature. These findings suggest that state-sponsored dental health services should be improved.

When the participants were asked if they knew the title of the physician who performed their treatment, 180 patients (62%) stated that they knew and 110 patients (38%) stated that they did not know. Of those who indicated that they knew, 110 patients indicated that they had undergone RCT with a dentist, 44 with an endodontic specialist and 26 with a dental intern. It is seen that most of the patients who underwent RCT have information about the title of the physicians who performed this treatment. I In the study by Janczarek et al. (22) it was reported that 95% of the participants had information about the titles of the physicians who performed RCT.

Past experiences or pain expectations are considered to be an important factor in patients avoiding dental treatments (25). Bansal and Jain (15) reported in their study that 16% of patients preferred tooth extraction instead of RCT. In the current study, the preference for tooth extraction over RCT was found to be lower at 2.2%. This can be attributed to the 37% who stated that they had no opinion. In order to improve the treatment approach, especially in patients who state that they have no idea, it is necessary to prevent misconceptions such as misinformation, fear and anxiety, that is, to increase knowledge and awareness about RCT.

It is noteworthy that patients' knowledge levels and perspectives on RCT may vary according to socioeconomic factors. It appears that the majority of patients receive information about RCT from their dentist. So that informing the patients before and after RCT is an issue that should be emphasized. More effective information may be beneficial in raising awareness on this issue. In addition, although it is less preferred by patients as a source of information, the use of mass media such as social media with the right strategies can help to increase awareness on this issue.

This study is a self-report survey. Therefore, there is a possibility of response bias in the data obtained. The more specific questions of the survey led to a reduction in the number of participants answering these questions, so not all participants were able to answer all the questions. This study is limited in its generalizability as it only represents the views of patients who visited AFSU Faculty of Dentistry. Patients in other regions of Türkiye may have different views. Further studies on the level of knowledge and awareness of RCT should be conducted on a larger scale, taking into account possible variations in responses among populations from different socioeconomic strata and different regions of the country.

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Kocatepe Tıp Dergisi
Kocatepe Medical Journal
25:525-535/Ekim 2024 Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

RATLARDA SİYATİK SİNİR YARALANMASINDA *MYRTUS COMMUNIS*'İN TERAPÖTİK ETKİNLİĞİ: BİR DENEYSEL ARAŞTIRMA

THERAPEUTIC EFFICACY OF *MYRTUS COMMUNIS* IN SCIATIC NERVE INJURY: AN EXPERIMENTAL RESEARCH IN RATS

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ÖZET

AMAÇ: Sinir yaralanmaları, genellikle çeşitli nedenlerden kaynaklanan ciddi sağlık sorunları olup, genellikle uzun süreli rehabilitasyon gerektirir. Bu yaralanmaların tedavisinde kullanılan geleneksel yöntemler çoğunlukla yetersiz kalmakta ve yeni tedavi yaklaşımlarının araştırılmasını gerektirmektedir. Bitkisel kökenli aktif bileşiklerin sinir rejenerasyonu üzerindeki etkileri üzerine yapılan araştırmalar, potansiyel yeni tedavi seçenekleri sunabilir. Bu bağlamda, *Myrtus communis*'in sinir rejenerasyonu üzerindeki etkilerini araştıran bu çalışma, sinir yaralanması tedavisi alanında önemli bir boşluğu doldurmayı amaçlamaktadır.

GEREÇ VE YÖNTEM: Bu çalışmada, *Myrtus communis*'in etkinliği deneysel siyatik sinir yaralanması modelinde değerlendirildi. Otuz iki dişi Wistar Albino sıçan dört gruba ayrıldı: Kontrol, Sham, Grup I ve Grup II. Siyatik sinir yaralanması indüklendi ve Myrtus communis tedavisi gastrik lavaj yoluyla uygulandı. Hayvanların motor fonksiyonları, duyusal fonksiyonları, elektrofizyolojik ölçümleri, biyokimyasal parametreleri ve histopatolojik değerlendirmeleri incelendi.

BULGULAR: *Myrtus communis*'in siyatik fonksiyonel indeks (SFI) değerlerinde hızlı iyileşmeye katkıda bulunduğunu gösterdi. Benzer şekilde, duyusal değerlendirme ve elektrofizyolojik ölçümlerde de olumlu etkiler gözlendi. Biyokimyasal analizler, Myrtus communis'in antioksidan kapasiteyi artırdığını ve oksidatif stresi azalttığını gösterdi. Histopatolojik incelemeler, *Myrtus communis* ile tedavi edilen gruplarda daha az akson dejenerasyonu, ödem ve vakuolizasyon olduğunu ortaya koydu.

SONUÇ: Bu çalışma, *Myrtus communis*'in siyatik sinir yaralanmasının tedavisinde potansiyel bir terapötik ajan olarak kullanılabileceğini sonucuna varmıştır. Bu bulgular, *Myrtus communis*'in sinir yaralanması sonrası iyileşme sürecinde destekleyici bir rol oynayabileceğini düşündürmektedir. Bununla birlikte, bu sonuçların klinik uygulamalara dönüştürülebilmesi için daha fazla araştırmaya ihtiyaç olduğu unutulmamalıdır.

ANAHTAR KELİMELER: *Myrtus Communis*, Siyatik sinir hasarı, Terapötik etkinlik, Periferik sinir rejenerasyonu, Anti-inflamatuar etkiler.

ABSTRACT

OBJECTIVE: Nerve injuries, often resulting from various causes, pose serious health issues that typically require prolonged rehabilitation. Conventional methods used in the treatment of these injuries are often inadequate, necessitating the exploration of new treatment approaches. Research on the effects of plant-derived active compounds on nerve regeneration may offer potential new treatment options. In this context, this study investigating the effects of *Myrtus communis* on nerve regeneration aims to fill an important gap in the field of nerve injury treatment.

MATERIAL AND METHODS: In this study, the efficacy of *Myrtus communis* was evaluated in an experimental sciatic nerve injury model. Thirty-two female Wistar Albino rats were divided into four groups: Control, Sham, Group I, and Group II. Sciatic nerve injury was induced, and Myrtus communis treatment was administered via gastric lavage. The animals' motor functions, sensory functions, electrophysiological measurements, biochemical parameters, and histopathological evaluations were examined.

RESULTS: The results demonstrated that *Myrtus communis* contributed to rapid improvement in sciatic functional index (SFI) values. Similarly, positive effects were observed in sensory assessment and electrophysiological measurements. Biochemical analyses indicated that *Myrtus communis* increased antioxidant capacity and reduced oxidative stress. Histopathological examinations revealed less axon degeneration, edema, and vacuolization in the groups treated with *Myrtus communis*.

CONCLUSIONS: This study concludes that *Myrtus communis* could be used as a potential therapeutic agent in the treatment of sciatic nerve injury. These findings suggest that *Myrtus communis* may play a supportive role in post-nerve injury recovery. However, it should be noted that further research is needed before these results can be translated into clinical applications.

KEYWORDS: *Myrtus Communis,* Sciatic nerve injury, Therapeutic efficacy, Peripheral nerve regeneration, Anti-inflammatory effects.

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Kabul Tarihi / Accepted:16.09.2024
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INTRODUCTION

Peripheral nerve injury (PNI) stands as a prevalent consequence of traumatic incidents (1), with an estimated incidence ranging from 13 to 23 cases per 100,000 individuals (2). These injuries can arise from various sources including mechanical, chemical, and thermal factors (3). PNI can disrupt motor and sensory functions, affecting both efferent (motor and autonomic) and afferent (sensory) pathways. This disruption can significantly impair a person's functional abilities and work capacity (4, 5). Treatment strategies for PNI focus on surgically repairing the damaged nerve or improving patients' quality of life through medical interventions (6). However, there remains a lack of consensus regarding the optimal approach for PNI treatment. Current methods for treating PNI include a range of interventions. These interventions encompass non-steroidal anti-inflammatory drugs, steroids, nerve growth factors, erythropoietin, thyroid hormone, growth hormone, adrenocorticotropic hormone, and insulin-like peptides, among others, used in experimental settings (7 – 12).

Myrtle (*Myrtus communis* L., MC) is a plant from the Myrtle family commonly found in the Mediterranean region (13). The primary compounds in MC leaves include phenolic acids (such as gallic acid, ferulic acid, caffeic acid, syringic acid, and vanillic acid), flavonoids, water-soluble tannins (gallotannins), proanthocyanidins, and essential oils (including a-pinene, myristenyl acetate, 1,8-cineole, limonene, and linalool) (14). Recently, plants with high levels of phenolic compounds, polyunsaturated fatty acids, and essential oils have gained attention for their potential health benefits, such as antioxidant, anticancer, and anti-inflammatory effects (15). MC leaves and fruits are known for their anti-inflammatory, antifungal, antibacterial, neuroprotective, hepatoprotective, anticancer, antidiabetic, and antiviral properties, as well as their ability to scavenge free radicals due to their antioxidant activity (16 – 20).

In this study, we aimed to evaluate the efficacy of Myrtus communis in sciatic nerve injury.

MATERIALS AND METHODS

Study Design

The research was conducted at the Experimental Animal Laboratory of Afyon Kocatepe University between January and March 2022. All animals involved in the study were treated with care and in accordance with the standards set forth in the National Institutes of Health's Guide for the Care and Use of Laboratory Animals.

Animals

The study used thirty-two female Wistar Albino rats, each weighing between 250-300 grams and aged 4-6 months. These rats were obtained from the Experimental Animal Production and Research Center in Afyonkarahisar, Turkey. Due to the unavailability of male rats and project timeline constraints, female rats were used. The rats received normal rat chow and unlimited water prior to the experiment. For a minimum of one week, they were kept in similar cages with regulated temperatures, 50% humidity, and a 12-hour light/dark cycle. Up to eight rats might be housed in each cage.

Anesthesia and surgical procedures

80 mg/kg of ketamine hydrochloride and 5 mg/kg of xylazine hydrochloride (both from Alfasan, The Netherlands) were injected intraperitoneally to induce anesthesia; further doses were given as needed. Throughout the procedure, electrocardiography (ECG) was monitored to keep the patient's heart rate between 190 to 260 beats per minute. An infrared lamp was used to maintain the rats' body temperature between 35.5 and 37.5°C, which was measured using a rectal probe. On a table, the rats were placed supine. Using microsurgical procedures, a single surgeon carried out each stage of the procedure.

After shaving, the right gluteal area was cleaned with a povidone-iodine antiseptic solution. The femoral biceps muscle was exposed through an oblique incision made in the right lower leg, which was made after the hip joint crease. The right sciatic nerve was exposed by blunt dissection, which released it from the tissues surrounding it from the sciatic process to the popliteal area. A bulldog clamp, measuring approximately 2 cm in length, was used to compress the nerve for 60 seconds at its midpoint. Following compression, 4-0 silk sutures were used to ligate the damaged area, and the wound was closed. Treatment for myrtus communis was started as soon as possible following nerve damage and continued for eight weeks using gastric gavage. After nerve injury, treatment for *myrtus communis* began immediately and involved once-daily gastric gavage for eight weeks.

Experimental groups

Four groups of eight rats each were randomly selected from the group of rats (n = 8).

Control: Absence of involvement.
Sham: Despite the exposed and damaged sciatic nerve, no more care was provided beyond the standard course of antibiotics.
Group I: 100 mg/kg (0.3 ml) of *Myrtus communis* was given daily along with a sciatic nerve damage.
Group II: 150 mg/kg (0.3 ml) of *Myrtus communis* was given daily along with a sciatic nerve damage.

Following the surgery, the rats received antibiotic therapy for seven days and were maintained for eight weeks. The rats were killed at the conclusion of this time by intracardiac injection of 150 mg/kg of sodium thiopental.

Evaluation Tests

Functional Gait Assessment

To ensure uniform walking direction, a 42x8.2x12 cm walking track ending in a dark room with a wooden floor was prepared. The rats' paws were dipped in ink, and paper was placed on the floor to capture their footprints. The rats were trained to walk on a track with closed sides and a dark shelter at one end, following the method described by De Medicanelli et al. (21). The footprints were used to measure the distance between the heel and toe (print length, PL), the distance between the first and fifth toes (stride width, TS), and the distance between the second and fourth toes (intermediate toe spread, IT) with a millimeter ruler. The obtained footprints were subjected to Sciatic Functional Index (SFI) evaluation, calculated using the Bain-Maccinon-Hunter Sciatic Functional Index formula (22).

SFI = [-38.5 (EPL-NPL/NPL) + 109.5 (ETS-NTS/NTS) + 13.3 (EIT-NIT/NIT)-8.8]

E: experimental, N: normal, PL: print length, TS: the total spread of toes (1st to 5th), IT: the spread of intermediate toes (2nd to 4th).

SFI ranges from 0 for a normal nerve to -100 for a nerve that has lost all motor function. The range of values is contingent upon the severity of the damage. SFI was determined prior to injury, 24 hours following injury, and one, two, three, four, five, six, seven, and eight weeks following injury.

Sensory Function Test (Pinch test)

Pinch test was used to evaluate the return of sensory function. A stimulus was given by squeezing the tip of the big toe towards the knee with forceps. Foot withdrawal reflex was evaluated between 0-3 points. Above the ankle was evaluated as 1 point, metatarsal area as 2 points, and pulling reflex at the level of the big toe as 3 points. A score of 0 was given if there was no pulling reflex. Using the pinch test, functional sensory recovery was examined. The foot's skin was squeezed with forceps, and the rats were handled gently and not subjected to stress (Splinter & Potts-Smith, Leica, NuŲloch, GmbH, Germany). The response levels were assigned a grade of 0 for no response, 1 for weak response, 2 for mild response, and 3 for strong response.

Electrophysiologic Evaluation

At 0 hours, 4 weeks, and 8 weeks, Electromyography (EMG) recordings were made of all the rats in the control, sham, group 1, and group 2 in order to evaluate nerve injury. Rats were given ketamine at a dose of 140 mg/kg without muscle relaxant. Using stainless steel needle electrodes, the recording was done with the active electrode inside the tibialis anterior muscle and the reference electrode, in accordance with the muscle-tendon concept, on the tendon of the same muscle. The ground electrode was placed between the stimulator and the active electrode. A 0.2 ms square wave stimulus at the lowest stimulus intensity (1.5-8 mA) that would supramaximally activate the sciatic nerve without propagating to the surrounding area was applied to the active electrode at the level of the "sciatic bulge," proximal to the nerve injury. For the sciatic nerve (right leg), at least three repeats of the amplitude and morphology were recorded. Then, the distal latencies and compound muscle action potential (CMAP) negative peak amplitude were measured.

Histologic Evaluation

Following the EMG testing, the rats were slaughtered by administering a fatal dosage of intracardiac Thiopental sodium injection. Subsequently, 2 cm long nerve samples were collected for histological analysis. To histological analyses, tissue samples obtained from the sciatic nerve were preserved in a 10% buffe-

red formalin solution. Tissue samples that had been fixed with formalin were trimmed to a thickness of 2-3 mm and acceptable dimensions, and then inserted into tissue tracking cassettes. Following an overnight rinse in tap water, the samples were immersed in 50%, 70%, 80%, 96% absolute alcohol, xylol, xylolised paraffin, and paraffin melted at 56-58ºC for 2 hours each. They were then sealed in paraffin. A 5-micron thick portion of each paraffin block was cut using a microtome (Leica, RM 2245) and then placed on slides using a water bath (Leica, HI 1210). Following a 10-minute drying period in a Thermo Histopathological oven, they were ready for use in histological techniques. Following a 10-minute drying period in a Thermo Histopathological oven, they were ready for use in histological techniques. Following the procedure described by Luna in 1968 (23), all sections were stained with haematoxylin-eosin (HE) in absolute, 96%, 80%, 70%, 50% alcohol series, and xylol series. The stained preparations were visualised using a binocular light microscope manufactured by Nikon, Eclipse Ci, based in Tokyo, Japan. Microscopic images were captured using the required equipment (Nikon DS FI3, Mikroscopic Digital Camera Systems, Tokyo, Japan). Evaluation of axonal degeneration, vacuolization, and edema was conducted **(Figure 1)**. Objective morphometric evaluations were conducted by two separate investigators using a 10X200µm magnification. Resolution of disagreements among the investigators was achieved by team deliberation.

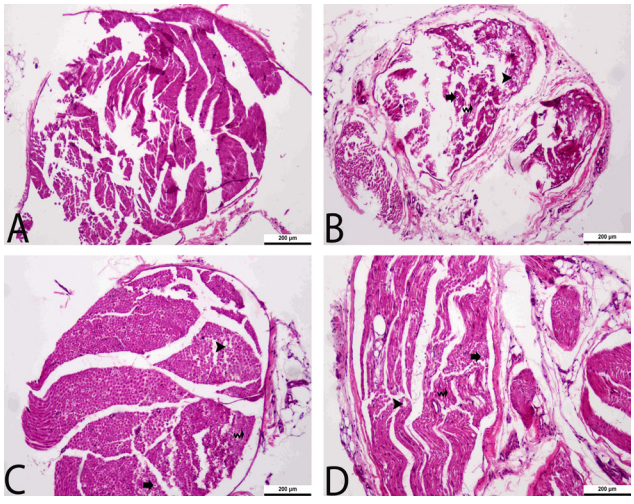


Figure 1: Histopathological findings. A, Control. B, Sham. Thick Arrow: Axonal degeneration. Arrowhead: Vacuolization. Curved Arrow: Edema. C, Group 1. Thick Arrow: Axonal degeneration. Arrowhead: Vacuolization. Curved Arrow: Edema. D, Group 2. Thick Arrow: Axonal degeneration. Arrowhead: Vacuolization. Curved Arrow: Edema.

Oxidant/Antioxidant Capacity Measurements in Blood Samples

Quantification of total antioxidant status (TAS) and total oxidant status (TOS) levels, as well as NGF and TGF-β levels, was conducted in nerve cells to examine the impact of *Myrtus communis* therapy on oxidant and antioxidant parameters. Following the procedure, venous blood was collected 8 weeks later, and the resulting serum samples were stored at a temperature of -80°C. Measurements of Nerve Growth Factor (NGF) in the serum (Bioassay Technology Laboratory, catalog No.: E0539Ra, Shanghai, China), TAS (Bioassay Technology Laboratory, catalog No.: E1710Ra, Shanghai, China), TOS (Bioassay Technology Laboratory, catalog No.: E1512Ra, Shanghai, China), and Transforming Growth Factor-Beta (TGF- β) (Bioassay Technology Laboratory, catalog No.: E1688Ra, Shanghai, China) were performed using the VGt Lambda Scan 200 ELISA device (Bio-Tech Instrument, Winooski, VT, USA).

Preparation of *Myrutus communis*

The leaves and stems of the myrtle tree are boiled at a concentration of 6 g/L in 100°C water for 15 minutes. The extracts are then subjected to a rotary evaporator to roughly remove the water, and the remaining portion is lyophilized to completely remove the water. Subsequently, solutions of 150 µg/mL are prepared from each of the samples and sterilized in an autoclave at 120°C for 1 hour. The solutions are stored in 50 mL Falcon tubes at +4°C for use in experiments. Alcohol extracts are prepared using a Soxhlet apparatus, and the alcohol is evaporated using a rotary evaporator (Aksay, 2016). The myrtle tree extract was provided by Ars Arthro Biotechnology Inc., Ankara. Note: Systemic toxicity studies of the myrtle tree extract were conducted in accordance with ISO 10993-11 standards, and no side effects were observed. Additionally, skin and eye irritation and sensitization tests showed that the plant extracts used did not cause irritation or sensitization on the skin (SANTEZ-0352.STZ.2013-2 project final report).

Variables

The main dependent variable of the research was the levels of SFI. Secondary outcome factors in the study included biochemical markers rela-

ted to oxidants and antioxidants, as well as histologic and neurophysiologic metrics. The groups of rats served as the independent study variable.

Ethical Committee

The study protocol received approval from the Local Ethics Committee for Animal Experiments at Afyon Kocatepe University in Afyonkarahisar, Turkey (Approval No: 49533702/04, Date: January 20, 2023).

Statistical Analysis

Computerized data were inputted and analysed using SPSS 25.0 software developed by SPSS Inc., based in Chicago, IL, USA. Quantitative data were displayed using frequencies, percentages, mean, and standard deviation (SD). An analysis of the normal distribution of numerical data was conducted using the Shapiro-Wilks test. An Independent Samples Analysis of Variance (One Way ANOVA) was employed to compare the groups based on each parameter. The Duncan multiple comparison test was employed to compare each group pairwise. Furthermore, a repeated measures ANOVA was used to compare each group based on time (Pre-op, Post-op 24 hours, 1. week, 2. week, 3. week, 4. week, 5. week, 6. week, 7. week, 8. week). The standard statistical significance level was set at 0.05..

RESULTS

Motor Function Evaluation

According to the results of this test, the SFI was between (0 and -10) in healthy rats, indicating normal motor function. When the sciatic nerve functional index results were analyzed, when the differences between all groups were examined, differences were found between the groups at 24th hour and 1st week. At 24 hours, the control group was significantly higher than groups 1 and 2 and similar to the sham group. The sham group was similar to all groups (p=0.028). At the 1st week evaluation, SFI values of the control and sham groups were similar. Group 1 and group 2 were similar to each other and had significantly lower SFI values than the other groups (p=0.024).

The SFI values of group 1 at 0th hour, 24th hour and 1st week were significantly lower and similar at 2nd week and later (p<0.001). SFI values of group 1 at 24 hours were significantly lower than SFI values measured at all other times (p<0.001). Group 1; 1st week SFI value was significantly higher than 24th hour and significantly lower than 0th hour, 7th and 8th week SFI values. Group 1; 1st week SFI value is similar to the SFI measurements at weeks 2-6.

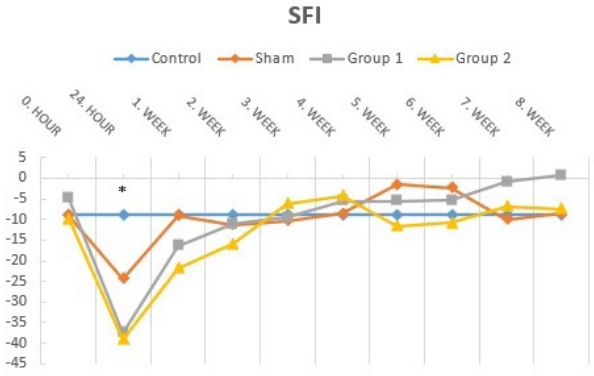
Group 2; SFI value at hour 0 is similar to the measurements at week 3 and later. The 24th hour SFI value is the lowest SFI values measured. Week 1 and week 2 SFI measurements are similar and significantly lower than all other times except 24 hours (p<0.001). **Table 1** and **Graph 1** show the evaluation of SFI values over time and between groups.

Table 1: Comparison of SFI measurements by time and groups

Groups	0th hour	24th hour	1th week	2nd week	3th week	4th week	5th week	6th week	7th week	8th week	F	p
Control	-8,90±0,28	-8,90±0,28	-8,90±0,28	-8,90±0,28	-8,90±0,28	-8,90±0,28	-8,90±0,28	-8,90±0,28	-8,90±0,28	-8,90±0,28	-	-
Sham	-9,10±9,19	-24,31^{AB}±9,10	-9,00^{A}±5,68	-11,36±5,37	-10,33±4,77	-8,51±16,58	-1,53±13,38	-2,36±18,42	-10,01±12,45	-8,53±15,09	1,426	0,197
Group 1	-4,88^{Ba}±5,99	-37,49^{Bc}±4,25	-16,46^{Bb}±2,53	-11,11^{ab}±14,83	-9,46^{ab}±8,60	-5,57^{ab}±10,9	-5,48^{ab}±13,16	-5,31^{ab}±9,38	-0,88±13,46	-0,70^{a}±12,82	6,268	**<0,001***
Group 2	-9,83^{a}±4,13	-39,13^{Bc}±8,79	-21,75^{Bb}±2,25	-15,90^{b}±13,97	-6,19^{a}±9,78	-4,19^{a}±5,57	-11,67^{a}±6,49	-10,83^{a}±5,00	-6,83^{a}±6,62	-7,42^{a}±6,86	9,022	**<0,001***
F	1,163	3,529	3,682	0,622	0,529	0,393	1,558	1,003	1,395	1,163		
p	0,342	**0,028***	**0,024***	0,607	0,666	0,759	0,222	0,406	0,265	0,236		

*: p<0.05 A, B: Differences between means with different letters in the same column are significant (p<0.05).

a, b, c: Differences between means with different letters in the same row are significant (p<0,05).



Graph 1: Evaluation of Sciatic Functional Index (SFI

Sensory Evaluation

At 24 hours, group 1 and group 2 are similar and significantly lower than the others, all other groups are different from each other (p<0.001). At 1-4 weeks, the control group is significantly higher than the others, all other groups are similar (p<0,001). At week 5, control group and group 2 are similar and higher than the others, all other groups are different from each other (p<0,001). At week 6, the sham group was significantly lower than the others and the other groups were similar (p<0,001).

The results of pinch test in the sham group were similar to hour 0 and higher than all other times at week 7 and week 8. The 24th hour pinch value was lower than all other times. Between 1st and 6th week, pinch tests were similar (p<0.001).

Group 1; pinch test results were similar and higher than other times at 0th hour and 4th week and all times thereafter. 24th hour was lower than all other times. Between 1st and 3rd week, pinch tests were similar (p<0.001).

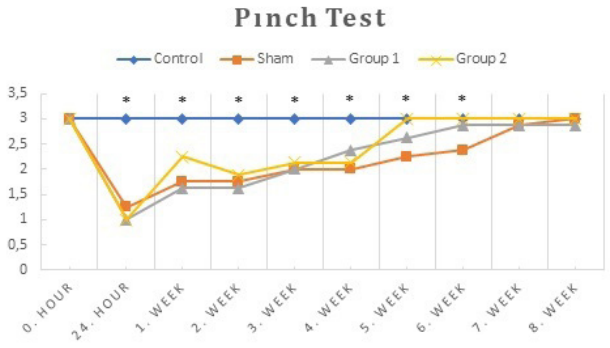
Group 2; pinch test results were similar and higher than all other times at 0th hour and 5th week and all times thereafter. 24th hour was lower than all other times. Between 1st and 4th week, pinch tests were similar (p<0.001). **Table 2** and **Graph 2** illustrate the comparison of pinch test measurements across time and groups. Comparison of CMAP Amplitude measurements

Table 2: Comparison of Pinch test measurements according to time and groups

Groups	0th hour	24th hour	1st week	2nd week	3th week	4th week	5th week	6th week	7th week	8th week	F	p
Control	3,00±0,00	3,00^{A}±0,00	3,00^{A}±0,00	3,00^{A}±0,00	3,00^{A}±0,00	3,00^{A}±0,00	3,00^{A}±0,00	3,00^{A}±0,00	3,00±0,00	3,00±0,00	-	-
Sham	3,00±0,00	1,25^{Bc}±0,46	1,75^{Bb}±0,46	1,75^{Bb}±0,46	2,00^{Bb}±0,00	2,00^{Bb}±0,00	2,25^{Cb}±0,46	2,38^{Bb}±0,52	2,88±0,35	3,00±0,00	**27,563**	**<0,001***
Group 1	3,00±0,00	1,00^{Cc}±0,00	1,63^{Bb}±0,52	1,63^{Bb}±0,52	2,00^{Bb}±0,53	2,38^{Ba}±0,74	2,63^{Ba}±0,52	2,88^{Aa}±0,35	2,88±0,35	2,88±0,35	**34,080**	**<0,001***
Group 2	3,00^{A}±0,00	1,00^{Cc}±0,00	2,25^{Ba}±0,71	1,88^{Bb}±0,35	2,13^{Ba}±0,35	2,13^{Ba}±0,35	3,00^{Aa}±0,00	3,00^{Aa}±0,00	3,00±0,00	3,00±0,00	**40,948**	**<0,001***
F	-	139,222	12,685	21,137	18,159	9,333	8,556	7,212	0,667	1,000		
p	-	**<0,001***	**<0,001***	**<0,001***	**<0,001***	**<0,001***	**<0,001***	**0,001***	0,580	0,407		

*: p<0,05 A, B, C: Differences between means with different letters in the same column are significant (p<0,05).

a, b, c: Differences between means with different letters in the same row are significant (p<0,05).



Graph 2: Evaluation of the Pinch Test

Comparison of CMAP Amplitude Measurements

In 24-hour measurements, the control group was similar to group 2 and significantly higher than the other groups. Sham group was similar to group 1 and significantly lower than all other groups and group 1 and group 2 were similar to each other (p=0.006). No difference was found between the groups in the 1st and 2nd month measurements (p=0.127, p=0.324, respectively). CMAP values measured at 24th hour and 1st month were similar in the sham group. The 2nd month CMAP value was significantly higher than the 24th hour (p=0.038).

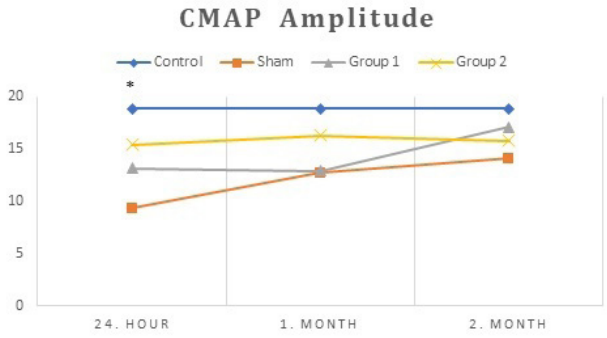
No difference was found in the measurements of the control group according to time. No significant difference was found in the CMAP values of group 1 and group 2 according to time (p=0.335, p=0.929, respectively). **Table 3** and **Graph 3** illustrate the comparison of CMAP amplitude measurements across time and groups.

Table 3: Comparison of CMAP Amplitude measurements according to time and groups

Groups	24th hour	1st month	2nd month	F	p
Control	*18,84^{A}±6,27 mV*	*18,84±6,27 mV*	*18,84±6,27 mV*	-	-
Sham	*9,33^{Cb}±1,95 mV*	*12,7^{ab}±3,95 mV*	*14,09^{a}±4,33 mV*	***4,151***	***0,038****
Gorup 1	*13,14^{BC}±5,24 mV*	*12,89±7,18 mV*	*17,11±5,93 mV*	*1,822*	*0,335*
Gorup 2	*15,43^{AB}±5,53 mV*	*16,31±5,26 mV*	*15,79±3,70 mV*	*0,074*	*0,929*
F	*5,051*	*2,072*	*1,212*		
p	***0,006****	*0,127*	*0,324*		

*: p<0,05 A, B, C: Differences between means with different letters in the same column are significant (p<0,05).

a, b: Differences between means with different letters in the same row are significant (p<0,05).



Graph 3: Evaluation of Compound Muscle Action Potential (CMAP)

Comparison of Latency Measurements

In 24-hour measurements, the control group was similar to group 2, and the latency value of the control group was significantly shorter than sham and group 1. Sham group was similar to group 1 and the latency value was significantly longer than group 2. Group 1 and group 2 were similar (p=0.002).

No difference was found in the measurements of the control group according to time. In the sham group, the 24 hour latency value was significantly longer than the 1st and 2nd month (p=0.001). Group 1; 24 hour latency value is significantly longer than the 1st and 2nd month (p<0.001). Group 2; 24 hour latency value is significantly longer than the 2nd month. Group 2 1st month latency value

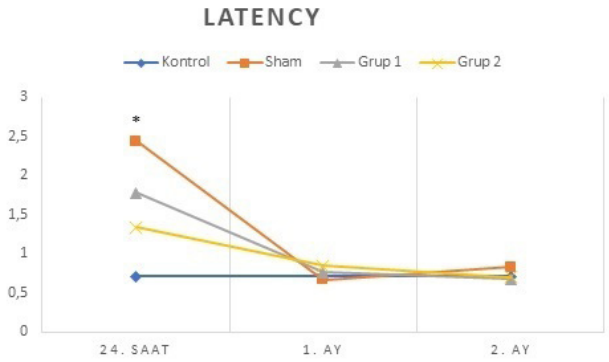
is similar to all times (p=0,003). **Table 4** and **Graph 4** illustrate the comparison of latency measurements according to time and groups.

Table 4: Comparison of Latency measurements according to time and groups

Groups	24th hour	1st month	2nd month	F	p
Control	0,71^{C}±0,29 ms	0,71±0,29 ms	0,71±0,29 ms	-	-
Sham	2,44^{Aa}±1,46 ms	0,67^{b}±0,2 ms	0,83^{b}±0,15 ms	11,371	0,001*
Group 1	1,78^{ABa}±0,58 ms	0,76^{b}±0,12 ms	0,68^{b}±0,12 ms	23,041	<0,001*
Group 2	1,34^{BCa}±0,41 ms	0,85^{ab}±0,26 ms	0,70^{b}±0,12 ms	8,735	0,003*
F	6,198	0,938	1,077		
p	0,002*	0,435	0,375		

*: p<0,05 A, B, C: Differences between means with different letters in the same column are significant (p<0,05).

a, b: Differences between means with different letters in the same row are significant (p<0,05).



Graph 4: Evaluation of Latency

Comparison of Biochemical Parameters According to Groups

TAS value in the control group was similar to sham and group 1 and significantly lower than group 2. Sham group TAS value was significantly lower than group 1 and group 2. Group 1 and group 2 were similar (p=0.002).

Control group TOS value was lower than sham group, group 1 and group 2. Sham group TOS value is higher than group 1 and group 2. Group 1 and group 2 are similar (p<0.001). Control group NGF value was similar to Sham and significantly lower than group 1 and group 2. Sham group; similar to all groups. Group 1 and group 2 are similar (p=0,058).

Control group TGF- β value; similar to Sham, significantly lower than group 1 and group 2. Sham group is similar to all groups. Group 1 and group 2 are similar (p=0,024). **Table 5** illustrate the comparison of biochemical parameters according to groups.

Comparison of Histopathological Parameters

All groups differ from each other in terms of axon degeneration. Axon degeneration was evaluated as Sham group, group 1 and group 2 in descending order. Axonal degeneration was not detected in the control group (p<0.001). In terms of edema, the control group was significantly lower than all other groups and no edema was detected. Sham and group 1 were similar to each other and significantly higher than group 2 (p<0,001). In terms of vacuolization, the control group was significantly lower than all other groups and no vacuolization was observed, Sham and Group 1 were similar and significantly higher than Group 2 (p<0,001). **Table 6** and **Graph 5** illustrate the comparison of histopathological parameters according to groups. In Figure 1, histopathological findings are shown.

Table 5: Comparison of biochemical parameters according to groups

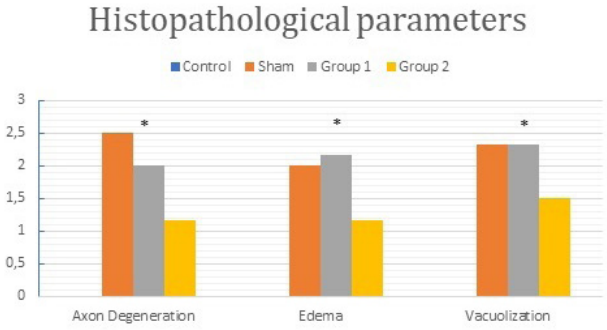
	Control	Sham	Group 1	Group 2	F	p
TAS (U/ml)	1,98±0,06^{bc}	1,82±0,04^{c}	2,12±0,11^{ab}	2,24±0,05^{a}		0,002*
TOS (U/ml)	7,10±0,32^{c}	11,09±0,46^{a}	9,70±0,25^{b}	9,33±0,30^{b}		0,001*
NGF (ng/L)	117,22±7,71^{b}	131,32±6,18^{ab}	137,29±5,74^{a}	140,94±4,91^{a}		0,058*
TGF- β (ng/L)	100,55±4,62^{b}	112,79±5,90^{ab}	116,66±4,88^{a}	123,28±4,37^{a}		0,024*

*: p<0.05 a, b, c: differences between means with different letters in the same row are significant (p<0.05).

Table 6: Comparison of histopathological parameters according to groups

Groups	Axonal Degeneration	Edema	Vacuolization
Control	0,00^{d}±0,00	0,00^{c}±0,00	0,00^{c}±0,00
Sham	2,50^{a}±0,55	2,00^{a}±0,00	2,33^{a}±0,52
Group1	2,00^{b}±0,00	2,17^{a}±0,41	2,33^{a}±0,52
Group 2	1,17^{c}±0,41	1,17^{b}±0,41	1,50^{b}±0,55
F	61,429	70,667	34,867
p	<0,001*	<0,001*	<0,001*

*: p<0.05 a, b, c: differences between means with different letters in the same column are significant (p<0.05).



Graph 5: Evaluation of Histopathological Parameters

DISCUSSION

In this study, different doses of *Myrtus communis* in sciatic nerve injury showed earlier improvement in SFI values, whereas no significant difference in this improvement was observed in those who did not receive treatment. In the SFI index evaluation, the sciatic nerve indices in group 1 and group 2 were similar to the sham but significantly worse than

the control group at 24 hours post-op. These results were similar in all groups on average at week 2. When the internal analysis of the treated groups was conducted, the indices were similar to baseline at week 2 in group 1 and similar to baseline at week 3 in group 2.

In the sensory evaluation, post-op, all groups were similarly worse than the control group; however, in group 1 at week 4, in group 2 at week 5, and in the sham group at week 7, sensory levels returned to values similar to baseline.

In the CMAP evaluation, sham had the lowest postoperative nerve conduction, followed by group 1 and, to a lesser extent, group 2. However, no significant difference was observed between the treated and untreated groups. When the latency values were analyzed, the post-op. latency was the longest in sham and no significant difference was observed between the treated and untreated groups.

In biochemical examination, TAS value was higher in treated than untreated patients. In group 1, it was similar to the control group. It was lower in the Sham group than the control group. TOS value was highest in Sham, similar and lower in groups 1 and 2, and lowest in the control group. NGF value was lower in the control group and similar in all other groups, but the highest NGF value was found in group 2. TGF-β values were also higher in groups 1 and 2 compared to the control but similar to sham.

In the histopathologic evaluation of our study, no damage was observed in the control group, whereas histopathologic changes were observed in sham and other treatment groups. Axon degeneration was the lowest in group 2 compared to the other groups, then in group 1 and the highest in sham. Edema was lowest in Group 2 and similar in Group 1 and sham group. Vacuolization was lowest in group 2 and similar in group 1 and sham group. When these results were taken into consideration, it was observed that 150 mg/kg dose provided histopathologically significant changes in the healing of nerve injury.

Injuries to peripheral nerves can arise from multiple causes (3). Particularly in cases of crush injuries, many complications may arise, including remyelination and demyelination, axonal regeneration and degeneration, focal, multifocal or diffuse nerve fiber loss, and endoneural edema (24). Loss of sensory and motor function after severe PNI severely affects patients' lives (4). As a result, it is critical to accelerate and improve the restoration of injured axons (25). To date, many surgical and non-surgical treatment approaches have been proposed for anatomical and functional recovery of injured peripheral nerves (5). The gold standard treatment of PNI is still widely accepted as axon-to-axon anastomosis (26), but factors such as the quality of axonal outgrowth, the number of viable neurons, the orientation of the regenerating axon and the condition of the axon are crucial for optimal nerve repair (27, 28). In addition, a number of pathophysiological events, including apoptosis (29), oxidative stress (30), inflammation (31), degradation of the extracellular matrix (27) and many more, can compromise the healing process in PNI. Microenvironmental conditions, cellular and molecular activation have proven to be really important in the nerve healing process (32). After nerve injury, ischemia-reperfusion injury due to dysfunction, microenvironmental macrophage activation via neutrophils and increased mitochondrial oxidative stress; the nerve healing process is negatively affected (33). Numerous experimental investigations have documented the efficacy of several pharmacological medications in the management of nerve damage (34 – 36). Alternative therapeutic approaches with phytochemicals including quercetin, ursocolic acid, curcumin and others have been suggested to be beneficial with experimental evidence, but most of them cause side effects at human doses (5). Therefore, newer approaches are needed for the treatment of peripheral nerve injury that manage the optimal properties for a drug, such as causing negligible side effects.

MC is a traditional medicinal plant used for treating stomach ulcers, inflammation, diarrhea, hemorrhoids, lung and skin disorders. Numerous research have shown the anti-diabetic, antioxidant, hepatoprotective, neuroprotective, anticancer, antiviral, antibacterial, and antimycotic properties of MC (37 – 41). The observed effects of MC can be attributed to biochemically active components, including phenolic chemicals, flavonoids, hydrolyzed tannins (galotanins), proanthocyanidins, and volatile oil (37).

The efficacy of *Myrtus communis* in peripheral nerve damage has not been previously assessed.

This work presents evidence of the antioxidant properties of oral MC administration through biochemical and histological responses of high-dose *Myrtus communis* treatment in peripheral nerve recovery. Specifically, the group with higher treatment dose showed increased levels of TAS, NGF, and TGF-β, and reduced vacuolization, edema, and axon degeneration in histological evaluations. The antioxidant activity of MC on the peripheral nerve may facilitate the early restoration of peripheral nerve healing following sciatic nerve injury. The responses of MC administration were recorded with two different drug doses and it was observed that both antioxidant response and histopathologic results were better in the group receiving the higher dose (MC 150 mg/kg).

NGF is one of the members of the neurotrophin family of neurotrophic factors (42). Upregulation of NGF synthesis during normal Wallerian degeneration enhances neuronal survival and axon growth in specific subgroups of sympathetic and sensory dorsal root neurons (43). In addition, many studies have shown that NGF induces the phagocytosis ability of Schwann cells. Thus, removal of damaged myelin sheaths is accelerated and the rate of regeneration is increased (44). In our study, similar to the literature, NGF value was expressed at a higher level in MC-treated groups compared to the control group and it was observed that it was expressed at a higher level in the group with higher MC dose than all other groups.

The transforming growth factor (TGF-β) is another group of neurotrophic factors that contributes to the process of regeneration. Transforming growth factor-β (TGF-β) is a cytokine that regulates cell growth, specialization, and programmed cell death. In the aftermath of neurological system damage, TGF-β controls the activity of neurons and glial cells, therefore facilitating the process of regeneration. Heightened production of TGF-β controls nerve regeneration by inhibiting the immune response, altering cellular activity, controlling the growth of nerve fibers, and facilitating the development of glial wounds (45).

One should evaluate this work considering the merits and drawbacks of experimental animal studies. A further constraint of this study is the limited sample size of the experimental animals. Given that experimental animal research involve live animals, we have included the number of experimental animals within relevant statistical boundaries. The generalizability of the results can only be achieved by clinical validation using suitable research.

There is still insufficient information about medical treatment options in the treatment of PNI. However, the role of Myrtus communis in early recovery has been demonstrated by the results of both biochemical and histopathological changes in the evaluation of functional recovery. Further studies on this subject will be guiding in the treatment of PNI.

This study was supported by Afyonkarahisar Health Sciences University Scientific Research Projects Coordination Unit with the project number 21.GENEL.016.

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Kocatepe Tıp Dergisi
Kocatepe Medical Journal
25:536-539/Ekim 2024 Sayısı

OLGU YAZISI / CASE REPORTS

KARIN DUVARINDA İZOLE KOLON ADENOKARSINOM METASTAZI: BIR OLGU SUNUMU

ISOLATED COLON ADENOCARSINOMA METASTASIS IN THE ABDOMINAL WALL: A CASE REPORT

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ÖZET

Kolorektal kanserlerde periton ve lenf düğümlerinin tutulumu olmaksızın ön karın duvarının izole local nüksleri nadirdir. Bu olguda 41 yaşındaki erkek hastanın rektus kasında kolon kanserinin izole metastazının klinik ve radyolojik bulguları sunulmuştur.

ANAHTAR KELİMELER: Adenokarsinom, Metakron tümör, Karın duvarı.

ABSTRACT

Isolated local recurrence of the anterior abdominal wall without peritoneum and lymph node involvement is rare in colorectal cancers. In this report, clinical and radiological findings of isolated metastasis of colon cancer in the rectus muscle of a 41-year-old male patient are presented.

KEYWORDS: Adenocarcinoma, Metachronous tumor, Abdominal wall.

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Kabul Tarihi / Accepted: 11.02.2022
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INTRODUCTION

Colorectal cancers (CC) are the third most common type of cancer in the world (1). In CC, approximately 20% of cases have metastasis at the time of diagnosis, most commonly in the liver and lungs. Depending on the hematogenous and lymphatic spread pattern, extra-abdominal metastasis is more common in rectal cancer, while abdominal metastasis rates are higher in CC (2).

Liver metastases are seen in more than 70% of CC, while less than 10% of metastases can be seen in other organs such as the central nervous system, adrenal gland, spleen and, skeletal system (3). In addition, it spreads non-hematological into the peritoneal cavity through peritoneal fluid (1). Metachrome abdominal wall metastasis in colorectal cancers is very rare and can be seen as a result of direct invasion, lymphatic and hematogenous pathways, or implantation of cancer cells (4).

In this report, clinical and radiological findings of a patient operated on sigmoid colon adenocarcinoma in whom an isolated rectus muscle metastasis was diagnosed and treated after 28 months without lymph node, abdominal, or extra-abdominal involvement, are presented.

CASE REPORT

A 41-year-old male patient applied to the hospital 28 months ago with complaints of chronic abdominal pain, constipation, rectal bleeding, and weakness. In the colonoscopy performed, a mass surrounding the lumen was observed at approximately 30th cm allowing the passage of the endoscope. Biopsy was taken from the mass which was reported as adenocarcinoma. There was no distant metastasis, local adjacent organ invasion or lymph node involvement observed in the contrast-enhanced abdominal and thorax computed tomography (CT) examinations. Anterior resection and primary anastomosis were performed as surgical procedures. The postoperative pathology result was reported as a 5x2 cm well-differentiated adenocarcinoma. It was also found that although the tumor did not have lymphovascular invasion, but showed perineural invasion. The tumor had passed through the muscularis propria and reached the perirectal fatty tissue; no tumoral involvement was observed in resected lymph nodes (pT3N0M0). The patient was referred for oncological treatment, receiving Kabestabin as a chemotherapeutic agent. Colonoscopy was evaluated as normal one year after follow-up. No distant metastasis was detected in abdominal and thoracic CT examinations. The control CEA (carsinoembryonic antigen) level was found to be normal. About 28 months later, in the control abdominal CT examination, a mass with a size of 6.4x5.6 cm invading the rectus abdominis muscle was detected in the anterior abdominal wall **(Figure 1)**.

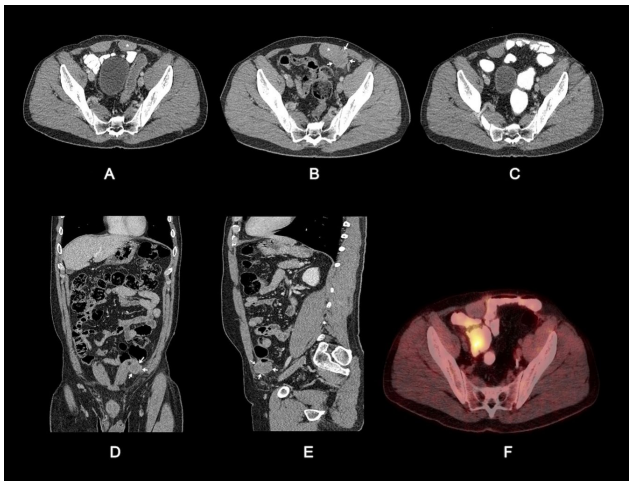

Figure 1: Contrast-enhanced axial CT image (A) in the preoperative period (October 2018). In multiplanar contrast-enhanced CT images (B, D, E) a solid lesion (arrows) with irregular border of soft tissue density that invades the left rectus abdominis muscle (asterisk) and where the planes in between are not visible. Postoperative period changes: axial CT (C) and PET-CT (F) (January 2021).

No other distant metastasis was detected in abdominal CT. No recurrence was detected in the colonoscopy and no finding in favor of distant metastasis elsewhere in the body was found in imaging modalities. There was no finding in favor of distant metastasis in thoracic CT. Percutaneous tru-cut biopsy from the lesion was assessed as adenocarcinoma metastasis and the patient without distant organ metastasis was evaluated as isolated rectus muscle metastasis. In the patient who underwent laparotomy for excision of the mass, there was no finding in favor of lymph nodes in the abdomen or tumor on the peritoneal surface during exploration. It was observed that the mass invaded the rectus muscle and bladder outside the peritoneum, the mass was excised with the lower part of the rectus muscle and part of the bladder wall. In the pathological examination of the removed mass, it was evaluated as adenocarcinoma metastasis. With these results, the patient was referred to oncological treatment.

No recurrence was observed in the patient's follow-up in the 8th postoperative month. Informed consent was obtained from the patient.

DISCUSSION

Metachronous abdominal wall metastases due to colorectal cancer are reported very rarely in the literature as case reports. Although colorectal cancers usually cause liver, lung, and other distant organ metastases in lymphatic and hematogenous ways, metastases are rarely seen as a result of the surgical incision, drainage area, implantation of cancer cells in the anastomosis area, and peritoneum (4). In previous studies, it was stated that there may be metastasis in the abdominal wall through the superficial lymph ducts and inferior epigastric arteries (3, 5). In other studies, it was thought that colon adenocarcinomas may rarely have metastasis to the abdominal wall muscle as a result of deterioration of physiology of muscle damage (6, 7). In our case, although there was no recurrence in the lymph nodes, anastomotic line, or peritoneum during the follow-up after primary treatment, the presence of metastasis only in the anterior abdominal wall rectus muscle suggests the possibility of spread as a result of the impaired muscle physiology after the first surgery.

Ultrasonography can be easily applied for imaging or biopsy in anterior abdominal wall lesions. Although imaging findings are nonspecific in abdominal wall metastases, CT or magnetic resonance imaging (MRI) is more advantageous in determining the exact location, size, and relationship of the lesion with other anatomical structures before surgical planning. The most important distinguishing feature is the presence of disease history and rapid growth of the lesion (8). In our study, abdominal CT was used as the imaging method for the patient, revealing an invasive mass to the left rectus muscle in the anterior abdominal wall. Due to the previous history of having a tumor, firstly metastasis was considered. Colonoscopy and PET-CT were performed to investigate the presence of metastatic foci in other locations than the abdominal wall. In the patient, no other focus was detected except for the lesion at the anterior abdominal wall.

The type of treatment to be applied is related to the extent of metastatic disease and the medical condition of the patient. In patients with limited disease, local control of the disease can be achieved with aggressive resection (6, 9). In the current case, prior to the surgical planning metastatic foci were investigated; since no other metastases were detected in other locations, surgical resection was planned and the lesion was resected with a clean surgical margin. In the literature, it is stated that wall defects caused by resection of abdominal wall metastases can be repaired by placing primary suture or mesh (4). In our case, the defect in the anterior abdominal wall after resection was primarily repaired.

Prognosis is related to the degree of malignancy of the primary lesion and its spread to other organs (9). For example, Lievre et al. (10) reported a mean survival of 12 months and postoperative 10-month survival in patients with colon cancer having thyroid metastasis, while Montero et al. (11) stated that the mortality rate was 50% due to cancer in less than one year in patients with thyroid metastasis. Our patient, who underwent metastasectomy, was in the 8th month postoperatively with normal abdominal CT studies.

Isolated metachronous metastasis in the anterior abdominal wall is very rare in colon adenocarcinomas. With the presence of a primary tumor history of the disease, imaging methods are helpful in diagnosis. In cases with isolated metastases, local control of the tumor can be achieved by resection with a clean surgical margin.

ACKNOWLEDGEMENTS

We are grateful to the staff of the Department of Pathology and General Surgery for their sincere assistance.

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Kocatepe Tıp Dergisi
Kocatepe Medical Journal
25:540-549/Ekim 2024 Sayısı

DERLEME/ REVIEW

TAKOTSUBO SENDROMUNA GÜNCEL BİR BAKIŞ

A CURRENT OVERVIEW OF TAKOTSUBO SYNDROME

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ÖZET

Takotsubo sendromu, kalbin sol ventrikülünün geçici işlev bozukluğu ile karakterize akut, geri dönüşümlü bir hastalıktır. Takotsubo sendromunun patogenezi tam olarak bilinmemektedir. Ancak Takotsubo sendromununpatogenezi ile ilgili çeşitli hipotezler ileri sürülmüştür. Takotsubo sendromunun patogenezi ile ilgili hipotezler; koroner mikrovasküler disfonksiyon, koroner arter spazmı, katekolamin kaynaklı miyokardiyal sersemleme, akut koroner sendromdan sonrası reperfüzyon hasarı, miyokardiyal mikroinfarktüs, endotel disfonksiyonu ve östrojen eksikliği ve kardiyak yağ asidi metabolizmasındaki anormallikler şeklinde adlandırılabilir. Takotsubo sendromu ile ilgili hipotez ve teoriler arasında en sık olarak katekolamin kaynaklı kardiyotoksisite ve koroner mikrovasküler disfonksiyon üzerinde durulmaktadır. Takotsubo sendromu bazı klinik semptom ve bulgularla kendini gösterir. Takotsubo sendromunda, başvuru sırasında görülen semptomlar, en yaygından en aza doğru göğüs ağrısı, nefes darlığı ve senkoptur. Klinik olarak akut göğüs ağrısı ve nefes darlığı gibi şikayetlere neden olduğu için akut miyokard enfarktüsü veya akut koroner sendrom ile karıştırılabilir. Bu nedenle bu hastalıklardan ayırt edilmesi önemlidir. Ayırıcı tanıda anamnez, fizik muayene, kardiyak troponin, kreatin kinaz, troponin, elektrokardiyografi (EKG), koroner anjiyografi kullanılır. Takotsubo sendromunun ayırıcı tanısında fiziksel veya duygusal stresin varlığı önemli bir rol oynar. Takotsubo sendromu için spesifik bir tedavi yoktur. Ancak tedavi akut ve kronik dönemler olarak ikiye ayrılabilir. Akut dönemde Takotsubo sendromuna bağlı gelişen komplikasyonlara yönelik tedaviler uygulanırken, kronik dönemde beta blokerler, anjiyotensin dönüştürücü enzim (ACE) inhibitörleri, anjiyotensin II reseptör blokerleri gibi ilaçlar kullanılmaktadır. Takotsubo sendromu yoğun bakım hastalarında da görülebilmektedir. Yoğun bakım hastalarında sıklıkla hemodinamik bozukluklar ve solunum yetmezliği ile kendini gösterir. Bu nedenle yoğun bakım hastalarında hemodinamik ve solunumsal değişiklikler gözlendiğinde Takotsubo sendromu düşünülmeli ve hastalar bu yönde takip edilmelidir.

ANAHTAR KELİMELER: Takotsubo Sendromu, Yoğun Bakım, Stres, Akut Hastalık.

ABSTRACT

Takotsubo syndrome is an acute, reversible disease characterized by transient dysfunction of the left ventricle of the heart. The pathogenesis of Takotsubo syndrome is not known precisely. However, various hypotheses regarding pathogenesis have been put forward. These hypotheses; coronary microvascular dysfunction, coronary artery spasm, catecholamine-induced myocardial stunning, reperfusion injury after acute coronary syndrome, myocardial microinfarction, endothelial dysfunction and estrogen deficiency, and abnormalities in cardiac fatty acid metabolism. Among these hypotheses and theories, catecholamine-induced cardiotoxicity and coronary microvascular dysfunction are most frequently emphasized. Takotsubo syndrome manifests itself with some clinical symptoms and signs. In Takotsubo syndrome, symptoms seen at presentation are chest pain, shortness of breath, and syncope, from the most common to the least. Clinically, it can be confused with acute myocardial infarction or acute coronary syndrome because it causes complaints such as acute chest pain and shortness of breath. Therefore, it is important to differentiate from these diseases. Anamnesis, physical examination, cardiac troponin, creatine kinase, troponin, electrocardiography (ECG), coronary angiography are used in the differential diagnosis. The presence of physical or emotional stress plays an important role in the differential diagnosis of Takotsubo syndrome. There is no specific treatment for Takotsubo syndrome. However, treatment can be divided into two parts as acute and chronic phases. While treatments for complications arising due to Takotsubo syndrome are applied in the acute phase, drugs such as beta blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers are used in the chronic phase. Takotsubo syndrome can also be seen in intensive care patients. In intensive care patients, it often manifests itself with hemodynamic disturbances and respiratory failure. Therefore, Takotsubo syndrome should be considered in intensive care patients when hemodynamic and respiratory changes are observed and patients should be followed up in this direction.

KEYWORDS: Takotsubo syndrome, Intensive care, Stress, Acute Disease.

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INTRODUCTION

Takotsubo syndrome (TCMP) (Stress-induced cardiomyopathy, Apical ballooning syndrome, Broken heart syndrome) is an acute disease characterized by transient left ventricular dysfunction (1, 2). It often causes reversible heart failure and resolves spontaneously within weeks (2 – 4). Patients often present with clinical signs such as acute chest pain and shortness of breath (2, 5). These complaints are similar to the presenting complaints of acute myocardial infarction or acute coronary syndrome. In addition, elevation of cardiac troponin and creatine kinase, ECG (Electrocardiography) changes (findings such as ST elevations in precordial leads) cause confusion with acute myocardial infarction and acute coronary syndrome in the early period of diagnosis (1). The fact that coronary stenosis is not observed in coronary angiography and there is a triggering emotional or physical stress in the anamnesis are helpful for TCMP (5, 6).

In TCMP, apical ballooning of the left ventricle is observed after systole (1). This is the classic pattern of left ventricular morphology. Apart from that, in TCMP; morphological features such as hypokinetic circumferential base (inverted Takotsubo variant), hypokinetic circumferential mid-ventricle (middle LV –Left Ventricule- variant), and focal variations can be traced (7 – 11).

An association between emotional or physical stress and cardiovascular events was recognized long ago. Stressful situations in population level cause a surge in cardiovascular mortality. Major non-cardiac surgeries, sepsis and subarachnoid hemorrhage increase cardiovascular mortality without an apparent coronary artery obstruction or cardiac structural abnormalities (12). One of the reasons for this increased cardiovascular mortality is Takotsubo syndrome. After the central Niigata Prefecture earthquake in Japan in 2004, a raised incidence of TCMP was reported (13).

Takotsubo syndrome can also be observed in intensive care patients. Most of the patients who are followed up in the intensive care unit initially present with serious diseases that lead to major stress such as respiratory distress, sepsis, convulsions and shock. Therefore, many of the patients followed up in the intensive care unit potentially have Takotsubo syndrome. This is why Takotsubo syndrome is not uncommon in intensive care. It is associated with particularly significant haemodynamic and respiratory instability in intensive care patients (14). Respiratory and hemodynamic deterioration with new onset arrhythmias are a warning for Takotsubo syndrome in intensive care patients. Therefore, when such conditions develop in patients followed in intensive care, patients should be followed up in terms of Takotsubo syndrome.

There is no specific treatment for Takotsubo syndrome. The treatment of Takotsubo syndrome is different in the acute phase and in the chronic phase and recurrence. In the acute phase, complications arising from Takotsubo syndrome are treated. In the chronic phase and recurrence, agents such as beta-blockers, angiotensin converting enzyme (ACE) inhibitors, Angiotensin II receptor blockers are used(1, 12).

EPIDEMIOLOGY

Takotsubo CMP (TCMP) is usually known as a disease that affects the older Asian women. While this assumption is mostly accurate, patients from all age groups have been reported, including a 2 years old girl with a malignancy (15). Several studies from Western countries reported that 90% of the patients were women between the ages 65-70 (15, 16). One study from Japan also reported the average age of the patients as 74 (15).

It is hard to detect the true incidence of TCMP, as it is a newly recognized disease, the information and clinical experience available is rapidly increasing. It should be noted that as the recognition of the disease increases, yearly incidence also increases. Minhas et al. reported a 20 fold increase in the incidence of TCMP between 2006 and 2012 (17). This is mostly due to the increased awareness of clinicians to the disease. This trend in the increased incidence was also reported in several other studies. For example, one center from Minneapolis reported an increased incidence in the last decade, with an incidence of 50 patients in the year of 2009 (15). Another study reports that 2% of the patients who were admitted with a suspected acute coronary sy-

ndrome were eventually diagnosed with TCMP. Annual incidence of TCMP in United States (US) may be estimated around 7000-14000 cases (13).

One of the large-scale studies about the epidemiology of TCMP comes from the United States of America (US). ⅕ of the US community hospitals were included in the study, and the incidence of TCMP was found to be 6,837 in 2008. The same cohort also emphasized that 70% of the patients were white and only 1% of them were Asian. This skew towards the Caucasians may be caused by the distribution of the sample population, however, this study shows that the TCMP is not restricted to Asians and may be seen in Caucasians too. As the reports and case series demonstrate, the incidence of TCMP is lower in Hispanics and African Americans. The recurrence rate of the disease varies between 0-22% in different patient groups (18). Additionally, recurrence rate was detected as 17.7% in patients with pheochromocytoma triggered TCMP (19).

There are no large scale epidemiological studies that correlate the combined incidence of neurological diseases and TCMP. However, several case series emphasize the causative relationship between neurological diseases and TCMP. One study from Italy reports that emotional triggers were seen in 27.7% of the cases, while physical triggers were seen in 36% of them. 7.8% of the patients had both physical and emotional triggers. Additionally, 55.6% of the patients had an acute or past history of the neurological or psychiatric diseases (20). In rare cases, TCMP may be triggered by viral diseases. there are 4 cases of TCMP triggered by viral gastroenteritis (21).

Takotsubo syndrome is not rarely observed in intensive care units. In a study conducted by Muratsu et al., 5 of the 5084 patients admitted to the intensive care unit were diagnosed with Takotsubo syndrome and 19 with clinical Takotsubo syndrome. The most common primary disease among the patients was sepsis (n=10), and secondary was subarachnoid hemorrhage (n=5), (22).

In the study conducted by Doyen et al., 13 of 280 patients admitted to the intensive care unit were diagnosed with Takotsubo syndrome using Mayo clinical criteria. Takotsubo syndrome was later confirmed by European Society of Cardiology (ESC) Heart Failure Association criteria. 69.2% of the patients diagnosed with Takotsubo syndrome were found to be female. In addition, the study found that Takotsubo syndrome is associated with high morbidity (14).

In another study from Korea, surprisingly high numbers of TCMP cases in Internal Care Unit (ICU) settings were reported. In a sample group of 92 patients, 28% were found to have TCMP (23). Rowell et al. reported only 4 cases of TCMP in their sample of 116 patients. In the same study, all of the patients were women (24). Lastly Oras et al. reported the incidence of 5% in a retrospective study in which more than 1000 patients were included (25).

Another article by Salah et al. presents 10 cases of TCMP in Coronavirus Disease-19 (COVID-19) patients. The mean age was 64.6 and 9 of the patients presented were women (26).

Also, after the COVID-19 pandemic, the rate of TCMP has increased in patients with initial diagnosis of acute coronary syndrome. As stated in this chapter, before the pandemic, this rate was near 2%, however after the start of the pandemic, this rate has risen to 7.75% (27). This significant increase is also supported by the study of European Association of Cardiovascular Imaging. In their study, 1216 COVID-19 positive patients were evaluated and 2% of them were diagnosed with TCMP (28). In another study, 118 COVID-19 positive patients were evaluated with clinically indicated transthoracic echocardiography and 4.2% of them were diagnosed with TCMP (29).

PATHOPHYSIOLOGY

The pathogenesis of TCMP is not known precisely (2, 30, 31). However, various hypotheses regarding pathogenesis have been put forward. These hypotheses; coronary microvascular dysfunction, coronary artery spasm, catecholamine-induced myocardial stunning, reperfusion injury after acute coronary syndrome, myocardial microinfarction, endothelial dysfunction and estrogen deficiency, and abnormalities in cardiac fatty acid metabolism (2, 31). Among these hypotheses and theories, catecholamine-induced cardiotoxicity and coronary microvascular dysfunction are most

frequently emphasized. Myocarditis is another theory about the pathophysiology of the TCMP, however, it is extremely unlikely due to absence of myocarditis in biopsies and absence of delayed gadolinium hyperenhancement with Cardiac magnetic resonance imaging (MRI).

1. Catecholamine-Induced Myocardial Stunning

It has been found that patients with TCMP experience an emotional loss or trauma before the diagnosis when questioned (2, 32). As a result of this study, it was suggested that excessive catecholamine release due to stress in TCMP leads to left ventricular dysfunction (30, 33 – 35). Various studies have been done to support this theory. One study found that patients with TCMP had higher circulating catecholamine levels compared to normal values (36, 37) and these levels persisted for 7-9 days after the initial presentation. Moreover, in a study of patients with TCMP (37), serum catecholamine concentrations were found to be two to three higher than in patients with myocardial infarction. This situation reveals that serious emotional stress is an accelerating factor in the development of TCMP. However, exogenous catecholamines, subarachnoid hemorrhage and pheochromocytoma have been reported to cause typical TCMP features such as wall motion abnormalities and depressed ejection fraction. (38, 39).

In addition to these, another study demonstrated that patients with hemodynamically unstable TCMP have a higher risk of heart attack when catecholamine supplementation is given, different complications associated with TCMP occur, and the risk of death is higher (1). Also, rat models showed that ST-segment elevations and apical ballooning may be prevented by the administration of alpha and beta receptor antagonists. These studies support the catecholamine theory.

Also, a study by Muratsu et al. demonstrated that subarachnoid hemorrhage was the second most frequent complication in ICU patients who had TCMP (22). This finding supports the hypothesis that sympathetic nervous system activation may induce TCMP. There is catecholamine-induced endothelial dysfunction in TCMP (40).

2. Endothelial Dysfunction and Estrogen Deficiency

Recent studies have shown that endothelial dysfunction is common in patients with TCMP (2). These studies are thought to explain the epicardial and/or microvascular coronary artery spasm seen in TCMP (2). Both age-related and estrogen deficiency coronary vasomotor abnormalities have been demonstrated in TCMP (41 – 43). This may explain the prevalence of TCMP in postmenopausal women. In physiological conditions, estrogen is beneficial on coronary microcirculation by various mechanisms (endothelium-dependent and endothelial-independent) and has a positive effect on coronary blood flow (43). In a study, it has been shown that stress-induced left ventricular apical ballooning can be prevented with estrogen supplementation (44). This situation supports the role of estrogen deficiency in the development of TCMP.

3. Coronary Microvascular Dysfunction

The majority of patients who undergo imaging for TCMP have normal coronary arteries or non-obstructive coronary artery disease on angiography (45). Therefore, obstructive coronary disease was excluded in the etiology of TCMP. Therefore, microvascular causes are thought to play a role in pathophysiology. Based on this, the theory of coronary microvascular dysfunction has been put forward. As a result of imaging methods performed for this theory, there are data in the literature indicating that microvascular dysfunction has a place in TCMP (40). However, coronary angiography is not used to visualize coronary microcirculation. Other focused methods such as thrombolysis in myocardial infarction (TIMI) frame count, corrected TIMI frame count (CTFC), TIMI myocardial perfusion grade (TMPG), and coronary flow reserve (CFR) have shown conflicting results. However, the limited imaging methods make it difficult to reveal new data.

CLINICAL PRESENTATION

Takotsubo syndrome constitutes approximately 1-2% of patients presenting with acute coronary syndrome (3, 46, 47). The majority of patients with Takotsubo syndrome are women (48). In the early stages of Takotsubo syndrome, ele-

ctrocardiographic findings and biomarkers are generally similar to acute coronary syndrome (3, 32, 49 – 52). In Takotsubo syndrome, symptoms seen at presentation are chest pain, shortness of breath, and syncope, from the most common to the least (48, 50, 53). Since chest pain and shortness of breath are common in acute myocardial infarction, Takotsubo syndrome may be confused with acute myocardial infarction. However, the severity of symptoms in Takotsubo syndrome is generally less severe than in acute myocardial infarction (53). Pulmonary edema can be observed in Takotsubo syndrome (48). However, cardiac arrest, cardiogenic shock, and severe arrhythmias are rarely observed at the onset of the disease (out-of-hospital settings) (48, 53). Apart from these symptoms, nonspecific symptoms such as weakness, cough and fever have also been reported (3, 32, 49, 51, 54, 55).

This syndrome may also develop in intensive care unit (ICU) patients. Usually first signs include pulmonary edema and ischemic changes in ECG. Cardiac biomarkers may also be elevated. In contrast with the other patients, most patients in the ICU are unable to experience chest pain due to continuous sedation or overlapping symptoms of other conditions. This makes the diagnosis more challenging. In a study by Haghi et al. 5 out of 6 patients were unable to report chest pain and for these 5 patients, hemodynamic deterioration was the key diagnostic clue (56). Another study by Doyen et al. reported that 69.2% of the ICU patients who developed TCMP presented with shock, 46.2% presented with arrhythmias and 92.3% presented with acute respiratory failure (14). In a study by Giustino et al. 118 laboratory-confirmed COVID-19 patients underwent a clinically indicated Trans-thoracic echocardiography and the results of 5 of them (4.2%) were found to be compatible with TCMP. The median age was reported to be 66 and all of them were men. At the time of the admission, 4 of them had shortness of breath and the other patient had chest pain (29).

One case report from Chicago describes a COVID-19 positive patient with rapid deterioration of cardiorespiratory status in her 4th day of hospitalization (57). It should be noted that during the hospital course, COVID-19 positive patients may experience symptoms that are consistent with TCMP.

DIAGNOSIS

Takotsubo CMP, manifests very similarly to acute coronary syndrome (ACS). In most cases, acute presentations are approached like ACS. In this section, diagnostic approaches and different criterions are explained. Firstly, ECG manifestations of TCMP mimic ACS and commonly cause misdiagnosis **(Figure 1)**.

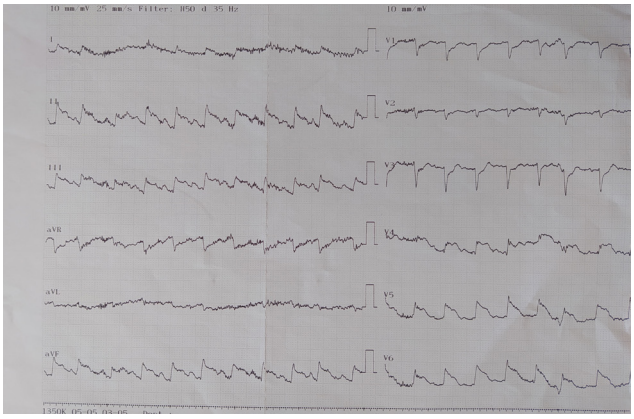

Figure 1: Takotsubo Syndrome Mimicking Acute Coronary Syndrome (Inferior MI) ECG Findings

Just like ACS, ST-segment elevations in precordial, inferior or lateral leads may be seen in TCMP. Elevations are most commonly seen in precordial leads, around 40-50% of the cases. Also, in some patients, new onset bundle branch blocks or non-specific T wave abnormalities may be detected. It is important to note that in the initial presentation, normal ECG findings don't rule out TCMP. In the following 2-3 days, ST-segment elevations tend to resolve and are replaced by diffuse deep T-wave inversions and QT-segment prolongation (57). Also, in some rare cases, transient pathological Q waves may be seen. Usually, these abnormalities are expected to resolve in 3-6 months (13).

In the acute settings, troponin level is usually measured for the ACS. Similarly to ACS, cardiac biomarkers are elevated in TCMP too, contributing to misdiagnosis. In 90% of the patients, at the initial presentation, the markers are found to be elevated (15). Compared to the ACS, peak troponin levels are usually found to be lower and creatine kinase (CK) level doesn't exceed 500 U/L (58). In contrast, brain natriuretic peptide (BNP) and N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP) levels peak around the 48 hour (h) after the initial presentation and are usually 3-4 folds greater than the levels found in ACS (59). However, 24 times higher than normal biomarker levels were also reported (60).

Ideally, patients with ACS should undergo angiography after the initial diagnosis. TCMP patients usually undergo angiography because of the initial misdiagnosis of ACS. During the angiography, no obstructions are detected in TCMP patients (61). However, in cardiac imaging, ventricular wall motion abnormalities are seen in these patients. These abnormalities are differentiated from ACS by their distributions. 3 different abnormal Left Ventricule (LV) contraction patterns are identified to be associated with TCMP. Most common type is apical ballooning type (75%) followed by mid ballooning type (25%) (15). Basal ballooning is seen very rarely (<1%), which is also called ''inverted TCMP"(18,62).

30% of the patients also show signs of right ventricular wall abnormalities(13, 61). These patients tend to develop congestive heart failure and have worse prognosis compared to patients with no right ventricular abnormalities (13).

In order to accurately diagnose TCMP, a detailed history must be obtained. As emphasized previously, different physical or emotional factors may trigger this syndrome. Also, it should be noted that TCMP may manifest in chronically ill patients who are admitted to the ICU for a long term. ICU patients who develop left ventricular systolic dysfunction in association with 1 or more of the factors such as hemodynamic compromise, pulmonary edema, troponin elevation, or ECG evidence of ischemia or infarction should be investigated for TCMP (23).

Also, it should be noted that ACS and TCMP may coexist and are not mutually exclusive (18).

Currently, there no universal diagnostic approach to TCMP. However, 4 different diagnostic criterions are used commonly **(Box 1 - 4)**.

Box 1: Mayo clinic criteria (63)

1. Transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present.

2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.

3. New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.

4. Absence of:
Pheochromocytoma, Myocarditis

Box 2: Swedish criterion (64)

Transient hypokinesis, akinesis, or dyskinesis in segments of the left ventricle, and frequently a stressful trigger (psychological or physical)

■ Absence of other pathological conditions (for example, ischemia, myocarditis, toxic damage, and tachycardia) that might more credibly explain the regional dysfunction

■ Slight or no increase in cardiac troponin levels (disparate with the amount of myocardial dysfunction)

Box 3: Italian criteria (65)

Typical transient LV wall-motion abnormalities extending beyond one epicardial vascular distribution, with complete functional normalization within 6 weeks

■ Absence of potentially culprit coronary stenosis or angiographic evidence of acute plaque rupture, dissection, thrombosis, or spasm

■ New and dynamic ST-segment abnormalities or T-wave inversion

■ Onset of transient or permanent left-bundle-branch block

■ Mild increase in myocardial injury markers (creatine kinase MB <50 U/L)

■ Clinical and/or instrumental exclusion of myocarditis

■ Postmenopausal woman (optional)

■ Antecedent stressful event (optional)

Box 4: MRI-based criteria from US and Europa (66)

■ An acute cardiac event typically presenting with chest pain and/or dyspnea

■ Transient systolic dysfunction with marked left ventricule(LV) contraction abnormality (akinesia or dyskinesia of the LV apical and/or midventricular or basal segments)

■ Absence of severe (>50%) obstructive coronary artery disease or angiographic evidence of acute plaque rupture

■ Electrocardiographic abnormalities (ST-segment elevation or T-wave inversion)

■ Slightly raised cardiac troponin level

■ Absence of pheochromocytoma

■ Absence of myocarditis or typical ischemic transmural late gadolinium enhancement on cardiovascular MRI (if available)

TREATMENT

Treatment in Acute Phase

There is no specific treatment for Takotsubo syndrome (67). Current treatment modalities applied in the acute phase are supportive therapies aimed at reducing the complications of Takotsubo syndrome (68).

In the acute phase of Takotsubo syndrome, serious cardiological complications occur in approximately 20% of patients (39). The most common complication in the acute phase is systolic heart failure (51, 52, 69). Complications occurring during this period can be confused with acute coronary syndrome (33).

When patients with Takotsubo syndrome present to the hospital, all patients should be followed up by ECG for at least 24 hours (70). However, patients with corrected QT interval (QTc) prolongation should also be followed up by ECG because of the increased risk of ventricular arrhythmias (58, 70).

It is important to determine the presence of hemodynamically significant left ventricular outflow tract obstruction in patients with Takotsubo syndrome who develop complications of cardiogenic shock. Inotropic agents should be discontinued immediately in the presence of left ventricular outflow obstruction to prevent an increase in obstruction (67, 70). Because left ventricular outflow tract obstruction is associated with basal hypercontractility in patients with Takotsubo syndrome (38, 70 – 72). In such patients, in the absence of severe heart failure, short-acting intravenous (IV) Beta-blockers may be used. However, attention should be paid to the use of catecholamines as well as inotropes in the treatment of patients with Takotsubo syndrome who develop cardiogenic shock without left ventricular outflow tract obstruction. Because it is thought that catecholamines are also involved in the pathogenesis of Takotsubo syndrome (36, 37). Levosimendan can be used as a positive inotrope for maintaining catecholamine levels (73). However, its use is controversial due to the lack of evidence. Therefore, early evaluation of mechanical support is necessary in patients with low cardiac output. Mechanical support devices such as a microaxial blood pump can be used in patients with Takotsubo syndrome who develop cardiogenic shock (50, 70). Afterload does not increase in microaxial blood pump treatment. This is one of the advantages of microaxial blood pump therapy. In patients with Takotsubo syndrome with refractory shock, extracorporeal membrane oxygenation and temporary left ventricular assist devices can be used if there are no contraindications (70, 74).

In patients with Takotsubo syndrome who develop congestive heart failure, diuretics or treatments such as nitroglycerin can be used to reduce preload (32, 37). ACE inhibitors or angiotensin II receptor blockers can be used in the presence of congestive heart failure, wall motion abnormality and impaired left ventricular ejection fraction. In the acute phase of Takotsubo syndrome, the use of Beta-blockers is beneficial in reducing in-hospital mortality, regardless of the presence of left ventricular outflow tract obstruction (75).

Another complication of Takotsubo syndrome is intraventricular thrombus. Intraventricular thrombus is especially seen in patients with severe apical ballooning and low left ventricular ejection fraction and is seen in approximately 2-5% of patients (66, 76). In order to prevent intraventricular thrombus formation, the use of prophylactic anticoagulants in patients with Takotsubo syndrome with impaired left ventricular ejection fraction is recommended by some experts until left ventricular ejection fraction is recovered (68, 70, 71, 77, 78). The prolongation of the QTc interval in Takotsubo syndrome is associated with the development of ventricular arrhythmia (58). Therefore, the use of drugs that cause QT prolongation in patients with Takotsubo syndrome should be avoided.

The prognosis of the TCMP is reported to be benign in most patients. This is also true for ICU patients. Despite the accompanying comorbidities, Haghi et al. reported that only 1 out of 6 patients died due to other conditions.

Treatment in Recurrence and Chronic Phase

Beta-blockers are used to prevent recurrence in Takotsubo syndrome (12, 67). Beta-blockers may protect against stress triggers and the ensuing catecholamine surges (67). Therefore, Beta-blockers are most frequently prescribed after discharge in patients with Takotsubo syndrome (67). However, recent studies have shown that post-discharge beta blocker use has no beneficial effect on mortality after 1 year of follow-up (50). In addition, two meta-analyzes did not confirm the hypothesis that beta blockers are useful in preventing the recurrence of Takotsubo syndrome (79, 80). However, the use of ACE inhibitors or angiotensin II receptor blockers in the chronic phase of Takotsubo syndrome is associated with decreased relapse rate in Takotsubo syndrome or improved survival at 1-year follow-up (50, 80). This association can be explained by the reduction of sympathetic activity or the anti-inflammatory effect on the myocardium via the renin-angiotensin system of ACE inhibitors and Angiotensin II receptor blockers (67).

Takotsubo syndrome is a disease with acute, transient left ventricular dysfunction (1, 2). Patients often present with shortness of breath and chest pain. Therefore, it can be confused with acute myocardial infarction(MI) and acute

coronary syndrome. Therefore, ECG, cardiac troponin and creatine kinase levels are important in the differential diagnosis (1). However, no stenosis is observed in the coronary angiography in Takotsubo syndrome. In addition, patients often have a history of emotional and physical stress.

There is no specific agent in the treatment of Takotsubo syndrome. Besides, treatment is divided into two: acute phase and chronic phase-recurrence. Symptomatic treatment is applied for complications in the acute phase. In the chronic phase and recurrence, agents such as beta-blockers, ACE inhibitors, angiotensin II receptor blockers are used. However, the exact effectiveness of these treatments has not been fully established. Therefore, further studies are needed for the treatment of Takotsubo syndrome.

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