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İçindekiler/*Contents*

Orijinal Araştırmalar / Original Articles

FORBES
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İçindekiler/*Contents*

Olgu Sunumu / Case Report

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Orijinal Araştırma / Original Article

Babaların Aşılar Hakkında Bilgi ve Tutumlarını Etkileyen Faktörler

Factors Affecting Fathers' Knowledge and Attitudes Towards Vaccinations

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ÖZ

Amaç: Aşılar, çocukluk çağı enfeksiyon hastalıklarını önlemede en etkili araçlardır. Ebeveynlerin aşılar hakkındaki bilgi ve tutumları, aşılanma oranlarını etkileyen temel faktörlerden biridir. Anneler hakkında çok sayıda çalışma olmasına karşın babaların aşılar konusunda bilgi ve tutumlarını inceleyen çalışmalar sınırlıdır. Çalışmamızın amacı, babaların ülkemizde uygulanan aşılar hakkındaki bilgi ve tutumlarını değerlendirerek aşılanmaya yaklaşımlarını belirlemek ve aşı karşıtlığına dair görüşleri öğrenmektir.

Yöntem: Mayıs-Temmuz 2022 tarihleri arasında çocuk polikliniğine başvuran babaların aşılarla ilgili bilgi ve tutumlarını değerlendiren kesitsel ve analitik bir çalışmadır. Etik kurul onayı alındıktan sonra babalara sosyo-demografik bilgiler, gelir, eğitim düzeyi, çocuk sayısı, babaların aşı tutumu, bilgi düzeyi ve rutin dışı aşı düşüncelerini içeren anket formu uygulanarak aşılar hakkındaki bilgi ve tutumları değerlendirildi.

Bulgular: Çalışmaya katılan babaların %33'ü aşılar hakkındaki bilgi düzeyinin iyi olduğunu düşünse de babaların %14,1'inin çocuklarına uygulanan aşıları, %23'ünün aşıların hangi zamanlarda yapıldığını bilmediği bulundu. Babaların büyük çoğunluğu aşılar hakkında bilgi kaynağı olarak sağlık kuruluşlarını ve hekimleri kullanıyordu. Babaların %17,3'ü bugüne kadar çocuklarına aşı yaptırma konusunda en az bir kez kararsızlık yaşadığını belirtirken, aşı reddeden baba yoktu. Aşı kararsızlığının en sık nedeni (%78,1) aşı yan etkisi korkusu bulundu. Anne babanın eğitim düzeyi arttıkça, babaların çocukluk çağı aşıları konusunda olumlu düşüncelerinin arttığı görülmüştür.

Sonuç: Aşılama, toplum sağlığını korumada önemli bir rol oynar. Ailelere doğru bilgi sağlanması, aşı karşıtlığını azaltmak ve aşı oranlarını artırmak için önemlidir. Sağlık çalışanlarının güvenilir bilgi sunması, ailelerin aşılara olumlu yaklaşımını ve aşı oranlarını artırma konusunda etkili bir faktördür.

Anahtar Kelimeler: Aşı, baba, aşı reddi, aşı kararsızlığı

ABSTRACT

Objective: Vaccines are the most effective tools in preventing childhood infectious diseases. Parents' knowledge and attitudes about vaccines are fundamental factors influencing vaccination rates. While there are numerous studies about mothers, research examining fathers' knowledge and attitudes on vaccines is limited. Our study aims to assess fathers' knowledge and attitudes about vaccines administered in our country, determine their approach to vaccination, and understand their views on vaccine hesitancy.

Methods: A cross-sectional and analytical study evaluating fathers' knowledge and attitudes about vaccines was conducted between May and July 2022 among fathers visiting the pediatric clinic. After obtaining ethical approval, fathers were administered a questionnaire covering sociodemographic information, income, education level, number of children, fathers' vaccine attitude, knowledge level, and non-routine vaccine considerations to assess their knowledge and attitudes about vaccines.

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Results: While 33% of participating fathers considered their vaccine knowledge good, 14.1% didn't know their children's vaccines, and 23% were unaware of vaccination timing. The majority of fathers used healthcare institutions and physicians for information about vaccines. While 17.3% experienced hesitancy about vaccinating their children, none outright refused. The most common reason for vaccine hesitancy (78.1%) was the fear of vaccine side effects. As parental education levels increased, the positive attitudes of fathers towards childhood vaccinations also increased.

Conclusion: Vaccination plays a crucial role in maintaining public health. Providing accurate information to families is important to reduce vaccine hesitancy and increase vaccination rates. Healthcare professionals offering reliable information is an effective factor in fostering positive attitudes toward vaccines and increasing vaccination rates.

Keywords: Vaccine, father, vaccine refusal, vaccine hesitancy

GİRİŞ

Sağlık alanındaki gelişmelere karşın enfeksiyon hastalıkları beş yaş altı çocuk ölüm nedenleri arasında ilk sıralardaki yerini korumaktadır. Aşılar, çocukluk çağında enfeksiyon hastalıklarının önlenmesi için kullanılan, etkinliği en yüksek araçlardır. Aşılama programları sayesinde her yıl yaklaşık iki milyon çocuk ölümünün engellendiği ve çok daha fazla sayıda çocuğun verem, çocuk felci, boğmaca, kızamık ve menenjit gibi sakat bırakan ya da süreğenleşen hastalıklardan korunduğu öngörülmektedir.[1,2] Aşılar yalnız hastalıklardan değil, dolaylı olarak hastalığın uzun dönem komplikasyonlarından da koruyarak çocukların sağlık niteliğini artırmakta, ağır tedavi ve rehabilitasyon giderlerini önlemektedir.[3] Ayrıca, yüksek aşılanma oranları aynı zamanda toplum immünitesi de oluşturduğu için aşılanmayan ya da aşılanamayan bireyler de hastalıklardan korunur. Örneğin, Amerika Birleşik Devletleri'nde yedi bileşenli konjuge pnömokok aşıları bebeklere yaygın olarak uygulanmaya başladıktan sonra 50 yaş üzeri erişkinlerde de pnömokok enfeksiyonlarının anlamlı oranda azaldığı gözlenmiştir.[3-5] Şu anda ülkemizde uygulanan ulusal aşı takviminde 13 farklı antijen yer almaktadır ve güncel verilere göre aşılama oranları %95-98 aralığındadır.[6,7]

Tüm bu başarılara karşın Dünya'da yaklaşık 25 milyon çocuk aşıya erişememekte ya da erişimde güçlük yaşamaktadır.[2] Aşılanma oranlarının istenilen düzeye gelememesinin pek çok nedeni olmakla birlikte özellikle son yıllarda toplumda yeniden popüler olan aşı kararsızlığı ve reddi nedenler orasında önemli bir yer tutmaktadır.[5,8-10] Anne babaların aşılar hakkındaki olumsuz düşünce ve endişelerinin artmasında aşı karşıtı toplulukların sosyal medyadaki olumsuz ifadelerinin ve yanlış bilgi paylaşımlarının oldukça etkili olduğu gösterilmiştir.[1,5]

Anne-babaların aşılar konusundaki bilgi ve tutumlarını bilmek, aşılanma oranlarını artırmak için yapılabilecek girişimlerin temelini oluşturmaktadır. Bu amaçla, annelerle yapılan çok sayıda çalışma olmasına karşın babaların aşılar ve aşı karşıtlığı konusunda bilgi ve tutumlarını inceleyen çalışmaların sınırlı sayıda olması bu çalışmayı planlamamızdaki temel etkendir. Çalışmamızın amacı, babaların ülkemizde uygulanan aşılar hakkında bilgi ve tutumlarını belirleyerek aşılanmaya yaklaşımlarını etkileyen etkenleri ortaya çıkarmak, aşı karşıtlığı hakkındaki görüşlerini öğrenmekti.

YÖNTEM

Bu kesitsel, analitik çalışmada Dokuz Eylül Üniversitesi Çocuk Sağlığı ve Hastalıkları Polikliniklerine 2022 yılı Mayıs-Temmuz ayları arasında herhangi bir nedenle başvuran çocukların babalarının aşılar hakkındaki bilgi ve tutumları değerlendirildi. Çalışmanın, bilinmeyen evrende %50 sıklık, %8 standart sapma ile %95 güven aralığında en az 151 kişilik örneklem grubu ile yapılması gerektiği hesaplandı. Ek olarak %10 yedek (15 kişi) hesaplandığında çalışmamızın en az 166 gönüllü ile yapılması planlandı. Çalışma öncesinde Dokuz Eylül Üniversitesi Girişimsel Olmayan Araştırmalar Yerel Etik Kurulu'ndan onayı alındı (karar no: 2022/12-01, karar tarihi: 30 Mart 2022). İlgili bilimsel yayınların taranması sonucu oluşturulan 23 soruluk Bilgi Toplama Formu, 2022 Mayıs ayında Dokuz Eylül Üniversitesi Çocuk Hastanesi' ne başvuran 0-18 yaş aralığındaki 234 çocuğun babasına uygulandı. Yabancı uyruklu olan aileler dil sorunu olabileceğinden çalışmaya alınmadı. Analizin sonuçlarında sapmalara neden olmaması açısından, soruların yarısından daha azını yanıtlayan babaların veri toplama formları veri analizine alınmadı. Bu nedenle, 43 geçersiz veri toplama formu çıkarılarak çalışılan 191 veri toplama formundan elde edilen bilgiler değerlendirildi.

Yirmi üç sorudan oluşan anket formu, ailelerin sosyo-demografik verileri, gelir ve eğitim düzeyleri, çocuk sayıları ile babaların aşılar konusundaki genel tutumu, bilgi düzeyi ve rutin dışı aşılar hakkındaki düşüncelerinden oluşmaktaydı. Ankete başlamadan önce gönüllü babalardan sözlü onam alındı. Anket babalara verilerek soruları yanıtlamaları istendi.

İstatistiksel Analiz

Elde edilen verilerin girişi ve değerlendirilmesi için Statistical Package for Social Sciences 24.0 (Chicago, IL, ABD) istatistiksel paket programı kullanıldı. Sonuçlar, sürekli ölçümlü değişkenler için aritmetik ortalama ve standart sapma, kategorik değişkenler için gözlem sayısı ve yüzde biçiminde ifade edildi. İstatistiksel analizde frekans değerleri, ortalama-minimum değer-maksimum değer-standart sapma değerleri, Spearman korelasyon testleri çalışıldı. Bağımsız iki grubun ortalaması Student's t-testi ile incelendi. İki grubun frekans dağılımları ki-kare ile test edildi. Sonuçların yorumlanmasında $p<0,05$ değeri istatiksel olarak anlamlı kabul edildi.

BULGULAR

Hastanemizin polikliniklerine herhangi bir nedenle çocuğunu getiren ve çalışmaya katılmayı kabul eden 191 babanın doldurduğu anket verisi çalışma kapsamında değerlendirilmeye alındı. Çalışmaya katılan babaların yaş ortalaması 36,38±6,22 yıldı. En genç baba 23 yaşındayken en yaşlı baba 53 yaşında idi. Annelerin yaş ortalaması 33,37±5,77 yıl iken, en genç anne 20, en yaşlı anne ise 53 yaşındaydı. Babaların yaklaşık yüzde kırk dokuzu, annelerin ise yüzde kırk ikisi üniversite ve üzeri eğitim almıştı. İki anne okur yazar değilken, bir anne okur yazardı, ancak bir okul bitirmemişti. Babalardan alınan bilgilere göre çalışmaya alınan ailelerin sosyo-demografik özellikleri Tablo 1'de özetlendi.

Tablo 1. Çalışmaya katılan ailelerin bazı sosyo-demografik özellikleri

	n	%
Baba yaşı		
≤35 yaş	95	49,7
>35 yaş	96	50,3
Anne yaşı		
≤35 yaş	123	64,4
>35 yaş	68	35,6
Baba eğitim düzeyi		
Yok	0	0
İlköğretim	28	14,7
Lise	70	36,6
Üniversite ve üzeri	93	48,7
Anne eğitim düzeyi		
Yok	3	1,6
İlköğretim	45	23,6
Lise	63	33
Üniversite ve üzeri	80	41,8
Baba çalışma durumu		
Çalışıyor	180	94,3
Çalışmıyor	5	2,6
Emekli	6	3,1
Anne çalışma durumu		
Çalışıyor	78	40,8
Çalışmıyor/ev hanımı	111	58,2
Emekli	2	1
Babanın gelir düzeyi algısı		
Gelir giderden düşük	38	19,9
Gelir ve gider eşit	103	53,9
Gelir giderden yüksek	50	26,2
Çocuk sayısı		
1	84	44
2	73	38,2
3	28	14,7
4 ve üzeri	6	3,1

Çocuklara uygulanan aşılar hakkındaki bilgi düzeyi algıları sorgulandığında, babaların %33'ü bilgisinin iyi düzeyde olduğunu düşündüğünü söyledi. Çocuklara uygulanan aşıların zamanlamaları hakkındaki bilgi düzey algıları sorgulandığında babaların %23'ü çocuklarına aşıların hangi zamanlarda yapıldığını hiç bilmediklerini söyledi (Tablo 2). Çalışmaya katılan babaların %55'i çocukları aşılamaya anne ile birlikte götürdüğünü bildirirken, %40,3'ü sadece annenin ve %4,7'si de sadece kendisinin götürdüğünü bildirdi. Babaların çocuklarına yapılan aşılar hakkındaki bilgileri sorgulandı. İki yaşından küçük çocuklara aşıların nereden uygulandığı sorusuna babaların %54,5'i "koldan" yanıtını verdi. Aynı soru iki yaşından büyük çocuklar için sorulduğunda "koldan" yanıtını veren baba oranı %71,7'ye yükseldi (Tablo 3). Hangi aşının hem ağız yoluyla hem de kas içi enjeksiyon yoluyla uygulanabildiği sorusuna 71 (%37,2) baba çocuk felci aşısı, 29 (%15,2) baba rotavirüs aşısı, 32 (%16,8) baba da Kızamık-Kızamıkçık-Kabakulak (KKK) aşısı yanıtını verdi. Babaların 59'u (%30,9) bu soruyu yanıtlamadı. Hangi aşının yapıldıktan sonra iz bırakarak iyileştiği sorusuna 112 (%58,6) baba verem aşısı yanıtını vermişken 44 (%23) baba KKK, sekiz (%4,2) baba rotavirüs aşısı yanıtını verdi. Babaların 27'si (%14,1) bu soruyu yanıtlamadı.

Çalışmaya katılan babaların yaklaşık %94'ü çocuklarının aşılarının Aile Sağlığı Merkezi'nde (ASM) yapıldığını bildirdi (Tablo 3). Bazı aileler birden fazla yerde aşı yaptırıyordu. Altı baba, çocuğunun aşılarının yalnızca devlet hastanesinde yapıldığını söylerken, üç baba üniversite hastanesinde ve iki baba özel hastanede yapıldığını söyledi. Altmış beş (%34) baba aşı sonrasında çocuklarında bir ya da daha fazla sayıda yan etki görüldüğünü bildirdi. En sık görülen yan etki ateş (n=51, %26,7) idi. Aşı sonrasında çocuğunda ateş görülen babaların %74,5'i ateş düşürücü ilaç kullandıklarını söyledi (Tablo 3).

Çocuklarına uygulanan aşılar ile ilgili bilgilerinin zaman faktöründen olumsuz etkilenebileceği düşünüldüğünden

Tablo 2. Babaların aşılar hakkındaki bilgi düzeyi algısı

	n	%
Çocuklarıma hangi aşıların uygulanacağı hakkındaki bilgim		
Hiç yok	27	14,1
Biraz var	81	42,4
İyi düzeyde	63	33
Çok iyi düzeyde	20	10,5
Çocuklarıma aşıların ne zaman uygulanacağı hakkındaki bilgim		
Hiç yok	44	23
Biraz var	79	41,4
İyi düzeyde	47	24,6
Çok iyi düzeyde	21	11

babalara son on yıl içinde doğan çocuklarına uygulanan aşılar soruldu. Çalışmaya katılan babaların son on yıl içinde doğan ilk çocuklarının yaş ortalaması 5,23±3,13 yıl (n=191), ikinci çocuklarının yaş ortalaması 2,93±2,33 yıl (n=65) ve üçüncü çocuklarının yaş ortalaması 1,63±1,41 yıl (n=10) bulundu. İlk çocukların %50,8'i, ikinci çocukların %55,4'ü, üçüncü çocukların %70'i erkekti. İlk çocuklarına yapılan aşılardan 1-3 aşı bilen baba oranı %28,8, 4-5 aşı bilen baba oranı %8,9; beşten fazla aşı bilen baba oranı %14,1'idi. İlk çocuklarına yapılan aşılar sorgulandığında babaların %48,2'si çocuklarına uygulanan hiçbir aşıyı bilemedi. İkinci çocuklarına uygulanan hiçbir aşıyı bilmeyen baba oranı %64,6, üçüncü çocuklarına uygulanan hiçbir aşıyı bilmeyen baba oranı %80 bulundu.

Tablo 3. Çalışmaya katılan babaların aşı uygulama ve yan etkileri hakkındaki bilgi durumları

	n	%
İki yaşından küçük çocuklara aşılar nereden uygulanır?*		
Koldan	104	54,5
Bacaktan (uyluktan)	81	42,4
Kalçadan	16	8,4
Ağızdan	11	5,8
İki yaşından büyük çocuklara aşılar nereden uygulanır?*		
Koldan	137	71,7
Bacaktan (uyluktan)	25	13,1
Kalçadan	9	4,7
Ağızdan	3	1,6
Çocuğunuza aşı nerede uygulandı?*		
ASM	180	94,2
Devlet Hastanesi	18	9,4
Üniversite Hastanesi	16	8,4
Özel hekim muayenehanesi	9	4,7
Özel hastane	6	3,1
Çocuğunuzda aşı sonrasında yan etki gözlendi mi?		
Evet	65	34
Hayır	126	66
Hangi yan etkiler gözlendi?*		
Ateş	51	26,7
Huzursuzluk	16	8,4
Aşı bölgesinde ağrı, şişlik, kızarıklık	13	6,8
Aşırı ağlama	3	1,6
Döküntü	1	0,5
Diğer	1	0,5
Çocuğunuzun aşı sonrası ateşi olduğunda ne yaptınız?*,&		
Ateş düşürücü ilaç verme	38	74,5
Soğuk kompres (alnına ıslak havlu koymak)	15	29,4
Ilık duş aldırma	12	23,5
Sağlık kuruluşuna gitmek	5	9,8
Sağlık kuruluşunu/doktorunu telefonla aramak	2	3,9

*Birden fazla cevap seçeneği işaretlenebilmiştir.
&Toplam çocuk sayısı 51 alınmıştır.
ASM: Aile Sağlığı Merkezi

Aşılar konusunda bilgi edindikleri, desteklendikleri ve kendilerini yönlendiren kaynaklar sorgulandığında babalar sağlık kurumları ve doktorları (%65,7) en çok bilgi edindikleri kaynak olarak bildirdi. Bu soruya birden çok yanıt verebilen babaların %15,5'i aile/akrabalarından bilgi aldığını ve desteklendiğini söylerken, %9,1 oranında "Arkadaşlar/Sosyal Çevre", %5,3 oranında "Sosyal Medya Uygulamaları", %4,5 oranında "Diğer (radyo, televizyon, gazete, dergi, internet vb.)" yanıtı verildi.

Babaların %17,3'ü bugüne kadar çocuklarına aşı yaptırma konusunda en az bir kez kararsızlık yaşadığını bildirdi. Aşı kararsızlığı yaşayan babaların %78,1'i aşıların yan etkilerinden korktuğunu, %21,9'u ise yeterince araştırılmadan uygulandıklarını düşündükleri için aşıların koruyucu olmayabileceğinden endişe ettiklerini belirtti. Çalışmaya katılan ve aşı karşıtı olduğunu söyleyen baba olmadı. Babaların 149'u (%78) aşıların kesinlikle yararlı olduğunu düşünürken, 40 (%21) baba yararlı olabileceğini, 2 (%1) baba da gereksiz olduklarını düşündüğünü bildirdi.

Babaların eğitim düzeyi arttıkça çocuklarına uygulanan aşılar hakkındaki bilgi düzeyi algıları artmaktaydı (p<0,001). Benzer biçimde, babaların gelir düzeyi algısı (p=0,032) ve anne eğitim düzeyi (p<0,001) arttıkça ve anneler çalışıyorsa (p=0,002) aşılar hakkındaki bilgi düzeyi algıları artmaktaydı. Babaların aşıların yararlılığı hakkındaki düşünceleri ise anne ve babanın eğitim düzeyi arttıkça istatistiksel olarak anlamlı ölçüde artıyordu (sırasıyla, p=0,048, p=0,008). Aşı kararsızlığı yaşayan babaları etkileyen faktörler incelendiğinde babanın aşıların yararlığı hakkındaki algısı dışında anlamlı bir sonuç bulunmadı (Tablo 4). Otuz beş yaşın altında, sekiz yıldan fazla eğitim görmüş olan babalar ile çocuğunda herhangi bir aşı sonrasında yan etki gelişen babalarda aşı kararsızlığı görülme sıklığının fazla olmasına karşın bu fark, istatiksel olarak anlamlı bulunmadı (p>0,05).

TARTIŞMA

Anne babaların aşılar hakkındaki bilgi düzeylerinin değerlendirildiği ülkemizde yapılan çalışmalarda, çocukluk dönemi aşılarını hiç bilmeyenlerin oranı %3,1 ile %21 arasında bulunmuştur.[11,12] Çalışmamıza katılan babaların %14,1'i çocuğuna uygulanan hiçbir aşıyı bilmediğini söyledi. Babaların aşılar hakkındaki bilgileri ayrıntılı incelendiğinde büyük çoğunluğunun aşının uygulama yeri hakkında yanlış bilgiye sahip olduğu görüldü. Babaların yaklaşık dörtte biri, aşıların ne zaman yapıldığını bilmemekteydi. En iyi

bilinen aşılar sırasıyla BCG, KKK ve Poliomiyelit aşıları idi. İzmir'de yapılan bir çalışmada anne babaların en çok bildikleri aşı kızamık aşısı idi.[10] Hatay'da gerçekleştirilen bir başka çalışmada ise anne babaların çoğunlukla KKK aşısını bildikleri, en az bilinen aşının ise Konjuge Pnömokok aşısı olduğu bulunmuştu.[11] Ankara'da yapılan bir çalışmada ise en çok bilinen aşının hepatit B aşısı olduğu saptanmıştı.[13]

Tablo 4. Aşı kararsızlığı yaşayan babaları etkileyen faktörler

	Aşı kararsızlığı yaşama durumu		
Faktörler	**Evet, n (%)**	**Hayır, n (%)**	**p**
Baba yaşı			
35 yaş ve altı	20 (21,1)	75 (78,9)	0,237
35 yaş üstü	13 (13,5)	83 (86,5)	
Baba eğitim düzeyi			
8 yıl ve altı	2 (7,1)	26 (92,9)	0,176
8 yıl üstü	31 (19)	132 (81)	
Aşı sonrası yan etki görülme durumu			
Evet	15 (23,1)	50 (76,9)	0,187
Hayır	18 (14,3)	108 (85,7)	
Babanın yaşadığı yer			
İl merkezi	22 (17,5)	104 (82,5)	
İlçe	10 (18,9)	43 (81,1)	0,681
Köy	1 (8,3)	11 (91,7)	
Babanın gelir düzeyi algısı			
Gelir giderden düşük	6 (15,8)	32 (84,2)	
Gelir ve gider eşit	20 (19,4)	83 (80,6)	0,682
Gelir giderden yüksek	7 (14)	43 (86)	
Babanın aşı yararlılığı hakkındaki düşüncesi			
Kesinlikle yararlı	12 (8,1)	137 (91,9)	
Yararlı olabilir	19 (47,5)	21 (52,5)	**<0,001**
Gereksiz/yararsız	2 (100)	0 (0)	
Babanın aşılar hakkındaki bilgi düzeyi algısı			
Hiç yok	4 (14,8)	23 (85,2)	
Biraz var	15 (18,5)	66 (81,5)	0,782
İyi düzeyde	12 (19)	51 (81)	
Çok iyi düzeyde	2 (10)	18 (90)	
Anne yaşı			
35 yaş ve altı	23 (18,7)	100 (81,3)	0,618
35 yaş üstü	10 (14,7)	58 (85,3)	
Anne eğitim düzeyi			
8 yıl ve altı	8 (16,7)	40 (83,3)	1,000
8 yıl üstü	25 (17,5)	118 (82,5)	

Anne babaların aşılar hakkındaki bilgi düzeylerinde bölgesel farklılıklar etkili olabilirse de genel olarak bilgi düzeylerinin yetersiz olduğu bulunmuştur. Baba ve anne eğitim düzeyinin, yüksek gelir algısının ve annenin çalışıyor olmasının babaların aşılar hakkındaki bilgi düzeyi algılarını olumlu etkilediği görülmüştür ($p<0,05$). Her ne kadar, çalışmamıza katılan babaların yaklaşık %40'ı çocuklarına yapılan aşılar hakkındaki bilgilerini iyi ya da çok iyi düzeyde bulsa da gerçekte bilgi düzeylerinin bu oranın çok altında olduğu görülmektedir.

İlginç bir şekilde çalışmamızda babalar en küçük çocuklarına uygulanan aşıları, en büyük çocuklarına uygulanan aşılardan daha az oranda biliyordu. Ülkemizde yapılan bir araştırmada da doğum sıra sayısı daha yüksek olan çocukların aşılanma oranları daha düşük bulunmuştu.[14] İngiltere'de 1-4 yaş çocuklar üzerinde yapılan bir çalışmada kardeş sayısının artması ile boğmaca aşısının geç yapılması ilişkilendirilmiştir.[15] Diğer araştırmaların tersine, yapılan bir başka çalışmada ise üç ya da daha fazla çocuklu ailelerde tam aşılanma oranlarının daha yüksek olduğu gösterilmiştir.[16] Çalışmamızda babaların küçük çocuklarına yapılan aşılar konusunda bilgisinin az olmasının nedenini çocuk sayısı arttıkça babaların çocuk sağlığı konusundaki sorumluluğu daha çok annelere bırakması olabileceğini düşünmekteyiz.

Son zamanlarda ülkemizde aşı reddinin arttığını, çocuklarına aşı yaptırmayan anne baba oranlarının hızla yükseldiğini gösteren çalışmalar mevcuttur.[17-19] Yıldız ve ark.[19] tarafından yapılan bir çalışmada aşı reddinde bulunan ve birden fazla çocuğu olan ailelerin yaklaşık yarısında önceki çocuklarında aşı reddinde bulunmadıkları gözlenmiş ve bu durum son yıllardaki aşı reddi artışının dikkat çekici bir göstergesi olarak yorumlanmıştır. Ülkemizde aşı reddinin sıfır yaş grubunda binde üç, ilköğretim okul çağında yüzde beş civarında olduğu, Doğu ve Güneydoğu Anadolu Bölgesi'nde diğer bölgelere göre yüksek oranda olduğu ve eksik aşılı olma oranının yaş arttıkça daha fazla olduğu bulunmuştur.[20] Çalışmamızda hiçbir baba kendisini aşı karşıtı olarak tanımlamamış, sadece %17,3'ü bir kez aşı yaptırma konusunda kararsızlık yaşadığını söylemişti. Çalışmamıza katılan babaların büyük çoğunluğu aşıların kesinlikle faydalı bir uygulama olduğunu düşünürken sadece iki baba aşıları gereksiz bir uygulama olarak değerlendirmişti. Yapılan bir başka çalışmada anne babaların %95,3'ü aşıların gerekli ve yararlı bir uygulama olduğunu düşündüklerini ifade etmiştir.[21] Giambi ve ark.'nın[22] İtalya'da yapmış olduğu çalışmada anne babaların %83,7'si aşının gerekliliği konusunda olumlu tutuma sahipken %15,6'sının kararsızlık yaşadığı görülmüştür.

Aşı çekimserliği ya da reddi yaşayan anne babalar çeşitli nedenler öne sürmektedir. Aşı sonrası istenmeyen yan

etki (ASİE), güvenlik kaygısı, hastalık riskinin olmadığını ya da çok az olduğunu düşünerek aşı uygulanmasını gerekli görmemek, zaman bulamamak, sağlık hizmetlerine karşı güvensizlik, medya aracılığıyla olumsuz bilgilenme ile kültürel, dini inançlar başlıca nedenleri oluşturmaktadır.[23-25] Ülkemizde yapılan bir çalışmada, aşı reddinin en sık nedeni olarak ASİE belirtilmiş, en sık bildirilen yan etkilerin ateş ve ağrı olduğu, kimi anne babanın kısırlığa yol açabileceğinden endişe duydukları kaydedilmiştir.[26] Çalışmamızda da benzer biçimde babaların en sık aşı yan etkisi endişesi nedeniyle kararsızlık yaşadıkları ortaya konmuştur. Bu babaların çocuklarının yaklaşık %45'inde bir ya da daha fazla sayıda ASİE gözlendiği kaydedildi.

Aşı kararsızlığı ve gelir durumu ilişkisine yönelik yapılan çalışmalarda aşı kararsızlığının daha yüksek gelire sahip anne babalar arasında daha yüksek olduğu gösterilirken[23,27,28], Migriño ve ark.[29] gelir durumunun aşı reddi ile ilişkili olmadığını bulmuştur. Çalışmamamızda da benzer şekilde gelir durumu ile aşı kararsızlığı arasında ilişki bulunmamıştır.

Anne baba eğitim ve gelir düzeyinin aşılama davranışını ve aşı reddini nasıl etkilediği ile ilgili farklı sonuçlar bulunmuştur. Topçu ve ark.[30] tarafından yapılan iki merkezli bir çalışmada anne ve babanın eğitim düzeyi arttıkça aşı ret oranlarının azaldığı gösterilmiştir. Anne eğitim düzeyinin yüksek olması çocuklarının tam aşılı olma durumunu olumlu yönde etkilemektedir.[31,32] Durmaz ve ark.[33] eğitim durumu, gelir ve aşı tutumu/çekimserliği arasında herhangi bir ilişki bulmamıştır. Çalışmamızda, anne babanın eğitim ve gelir düzeyi ile babaların çocukluk çağı aşıları konusunda bilgi düzeyi algılarının doğru orantılı olarak etkilendiği görüldü.

Babaların büyük çoğunluğu aşılar hakkında bilgi kaynağı olarak hekimleri ve sağlık kuruluşlarını göstermişti. Anne babaların önemli bir kısmı farklı kaynaklardan bilgi almak istemekte, az bir kısmı medyadan önemli ölçüde etkilenmektedir.[34] Çalışmamıza katılan babaların %10'u bilgi kaynağı olarak dijital ve basılı medyayı kullanıyordu. Medya, bilgi aramak için yaygın olarak kullanılmakla birlikte özellikle dijital medyada paylaşılan pek çok yanlış bilginin hızla yayıldığı ve geniş kitleleri etkilediği bilinmektedir. Özellikle, dijital medya kanallarında aşılar ile ilgili paylaşılan çoğu yanlış bilginin aşı konusunda kararsızlık yaşayan anne babaları etkilediği gösterilmiştir.[35-37] Oysa, aşılar konusunda temel bilgi kaynağı olarak hekimlere başvurulduğunda, daha yüksek oranda doğru bilgi edinildiği ve aşılama konusunda anne babalarda olumlu bir tutum olduğu gösterilmiştir.[38] Yeni Zelanda'da yapılan bir çalışma babaların %78'inin aşı konusuna hamilelik döneminde karar verdiğini, aşılama konusunda kararsız kaldıklarında ise çocukluk çağı aşılarını zamanında yaptırma olasılığının azaldığını göstermiştir.[39] Anne babaların aşılara ve çocuklarını aşılatmaya olumlu yaklaşımında ve aşı oranlarının artmasında en etkili ögelerin başında ailelerin sağlık çalışanları tarafından doğru bilgilendirilmeleri gelmektedir.

Çalışmanın Kısıtlılıkları

Çalışmamızın bazı kısıtlılıkları bulunmaktadır. Öncelikle, kısıtlı bir süre içinde sınırlı bir örnekleme dayanmaktadır ve soruların yarısından azını yanıtlayan babaların çalışmadan çıkarılmasıyla 191 babanın verisi değerlendirilerek gerçekleşmiştir. İkinci olarak belirli bir coğrafi bölgedeki babaları temsil etmektedir. Ayrıca çalışmaya katılan babalar çocuklarının aşı uygulamaları için düzenli olarak annelere eşlik etmediklerinden aşılar isimleriyle ve uygulama biçimleriyle sorulduğunda hatırlama ve doğru bilgi alma oranı yetersiz kalmıştır.

Bununla birlikte çalışmamızın bazı üstünlükleri de vardır. Üçüncü basamak sağlık kuruluşunda, bir proje dahilinde hekim ve hemşire gözetiminde yürütülmüş olması önemlidir. Ayrıntılı ve özgün bir veri toplama formu hazırlanıp kullanılmış, çalışmaya katılan babalarla bire bir görüşülmüştür. Babaların çocukluk çağı aşıları ve çocuklarının aşılanma durumu hakkında bilgi ve tutumlarını araştıran az sayıda çalışma vardır. Gelecekte, bu kısıtlılıklar ele alınarak daha kapsamlı çalışmalar yapılabilir.

SONUÇ

Sonuç olarak, çalışmamıza katılan babalarda aşı reddiyle karşılaşılmamış olması sevindiricidir. Anne babanın eğitim düzeyi arttıkça, babaların çocukluk çağı aşıları konusunda olumlu düşüncelerinin arttığı görülmüştür. Çocukların aşılarının büyük bir bölümü ASM yapıldığından, birinci basamakta çocuk sağlığı izleminde yaygın ve sürekli olarak, her aileye aşılar hakkında gereken bilginin verilmesi önemlidir. Sağlık çalışanlarının, ASİE ve yönetimi konusunda aileleri bilgilendirmesi anne babanın endişelerini azaltacak, aşı konusunda kararsızlık yaşamalarını engelleyecektir.

Etik

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Hasta Onayı: Ankete başlamadan önce gönüllü babalardan sözlü onam alındı.

Yazarlık Katkıları

Konsept: T.İ., S.U.B., Dizayn: T.İ., G.T., S.U.B., Veri Toplama veya İşleme: T.İ., B.B.A., Analiz veya Yorumlama: T.İ., G.T., S.U.B., Literatür Arama: T.İ., B.B.A., G.T., Yazan: T.İ., G.T., S.U.B.

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Original Article / Orijinal Araştırma

Relationship Between Dihydropyrimidine Dehydrogenase Gene Polymorphism and Toxicities in Cancer Patients Receiving 5-Fluorouracil

5-Florourasil Alan Kanser Hastalarında Dihidropirimidin Dehidrojenaz Gen Polimorfizmi ile Toksisiteler Arasındaki İlişki

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ABSTRACT

Objective: Dihydropyrimidine dehydrogenase (DPD) is a rate-limiting enzyme that degrades uracil, thymine, and 5-fluorouracil, which are important for treating gastric, colorectal, and breast cancers. In this study, we aimed to determine the association between chemotherapy-related toxicities and DPD gene variants; evaluate the consequences of these genetic differences; and integrate DPYD genetic screening into conventional cancer treatment regimens.

Methods: Sixty-two patient files from 2015 to 2018 were retrospectively reviewed to investigate whether the DPYD gene causes toxicity before or during treatment. A total of 50 patients were enrolled after receiving informed consent and ethical clearance for the comprehensive examinations. The aim of this study was to reveal the genetic causes of adverse effects and better understand treatment responses.

Results: Our analysis of 50 patients with cancer revealed that the severity of response to fluoropyrimidine compounds used in chemotherapy varied depending on DPYD gene polymorphisms. These mutations increased susceptibility to severe neutropenia -which can weaken immune systems- among other negative effects. It also found that IVS14 + 1G>A had a significant effect on treatment outcome, indicating that genetic screening should be included in planning therapy as it can prevent major side effects.

Conclusion: Dihydropyrimidine connected to dehydrogenase gene polymorphism occurred in patients with gastrointestinal cancer who developed diarrhea, nausea, anemia, thrombostitopenia, and grade 3-4 neutropenia side effects while receiving 5-FU.

Keywords: Dihydropyrimidine dehydrogenase, 5-fluorouracil, gene polymorphism

ÖZ

Amaç: DPD (dihydropyrimidine dehydrogenase), mide, kolorektal ve meme kanserlerinin tedavisinde urasil, timin ve 5-florourasili parçalayan hız sınırlayıcı bir enzimdir. Bu çalışmada kemoterapiye bağlı toksisiteler ile DPD gen varyantları arasındaki ilişkiyi belirlemeyi, bu genetik farklılıkların sonuçlarını değerlendirmeyi ve DPYD genetik taramasını geleneksel kanser tedavi rejimlerine entegre etmeyi amaçladık.

Yöntem: DPYD geninin tedavi öncesi veya tedavi sırasında toksisiteye neden olup olmadığını araştırmak için 2015'ten 2018'e kadar altmış iki hasta dosyası geriye dönük olarak gözden geçirildi. Kapsamlı muayeneler için bilgilendirilmiş onam ve etik izin alındıktan sonra toplam 50 hasta alındı. Amaç, yan etkilerin genetik nedenlerini ortaya çıkarmak ve tedavi yanıtlarını daha iyi anlamaktır.

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Bulgular: Elli kanser hastası üzerinde yaptığımız analiz, kemoterapide kullanılan floropirimidin bileşiklerine yanıt şiddetinin DPYD gen polimorfizmlerine bağlı olarak değiştiğini ortaya koydu. Bu mutasyonlar, diğer olumsuz etkilerin yanı sıra bağışıklık sistemlerini zayıflatabilen şiddetli nötropeniye duyarlılığı artırdı. Ayrıca IVS14 + 1G>A'nın, majör yan etkileri önleyebileceği için genetik taramanın planlama tedavisine dahil edilmesi gerektiğini gösteren yönetim üzerinde önemli bir etkisi olduğunu bulduk.

Sonuç: Dehidrojenaz gen polimorfizmine bağlı dihidropirimidin, 5-FU ile tedavi edilirken ishal, bulantı, anemi, tyrostitopeni, nötropeni grade 3-4 yan etkileri gelişen gastrointestinal kanser olgularında ortaya çıkmıştır.

Anahtar Kelimeler: Dihidropirimidin dehidrojenaz, 5-florourasil, gen polimorfizmi

INTRODUCTION

Dihydropyrimidine dehydrogenase (DPD) (EC 1.3.1.2) is a rate-limiting enzyme that degrades uracil, thymine, and 5-fluorouracil.[1] Intracellular 5-FU phosphorylation and activation inhibit DNA synthesis and RNA dysfunction.[2] In 10-30% of patients, an important treatment for gastric, colorectal, and breast malignancies causes significant side effects, such as neutropenia, thrombocytopenia, mucositis, diarrhea, and hand-foot syndrome.[3] A DPD-mediated three-step metabolic process excretes more than 80% of 5-FU.[4] DP puts the first step by converting 5-FU to dihydro-5-FU. DHP (EC 3.5.2.2) hydrolyzes FUH2, which is then converted into fluoro-β-alanine after β-ureidopropionase (β-UP, EC 3.5.1.6) converts fluoro-β-ureidopropionic acid created in the previous steps.[5] A severe 5-FU poisoning can be caused by any of these enzymes, but DPD, the rate-limiting enzyme, is most important.[5] Due to 5-FU accumulation and blood levels, DPD deficiency can increase antitumor effects or toxicity.[6]

DPD is expressed by more cells, but liver and lymphocytes seem to be more active.[7] DPYD, which is on chromosome 1p21 has an open reading frame of 3,078 bp and 1,025 amino acid residues.[8] It is made up of 23 exons. Amino acid sequences and enzymatic activities can be modified by DPYD SNVs, deletions and insertions. Clinical symptoms such as seizures, mental illness, microcephaly, autism in sick people and asymptomatic people in DPD deficiency.[9,10] Microdeletion and chromosomal instability in the 1p21 region of DPYD also lead to this autosomal recessive genetic disorder. DPD deficit can only be detected after 5-FU treatment, which causes significant toxicity in asymptomatic individuals; thus, predicting the toxicity risk is vital. In addition to four Caucasian risk variants of DPYD: C.1905+1G>A (IVS14+1G>A, DPYD*2A), C.1129-5923C>G/hapB3, C.1679T>G (DPYD*13, p. I560S), and C.2846A>T, there have been more than 450 variations of the gene.[11,12] Splicing mistakes or amino-acid alterations affect the enzymatic activity.[13,14] The Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group recommend modifying 5-FU doses for DPYD genetic variations.[15]

Our research shows that comprehensive studies are rare that could help prove the clinical benefits of DPYD polymorphism screening as part of cancer treatment planning. Although current studies have provided a basic understanding of the correlation between DPD variants and chemotherapy toxicity; no consensus has been reached regarding the effects of these genetic tests on treatment outcomes and patient management strategies. To enable personalized medicine approaches in oncology, we need to further investigate the prevalence of DPYD polymorphisms among different populations and cancer types and their effects on toxicity profiles.

However, this study sets out to clarify the situation by examining chemotherapy toxicity resulting from a mix of certain Dec gene polymorphisms in patients. The overall goal is to determine whether it is worth integrating genetic tests into routine cancer treatment protocols. This will increase the effectiveness of treatments, reduce negative effects, and improve the overall quality of life of patients with cancer.

METHODS

The study was approved by the Ethical Review Board of Harran University Faculty of Medicine, Şanlıurfa (approval number: E13607, date: 25.03.2019). From January 1st 2015 through January 1st 2018 at our University Faculty of Medicine Research and Application Hospital Department of Medical Oncology were examined as part of a preliminary trial (62 patient files). Evaluation for inclusion in the study was given regardless of whether the patient was admitted as a hospitalized or outpatient but had to be set up for chemotherapy. With approval from the ethics committee and after informed consent was obtained from each patient, the boundaries were determined so that only those who could reliably report chemotherapy symptoms and the effects of DPYD gene polymorphism on treatment outcomes (Figure 1), which included 50 patients after removing untraceability (n=2), prestudy death (n=3) and inadequate data records (n=7) (Figure 1).

Patients were informed of the study design and its objective. The study was approved by the Ethical Review Board of Harran University Faculty of Medicine, Şanlıurfa (approval number: E13607, date: 25.03.2019), in accordance with national patient care guidelines, and met international ethical standards for research involving humans. Patients

received full disclosure of the tests that would be performed on them and any potential side effects caused by these tests. Before and 10 days after chemotherapy, patients underwent complete blood counts and biochemical testing to evaluate their baseline health status and detect any changes. Just before treatment, a blood sample was collected from each patient for genetic polymorphism analysis, especially for DPYD gene polymorphisms, and kept at -80 ºC until DNA extraction followed by real-time polymerase chain reaction (PCR) analysis.

To analyze the association between genetic polymorphism (DPYD * 2A, * 13, *9B) and toxicity during two periods: pre-chemotherapy assessment 10 days before chemotherapy; post-chemotherapy assessment 10 days after chemotherapy to identify genetic factors responsible for adverse reactions to drugs currently used in clinical practice (chemotherapies) as well as those used separately or associated with other drugs in individual patients; detailed protocols were used according to manufacturer instructions to extract blood DNA from each patient. After homogenization for at least 2 h at room temperature together with the addition of QIAGEN protease to the buffer AL + ethanol mixture (spin column), centrifugation

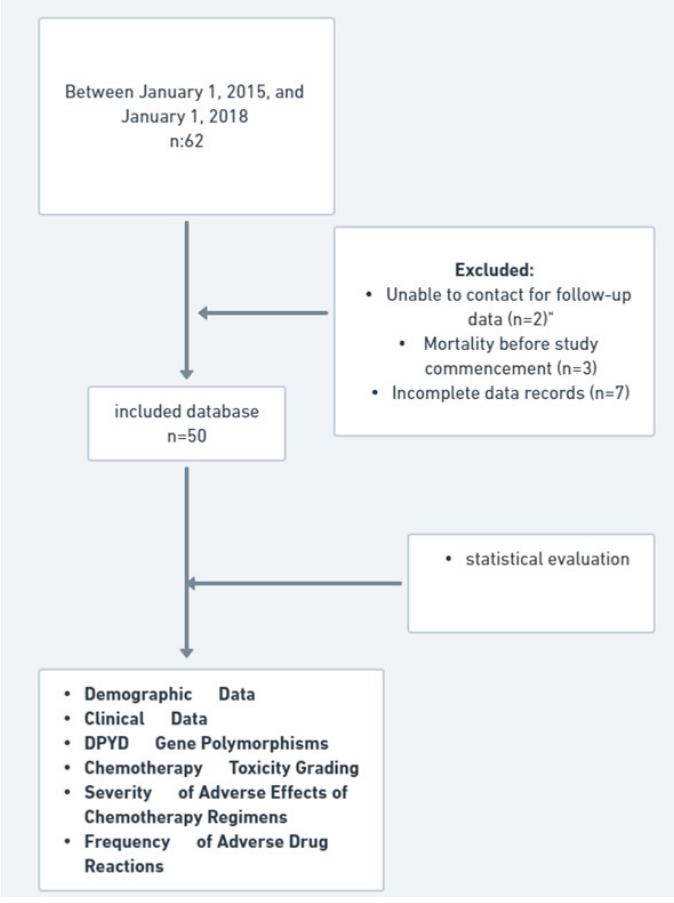

Figure 1. Study design

occurred. Polymorphism screening needs high-quality DNA-which was what our protocol provided. DPYD gene variants were detected using a Taqman Genotyping Assay and Master Mix polymorphism screening using qPCR.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences for Windows version 20.0; continuous variables are presented as mean±standard deviation; categorical variables are presented as frequency (%) or number (%); parametric variables were compared using Student's t-test or Mann-Whitney U test; categorical variables were compared using chi-square test or Fisher's exact test. P values <0.05 were considered statistically significant.

RESULTS

We collected and analyzed the medical records of 50 patients, including personal data such as age, sex, anthropometric measurements, tumor type, cancer staging, and chemotherapy treatment regimens. The sample consisted of 27 men (54%) and 23 women (46%), with a mean age of 54.18±14.40 years; the prevalence rate reflects that cancer is more common in women than in men: breast cancer was the most frequent among women, while prostate cancer was the most frequent among men; The mean weight was 66.88 kg (±15.47 kg), and the mean height was 164.50 cm (±7.22 cm), reflecting the fact that each patient had their own health condition; cancer stages ranged from 2 to 4: Stage 2 corresponded to 20% of the sample, Stage 2 corresponded to 25%, Stage 3 corresponded to another third (30%), and Stage 4 corresponded to another quarter (25%), highlighting that although all have cancer - it doesn't always mean they have the same stage - making it even more important to personalize treatments in order to obtain better results by reducing possible side effects associated with them; chemotherapy regimens included FEC, FOLFOX, and cisplatin-based treatments tailored according to tumor type and stage. We have now included a detailed analysis of the side effects according to the chemotherapy regimens to enhance the understanding and management of patient care (Table 1).

Our analysis using genotyping showed higher rates of DPYD gene variant detection than expected for variants DPYD *2A rs3918290 c.-166G>T rs55886062 c.-96T>G rs67376798 c.-1103C>G HapB3c.-1601C>A. These results are meaningful because these polymorphisms are associated with severe reactions to fluoropyrimidine, which are widely used in chemotherapy. In the future, it will be necessary to screen and identify people at risk of adverse responses and reduce the dosage of such drugs (Table 2). Patients with these polymorphisms have a greater risk of developing severe neutropenia and other side effects.

Table 1. Demographics and clinical data of the patients			
Parameter	**Total (n=50)**	**Male (n=27)**	**Female (n=23)**
Gender	Male: 54% (27) Female: 46% (23)	-	-
Average age	54.18±14.40 years	56±14 years	52±14 years
Weight (kg)	66.88±15.47 kg	70±15 kg	63±15 kg
Height (cm)	164.50±7.22 cm	170±7 cm	159±6 cm
The type of cancer	Breast (25.8%), lung (15.4%), colorectal (10.7%), prostate (15.1%), and other (33%)	Prostate (30%), lung (20%), colorectal (15%), and others (35%)	Breast (30%), lung (20%), colorectal (15%), and others (35%)
Cancer stage	Stage 1 (20%), Stage 2 (25%), Stage 3 (30%), Stage 4 (25%)	Stage 1 (22%), Stage 2 (25%), Stage 3 (28%), Stage 4 (25%)	Stage 1 (18%), Stage 2 (25%), Stage 3 (32%), Stage 4 (25%)
Chemotherapy regimen	FEC (20%), FOLFOX (20%), cisplatin-based (25%), and others (35%)	FOLFOX (25%), cisplatin-based (30%), others (45%)	FEC (25%), FOLFOX (20%), and others (55%)

Table 2. Prevalence of DPYD gene polymorphisms					
DPYD variant	**Allelic frequency in the general population**	**Frequency in the study population (n=50)**	**Homozygous**	**Heterozygous**	**Notes**
DPYD*2A (rs3918290)	0.7%	2 (4%)	0 (0%)	2 (4%)	Associated with severe toxicity to fluoropyrimidine.
c.1679T>G (rs55886062)	0.2%	1 (2%)	0 (0%)	1 (2%)	Rare but significant when present.
c.2846A>T (rs67376798)	1.4%	3 (6%)	0 (0%)	3 (6%)	Linked to increased risk of severe neutropenia and other toxicities.
c.1129-5923C>G (HapB3)	2.9%	4 (8%)	0 (0%)	4 (8%)	The most frequently identified variant.
Compound heterozygous	N/A	1 (2%)	N/A	1 (2%)	Carrying two different DPYD risk variants.
N/A: Not applicable					

Tablo 3. Chemotherapy toxicity grading					
Toxicity type	**Grade 0 (none)**	**Grade 1 (mild)**	**Grade 2 (moderate)**	**Grade 3 (severe)**	**Grade 4 (life-threatening)**
Anemia (g/dL)	>12	10-12	8-9.9	6.5-7.9 (transfusion needed)	<6.5 (immediate intervention required)
Thrombocytopenia (per µL)	>142,000	75,000-142,000	50,000-74,000	25,000-49,000	<25,000
Neutropenia (per µL)	>1,630	1,400-1,630	1,000-1,400	500-900	<500
Diarrhea	None	<4 episodes/day	4-6 episodes/day	>6 episodes/day (hospitalization indicated)	Life-threatening complications
Nausea	None	Appetite loss without altering eating habits	Reduced oral intake without weight loss	Inadequate oral intake requiring intravenous hydration or hospitalization	-
Vomiting	None	1-2 episodes in 24 h	3-5 episodes in 24 h	≥6 episodes in 24 h or requiring IV hydration	Life-threatening complication

Grades of chemotherapy toxicity in our patients indicated how much their health was affected by the treatment. Categorizing anemia, thrombocytopenia, and neutropenia as well as rating symptoms like diarrhea, nausea, and vomiting helped us measure the side effects of therapy. This classification is key to finding and preventing serious consequences early in life. To ensure safe treatment and effective care, chemotherapy toxicities must always be monitored and managed (Table 3).

In relation to DPYD gene polymorphisms in our study of the side effects of chemotherapy, we found that genetic factors were responsible for different responses to treatment. We found solid links between certain DPYD variants and the severity of anemia, neutropenia, thrombocytopenia, diarrhea, nausea, and vomiting. Patients with these polymorphisms were more likely to have serious side effects, supporting the idea of pre-treatment genetic testing. If this test is passed, it can tell doctors whether a patient will have bad reactions or not so they can adjust the therapy plan accordingly to lower those risks down and improve patient outcomes (Table 4).

To show just how big of an effect IVS14 + 1G > A has when it comes to handling drugs we compared bad treatment reactions in IVS14 + 1G > A patients with those not carrying it and showed its influence over standard doses of chemotherapy. People with this variant had a much higher risk of developing neutropenia and diarrhea, which shows a good chance of using detailed genetic profiling outside of cancer treatment planning to identify people who need dose adjustments etc. because they might also experience severe side effects (Table 5).

DISCUSSION

DPD comprises five domains, which are like sections. The first and fifth ones both have two 4Fe-4S clusters containing two molecules each. The second mutant has the FAD binding site. The fourth site holds the FMN binding site. In domain four, there is an active site. NADPH sends

Table 4. Severity of adverse effects of chemotherapy regimens based on DPYD gene polymorphisms

Adverse effect	FEC regimen	FOLFOX regimen	Cisplatin-based regimen
Anemia	Grade 2	Grade 1-2	Grade 2-3
Neutropenia	Grade 3	Grade 2-3	Grade 4
Thrombocytopenia	Grade 1	Grade 1-2	Grade 2-3
Diarrhea	Grade 1-2	Grade 2	Grade 3-4
Nausea	Grade 1	Grade 2	Grade 1-2
Vomiting	Grade 1	Grade 2	Grade 3

DPYD gene polymorphisms significantly influence the severity of adverse reactions to fluoropyrimidine-based chemotherapy, with variations like DPYD*2A, c.1679T>G, and c.2846A>T increasing the risk of severe toxicities such as neutropenia and diarrhea. Genotyping is crucial for tailoring treatment strategies to mitigate these polymorphisms

Table 5. Frequency of adverse drug reactions in patients with IVS14 + 1G > A polymorphism

Adverse effect	Patients with IVS14 + 1G> polymorphism (%)	Patients without IVS14 + 1G > polymorphism (%)	Notes
Neutropenia	40% (2 out of 5)	20% (9 out of 45)	The presence of IVS14 + 1G> polymorphism doubles the risk of severe neutropenia compared with that in patients without the variant.
Anemia	20% (1 out of 5)	15.6% (7 out of 45)	A slight increase in the risk of anemia in patients with polymorphism, indicating a marginal effect.
Thrombocytopenia	0% (0 out of 5)	6.7% (3 out of 45)	No cases of thrombocytopenia were observed in patients with the polymorphism, suggesting minimal impact.
Diarrhea	60% (3 out of 5)	24.4% (11 out of 45)	Significantly higher occurrence in patients with polymorphism, indicating a strong influence on gastrointestinal toxicity.
Nausea	40% (2 out of 5)	33.3% (15 out of 45)	Slightly increased risk in patients with polymorphism, although within a close range to that in patients without polymorphism.
Vomiting	40% (2 out of 5)	22.2% (10 out of 45)	Increased risk of nausea in patients with polymorphism, consistent with an elevated incidence of nausea.

electrons to domain three when DPD is being used.[16] These domains' amino acid sequences are similar in all of the animal species studied so far, and they only start working after dimerization occurs and electrons from the 4Fe-4S clusters move.[17] We used a technique called immunoblotting with blue native PAGE to determine how small changes to certain amino acids affected dimer formation in DPD. This allowed us to look at DPD versions we already knew couldn't turn on, see that they didn't make dimers, and then figure out what happened when others did work but worse for whatever reason.[18] All our normal-looking versions, except for DPYD*2A and G926V, produced the same dimer band at approximately 242 kDa. Seven other versions were fainter or absent while their bands were still there too, which told us those ones either barely or never turned on at all (N151D, R353C, R592W, G748D, T768K, H807R, T990I).[19] Four of these seven had higher electrophoretic mobility than usual because of amino acid charge changes (N151D, R592W, G748D and H807R) - this means that they moved faster from left to right as electric charges pushed them along while we did blue native PAGE - before also becoming less reactive[20].

To elaborate on the variation in patient outcomes mentioned earlier, this study presents a more detailed account of how DPYD gene polymorphisms determine toxicity patterns across various cancer types and chemotherapy regimens. This analysis showed that some polymorphisms were consistently associated with increased toxicity in specific cancer populations. As an illustration, colorectal cancer patients with DPYD*2A polymorphism had significantly higher rates of severe neutropenia than other malignancies when treated with 5-FU-based regimens. This underscores the importance of personalized treatment based on genetic testing results by recognizing the intricate interplay between disease type, therapeutic regimen, and genetic makeup.

This research is limited by the small number of patients. It is important to note the different works on this topic in this part of the paper and discuss their outcomes. For example, Rai et al.[21] (2019) and Li et al.[22] (2014) also studied DPYD polymorphisms but used greater samples, making diverse recommendations that are consistent with our findings and indicated that differences exist for our smaller population sample size may not capture fully it's response variability.

Stuff in lane one was especially bad here because it had more than double the amount of protein than anything else but looked about half as bright "inside" where light can get absorbed, which is how we know these products of chemical reactions were also made in smaller amounts. R592W, T768K, and G926V versions had much less activity than normal, just like some other versions we tested before.[22] C29R, Y304H, and F438V all cut the same DNA linkages as regular DPD but at less than 50% the speed. This does not mean they work half as well: they still make a lot of this drug-destroying enzyme, but it doesn't move fast enough to protect people from getting hurt by it while taking therapeutic doses of 5-FU.[20-23]

We cannot draw any conclusions regarding whether the patients did or did not experience very bad side effects. However, because of what we know about cancer cells' metabolism and drug properties, it seems important that their body's most active proteins are already compromised. In cases in which the family has never been diagnosed with cancer before, it makes sense for a doctor to wonder why someone unexposed to anything else could have so many problems after only one treatment. Using our genetic testing on more families like this lets us calculate odds ratios that help doctors advise them against giving toxic drugs to people with abnormally low enzyme activities or making up new rules so they are allowed to use lower doses in future.[23,24]

Our study also had some limitations because each patient was selected from a single hospital; each sample represented a limited population that may differ genetically from the population found in larger groups. Additionally, we only examined certain DPYD polymorphisms; we didn't take into account other genetic factors that could influence an individual's response chemotherapy.[25,26]

Toxin-absorbing enzymes made by your liver clean out many things you do not want in your blood, including the actions of cells -whether healthy or not- during normal living and dying. Sometimes you need to put a lot more into them though to kill cancer cells without killing you. The simplest 5-fluorouracil (5-FU) is a powerful molecule until toxic chemicals produced by your liver turn it into things that break up DNA. This only occurs in cancer cells because their mitochondria no longer can generate ATP energy for them. Your normal ones still can and they even use extra hydrogen atoms from the enzyme DPD to regenerate nicotinamide adenine dinucleotide phosphate (NADPH), which lets them keep breaking up 5-FU waste with dihydropyrimidine dehydrogenase NADP+ intermediate oxidoreductase (DPYD).[26,27]

This makes it possible to kill tumor cells without killing the rest of the body, but some people make a lot less DPD and are poisoned by accident while on what should be safe doses of 5-FU-based drugs like capecitabine. These patients usually die when their immune system gets turned on instead of breaking up uracil nucleotides into harmless parts that get peeped out, which generates enough active oxygen forms to cause adult respiratory distress syndrome and liver failure earlier than usual in humans who do not have mutations in either DPYD gene.[27,28]

But sometimes going through these steps takes longer than it should, so you might wonder if this stuff is really necessary at all or if there's another way to make as much DNA damage as we want with fewer side effects during chemotherapy using other stuff. At least one expert thinks the results from this study can help researchers find out before this month ends.[29,30]

In combination with irinotecan, some versions of DPYD also lower the production of inactive drug metabolites called SN-38G and APC:SN-38G conjugates so much that UGT1A1 cannot clear enough away in time for them to finish being turned into active toxins by gut bacteria. A typical human body might eat 0.1-0.3 g of feces per day, which contains DPD NADPH and other things that make DNA-damaging products with no regard for what they do because they do not have a brain.[31]

Irinotecan's active metabolite of irinotecan is SN-38, the most powerful DNA poison in use today. It should be trapped inside cells by UGT1A1 conjugation, so it can only damage DNA once before being turned back into irinotecan.[17] Two SN-38 molecules turning back into one irinotecan molecule per second while your liver turns food into ATP energy is a lot faster than the rate at which you can damage DNA, so this should keep you from dying while giving some muscle to chemotherapy by letting it happen more often than mistakes during DNA replication - about every 10^{7} cycles through the bases without repair compared to 10^{-4}.[32]

One thing both versions of DPYD would accomplish is lower blood levels of SN-38G thanks to less production but also because some of it gets peed out along with aberrant concentrations of other things -such as NADPH- that we think are made specifically to prevent all tissues from being poisoned when certain events occur at times and places where they shouldn't be happening even if there was an errant signal instructing all tissues to do whatever we are seeing. Another version could change how these enzymes work in too complex a way to predict based on what amino acids are present or not, so a study like this that directly measures chemical reaction rates is necessary to see if these patients will get hurt worse than usual if treated with either drug.[33,34]

Our results provide evidence for nine new pathogenic DPYD variants, five polymorphisms associated with partial loss of activity, and six linked to complete loss. We hope that these data will aid future research by enabling the selection of patients who can be administered appropriate doses based on genetic and clinical information.

Study Limitations

The limitation of this study is that it was a prospective study with a small patient population.

CONCLUSION

In patients undergoing the 5-FU treatment protocol due to a diagnosis of gastrointestinal cancer, developing diarrhea, nausea, anemia, thrombostitopenia, and neutropenia grade 3, 4 side effects of this, it was found that dihydropyrimidine in patients had a significant association with the dehydrogenase gene polymorphism. When we look at the literature, we usually see that similar results have been obtained. But nevertheless, it is too centralized to come to firm conclusions on this issue in the long term; with more patients, it needs to be done.

Ethics

Ethics Committee Approval: The study was approved by the Ethical Review Board of Harran University Faculty of Medicine, Şanlıurfa (approval number: E13607, date: 25.03.2019).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: T.Y., Concept: T.Y., Design: T.Y., Data Collection or Processing: T.Y., Analysis or Interpretation: Ç.C., Literature Search: T.Y., Writing: T.Y.

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Orijinal Araştırma / Original Article

Palyatif Bakım Veren Hemşirelerin Hasta Merkezli Bakım Yetkinliğinin Bakım Kalitesine Etkisi

The Effect of Patient-centred Care Competence of Palliative Care Nurses on Quality of Care

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ÖZ

Amaç: Bu çalışmanın amacı palyatif bakım veren hemşirelerin hasta merkezli bakım yetkinliğinin bakım kalitesine etkisinin belirlenmesidir.

Yöntem: Tanımlayıcı ve kesitsel tipteki araştırma, Haziran-Ağustos 2023 arasında İzmir İl Sağlık Müdürlüğü'ne bağlı sağlık kurumlarında yürütülmüştür. Araştırma sağlık kurumlarının palyatif bakım birimlerinde aktif olarak görev alan 130 hemşire ile gerçekleştirilmiştir. Veriler "Kişisel Bilgi Formu", "Hasta Merkezli Bakım Yetkinliği Ölçeği" ve "Hemşireler için Palyatif Bakım Kalitesi Ölçeği" kullanılarak toplanmıştır. Verilerin analizinde tanımlayıcı istatistikler, nicel değişkenler arasındaki ilişkinin değerlendirilmesinde Pearson korelasyon katsayısı kullanılmıştır.

Bulgular: Araştırmaya katılan hemşirelerin yaş ortalaması 36,69±7,5 olup, %94,6'sı kadındır. Hemşirelerin Hasta Merkezli Bakım Yetkinliği Ölçeği toplam puan ortalamaları 4,02±1,04; hasta bakış açılarına (perspektifine) saygı duymak, bakım süreçlerinde hasta katılımını teşvik etmek, hasta konforu sağlamak ve hastaları haklarını savunmak alt boyutlarına yönelik puan ortalamaları sırasıyla 4,01±1,05; 4,01±1,05; 4,08±1,11ve 3,98±1,08; Hemşireler için Palyatif Bakım Kalitesi Ölçeği'nden aldıkları toplam puan ortalaması ise 74,80±11,98 olarak tespit edilmiştir. Araştırmada Hemşirelerin Hasta Merkezli Bakım Yetkinliği Ölçeği ve Hemşireler için Palyatif Bakım Kalitesi Ölçeği toplam puan ortalamaları arasında pozitif yönlü orta düzeyde istatistiksel olarak anlamlı bir ilişki tespit edilmiştir (r=0,319; p<0,001).

Sonuç: Bu çalışmada palyatif bakım hemşirelerinin hasta merkezli bakım yetkinliklerinin ve yürüttükleri palyatif bakım hizmetleri kalitesinin yüksek düzeyde olduğu belirlenmiş, hasta merkezli bakım yetkinliklerinin palyatif bakım kalitesine etkisi olduğu gösterilmiştir.

Anahtar Kelimeler: Palyatif bakım, hasta merkezli bakım yetkinliği, sağlık bakım kalitesi, sağlık yönetimi

ABSTRACT

Objective: The aim of this study is to determine the effect of patient-centered care competence of palliative care nurses on the quality of care.

Methods: The descriptive and cross-sectional study was conducted between June and August 2023 in health institutions affiliated to Izmir Provincial Health Directorate. The study was conducted with 130 nurses actively working in palliative care units of health institutions. Data were collected using "Personal Information Form", "Patient-centered Care Competency Scale" and "Palliative Nursing Care Quality Scale". Descriptive statistics were used to analyze the data and Pearson correlation coefficient was used to evaluate the relationship between quantitative variables.

Results: The mean age of the nurses participating in the study was 36.69±7.5 years and 94.6% of them were female. The mean total scores of the nurses on the Patient-centered Care Competency Scale were

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4.02±1.04; the mean scores for the sub-dimensions of respecting patient perspectives, promoting patient involvement in care processes, providing for patient comfort and advocating for patients were 4.01±1.05, 4.01±1.05, 4.08±1.11 and 3.98±1.08, respectively; and the mean total score on the Palliative Nursing Care Quality Scale was 74.80±11.98. In the study, a positive moderate statistically significant relationship was found between the mean total scores of the Patient-centered Care Competency Scale and the Palliative Nursing Care Quality Scale (r=0.319; p<0.001).

Conclusion: In this study, it was determined that palliative care nurses' Patient-centered Care Competencies and the quality of palliative care services they provide are at a high level, and it was shown that Patient-centered Care Competencies have an effect on palliative care quality.

Keywords: Palliative care, patient-centered care competency, quality of care, health management

GİRİŞ

Palyatif bakım, yaşamı tehdit eden bir hastalıkla ilişkili sorunla karşılaşan hastaların ve ailelerinin yaşam kalitesini, acılarının erken saptanması ve kusursuz bir değerlendirme ile önlenmesi ve dindirilmesi ve ağrının, fiziksel, psiko-sosyal ve manevi diğer sorunlarının tedavisi yoluyla geliştiren bir yaklaşım olarak tanımlanmaktadır. Son yıllarda yaşamı tehdit eden ya da sınırlayan hastalıkların yükü küresel olarak artış göstermiş ve palyatif bakıma olan gereksinim artmıştır.[1-3] Dünya Sağlık Örgütü (DSÖ) palyatif bakımın bir seçenek olmayıp tıbbi ve etik bir zorunluluk olduğunu ve tüm sağlık sistemleri düzeylerinde ulaşılabilir olmasının önem taşıdığını bildirmektedir. Bununla birlikte DSÖ tahminlerine göre dünyada 56,8 milyon kişi palyatif bakıma gereksinim duymakta ve bunlardan sadece %14'ü palyatif bakımdan yararlanabilmektedir. Palyatif bakım hizmetlerinin, hastalar için sıkıntı verici sağlık sorunlarının değerlendirilmesi ve çözümüne odaklı olması nedeniyle hasta merkezli olması öncelikli olmalıdır. Dame Cicely Saunders'ın *"her bireyin kendine özgü deneyimi, geçmişi, ilişkileri ve kültürü olduğu ve bireyin eşsiz bir varlık olarak saygı görmeye değer olduğu anlayışıyla başlar"* şeklindeki açıklamaları palyatif bakım felsefesini özetlemektedir.[1,4]

Hasta merkezli bakım "paylaşılan karar verme", "hasta odaklılık" ve "toplum ve hasta katılımı" gibi farklı kavramları kapsamakta ve hasta ile ilgili tüm girişimlerde veya sağlık sorunlarının yönetiminde hasta ve yakınlarının karar verme sürecine dâhil edilmesini, sağlık profesyonelleri ile hasta arasında ortak kararlar almayı ifade etmektedir.[5,6] Hasta merkezli bakım hastayı bireysel tercihleri olan bir bütün olarak değerlendirip ele alır. Hastaların tercihlerini, değerlerini ve gereksinimlerini tanımlamak ve bunlara saygı duymak; uygun tedavi ve bakıma ulaşmalarını sağlamak; fiziksel ve duygusal iyilik hallerini sürdürmek; alınacak tüm kararlarda hasta ve yakınları arasında iş birliğini desteklemek ve hasta savunuculuğu yapmak hasta merkezli bakımın temel ilkeleridir.[7-9] Literatürde hasta-merkezli bakımın, kaliteli bakımın temel bir özelliği olarak kabul edilmekte, hasta memnuniyetini geliştirdiği ve sağlık erişimindeki eşitsizlikleri azaltarak sağlık çıktılarına olumlu katkı sağladığı bildirilmektedir.[10-13] Hasta merkezli bakım, sağlık bakım hizmetlerinde kaliteyi geliştirme ve hasta güvenliğinin sağlanmasında önem kazanan yaklaşımlar arasında olup hemşirelik eğitimlerinde temel bir yetkinlik olarak belirtilmektedir.[14]

Bakım, hemşirenin bağımsız fonksiyonu ve en önemli işlevidir. Hemşirelik bakımı, günümüzde önemi gittikçe artan sağlık hizmetlerindeki kalitenin temel göstergelerindendir. Amerikan Hemşireler Birliği, bakımın kalite belirleyicilerini *"Hastaya mümkün olabilecek en iyi hemşirelik bakımını sağlamada yer alan aktiviteler"* olarak bildirmektedir. Hemşirelikte bakımın kalitesi, hasta bakım ve tedavi süreçlerinde güvenli bir bakım ortamının oluşturulması ve hasta gereksinimlerinin diğer ekip üyeleriyle iş birliği halinde bütüncül olarak karşılanmasını ifade eder.[15,16] Bu bağlamda palyatif bakımda hemşirelik bakım kalitesini etkileyebilecek bir faktör olarak hasta merkezli bakım yetkinliğinin değerlendirilmesinin önemli olduğu düşünülmüştür. Bununla birlikte hemşirelik bakım yaklaşımlarının tanımlanmasının palyatif bakım kalitesinin iyileştirilmesi ve geliştirilmesine katkıda bulunabileceği öngörülmüştür.

YÖNTEM

Araştırma Tasarımı ve Amacı

Tanımlayıcı ve kesitsel tipte olan bu araştırmada palyatif bakım veren hemşirelerin hasta merkezli bakım yetkinliğinin bakım kalitesine etkisinin belirlenmesi amaçlanmıştır.

Araştırmanın Evren ve Örneklemi

Araştırmanın evrenini Haziran-Ağustos 2023 tarihleri arasında İzmir İl Sağlık Müdürlüğü'ne bağlı sağlık kurumları bünyesindeki palyatif bakım birimlerinde aktif olarak görev yapan 248 palyatif bakım hemşiresi oluşturmuştur. Araştırmanın örneklem büyüklüğü %90 güç, 0,15 (orta) etki büyüklüğü ve %5 tip 1 hata düzeyi kabul edilerek hesaplandığında en az 130 bireye ulaşılması gerektiği saptanmıştır. Bu kapsamda araştırmanın yürütüldüğü kurumlarda Haziran-Ağustos 2023 tarihleri arasında aktif olarak görev yapan, akıllı telefon kullanan ve araştırmaya katılmaya gönüllü 130 palyatif bakım hemşiresi çalışmaya dahil edilmiştir. Çalışma verileri, kartopu örnekleme yöntemi kullanılarak ve WhatsApp uygulaması üzerinden toplanmıştır.

Veri Toplama Araçları

Kişisel Bilgi Formu: Araştırmacılar tarafından literatür taraması sonucunda hazırlanmış olan bu formda palyatif bakım hemşirelerinin yaş, cinsiyet, eğitim durumu, mesleki çalışma süresi, birimde çalışma süresi ve haftalık çalışma süresine ilişkin sorular yer almaktadır.[6,14]

Hasta Merkezli Bakım Yetkinliği Ölçeği (HMBYÖ): Hwang[6] (2015) tarafından geliştirilen ölçeğin, Türk toplumu için uyarlama çalışması Arslanoğlu ve Kırılmaz[17] (2019) tarafından yapılmıştır. Ölçek, "hasta bakış açılarına (perspektifine) saygı duymak" (6 madde), "bakım süreçlerinde hasta katılımını teşvik etmek" (5 madde), "hasta konforu sağlamak" (3 madde) ve "hastaların haklarını savunmak" (3 madde) olmak üzere 4 alt boyut ve 17 maddeden oluşmaktadır. Beşli Likert tipte olan ölçekte "(1) kesinlikle katılmıyorum" ve "(5) kesinlikle katılıyorum" ifadeleri arasında değişen bir sıklık aralığı kullanılmaktadır. Arslanoğlu ve Kırılmaz[17] (2019) tarafından yapılan çalışmada ölçeğin tamamı için Cronbach alfa katsayısı 0,85 olarak bildirilmiştir. Bu çalışmada ölçek Cronbach alfa katsayısı ise 0,99 olarak hesaplanmıştır.

Hemşireler için Palyatif Bakım Kalitesi Ölçeği (HİPBK): Zulueta Egea ve ark.[18] (2020) tarafından geliştirilmiş ve Mollaoğlu ve Boy[19] (2023) tarafından Türkçe geçerlik ve güvenirlik çalışması yapılmıştır. Alt boyutları bulunmayan ve toplam puan üzerinden değerlendirilen ölçekten en az 18 puan ve en çok ise 90 puan alınabilmektedir. Ölçekten alınan puanların artması hemşireler tarafından verilen palyatif bakımın kaliteli olduğunu göstermektedir. Mollaoğlu ve Boy[19] (2023) çalışmalarında ölçek Cronbach alfa katsayısı 0,92 olarak hesaplanmıştır. Bu çalışmada ise tespit edilen ölçek Cronbach alfa katsayısı 0,97'dir.

Verilerin Toplanması

Araştırma verileri Haziran-Ağustos 2023 tarihleri arasında toplanmıştır. Araştırmada veri güvenliğinin sağlanmasına yönelik araştırmacılar tarafından güvenilir çevrimiçi anket oluşturma bağlantıları incelenmiş ve veri toplama formlarının "surveey.com" bağlantısı üzerinden düzenlenmesine karar verilmiştir. Formlara ilişkin bağlantı adresi başlangıçta İzmir İl Sağlık Müdürlüğü'ne bağlı ve palyatif bakım kliniklerinin bulunduğu hastanelerde yönetici hemşireler ile WhatsApp uygulaması üzerinden paylaşılmıştır. Yönetici hemşireler bulundukları kurumlarda hizmet yapmakta olan palyatif bakım hemşireleri ile veri toplama formlarına ilişkin bağlantı adreslerinin paylaşılması hususunda teşvik edilmiştir. Örnekleme ulaşmada kullanılan kartopu örnekleme yöntemi verilerin toplanmasında hızlı ve maliyet etkin bir yöntem olup, daha geniş kitlelere ulaşmaya olanak sağlamaktadır.[20] Katılımcılar araştırma formlarının yanıtlanmasından önce çalışmanın amacı ve kapsamı hakkında bilgilendirilmiş ve onayları alınmıştır. Araştırma verileri, araştırmacılar tarafından günlük olarak yedeklenmiş, tekrarlı veri girişinin önlenmesi için IP denetlenmesi sağlanmıştır.

Verilerin Analizi

Araştırma verilerinin analizinde Statistical Package for Social Sciences (SPSS) 25.0 (SPSS statistics for Windows, version 25.0, IBM Corp. Armonk, NY) paket programından yararlanılmıştır. Verilerin değerlendirilmesinde tanımlayıcı istatistikler (sayı, yüzde, ortalama, standart sapma, minimum, maksimum) kullanılmıştır. Kullanılan parametrelerin normal dağılım gösterip göstermediği çarpıklık basıklık katsayıları dikkate alınarak incelenmiştir. Buna göre araştırmada kullanılan ölçeklere ilişkin çarpıklık ve basıklık katsayılarının -2 ve +2 aralığında olduğu tespit edilmiş ve dağılımın normal olduğu kabul edilmiştir.[21] Nicel değişkenler arasındaki ilişki Pearson korelasyon katsayısı kullanılarak değerlendirilmiştir. İstatistiksel önemlilik için $p<0,05$ ve ve $p<0,001$ anlamlılık düzeyleri kabul edilmiştir.

Araştırmanın Etik Yönü

Araştırmanın yürütülebilmesi için, İzmir Bakırçay Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'ndan (karar no: 997, tarih: 26.04.2023), İzmir İl Sağlık Müdürlüğü Sağlık Hizmetleri, İlaç ve Tıbbi Cihaz Hizmetleri Başkanlığı Arge ve Sağlık İnovasyonu Birimi Araştırma İzin Taleplerini Değerlendirme Komisyonu'ndan (16.06.2023 ve 2023/60 karar sayılı), araştırma verilerinin toplanmasında kullanılan ölçeklerin Türk toplumu için uyarlama çalışmalarını yapan yazarlardan ve araştırmaya katılan bireylerden gerekli izinler alınmıştır. Çalışmada yer alan katılımcılardan anket formlarının cevaplandırılmasından önce araştırmanın amaç/kapsamı hakkında bilgilendirilmiş onamları alınmıştır. Araştırma Helsinki Bildirgesi'ne uygun olarak gerçekleştirilmiştir.

BULGULAR

Araştırmaya katılan hemşirelerin tanımlayıcı özellikleri Tablo 1'de gösterilmiştir. Hemşirelerin çoğunluğunun kadın (%94,6) ve eğitim durumunun lisans seviyesinde (%88,5) olduğu, yarıdan fazlasının meslekte çalışma sürelerinin (%65,4) 10 yılın üzerinde ve palyatif bakım kliniğinde çalışma deneyimlerinin (%50,8) 3 yılın üzerinde olduğu belirlenmiştir. Araştırmada yer alan palyatif bakım hemşirelerinin çoğunluğu haftalık çalışma saatlerinin (%74,6) 40 saatin üzerinde olduğunu bildirmiştir (Tablo 1).

Palyatif bakımda görev alan hemşirelerin HMBYÖ'den aldıkları toplam puan ve alt boyut puan ortalamaları ile HİPBK toplam puan ortalamaları Tablo 2'de sunulmuştur. Hemşirelerin HMBYÖ toplam puan ortalamaları 4,02±1,04; hasta bakış açılarına (perspektifine) saygı duymak alt boyut puan ortalaması 4,01±1,05; bakım süreçlerinde hasta

katılımını teşvik etmek alt boyut puan ortalaması 4,01±1,05; hasta konforu sağlamak alt boyut puan ortalaması 4,08±1,11; hastaları haklarını savunmak alt boyut puan ortalaması 3,98±1,08; HİPBK'den aldıkları toplam puan ortalaması ise 74,80±11,98 olarak belirlenmiştir (Tablo 2).

Hemşirelerin HMBYÖ ve HİPBK puan ortalamaları arasındaki ilişkiler Tablo 3'te gösterilmiştir. Hemşirelerin HİPBK puan ortalamaları ile HMBYÖ alt boyutlarından hasta bakış açılarına (perspektifine) saygı duymak alt boyutu (r=0,313; p<0,001); bakım süreçlerinde hasta katılımını teşvik etmek alt boyutu (r=0,305; p<0,01); hasta konforu sağlamak alt boyutu (r=0,325; p<0,001) ve hastaları haklarını savunmak alt boyutu (r=0,314; p<0,001) puan ortalamaları arasında ve ölçek toplam puanı (r=0,319; p<0,001) arasında pozitif yönlü orta düzeyde istatistiksel olarak anlamlı bir ilişki tespit edilmiştir (Tablo 3).

TARTIŞMA

Hasta merkezli bakım, sağlık kurumlarında kaliteli bakım hizmetinin sunulmasında önemli bir yaklaşımdır.[22] Hasta merkezli bakımının sağlık çıktılarına ve bakım giderlerinin azaltılmasına olumlu katkıda bulunduğu bildirilmektedir.[23] Kronik hastalıklar ve bunların karmaşık semptom yükü tüm toplumlarda yaygınlaştıkça, hasta merkezli bakım, özellikle yaşam sonu da dahil olmak üzere palyatif bakım bağlamında giderek önem kazanmıştır.[24] Tanı anından itibaren erken dönemde sağlanan hasta merkezli palyatif bakım hizmetleri, tedavi ve bakımın planlanmasında

Tablo 1. Katılımcıların tanımlayıcı özellikleri (n=130)

Tanımlayıcı özellikler		**Ortalama±SS**	**Minimum-maksimum**
Yaş (yıl)		36,69±7,5	24,00-53,00
		n	**%**
Cinsiyet	Kadın	123	94,6
	Erkek	7	5,4
Eğitim durumu	Sağlık meslek lisesi	4	3,1
	Lisans	115	88,5
	Lisansüstü	11	8,5
Meslek yılı	1-5 yıl	26	20,0
	6-10 yıl	19	14,6
	>10 yıl	85	65,4
Palyatif bakım kliniğinde çalışma süresi	6 ay-1 yıl	18	13,8
	1-2 yıl	19	14,6
	2-3 yıl	27	20,8
	>3 yıl	66	50,8
Haftalık çalışma saati	40 saat	33	25,4
	>40 saat	97	74,6

SS: Standart sapma

Tablo 2. Katılımcıların Hasta Merkezli Bakım Yetkinliği Ölçeği ve Hemşireler için Palyatif Bakım Kalitesi Ölçeği puan ortalamaları (n=130)

Ölçekler		**Ortalama±SS**	**Minimum-maksimum**
Hasta Merkezli Bakım Yetkinliği Ölçeği toplam		4,02±1,04	1,00-5,00
Ölçek alt boyutları	Hasta Bakış Açılarına (Perspektifine) Saygı Duymak	4,01±1,05	1,00-5,00
	Bakım Süreçlerinde Hasta Katılımını Teşvik Etmek	4,01±1,05	1,00-5,00
	Hasta Konforu Sağlamak	4,08±1,11	1,00-5,00
	Hastaları Haklarını Savunmak	3,98±1,08	1,00-5.00
Hemşireler için Palyatif Bakım Kalitesi toplam		74,80±11,98	33,00-90,00

SS: Standart sapma

Tablo 3. Hemşirelerin Hasta Merkezli Bakım Yetkinliği Ölçeği ve Hemşireler için Palyatif Bakım Kalitesi Ölçeği puan ortalamaları arasındaki ilişki (n=130)

Değişkenler	**Hemşireler için Palyatif Bakım Kalitesi Ölçeği**	
Hasta Merkezli Bakım Yetkinliği Ölçeği	**r**	**p**
Hasta Bakış Açılarına (Perspektifine) Saygı Duymak	0,313**	0,000*
Bakım Süreçlerinde Hasta Katılımını Teşvik Etmek	0,305	0,000
Hasta Konforu Sağlamak	0,325	0,000
Hastaların Haklarını Savunmak	0,314	0,000
Toplam	0,319	0,000

**p<0,001; r: Pearson korelasyon katsayısı

rehber niteliğinde olup bireylerin yaşam kalitelerinin korunmasında esastır.[25,26] Hasta merkezli palyatif bakımın hasta ve yakınlarının gereksinimlerinin bütüncül ve etkili bir şekilde karşılanmasında, gelecekteki uygulamalar ile ilgili net kararlar alınmasında ve gereksiz hastane yatışlarının azaltılmasında etkili olduğu bildirilmektedir.[27]

Palyatif bakım kliniklerinde görev alan hemşirelerin hasta merkezli bakım yetkinliğinin bakım kalitesine etkisinin değerlendirildiği bu çalışmada, hemşirelerin hasta merkezli bakım yetkinliklerinin yüksek düzeyde olduğu belirlemiştir. Literatürde hemşirelerle yürütülen ve hasta merkezli bakım yetkinliğinin değerlendirildiği çalışmalarda benzer sonuçlar elde edilmiştir.[27-30] Çalışmada hemşirelerin, HMBYÖ hasta konforu sağlamak alt boyutundan en yüksek puan ortalamasını alırken, hasta haklarını savunmak alt boyutundan en düşük puan ortalamasına sahip oldukları görülmüştür. Sançar ve ark.'nın[27] (2023) cerrahi hemşireleri ile; Pakkonen ve ark.'nın[30] (2023) geriatrik hastalara bakım veren hemşirelerle yürüttükleri çalışmaların sonuçlarında da katılımcıların hasta konforu sağlamak alt boyut puan ortalamalarının yüksek olduğu bildirilmiştir. Hasta konforunu sağlamak alt boyutu, hastaların ağrı, rahatsızlık gibi semptomlarının değerlendirilmesi ve giderilmesi, fiziksel ve duygusal rahatlık düzeylerinin değerlendirilmesi ve hasta beklentilerinin sorgulanarak karşılanması gibi hemşirelik uygulamalarını kapsamaktadır. Palyatif bakım gereksinimi olan hastalar için ağrı, en sık bildirilen (%70-90), fiziksel, duygusal ve psikolojik bileşenleri nedeniyle korkutucu ve ıstırap verici bir semptomdur ve özellikle yaşamın son dönemindeki hastaları sıklıkla etkilemektedir.[31,32] Palyatif bakımda uygun değerlendirmeler ve hasta gereksinimlerinin saptanması ile ağrının tedavi ve bakım yönetimi sağlanabilmektedir.[33] Hemşirelik disiplini hastanın fizyolojik, psikolojik ve ruhsal rahatlık elde etmelerini sağlamak üzere hasta bakımına yönelik uygulamaları içerir. Palyatif bakımda hemşirelerin bütüncül yaklaşımla birey ve ailenin gereksinimlerini belirlemeleri, karşılanmamış bakım gereksinimlerine yönelik destekleyici bakım yaklaşımlarını uygulanmaları ve optimum düzeyde hasta konforunu sağlamaları, yaşam kalitesine katkı sağlayacak yaklaşımlardır.[34,35]

Çalışmada hemşirelerin HİPBKÖ puan ortalamalarının yüksek düzeyde olduğu belirlenmiştir. Palyatif bakım profesyonellerinden oluşan interdisipliner ekip içinde hemşireler, hasta ve ailesinin bakımına ayırdıkları zaman ve hemşirelik bakımının temeli olarak yaşama saygı ve kişinin onuru değerlerinin savunulmasını etik kodlar içerisinde benimsemeleri nedeniyle öncelikli role sahiptir.[35] Palyatif bakımda verilen hemşirelik bakımının kalitesinin değerlendirilmesinin mesleğin profesyonel gelişiminde gerekli olduğu bildirilmekte, rutin bakım uygulamalarında mükemmellik arayışı olarak kabul edilmektedir.[36] Literatürde palyatif bakım kalitesi farklı ölçüm araçlarıyla ve hemşirelik profesyonellerinin bilgi, beceri ve yetkinlikleri üzerinden değerlendirilmiştir. Soikkeli-Jalonen ve ark.'nın[36] (2020) çalışmalarında, hemşirelerin hasta ve ailesinin bakımına yönelik uyguladıkları bakımda bilgi ve beceriye yönelik yetkinliklerini değerlendiren 10 farklı ölçüm aracı saptanmış ve bu araçların değerlendirdikleri alanlar palyatif bakımın genel yönleri, hastanın öz bakıma katılımı, psikososyal destek, maneviyat, bakımın kültürel yönleri, farmakolojik tedavi, semptom yönetimi ve yaşam sonu bakım olarak belirlenmiştir. Çalışmaların genelinde palyatif bakımda uygulanan hemşirelik bakımının kalitesinde iş birliği ve iletişim, kişisel ve mesleki konular, karar verme, bakımın sürekliliği ve örgütsel desteğin önemini vurgulanmıştır.[19,37-39]

Çalışmada hemşirelerin hasta merkezli bakım yetkinlikleriyle palyatif bakım kalitesi arasında ilişki olduğu tespit edilmiştir. Bununla birlikte hasta merkezli bakım yetkinliği kapsamında değerlendirilen, hasta bakış açılarına saygı duyulması, katılımının teşvik edilmesi, konforunun sağlanması ve haklarının savunulması gibi uygulamaların da palyatif bakımın hizmetlerinin kalitesini olumlu etkilediği belirlenmiştir. Literatürde hasta merkezli bakım yetkinliğine sahip hemşirelerin, hasta değerleri ve tercihleri ile uyumlu bireyselleştirilmiş bakım yönetimini sağlamada etkili olabildikleri bildirilmiştir.[39] Bireyselleştirilmiş

bakım, palyatif bakım müdahalelerinin yalnızca etkili olmasını değil, aynı zamanda her hastanın kendine özgü ihtiyaçlarını karşılayacak şekilde düzenlenmesini de sağlayabilmektedir.[40] Çalışmamızda hemşirelerin hasta merkezli bakım yetkinliklerinin yüksek düzeyde olmasının palyatif bakım kalitesini olumlu yönde etkilemesi literatürle uyumludur. Bununla birlikte literatürde hasta ve yakınlarının palyatif bakımda ortak karar verme ve bakıma aktif katılım konusunda teşvik edilmesinin hasta deneyiminin artırılmasında ve olumlu sağlık çıktılarının elde edilmesinde önemli olduğu vurgulanmaktadır.[12-14] Hasta merkezli bakımda yetkin hemşirelerin mevcut palyatif bakım seçenekleri hakkında hasta ve yakınlarına eğitim ve danışmanlık verilmesi, girişimlere yönelik potansiyel sonuçların tartışılması ve hasta hedefleriyle uyumlu kararların iş birliği halinde alınmasında etkin oldukları bildirilmektedir.[11,40] Çalışmamızda hasta bakış açılarına saygı duyma ve katılımı teşvik etme gibi yaklaşımların palyatif bakım kalitesini olumlu etkilediği görülmüştür.

Çalışmanın Kısıtlılıkları

Bu çalışmanın bazı sınırlılıklar bulunmaktadır. Öncelikle çalışma verileri çevirimiçi ortamda toplanmıştır. Bu nedenle elektronik ortamı güvenli bulmayan ya da internet kullanımı/bağlantı sorunları nedeniyle veri toplama formlarına erişemeyen grup örnekleme dahil edilememiştir. İkinci olarak verilerin yüz yüze toplanmaması nedeniyle araştırma konusunun önemi ulaşılması hedeflenen grup tarafından anlaşılmamış olabilir. Bununla birlikte araştırmanın çok merkezli yürütülmesi ve farklı sağlık kurumlarında görev alan palyatif bakım hemşirelerine ulaşılması araştırmanın güçlü yönü olup, sonuçların genellenebilirliğini artırmaktadır.

SONUÇ

Sağlık hizmetlerinin sunumundaki gelişmelerle birlikte, hemşirelik profesyonellerinin rolü, hastaların yalnızca fiziksel gereksinimlerin karşılanmasına yönelik sağlanan bakımla yeterli olmayıp, aynı zamanda benzersiz ihtiyaçlarına, değerlerine ve gereksiimlerine hitap eden bakım uygulamalarının sağlanmasında giderek daha önemli hale gelmiştir. Hemşirelik profesyonellerinin bu ilkeleri benimseyerek uyguladıkları palyatif bakım bireylerin yaşam kalitelerinin artırılmasında fark yaratabilir, yaşamı tehdit eden hastalıklar karşısında konfor, destek ve saygınlık sağlayabilirler. Bu çalışmada hemşirelerin hasta merkezli bakım yetkinliklerinin ve yürüttükleri palyatif bakım hizmetleri kalitesinin yüksek düzeyde olduğu belirlenmiş; hasta merkezli bakım yetkinlikleri ve palyatif bakım kalitesine etkisi olduğu gösterilmiştir. Bu bağlamda lisans ve lisansüstü düzeyde verilen hemşirelik eğitim programlarında ve kurumlarda yürütülen sürekli gelişim faaliyetlerinin, hemşirelerin bu yetkinliklerini kazanmalarına yönelik planlanması ve yürütülmesi önemlidir. Palyatif bakımın sunulduğu merkezlerde multidisipliner ekip tarafından sağlanan hasta merkezli bakımın güçlendirilmesi, sunulan bakımın daha etkin ve insan odaklı hale gelmesine katkı sağlayabilir.

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Original Article / Orijinal Araştırma

Role of COHb Level in Newborns with ABO Blood Group Incompatibility in Predicting Newborn Jaundice Risk

ABO Kan Grubu Uyuşmazlığı Olan Yenidoğanlarda Kord Kan COHb Düzeyinin Yenidoğan Sarılığı Riskini Öngörmedeki Rolü

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ABSTRACT

Objective: Neonates with hyperbilirubinemia are at risk of brain damage, and at least two-thirds of neonates show clinical signs of jaundice in the first week of life. To predict the correlation between cord carboxyhemoglobin (COHb) with postnatal 24th-hour total serum bilirubin (TSB) level in newborns with ABO incompatibility.

Methods: This retrospective cohort study included newborns older than 35 weeks of gestation who were followed up in the Neonatal Intensive Care Unit of Tokat Gaziosmanpaşa University Hospital between January 2019 and December 2023. Patients were divided into three groups; Group 1: ABO incompatibility with direct Coombs (DC) positive newborns, Group 2: ABO incompatibility and DC negative newborns, and Group 3: ABO incompatibility with no known hemolysis risk factors.

Results: A total of 292 patients in 3 groups were included in the study. Group 1 consisted of 93 patients, Group 2 consisted of 99, and Group 3 consisted of 100. The mean newborn cord COHb was 1.59±0.56%, the mean cord bilirubin was 3.12±2.05 mg/dL, the mean 24-h TSB was 6.40±1.99 mg/dL, and the mean cord blood gas hemoglobin was 18.06±2.57 g/dL. In the first group, the correlation between cord COHb and 24-h TSB was high and statistically significant. In the second group, the correlation between cord COHb and 24-h PTH was low and statistically significant.

Conclusion: The use of COHb as a predictor of 24-h postnatal TSB levels in ABO-incompatible neonates is plausible.

Keywords: Neonatal jaundice, COHb, ABO incompatibility, Kernicterus

ÖZ

Amaç: Hiperbilirubinemili yenidoğanlarda potansiyel beyin hasarı riski vardır ve yenidoğanların en az üçte ikisi yaşamlarının ilk haftasında klinik sarılık belirtileri gösterir. ABO uyuşmazlığı olan yenidoğanlarda kord karboksihemoglobin (COHb) ile postnatal 24. saat total serum bilirubin (TSB) düzeyi arasındaki ilişkiyi öngörmeyi hedefledik.

Yöntem: Retrospektif kohort analizi kullanılarak yapılan bu çalışma, Ocak 2019 ile Aralık 2023 tarihleri arasında Tokat Gaziosmanpaşa Üniversite Hastanesi Yenidoğan Yoğun Bakım Ünitesi'nde takip edilmiş 35. gebelik haftasından büyük yenidoğanlar ile gerçekleştirildi. Hastalar üç gruba ayrıldı; Grup 1: ABO uyuşmazlığı ve direkt Coombs (DC) pozitif yenidoğanlar, Grup 2: ABO uyuşmazlığı ve DC negatif yenidoğanlar, Grup 3: ABO uyuşmazlığı olmayan ve bilinen hemoliz risk faktörü olmayan yenidoğanlar.

Bulgular: Çalışmaya 3 grupta toplam 292 hasta dahil edildi. Grup 1, 93 hastadan, Grup 2, 99 hastadan ve Grup 3, 100 hastadan oluşuyordu. Yenidoğan kord COHb ortalaması %1,59±0,56, kord bilirubini ortalaması 3,12±2,05 mg/dL, 24. saat TSB ortalaması 6,40±1,99 mg/dL, kord kan gazındaki hemoglobin ortalaması 18,06±2,57 g/dL olarak belirlendi. Birinci grupta kord COHb ile 24. saat TSB arasındaki korelasyon yüksek ve istatistiksel olarak anlamlıydı. İkinci grupta kord COHb ve 24. saat TSB korelasyonu düşük ve istatistiksel olarak anlamlıydı.

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Sonuç: Bu çalışma, ABO uyuşmazlığı olan yenidoğanlarda doğum sonrası 24. TSB düzeyini tahmin etmede COHb kullanımının akla yatkın olduğu sonucunu ortaya koymaktadır.

Anahtar Kelimeler: Yenidoğan sarılığı, COHb, ABO uyuşmazlığı, Kernikterus

INTRODUCTION

Neonatal jaundice is frequently noted within the first 2 weeks of life and is the most common reason for hospital admission of neonates. As such, it is a major issue for clinicians and families.[1,2] Approximately 5-10% of neonatal jaundice is pathological and requires treatment.[3] Neonatal jaundice is generally a consequence of unconjugated hyperbilirubinemia, a condition that results from a limited ability to conjugate the increased bilirubin levels that occur in the first days of life. Severe cases may lead to serious neurological complications, kernicterus, and even death.[4,5]

The potential risk of bilirubin-induced brain damage underscores the critical importance of early detection of neonatal jaundice.[6,7] Identification of infants at risk of severe hyperbilirubinemia and early diagnosis are critical and can reduce the need for rehospitalization and prevent possible complications.[8,9]

For social, economic, and medical reasons, the duration of post-birth hospitalization among newborns and their mothers has reduced, and early discharge rates have increased. Because this increases the risk of severe hyperbilirubinemia and its complications, various methods are used to predict each infant's risk of neonatal jaundice prior to hospital discharge.[10]

ABO blood group incompatibility is an important risk factor for neonatal jaundice.[11] Bilirubin is a byproduct of heme molecule metabolism. However, in newborns with ABO blood group incompatibility, there is an enzymatic reaction between heme molecules, heme oxygenase, and iron during the breakdown of hemoglobin that causes the release of carbon monoxide (CO) and bilirubin into the body.[12] This catabolism indicates that measurement of carboxyhemoglobin (COHb) levels in cord blood may be a useful tool for detecting risk and early diagnosis of hyperbilirubinemia in newborns.[13]

This study aimed to investigate the correlations between cord blood gas COHb and total serum bilirubin (TSB) levels and ABO blood group incompatibility in newborns at postnatal hour 24 and the neonatal jaundice risk prediction accuracy.

METHODS

This retrospective cohort study included neonates born after >35 weeks of gestation who were hospitalized in the Neonatal Intensive Care Unit at Tokat Gaziosmanpaşa University Hospital between January 2019 and December 2023. The study was conducted with the permission of Tokat Gaziosmanpaşa University Hospital Ethics Committee (date: 18.01.2024, decision no: 83116987-039). Data were collected from patient medical records. Three patient groups were analyzed. Group 1 comprised patients with ABO blood group incompatibility between mothers and infants and positive direct Coombs (DC) results in newborns. Group 2 comprised patients with ABO blood group incompatibility and DC-negative newborns. Group 3 comprised patients without known ABO blood group incompatibility and hemolysis risk factors.

Exclusion criteria:

1. Maternal thyroid function test abnormalities;
2. Inadequate oral intake;
3. Congenital anomalies;
4. Sepsis or suspected sepsis;
5. Rh incompatibility;
6. Glucose-6-phosphate deficiency;
7. Incomplete patient data;
8. Hospitalization beyond postnatal hour 24;
9. Metabolic disorder.

Inclusion criteria:

1. Delivery after 35 week gestation;
2. ABO-incompatible neonates with or without positive results on a DC test;
3. Newborns without possible jaundice, such as those with transient respiratory tachypnea and congenital pneumonia, were included as a control group;
4. Delivery took place in our hospital;
5. TSB measurement 24 hours after birth and cord blood gas analysis at birth;
6. Complete patient data.

Only patients with blood ABO blood group incompatibility were included. Patients with other causes of hemolysis were excluded to reduce possible variables affecting outcomes. The use of phototherapy was based on the guidelines of the Turkish Neonatal Society and the American Academy of Pediatrics.[14,15]

Demographic, clinical, and pathological information included sex, gestational age, birth weight, cord blood gas values (COHb, Hb, hematocrit, and bilirubin), TSB measured at the 24th hour, DC test result, mode of delivery, and whether or not phototherapy was administered.

Among patients whose TSB levels identified them as having a medium-high risk of jaundice, we determined whether they had received phototherapy based on the record of their daily progress reports.

Blood bilirubin was measured using an ABL 800 Flex (Danaher Corp., Washington DC, USA) (195 µL). TSB was measured using a Roche Diagnostics COBAS six thousand AutoAnalyzer (Roche Diagnostics, Indianapolis, IN, USA).

Statistical Analysis

Quantitative variables were presented as mean and standard deviation and qualitative variables as number (n) and percentage (%). Differences in quantitative measurements between independent groups were determined using one-way analysis of variance (ANOVA). Qualitative values were analyzed using chi-square tests. Tukey's honestly significant difference test and Tamhane's T2 test were used for multiple comparisons. Pearson's correlation coefficient was used to identify relationships between quantitative variables. Receiver operating characteristics (ROC) curves were applied to determine the cut-off values of the variables by group; the area under the curve (AUC) was also evaluated. P values <0.05 were considered statistically significant. All analyses were performed using Statistical Package for Social Sciences (SPSS) v.22. statistical software (SPSS Inc., IBM Corp., Armonk, NY, USA).

RESULTS

A total of 292 patients were included in the study. Group 1 (ABO incompatibility and positive DC) comprised 93 patients, Group 2 (ABO incompatibility and negative DC) comprised 99 patients, and group 3 (no known risk factor for blood incompatibility) comprised 100 patients.

Of the 292 patients, 161 (55.8%) were male and 129 (44.2%) were female. There were 199 (68.2%) patients with negative neonatal DC test results, 29 (9.9%) with 1+ results, 42 (14.4%) with 2+ results, 21 (7.2%) with 3+ results, and 1 (0.3%) with a score of 4+ on the DC test. Among the deliveries, 255 (87.3%) were cesarean section (C/S) and 37 (12.7%) were normal vaginal deliveries. Among the included patients, 174 (59.6%) received phototherapy while 118 (40.4%) did not (Table 1).

The mean gestational week at birth was 37.27 (±1.63) and the mean birth weight was 3036.65 (±548.12) g. The mean newborn cord COHb level was 1.59 (±0.56)%, the mean cord bilirubin level was 3.12 (±2.05) mg/dL, and the mean 24-hour TSB level was 6.40 (±1.99) mg/dL. The mean cord blood gas concentration (Hb) was 18.06 (±2.57) g/dL, and the mean cord heart rate (HTH) was 54.57 (±7.95)% (Table 2).

In Group 1, there was a strong significant correlation between cord COHb and 24-h TSB (p<0.001*, r=0.603). In Group 2, there was a weak but significant correlation between cord COHb and 24-h TSB (p<0.001*, r=0.378). In Group 3, there was no correlation between cord COHb and 24-h TSB (p=0.675, r=0.042).

ROC analysis of cord COHb and 24-h TSB in Group 1 revealed a significant relationship (p<0.001). The threshold

Table 1. Distributions of qualitative values (n=292)

		n	%
Group	1. Group	93	31.8
	2. Group	99	33.9
	3. Group	100	34.2
Sex	Male	163	55.8
	Female	129	44.2
Neonatal direct Coombs	Negative	199	68.2
	1+	29	9.9
	2+	42	14.4
	3+	21	7.2
	4+	1	0.3
Mode of delivery	C/S	255	87.3
	NVD	37	12.7
Phototherapy	No	118	40.4
	Yes	174	59.6

N: Number, %: Percent, +: Positive.
C/S: Cesarean section, NVD: Normal vaginal delivery

Table 2. Distributions of quantitative measures (n=292)

	Average	Standard deviation	Minimum	Maximum
Gestational week	37.27	1.63	33.00	42.00
Birth weight (grams)	3036.65	548.12	2000.00	5000.00
Cord COHb (%)	1.59	0.56	0.10	3.70
Cord bilirubin (mg/dL)	3.12	2.05	0	10.40
24th hour TSB (mg/dL)	6.40	1.99	1.00	11.80
Cord HB (gr/dL)	18.06	2.57	10.10	25.30
Cord HTC (%)	54.57	7.95	30.30	77.10

N: Number, %: Percent, Cord HB: Cord hemoglobin, Cord HTC: Cord hematocrit, mg/dL: Milligram/deciliter, TSB: Total serum bilirubin, COHb: Carboxyhemoglobin

value of cord COHb was 1.8%. The specificity and sensitivity were 100% and 54.88, respectively (Figure 1). There was also a significant relationship between these two variables in Group 2 ($p<0.009$). In this group, the threshold cord COHb level was 1.7%. The specificity and sensitivity were 80.39% and 45.83%, respectively (Figure 2).

The relationship between cord COHb level and receipt of phototherapy treatment was analyzed in Group 1, and a moderately significant correlation was found ($p<0.001$, $r=0.568$).

The number of patients in groups 1, 2, and 3 whose cord blood gas bilirubin and subsequent TSB levels exceeded 5 mg/dL were 18 (19%), 14 (14%), and 6 (6%) patients, respectively.

DISCUSSION

We found a significant correlation between cord COHb levels and 24-h TSB levels in newborns with ABO incompatibility. This correlation was significant regardless of whether the patient had a positive DC test result although it was stronger in those with positive DC results.

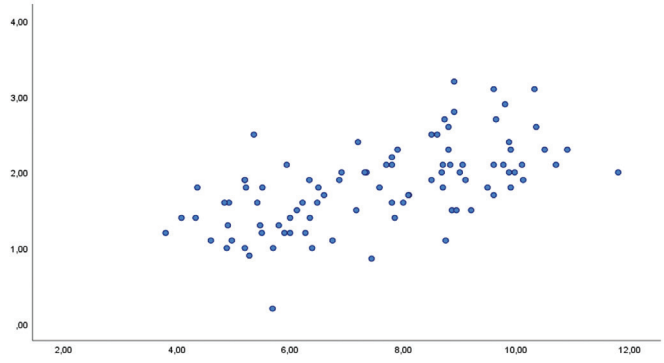

Figure 1. The scatter plot shows the relationship between the cord capillary tube COHb level (vertical axis) and 24th-hour TSB (horizontal axis) in Group 1

TSB: Total serum bilirubin, COHb: Carboxyhemoglobin

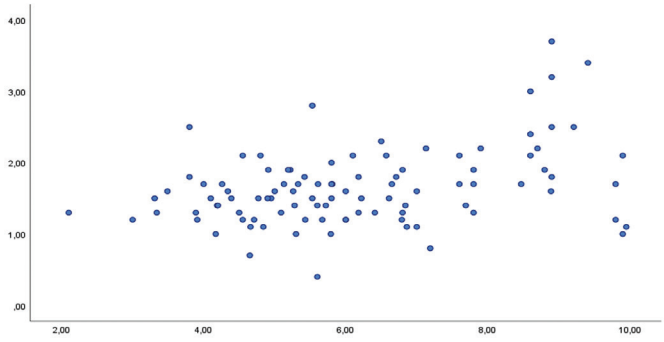

Figure 2. The scatter plot shows the relationship between the cord capillary tube COHb level (vertical axis) and 24th-hour TSB (horizontal axis) in Group 2

TSB: Total serum bilirubin, COHb: Carboxyhemoglobin

A 2021 study by Tıraş et al.[16] divided patients into the same three groups as in the present study to determine whether cord blood COHb levels can be used as a predictor of severe hyperbilirubinemia in jaundiced term neonates with and without positive DC test results. However, the authors did not find COHb levels to be a better predictor than the DC test of severe hyperbilirubinemia in term infants. The differing results between this study and ours may be due to the higher number of patients in the present study.

There are numerous national and international recommendations and guidelines and a plethora of studies on the early detection and monitoring of hyperbilirubinemia.[17] For example, the approach, follow-up, and treatment guidelines for neonatal jaundice were revised by the Turkish Neonatology Association in 2023. Hyperbilirubinemia can cause severe and irreversible brain damage in newborns. To define physiological-pathological jaundice, it is important to consider the gestational and postnatal ages of the infant, assess the risks, and evaluate TSB hourly using the bilirubin nomogram. Although progress has been made in neonatal health in recent years, some health system-related problems remain. These include high C/S rates, early discharge after birth (less than 24 hours), inadequate checkup policies for 48 hours after discharge, and checks performed by family physicians with insufficient knowledge of neonatal health.[14] For these reasons, we aimed to analyze the use of cord COHb as a potential risk predictor of neonatal jaundice.

TSB levels are currently the gold standard for diagnosing neonatal jaundice. According to the bilirubin nomogram, bilirubin values should be interpreted according to the patient's age in hours. This nomogram allows us to monitor changes in bilirubin values over time and predict the development of hyperbilirubinemia. However, adequate samples are not always obtained, and the procedure can be uncomfortable or painful for patients. An alternative method for measuring bilirubin levels at the bedside is the capillary tube method, which requires only a small blood sample. This method is less painful and more accessible. Bilirubin can also be measured on the skin surface using transcutaneous bilirubin measurement, eliminating the need for a blood sample. The ubiquitous use of this method decreased the incidence of severe hyperbilirubinemia and rehospitalization for phototherapy treatment. However, this method is unreliable for newborns receiving phototherapy and for those with darker skin.[18]

ABO blood group incompatibility is one of many conditions that can cause neonatal hyperbilirubinemia. COHb and

bilirubin, which are produced as a result of the catabolism of hemoglobin, can be measured concurrently by blood gas analysis. A recent study investigated the relationship between cord COHb levels and severe hyperbilirubinemia. The study found that cord COHb can be used for the early diagnosis and treatment of hemolysis. When the cord COHb cut-off value was set at 2.2%, the authors found a sensitivity of 80.8% and a specificity of 95.5% in its ability to predict severe hyperbilirubinemia.[19] In our study, a cord COHb cut-off value of 1.8% in patients with ABO blood incompatibility who were also DC-positive produced a specificity of 100% and sensitivity of 54.88%. A cord COHb cut-off value of 1.7% in patients with ABO blood incompatibility that were also DC-negative produced a sensitivity of 80.39% and specificity of 45.83%. In a similar study, the correlation between cord COHb levels and TSB levels during follow-up in patients with ABO blood group incompatibility and DC test positivity was found to be significantly higher compared with the control group.[11] The findings of this study are consistent with the present findings.

Lozar-Krivec et al.[20] found that newborns with ABO blood group incompatibility who were later diagnosed with hyperbilirubinemia had significantly higher cord COHb values than those without ABO blood group incompatibility. In the same study, a cord COHb cut-off value of 1.7% for confirming hemolysis in ABO alloimmunization of 1.7% resulted in 72% sensitivity and 97% specificity.[20] This cord COHb cut-off value was close to our own but had a pronounced difference in sensitivity and specificity. While sensitivity was higher in our study, specificity was significantly higher in their study.

Guney Varal et al.[21] found that newborns who received phototherapy treatment upon admission had significantly higher cord COHb levels than those who did not receive treatment. This trend continued in the following hours. They also found a positive correlation between the first and subsequent cord COHb levels and TSB and that direct antiglobulin test positivity significantly affected the need for phototherapy. They showed that cord COHb levels ≥0.95% had a sensitivity of 90% and a specificity of 88% in terms of the need for phototherapy (TSB ≥95% percentile). Although the cord COHb cut-off value was much lower than that of our study, they achieved high sensitivity and specificity.

Blood CO can be measured invasively from cord blood gas, and end-tidal CO corrected for inhaled CO concentration (ETCOc) can be measured noninvasively. In our study, COHb levels were measured using an invasive method. We compared our study data with that of previous research using the ETCOc method. In a study by Christensen et al.[22] based on ETCOc measurements, 11 of 100 patients had ABO blood incompatibility. None of the 100 were rehospitalized for jaundice treatment compared with 2.99 rehospitalizations per 100 control neonate who had TSB values >75th percentile. Bhutani et al.[23] measured ETCOc and TSB in 641 newborns 30 (±6) hours before discharge and in patients with ETCOc ≥1.7 ppm. TSB was significantly higher. These two studies using ETCOc had different COHb results from one another, with Christensen et al.[22] finding results that differed from our own and Bhutani et al.[23] producing similar outcomes to ours.

Maisels and Kring[24] the relationship between TSB and ETCO levels between the first and fifth days of life in patients diagnosed with neonatal jaundice and 164 healthy newborns. A positive correlation was found for ETCO based on the 75th percentile of TSB, and a statistically significant difference was observed between the two groups. The study also found a positive relationship between newborn COHb levels measured by ETCO and TSB levels.

Bhatia et al.[25] found that hemolysis was more commonly observed in babies with an ETCOc ≥1.8 ppm than those with an ETCOc <1.8 ppm. This was linked to higher TSB levels, a rapid increase in TSB, and longer phototherapy duration. ETCOc values can be used as an indicator of hemolysis and a predictor of significant hyperbilirubinemia development in newborns. Although the CO measurement method was different, our results suggest that COHb and ETCOc measurements are similarly effective in predicting the risk of neonatal jaundice.

Study Limitations

Our study has some limitations. Newborns born at less than 35 weeks' gestation were excluded. Only hemolysis patients with ABO blood group incompatibility were examined, and the data were gathered retrospectively. A more comprehensive prospective study is needed to verify our findings.

CONCLUSION

We found the cord blood gas COHb level to be a meaningful parameter for predicting the TSB level within the first 24 hours after birth in DC-positive and DC-negative patients with ABO incompatibility. The accuracy of hyperbilirubinemia prediction using COHb levels needs to be verified in further research, which should investigate causes beyond ABO incompatibility.

Ethics

Ethics Committee Approval: The study was conducted with the permission of Tokat Gaziosmanpaşa University Hospital Ethics Committee (date: 18.01.2024, decision no: 83116987-039).

Informed Consent: Because the study was designed retrospectively, no written informed consent forms were obtained from the patients.

Authorship Contributions

Surgical and Medical Practices: K.D., Ş.T., Concept: K.D., Ş.T., Design: K.D., Ş.T., Data Collection or Processing: K.D., Ş.T., Analysis or Interpretation: K.D., Ş.T., Literature Search: K.D., Ş.T., Writing: K.D.

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

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Original Article / Orijinal Araştırma

View of Perceived Symptoms Associated with Chemotherapy-induced Peripheral Neuropathy in Patients with Breast Cancer: A Cross-sectional Study

Meme Kanseri Hastalarında Kemoterapiye Bağlı Periferik Nöropati ile İlişkili Algılanan Semptomlara Bir Bakış: Kesitsel Bir Çalışma

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ABSTRACT

Objective: This cross-sectional study aimed to assess the perceived chemotherapy-induced peripheral neuropathy (CIPN) symptoms in patients with breast cancer who received taxane-based chemotherapy.

Methods: A total of 74 patients with breast cancer who underwent taxane-based chemotherapy were screened and invited to participate in this study. Perceived symptoms of CIPN were assessed via the European Organization for Research and Treatment of Cancer-Chemotherapy Induced Peripheral Neuropathy (EORTC-CIPN20) questionnaire after the completion of systemic treatment within a month and a half. Sensory, motor, and autonomic subscale scores were calculated and analyzed for each patient.

Results: This study included 52 patients with breast cancer. The mean total exposure dose was 2093.92±1266.22 mg. The rates of adjuvant and neoadjuvant chemotherapy were similar (n=25 vs. n=27). Most patients underwent breast-conserving surgery (65.4%). The types of chemotherapy regimen were combined anthracycline and paclitaxel (n=28), docetaxel (n=14), and combined anthracycline, pertuzumab, trastuzumab, and docetaxel (n=10). Patients who underwent modified radical mastectomy had significantly higher scores in the perceived symptoms of CIPN motor function subscale of EORTC-CIPN20 (z=-2.838, p=0.005). The autonomic subscale of EORTC-CIPN20 was significantly correlated with age (r=-0.373, p=0.006) and with the total exposure dose of chemotherapy (r=0.295, p=0.034).

Conclusion: The type of surgery, specifically MRM, which has been emphasized as a contributing factor to CIPN, should be taken into consideration for further potential deterioration. By this means, it is reasonable to state that not only ongoing monitoring of the CIPN is of utmost importance, but also potential contributors to the management of the CIPN are of great importance.

Keywords: Breast cancer, chemotherapy, taxane, peripheral neuropathy

ÖZ

Amaç: Bu kesitsel çalışmanın amacı, taksan bazlı kemoterapi uygulanan meme kanserli hastalarda algılanan kemoterapi ilişkili periferik nöropati (CIPN) semptomlarını değerlendirmektir.

Yöntem: Taksan bazlı kemoterapi uygulanan toplam 74 meme kanseri hastası tarandı ve bu çalışmaya katılmaya davet edildi. Algılanan CIPN semptomları, sistemik tedavilerinin bir buçuk ay içinde tamamlanmasının ardından Avrupa Kanser Araştırma ve Tedavi Örgütü-Kemoterapiye Bağlı Periferik Nöropati (EORTC-CIPN20) anketi aracılığıyla değerlendirildi. Her hasta için duyusal, motor ve otonom alt ölçek puanları hesaplandı ve analiz edildi.

Bulgular: Bu çalışma 52 meme kanseri hastası ile tamamlandı. Ortalama maruz kalınan toplam doz 2093,92±1266,22 mg idi. Adjuvan ve neoadjuvan kemoterapi oranı benzerdi (n=25 vs. n=27). Hastaların çoğu meme koruyucu cerrahi geçirmiş idi (%65,4). Kemoterapi rejimi sırasıyla kombine antrasiklin ve

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paklitaksel (n=28), dosetaksel (n=14) ve kombine antrasiklin, pertuzumab, trastuzumab ve dosetaksel (n=10) idi. Modifiye radikal mastektomi (MRM) uygulanan hastalar, EORTC-CIPN20'nin motor fonksiyon alt ölçeğinin algılanan semptomlarında anlamlı derecede daha yüksek skorlar gösterdi (z=-2,838, p=0,005). EORTC-CIPN20'nin otonomik alt ölçeği yaş ile (r=-0,373, p=0,006) ve maruz kalınan toplam kemoterapi dozuyla (r=0,295, p=0,034) anlamlı korelasyon gösterdi.

Sonuç: CIPN'ye katkıda bulunan bir faktör olarak kendini gösteren ameliyat türünde, özellikle MRM, daha fazla potansiyel kötüleşme için dikkate alınmalıdır. Bu sayede, sadece CIPN'nin sürekli takibinin değil, aynı zamanda CIPN'ye katkıda bulunan potansiyel faktörlerin yönetiminin de büyük önem taşıdığını belirtmek makul olacaktır.

Anahtar Kelimeler: Meme kanseri, kemoterapi, taksanlar, periferal nöropati

INTRODUCTION

Breast cancer (BC) is the most common type of cancer observed in women worldwide. The reported incidence of BC nearly equals 13%.[1] However, the disease-free survival rate of BC has increased to up to 90%, highlighting the utmost need for management strategies regarding the potential side effects of BC treatment to improve survival in BC survivors.[2,3]

Chemotherapy, which has proven efficacious for treating BC, is widely used. However, due to its potential neurotoxic side effects, BC patients who undergo systemic chemotherapy can experience sensory, motor, and autonomic disturbances in the distal part of their extremities, showing themselves as "stock and glove" like sensorial impairments in the initial stages.[4-7] This situation is called Chemotherapy-induced peripheral neuropathy (CIPN), and it is one of the most cumbersome and well-recognized side effects of systemic chemotherapy. The incidence of CIPN can be as high as 30%, even years after the completion of systemic chemotherapy.[4,7] Patients who suffer from CIPN may experience tingling, numbness, pain, and a wide range of symptoms in their hands and feet, which in turn could lead to diminished functional performance, deteriorated gross and fine motor skills, balance loss and so forth.[8-10]

There are well-known risk factors that have been identified in the context of CIPN onset, such as increased dosage, genetic factors, preexisting neuropathy, and so forth.[6,11,12] To the best of our knowledge, there is a gap regarding the potential association between the type of surgery and chemotherapy [adjuvant (ACT) vs. neoadjuvant NACT)] in the context of perceived CIPN, which needs to be addressed further to draw and conclude a sensitive approach in patients with BC who are at risk for CIPN. Therefore, this cross-sectional study aimed to assess the perceived CIPN symptoms in patients with BC who underwent taxane-based chemotherapy.

METHODS

Study Design

This prospective observational study was conducted in the Medical Oncology Unit of İzmir Bakırçay University Faculty of Medicine, according to the 1964 Helsinki Declaration and its later amendments or comparable ethical standards between January 2024 and March 2024. Ethical approval was granted from the İzmir Bakırçay University Ethical Board of Clinical Studies with the following number (decision no: 1414, date: 17.01.2024). The non-probability sampling method was used. This study was conducted according to the Strengthening of the Reporting of Observational Studies in Epidemiology guideline.[13]

Patients

Patients diagnosed with BC and referred to the medical oncology unit for systemic chemotherapy were screened and invited to participate in this study. The inclusion criteria were being a volunteer to participate, being over 18 years old, being female, and being a candidate for systemic chemotherapy. Having distant metastasis, comorbidities that might contribute to or cause sensory and motor deficits, such as multiple sclerosis, diabetes, polyneuropathy, etc., and prolonged surgical (if any) complications (i.e. pain, seroma, etc.) were set as exclusion criteria. Signed informed consent was obtained from each patient.

Assessments

The assessment time frame was set to one month and a half after the completion of systemic chemotherapy.

Data Form

A simple data form was used to gather information about the patients' age, weight, height, marital status, and smoking status. In addition, the clinical features of the patients were gathered and checked based on the current medical examination and systemic chemotherapy reports.

Calculation of Mean Exposure Dose

The mean exposure for chemotherapy drugs was calculated according to the body surface area (BSA) and the Du Bois formulation. The BSA was gathered according to the following formula: BSA [m^2] = Weight [kg]$^{0.425}$ × height (cm)$^{0.725}$ × 0.007184. Universal dose calculations were used to calculate the mean exposure according to the following doses for each patient-specific to their chemotherapy regimen: Four cycles of anthracycline were applied 14 days

apart 60 mg/m^2 intravenous (IV), 12 cycles of paclitaxel were applied seven days apart 80 mg/m^2 IV, and four cycles of docetaxel were applied 21 days apart 75 mg/m^2 IV.

Assessment of Chemotherapy Induced Peripheral Neuropathy

The European Organization for Research and Treatment of Cancer-Chemotherapy Induced Peripheral Neuropathy (EORTC-CIPN20) was developed to assess potential symptoms associated with CIPN in 2005. The questionnaire has been widely used and reported to be valid and reliable due to its robust psychometric properties.[14] Therefore, EORTC-CIPN20 was used to assess the perceived symptoms of CIPN in this study. The test consists of a total of 20 items each is scored from "1: not at all" to "4: very much" in a 4-point Likert scale. Individuals are requested to fill out the survey by considering their last week. Sensory, motor, and autonomic subscales are reported within the constructs. A total of 9, 8, and 3 items were referred to as sensory, motor, and autonomic disturbances, respectively. The last question of EORTC-CIPN20 evaluates erectile dysfunction that is not suitable for females. Therefore, it should be excluded from women. Raw scores range between 1-36 and 1-32 for the sensory and motor subscales, whereas the range of raw scores of the autonomic subscales is 1-12 for men and 1-8 for women, respectively. When reporting on the EORTC-CIPN20, it is recommended to convert all scores in a 0-100 linear scale. Higher scores indicate worse, and vice versa.[15]

Statistical Analysis

The data are presented as means and standard deviations or numbers and percentages according to the type of data. The normality of the data was checked using the Shapiro-Wilk tests, skewness, and kurtosis as well as graphical representation. Continuous data between groups were analyzed using the independent samples t-test or the Mann-Whitney U test in case of the violation of normality assumptions (i.e. patients with MRM or breast-conserving surgery). Pearson's r or Spearman's rho correlation analyses were performed between parameters according to the assumptions that the distribution met normality. All analyses were two-tailed, and p=0.05 was considered significant. The statistical analysis was performed using IBM Statistical Package for the Social Sciences v.20. (IBM Corp, NY).

RESULTS

Seventy four patients with BC who had completed their systemic treatments (chemotherapy, radiotherapy, surgery) were screened and invited to participate in this study. However, according to the predefined inclusion and exclusion criteria, 22 of them (29.7%) were excluded for various reasons. A detailed participation process is shown in (Figure 1) as a flowchart. Therefore, this study was completed with 52 BC patients [mean age and body mass index (BMI): 48.67±8.21 years and 27.03±4.31 kg/m^2]. ACT was applied in 25 of 52 patients (48.1%), while the rest of the patients underwent NACT (51.9%). Most patients underwent breast-conserving surgery (65.4%). The type of chemotherapy regimen was a combination of anthracycline and paclitaxel (28 out of 52), docetaxel (14 out of 52), or a combination of anthracycline, pertuzumab, trastuzumab, and docetaxel (10 out of 52). The mean total exposure dose was 2093.92±1266.22 mg. Only 13 (25%) reported being an active smoker during the data collection

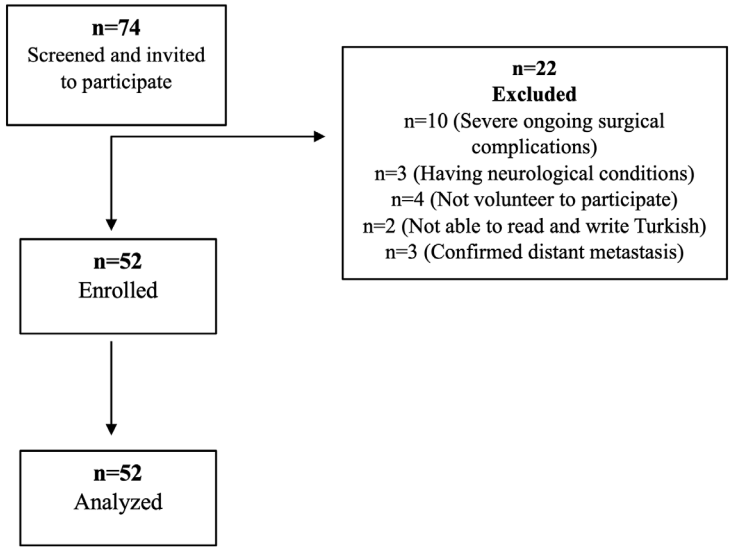

Figure 1. Flow chart of the study participants

period. The clinical and sociodemographic characteristics of patients are shown in (Table 1).

According to the linear converted scale scores of CIPN (0-100), the mean sensory, motor, and autonomic scores of CIPN were 21.50±18.68, 22.02±19.27 and 24.67±22.01, respectively. The total cumulative scores of the same subscales were 14.80±5.04, 12.69±4.27, and 3.48±1.32, respectively. Setting threshold 35 as discriminative of potential CIPN presence in the total score, 16 out of 52 patients (30.7%) had scores higher than this threshold. Patients who underwent MRM showed higher scores in the perceived symptoms of CIPN in all subscales compared with patients who underwent breast-conserving surgery; however, a significant result was only obtained in the motor function subscales of EORTC-CIPN20 (z=-2.838, p=0.005). When the mean scores of these subscales were compared between patients with ACT and NACT, the autonomic subscale of EORTC-CIPN20 was significantly higher in patients with NACT (z=-2.238, p=0.025). Although age and BMI were seen as lower in the NACT group compared with those with ACT, remarkably higher means were observed in both motor (27.06 vs. 16.56) and sensory subscales (24.00 vs. 18.81) of EORTC-CIPN20 in the NACT group compared with the ACT, yet those did not reach statistical significance (p>0.05). Yet, the mean exposure of chemotherapy was nearly two-fold higher in patients with NACT compared with the patients with ACT (2792.26 mg vs. 1339.72 mg) (z=-3.315, p=0.001). The detailed mean scores and comparisons of EORTC-CIPN20 between groups (MRM vs. breast-conserving surgery or ACT vs. NACT) are shown in (Table 2). Thirteen patients (25%) who were active smokers showed higher mean scores in the sensory and autonomic subscales of EORTC-CIPN20 compared with non-smokers; however, between-group comparisons

Table 1. Clinical and sociodemographic characteristics of patients

Marital status	**n (%)**
Married	39 (75)
Single or divorced	13 (25)
Smoking	
Yes	13 (25)
No	39 (75)
Alcohol consumption	
Yes	4 (7.7)
No	48 (92.3)
Type of chemotherapy	
ACT	25 (48.1)
NACT	27 (51.9)
Type of surgery	
BCS	28 (66.7)
MRM	14 (33.3)
Type of chemotherapy regimen	
AC+PAXL	28 (53.8)
Docetaxel	14 (26.9)
AC+docetaxel+pertuzumab+trastuzumab	10 (19.3)

BCS: Breast-conserving surgery, MRM: Modified radical mastectomy, ACT: Adjuvant chemotherapy, NACT: Neoadjuvant chemotherapy

Table 2. Detailed scores and comparisons of EORTC-CIPN20

EORTC-CIPN20				
Total score	**n (%)**			
<35	36 (69.3)			
>35	16 (30.7)			
	Median (IQR$^{25-75}$)	**Median (IQR$^{25-75}$)**		
EORTC-CIPN20	**MRM**	**BCS**	**z**	**p**
Sensory	25.92 (11.11, 41.66)	14.81 (3.70, 26.84)	-1.468	0.142
Motor	33.33 (13.83, 43.74)	12.5 (4.16, 23.80)	-2.838	0.005
Autonomic	33.33 (12.49, 50.00)	16.66 (0.00, 33.33)	-1.418	0.156
EORTC-CIPN20	**ACT**	**NACT**		
Sensory	14.81 (5.55, 25.92)	18.51 (3.70, 44.44)	-0.717	0.473
Motor	12.50 (4.16, 27.08)	20.83 (8.33, 41.66)	-1.884	0.060
Autonomic	16.66 (0.00, 24.99)	33.33 (16.66, 50.00)	-2.238	0.025
Mean exposure time (mg)	618.15 (516.71, 2245.20)	2213.01 (1935.98, 4087.66)	-3.315	0.001

p<0.05.

EORTC-CIPN20: European Organization for Research and Treatment of Cancer-Chemotherapy Induced Peripheral Neuropathy (EORTC-CIPN20) questionnaire, BCS: Breast-conserving surgery, MRM: Modified radical mastectomy, ACT: Adjuvant chemotherapy, NACT: Neodjuvant chemotherapy, mg: Milligram, z: Mann-Whitney U test, IQR: Interquartile range

showed no significant difference (p>0.05). When floor and ceiling effects were analyzed, 13.4% and 94.2% of patients scored "1=not at all" in 10th item (Did you have difficulty distinguishing between hot and cold water?) and "4=very much" in 13th item (Did you have difficulty opening a jar or bottle because of weakness in your hands?) in EORTC-CIPN20, respectively.

There were also significant correlations, which should be discussed in detail. Age was significantly correlated with the mean scores of the autonomic subscale of EORTC-CIPN20 (r=-0.373, p=0.006). The total exposure dose of chemotherapy was also significantly correlated with the autonomic subscale of EORTC-CIPN20 (r=0.295, p=0.034). No significant differences were observed between the sensory and motor subscales as well as age, BMI, and exposed dose, respectively (p>0.05).

DISCUSSION

There is no standardized consensus or gold standard for diagnosing and evaluating CIPN. Patient-reported outcomes, such as EORTC-QLQ-CIPN20, are reported to be useful and reliable for assessing the general picture of patients who suffer from or are at risk for CIPN, especially in the context of potential functional limitations.[14] In addition, when considering the total cumulative score, the sensory scale had higher mean scores than the motor and autonomic subscales. This result was expected because CIPN frequently presents with a sensory-dominant impairment. Other studies have also found higher means of sensory subscale scores compared to the others.[9,16] Yeo et al.[17] reported the highest mean changes in the sensory subscale in patients receiving taxane-based chemotherapy during the chemotherapy treatment trajectory. On the other hand, the effect of the type of surgery, especially on the motor subscale, deserves further study due to the fear avoidance attitude, ongoing pain, and/or pain catastrophizing that might contribute more to perceived CIPN symptoms in patients with MRM. In line with the literature findings, higher exposure doses of chemotherapy were significantly associated with increased perceived autonomic symptoms of CIPN. In this regard, it should be noted that the timing of measurement might also act as a major contributing factor in the context of perceived CIPN symptoms according to the patient-reported outcome(s).

Studies indicated that the prevalence of CIPN gradually decreases from nearly 70% to 30% within the first month and after six months of completion of chemotherapy.[4] Although we assessed our patients within a month and a half, our results seem parallel and comparable with the findings of Seretny et al's.[4] study in which nearly the same rate of prevalence was reported in a six-month or more time frame (30.7% vs 30%) according to the setting of threshold as 35 in the total cumulative score of EORTC-CIPN20 in our study. However, we found this rate earlier than those reported in six months or more. This can be attributable to the timing of measurements in our study, which corresponded nearly to two months after the completion of chemotherapy. In parallel with this, the onset and severity of CIPN were reported to be highest during and after the completion of systemic chemotherapy.[18] Though there have been no reports of useful cut-off values or thresholds for EORTC-CIPN20, we set this threshold as 35 in the total score according to the study of Alberti et al.[9], in which scores above 35 relatively correspond to grades two or more in the Total Neuropathy Score (TNSc) classification. Other studies also indicated significant correlations between clinician-assessed and patient-reported outcomes in the context of perceived CIPN.[18] For instance, Zhi et al.[5] reported diminished tactile and vibration perception in the Quantitative Sensory Testing (QST) method in patients with mild to moderate CIPN according to patient-reported outcomes. However, available methods in the literature on the assessment of CIPN do not show any superiority. By way of instance, QST evaluates large, myelinated fibers,[19] associated with sensory input, which is a predominant loss, especially in the initial stages of CIPN, which can be accounted for as an advantage. However, focusing only on sensory disturbance(s) using the QST may fail to detect and/or interpret potential motor disturbances. Thus, previous studies have indicated that using combined measurement methods is preferable for detecting and interpreting the potential consequences of CIPN.[10]

Not only the primary symptoms but also the associated consequences of perceived CIPN, such as falls, balance loss, increased energy expenditure, depression and anxiety, and sleep disorders, during functional abilities can significantly cause a deteriorated quality of life for patients undergoing taxane-based CT.[4,6,20] Moreover, some clinical and individual factors are known to have affected CIPN, such as the presence of comorbidities, nutrition, previous psychological status, obesity, the level of physical activity, as well as the amount of exposed dose, and so forth.[21-24] The main risk factor for CIPN is the cumulative dosage of chemotherapy.[6,11] We also found that patients who underwent NACT with higher doses showed higher but insignificant scores in each subscale of EORTC-CIPN20 compared to the ones who underwent ACT with significantly lower doses exposed. This might be relatively expected because all our patients with NACT underwent a combination of chemotherapy including HER2 antibodies such as pertuzumab and/or trastuzumab, which further contribute to an increased exposure dose of chemotherapy. Candelario et al.[25] reported a two-fold higher risk of experiencing CIPN in patients with HER2 positivity (odds

ratio: 2.11). The same authors also reported a nearly threefold increased risk of CIPN in patients who received paclitaxel compared with that in patients who received docetaxel alone (odds ratio: 2.89). The current literature also supports this hypothesis that patients who underwent paclitaxel are much more likely to experience CIPN.[7,12] Although the chemotherapy regimen was combined with anthracycline and paclitaxel in nearly half of our sample, we did not find any significant difference in terms of sensory and motor subscales except for the autonomic subscale of EORTC-CIPN20, which was significantly higher compared with patients who underwent docetaxel only. Although higher mean scores were observed for each subscale, the results were insignificant except for the autonomic subscale. These findings may be attributed to the highly skewed results of EORTC-CIPN20, which was also reported in other studies.[26] In addition, other uncontrollable factors might also cause these insignificant results, such as EORTC-CIPN20, to be filled out by considering the last week, which is relatively narrow and vulnerable to detect a complete picture of potential CIPN. On the other hand, we also found a weak but significant correlation between the autonomic subscale of EORTC-CIPN20 and the exposure dose. The motor and sensory subscales did not significantly correlate with EORTC-CIPN20. However, this finding should be thoroughly interpreted because of the relatively lower levels of reliability and validity of the autonomic subscale of EORTC-CIPN20 compared with other subscales.[26,27] Besides, there is only a set of three items associated with autonomic disturbance in EORTC-CIPN20 (i.e. blurred vision, hypotension, and erectile dysfunction), and we could not evaluate the last item as it is only for males. Studies have also indicated that experiencing hypotension and/or blurred vision can also originate from prolonged side effects of systemic chemotherapy.[27] Furthermore, Rattanakrong et al.[16] reported no significant difference in the autonomic scale scores between patients with BC and healthy controls. Yet, a weak but significant correlation between the autonomic subscale of EORTC-CIPN20 and age should be considered, especially for older patients who are expected to be more vulnerable to neurotoxic chemotherapy and thereby suffer more from CIPN. Indeed, secondary complications, such as increased fall risk[8], should be seriously considered in these older patients since they might cause devastating complications for functionality.[26] Bao et al.[8] reported a nearly two-fold increased risk of CIPN in patients with obesity. Yet, controversial results were also reported in which individual (i.e. age, race, smoking, alcohol) and clinical factors (i.e. diabetes, renal disease) were not found as significant factors in the context of the severity of CIPN.[25] In parallel with the previous findings of Candelario et al.[25], we also did not find any significant correlation between BMI and each subscale of EORTC-CIPN20. This insignificant finding can be attributed to the timing of our measurement, and it might be reasonable to conclude that the cumulative effects of neurotoxic chemotherapy might not have occurred at the time of data collection. On the other hand, the most prominent finding of our study was that patients who underwent MRM showed significantly higher scores on the motor subscale of EORTC-CIPN20 compared with those who underwent breast-conserving surgery. MRM can be accounted for in more extensive surgery not only by losing the breast but also by experiencing ongoing surgical complaints (i.e. pain in the surgical incision) might have contributed to this result. Lavoie Smith et al.[27] reported that those with a more proximal extension of CIPN associated with upper extremity dysfunction were prone to have higher CIPN scores. Therefore, patients who underwent MRM should be closely monitored due to worsening CIPN symptoms by aggravating both sensory and motor disturbances, which in turn might result in a remarkable decrease in functionality. Notably, patients with MRM are particularly prone to avoid their affected upper extremities due to false beliefs upon the manifestation of lymphedema, which ultimately results in fear avoidance patterns.[28] Nonetheless, a ceiling effect was also found at a rate of 94.2% in the 13th item of EORTC-CIPN20 ("Did you have difficulty opening a jar or bottle because of weakness in your hands") which might also be considered to have originated from the relatively notable number of patients with MRM (~35%) in our study. Mols et al.[26] reported that the most frequent symptom was the same item in the EORTC-CIPN20. This finding carries a noticeable importance because patients with BC might likely face problems associated with gross and fine motor skills of the upper extremity, which can end in loss of work and devastating financial toxicity.[29] Therefore, not only the perception of CIPN but also secondary consequences, such as diminished fine motor ability, should be integrated into the trajectory of survivorship.[10] We were also able to report a decrease in handgrip and peripheral muscle strengths as well as diminished fine motor ability in the trajectory of systemic chemotherapy in patients with BC.[30] In our study, we also found higher mean scores of the EORTC-CIPN20 motor and autonomic subscales in patients who presented themselves as active smokers compared with non-smokers during data collection, yet the difference did not reach statistical significance for each subscale. However, we only asked respondents whether they were smoker or not and did not collect the cumulative amount of smoking in a day or duration. However, we think that this finding is worthy of future study because the mean exposure dose of chemotherapy (1908 mg vs. 2155 mg) and age (45 vs. 50) were lower in smokers.

Study Limitations

This study has some strengths and limitations. Establishing a real-time environment for patient-reported outcomes, a homogeneous sample of BC, and using non-biased clinical data (i.e. the cumulative dose, surgery, chemotherapy regimen, etc.) to compare patients with ACT and NACT in terms of discriminating surgical effects can be considered the strengths of this study. However, the relatively small sample size and the cross-sectional nature of the design of this study, which hampered us from comparing before and after, can be considered limitations of this study. In addition, since this study was conducted in a single outpatient clinic and relatively included Caucasian women, the generalizability of our results might be arguable. Besides, since we included only female patients with BC, the last item of EORTC-CIPN20 could not be calculated because it directly evaluates erectile dysfunction. Our results need to be clarified in further studies, especially when combined with objective assessments of motor and sensory disturbances.

CONCLUSION

The findings of this study highlighted the need for further and ongoing evaluation of perceived CIPN symptoms, particularly in patients who received higher doses of chemotherapy and/or were older. However, the autonomic reflections of potential CIPN should be carefully interpreted in terms of their clinical implications. The type of surgery, specifically MRM, which has been emphasized as a contributing factor to CIPN, should be taken into consideration for further potential deterioration. By this means, it is reasonable to state that not only ongoing monitoring of the CIPN is of utmost importance, but also potential contributors to the management of the CIPN are of great importance.

Ethics

Ethics Committee Approval: Ethical approval was granted from the İzmir Bakırçay University Ethical Board of Clinical Studies with the following number (decision no: 1414, date: 17.01.2024).

Informed Consent: Written informed consent was obtained from each patient.

Authorship Contributions

Surgical and Medical Practices: M.A., Concept: M.A., Design: A.T., M.A., Data collection or Processing: A.T., M.A., Analysis or interpretation: A.T., M.A., Literature Search: A.T., Writing: A.T., M.A.,

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Original Article / Orijinal Araştırma

Investigation of Inflammation and Autophagy due to Biglycan-mediated TLR2/4 Signaling in Oral Lichen Planus Tissues

Oral Liken Planus Dokularında Biglikan Aracılı TLR2/4 Sinyallemesine Bağlı Enflamasyon ve Otofaji Aktivasyonunun Araştırılması

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ABSTRACT

Objective: Oral lichen planus (OLP) is a chronic oral mucosal disease of unknown etiology. Cellular immune response, basement membrane, and extracellular matrix (ECM) molecules are also noteworthy in the pathogenesis. We aimed to investigate the role of Biglycan (BGN) in Toll-like receptors (TLR)2/4-CD14 and TLR4-CD44 mediated signaling mechanisms in the pathogenesis of OLP.

Methods: Twenty-one patients with a previous diagnosis of OLP and 21 patients with normal oral mucosa were included. RNA was isolated from biopsy samples of patients, and the gene expression of BGN, TLR2, TLR4, CD14, and CD44 was analyzed by quantitative real-time polymerase chain reaction and immunohistochemistry.

Results: According to our findings, the fold change rates of BGN, TLR2, TLR4, and CD14 mRNA levels in tissues obtained from patients with OLP were higher compared with the control group. TLR2, TLR4, and CD14 fold change rates were statistically significant ($p<0.05$). CD44 co-receptor mRNA levels were higher in the control group ($p<0.05$). Similar results were obtained by immunohistochemical analysis.

Conclusion: BGN expression has a pro-inflammatory effect in various disease models. The BGN levels in the tissues of patients with OLP were higher than those of the control group, but the difference was not statistically significant. However, TLR2/4-CD14 and CD44 levels were upregulated, as well as CD44 levels were downregulated. We suggest that inflammation signaling is activated and autophagy is inhibited in OLP. BGN-dependent inflammation and autophagy signaling in OLP are evaluated for the first time.

Keywords: Biglycan, oral lichen planus, inflammation, autophagy, TLR

ÖZ

Amaç: Oral liken planus (OLP), etiyolojisi bilinmeyen, kronik enflamatuvar bir oral mukoza hastalığıdır. OLP patogenezinde hücresel immün yanıt, bazal membran ve hücre dışı matriks (ECM) molekülleri de dikkat çekmektedir. Biglikan (BGN), ECM'nin yapısal bir bileşenidir ve aynı zamanda bir sinyal molekülü olarak da görev yapar. Bu çalışmada OLP hastalarının patogenezinde BGN'nin Toll-like reseptörler (TLR)2/4-CD14 ve TLR4-CD44 aracılı sinyalleşme mekanizmaları üzerindeki rolünü, enflamasyon ve otofaji ile ilişkisini araştırmayı amaçladık.

Yöntem: Çalışmamıza daha önceden OLP tanısı almış 21 hasta ve oral mukozası normal olan 21 hasta dahil edildi. Hastaların biyopsi örneklerinden RNA izole edildi ve BGN, TLR2, TLR4, CD14 ve CD44 moleküllerinin gen ekspresyonları kantitatif gerçek zamanlı polimeraz zincir reaksiyonu ve immünohistokimya ile analiz edildi.

Bulgular: Bulgularımıza göre OLP hastalarından elde edilen dokularda BGN, TLR2, TLR4, CD14 mRNA düzeylerinin kat değişim oranları kontrol grubuna göre daha yüksekti. TLR2, TLR4, CD14 kat değişim oranları istatistiksel olarak anlamlıydı ($p<0,05$). CD44 ko-reseptör mRNA düzeyi kontrol grubunda daha yüksekti ($p<0,05$). İmmünohistokimyasal analize göre de benzer sonuçlar elde edildi.

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Sonuç: Dolaşımdaki çözünür BGN ekspresyonunun çeşitli hastalık modellerinde proenflamatuvar etkiye sahip olduğu bulunmuştur. Bu çalışmada OLP hastalarının dokularındaki BGN düzeyleri kontrol grubuna göre daha yüksekti ancak bu istatistiksel olarak anlamlı değildi. Ancak OLP dokularında TLR2/4-CD14 seviyeleri yukarı doğru düzenlenirken, CD44 seviyeleri de aşağı doğru düzenlenmiştir. OLP'de enflamasyon sinyalinin aktive olduğunu ve otofajinin inhibisyon olduğunu öneriyoruz. OLP'de BGN'ye bağlı enflamasyon ve otofaji sinyali ilk kez değerlendirildi.

Anahtar Kelimeler: Biglikan, oral liken planus, enflamasyon, otofaji, TLR

INTRODUCTION

Oral lichen planus (OLP) is a chronic inflammatory oral mucosal disease of unknown etiology.[1] It is more common in women than men (female/male: 2/1). This disease manifests as white streaks, papules, plaques, erythema, erosions, or blisters that predominantly affect the buccal mucosa, tongue, and gingiva.[2,3] OLP has been defined as a premalignant condition by the World Health Organization, and malignancy has been identified in approximately 10% of cases. Therefore, the elucidation of the pathogenesis of OLP has gained importance.[4,5]

Besides the cellular immune response, the basement membrane, intercellular connections, and extracellular matrix (ECM) molecules draw attention to the pathogenesis of OLP. The ECM is a non-cellular and highly specialized three-dimensional skeletal structure in all tissues and organs. ECM molecular composition and structure can change significantly during normal tissue repair or during the progression of various diseases.[6] Therefore, explaining the relationship between ECM molecules and inflammation in OLP is essential in elucidating the disease's pathogenesis and supporting diagnostic criteria. It was determined that the expression of ECM molecules such as fibronectin, integrin, keratin, collagen, and E-cadherin differs in OLP. Various studies have been conducted on the receptors and signaling pathways of these molecules.[7]

Studies have shown that OLP is a T cell-mediated autoimmune disease and that ECM molecules play important roles in the pathogenesis of the disease.[3,8] In OLP histopathology, oral mucosal basal keratinocyte become sensitized, and the severity of the disease increases with the stimulation of the inflammatory process, which tends to become chronic.[4,9]

Small leucine-rich proteoglycans (SLRP) comprise a large 18-member ECM proteoglycan family.[5] Biglycan (BGN) is a member of the SLRP family of ECM.[10,11] Under normal conditions, BGN is a structural protein. Nevertheless, in situations such as tissue injury and stress, it is cleaved by the proteolytic pathway or released de novo and then acts as a direct signaling molecule in inflammation.[12] It has been reported that BGN stimulates macrophages, some chemokine, and cytokines, especially in inflammation, and causes an increase in inflammation.[6,7,12] In pathogenic inflammation or pathological conditions, BGN binds toll-like receptor (TLR)2 and TLR4 receptors on macrophages and dendritic cells, induces various pro-inflammatory cytokines or chemokine, and causes increased inflammation. Thus, it plays an important role in the endogenous proinflammatory response.[13-15] Recent studies have shown that molecules such as CD14 and CD44 act as co-receptors in BGN-mediated TLR2 and 4 signaling.[12] However, these pathways result in different cellular processes; TLR2/4-CD14 signaling induces inflammation[12] while TLR4-CD44 signaling has been shown to result in autophagy.[10,16,17] CD44 isoform in epithelial cells, active lymphocytes, and tumor cells are associated with inflammation. However, the mechanism by which CD44 expression is signaled remains unclear.[18]

Although BGN has been studied in many inflammatory diseases, only one study has shown its relationship with OLP. This study showed that BGN is overexpressed in OLP and oral squamous cell carcinoma, and it was interpreted that it might increase the release of the immune system and cytokines, thereby causing inflammation.[10] However, there are no studies on the role of BGN in OLP and its effect on inflammation, which is associated with many inflammatory diseases. In this study, we aimed to investigate the role of BGN in TLR2/4-CD14- and TLR4-CD44-mediated signaling mechanisms in patients with OLP and the relationship with inflammation and autophagy.

The data obtained from our study will make important contributions to the literature regarding whether BGN is associated with inflammation in OLP and evaluate the signaling mechanisms associated with BGN as a biomarker.

METHODS

Patient Selection and Criteria

Ethical approval was obtained from the Clinical Research Ethics Committee of the Alanya Alaaddin Keykubat University (ALKU) Faculty of Medicine (date: 19.11.2020, decision no: 25/10). This study applied the principles of the Declaration of Helsinki and local laws. Written informed consent forms were obtained from the participants included in the study.

Our study included 21 patients previously diagnosed with OLP at the ALKU Faculty of Medicine Ear Nose and Throat Polyclinic and oral mucosal tissue samples of 21 patients whose biopsies were previously taken with the preliminary diagnosis of OLP and reported as normal tissue. Patients who were pregnant, <18 years of age, or diagnosed with any

malignancy were excluded from the study. The expression levels of BGN, TLR2, TLR4, CD14, and CD44 genes were evaluated by quantitative real-time polymerase chain reaction (RT-qPCR) and immunohistochemistry analyses of paraffin-embedded tissues from patients and volunteers.

Immunohistochemical Analyzes

Sections of 5 µm thickness were taken from each paraffin block of the oral mucosa in all groups using a microtome. After being flattened in a water bath at the appropriate temperature, the sections were transferred onto superfrosted slides. The following primary antibodies were used: anti-BGN (Cat#FNab00895, Fine Test, China) (1:50 dilution), anti-TLR2 (Cat#BT-AP09061, BT Lab, China) (1:100 dilution), anti-TLR4 (Cat#BT-AP09062, BT Lab, China) (1:100 dilution), anti-CD14 (Cat#FNab01426, Fine Test, China) (1:50 dilution), and anti-CD44 (Cat#BT-AP01504, BT Lab, China) (1:50 dilution). Samples were classified as stained with strong density, medium density (similar to normal laryngeal squamous epithelium), and weak density. All immunohistochemical sections were scored according to staining intensity as follows: (-): No Staining, (+): Poor Staining, (++): Medium staining, (+++): Strong staining.

Determination of Gene Expression Levels

Total RNA Isolation from Paraffin-embedded Tissue

To study mRNA expression profiles in formalin-fixed and paraffin-embedded (FFPE) tissues, 8 sections of 10 µm thickness were taken for each patient. According to the manufacturer's instructions, total RNA was extracted from the prepared samples using the PureLink™ FFPE Total RNA Isolation Kit (Cat#K156002, Invitrogen, USA). After measuring the purity and concentrations (ng/µL) of the isolated RNAs with an ELISA Plate Reader (Synergy H1, BioTek, USA) (260/280=1.8-2.1), total RNA samples were stored at -80 °C until use.

cDNA Synthesis

Using reverse transcriptase PCR (RT-PCR), cDNA synthesis was performed from mRNAs. For cDNA synthesis, an ABT cDNA synthesis kit (Cat#C03-01-20, ABT, Türkiye) was used, and cDNA synthesis was performed in a total volume of 20 µL according to the manufacturer's instructions. The obtained cDNAs were stored at -20 °C for real-time PCR reaction.

Gene Expression Measurement by Quantitative Real-time PCR

The gene expression levels of BGN, TLR2, TLR4, CD14, and CD44 genes, which are believed to play a role in the pathogenesis of OLP, were determined using the relative gene expression RT-qPCR method. Beta-actin (β-actin) was used as the housekeeping gene. RT-qPCR reactions were performed using a QRT-PCR master mix kit (Cat#Q03-02-01, ABT. 2X qPCR SYBR Green Master Mix, Türkiye) and a LightCycler 96 system (Roche Diagnostics, Basel, Switzerland). The relative expression values were calculated using the cycle threshold (Ct) method according to the $2^{-\Delta\Delta Ct}$ formula and the fold change in the mRNA expression of the target genes was determined.[19]

Statistical Analysis

Statistical Package for the Social Sciences, a Windows version 17.0 computer program, was used for statistical analysis. The immunohistochemical analysis was performed using Fisher's exact test. In addition, differences between the paired groups were compared with the independent sample t-test or Mann-Whitney U test for parametric or nonparametric samples. Chi-square analysis and frequency analysis were used for categorical variables. The significance level was set as $p<0.05$ in all statistical comparisons.

RESULTS

The study included 42 individuals; there were 15 female and 6 male patients in the patient group and 11 female and 10 male patients in the control group. The lowest age was 19 years, and the oldest was 68 years. Mean age were 44.5 (±11.08) and 49.2 (±13.51) in the patient and control groups. To gain an understanding of the relationship between inflammation and BGN in OLP, we evaluated BGN, TLR2, TLR4, CD14, and CD44 gene expression levels in paraffin-embedded tissues using immunohistochemistry and RT-qPCR in all study groups.

Quantitative Real-time PCR Findings

The mRNA expression levels of BGN, CD14, CD44, TLR2, and TLR4 proteins in the tissues of patients with OLP and the control group were compared using RT-qPCR. The relative expression levels of these genes are presented in Figure 1. In the results obtained, there was no statistically significant difference between the OLP patients and the control group in terms of BGN mRNA expression level (1.14 fold) (p=0.438) (Figure 1A). The relative expression levels of CD14, TLR2, and TLR4 mRNA in the OLP samples were significantly elevated to 1.95 (p=0.001), 2.34 (p=0.04), and 1.96 (p=0.005) folds, respectively, compared with the control group (Figure 1B, 1D, 1E). In contrast, CD44 gene expression levels were significantly decreased (3.7 fold) in OLP patients compared with controls (p=0.001) (Figure 1C).

Immunohistochemical Findings

In histological examinations, intense subepithelial inflammatory cell infiltration, epithelial atrophy, and basement membrane degeneration were observed in OLP

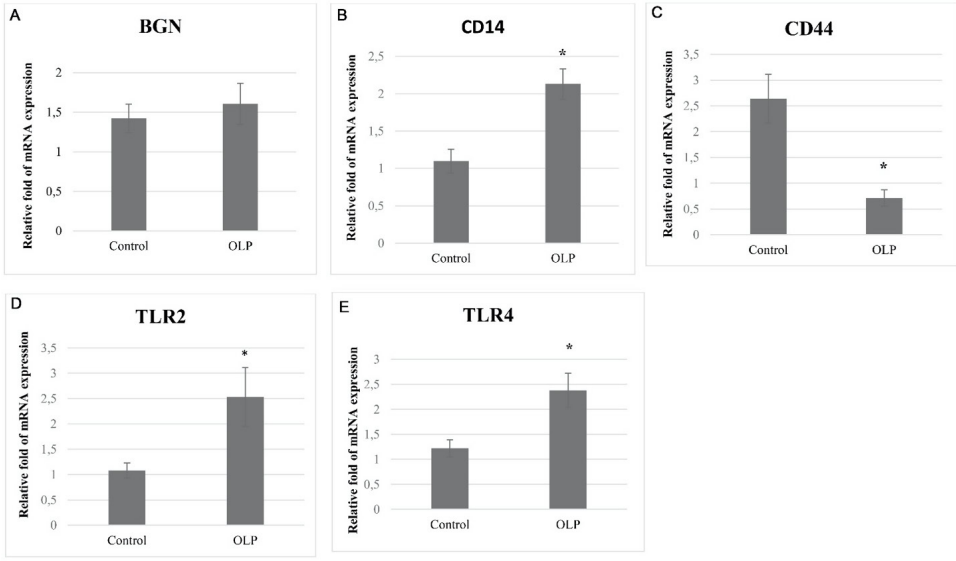

Figure 1. Relative fold to mRNA expression levels of BGN, CD14, CD44, TLR2, and TLR4 in tissues of OLP patients and the control (mean value±standard error). Significance level compared to control **p<0.05 vs. significant differences in CD14, CD44, TLR2, and TLR4 expression between OLP and control were found

OLP: Oral lichen planus, BGN: Biglycan

tissues. BGN, TLR2, TLR4, CD14, and CD44 findings obtained from the OLP and control groups by immunostaining are shown in Figures 2 and 3. Accordingly, no significant immunohistochemical staining was obtained for BGN in both groups (-) (Figure 2A, Figure 3A). CD14 (Figure 2B, Figure 3B), TLR2 (Figure 2D, Figure 3D), and TLR4 (Figure 2E, Figure 3E) stained weakly (+) in normal tissues and moderately (++) in OLP tissues. CD44 stained strongly (+++) in normal tissues and weakly (+) in OLP tissues (Figure 2C, Figure 3C).

DISCUSSION

OLP is an inflammatory disease, and it is thought that the basement membrane and ECM molecules also play a role in its pathogenesis in addition to the cellular immune response. Many endogenous and exogenous inflammatory processes are known to be involved in the pathogenesis of OLP, but the mechanisms involved in these processes need to be elucidated.[2,3,9] It has been determined that the expression of ECM molecules such as fibronectin, integrin, keratin, collagen, and E-cadherin differ in OLP.[6,7,12] In this study, we investigated the effects of BGN on TLR2/4-CD14- and TLR4-CD44-mediated signaling mechanisms in patients with OLP as a relationship with inflammation and autophagy. To understand the relationship between these signaling mechanisms and the pathogenesis of the disease, we examined the gene expression of these molecules at the mRNA level by RT-qPCR and protein level by IHC staining.

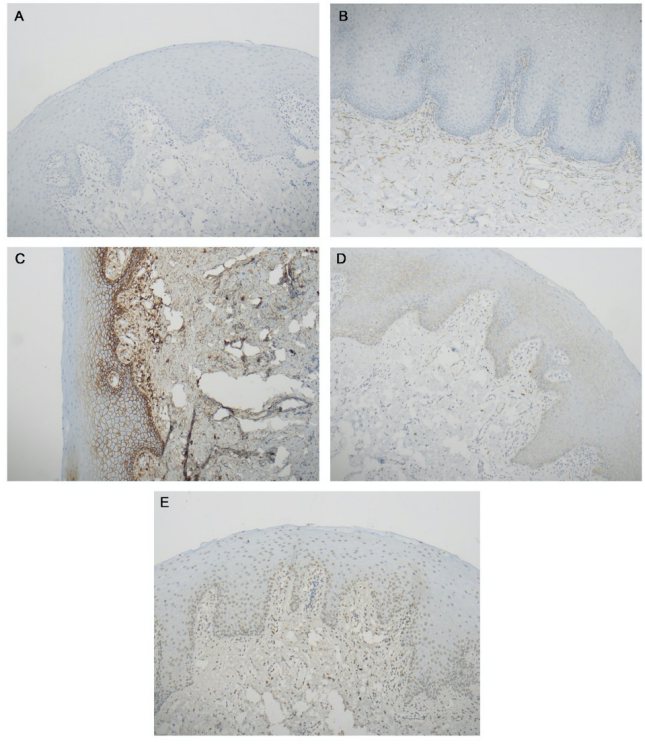

Figure 2. Representative images of the IHC staining of BGN, CD14, CD44, TLR2, and TLR4 from the control group. IHC staining of NOM tissue sections showed BGN (-) (A), CD14 (+) (B), CD44 (+++) (C), TLR2 (+) (D), and TLR4 (+) (E)

Original magnification ×10, IHC: Immunohistochemistry, NOM: Normal oral mucosa

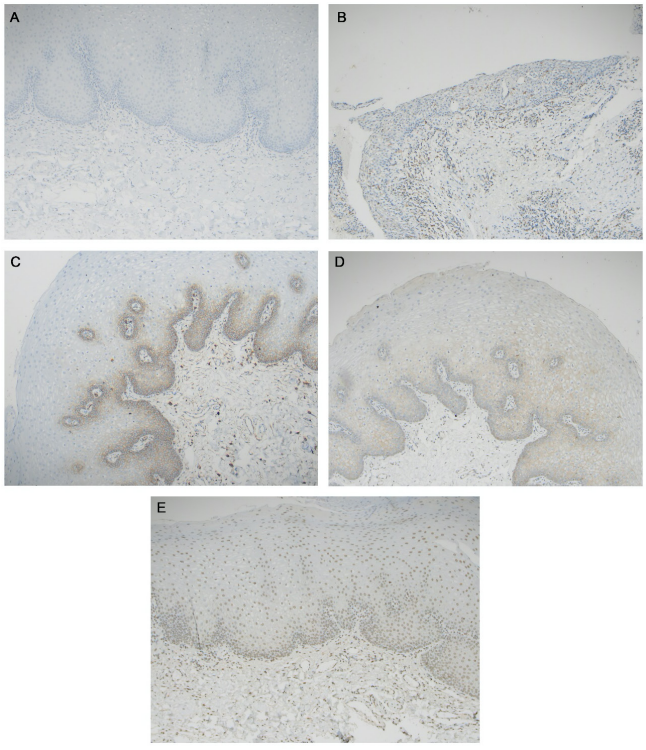

Figure 3. Representative images of the IHC staining of BGN, CD14, CD44, TLR2, and TLR4 from the OLP group. IHC staining of OLP tissue sections showed BGN (-) (A), CD14 (++) (B), CD44 (+) (C), TLR2 (++) (D), and TLR4 (++) (E)

Original magnification ×10, IHC: Immunohistochemistry, OLP: Oral lichen planus

BGN is known to play a role in maintaining the integrity of the ECM under normal physiological conditions. In addition, proteolytic cleavage from the ECM stimulates macrophages, some chemokine, and cytokines, especially in tissue damage and inflammation. Increases inflammation by sending a signal via TLR4.[7,10,12] According to our studies, only one study investigated the relationship between BGN and OLP. This study showed that the BGN level was increased in tissues adjacent to OLP tissues but histologically remained unchanged, whereas it was lower in OLP tissues. Based on these findings, it has been suggested that high BGN expression in adjacent tissues of the OLP contributes to the enhanced infiltration of immune cells in the OLP region.[10] In our study, BGN was less stained in OLP tissue immunohistochemically than in control tissue, but the difference was not statistically significant. In addition, the mRNA expression level of BGN was decreased in OLP tissues compared with the control group, but the results were not statistically significant. Our results show that BGN is less in OLP patients, which supports the current study, but it would be useful to examine samples from adjacent tissues for mRNA expression. This study contributes to the evaluation of the reduction of BGN, which supports the mucosal structure in terms of its effect on the etiology of OLP, independent of signaling molecules.

Previous studies have shown that BGN plays a role in initiating and maintaining the inflammatory response. This molecule has been implicated in proinflammatory signaling in various diseases, causing an increase in cytokines such as tumor necrosis factor-α, IL-6 and IL-1β.[20] It is involved in the pathogenesis of rheumatoid arthritis, lupus nephritis, ischemic acute kidney injury,[14] osteoarthritis,[21] and insulin-dependent diabetes mellitus type 1.[12,20] By stimulating various signaling mechanisms and increasing proinflammatory activity. Based on these findings, we examined the mRNA levels and immunoreactivity of BGN in OLP, an inflammatory disease. The BGN levels in the tissues of patients with OLP were higher than those of the control group, but the difference was not statistically significant. According to the study by Lonar-Brzak et al.[10], BGN was increased to a greater extent in healthy adjacent tissues than in inflammation-positive tissues in patients with OLP. This was interpreted as supporting the progression of the disease and increasing the risk of malignancy. Increases in BGN levels in adjacent tissues may be intended to modulate inflammation. We directly studied the lesioned tissues, so a comprehensive examination of the adjacent tissues is recommended.

Various studies have reported that TLR2 and TLR4 are important in regulating the inflammatory response in the epithelial tissues of patients with OLP. However, different studies have reported that TLR2 or TLR4 are downregulated or upregulated, and no definite conclusion has been reached on this issue.[22,23] In the present study, TLR2 and TLR4 transcripts and protein levels were significantly increased in OLP samples with inflammation. This supports the idea that inflammatory mediators play an active role in inflammation.

In some disease models, BGN has been reported to act as a ligand of TLR2 and TLR4 in inflammation, whereas CD14 and CD44 molecules act as co-receptors and stimulate different signaling mechanisms.[12,24] In recent studies, binding of BGN with a TLR2/4-CD14 co-receptor with high affinity was reported to induce immune cell infiltration and increase inflammation in inflamed tissues.[15,17] Conversely, BGN overexpression in macrophages has been shown to activate autophagy through TLR4-CD44 signaling which is very interesting.[17] Accordingly, the selection of BGN to TLR2/4 receptors and co-receptors may be decisive in directing tissue toward chronic inflammation or regeneration.[15] According to our research, the effects of TLR2/4 receptors and CD14-CD44 co-receptors on OLP in the BGN-induced inflammation pathway have not been

studied. Our results showed that TLR2/4 and CD14 levels were increased at the mRNA and immunohistochemical levels in OLP tissues. In support of the data from various diseases previously analyzed, we found that the TLR2/4-CD14 signaling pathway increased inflammation in patients with OLP. Although the course of BGN was insignificant, our results suggest that it is increased in OLP tissues and may be related to the TLTR2/4-CD14 inflammation signaling pathway.

Autophagy promotes cell survival against various stressors, negatively regulates inflammation, and prevents excessive tissue damage.[25] In addition, the inhibition of autophagy leads to increased inflammation and cellular damage.[26] Zhang et al.[25] showed that autophagy is activated via the Akt/mTOR pathway in OLP tissues. In contrast, Tan et al.[26] reported that autophagy-related gene expression was downregulated in OLP. Recent studies suggest that TLR4/CD44 signaling activates autophagy.[17] Ghazi et al.[27] showed increased CD44 immunoexpression in the epithelium of dysplastic OLP and interpreted that it may contribute to inflammation. However, some CD44 isoform were reported to be decreased in OLP tissue compared with controls or did not differ between these two groups in different studies.[16,18,28] In our study, although TLR4 expression was increased, the level of CD44 co-receptor, which regulates the autophagy pathway, was significantly decreased in OLP tissues. This result shows that TLR/4 CD44 signaling is downregulated in OLP, suggesting the inhibition of autophagy.

Study Limitations

There are two main limitations to our study. First, paraffin-embedded tissues from 21 patients previously diagnosed with OLP were studied. Increasing the number of patients will increase the study reliability. Additionally, studies examining signaling pathways at the molecular level are needed to better understand how BGN, TLR2, TLR4, CD14, and CD44 affect the molecular mechanisms underlying OLP.

CONCLUSION

According to the results of the present study, BGN-mediated TLR2/4 and CD14 signaling may promote inflammation in OLP. In addition, we suggest that inflammation signaling is upregulated by increased TLR2/4-CD14 levels in OLP tissues, and autophagy inhibition may occur by downregulating TLR2/4-CD44 signaling. We recommend that inflammation and autophagy in the OLP should be investigated in more comprehensive studies.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Clinical Research Ethics Committee of the Alanya Alaaddin Keykubat University (ALKU) Faculty of Medicine (date: 19.11.2020, decision no: 25/10).

Informed Consent: Written informed consent forms were obtained from the participants included in the study.

Authorship Contributions

Surgical and Medical Practices: H.G., Concept: Ö.C.G., H.E., F.Y., Design: Ö.C.G., H.E., F.Y., Data Collection or Processing: H.G., Analysis or Interpretation: Ö.C.G., H.G., H.E., F.Y., Literature Search: Ö.C.G., H.G., H.E., F.Y., Writing: Ö.C.G., H.G., H.E., F.Y.

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

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Original Article / Orijinal Araştırma

The Worrying Mystery in Children with ADHD: Autonomic Nervous System Dysregulation and Methylphenidate Use

DEHB'li Çocuklarda Endişe Verici Gizem: Otonom Sinir Sistemi Disregülasyonu ve Metilfenidat Kullanımı

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ABSTRACT

Objective: Children with attention deficit and hyperactivity disorder (ADHD) may have an increased risk of cardiovascular complications due to reduced vagal tone and increased heart rate (HR). Methylphenidate (MPH) is a frequently used drug, and its sympathomimetic effects often cause pediatricians to be concerned when making diagnostic and treatment decisions. We aimed to assess the effects of MPH on the cardiovascular system and autonomic activity of the heart using heart rate variability (HRV) in ADHD patients.

Methods: We retrospectively analyzed physical examination, blood pressure (BP), and 24-hour Holter monitoring in 33 patients (9.7±2.6 years) and 36 healthy subjects (9.54±2.8 years). The results of the examinations at the end of the first month of MPH treatment were compared with the pre-treatment findings in the patient group.

Results: Systolic and diastolic BP measurements were similar between the groups at diagnosis. The patients showed a mild increase in systolic and diastolic BP after treatment, but the differences were not statistically significant (p=0.059 and p=0.063, respectively). However, increase in heart rate and QTc duration on ECG was statistically significant in the patient group (p=0.001 and <0.001, respectively). We did not detect any significant differences in the time-domain analyses. Only the low-frequency index decreased significantly as a frequency domain parameter [871 ms2 (316.6-2198.6) vs. 788.1 ms2 (228.9-1950.3); p=0.039].

Conclusion: MPH has no significant cardiovascular side effects in ADHD. Attention should be paid when prescribing drugs that may prolong the duration of QTc; rhythm and BP should also be monitored during follow-up.

Keywords: Attention deficit and hyperactivity disorder, cardiovascular risk, variability in heart rate, methylphenidate

ÖZ

Amaç: Dikkat eksikliği ve hiperaktivite bozukluğu (DEHB) olan çocuklarda azalmış vagal tonus ve artmış kalp hızları nedeniyle kardiyovasküler komplikasyon riskinde artış gözlenebilir. Metilfenidat (MPH) sık kullanılan bir ilaçtır ve sempatomimetik etkileri çocuk doktorlarının tanı ve tedavi kararları verirken sıklıkla endişe duymalarına neden olmaktadır. Bu nedenle çalışmamızda, DEHB hastalarında kalp hızı değişkenliğini kullanarak MPH'nin kardiyovasküler sistem ve kalbin otonomik aktivitesi üzerindeki etkilerinin değerlendirmesi amaçlanmıştır.

Yöntem: Çalışmamızda 33 hasta (9,7±2,6 yıl) ve 36 sağlıklı çocuğun (9,54±2,8 yıl) fizik muayene, kan basıncı (KB) ve 24 saatlik Holter monitörizasyonu bulguları retrospektif olarak değerlendirilmiştir. Ayrıca, MPH tedavisinin birinci ayının sonundaki bulgular hasta grubunda tedavi öncesi bulgularla karşılaştırılmıştır.

Bulgular: Tanı anında sistolik ve diyastolik KB ölçümleri gruplar arasında benzerdi. Hastalarda tedavi sonrasında sistolik ve diyastolik KB'de hafif bir artış görüldü ancak istatistiksel olarak anlamlı değildi

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(sırasıyla p=0,059 ve p=0,063). Ancak, hasta grubunun kalp hızı ve QTc süresindeki artış istatistiksel olarak anlamlıydı (sırasıyla p=0,001 ve p<0,001). Zaman alanı analizlerinde anlamlı bir fark tespit edilmedi. Frekans alanı parametresi olarak sadece düşük frekans indeksi anlamlı şekilde azaldığı görüldü [871 ms^2 (316,6-2198,6) vs. 788,1 ms^2 (228,9-1950,3); p=0,039].

Sonuç: MPH tedavisinin DEHB tedavisinde önemli majör bir kardiyovasküler yan etkisi olmadığı gösterilmiştir. İlacın QTc süresini uzatabilecek diğer ilaçlarla birlikte reçete edilirken dikkat edilmesi gerekliliği; tedavi süresince ritim ve KB değerlerinin izlemi önerilmektedir.

Anahtar Kelimeler: Dikkat eksikliği ve hiperaktivite bozukluğu, kardiyovasküler risk, kalp hızı değişkenliği, metilfenidat

INTRODUCTION

Attention deficit and hyperactivity disorder (ADHD) is a neurobiological syndrome that affects approximately 5% of school-age children and often persists into adulthood.[1-5] It is more common in boys and is characterized by increased activity, an inability to concentrate, and poor school performance.[6,7]

ADHD is one of the most common psychiatric disorders in children and is also one of the most common challenges that pediatricians face during outpatient visits for various reasons (prescribing certain antibiotics or antihistamines, screening of athletes, pre-operative screening, etc.). In light of previous studies, children with ADHD might have an increased baseline risk of cardiovascular complications due to decreased vagal tone and increased heart rates (HR).[1,8,9] In addition, methylphenidate (MPH), which is the drug of choice worldwide for patients with ADHD, is also of concern to pediatricians due to its sympathomimetic effects. It has been reported that the sympathomimetic (noradrenergic and dopaminergic) effects of MPH may cause increases in systolic and diastolic blood pressure (BP) and HR, QTc prolongation, arrhythmias, and even sudden death.[10,11] Conversely, cardiovascular side effects are primarily transient, dose-dependent, and easily rectified with dosage adjustments.[6] In addition, they are considered minor from a clinical perspective, considering the level of improvement in behavior and cognitive functioning observed in most children. The primary evaluation of these patients for screening for possible adverse effects of MPH treatment involves an investigation of cardiac symptoms, physical examination, electrocardiogram (ECG), measurement of QTc duration and BP, and a detailed family history.

HR variability (HRV) is the degree of variation in the beat-to-beat differences in heart rhythm. It is a non-invasive marker of autonomic nervous system (ANS) activity based on the dynamic interplay of sympathetic and parasympathetic inputs to the sinus node.[12] High HRV indicates adaptability to environmental and physiological demands and low HRV indicates autonomic dysfunction. A sympathovagal imbalance, which is characterized by a decrease in vagal activity or an increase in sympathetic activity, is a marker of cardiovascular morbidity.[13,14] There is controversy regarding the sympathovagal imbalance in patients with ADHD, as illustrated by HRV in previous studies.[1,9,15-17] In the present study, we aimed to assess the effects of MPH treatment on the cardiovascular system and autonomic activity of the heart using HRV analysis in this patient group.

METHODS

This retrospective study evaluated 33 patients (24 males) and 36 healthy controls (21 males) using our hospital's computerized database. The patient group consisted of patients referred to the pediatric cardiology department for baseline evaluation with a diagnosis of ADHD on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; American Psychiatric Association 2013. We analyzed the results of physical examination, systolic and diastolic BP measurements, ECG, and 24-hour Holter monitoring in all patients and the control group. In addition, the results of physical examination, ECG, and 24-hour Holter monitoring at the end of the first month of MPH treatment were compared with the pre-treatment findings in the patient group. Subjects with congenital heart defects, dysrhythmia, systemic illness, hypothyroidism, or hyperthyroidism were excluded from the study. The confidentiality of the information was assured, and no incentives or inducements were offered to participants during the study. The study was approved by the Ankara Child Health and Diseases Oncology Training and Research Hospital Clinical Research Ethics Committee (protocol no: 2013/059, date: 22.10.2013).

QTc Interval Measurements

All standard 12-lead ECGs were acquired simultaneously at a paper speed of 25 mm/s and standardized to 1 mV/cm (0.08-35 Hz, 500 sps) using the same recorder (MAC 400; GE Medical Systems, Milwaukee, WI, USA). The ECG recordings were analyzed by a single investigator in a blinded manner. QTc intervals were measured manually using calipers to improve accuracy. QT was defined as the time from the onset of the QRS complex to the end of the T-wave, with a return to the isoelectric line. In the presence of U waves, the offset of the T wave was defined as the nadir between the T and U waves. If it was not possible to identify the end of the T wave, the lead was ruled out. Three successive QT intervals were measured, and the average was calculated for each lead.

24-h Holter Monitoring

The 24-hour Holter recordings were performed using a three-channel DMS 300-3 A Holter system (DM Software, Inc., Stateline, NV, USA). HRV analysis was based on changes in consecutive RR intervals, where measurements were performed dynamically on 24-h recordings. Abnormal beats and artifact areas were rejected. Recordings less than 18 h and those with significant arrhythmias were excluded to avoid effects caused by circadian variation in HRV. HRV was measured by calculating the time and frequency domain indices from 24-h recordings. The same qualified cardiologist carefully analyzed the Holter ECGs. Measurements of HRV were performed using only normal-to-normal intervals according to the standards of the Task Force of the European Society of Cardiology and the American Society of Pacing and Electrophysiology.[14]

The time domain indices of HRV were examined as follows: standard deviation of all normal sinus R-R intervals (SDNN); mean of the standard deviations of all normal sinus R-R intervals for all 5-minute segments of the entire recording (SDNNI); standard deviation of the averages of R-R intervals in all 5-minute segments of the entire recording (SDANN); square root of the mean of the sum of square differences between adjacent filtered RR intervals (rMSSD); and percentage of the difference between adjacent RR intervals greater than 50 milliseconds for the whole period of analysis (PNN50). Although rMSSD and pNN50 primarily reflect parasympathetically mediated changes in HR, other time domain variables reflect a mixture of parasympathetic, sympathetic, and other physiological influences.

Frequency domain analysis was performed on 300-s segments selected at the time of lowest HR during the entire recording period and free of abnormal data. We determined the spectral power over three frequency regions of interest: VLF, very low-frequency index (0.017-0.05 Hz range); LF, low-frequency index (0.05-0.15 Hz range); HF, high-frequency index (0.15-0.50 Hz range). We also determined the total power (all frequencies greater than 0.017 Hz) and LF/HF ratio. HF reflects cardiac vagal activity, and LF is affected by both the vagal and sympathetic systems. LF/HF is an indicative parameter for assessing autonomic balance.

Statistical Analysis

Results were analyzed using commercial statistical software [Statistical Package for the Social Sciences (SPSS) for Windows, version 21.0; SPSS Inc, Chicago, IL, USA]. Continuous variables are presented as mean (standard deviation) or median (minimum-maximum), where appropriate, and categorical variables are presented as numbers (%). Continuous variables were compared between groups using Student's t-test or Mann-Whitney U test, depending on whether they were normally distributed or otherwise, as tested using the Shapiro-Wilk test. Statistics obtained by Wilcoxon signed rank test or Paired samples t-test for dependent variables. A value of $p<0.05$ was considered statistically significant.

RESULTS

We studied 33 children diagnosed with ADHD (24 boys, 9 girls) and 36 healthy children (21 boys, 15 girls) with a similar gender distribution (p=0.317). The mean ages of the patient and control groups were 9.72.6± and 9.542.8± years, respectively (p=0.75) (Table 1).

HR, QTc duration, and systolic and diastolic BP measurements were not significantly different between the control and patient groups at diagnosis (p=0.71, p=0.314, p=0.597, and p=0.646, respectively). After MPH treatment, the patients' systolic and diastolic BP slightly increased, but this was not statistically significant (p=0.059, p=0.063, respectively) (Table 1). However, the HR and QTc duration increase was statistically significant in the patient group (p=0.001, p<0.001, respectively). HR increased from 87±12 beats/min to 96±15 beats/min; QTc duration increased from 387±15 msec to 416±22 msec at the end of 1st month of MPH treatment. No patients required discontinuation

Table 1. Descriptive and clinical data of the patient and control groups

	Controls (n=36)	Pre-treatment (n=33)	Value	p	After treatment (n=33)	t value	p¥
Age	9.5±2.8	9.7±2.6	-0.264	0.793	N/A	N/A	N/A
Male (%)	21 (58.3)	24 (72.7)	1.002*	0.317	N/A	N/A	N/A
Heart rate (min^{-1})	92±14	87±12	-1.833	0.71	96±15	-3.598	**0.001**
QTc (ms)	391±19	387±15	-1.015	0.314	416±22	-7.820	**<0.001**
Systolic blood pressure (mmHg)	103±15	99±14	-0.532	0.597	107±13	-1.960	0.059
Diastolic blood pressure (mmHg)	61±10	60±11	-0.462	0.646	65±7	-1.924	0.063

*Chi-square value. Other values in this column indicate t-values; ¥Comparison of patient group before and after treatment.
BP: Blood pressure, N/A: Not applicable

of MPH treatment due to significant cardiovascular complaints or drug-related dysrhythmia.

24-h Holter monitoring revealed similar minimal, maximal, and average HRs between the patient and control groups upon diagnosis (p=0.849, p=0.777, and p=0.763, respectively). However, there was a slight but statistically significant increase in the average HR after MPH treatment in the patient group (p=0.044). Although rare supraventricular extrasystoles were observed in 5 patients and rare ventricular extrasystoles in 2 patients on pre-treatment Holter monitoring, similar findings were observed after MPH treatment in the patient group. In the control group, rare supraventricular extrasystoles were noted in 3 children. HRV analyses revealed no statistically significant difference between the time and frequency domain indices between the control subjects and patients with ADHD (Table 2). Similarly, these parameters were not different between the control subjects and patients in the first month of treatment. RMMSD, pNN50, and HF, which reflect predominantly parasympathetic activity in the heart, were slightly higher in the patient group than in the healthy controls before MPH treatment (p>0.05). After the first month of medical treatment, no significant difference was observed in the time domain analyses. However, only LF decreased significantly as a frequency domain parameter (993.2±510 ms^2 vs. 875.1±434 ms^2, p=0.039).

DISCUSSION

Although the exact mechanism of ADHD has not been completely understood, it is suggested that a genetic imbalance in catecholamine metabolism in the cerebral cortex and ANS dysregulation may play a primary role. However, reports regarding the imbalance between vagal tonus and sympathetic activity in ADHD are confusing.[1,9,18-20] In addition, several factors, including the social environment, chemicals, drugs, nutrition, and some neuro-metabolic disorders, may contribute to disease development.[5]

Inattention, hyperactivity, and emotional and behavioral abnormalities are the clinical characteristics of ADHD. The symptoms are associated with serious cognitive, academic, and social problems in affected children. It has been suggested that reduced function of the prefrontal cortex plays a significant role in the occurrence of these findings in patients with ADHD.[6] Different parts of the prefrontal cortex are responsible for various functions, including higher-order autonomic control. According to various neuropsychological and neuroimaging studies, an alteration in these functions is believed to be the neurobiological basis for the symptoms observed in ADHD patients.[21] Furthermore, it has been suggested that characteristic symptoms of ADHD reflect impairment in emotional self-regulation, which the ANS predominantly regulates.[13] Thus, it is reasonable to expect dysregulation of

Table 2. Comparison of the time- and frequency-domain HRV parameters between the patient and control groups

	Controls (n=36)	Pre-treatment (n=33)	Value	p	After treatment (n=33)	Value	p¥
Maximum HR (min^{-1})	166±17	165±12	0.285	0.777	170±14	0.285	0.077
Minimum HR (min^{-1})	51±6	52±6	-0.191	0.849	52±7	-0.191	0.586
Average HR (min^{-1})	90±12	89±9	0.303	0.763	91±9	0.303	**0.044**
SDNN (ms)	131.5±43.1	137.1±33.5	-0.601	0.550	133.7±36.5	-0.601	0.353
SDANN (ms)	112.4±41.4	121.7±32.7	-1.034	0.305	120.2±38.6	-1.034	0.737
SDNN index (ms)	64.5±19.7	65.8±18.1	-0.295	0.769	63.2±18	-0.295	0.086
RMSSD (ms)	43 (18-87)	45 (15-93)	-0.557	0.580	43 (12-97)	-0.557	0.608
PNN50 (%)	18.4±10.7	19.1±10.3	-0.278	0.782	19.2±12	-0.278	0.963
Total power (ms^2)	3881.5 (790.3-11880)	3903.1 (1070.4-10129.9)	-0.432*	0.665	3661.2 (958.9-7943)	-1.706*	0.088
VLF (ms^2)	2392.4 (450.5-8804.4)	2367.2 (694-6933)	-0.372*	0.710	2412.9 (603.7-5476.6)	-1.867*	0.062
LF (ms^2)	892.8±464	993.2±510	-0.857	0.395	875.1±434	2.150	**0.039**
HF (ms^2)	568.1±293.3	657.1±384.1	-1.075	0.286	619.6±367.1	-1.075	0.352
LF/HF	1.7 (0.9-2.8)	1.5 (0.9-5.9)	-0.877	0.384	1.5 (0.9-6.45)	-0.877	0.372

*Z-value. Other values in this column indicate t-values. ¥Comparison of patient group before and after treatment.

HR: Heart rate, SDNN: Standard deviation of all NN intervals, SDANN: Standard deviation of all 5-minute NN intervals, rMSSD: Square root of the mean of the sum of squares of differences between adjacent NN intervals, PNN50: Percentage of the difference between adjacent RR intervals that was greater than 50 milliseconds for the whole period of analysis, VLF: Very low frequency, LF: Low frequency, HF: High frequency, LF/HF: Low frequency/high frequency

cardiac autonomic functions. Most efforts to assess these effects in these patients are accomplished by evaluating autonomic regulation.

HRV, the beat-to-beat variation of HR, is a simple and noninvasive method for evaluating the effect of ANS on sinus nodes. Lower HRV due to sympathovagal imbalance is associated with cardiovascular morbidity, whereas higher HRV reflects good adaptability to environmental and physiological demands. It can be measured using continuous ECG, which provides information about the autonomic balance.[9,14]

MPH is one of the most preferred psychostimulants for the treatment of patients with ADHD.[6,8,11,22-25] The potential cardiovascular side effects of MPH due to its sympathomimetic effects have been a major concern for treatment. However, MPH treatment is highly effective in relieving symptoms and increasing school success, and data from clinical trials can guide the concerns of physicians and families.

In our study, contrary to previous studies, no significant difference was found between children with ADHD and healthy controls regarding the ANS indices obtained using HRV. 24-h Holter monitoring showed a slight but significant increase in average HR after MPH treatment in the patient group. Although LF decreased significantly after the first month of MPH treatment in the patient group, the clinical value of this finding should be assessed.

Buchhorn et al.[1] revealed that MPH treatment caused a significant decrease in circadian HR and increased the expression of markers reflecting vagal tone, sNN50, and rMSSD in 24-h Holter recordings. Similar findings were reported in another study using a different methodology: 5-min Holter ECG recordings from a 12-week prospective study. A meta-analysis by Robe et al.[18] concluded that the findings provide evidence for associations between ADHD and autonomic dysregulation. However, another meta-analysis presented a conflicting result. Koenig et al.[19] found no differences in short-term measures of vagally-mediated HRV, and concluded that ADHD is not associated with altered resting-state vagal tone, unlike other psychiatric disorders.

In 2006, the U.S. the Food and Drug Administration added a black box warning that stimulants may cause severe cardiovascular effects, such as increased BP and HR, severe cardiac arrhythmias, and even sudden death. However, MPH remains the treatment choice for children with ADHD, and several reports have reported conflicting results regarding side effects.[23,24] Our 24-h Holter monitoring revealed that minimal HR, maximal HR, and HRV indices reflecting sympathetic and parasympathetic influences were similar between patients and controls. In addition, we did not observe any cardiovascular side effects during treatment.

Another concern for pediatricians and child psychiatrists is the increase in BP during MPH treatment in children with ADHD. In our study, a slight increase in systolic and diastolic BP was observed in the MPH-treated patient group; however, this increase was neither statistically significant nor exceeded the 95th percentile. Although this sympathomimetic drug has the potential to cause systemic hypertension, the risk does not appear to be significant at therapeutic doses.[10,20,25] Finding et al.[20] examined the cardiovascular effects of MPH and Adderall in a clinic-based group of youth with ADHD. They found that the short-term cardiovascular effects of both drugs were modest, without any significant changes in the cardiovascular measurements. Buitelaar et al.[25] and Bhat et al.[26] reported statistically significant increases in systolic and diastolic BP 45 min after MPH administration during the daytime without any clinical symptoms. These clinically insignificant differences may be attributable to differences in the design of the studies and the number or age of subjects. Furthermore, Schelleman et al.[23] investigated cardiovascular events and mortality in children exposed to and unexposed to ADHD agents. They reported that the rate of cardiovascular events in exposed children was very low and generally not higher than that in unexposed control subjects.

Study Limitations

Our study has several limitations. First, the study has a retrospective design. Second, the number of patients in the trial was relatively small, possibly affecting the power of the study. Third, BP was measured at outpatient visits, and 24-h BP monitoring was not performed. However, we repeated the BP measurements to rule out white-coat hypertension in cases of abnormal results. Finally, medication adherence could not be checked because the patients were followed up at outpatient visits. We continued medication according to the parents' reports and excluded patients who were not adequately adherent to MPH treatment.

CONCLUSION

Children with ADHD are prevalent worldwide, and pediatricians and child psychiatrists often encounter these patients during their daily work. Although recent pediatric data demonstrate the efficacy and safety of MPH treatment, physicians still have concerns when making diagnostic and treatment decisions. This study supports the contemporary outcomes that MPH had no significant cardiovascular effects in children with ADHD, except for an increase in HR and prolongation of QTc duration. Drugs that may prolong QTc interval should be prescribed, and

rhythm and BP should be monitored regularly in patients receiving sympathomimetic agents.

Ethics

Ethics Committee Approval: The study was approved by the Ankara Child Health and Diseases Oncology Training and Research Hospital Clinical Research Ethics Committee (protocol no: 2013/059, date: 22.10.2013).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Ö.T., A.K., Concept: Ö.T., A.K., Design: Ö.T., A.K., Data Collection or Processing: Ö.T., A.K., Analysis or Interpretation: Ö.T., A.K., Literature Search: Ö.T., A.K., Writing: Ö.T.

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Original Article / Orijinal Araştırma

Analysis of Amniocentesis Results in a Tertiary Care Center: A Retrospective Cohort Study

Üçüncü Basamak Bir Merkezde Amniyosentez Sonuçlarının Analizi: Retrospektif Bir Kohort Çalışması

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ABSTRACT

Objective: To investigate the results of patients who underwent amniocentesis.

Methods: Information about patients who underwent amniocentesis between May 2021 and May 2022 at the perinatology department of training and research hospital was obtained from the database and evaluated. The demographic characteristics of the patients, indications for amniocentesis, and clinical results of the procedures were also evaluated. Maternal age, gestational age at the time of amniocentesis, amniocentesis indication, and karyotyping results were reviewed and analyzed.

Results: A total of 579 patients were included in the study. The mean ages of the patients and weeks of gestation at the time of the procedure were 32.28 (minimum 17, maximum 50) and 16.32 (minimum 14, maximum 32), respectively. Amniocentesis was most frequently performed in our clinic, with an indication for increased risk according to the dual screening test. Clear chromosome analysis could not be performed using the quantitative fluorescent polymerase chain reaction method in 17 patients, and 38 patients had an abnormal result for long-term cell culture.

Conclusion: Amniocentesis is a frequently used fetal invasive karyotyping procedure. Amniocentesis indications are increasing with the progress of prenatal diagnosis. It is a relatively safe procedure when performed by experienced hands.

Keywords: Amniocentesis, fetal invasive karyotyping, increased risk in screening test, QF-PCR

ÖZ

Amaç: Amniyosentez yapılan hastaların retrospektif olarak değerlendirilmesidir.

Yöntem: Eğitim ve araştırma hastanesiperinatoloji bölümünde, Mayıs 2021 ile Mayıs 2022 tarihleri arasında yapılan amniyosentez vakaları retrospektif olarak değerlendirildi. Hastane veri tabanı incelenerek veriler toplandı. Hastaların demografik özellikleri, amniyosentez endikasyonları, yapılan işlemlerin klinik sonuçları incelendi.

Bulgular: Mayıs 2021 ile Mayıs 2022 tarihleri arasında kliniğimizde toplam 579 hastaya amniyosentez işlemi yapıldı. Hastaların yaşlarının ve işlem anındaki gebelik haftalarının ortalamaları sırasıyla 32,28 (minimum 17, maksimum 50), 16,32 (minimum 14, maksimum 32) olarak saptandı. Amniyosentez işlemi; kliniğimizde en sık ikili tarama testinde risk artışı endikasyonu ile uygulandı. Amniyosentez materyalinden alınan örnekle yapılan kantitatif floresan polimeraz zincir reaksiyonu yöntemiyle yapılan anöploidi taramasında 17 hastanın kromozom analizi net yapılamamıştır. Uzun süreli hücre kültürü sonuçları 38 hastanın anormal olarak tespit edildi.

Sonuç: Amniyosentez sıklıkla uygulanan bir fetal invaziv karyotipleme işlemidir. En sık tarama testlerindeki risk artışı endikasyonları ile yapılır. Tecrübeli eller tarafınca uygulandığında oldukça güvenli bir prosedürdür.

Anahtar Kelimeler: Amniyosentez, fetal invaziv karyotipleme, tarama testinde risk artışı, QF-PCR

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INTRODUCTION

Amniocentesis is used for diagnostic and therapeutic purposes, including chromosomal, biochemical, histopathological, and microbial assessments.[1-3] This process aids families in making informed decisions about continuing the pregnancy, preparing for birth, and understanding the newborn's prognosis while also assisting the physician in diagnosis.[4,5] Counseling should be provided to the family regarding the indications, risks, benefits, and limitations of the procedure.[6]

Although the risks associated with amniocentesis are considered minimal, this procedure is invasive and not entirely free of complications. These complications can include the loss of amniotic fluid during or after the test, fetal injury during the procedure, and pregnancy loss, which is one of the most feared complications. Current studies indicate that the rate of fetal loss related to the procedure is less than 1%.[5,7,8] Recent research shows that the complication rate associated with amniocentesis may depend on factors such as the needle thickness used, whether the puncture is performed transplacentally, the number of punctures, and the experience of the operator. Literature data suggest that at least 30 tests per year are necessary to maintain proficiency and minimize risks associated with practitioner experience.[5,7]

The aim of our study was to examine the indications for amniocentesis, demographic characteristics of patients, and clinical outcomes of amniocentesis in a tertiary hospital.

METHODS

This retrospective cohort study included all patients who underwent amniocentesis at the perinatology clinic of the research hospital between May 2021 and May 2022. Ethical approval was obtained from the Ethics Committee of University Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital Ethics Committee (approval no: 2022/11-24, date: 09.12.2022). Written informed consent was secured from each participant.

Amniocentesis is generally performed in the second trimester. Prior to the procedure, an ultrasound examination is conducted to verify fetal viability, determine gestational age, count the number of fetuses, evaluate placental position, measure amniotic fluid volume, perform fetal anatomical assessment, and identify any uterine cavity abnormalities or fibroids.[9]

The maternal abdomen is disinfected with an antiseptic solution and draped. Due to the possibility of fetal movements altering the locations of amniotic fluid pockets, a larger area of the maternal abdomen is prepped than the designated needle insertion site. A 20-gauge, 9-14 cm long sterile spinal needle is used for the procedure. The ultrasound probe is placed in a sterile cover, with non-sterile gel applied inside and sterile gel on the outside, in contact with the mother's skin. All procedures were conducted by fellows under the supervision of experienced specialists. We use the freehand technique in our clinic, which allows adjustment of the needle entry route. The transducer was held by the fellows while inserting the needle, continuing to visualize the needle tip until an assistant collected the amniotic fluid samples. If the needle tip position is indiscernible on the screen, the needle is not advanced. Using the fellow's wrist, a sudden thrust as the needle passes through the uterine muscle into the amniotic cavity prevents tenting of the membrane.

The extracted amniotic fluid consists of shed fetal cells, transudates, fetal urine, and lung secretions.[7,10-12] As the initial drop of amniotic fluid may contain maternal cells adhering to the needle from the mother's skin, it is discarded to avoid maternal cell contamination in cytogenetic studies. After replacing the syringe, the aspiration of the amniotic fluid was continued. Approximately 20-30 mL of amniotic fluid is aspirated using sterile syringes or vacuum tubes. Several reports have suggested that prolonged contact of the fluid with the syringe stopper can inhibit cell growth in cultures; therefore, we used poisonless syringes to mitigate this risk.

Post-procedure, the fetal heart rate is evaluated and recorded. Patients will be instructed to report any vaginal fluid loss, bleeding, severe uterine cramping lasting for several hours, or fever. There are no restrictions on physical or sexual activity following the procedure. RhD-negative patients who were not alloimmunize will receive Rh(D) immune globulin to prevent RhD sensitization.

Maternal and fetal data were retrieved from the medical records department, including maternal age, indications for amniocentesis, gestational age at the time of amniocentesis, quantitative fluorescent polymerase chain reaction (QF-PCR) results, karyotyping results, and any intra- or postprocedural complications. Data tables were created to calculate mean and median values, including averages for maternal and gestational ages at the time of amniocentesis.

Statistical Analysis

Statistical data were analyzed using the Statistical Package for the Social Sciences software version 26.0. Categorical data were obtained using frequency analysis and are presented as numbers and percentages. Numeric data were obtained by descriptive analysis and presented as means, standard deviations, and minimum-maximum values.

RESULTS

The mean ages of the patients and gestational weeks at the time of the procedure were 32.28 (minimum 17, maximum 50), 16.32 (minimum 14, maximum 32), respectively. Six of the patients who underwent amniocentesis had multiple pregnancies (5 twice, 1 triplet).

Amniocentesis procedure; was performed in our clinic with the most frequent indications of increased risk according to the double screening test in 270 (46.6%) patients, increased risk according to the triple screening test in 59 (10.2%) patients, and maternal anxiety in 37 (6.4%) patients (amniocentesis indications are shown in Table 1). In addition, amniocentesis procedure was performed to affected in previous pregnancy 19 (3.2%) patients, abnormal non-invasive fetal test (NIFT) results in 9 (1.6%) patients, increased risk in quadruple screening test 7 (1.2%) patients, maternal infection in 18 patients (10 toxoplasma, 8 cmv), maternal translocation in 1 patient, carrier of both maternal and paternal muscle disease in 1 patient, and ultrasonographic findings (major fetal anomaly, soft marker) in 158 patients. Details regarding the indications to be affected in previous pregnancy are presented in Table 2.

In the aneuploidy screening performed using the QF-PCR method with the sample taken from the amniocentesis material, a clear chromosome analysis of a total of 20 patients could not be performed; the data are shown in detail in Table 3. The sex chromosomes of 9 patients, the 18th chromosome of 4 patients, the 13th chromosome of 3 patients, and the 21st chromosome of 1 patient could not be made clearly, and contamination was detected in 3 patients.

The final result of 7 cases whose sex chromosome could not be analyzed clearly by QF-PCR was reported as normal karyotype, the definitive karyotype of 1 case was 47 XYY, and the definitive karyotype of 1 case was 47 XXY. In 3 of 4 cases whose chromosome 18 could not be clearly analyzed by QF-PCR, the cytogenetic result was normal karyotype, and Leigh syndrome was detected in 1 case. The final results of 3 cases whose 13th chromosome could not be clearly analyzed by QF-PCR and 1 case whose 21st chromosome could not be clearly analyzed were reported as normal karyotype. The final result of 2 of 3 patients whose QF-PCR result was uncertain due to contamination was a normal karyotype, and the result of 1 patient was 46 der[20]. Long-term cell culture results confirmed trisomy 21 in 11 patients, trisomy 18 in 8 patients, and trisomy 13 in 2 patients. Sex chromosomal anomalies (1 45 X0, 1 47 XXY, 1 47 XYY, 1 47 XXX) were found in 4 patients, structural chromosomal anomaly in 6 patients, and Leigh syndrome in 2 patients.

Table 1. Amniocentesis indications

Indications	Number (n)	Percentage (%)
Increased risk in double-screening	270	46.6
Ultrasonography finding	158	27.28
Increased risk in triple-screening	59	
Maternal anxiety	37	10.2
Affected in previous pregnancy	19	6.4
Abnormal NIFT test result	9	3.2
Increased risk in quad screening	7	1.6
Maternal infection	18	1.2
Maternal translocation	1	3.2
Carrier of both maternal and paternal muscle diseases	1	
Total	579	100

NIFT: Non-invasive fetal test

Table 2. Details regarding the indications to be affected in previous pregnancy

	Number (n)	Percentage (%)
Trisomy 21	6	33
History of trisomy 18	1	5.5
History of trisomy 13	1	5.5
Structural chromosomal anomaly	1	5.5
SMA type 1	3	16.5
Prader-Willi syndrome	1	5.5
Leigh syndrome	2	11
Genetic mutation	2	11
History of triploidy in previous miscarriage	1	5.5
Total	18	100

SMA: Spinal muscular atrophy

The results of 4 patients were unsatisfactory. Mosaicism was detected in 1 patient. The results are presented in Table 4.

No false-positive results were observed for the QF-PCR test. Of the 38 abnormalities detected by cytogenetic analysis, 24 fetuses were diagnosed as chromosomal abnormal (63.15%). A clear analysis of 3 cases with genetic abnormalities could not be performed using QF-PCR test (7.89%). The final result of 7 of 9 cases for which sex chromosome analysis could not be performed by QF-PCR test was normal karyotype and normal sex chromosome, and sex chromosome anomaly (1 patient 47, XXY, 1 patient 47, XXY) was detected in 2 patients. QF-PCR showed 100% specificity for chromosome 21, 18, 13, and X and Y aneuploidies, with 100% positive predictive value and 99.7% negative predictive value. No premature rupture of membranes or vaginal/intrauterine bleeding occurred in the early postoperative period in patients undergoing amniocentesis.

DISCUSSION

Our study identified increased risk in the double screening test as the most common indication for amniocentesis, followed by increased risk in the triple screening test. These findings contrast with those of earlier studies in which advanced maternal age was the predominant indication for the procedure.[13,14] In our study, the second trimester was the most frequent gestational period for amniocentesis, which is consistent with the findings of other studies. The chromosomal anomaly rate in our cohort was 6.5% (38 cases), which is consistent with the rates reported by Ercan et al.[15]

The most prevalent chromosomal abnormality detected was trisomy 21 (Down syndrome), representing 28.94% of cases, followed by trisomy 18 (Edwards syndrome) at 21%, and structural chromosomal abnormalities at 15.78%. Unlike the study by Zhang et al.[16], our study found a higher frequency of structural chromosomal anomalies compared with trisomy 13 (Patau syndrome).

Amniocentesis is an invasive procedure that carries certain risks, such as amniotic fluid leakage, miscarriage, and preterm birth. Procedures performed before 15 weeks are associated with higher rates of fetal loss and complications, including culture failure, and should be delayed if possible.[17] In our study, the mean gestational age during the procedure was 16.32 weeks, and the procedure was performed on three patients after 14 weeks. The cytogenetic results for two of these three patients were unsatisfactory. No cases of premature membrane rupture or vaginal/intrauterine bleeding were observed in the early postoperative period.

Later second-trimester procedures are generally safe, but they may pose challenges if pregnancy termination is planned based on abnormal results. In our study,

Table 3. Quantitative fluorescent polymerase chain reaction; details of cases for which clear chromosomal analysis could not be performed

	Number (n)	Percentage (%)
The sex chromosome cannot be clearly analyzed 18th chromosome could not be analyzed	9 4	45 20
13th chromosome could not be clearly analyzed	3	15
21st chromosome cannot be clearly analyzed	1	5
Contamination	3	15
Total	20	100

Table 4. Patients with abnormal amniocentesis culture results

	Number (n)	Percentage (%)
Trisomy 21	11	28.94
Trisomy 18	8	21
Trisomy 13	2	5
Sex chromosomal anomaly	4	10.52
Structural chromosomal abnormalities	6	15.78
Leigh syndrome Insufficient result	2 4	5.26 10.52
Mosaicism	1	2.63
Total	38	100

amniocentesis was performed in eight patients in the late second trimester. The ethics committee recommended termination for two patients with hydrops fetalis and one patient with multiple anomalies.

Amniocentesis is also used as a therapeutic procedure to reduce amniotic fluid volume in conditions such as symptomatic polyhydramniosis or twin-to-twin transfusion syndrome.[18] In our clinic, amnioreduction was performed in three patients due to polyhydramnios in the last trimester.

The efficacy of prophylactic antibiotics for reducing pregnancy loss associated with amniocentesis has not been comprehensively evaluated. One study involving 33,748 patients randomly assigned to receive azithromycin or no antibiotic treatment before amniocentesis found fewer fetal losses in the prophylaxis group.[19] A single operator conducted all the procedures. During the first 4 weeks post-procedure, the prophylaxis group experienced fewer fetal losses than the control group. Nearly half of the fetal losses (21 out of 43) were associated with preterm prelabor rupture of membranes, which was also less frequent in the prophylaxis group. In our clinic, we administered prophylactic antibiotic therapy to all patients undergoing amniocentesis.

Risk factors for pain during amniocentesis include maternal anxiety, lower uterine needle insertion, history of menstrual cramps, and previous amniocentesis.[20] Local anesthesia is optional and usually unnecessary, as most patients experience no or mild discomfort.[20-23] In our clinic, local anesthesia was not administered to any patients.

The use of simultaneous ultrasound guidance rather than pre-amniocentesis ultrasound evaluation has not been associated with a reduced rate of fetal loss in controlled studies.[3] However, to avoid direct fetal damage and reduce the number of punctures and the possibility of bloody fluid, we perform amniocentesis on all patients with ultrasonographic monitoring, in which the needle is constantly monitored throughout the procedure.

The optimal needle insertion site for amniocentesis should avoid the placenta if possible. Some studies have suggested a higher risk of fetal complications with transplacental amniocentesis, though this has been contested by other studies.[24-35] When a transplacental approach is necessary, there are two options: crossing the placenta or delaying the procedure to allow for a larger intrauterine volume. In our clinic, we preferred the first option of transplacental insertion in 300 out of 579 patients, with no complications observed in either group.

Aneuploidy was detected in five of nine patients who underwent amniocentesis due to abnormal NIFT test results. The amniocentesis QF-PCR and culture results of four patients at high risk of trisomy 21 according to NIFT were consistent with trisomy 21. Four patients with NIFT results indicating a high risk of sex chromosome or structural chromosomal anomalies were found to have normal karyotypes upon amniocentesis. One patient with a high risk of trisomy 13 according to NIFT was confirmed to have trisomy 13 due to a Robertsonian translocation in chromosome 13.

In our study, 536 out of 541 cases diagnosed as having normal karyotype according to long-term cell culture results were confirmed as chromosomal normal by QF-PCR, a rate higher than that reported in the literature.[36] This discrepancy may be due to NIFT not being included in the free national prenatal screening program in our country, leading pregnant women at risk for increased risk for double tests or sonographic markers to seek diagnostic testing.

Study Limitations

Our study has some limitations. It is single-centered and covers the early period in terms of complications.

CONCLUSION

Amniocentesis is a frequently performed fetal invasive karyotyping procedure. It has become increasingly safe with a low rate of pregnancy loss and is considered a reliable and low-risk method for obtaining genetic material. Our results indicate that the procedure is safe and should be offered to all women requesting diagnostic testing, regardless of risk factors or anomalies.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital Ethics Committee (approval no: 2022/11-24, date: 09.12.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: R.T., B.S., S.T.C., C.S., M.Ö., Z.E.Ç., A.G.Ş.Y., A.E., Concept: R.T., Design: R.T., Data Collection or Processing: R.T., B.S., S.T.C., C.S., M.Ö., Z.E.Ç., A.G.Ş.Y., A.E., Analysis or Interpretation: R.T., B.S., Literature Search: R.T., Writing: R.T.

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Original Article / Orijinal Araştırma

A Life-threatening Environmental Emergency: Childhood Drowning

Hayatı Tehdit Eden Bir Çevresel Acil: Çocukluk Çağı Boğulmaları

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ABSTRACT

Objective: Childhood drowning is a common environmental emergency worldwide. In this study, we examined drowning and non-fatal drowning (NFD) cases and tried to determine which parameters could predict prognosis during follow-up.

Methods: This study was conducted in a tertiary pediatric emergency room. The study population comprised cases of drowning/NFD between 2008 and 2021. Age, gender, and drowning mechanisms. Laboratory examinations, and the outcomes of these cases were analyzed. The data were obtained from the hospital automation system. The Szpilman score (SC) of each patient was calculated.

Results: A total of 150 cases were included in the study. The ages of the cases were 5.2±3.8. The mean Glasgow Coma Scale (GCS) score was found to be 12.2±3.8. Cardiopulmonary resuscitation (CPR) was performed in 75 cases (50%), and 30 cases (20%) patients were intubated. Cases were divided into two groups: those in the intensive care unit and those followed in the emergency department. The mean SC of the follow-up group was 1.4±0.6, and the mean SC of the intensive care group was 4.6±1.4 ($p<0.01$, $T=19.3$). A strong negative correlation was found between the SC and GCS ($p<0.01$, $r=-929$) and a strong positive correlation was found between the respiratory support system ranking-from simple to complex-and the SC ($p<0.01$, $r=827$).

Conclusion: High SC, CPR, low GCS, young age, and low blood pH were associated with an increased rate of intensive care unit admission.

Keywords: Environmental emergency, childhood drowning, Szpilman score

ÖZ

Amaç: Çocukluk çağında boğulma, dünya çapında yaygın bir çevresel acil durumdur. Bu çalışmada boğulma ve ölümcül olmayan boğulma (ÖOB) olgularını inceleyerek takip sırasında hangi parametrelerin prognozu tahmin edebileceğini belirlenmeye çalışılmıştır.

Yöntem: Bu çalışma üçüncü basamak bir pediatrik acil serviste gerçekleştirilmiştir. Araştırmanın evrenini 2008-2021 yılları arasında boğulma/ÖOB olguları oluşturmuştur. Yaş, cinsiyet, boğulma mekanizmaları, laboratuvar tetkikleri ve sonuçları analiz edilmiştir. Veriler hastane otomasyon sisteminden elde edilmiştir. Her olgu için Szpilman skoru (SC) hesaplanmıştır.

Bulgular: Çalışmaya toplam 150 olgu dahil edildi. Olguların yaşları 5,2±3,8 idi. Ortalama Glasgow Koma Skalası (GCS) skoru 12,2±3,8 olarak bulundu. Olguların 75'ine (%50) kardiyopulmoner resüsitasyon (CPR) uygulandı ve 30 olgu (%20) entübe edildi. Olgular yoğun bakımda yatanlar ve acil serviste takip edilenler olmak üzere iki gruba ayrıldı. Takip grubunun ortalama SC'si 1,4±0,6, yoğun bakım grubunun ortalama SC'si 4,6±1,4 idi ($p<0,01$, $T=19,3$). SC ve GCS arasında güçlü bir negatif korelasyon bulundu ($p<0,01$, $r=-929$) ve solunum destek sistemleri sıralaması (basitten karmaşığa) ile SC arasında güçlü bir pozitif korelasyon bulundu ($p<0,01$, $r=827$).

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Sonuç: Yüksek SC, CPR, düşük GCS, genç yaş ve düşük kan pH'sının yoğun bakıma yatış oranını artırdığı görüldü.
Anahtar Kelimeler: Çevresel acil, çocukluk çağı boğulmaları, Szpilman skoru

INTRODUCTION

Every year, approximately 500,000 people worldwide and 4.000 people in the United States (US) die from drowning.[1,2] Mortality due to drowning was found to be 0.003% for individuals between the ages of 1 and 4 in a study in the US, and 0.1% in children under the age of 2 in a study in Thailand.[3,4] More than 90% of all drowning deaths occur in low-and middle-income countries.[5-9] Although it is difficult to obtain statistics on non-fatal drowning (NFDs), it is a fact that NFDs are several hundred times greater than reported drowning deaths.[10,11] Many terminologies related to drowning have been defined in the literature in recent years, but this approach has also led to serious confusion. In the nomenclature that is accepted today, the condition of death due to respiratory causes as a result of exposure to a liquid environment is simplified as "drowning." If this does not result in death, it is termed NFD.[12] Global age-standardized drowning death rates have decreased from 9.3% in 1990 to 0.004% per year in 2017, but they remain a major preventable cause of pediatric morbidity and mortality.[13-15]

Because of the complexity of the situation, many researchers have developed classification systems to predict prognosis in drowning cases. These studies used large case series data and generally covered the adult age group.[16-19] For example, Menezes and Costa[20] (1972) divided all cases into four grades according to severity and prognostic predictions. The Semple-Hess and Campwala classification systems categorize pediatric drowning patients according to respiratory distress, hypothermia, and the Glascow Coma Scale (GCS) score.[21] In our study, we preferred to use the Szpilman[22] (1997) classification, in which 2.304 cases were examined, including pediatric cases, because this classification system provided a more sensitive grading system compared with Menezes and Costa's[20] classification. According to this classification, Grade 1 has only cough, Grade 2 has occasional crepitant rales on lung auscultation, Grade 3 has crepitant rales in all parts of the lung and a pink foam near the mouth/nose, Grade 4 has Grade 3 auscultation findings in addition to hypotension, Grade 5 has respiratory arrest/apnea, and Grade 6 is classified as "cardiopulmonary arrest."[22]

The aim of the current study was to investigate the characteristics of this life-threatening environmental emergency on the west coast of Turkey. The secondary aim is to determine whether the clinical and laboratory findings at presentation can provide insights regarding prognosis.

METHODS

This was a cross-sectional, observational, and retrospective study. The study was performed at the University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital pediatric emergency clinic, which is the largest trauma reference center in the region of İzmir, a seaside port city located in the west of the Republic of Turkey, a peninsula surrounded by sea. The period examined was 01.01.2008-31.12.2021. Information about the cases was obtained from the hospital's automation system. After obtaining permission from İzmir Kâtip Çelebi University, Non-Interventinal Clinical Studies Ethics Committee (decision no: 0492, date: 18.11.2021) and other necessary approvals, the study began.

All patients admitted to the pediatric emergency department with a complaint of drowning were included in the study. Patients whose data could not be obtained or those referred to a different center during the treatment process were excluded from the study. The dependent variable of the study was fatal or NFD cases, and the independent variables were fatal or NFD case mechanisms, physical and chemical properties of the exposed water, clinical and laboratory findings, and clinical progression of the cases, in addition to demographic information such as age and gender. The cases were assigned to the appropriate Szpilman classification grade according to the available information. Cases were divided into two groups: those in the intensive care unit and those followed in the emergency department. The parameters of these two groups were compared. The cases were also divided into two groups according to whether the water to which they were exposed was salty. The analyses were repeated in these groups as well.

Statistical Analysis

The data obtained were analyzed using the Statistical Package for the Social Sciences 22 package program, and the frequency information of the numerical data was presented as a percentage and mean standard deviation. Chi-square analysis was used for categorical data, Fisher's exact test was used in cases where the chi-square assumption could not be provided, and the T-test was used for numerical data in the comparisons of the two groups. In cases in which normality could not be achieved, non-parametric tests were used. Pearson's correlation coefficient was applied to determine the relationship between the numerical data. Logistic regression modeling was performed. The receiver operating characteristic (ROC) curve was drawn to determine the cut-off value.

RESULTS

A total of 150 patients were included in the study. Ninety (60%) patients were males. The mean age of patients was 5.2±3.8 (1-13). The mean age of the female patients was significantly lower than that of the male patients (mean age of female cases 3.7±1.9, male cases 6.3±4.9 years; p<0.01, T=-4.1). Ninety cases (60%) were in seawater (75 males, 15 females), 30 (20%) were in swimming pools (all girls), and 30 (20%) occurred by falling into a mop bucket (15 girls and 15 boys). The mean GCS was found to be 12.2±3.8 (3-15). Cardiopulmonary resuscitation (CPR) was performed in 45 cases (30%) patients in the field and in 30 cases (20%) patients in the emergency department. Treatment with vasoactive agents was provided in 30 cases (20%) cases, and antibiotics were provided in 75 cases (50%). Sixty cases (40%) were monitored in normal room air, 45 cases (30%) were followed up with a simple oxygen mask, 15 cases (10%) were followed up with high-flow nasal cannula oxygen therapy, and 30 cases (20%) were intubated. Forty-five cases (30%) were followed in the emergency department for 6 hours, 45 cases (30%) were followed for 24 hours in the emergency department, and 60 cases (40%) were followed in the pediatric intensive care unit. None of the cases resulted in death. Chest X-ray of 75 patients (50%) was abnormal. In the physical examination of 75 patients (50%), an abnormal respiratory pattern was detected. In 45 patients (30%), hypothermia was present at admission (Table 1).

Cases of drowning by falling into a swimming pool or bucket were considered drowning in fresh water. When the rates of drowning in fresh and saltwater were compared according to age, the mean age of cases in saltwater was 6.5±4.3 years, whereas the mean age of cases in freshwater was 2±2.3 years (p<0.01, T=-5.6). The mean GCS of cases in freshwater (10.2±4.5) was significantly lower than that in saltwater (13.5±2.5) (p<0.001, T=5.5). There were significant differences in white blood cell counts, hemoglobin levels, blood creatin kinase levels, blood sodium levels, blood potassium levels, blood C-reactive protein levels, partial corbondioxide levels, blood lactate levels, and blood glucose levels between the groups (Table 2). Szpilman scores (SC) were 3.1±1.9 on average in freshwater samples and 2.4±1.8 in saltwater samples (p=0.02, T=2.2) (Table 2).

If we divide the cases into two groups-patients followed for 24 hours and patients hospitalized in the pediatric intensive care unit-the mean age of the follow-up group (6.3±4 years) was significantly higher than that of the intensive care group (3.5±2.5 years) (p=0.001, T=4.7). The mean GCS score of the follow-up group (14.6±0.7 years) was significantly higher than that of the intensive care group (8.5±3.6) (p<0.001, T=15.4). There were significant values in terms of white blood cell counts, blood creatin kinase levels, blood sodium, potassium, calcium, chlorur, C-reactive protein levels, blood pH, partial corbondioxide levels, and blood glucose, urea, creatinin, alanine amino transferase, and aspartat amino transferase levels between the groups. The mean SC of the follow-up group (1.4±0.6) was significantly lower than that of the intensive care group (4.6±1.4) (p<0.01, T=19.3) (Table 3).

ROC curve analysis was performed to determine the cut-off value for the SC. Accordingly, the cut-off point was 3.5, the area under the curve was 0.99, sensitivity was 82%, and specificity was 92%. In subsequent analyses, the cutoff point was 3 because it was an integer. When the correlation between the SC and GCS was examined, a strong negative correlation was found between them (p<0.01, r=-29). When respiratory support systems were ranked from simple to complex, a strong positive correlation was found when this order was compared with the SC (p<0.01, r=827) (Table 4). When CPR performance was compared with the SC, CPR was not performed in any of the cases with a SC 3, and the cases with a SC >3 resulted in 66.7% of all CPR cases (p<0.01, x^2=87). It was observed that all patients in whom vasoactive agents were initiated had a SC >3 (Table 5).

When the relationship between chest X-ray findings and antibiotic use was evaluated, 80% of the patients with abnormal chest X-ray findings started on antibiotic therapy (p<0.01, x^2=54). Antibiotic treatment was started in 75% of the pediatric intensive care unit patients. This value was significantly higher than that of the follow-up group (p<0.01, x^2=25). It was observed that 66.6% of the patients with hypothermia upon admission were admitted to the pediatric intensive care unit (p<0.01, x^2=19). It was observed that 66.6% of the patients with hypothermia upon admission drowned in salt water (p=0.27, x^2=1.1). It was determined that 66.6% of the hypothermic patients received CPR (p=0.01, x^2=41) (Table 6).

In the logistic regression modeling we carried out to determine which variable increased the risk of admission to the intensive care unit, being male resulted in a 3.18-fold increase [95% confidence irterval (CI)=0.941-0.161, p=0.01], freshwater resulted in a 7.9-fold increase (95% CI=4.327-33.010, p=0.01), low pH resulted in a 3.17-fold increase (95% CI=1.005-24.198, p=0.02), a high SC resulted in a 2.3-fold increase (95% CI=4.762-10.192, p<0.01), a low GCS score resulted in a 2.3-fold increase (95% CI=2.751-10.152, p<0.01), and exposure to CPR resulted in a 7.5-fold increase (95% CI=3.761-101.112, p<0.01).

DISCUSSION

The primary aim of this study was to examine the clinical and laboratory parameters of drowning/NFD cases in

Turkey. The aim of this study was also to determine which prognostic factors had a significant effect on outcomes. As a result, we found that being young, drowning in fresh water, receiving CPR, having a low GCS score, and having a low pH were associated with worse prognosis. The secondary aim was to determine how prognosis could be predicted. We conclude that the Szpilman classification is useful in terms of the necessity for respiratory support systems and admission to intensive care units.

By examining the cases of drowning/NFD in terms of average age, the mean age in this study was 5.2 years. This average age has been observed in many studies in the literature. For example, Loux et al.[23] examined 153 drowning/NFD cases in the US and found that the mean age was 4 years. Another study conducted by Moffett et al.[24] in the US, in which they examined 114 cases, the mean age was 4.2 years. Another study conducted by Salas Ballestín et al.,[27] the mean age was 5.3 years, and a mean age of 3.5 years was found according to Habib et al.'s[26] study.

Table 1. The properties of whole-group

		N	%
Gender	Female	60	40
	Male	90	60
Age (mean)	5.2±3.8 (1-13) (whole group)	3.7±1.9 (girls) 6.3±4.9 (boys)	p<0.01 T=-4.1
Drowning mechanism	Sea	90 (75 boys + 15 girls)	60
	Swimming pool	30 (all girls)	20
	Mop bucket	30 (15 boys + 15 girls)	20
CPR in the field	Yes	45	30
	No	105	70
CPR in the ER	Yes	30	20
	No	120	80
Vasopressor agent	Yes	30	20
	No	120	80
Antibiotic	Yes	75	50
	No	75	50
Abnormal breathing	Yes	75	50
	No	75	50
Hypotermia	Yes	45	30
	No	105	60
Breathing support	Normal room O2	60	40.0
	O2 with masc	45	30.0
	High-flow nasal cannula	15	10.0
	IV	30	20.0
GCS (mean)	12.2±3.8 (3-15)		
Spilzman score	1	60	40
	2	28	18.7
	3	24	16
	4	4	2.7
	5	4	2.7
	6	30	20
Observation conditions	6 h in the ER	45	30.0
	6-24 h in the ER	45	30.0
	PICU	60	40.0

GCS: Glasgow Coma Scale, CPR: Cardiopulmonary resuscitation, ER: Emergency room, PICU: Pediatric intensive care unit

By examining the drowning/NFD cases in terms of sex, we found that the number of male cases was higher in both the literature and this study. The rate of male patients in this study was 60%; the rates were 70%, 65%, 60%, 72.5%, and 69%, respectively, in other studies examining childhood drowning/NFD cases.[23-27]

When examining drowning/NFD cases, it is also important to note in which waters these events take place. Undoubtedly, the geographical location of the study site, its distance from the sea, and the temperatures in the summer months will impact this rate. For example, Şık et al.[27] examined 89 drowning/NFD cases on the West Coast of Turkey, of which 58.5% were drowned in salt water. In this study, similarly, the NFD in salt water was found to be 60%. In a study conducted in Florida, US, 93.5% of drowning/NFD cases occurred in fresh water.[23] In a study conducted far from the coast of Texas, 93.4% of cases occurred in fresh water. In a study conducted in Spain, 90% of cases occurred in fresh water.[23-25]

In this study, we evaluated the cases according to their follow-up periods. We evaluated them by dividing them into three groups: those who were discharged from the emergency room (ER) after less than 24 hours, those who were followed up in the ward/ER for more than 24 hours, and those who needed intensive care for any reason. Undoubtedly, the most severe patient group was those admitted to the intensive care unit. In this study, although the rate of hospitalization in the intensive care unit was 40% of all cases, similar values were found in the literature. For example, the percentage of patients hospitalized in the intensive care unit was 31.7%, 44.2%, and 50%, respectively.[23,25,28] Similarly, although the number of cases followed in the ER for 24 hours in this study constituted 30% of all cases, this rate was 60% and 48% in studies in the literature.[27,29]

Table 2. Differences according to salty and fresh water

	Whole group	Fresh water	Salty water	T	p
Age (year) mean	5.2±3.8	2±2.3	6.5±4.3	5.6	**0.01**
Gender	N=120	45 girls+15 boys	15 girls+75 boys	x^2=51	**<0.01**
GCS (mean)	12.2±3.8	10.2±4.5	13.5±2.5	5.5	**0.001**
WBC/µL	11900±3.8	3600±5068	10800±2255	4.6	**0.001**
Hb g/dL	11.2±1	10.7±1.1	11.6±0.6	6.1	**0.001**
Platelet/µL	245900±73960	249000±83821	243833±67002	0.4	**0.6**
CK U/L	530±485	1032±351	196±172	19.3	**0.001**
Na mmol/L	137.2±8.4	133±5.1	139±9.2	5	**0.001**
K mmol/L	3.8±0.3	3.9±0.5	3.8±0.2	5	**0.001**
Ca mg/dL	9.2±0.3	9.27±0.3	9.2±0.3	1.2	**0.2**
Cl mmol/L	105.4±7.1	102.0±5.2	107.6±7.4	1.2	**0.2**
CRP mg/L	8.3±11.5	5.3±5.6	10.7±14.2	2.7	**0.001**
pH	7.26±.09	7.23±0.1	7.28±0.1	3.1	**0.01**
Pa CO_2, mmHg	44.5±6.1	43.7±8.2	45±4.3	1.2	**0.001**
HCO_3 mmol/L	20.8±4.4	21.0±3.7	20.6±4.9	0.4	**0.6**
Lactate mmol/L	2.7±1.6	3.3±1	2.4±1.8	3.1	**0.001**
Glucose mg/dL	129.8±49.3	159.2±57.9	110.1±29.6	6.1	**<0.01**
Ure mg/dL	25.3±9.3	26.5±7.8	24.5±10.2	1.2	**0.2**
Creatinin mg/dL	0.5±0.1	0.4±0.1	0.5±0.1	2.5	**0.1**
AST U/L	44.8±16.3	59.0±12.7	35.3±10.5	12	**0.05**
ALT U/L	19.9±7.9	24.0±6.6	6.6±7.6	5.6	**0.8**
Szpilman score	2.7±1.9	3.1±1.9	2.4±1.8	2.2	**0.02**
Outcome					
Observation group PICU group	N=150	N=30 N=30	N=60 N=30	x^2=4.1	**0.04**

GCS: Glasgow Coma Scale, WBC: White blood cell, Hb: Hemoglobin, CK: Creatine kinase, Na: Sodium, K: Potassium, Cl: Clorur, CRP: C-reactive protein, $PaCO_2$: Partial carbon dioxide pressure, HCO_3: Bicarbonate, AST: Aspartate amino transferase, ALT: Alanine amino transferase, PICU: Pediatric intensive care unit, x^2: Chi-square

Table 3. Differences between the PICU and observation groups				
	Observation group	**PICU group**	**T**	**p**
Age (year) mean	6.3±4	3.5±2.5	4.7	**0.001**
GCS mean	14.6±0.7	8.5±3.6	15.4	**<0.001**
WBC /µL	10025±2156	13181±4200	5.3	**<0.001**
Hb g/dL	11.2±0.5	11.2±11.2	0.1	0.8
Platelet /µL	203333±59252	309750±40061	12.1	0.1
CK U/L	459.3±479.2	637.5±478.8	2.2	**0.02**
Na mmol/L	134±3.5	140±11	T=4.4	**<0.001**
K mmol/L	3.7±0.2	3.9±0.5	2.6	**<0.001**
Ca mg/dl	9.3±0.3	9.05±0.3	5.2	**<0.01**
Cl mmol/L	103±3.3	108±9.8	4.5	**<0.001**
CRP mg/L	3.9±2.2	13.9±15	5.4	**<0.001**
pH	7.30±0.6	7.20±0.1	7.8	**<0.001**
Pa CO_2, mmHg	43.2±9.2	45.3±3.3	2.4	**<0.001**
HCO_3 mmol/L	23.3±3.5	17.0±2.7	11	0.3
Laktat mmol/L	2.5±1.6	2.9±1.6	1.2	0.2
Glucose mg/dL	121±26	143±69	2.7	**<0.001**
Ure mg/dL	23.3±7.9	28.2±10	3.2	**<0.001**
Creatinine mg/dL	0.4±0.1	0.5±0.01	5.4	**<0.001**
AST U/L	42±12	48±20	2.3	**<0.001**
ALT U/L	17.5±9.4	21±4.1	3.08	**<0.001**
Szpilman score	1.4±0.6	4.6±1.4	19.3	**<0.01**

GCS: Glasgow Coma Scale, WBC: White blood cell, Hb: Hemoglobin, CK: Creatine kinase, Na: Sodium, K: Potassium, Cl: Clorur, CRP: C-reactive protein, $PaCO_2$: Partial carbon dioxide pressure, HCO_3: Bicarbonate, AST: Aspartate amino transferase, ALT: Alanine amino transferase, PICU: Pediatric intensive care unit

Table 4. Correlation between the Szpilman score and GCS and respiratory support system ranking		
	Szpilman score	
	R	**p**
GCS	-0.929	0.01
Respiratory support system ranking from simple to complex	0.827	0.01

GCS: Glasgow Coma Scale

Table 5. Qui-square analyses between Szpilman and categoric parameters					
		Szpilman score <3 N=120 %(coloumn)	**Szpilman score >3 N=30**	**χ^2**	**p**
CPR	No	105 (87.5)	0 (0)	87	**<0.01**
	Yes	15 (12.5)	30 (100)		
Vasoactive agent 1		120 (100)	0 (0)	150	**<0.01**
	Yes	0 (0)	30 (100)		
Observation group		90 (75)	0 (0)	56	**<0.01**
PICU group		30 (25)	30 (100)		
Fresh water		45 (37.5)	15 (50)	1.5	0.2
Salty water		75 (62.5)	15 (50)		
Antibiotic	Yes	45 (37.5)	30	37.5	**<0.01**
	No	75 (62.5)	0		

CPR: Cardiopulmonary resuscitation, PICU: Pediatric intensive care unit, x^2: Chi-square

Table 6. Chi-square analyses between hypothermia and categoric parameters					
		Hyopothermic N=45 %(coloumn)	**Normothermic N=105**	**χ^2**	**p**
Fresh water		15 (33.3)	45 (42.8)	1.1	0.2
Salty water		30 (66.6)	60 (57.1)		
Observation group		15 (33.3)	75 (71.4)	19	<0.01
PICU group		30 (66.6)	30 (28.5)		
CPR	No	15 (33.3)	90 (85.7)	41	<0.01
	Yes	30 (66.6)	15 (14.3)		
CPR: Cardiopulmonary resuscitation, PICU: Pediatric intensive care unit, x^2: Chi-square					

CPR in cases of drowning is commonly reported in the literature. For example, in Şık et al.'s[27] study, CPR was applied to 15.7% of the cases, and 13.4% of them were intubated. Similarly, in this study, 20% of our patients received CRP in the ER, and these patients were followed up as they were intubated. Cohen et al.[28] examined 70 drowning cases and determined that CPR was performed in 23% of surviving cases.

None of the cases included in this study resulted in death. However, mortality has been reported for both freshwater and saltwater drowning events in the literature. For example, Szpilman's[22] (1997) study examined 1.831 drowning/NFD cases over 20 years, found that 12% occurred in seawater and 16% occurred in freshwater. The high mortality rate can be explained by the outdated medical data used in this study. However, Şık et al.'s[27] (2020) mortality rate was 4.4%. When the cases resulting in death in this study were examined, most deaths occurred in individuals with chronic diseases and neurological deficits. Another reason for the absence of exitus cases in our study may be that cases involving exitus in the area were not brought to the ER. In addition, given that this study did not include data pertaining to cases undergoing the intensive care process due to its design, individuals who died after being admitted to the intensive care unit from the ER were not mentioned in the study.

Moffett et al.[24] examined 114 NFD cases and investigated the antibiotic initiation status. Antibiotics were started empirically in 50% of the cases, but they were also given to all intubated individuals who had undergone CPR. Similarly, in this study, antibiotics were given in 50% of the cases, and 75% of those admitted to the intensive care unit were given antibiotic treatment.

In NFD cases, the temperature of the water to which the individual is exposed and the duration of exposure are important. The literature indicates that the prognosis of individuals admitted as hypothermic is worse than normothermics.[29] In this study, patients who were found to have hypothermia at the time of first admission had higher CPR administration and intensive care unit admission rates than those who were normothermic. However, one limitation of our study is that information on how long the individual remained in the water and the temperature at which they did so was not noted.

When we look at the literature, we see scoring schemes used to predict prognosis in drowning/NFD cases. For example, Blasco Alonso et al.[29] used the Conn Modell and Orlowski classifications in their study, which examined 62 drowning cases in Spain. The Conn Model classification was not sufficient for our study because it was based only on the neurological status of the cases.[26] Orlowski's classification was developed in 1979 to determine prognostic factors for childhood drowning; it was mainly based on age, immersion duration, CPR duration, consciousness, and pH. This classification is more comprehensive than the Conn Model, but it does not include pulmonary findings.[30] For this reason, we decided to use the Szpilman scoring system, as described above. According to Şık et.[27] al's studies, 37% of the cases were classified as Grade 1, 10% as Grade 2, 31% as Grade 3, 6% as Grade 4, 12% as Grade 5, and 2% as Grade 6. In other words, 78% of the cases were in the first three grades in their studies. In our study, 40% of the cases were in Grade 1, 18.7% were in Grade 2, 16% were in Grade 3, 2.7% were in Grade 4, 2.7% were in Grade 5, and 20% were in Grade 6. Similarly, in our study, 74.7% of the cases were in the first three grades. Salas Ballestín et al.'s[25] study of the prognostic factors of 131 drowning/NFD cases in Spain indicated that "low GCS, change in pupil size, choking without witnesses, low pH, need for CPR" were poor prognostic factors. In this study, we found a significant correlation between the Szpilman classification score, the need for respiratory support, and the need for inotrope; however, we did not encounter such data in the literature.

According to a study comparing the laboratory data of hospitalized and nonhospitalized drowning cases, blood glucose, alanine transaminase, and lactate levels were found to be significantly higher, and blood pH was found to be significantly lower in hospitalized patients.[27] Similarly, in our study, blood glucose, alanine

transaminase, and lactate levels were higher, and blood pH was lower in intensive care patients. In the same study, similar to this current study, the SC was found to be higher and the GCS score was lower in the hospitalized group. In addition, a strong negative correlation was found between the SC and GCS, which is similar to the results of our study.[27]

Many studies have shown that there is no difference in laboratory and clinical parameters between the victims of drowning in freshwater and saltwater, except for those who died in the field.[31-34] However, an interesting study in the literature provided the autopsy results of 118 drowning cases; autopsies were performed on 74 cases that drowned in freshwater and 44 cases that drowned in saltwater within an average of 750 minutes. The mean age of those who drowned in freshwater was lower than that of those who drowned in saltwater, and those who drowned in saltwater had higher mean serum sodium and chlorine levels and lower mean serum potassium levels than the other group (same as in our study).[17]

Study Limitations

In this study, although there were differences between fresh and saltwater waters regarding white blood cell count, hemoglobin level, potassium level, pH, and glucose level, these were not clinically significant, as the average of all values were within normal limits. The missing data in this study, especially the inaccessibility of data on the patients who underwent CPR in the field, the characteristics of the water to which the patients were exposed, and the neurological outcomes of the patients after discharge, created serious limitations. We believe that a larger study on this topic will contribute to the literature. However, we believe that this study can serve as a guide, as there are not many studies in this field pertaining to childhood.

CONCLUSION

In conclusion, as a result of an examination of drowning cases in Turkey, we found that the prognosis was poor for those who drowned in freshwater, had low GCS, had low blood pH upon admission, had high blood lactate levels, and received CPR. In addition, we conclude that the Szpilman classification, which was created at admission, may be a prognostic guide.

Ethics

Ethics Committee Approval: The study was approved by the İzmir Kâtip Çelebi University, Non-interventinal Clinical Studies Ethics Committee (decision no: 0492, date: 18.11.2021).

Informed Consent: Retrospective study.

Authorship Contributions

Concept: G.G., Design: G.G., Data Collection or Processing: G.G., T.N., Y.B., G.D., Analysis or Interpretation: G.G., T.N., Ş.B., A.Ç., Literature Search: G.G., Y.B., Ş.B., E.B., Writing: G.G.

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Case Report / Olgu Sunumu

Rare Case of Mechanical Intestinal Obstruction: Cecal Endometriosis

Mekanik Barsak Obstruksiyonun Nadir Bir Sebebi: Çekal Endometriozis

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ABSTRACT

Cecal endometriosis is an extremely rare condition. Mechanical intestinal obstruction is a rare clinical entity, particularly due to cecal endometriosis. We discuss a case of mechanical intestinal obstruction due to cecal endometriosis. A 28-year-old woman was admitted to the general surgery department with complaints of abdominal pain, nausea, vomiting, and obstipation for 1 week. A mass in the cecum was found, and right hemicolectomy was performed. Pathological examination revealed cecal endometriosis. Intestinal endometriosis is a diagnosis that should be considered in patients with nonspecific gastrointestinal complaints and masses causing mechanical intestinal obstruction in women of reproductive age.

Keywords: Endometriosis, bowel obstruction, cecal endometriosis

ÖZ

Çekal endometriozis nadir görülen klinik bir tablodur. Rektosigmoid bileşke tutulumuna bağlı olarak gelişen mekanik barsak obstruksiyonu görece sık görülebilse de çekal endometriozise bağlı mekanik barsak obstruksiyonu karşımıza ender olarak çıkmaktadır. Olgumu sunumumuzda çekal endometriozise bağlı gelişen mekanik barsak obstruksiyonu gelişen bir olguyu tartışacağız. Yirmi sekiz yaşında kadın hasta bir haftadır devam eden karın ağrısı, bulantı, kusma ve kabızlık şikayetleriyle genel cerrahi servisine başvurdu. Çekum tümörü ön tanısıyla hastaya sağ hemikolektomi uygulandı. Patolojik incelemede çekal endometriozis saptandı. Barsak endometriozisi, spesifik olmayan gastrointestinal şikayetleri olan ve üreme çağındaki kadınlarda mekanik barsak tıkanıklığına neden olan kitleleri olan hastalarda akılda tutulması gereken bir tanıdır.

Anahtar Kelimeler: Endometriozis, barsak obstruksiyonu, çekal endometriozis

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INTRODUCTION

Endometriosis is the presence of endometrial tissues outside the uterus. It is a chronic estrogen-dependent condition that affects 10% of reproductive women.[1] It often causes complaints such as dysmenorrhea, heavy and irregular menstrual bleeding, pelvic pain, or dyspareunia.[2] Although the most common site of involvement is in the pelvic region, extrapelvic involvement may occur in the gastrointestinal, pulmonary, abdominal wall, and even the central nervous system.[3] Rectum and colon are the most common sites of involvement in the gastrointestinal system. Cecal endometriosis is extremely rare. Cramping abdominal pain, tenesmus, abdominal distension, changes in bowel habits, and hematochezia may occur due to gastrointestinal system endometriosis.[4] Mechanical intestinal obstruction is a rare clinical entity, especially due to cecal endometriosis. We discuss a case of mechanical intestinal obstruction due to cecal endometriosis.

CASE REPORT

A 28-year-old woman (Gravida: 0, Parida: 0, Abortus: 0) was admitted to the general surgery department with complaints of abdominal pain, nausea, vomiting, and obstipation for 1 week. When the patient's history was further investigated, it was determined that her complaints had been going on for approximately 3 months, with occasional cramping and abdominal pain and bloody mucous stool. Three months ago, colonoscopy was performed due to complaints of abdominal bloating, abdominal pain, nausea, vomiting and bloody mucous stool. During colonoscopy, the colonic loops were suboptimally examined with a dirty appearance. The colonoscope was advanced to the cecum, visualizing the ileocecal valve, and advancing 10 cm into the terminal ileum. The terminal ileum mucosa was normal, as well as the mucosa in the cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, and rectum. The submucosal vascular appearance was also normal. The patient had been investigated for infertility, although the specific details of the infertility investigation are unknown; the patient's history indicates a history of infertility.

Diffuse abdominal distension and metallic bowel sounds were found during physical examination, and computed tomography revealed a 4.5-cm mass in the cecum causing mechanical obstruction. The patient was surgically explored with a preliminary diagnosis of mechanical bowel obstruction due to a cecal mass. On exploration, a 4-cm mass was found in the ileocecal region, causing obstruction. There were no signs of carcinomatosis in the peritoneal cavity or liver metastasis; however, bulging lymph nodes were observed in the colon mesentery.

Right hemicolectomy and end-to-end anastomosis were performed; the right hemicolectomy material is shown in Figure 1. Postoperatively, the patient was discharged on 6th day without any complications. The patient had no complaints at the outpatient clinic control at the 3rd postoperative week. Pathological examination revealed bowel obstruction caused by diffuse endometriosis in the bowel wall and 80 reactive lymph nodes. Macroscopically, a 2.5-cm long colon segment was observed from the pathology container. A mucosal surgical border of 2.5 cm in diameter was observed on one side of the material and 4 cm in diameter on the other side. When examined by cutting from the anteroenteric line, a 3.8x3.2x3 cm sized fibrotic lesion with completely narrowed lumen was observed. Diffuse endometriosis, endometriosis-related fibrosis, and almost complete bowel obstruction were observed in the bowel wall. In addition, histopathological examination of the lymph nodes revealed significant dilatation in the sinuses, histiocyte proliferation, and increased vascularity. The patient provided an informed consent form.

DISCUSSION

Intestinal endometriosis is an unexpected diagnosis in right hemicolectomy material. This condition is related to low clinical suspicion, which is an unusual cause of bowel obstruction. However, it should be kept in mind, especially among young women.[5]

Although the pathophysiology of endometriosis is not clear, the generally accepted theory is that endometrial tissue attaches to different sites via retrograde menstruation.[1] The clinical features of intestinal endometriosis vary according to the extent and location of involvement. It is more common in the premenopausal period when endometrial cells are sensitive to hormonal changes during menstrual cycles. Intestinal endometriosis presents with different clinical features depending on the site of involvement. Acute appendicitis, gastro-intestinal system bleeding, intermittent abdominal pain, and, rarely, mechanical intestinal obstruction may occur.[6-8]

Intestinal endometriosis is often localized to the serosal surface of the intestine, and it may sometimes invade the subserosa.[9] Colonoscopic investigation will be normal

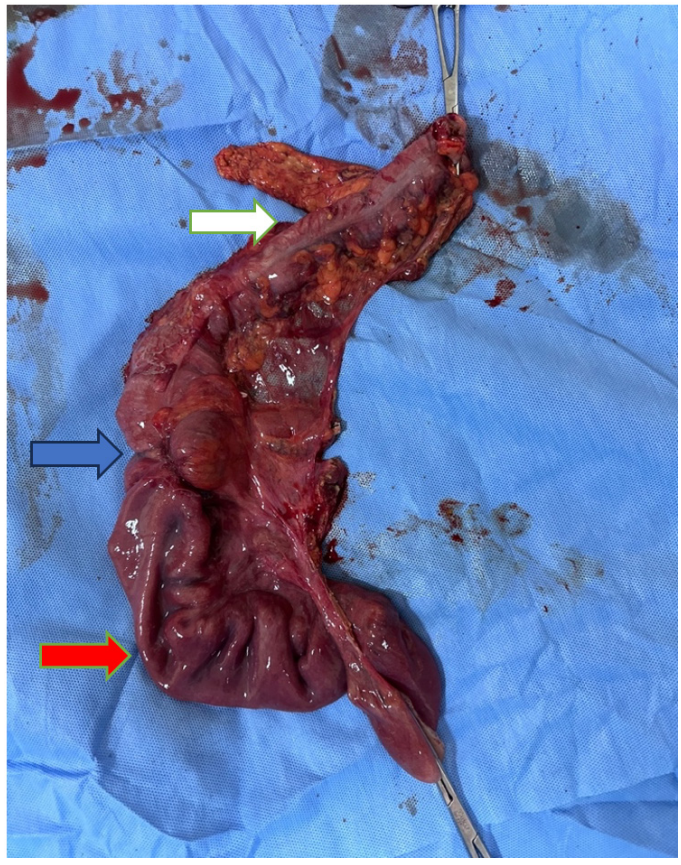

Figure 1. Right hemicolectomy material

White arrow: Transverse colon. Blue arrow: Endometriosis tissue causing intestinal obstruction. Red arrow: Dilated intestinal loops

if there is no mucosal involvement; however, a stenotic lesion may be observed in the intestinal wall. Mucosal involvement by endometriosis nodules is very rare, and endoscopy is usually aspecific and shows extrinsic compression of the mucosa, submucosal mass, and/or eccentric wall thickening.[5] In our case, colonoscopy performed 3 months previously was normal. Because there was no mucosal lesion and the endometriosis tissue was hormone-active tissue, it was expected that the colonoscopy performed 3 months ago would be considered normal, even though it was a suboptimal evaluation. Additionally, serosal lesions are not visible on colonoscopy, but they can be detected on diagnostic laparoscopy. Endometriosis tissue stimulated by hormonal stimulation obstructed the cecum and caused mechanical bowel obstruction.

Although thickening of the intestinal wall and adhesions to the uterus or adnexa can be visualized on radiological imaging, there are no clear pathognomic features. Laparoscopy is the most effective method for demonstrating both gastrointestinal and pelvic involvement.[1] Intestinal endometriosis should be considered in infertile patients with complaints such as intermittent abdominal pain and bloody mucous stools. It has been reported that intestinal endometriosis may also develop in patients who undergo bilateral salpingoophorectomy with hysterectomy.[7]

It can be very difficult to differentiate intestinal endometriosis from other gastrointestinal pathologies because the disease has no pathognomic symptoms. It is often associated with irritable bowel syndrome, inflammatory bowel disease, ischemic colitis, and malignancy when it presents with signs of obstruction, as in the present case. Mechanical bowel obstruction is a rare complication of endometriosis that often develops due to the involvement of the rectosigmoid region.[3] All three cases reported by Pramateftakis had involvement of the rectosigmoid region.[6] Ruffo et al.[5] showed that 1.7% of patients who underwent colorectal resection due to endometriosis involvement had mechanical bowel obstruction. In all of these cases, the rectosigmoid region was involved. As observed in our case, the development of mechanical bowel obstruction due to cecal endometriosis is extremely rare. Surgical removal of all visible intestinal endometriosis and bowel resection are recommended in cases of severe endometriosis with bowel obstruction.[8]

CONCLUSION

Intestinal endometriosis is a diagnosis that should be considered in patients with nonspecific gastrointestinal complaints and masses causing mechanical intestinal obstruction in women of reproductive age.

Ethics

Informed Consent: The patient provided an informed consent form.

Authorship Contributions

Surgical and Medical Practices: C.U., Concept: C.U., Design: C.U., P.E.U., O.B., Data collection or Processing: C.U., P.E.U., Analysis or interpretation: C.U., P.E.U., O.B., Literature search: C.U., P.E.U., Writing: C.U., P.E.U.

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