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ÖZGÜN ARAŞTIRMA

Üçüncü Düzey Bir Ünitede Germinal Matriks-İntraventriküler Kanama Tanısı Alan Pretermlerin İncelenmesi: 4 Yıllık Deneyim

Ezgi Deniz AÇAR ÇELİK[1], İpek GÜNEY VARAL[2], Pelin DOĞAN[2], Elif GÜLER KAZANCI[3]

[1] Sağlık Bilimleri Üniversitesi Bursa Yüksek İhtisas Eğitim Araştırma Hastanesi, Bursa, Türkiye.
[2] Sağlık Bilimleri Üniversitesi Bursa Yüksek İhtisas Eğitim Araştırma Hastanesi Neonatoloji, Bursa, Türkiye.
[3] Sağlık Bilimleri Üniversitesi Bursa Yüksek İhtisas Eğitim Araştırma Hastanesi Çocuk Hematoloji, Bursa, Türkiye.

ÖZET

Germinal matrix kanaması-intraventriküler kanama, özellikle erken doğumların önemli bir komplikasyonu olup pretermlerde görülen beyin hasarının en sık nedenidir. Etiyolojisi karmaşık ve multifaktöriyel olup yenidoğanlarda sık görülen morbidite ve mortalite nedenlerindendir. Hastanemiz Yenidoğan Yoğun Bakım Ünitesinde doğum ağırlığı 1500 gramın ve gestasyon yaşı 32 haftanın altında doğan toplam 391 yenidoğan (n=119 prematüre germinal matrix kanaması-intraventriküler kanama, n=27 prematüre ileri evre kanama tanılı) çalışmaya dahil edilmiştir. Çalışmaya dahil edilen pretermlerin %30,4'ü germinal matrix kanaması-intraventriküler kanama, bu bebeklerin %6,9'u ileri evre kanama tanısı almıştır. Hastaların doğum ağırlığı ve gestasyon haftası azaldıkça germinal matrix kanaması-intraventriküler kanama ve ileri evre kanama riskinin anlamlı düzeyde arttığı ve mortalite üzerine olumsuz etkisi gösterilmiştir. Yenidoğan Yoğun Bakım Ünitesinde yatış süresi boyunca kanama riski olan bebekler ve eşlik eden morbideteler değerlendirilmiştir. Biz bu çalışmada ileri derece preterm bebeklerin hayatta kalma şansı arttıkça, güncel bir problem olan germinal matrix kanaması-intraventriküler kanamanın önlenmesi için riskli grupları gösterdik.

Anahtar Kelimeler: Germinal matriks kanaması-intraventriküler kanama. Prematürite. Risk faktörleri.

Investigation of Preterms Diagnosed with Germinal Matrix Hemorrhage-Intraventricular Haemorrhage in the Third Level Intensive Care Unit: 4-Years Experience

ABSTRACT

Germinal matriks hemorrahage-intraventricular hemorrhage is an serious complication of premature births and is the most common cause of brain damage in preterm babies. The etiology of germinal matrix hemorrhage and intraventricular hemorrhage is complex and multifactorial. Germinal matriks hemorrahage-intraventricular hemorrhage are common causes of morbidity and mortality in neonates. A total of 391 neonates (n=119 preterms with germinal matrix hemorrhage and intraventricular hemorrhage, n=27 preterms with high grade hemorrhage with born in the our Neonatal Intensive Care Unit, birth weight <1500 grams and <32 weeks of gestation were included in the study. Of the included infants, 30.4% had germinal matrix hemorrhage and intraventricular hemorrhage, and 6.9% of germinal matriks hemorrahage-intraventricular hemorrhage diagnosed infants had high grade hemorrhage. Germinal matriks hemorrahage-intraventricular hemorrhage were found to be higher in premature babies with gestational week and birth weight decreased. At risk of germinal matriks hemorrahage-intraventricular hemorrhage and the clinical morbidities they experienced were evaluated during their stay in the Neonatal Intensive Care Unit. In this study, we demonstrated the risk groups for the prevention of germinal matriks hemorrahage-intraventricular hemorrhage, which is a current problem as the chance of survival of severe preterm infants increases.

Keywords: Germinal matrix hemorrhage-intraventricular hemorrhage. Prematurity. Risk factors.

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İpek GÜNEY VARAL
Sağlık Bilimleri Üniversitesi Bursa Yüksek İhtisas Eğitim Araştırma Hastanesi, Bursa, Türkiye
Tel: 0532 341 33 89
E-posta Adresi: ipekguneyvaral@gmail.com

Yazarların ORCID Bilgileri:
Ezgi Deniz AÇAR ÇELİK: 0000-0003-2845-4314
İpek GÜNEY VARAL: 0000-0002-3298-066X
Pelin DOĞAN: 0000-0003-4926-7657
Elif GÜLER KAZANCI: 0000-0003-0910-1142

Germinal matrix kanaması-intraventriküler kanama (GMK-IVK), özellikle erken doğumların önemli bir komplikasyonu olup pretermlerde görülen beyin hasarının en sık nedenidir[1]. Günümüzde perinatoloji ve neonatolojideki tüm yeniliklere ve gelişmelere rağmen mortalite ve nörolojik gelişimi olumsuz etkileyen ciddi bir sorun olmaya devam etmektedir[2]. Hayatın ilk günlerinde gerçekleşen bu GMK-İVK'lar erken dönemde ölüme, uzun vadede ise ömür boyu kalıcı hasar bırakarak nörolojik hasara yol açmaktadır. GMK-İVK sıklığı maturasyon ile ters orantılıdır ve

32. gestasyonel hafta ve 1500 gramın altında doğan preterm bebeklerde daha sıktır. Güncel literatürde insidans, %20-25 olarak bildirilmektedir[1,2] Prematürelerin gestasyon haftaları azaldıkça bu insidansın daha da arttığı, özellikle yirmi altı gestasyon haftasından önce doğan çok küçük preterm grubunun ise yaklaşık %45'i GMK-İVK'dan etkilendiği bilinmektedir[1].

Prematüre bebeklerde solunum sistemi, gastrointestinal, kardiyovasküler sistem gibi birçok sistem gelişimi immatür olup çeşitli problemlerle karşımıza gelse de; uzun vadede prognoz üzerine en olumsuz sonuçlara neden olan GMK-İVK'dır. Bu nedenle neonatolojideki güncel yaklaşım öncelikle riskli grupların belirlenmesi ve gereken önlemlerin alınmasıdır. Germinal matriks kanaması ve intraventriküler kanamanın en önemli risk faktörü prematürite olduğundan, önlemenin en etkili yolu da prematüritenin de önlenmesidir[3]. Bizim çalışmamızdaki amacımız GMK-İVK ve ileri evre GMK-İVK tanısı alan bebeklerin etiyolojisi, morbidite ve mortaliteyle ilişkisini değerlendirmek ve riskli grupları belirlemektir.

Gereç ve Yöntem

Çalışmaya Sağlık Bilimleri Üniversitesi Bursa Yüksek İhtisas Eğitim ve Araştırma Hastanesi doğum salonu ve sezaryen ameliyathanesinde doğan ve YYBÜ'de 1 Ocak 2018-1 Ocak 2022 tarihleri arasında 32. gestasyonel haftanın altında veya 1500 gram altında doğan preterm bebekler dahil edildi. Dışlanma kriterlerine uymayan, bilgilerine ulaşılamayan ve ailesinden onam alınamayan hastalar çalışma dışı bırakıldı. Çalışmaya dahil edilen hastalar belirlenen preterm ultrasonografik izlem protokolüne göre aynı iki neonatolog tarafından çift kör değerlendirilmiştir. Tüm hastalara ilki yatış sonrası ilk 24 saatte olmak üzere iki veya üç kez kranial ultrasound görüntülemesi (kUS) yapıldı. Daha sonra haftalık kUS izlemine alındı. GMK-İVK sınıflaması Volpe' ye göre yapıldı. Hastaların izlemde görülen en yüksek evre GMK-İVK dereceleri kaydedildi. Volpe sınıflaması patofizyoloji zeminine dayanır ve kUS görüntülerini baz alır. Evre 1'de GMK ventrikülün içine taşabilir ancak ventrikülün <%10'unu doldurur. Evre 2, ventrikül alanının %10-50'sini dolduran kanamadır. Evre 3, ventrikül alanının >%50'sini dolduran kanamadır. Periventriküler hemorajik infarkt ise kanamanın olduğu tarafta parankimal kanamadır ve herhangi bir evreye eşlik edebilir[2]. Çalışmaya dahil edilen hastalar GMK-İVK tanısı alanlar ve almayanlar olarak iki gruba ayrıldı. GMK-İVK tanısı alan hastalarda düşük evre (Evre 1 ve 2), ileri evre kanama (Evre 3, periventriküler hemorajik infarkt) olarak iki gruba ayrıldı. Tüm hastalar antenatal ve postnatal özellikleri, risk faktörleri ve eşlik eden anomaliler açısından değerlendirildi. Araştırma Helsinki Deklarasyonu prensiplerine uygun olarak yapılmıştır. Bu çalışma için Sağlık Bilimleri Üniversitesi Bursa Yüksek İhtisas Eğitim Araştırma Hastanesi Klinik Araştırmalar Etik Kurulundan (tarih: 01.06.2022, no: 2022/03-22 kararı) onay alınmıştır.

İstatistiksel Analiz

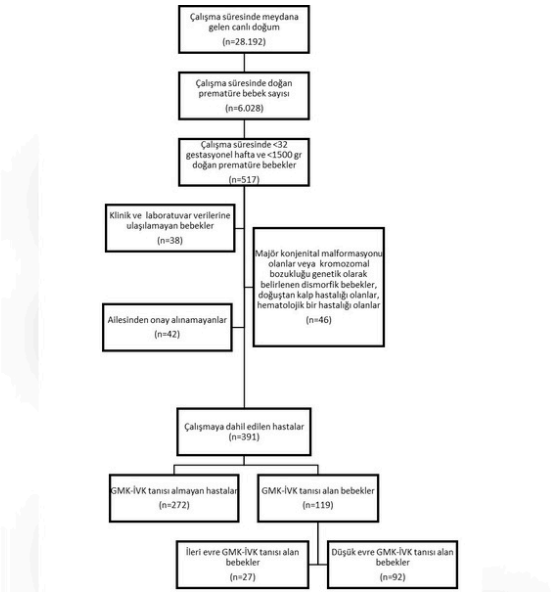
Araştırmada elde edilen verilerin istatistiksel analizleri IBM SPSS V 25.0 (IBM SPSS, Türkiye) istatistiksel paket programı ile değerlendirildi. Bağımsız iki grup karşılaştırmalarında veriler normal dağıldığı durumda bağımsız örneklem t testi, normal dağılmadığı durumda ise Mann-Whitney U testi uygulanmıştır. Betimleyici istatistikler olarak ortalama ± standart sapma, medyan (IQR) değerleri verilmiştir. Kategorik değişkenler için betimleyici istatistikler n (%) ile ifade edilmiştir. Kategorik değişkenlerin gruplar arası karşılaştırmasında ise Pearson ki-kare, Fisher'in kesin ki-kare testi ve Fisher-Freeman-Halton testleri kullanılmıştır. Çok değişkenli lojistik regresyon analizi yapılarak odds oranları (OR) hesaplamaları yapıldı. Anlamlılık düzeyi α=0,05 olarak belirlendi.

Bulgular

Çalışma süresince hastanemizin kadın doğum ameliyathanesinde ve doğum salonunda toplam 28.192 canlı doğum, 6.028 prematüre bebek, <32 gestasyonel hafta ve <1500 gram 517 bebek dünyaya gelmiştir. Çalışmaya, dışlama kriterlerine uyan bebekler, verilerine ulaşılamayanlar ve ailesi tarafından onam verilmeyenler elendikten sonra 391 prematüre bebek dahil edilmiştir. Dışlanma kriteri olarak majör konjenital anomali, doğuştan kalp hastalığı, kromozomal bozukluğu, hematolojik hastalıklar belirlendi. Çalışmaya dahil edilen tüm prematüre bebeklerin yüzde 30,4'ünde germinal matriks kanaması-intraventriküler kanama görülürken, yüzde 6,9'unda ileri evre germinal matriks kanaması-intraventriküler kanama görüldü. Çalışmaya dahil edilen hastaların ayrıntılı akış şeması şekil 1'de gösterilmektedir.

GMK-İVK tanısı alan ve almayan bebekler karşılaştırıldığında, doğum ağırlığı ve gestasyonel hafta azaldıkça GMK-İVK daha çok görülmektedir ($p<0,001$). GMK-İVK tanısı alan bebeklerde APGAR 1. dakika ve 5. dakika değerleri düştükçe GMK-İVK daha sık ortaya çıkmaktadır ($p<0,001$). Antenatal kortikosteroid tedavisi, çalışmamızda eksik ve tam doz olarak değerlendirildiği için GMK-İVK ile arasında istatistiksel ilişki gösterilemese de GMK-İVK oluşmasını azalttığı bilinmektedir. GMK-İVK tanısı alan ve almayan bebeklerin demografik özelliklerine göre karşılaştırılmasına ilişkin veriler Tablo I'de yer almaktadır. Çok değişkenli lojistik regresyon analizi ile diğer faktörler dahil edildiğinde,

gebelik haftasının azalmasının GMK-İVK gelişiminde bağımsız rol oynadığı görüldü. Aynı şekilde APGAR 1. ve 5. Dakika değerinin düşük olmasının GMK-İVK gelişiminde bağımsız risk faktörü olduğu görüldü. Diğer değişkenler çoklu regresyon analizinde anlamlı bulunmadı.



Şekil 1.
Çalışmaya dahil edilen hastaların akış şeması. YYBÜ: yenidoğan yoğun bakım ünitesi; GMK-İVK: germinal matriks-intraventriküler kanama

Tablo I. GMK-İVK Tanısı Alan ve Almayan Bebeklerin Demografik Özelliklerine Göre Karşılaştırılması

	GMK-İVK		p
	Yok (n=272)	Var (n=119)	
Cinsiyet (Kız), n (%)	112 (%41,2)	59 (%49,6)	0,123**
Doğum Ağırlığı gr	1130 (900-1391)	730 (620-850)	**<0,001***
Doğum Şekli (C/S)	222 (%81,6)	109 (%91,6)	**0,012****
Gestasyonel Hafta (hf)	29 (27-31)	25 (24-27)	**<0,001***
APGAR 1.-5. Dakika	7 (5-8)	4,5 (3-6)	**<0,001***
IUGR, n (%)	41 (%15,1)	13 (%10,9)	0,274**
Anne Yaşı	27 (24-32)	28 (24-32)	0,710**
Multiparite, n (%)	133 (%48,9)	77 (%64,7)	**0,004****
Çoğul Gebelik, n (%)	42 (%15,4)	20 (%16,8)	0,734**
Maternal Hastalık, n (%)	52 (%19)	25 (%21)	0.268**
Oligoanhidroamnios, n (%)	40 (%14,7)	19 (%16,0)	0,749**
EMR, n (%)	48 (%17,6)	20 (%16,8)	0,840**
AKS Yok	134 (%49,3)	63 (%52,9)	0,068**
AKS Eksik	52 (%19,1)	31 (%26,1,)	
AKS Tam	86 (%31,6)	25 (%21)	

Tanımlayıcı istatistikler medyan (minimum-maksimum), frekans (n) ve yüzde (%) olarak belirtildi.
*Mann-Whitney U testi, ** Pearson ki-kare testi. (C/S: Sezaryen Doğum, IUGR: İntrauterin Gelişme Geriliği, EMR: Erken Membran Rüptürü, AKS: Antenatal Kortikosteroid)

Düşük evre ve ileri evre GMK-İVK tanısı alan bebekler karşılaştırıldığında, ileri evre GMK-İVK tanısı alan bebeklerde erkek cinsiyet daha fazla görülmektedir (p=0,03). GMK-İVK tanısı alan bebeklerde gestasyonel hafta ve doğum ağırlığı azaldıkça ileri evre GMK-İVK daha fazla ortaya çıkmaktadır (p=0,005). İleri evre GMK-İVK tanısı alan bebeklerde, düşük evreye göre daha fazla çoğul gebeliğe rastlanmaktadır (p=0,01). Düşük evre GMK-İVK'da maternal hastalıklardan preeklampsi en sık görülmektedir. İleri evre GMK-İVK tanısı alan bebeklerde ise koryoamniyonit, preeklampsiye göre daha sık görülmektedir (p=0,04). Düşük evre ve ileri evre GMK-İVK tanısı alan bebeklerin demografik özelliklerine göre karşılaştırılmasına ilişkin veriler Tablo II'de yer almaktadır. Çok değişkenli lojistik regresyon analizi ile diğer faktörler dahil edildiğinde, erkek cinsiyetin ileri evre GMK-İVK oluşumunda bağımsız risk faktörü olduğu görüldü. Yine doğum ağırlığının azalması ve çoğul gebeliğin de ileri evre GMK-İVK gelişimi için bağımsız risk faktörü olduğu görüldü. Diğer değişkenler çoklu regresyon analizinde anlamlı bulunmadı.

Tablo II. Düşük Evre ve İleri Evre GMK-İVK Tanısı Alan Bebeklerin Demografik Özelliklerine Göre Karşılaştırılması

	GMK-İVK (n=119)		
	Düşük evre (n=92)	İleri evre (n=27)	p
Cinsiyet (Kız), n (%)	51 (%55,4)	8 (%29,6)	**0,018****
Doğum Ağırlığı (gr)	735 (637-900)	650 (530-755)	**0,005***
Doğum Şekli (C/S), n (%)	84 (%91,3)	25 (%92,6)	**1,000*****
Gestasyonel Hafta (hf)	26 (25-27)	24 (24-26)	**0,006***
APGAR 1.-5. Dakika	5 (3-6)	4 (3-5)	0,351*
IUGR, n (%)	9 (%14)	4 (%14,8,)	0,488**
Anne Yaşı, n (%)	27 (25-32)	28 (24-32)	0,145**
Multiparite, n (%)	58 (%63)	19 (%70,4)	0,484**
Çoğul Gebelik, n (%)	11 (%12)	9 (%33,3)	**0,017*****
Maternal Hastalık, n (%)	20 (%21)	5 (%18,5)	0.87***
Oligoanhidroamnios, n (%)	17 (%18,5)	2 (%7,4)	0,236***
EMR, n (%)	16 (%17,4)	4 (%14,8)	1,000***
AKS Yok	46 (%50)	17 (%63)	0,473**
AKS Eksik	25 (%27,2)	6 (%22,2)	
AKS Tam	21 (%22,8,)	4 (%14,8)	

Tanımlayıcı istatistikler medyan (minimum-maksimum), frekans (n) ve yüzde (%) olarak belirtildi.
*Mann-Whitney U testi, ** Pearson ki-kare testi, *** Fisher'in kesin ki-kare testi. (C/S: Sezaryen Doğum, IUGR: İntrauterin Gelişme Geriliği, EMR: Erken Membran Rüptürü AKS: Antenatal Kortikosteroid

GMK-İVK tanısı alan ve almayan bebeklerin eşlik eden morbiditeleri karşılaştırıldığında GMK-İVK tanısı alan bebeklerde respiratuar distress sendrom

(RDS), orta-ağır bronkopulmoner displazi (BPD), pulmoner hipertansiyon, ventilatör ilişkili pnömoni, tedavi gerektiren patent duktus arteriosus (PDA) ve evre 3-4 prematüre retinopatisi (ROP) daha fazla görülmektedir (p<0,001). GMK-İVK tanısı alan bebeklerde inotrop ihtiyacı olan hipotansiyon ve böbrek yetmezliği daha fazla görülmektedir (p<0,001). GMK-İVK tanısı alan bebeklerde periventriküler lökomalazi ve konvulziyon daha fazla görülmektedir (p<0,001). GMK-İVK tanısı alan bebekler daha uzun süre TPN almakta ve daha uzun süre invaziv ve non invaziv mekanik ventilasyona ihtiyaç duymaktadır (p<0,001). GMK-İVK tanısı alan bebeklerin YYBÜ yatış süresi daha uzundur (p<0,001). GMK-İVK tanısı alan bebeklerde mortalite oranı daha fazladır (p<0,001). GMK-İVK tanısı alan ve almayan bebeklerin eşlik eden morbiditelere göre karşılaştırılmasına ilişkin veriler Tablo III'te yer almaktadır.

Tablo III. GMK-İVK Tanısı Alan ve Almayan Bebeklerin Eşlik Eden Morbiditelere Göre Karşılaştırılması

	GMK-İVK		
	Yok (n=272)	**Var (n=119)**	**p**
RDS, n (%)	149 (%54,8)	106 (%89,1)	**<0,001****
Orta-Ağır BPD, n (%)	36 (%13,2)	34 (%28,6)	**<0,001****
Pulmoner hipertansiyon, n (%)	20 (%7,4)	23 (%19,3)	**<0,001****
VİP, n (%)	16 (%5,9)	24 (%20,2)	**<0,001****
Tedavi Gerektiren PDA, n (%)	58 (%21,3)	73 (%61,3)	**<0,001****
PDA Tedavi Şekli İbuprofen Parasetamol	34 (%58,6) 24 (%41,4)	11 (%15,3) 61 (%84,7)	**<0,001****
Evre 2-3 NEK, n (%)	12 (%4,4)	8 (%6,7)	0,340**
İnvaziv mekanik ventilasyon süresi (gün)	2 (2-7)	14 (4-15)	**<0,001***
Noninvaziv mekanik ventilasyon süresi(gün)	4 (1-13)	13 (2-16)	**<0,001***
Evre 3-4 ROP, n (%)	13 (%4,8)	33 (%27,7)	**<0,001****
İnotrop ihtiyacı Olan Hipotansiyon, n (%)	38 (%14,0)	45 (%37,8)	**<0,001****
Böbrek Yetmezliği, n (%)	4 (%1,5)	11 (%9,2)	**<0,001****
TPN Alma Süresi, n (%)	9 (6-14)	16 (7-17)	**<0,001***
Konvulziyon, n (%)	4 (%1,5)	16 (%13,4)	**<0,001****
PVL, n (%)	54 (%19,9)	44 (%37)	**<0,001****
Hastane yatış süresi (gün)	34 (21-57)	61 (13-101)	**<0,001****
Mortalite, n (%)	54 (%19,9)	52 (%43,7)	**<0,001****

Tanımlayıcı istatistikler medyan (minimum-maksimum), frekans (n) ve yüzde (%) olarak belirtildi.
*Mann-Whitney U testi, ** Pearson ki-kare testi. (RDS: Respiratuar Distres Sendromu, BPD: Bronkopulmoner Displazi, VİP: Ventilatör İlişkili Pnömoni, PDA: Patent Duktus Arteriozus, NEK: Nekrotizan Entrokolit, ROP: Prematüre Retinopatisi, PVL: Periventriküler Lökomalazi)

Düşük evre ve ileri evre GMK-İVK tanısı alan bebeklerin eşlik eden morbiditelerine göre karşılaştırıldığında, ileri evre GMK-IVK tanısı alan bebeklerde RDS (p<0,001) ve tedavi gerektiren PDA (p=0,002) daha fazla görülmektedir. İleri evre GMK-İVK tanısı alan bebeklerde mortalite oranı daha fazladır (p<0,001). Düşük evre ve ileri evre GMK-İVK tanısı alan bebeklerin eşlik eden morbiditelerine göre karşılaştırılmasına ilişkin veriler Tablo IV'te yer almaktadır.

Tablo IV. Düşük Evre GMK-İVK ve İleri Evre GMK-İVK Tanısı Alan Bebeklerin Eşlik Eden Morbiditelerine Göre Karşılaştırılması

	GMK-İVK (n=119)		
	Düşük evre (n=92)	**İleri evre (n=27)**	**p**
RDS, n (%)	63 (%68,5)	27 (%100)	**<0,001****
Orta Ağır BPD, n (%)	18 (%19,6)	5 (%18,5)	0,904**
Pulmoner Hipertansiyon, n (%)	10 (%10,9)	6 (%22,2)	0,195***
VİP, n (%)	10 (%10,9)	4 (%14,8)	0,519***
Tedavi Gerektiren PDA, n (%)	31 (%33,7)	18 (%66,7)	**0,002****
PDA Tedavi Şekli İbuprofen Parasetamol	9 (%17) 44 (%83)	1 (%5,6) 17 (%94,4)	0,434***
Evre 2-3 NEK, n (%)	5 (%5,4)	3 (%11,1)	0,379***
Evre 3-4 ROP, n (%)	11 (%12)	7 (%25,9)	0,122***
İnotrop İhtiyacı Olan Hipotansiyon	19 (%20,7)	15 (%55,6)	**<0,001****
Böbrek Yetmezliği, n (%)	8 (%8,7)	3 (%11,1)	0,711***
Konvulziyon, n (%)	8 (%8,7)	8 (%29,6)	**0,009****
PVL, n (%)	30 (%32,6)	14 (%51,9)	0,069**
Mortalite, n (%)	24 (%26,1)	19 (%70,4)	**<0,001****

*Mann-Whitney U testi, ** Pearson ki-kare testi, *** Fisher'in kesin ki-kare testi (RDS: Respiratuar Distres Sendromu, BPD: Bronkopulmoner Displazi, VİP: Ventilatör İlişkili Pnömoni, PDA: Patent Duktus Arteriozus, NEK: Nekrotizan Entrokolit, ROP: Prematüre Retinopatisi, PVL: Periventriküler Lökomalazi)

GMK-İVK tanısı alan bebeklerde çok değişkenli Lojistik Regresyon Analizi Tablo V'te yer almaktadır. Modele gestasyonel hafta, doğum ağırlığı, APGAR 1.-5. dakika skoru, RDS, tedavi gerektiren PDA, orta-ağır BPD, mortalite eklendi. Analiz sonucunda gestasyonel haftanın, doğum ağırlığının ve APGAR 1.-5. dakika skorunun azalmasının, GMK-İVK sıklığını anlamlı derecede arttırdığı bulundu.

Tablo V. GMK-İVK Tanısı Alan Bebeklerde Çok Değişkenli Lojistik Regresyon Analizi

	p	Odds Oranı	Odds Oranı (%95 Güven aralığı)
Doğum Ağırlığı	<0,001	0,995	0,993-0,997
Tedavi Gerektiren PDA	0,084	1,833	0,924-3,664
Mortalite	0,126	1,818	0,844-3,928
Apgar 1.-5. Dakika	0,002	0,751	0,622-0,901
Orta-ağır BPD	0,071	2,187	0,941-5,188

Tartışma ve Sonuç

Daha küçük bebekler hayatta kalmayı başardıkça GMK-İVK, yenidoğan yoğun bakımlar için daha büyük sorun oluşturmaya başlamıştır[4]. Doğum sonrası ilk günlerinde gerçekleşen bu durum hem hayatta kalma şansını azaltmakta hem de hayat boyu kalıcı hasarlara neden olmaktadır. Bu amaçla çalışmamız en riskli ve prematür bebeklerin izlendiği üçüncü düzey merkezlerdeki güncel GMK-İVK oranlarını belirlemeyi ve riskli bebekleri bulmayı hedeflemiştir. Çalışmamızda, <32. gestasyonel hafta, <1500 gr bebeklerin %30,4'ü GMK-İVK tanısı almış olup, tüm bebeklerin %6,9'u ileri evre, %23,5'i erken evre GMK-İVK tanısı almıştır. Literatürle uyumlu olarak ileri evre GMK-İVK tanısı alan bebeklerde erkek cinsiyeti bağımsız risk faktörü olarak gösterdik[5].

Bilindiği üzere düşük doğum ağırlığı ve gestasyon haftası; GMK-İVK risk faktörleri arasında en bilinenlerinden birisidir[6]. Bizim çalışmamızda GMK-İVK tanısı alan bebeklerin ortalama doğum ağırlığı 730 gram, ortalama gestasyon haftası 25 haftaydı. Doğum ağırlığı ve gestasyon haftası azaldıkça GMK-İVK sıklığında artış görüldü. Sezaryen doğum şeklinin, normal doğum şekline göre GMK-İVK sıklığını azalttığına dair yeterli çalışma yoktur. Humberg ve ark.[6] tarafından yapılan bir çalışmada, GMK-İVK prevelansı vajinal doğumda %26,6, acil sezaryen doğumda %31,1 ve planlı sezaryen doğumda %17,2 olarak bulundu. Vajinal doğum ve acil sezaryen doğum, bağımsız olarak GMK-İVK ile ilişkilendirildi. Bizim yaptığımız çalışmada GMK-İVK tanısı alan bebeklerin sezaryen doğum oranını %91,6, vajinal doğum oranını %8,4 olarak bulduk. Doğum yöntemi kararı sadece prematüriteye bağlı olarak verilmemeli diğer risk faktörleri de göz önüne alınarak karar verilmelidir.

Prematüre bebeklerde germinal matriks ve germinal matriksi çevreleyen destekleyici tabakalar tam olgunlaşmamıştır[7]. Asfiksi ve hipoksi gibi durumlarda olgunlaşmamış yapıların spontan perforasyonu GMK-İVK oluşumuna yol açar. Düşük APGAR skorları hipoksi ve asfiksiye neden olarak, GMK-İVK oluşumuna zemin hazırlar[7]. Çalışmamızda literatüre uygun olarak GMK-İVK tanısı alan prematüre bebeklerde, APGAR 1. ve 5. Dakika skorları düşüktür. Özdemir ve ark.'nın[8] prematüre bebeklerle yaptıkları çalışmada, GMK-İVK tanısı alan bebeklerde çoğul gebelik oranı %12.5 olarak bulundu. Bizim çalışmamızda da GMK-İVK tanısı alan ve GMK-İVK tanısı almayan bebeklerde çoğul gebeliğe rastlanma açısından fark yoktu. Biz bu durumu, doğum öncesi kadın hastalıkları ve doğum ekibinden çoğul gebelik bilgisi aldıktan sonra yenidoğan canlandırması ve resüsitasyonunu etkin bilen bir ekiple doğuma katılmamıza bağladık. Fakat bu bebekler çoğunlukla düşük doğum ağırlıklı ve prematür olduğu için takiplerinde GMK-İVK'ya yatkındır ve ileri evre GMK-İVK'ya ilerlemesi muhtemeldir[9]. Çalışmamızda çoğul gebeliğin ileri evre GMK-İVK gelişimi için bağımsız risk faktörü olduğu gördük.

Enflamasyonun ve koryoamniyonitin GMK-İVK patogenezindeki yeri hala açıklanabilmiş değildir. Literatürde birbirinden farklı bulgular bulunmakla beraber, bizim çalışmamızda da GMK-İVK tanısı alan bebeklerde koryoamniyonitte artış yoktu. Kim ve ekibinin yaptığı çalışmada preeklampsili annelerdeki uteroplasental disfonksiyona karşı bebeğin adaptasyon sağladığı ve bu bebeklerde GMK-İVK ve ileri evre GMK-İVK riskinin azaldığını söylediler[10]. Yapılan başka bir çalışmada preeklampsinin ileri evre GMK-İVK için potansiyel koruyucu faktörlerden olduğu, nöroprotektif etkili ve nöronal maturasyonu hızlandırdığı söylendi[11]. Çalışmamızda GMK-İVK tanısı alanlar daha fazla preeklamptik anne bebeğiydi fakat istatiksel açıdan fark yoktu. GMK-İVK tanısı alan preeklamptik anne bebekleri, prematüre bebekler olmaların rağmen ileri evre kanamaya daha az rastladık. Bu durumu da bebeklerin uteroplasental disfonksiyona adaptasyon sağlamasına ve preeklampsinin nöroprotektif etkisine bağladık. Bununla beraber erken membran rüptüründe (EMR) insidans artışı yoktu. Bunun nedeninin EMR' de hızlı antibiyoterapiye başlamımız olduğunu düşünmekteyiz.

İnvaziv ve noninvaziv mekanik ventilasyon serebral kan akışını bozabilir ve lokal inflamatuar yanıtı indükleyebilir; böylece GMK-İVK'ya eğilim artar[12]. Biz de GMK-İVK tanısı alan bebeklerin daha uzun süre invaziv ve noninvaziv mekanik ventilasyona ihtiyaç duyduğunu ve daha uzun süre oksijen desteği aldığını bulduk. RDS; hipoksemi, hiperkarbi ve hipotansiyona yol açarak beyine hasar veren mekanizmalardan biridir ve bunu GMK-İVK'ya yol açarak yapar[13]. Biz de literatürle uyumlu olarak GMK-İVK ve ileri evre GMK-İVK tanısı alan bebeklerde RDS'yi daha fazla bulduk. BPD solunum iş yükünü, hipoksi ve hiperkarbiyi, mekanik ventilasyon ihtiyacını arttıran bir diğer hastalıktır. GMK-İVK oluşumunu kolaylaştırır[14]. Bizim çalışmamızda da GMK-İVK tanısı alan bebeklerde BPD daha fazladır.

Pulmoner hipertansiyon (PHT) doğumdan sonra gelişen değişken hipoksemi ve diferansiyel siyanoz (preduktal spo2'nin, postduktal spo2'den yüksek olması) şeklinde kliniğe yansır[15]. Bizim çalışmamızda da GMK-İVK tanısı alan bebeklerde PHT daha sık görülmüştür. Zamanında ve etkili kapatılmayan PDA sonucunda soldan sağa şant meydana gelebilir. Soldan sağa şant ise böbrek yetmezliği, osteodisplazi, NEK, GMK-İVK, PVL, BPD, konjestif kalp yetmezliği ve pulmoner kanamaya neden olabilir[16]. Bizim çalışmamızda da GMK-İVK tanısı alan bebeklerde tedavi gerektiren PDA daha fazlaydı.

Beslenme problemleri ve nekrotizan enterokolit (NEK), GMK-İVK için bilinen bir risk faktörleri

değildir; fakat bu hastalıklar riskli bebeklerde görüldüğü için birbirine sık eşlik ederler[17]. Bizim çalışmamızda GMK-İVK tanısı alan bebeklerde daha çok beslenme problemleri görülmektedir, daha uzun süre TPN almaktadır ve tam enteral beslenmeye daha uzun sürede geçmektedir. Çalışmamızda GMK-İVK ve ileri evre GMK-İVK tanısı alan bebeklerde NEK daha fazla görülmüştür. Preterm doğum öncesi AKS tedavisinin RDS, GMK-İVK, NEK ve mortalite sıklığını azalttığı bilinmektedir[17]. Çalışmamızda literatürle uyumlu olarak GMK-İVK tanısı alan bebeklerde AKS tedavisinin %55,2, ileri evre GMK-İVK tanısı alan bebeklerde %64 oranında verilmediğini bulduk. Asfiksi, apne, RDS, BPD, asidoz varlığı gibi ciddi oksijen tedavisi gerektiren hastalıklarda ROP gelişime riski artar[17]. Bizim çalışmamızda GMK-İVK tanısı alan hastalarda RDS, BPD, oksijen ihtiyacı, mekanik ventilasyon ihtiyacı dolayısıyla da ROP insidansı artmış olarak bulundu.

Al-Muqdad ve ekibinin, Yenidoğanlarda Dünya Çapında Akut Böbrek Hasarı Epidemiyolojisinin Değerlendirilmesi çalışmasını dikkate alarak yaptıkları çalışmada, GMK-İVK tanısı alan hastalarda ABY daha fazla görüldü[18]. Bizim yaptığımız çalışmada da GMK-İVK tanısı alan bebeklerde ABY daha fazladır. Prematüre bebekler için GMK-İVK ve PVL risk faktörleri yaklaşık olarak aynıdır[19]. Bizim yaptığımız çalışmada GMK-İVK ve ileri evre GMK-İVK tanısı alan bebeklerde PVL fazlaydı.

Ohlin ve arkadaşlarının İsveç'te yaptıkları çalışmada sepsis ve GMK-İVK arasında istatiksel olarak anlamlı ilişki bulunmadı[20]. Bizim çalışmamızda GMK-İVK tanısı alan bebeklerde sepsis, tanı almayanlara göre fazla değildi; son zamanlardaki yenidoğan yoğun bakım ünitemizdeki gelişmelerin bunda etkisi vardır. Bizim çalışmamızda GMK-İVK tanısı alan bebeklerde geç sepsis oranı daha yüksek bulundu; çünkü prematüre ve GMK-İVK'lı bebekler, YYBÜ'de uzun süre yatmaktadır. Bu sebeple geç sepsis olma ihtimalleri de artmaktadır. Bizim ünitemizde sepsis etkeni olarak gram pozitif erkenler fazla olmasına rağmen GMK-İVK tanısı alan bebeklerde gram negatif etkenler fazla görüldü. Bu nedenle özellikle bu hastaların geç sepsis tanısında gram negatif etkenler akla gelmelidir.

GMK-İVK, bilindiği üzere mortalite üzerindeki en önemli faktörlerden birisidir[17]. Ülkemizde Kazan ve ark.'nın prematüre bebeklerle yaptıkları çalışmada GMK-İVK olan bebeklerde mortalite oranı %38 bulundu[21]. Christian ve ark.'nın prematüre bebeklerle yaptıkları çalışmada düşük evre GMK-İVK'nın mortalite oranını %14; ileri evre GMK-İVK oranını %60'dı[1]. Bizim çalışmamızda GMK-İVK tanısı alan bebeklerin mortalite oranı %43,7, ileri evre GMK-İVK tanısı alan bebeklerin mortalite oranı %70,4 bulunmuş olup literatürle uyumludur.

Çalışmamızın en önemli kısıtlılığı retrospektif olmasıdır. Ayrıca ünitemizin üçüncü düzey bir merkez olması ve hastanemize riskli bebeklerin sevk edilmesi nedeniyle yatan prematüre hastalarımızın mortalitesi ve morbiditesi genel popülasyondan daha yüksektir. Çalışmamızın güçlü yanları ise hasta öncelikle sayımızın çok olması ve takipte radyolojik izlemin aynı 2 neonatolog tarafından yapılması ile tanıların benzer konulmasıdır.

Sonuç olarak biz bu çalışmada günümüzde çok küçük pretermlere bakım veren üst düzey yenidoğan yoğun bakım merkezlerinin önemli bir problemi olan GMK-İVK tanısı alan bebeklerin, risk faktörlerini ve eşlik eden klinik durumlarını ayrıntılı olarak değerlendirdik. GMK-İVK ve ileri evre GMK-İVK'nın mortalite ile birebir ilişkili olduğunu göstermiş olup, çakışmamızın bunların önlenmesi için riskli grupların belirlenmesinde literatüre katkıda bulunacağını düşünmekteyiz.

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ÖZGÜN ARAŞTIRMA

Tip 1 Diabetes Mellitus Hastalarında Magnezyum Düzeylerinin Glisemik Parametreler ve Mikrovasküler Komplikasyonlarla İlişkisi*

Murat ÇALAPKULU, Merve TEKİNYILDIZ

Iğdır Dr. Nevruz Erez Devlet Hastanesi, Iğdır, Türkiye.

ÖZET

Bu çalışma, Tip 1 Diyabet (T1D) hastalarında serum magnezyum düzeylerinin glisemik kontrol ve mikrovasküler komplikasyonlarla olan ilişkisini değerlendirmeyi amaçlamaktadır. Retrospektif kesitsel olarak tasarlanan çalışmada, Temmuz 2022 - Haziran 2024 tarihleri arasında 262 T1D hastası ve 120 sağlıklı birey incelenmiştir. Çalışmanın verileri hastaların dosyalarından elde edilmiş olup, serum magnezyum düzeyleri atomik absorpsiyon spektrofotometresi kullanılarak ölçülmüştür. Magnezyum eksikliği, 1.6 mg/dL'nin altındaki serum magnezyum düzeyi olarak kabul edilmiştir. Çalışmada, T1D hastalarında kontrol grubuna göre anlamlı olarak düşük magnezyum seviyeleri tespit edilmiştir ($p < 0.001$). T1D hastalarının %6.1'inde ($n = 16$) magnezyum eksikliği saptanmıştır. Serum magnezyum düzeyi ile HbA1c arasında negatif bir korelasyon bulunmuş ($r = -0.286$, $p < 0.001$) ve magnezyum eksikliği olan hastalarda HbA1c seviyelerinin daha yüksek olduğu gözlenmiştir ($p = 0.02$). Bununla birlikte, mikrovasküler komplikasyonlar (retinopati, nefropati, nöropati) ile magnezyum düzeyleri arasında anlamlı bir ilişki bulunmamıştır. Bu sonuçlar, magnezyum eksikliğinin kötü glisemik kontrol ile ilişkili olabileceğini ancak mikrovasküler komplikasyonlara doğrudan etkisinin olmayabileceğini göstermektedir. Bu bulgular, glisemik profili kötü T1D hastalarında magnezyum seviyelerinin izlenmesinin kan şekeri regülasyonu açısından önemini vurgulamaktadır.

Anahtar Kelimeler: Glisemik kontrol. Mikrovasküler komplikasyonlar. Tip 1 Diyabet. Magnezyum.

Association of Magnesium Levels with Glycemic Parameters and Microvascular Complications in Type 1 Diabetes Mellitus Patients

ABSTRACT

This study aims to evaluate the relationship between serum magnesium levels, glycemic control, and microvascular complications in Type 1 Diabetes (T1D) patients. Designed as a retrospective cross-sectional study, data from 262 T1D patients and 120 healthy individuals between July 2022 and June 2024 were analyzed. Patient records provided the data, and serum magnesium levels were measured using atomic absorption spectrophotometry, with magnesium deficiency defined as serum levels below 1.6 mg/dL. The study found significantly lower magnesium levels in T1D patients compared to controls ($p < 0.001$). Magnesium deficiency was observed in 6.1% ($n = 16$) of T1D patients. A negative correlation was found between serum magnesium levels and HbA1c ($r = -0.286$, $p < 0.001$), with higher HbA1c levels in patients with magnesium deficiency ($p = 0.02$). However, no significant relationship was identified between magnesium levels and microvascular complications (retinopathy, nephropathy, neuropathy). These findings suggest that magnesium deficiency may be associated with poor glycemic control but may not have a direct effect on microvascular complications. These findings highlight the importance of monitoring magnesium levels in poorly controlled type 1 diabetes patients in terms of glycemic regulation.

Keywords: Glycemic control. Microvascular complications. Type 1 Diabetes. Magnesium.

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Dr. Murat ÇALAPKULU
Iğdır Dr. Nevruz Erez Devlet Hastanesi, Iğdır, Türkiye.
Tel.: 0506 611 01 16
E-posta: calapkulumurat89@gmail.com

Yazarların ORCID Bilgileri:
Murat ÇALAPKULU: 0000-0002-7445-2275
Merve TEKİNYILDIZ: 0000-0002-6356-030X

Tip 1 Diyabet (T1D), insülin üreten pankreatik beta hücrelerinin otoimmün bir reaksiyon sonucu hasar görmesiyle ortaya çıkan ve insülin eksikliğiyle karakterize kronik bir hastalıktır[1]. Uluslararası Diyabet Federasyonu'na (IDF) göre, dünya genelinde yaklaşık 537 milyon kişi diyabetle yaşamaktadır ve bunun %10'u T1D hastasıdır[2]. IDF verilerine göre, Türkiye'de T1D'nin yaygınlığı son 20 yılda yaklaşık 2,48 kat artmıştır[2]. Magnezyum hücre içindeki birçok önemli metabolik ve biyokimyasal süreçte yer alır. Kemik gelişimi, nöromüsküler fonksiyon, sinyal yolları, enerji depolama ve transferi, glikoz, lipid ve protein metabolizması ve hücre çoğalması gibi vücuttaki çok sayıda fonksiyondan sorumludur[3].

Özellikle glukoz metabolizması ve insülin sinyal iletimi süreçlerinde kritik bir öneme sahiptir. Magnezyum eksikliği, insülinin hücresel etkinliğini azaltarak glisemik kontrolü olumsuz etkileyebilir ve kan şekeri seviyelerinin yükselmesine yol açabilir[4,5]. Bu bağlamda, magnezyumun eksikliğinin diyabet hastalarındaki olası etkileri üzerine yapılan çalışmalar artan bir ilgi görmektedir.

Diyabetli hastalarında hipomagnezemi prevelansı %10-48 arasında değişmektedir[6,7]. Bu hasta grubunda hipomagnezeminin en sık sebebi ozmotik diürez veya belirli tübüler defektlerin neden olduğu böbreklerden magnezyum atılımıdır[8]. Magnezyum takviyesinin insülin direncini azalttığı ve glikoz metabolizmasını iyileştirdiği önceki çalışmalarda raporlanmıştır[9,10]. Daha da önemlisi, magnezyumun inositol taşınması üzerindeki etkisiyle diyabetin uzun süreli komplikasyonlarının gelişiminde önemli bir role sahip olabileceği öne sürülmüştür[11]. Magnezyum eksikliğini komplikasyonlarla ilişkilendiren çalışmalarda, altta yatan mekanizmalar arasında daha yüksek tümör nekrozis faktörü (TNF) alfa seviyeleri ve ileri glikozilasyon son ürünlerinin oluşumunun artması yer almaktadır[6,12].

Magnezyumun diyabetteki rolüne yönelik çalışmaların çoğu tip 2 diabetes mellitus (T2D) hastaları arasında gerçekleştirilmiştir[5,7,10]. T1D hastalarında hipomagnezemi prevelansı ve magnezyum düzeyinin glisemik parametrelerle ilişkisini araştıran kısıtlı sayıda çalışma mevcuttur[6,13]. Ayrıca literatürde hipomagnezemi ile mikrovasküler komplikasyonlar arasındaki ilişki az sayıda çalışmada araştırılmış olup çelişkili sonuçlar raporlanmıştır[6,14–17]. Bu çalışmanın amacı, T1D hastalarında serum magnezyum seviyelerinin değerlendirilmesi ve bu seviyelerin glisemik kontrol ve mikrovasküler komplikasyonlar üzerindeki etkilerini incelemektir.

Gereç ve Yöntem

Çalışma Tasarımı ve Hasta Seçimi

Çalışmaya Temmuz 2022 ile Haziran 2024 tarihleri arasında Iğdır Dr. Nevruz Erez Devlet Hastanesi, Endokrinoloji ve Metabolizma Kliniği'nde 18 yaşından büyük T1D tanısı ile takipli 262 hasta ve 120 sağlıklı kontrol grubu dahil edilmiştir. Çalışma T1D'li ayaktan polikliniğe başvuran hastalarda retrospektif, kesitsel bir çalışma olarak yürütülmüştür. Çalışma protokolü Kafkas Üniversitesi Tıp Fakültesi Etik Kurulu tarafından 26.06.2024 tarihinde 471/10 karar numarası ile onaylanmıştır. Çalışma Helsinki Deklarasyonu'na uygun olarak yürütülmüştür. Yaş, cinsiyet, vücut boyu ve kilosu, diyabet süresi ve mikrovasküler komplikasyonlar hasta dosyaları taranarak elde edilmiştir. Son klinik ziyarette kaydedilen HbA1C, açlık plazma glukozu (APG), serum kreatinin, serum magnezyum, açlık total kolesterol (TK), düşük yoğunluklu lipoprotein kolesterol (LDL-K), trigliserid (TG) ve yüksek yoğunluklu lipoprotein kolesterol (HDL-K) düzeyleri tıbbi kayıtlardan elde edilmiştir. T2D hastaları, MODY hastaları, gebeler veya emzirenler, magnezyum takviyesi kullanan hastalar, magnezyum metabolizmasını etkileyen diüretik ve benzeri ilaç kullanımı olan hastalar ve verileri eksik olan hastalar çalışmadan çıkarılmıştır. Kontrol grubu, yakın akrabalarında hastalık bulunan, kontrol için hastanemize başvuran ve yapılan tetkiklerde herhangi bir hastalık saptanmayan rastgele seçilmiş sağlıklı bireylerden oluşturulmuştur.

Klinik ve Biyokimyasal Ölçümler

Vücut kitle indeksi (VKİ), kilogram cinsinden ağırlığın metre cinsinden boyun karesine bölünmesi yoluyla hesaplanmıştır. Analizler merkezimiz biyokimya laboratuvarında biyokimyasal analiz cihazı kullanılarak gerçekleştirilmiştir. Kan örnekleri, en az 8 saatlik açlıktan sonra, gece boyunca aç kaldıktan sonra, sabah 8:00 ile 9:00 arasında alınmıştır. Değerlendirmeler HbA1c, APG, serum kreatinin düzeyi, serum magnezyum düzeyi ve lipid profili üzerinden yapılmıştır. Serum magnezyum seviyeleri atomik absorpsiyon spektrofotometrisi, HbA1c ise yüksek performanslı sıvı kromatografisi yöntemi kullanılarak ölçülmüştür. TG, LDL-K, HDL-K ve TG değerleri, spektrofotometri ile enzimatik kolorimetrik analizlerle belirlenmiştir. En az iki ardışık idrar örneğinde proteinüri saptanan (idrar albümin/kreatinin oranı $\geq$ 30 μg/mg) veya son dönem böbrek hastalığı olan hastalar diyabetik nefropati olarak kabul edilmiştir. Magnezyum eksikliği, 1.6 mg/dL'nin altındaki serum magnezyum düzeyi olarak kabul edilmiştir.

İstatistiksel Analiz

İstatistiksel analizler SPSS yazılımı (sürüm 23.0, SPSS, IBM Corporation, NY, ABD) kullanılarak yapılmıştır. Cinsiyet ve hipomagnezemi gibi kategorik veriler frekans ve yüzde (%) ile özetlenmiştir. Öncelikle değişkenler Kolmogorov-Smirnov testi ile normal dağılıma sahip olup olmadıkları açısından incelenmiştir. Normal dağılıma sahip sürekli değişkenler ortalama ± standart sapma (SD) olarak ifade edilmiştir ve normal dağılım sağlamayan değişkenler medyan (aralık) değerleri olarak verilmiştir. Normal dağılıma sahip değişkenleri karşılaştırmak için Student's t testi kullanılmıştır. Normal dağılıma uymayan değişkenleri karşılaştırmak için Mann-Whitney U testi kullanılmıştır. Kategorik değişkenler arasındaki karşılaştırmalar Ki-kare analizi ile, sayısal değişkenler arasındaki farklar Pearson korelasyon analizi ile analiz edilmiştir. İstatistiksel anlamlılık düzeyi olarak p değerinin 0.05'den küçük olması anlamlı kabul edilmiştir.

Bulgular

Çalışma 262 T1D ve 120 sağlıklı gönüllünün değerlendirilmesi ile yapılmıştır. Hastaların ve kontrol grubunun demografik verileri ve laboratuvar bilgileri Tablo I'de verilmiştir. T1D hastalarının %57.6'sının (n = 151) kadın ve ortalama yaşının 31.8 ± 15.6 yıl olduğu saptanmıştır. Kontrol grubunun ise %67.5'inin (n = 81) kadın ve ortalama yaşının 33.4 ± 9.7 yıl olduğu saptanmıştır. İki grup arasında yaş ve cinsiyet açısından farklılık saptanmamıştır (p = 0.07). VKİ bakımından da gruplar arasında istatistiksel olarak anlamlı bir fark bulunmamıştır (p = 0.1). T1D hastalarında medyan hastalık süresi 8 (1-39) yıl olarak saptanmıştır. Bununla birlikte, serum kreatinin düzeyleri T1DM grubunda kontrol grubuna kıyasla hafifçe yüksek saptanmıştır (p = 0.04). Serum magnezyum düzeyi T1DM hastalarında (1.8 ± 0.2 mg/dL) kontrol grubu (2 ± 0.1 mg/dL) ile karşılaştırıldığında daha düşük saptanmıştır (p < 0.001). Serum magnezyum düzeyi ile APG (r:-0.187, p=0.004) ve HbA1c (r:-0.286, p<0.001) arasında negatif korelasyon gözlenmiştir.

Tablo I: Katılımcıların demografik ve laboratuvar verileri

Parametreler	T1D (n= 262)	Kontrol (n=120)	p
Yaş (yıl)	31.8 ± 15.6	33.4 ± 9.7	0.3
Cinsiyet (K)	151 (%57.6)	81 (%67.5)	0.07
VKİ (kg/m²)	22.7 ± 3.4	23.3 ± 3	0.1
Kreatinin (mg/dl)	0.78 (0.4-3.5)	0.74 (0.48-1.17)	**0.04**
AST (U/L)	16.16 (2-177)	17.7 (10.4-56.8)	0.13
ALT (U/L)	15 (1-132)	17.8 (4.9-70.6)	0.26
Açlık kan şekeri (mg/dl)	241.8 ± 113.2	88.4 ± 8.4	**<0.001**
HbA1c (%)	10.3 ± 2.8	5.5 ± 0.4	**<0.001**
Total kolesterol (mg/dl)	170 (42-379)	166 (109-243)	0.58
LDL-K (mg/dl)	117.9 ± 37.3	111.5 ± 28.9	0.11
HDL-K (mg/dl)	51.7 ± 15.7	49.8 ± 15.1	0.27
Trigliserid (mg/dl)	98.3 (26-705)	82.6 (27-397.2)	0.22
Magnezyum (mg/dl)	1.8 ± 0.2	2 ± 0.1	**<0.001**

T1D: Tip 1 Diyabet, K:Kadın, VKİ: Vücut kitle indeksi, AST: Aspartat Aminotransferaz, ALT: Alanin Aminotransferaz, LDL-K: Düşük yoğunluklu lipoprotein kolesterol, HDL-K: Yüksek yoğunluklu lipoprotein kolesterol

T1D hastalarının %6.1'inde (n = 16) magnezyum eksikliği saptanmıştır. Magnezyum eksikliği olan T1D hastaları ile normal magnezyum seviyesine sahip T1D hastaları karşılaştırıldığında, yaş, cinsiyet dağılımı, VKİ ve diyabet süresi gibi parametrelerde istatistiksel olarak anlamlı bir fark bulunmamıştır (Tablo II). Lipid profili açısından da iki grup arasında anlamlı bir farklılık saptanmamıştır (Tablo II). Ancak, magnezyum eksikliği olan hastaların HbA1c seviyeleri istatistiksel açıdan anlamlı düzeyde daha yüksek bulunmuştur (p = 0.02).

Tablo II: Tip 1 diyabetik hastalarda klinik ve laboratuvar verilerinin magnezyum eksikliği durumuna göre değerlendirilmesi

Parametreler	Mg düzeyi normal olan hastalar (n=246)	Mg eksikliği olan hastalar (n=16)	p
Yaş (yıl)	32.3 ± 19.2	29.8 ± 8.9	0.61
Cinsiyet (K)	139 (%56.5)	11 (%68.8)	0.34
VKİ (kg/m²)	22.8 ± 3.2	22.6 ± 7.3	0.83
Diyabet Süresi (yıl)	8 (1-39)	7 (1-20)	0.31
Kreatinin (mg/dl)	0.79 (0.43-3.5)	0.76 (0.4-1.13)	0.29
HbA1c (%)	10.5 ± 2.9	12.3 ± 2.9	**0.02**
Total kolesterol (mg/dl)	169 (42-379)	148 (73-207)	0.07
LDL (mg/dl)	116.3 ± 35.4	112.1 ± 47	0.65
HDL (mg/dl)	50.5 ± 15.1	44.5 ± 14.1	0.12
Trigliserid (mg/dl)	109.3 (26-705)	104 (40.7-395)	0.45

Mg: Magnezyum, K:Kadın, VKİ: Vücut kitle indeksi, LDL-K: Düşük yoğunluklu lipoprotein kolesterol, HDL-K: Yüksek yoğunluklu lipoprotein kolesterol

Mikrovasküler komplikasyon oranı %30.2 (n = 79) olarak saptanmıştır. Hastaların %14.1'inde (n = 37) retinopati, %14.5'inde nefropati (n = 38), %20.6'sında (n = 54) nöropati saptanmıştır. T1D hastalarında mikrovasküler komplikasyonların varlığı ile magnezyum düzeyleri arasındaki ilişki Tablo III'te verilmiştir. Mikrovasküler komplikasyonları olan hastaların magnezyum düzeyleri, komplikasyonu olmayanlara kıyasla istatistiksel olarak anlamlı bir farklılık göstermemiştir.

Tablo III: Tip 1 diyabet hastalarında mikrovasküler komplikasyonlar ile magnezyum düzeyi arasındaki ilişkinin değerlendirilmesi

Komplikasyon	Komplikasyon olanlarda magnezyum düzeyi	Komplikasyon olmayanlarda magnezyum düzeyi	p
Retinopati	1.85 ± 0.21	1.91 ± 0.22	0.12
Nefropati	1.92 ± 0.23	1.85 ± 0.21	0.06
Nöropati	1.88 ± 0.29	1.86 ± 0.18	0.53

Tartışma ve Sonuç

Bu çalışmada T1D hastalarında magnezyum düzeylerinin glisemik kontrol ve mikrovasküler komplikasyonlarla ilişkisi incelenmiştir. T1D hastalarında serum magnezyum düzeyi kontrol grubuna göre daha düşük bulunmuş ancak hastaların %6.1'inde hipomagnezemi olduğu gözlenmiştir. Serum magnezyum düzeyi ile HbA1c ve APG arasında negatif korelasyon saptanmıştır. Bulgularımız, magnezyum eksikliğinin kötü glisemik kontrol ile ilişkili olduğunu ancak mikrovasküler

komplikasyonlar ile anlamlı bir ilişkisinin olmadığını göstermiştir.

Literatürde T1D hastalarında hipomagnezemi prevalansı değişmektedir[6,13,18,19]. Eski çalışmalarda T1D'li kişilerde hipomagnezemi yüzdesinin %38,6'ya kadar çıktığı bildirilmiştir[19]. Ancak, bu sonuçlar günümüze genelleştirilemez çünkü T1DM tedavisi son on yıllarda önemli ölçüde iyileşmiş ve daha iyi glisemik kontrol sağlanmıştır. Gerçekten de, yakın zamanda Hollanda'da yapılan ve 207 hastayı içeren prospektif bir kohortta hipomagnezemi oranı %4.3 olarak raporlanmıştır[6]. Pakistan'da yürütülen bir başka çalışmada hipomagnezemi oranı %14.5 bulunmuştur[18]. Oost ve arkadaşlarının 241 hastayı değerlendirildiği bir çalışmada ise hastaların %2.9'unda hipomagnezemi olduğu gösterilmiştir[13]. Bu çalışmada %6.1 olan hipomagnezemi oranı son yıllarda yayınlanan çalışmalardaki oranlarla benzerlik göstermektedir.

Bu çalışmada magnezyum eksikliğinin daha yüksek HbA1c düzeyleri ile ilişkili olduğu ve bunun kötü glisemik kontrolü işaret ettiği gözlemlenmiştir. Literatürde magnezyum eksikliği ile kötü glisemik kontrol arasında ilişki olduğunu rapor eden çalışmalar olsa da bunun aksini ifade eden yayınlarda mevcuttur[6,12,13,17]. Dijk ve arkadaşlarının yaptığı bir çalışmada T1D hastalarında magnezyum düzeyi ile HbA1c arasında bir ilişki olmadığı raporlanmıştır[6]. Buna karşın yakın zamanda yapılan bir meta-analizde, magnezyum ve glisemik kontrol arasındaki ilişkiyi değerlendirmek üzere tasarlanmış yedi çalışmadan beşinde azalan magnezyum seviyeleri ile zayıf glisemik kontrol arasında bir ilişki olduğu raporlanmıştır[12]. Oost ve arkadaşları ise serum magnezyum düzeyinin kötü glisemik kontrolle ilişkili olduğunu ve bunun muhtemel sebebinin insülin direnci olduğunu öne sürmüşlerdir[13]. Benzer şekilde, Galli-Tsinopoulou ve arkadaşları tarafından yapılan bir çalışmada da magnezyumun, glisemik kontrol mekanizmaları üzerinde doğrudan bir etkisi olduğu ve eksikliğinde kan şekeri seviyelerinde bozulma görüldüğü ifade edilmiştir[17]. Magnezyum, insülinin hücre içi glukoz alımı üzerindeki etkisini artırarak glisemik kontrolün sağlanmasında önemli bir rol oynamaktadır[20]. Azalmış magnezyum konsantrasyonları, tirozin kinaz aktivitesinin bozulmasına ve insülin direncinin kötüleşmesine neden olmaktadır. Bu bivalent iyonun sürekli eksikliği ise insülin direncine de katkıda bulunan daha yüksek TNF alfa seviyeleriyle ilişkilidir[21]. Çalışmamızda T1DM hastalarının ortalama magnezyum seviyesinin kontrol grubuna göre daha düşük bulunması ve hipomagnezemi olan grupta HbA1c düzeyinin daha yüksek bulunması diyabet yönetiminde magnezyum takviyesinin faydalı olabileceğini ve glisemik kontrolün sağlanmasına katkıda bulunabileceğini göstermektedir.

Çalışmanın bir başka sonucu da T1DM hastalarında retinopati, nefropati ve nöropati gibi mikrovasküler komplikasyonlar ile magnezyum düzeyleri arasında anlamlı bir ilişki bulunamamasıdır. Mikrovasküler komplikasyonların gelişiminde hiperglisemi, oksidatif stres ve vasküler inflamasyon gibi birçok faktör rol oynar[22]. Magnezyum eksikliğinin oksidatif stres ve inflamasyon mekanizmalarını tetikleyerek vasküler fonksiyonları etkilediği bilinse de, T1DM hastalarında bu etkinin doğrudan mikrovasküler komplikasyonlara yansıması literatürde tam olarak kanıtlanamamıştır[12,23]. Arslanoğlu ve arkadaşlarının yaptıkları çalışmada hipomagnezemi ile mikroalbüminüri arasında ilişki olduğu raporlansa da bu ilişki sonraki çalışmalarda doğrulanamamıştır[6,12,15,16]. T1D hastalarında retinopati ile serum magnezyum düzeyi arasındaki ilişkiyi inceleyen iki farklı çalışma, retinopati ile serum magnezyum düzeyleri arasında anlamlı bir ilişki olmadığını göstermiştir[14,24]. Rodrigues ve arkadaşları tarafından yapılan meta-analizde de benzer sonuçlar elde edilmiş, magnezyum eksikliğinin kötü glisemik kontrol ile ilişkili olduğu ama mikrovasküler komplikasyonlar üzerindeki doğrudan etkisinin net olarak kanıtlanamayacağı bildirilmiştir[12]. Hollanda'da yapılan prospektif bir çalışmada da magnezyum eksikliği ile mikrovasküler komplikasyonlar arasında doğrudan bir bağlantı bulunmadığı rapor edilmiştir[6]. Genel olarak bakıldığında çalışmamızın sonuçlarının güncel literatür ile uyumlu olduğu görülmektedir. Ancak magnezyumun mikrovasküler komplikasyonlardaki rolünün daha kapsamlı ve uzun dönemli çalışmalarla açıklığa kavuşturulması gerekmektedir

Bu çalışmanın güçlü yönlerinden biri, geniş bir hasta grubunun dahil edilmesi ve kontrol grubunun varlığıdır. Bu durum, magnezyum düzeylerinin T1DM hastalarında nasıl değiştiğini anlamak için sağlıklı bireylerle karşılaştırma yapmamıza olanak sağlamıştır. Ayrıca, mikrovasküler komplikasyonların detaylı bir şekilde değerlendirilmesi, bu çalışmayı literatürdeki diğer benzer çalışmalardan ayırmaktadır. Magnezyum eksikliğinin glisemik kontrol üzerindeki etkileri bu çalışma ile desteklenmiş olup, magnezyumun T1DM yönetiminde potansiyel bir hedef olabileceğini göstermektedir. Ancak çalışmanın bazı sınırlamaları da bulunmaktadır. Çalışmamız retrospektif olarak tasarlandığı için, nedensel ilişkiler kurmak zor olmuştur. Ayrıca, bu çalışma tek bir merkezde yapılmış olup, bulguların genelleştirilebilirliği sınırlıdır. Çalışmada yalnızca mikrovasküler komplikasyonlar değerlendirilmiş olup, makrovasküler komplikasyonlara ilişkin veri bulunmamaktadır. Magnezyum takviyesinin glisemik parametreler üzerindeki etkisi değerlendirilememiştir. Son olarak çalışma popülasyonunda insülin direnci varlığı, TNF-alfa ve yüksek duyarlıklı C-reaktif protein gibi inflamasyon belirteçleri incelenememiştir.

Bu çalışma T1D hastalarında magnezyum eksikliğinin glisemik kontrol ile ilişkili olduğunu ve özellikle kötü glisemik profile sahip hastalarda magnezyum seviyelerinin diyabet yönetiminde değerlendirilmesinin önemli olabileceğini göstermektedir. Ancak, T1D hastalarında magnezyumun mikrovasküler komplikasyonların gelişimine olan etkisini netleştirmek için ileriye dönük çalışmalar gerekmektedir. Gelecekte yapılacak çok merkezli, prospektif ve geniş kapsamlı çalışmalar, magnezyumun T1DM'deki rolünü daha net bir şekilde ortaya koyabilir.

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ORIGINAL RESEARCH

A Contemporary Series on Retropubic Radical Prostatectomy and an Analysis of Factors Influencing Biochemical Recurrence-Free Survival

Yavuz Mert AYDIN, Necmettin Aydın MUNGAN

Zonguldak Bulent Ecevit University Faculty of Medicine, Department of Urology, Zonguldak, Türkiye.

ABSTRACT

This study investigates outcomes and identifies factors influencing biochemical recurrence and biochemical recurrence-free survival (BRFS) rates in patients undergoing retropubic radical prostatectomy (RRP) at a tertiary university hospital over 10 years. Data of patients who underwent RRP between 2012 and 2022 were analyzed retrospectively. Variables included demographic information, preoperative prostate-specific antigen (PSA) levels, prostate volume, PSA density, operative details, histopathological findings, and postoperative follow-up data. Patients without at least three years of regular follow-up were excluded from the study. The Cox regression analyses were performed to determine the independent risk factors for BRFS. Survival analysis was performed using Kaplan-Meier and the log-rank test. The final analysis included 115 patients. The median follow-up duration was 77.2 months (range: 36.3–153.6), and the median BRFS was 47.3 months (range: 0–153.6). The 3-year BRFS rate was 61.8%. Positive surgical margins were identified as a significant predictor of BRFS (HR: 2.388, p=0.004), while higher PSA density and the ISUP grade groups also showed associations with recurrence risk (p= 0.033 and 0.048, respectively). Survival analyses confirmed shorter BRFS in patients with positive surgical margins (p=0.000). This study highlights the effectiveness of RRP in the surgical management of localized PCA. Surgical margin status emerged as the primary predictor of BRFS. PSA density may be a promising parameter in predicting biochemical recurrence, but further studies are needed.

Keywords: Retropubic radical prostatectomy. Prostate cancer. Biochemical recurrence-free survival.

Retropubik Radikal Prostatektomi Üzerine Çağdaş Bir Seri ve Biyokimyasal Nükssüz Sağkalımı Etkileyen Faktörlerin Analizi

ÖZET

Bu çalışmanın amacı üçüncü basamak sağlık hizmeti veren bir üniversite hastanesinde son 10 yılda yapılan retropubik radikal prostatektomi (RRP) ameliyatlarının sonuçlarını değerlendirmek ve cerrahi tedavi alan hastalarda biyokimyasal nüksüz sağkalımı (BNS) etkileyen faktörleri belirlemektir. Bu çalışma için kliniğimizde 2012-2022 yılları arasında RRP geçiren hastaların verilerini retrospektif olarak analiz edildi. İncelenen veriler arasında; hastaların demografik bilgileri, preoperatif prostat spesifik antijen (PSA) düzeyi, prostat hacmi, PSA dansitesi, operatif veriler, histopatolojik sonuçlar ve postoperatif takip bilgileri mevcuttu. En az üç yıllık düzenli takibi olmayan hastalar çalışma dışı bırakıldı. BNS üzerine etki eden faktörleri belirlemek için Cox regresyon analizi uygulandı. Sağkalım analizi log-rank testi uygulanarak Kaplan-Meier grafi ile verildi. Analize 115 hasta dahil edildi. Medyan takip süresi 77,2 ay (36,3–153,6) ve medyan BNS 47,3 aydı (0–153,6). 3 yıllık BNS oranı 61.8%' olarak bulundu. Cerrahi sınır pozitifliği BNS etkileyen önemli bir faktör olarak tespit edildi (HR: 2.388, p=0.004). Ayrıca yüksek PSA dansitesi ve yüksek ISUP derece grup varlığı biyokimyasal rekürrens ile ilişkili bulunmuştur (p sırasıyla = 0,033 ve 0,048). Sağkalım analizi cerrahi sınırı pozitif olan hastaların daha kısa BNS süresine sahip olduklarını göstermiştir. (p=0.000). Bu çalışa RRP' nin lokalize prostat kanseri tedavisindeki yerini vurgulamıştır. Cerrahi sınır durumu BNS' yi öngörmede anlamlı bir parametredir. PSA dansitesi biyokimyasal rekürrensi öngörmede umut vaat eden bir parametredir; ancak bu konuda daha ileri çalışmalara gereksinim vardır.

Anahtar Kelimeler: Retropubik radikal prostatektomi. Prostat kanseri. Biyokimyasal nükssüz sağkalım.

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Dr. Yavuz Mert AYDIN
Zonguldak Bülent Ecevit Üniversitesi Tıp Fakültesi,
Üroloji, ABD. Kozlu, 67639,
Zonguldak, Türkiye
Phone: 0506 956 77 45
E-mail: yavuzmertaydin@gmail.com,
mert.aydin@beun.edu.tr

Authors' ORCID Information:
Yavuz Mert Aydın: 0000-0002-6287-6767
Necmettin Aydın Mungan: 0000-0002-1985-4212

Prostate cancer (PCA), which has an age-standardized incidence rate of 29.4 per 100,000, ranks as the second most frequently diagnosed cancer globally, following breast cancer[1]. Considering only the male population, PCA ranks as the second most commonly diagnosed cancer after lung cancer[1]. Definitive treatment options for localized PCA include surgery (radical prostatectomy) and external beam radiation therapy[2]. Radical prostatectomy involves the excision of the whole prostatic gland with the prostate capsule, the distal segments of the bilateral vas deferens, and the

seminal vesicles. The procedure is subsequently followed by vesicourethral anastomosis. The application of radical prostatectomy dates back to 1905 when Hugh Hampton Young introduced the perineal approach[3]. Later, in 1948, Milin described the extraperitoneal radical prostatectomy using an abdominal infra umbilical incision[4]. In 1979, Walsh developed a technique for managing the dorsal venous complex, significantly reducing intraoperative blood loss and enhancing procedural safety[5]. Furthermore, Walsh introduced the concept of nerve-sparing radical prostatectomy[6]. The nerve-sparing retropubic radical prostatectomy (RRP) became the standard surgical procedure for prostate cancer treatment for many years. While laparoscopic radical prostatectomy (LRP) and robot-assisted radical prostatectomy (RARP) are now widely utilized, open RRP continues to hold its place in the management of PCA treatment[7].

Systematic reviews have demonstrated that laparoscopic and robot-assisted radical prostatectomy do not provide superior oncological outcomes compared to RRP[8,9]. Although LRP and RARP offer advantages in terms of complication rates and length of hospital stay, some LRP series have reported higher incidences of anastomotic leakage, organ injury, and ileus than RRP[2,8,9]. Furthermore, the significantly greater cost-effectiveness of RRP and its ability to be performed with fewer technological instruments compared to the other two methods represent a critical advantage in favor of RRP[7].

This study aims to present the outcomes of a 10-year RRP series conducted at a university hospital delivering tertiary healthcare services and to identify factors influencing biochemical recurrence-free survival (BRFS) in these patients.

Material and Method

In this study, we retrospectively analyzed the data of 125 patients who underwent RRP for prostate cancer in our clinic between January 1, 2012, and January 1, 2022. The analyzed parameters included patient demographic data (age, weight), preoperative prostate-specific antigen (PSA) levels, prostate volume, PSA density, American Society of Anesthesiologists (ASA) scores, postoperative complications, preoperative and postoperative hematocrit level, estimated blood loss, operation time, length of hospital stay, Gleason scores and International Society of Urological Pathology (ISUP) grade group of the radical prostatectomy specimens, presence of perineural invasion (PNI), presence of lymphovascular invasion (LVI), lymph node status, surgical margin status, postoperative PSA follow-up results, bladder neck contracture rate, last follow-up date, the date of biochemical recurrence (BCR), 3-year BRFS status, BRFS time. PSA density was determined by dividing the PSA level by the prostate volume. Estimated blood loss was calculated using the formula: the difference between the preoperative and postoperative hematocrit values was divided by the preoperative hematocrit, and the result was multiplied by the total blood volume. Total blood volume was calculated by multiplying the body weight by 70 ml/kg. Postoperative complications were classified according to the Clavien-Dindo classification system[10]. Patients who underwent radical prostatectomy surgery out of abdominal RRP technique and those with less than three years of follow-up were excluded from the study. As our department serves as a training clinic for urology, residents also participated in these surgeries.

Surgical Procedure

Following field preparation and sterilization in the supine position under general anesthesia, a sub-umbilical midline incision was made, traversing the skin, subcutaneous tissue, and fasciae, and finally reached the peritoneum. The endopelvic fascia was incised to expose the prostate capsule. The puboprostatic ligament and dorsal venous complex were ligated and transected using a 1/0 Vicryl suture. Subsequently, the urethra was incised at the prostate apex, rotated 180 degrees, and the foley catheter was clamped and cut distal to the external urethral opening. The lateral pedicles were then dissected using both blunt and sharp dissection techniques. The bladder neck was dissected and preserved, allowing the prostate base to be separated through a combination of blunt and sharp dissection. Posteriorly, the vas deferens were bilaterally ligated and transected at the level of the seminal vesicles, which were subsequently dissected. The Denonvilliers fascia was identified, enabling the separation of the prostate from the rectum. After removing the radical prostatectomy specimen from the surgical site, meticulous hemostasis was achieved. A 20F Foley catheter was then inserted before vesicourethral anastomosis. The anastomosis of the bladder neck to the urethra was performed using six 2/0 Vicryl sutures corresponding to 1, 3, 6, 9, 11, and 12 o'clock. A drain was placed in the surgical site, and the surgical layers were closed in alignment with the anatomical planes.

Ethics Statement

The study protocol was approved by the Clinical Research Ethics Committee of Zonguldak Bülent Ecevit University (approval number: 2024/20) and complied with the tenets of the Helsinki Declaration.

Biostatistical Analysis

Categorical variables were compared using the chi-square test, continuity correction, and Fisher's exact test. Shapiro–Wilk and Kolmogorov–Smirnov tests were performed to evaluate the normality of continuous data. The Mann–Whitney U and Kruskal–Wallis test was used for nonnormally distributed variables. Continuous data are expressed as the median and minimum-maximum values. The Cox regression analyses were performed to determine the independent risk factors for BRFS. Survival analysis was performed using Kaplan-Meier and the log-rank test. $P<0.05$ was considered to indicate a statistically significant result. SPSS software (IBM SPSS Statistics for Windows, version 25.0; IBM Corp) was used for the analyses.

Results

After applying exclusion criteria, 115 patients were included in the final analysis. The median age of the patients was 64.5 years (range: 47.5–75.3), with a median body weight of 78.5 kg (range: 55–106). The median prostate volume was 41 ml (range: 20–120), the preoperative PSA level was 8.9 ng/ml (range: 3.1–27.5), and the PSA density was calculated as 0.21 ng/ml^2 (range: 0.09–1.17). The median duration of the surgeries was 175 minutes (range: 115–230), and the median estimated blood loss was calculated as 742 ml (range: 525–1375). The median length of hospital stay was 5 days (range: 3–9), with most postoperative complications being minor (13% vs. 2.7%). During clinical follow-up, one patient presenting with acute chest pain was diagnosed with acute myocardial infarction following cardiac evaluation and underwent percutaneous transluminal coronary angioplasty performed by the cardiology team. Another patient developed a hematoma at the incision site, necessitating re-exploration and hemostasis under general anesthesia. Additionally, one case of bowel evisceration at the surgical wound site required surgical repair under general anesthesia. During long-term follow-up, bladder neck contracture was observed in 10 patients (8.7%). (Table I)

The evaluation of RRP specimens revealed that most patients (57.4%) were classified as ISUP grade group 1 (Gleason 3+3). Of the patients, 93 (80.8%) were staged as pT2, while 19.2% were pT3. PNI positivity was observed in 64 patients (55.7%), and LVI positivity was noted in 6 (5.2%). Extended pelvic lymph node dissection (including external iliac, internal iliac, and obturator zones) was performed in 21 patients (18.3%), with malignant lymph nodes identified in only one case. Positive surgical margins were identified in 42 patients (36.5%). The median follow-up duration was 77.2 months (range: 36.3–153.6), and the median BRFS was 47.3 months (range: 0–153.6). (Table I)

Table I: The Clinicopathological characteristics of the entire patients.

Age (median, min&max; years)			64.5 (47.5-75.3)
Body Weight (median, min&max; kg)			78.5 (55-106)
Prostate Volume (median, min&max; ml)			41 (20-120)
Preop PSA Level (median, min&max; ng/ml)			8.9 (3.1-27.5)
PSA Density (median, min&max; ng/ml^2)			0.21 (0.09-1.17)
Estimated Blood Loss (median, min&max; ml)			742 (525-1375)
Operation Time (median, min&max; min)			175 (115-230)
Length of hospital stay (median, min&max; days)			5 (3-9)
Follow-up duration (median, min&max; months)			77.2 (36.3-153.6)
Biochemical recurrence-free survival (median, min&max; months)			47.3 (0–153.6)
Postoperative Complication			15 (13%)
Minor (I—II) (*n*, %)			3 (2.7%)
Major (≥ III) (*n*, %)			1 (0.9%)
(IIIa) Percutaneous transluminal coronary angioplasty			1 (0.9%)
(IIIb) Surgical intervention due to hematoma			1 (0.9%)
(IIIb) Surgical intervention due to bowel evisceration			1 (0.9%)
Bladder neck contracture *(n,%)*			10 (8.7%)
ISUP Grade Group	*1*	*3+3 (n,%)*	66 (57.4%)
	2	*3+4 (n,%)*	26 (22.6%)
	3	*4+3 (n,%)*	14 (12.2%)
	4	*4+4 (n,%)*	3 (2.6%)
	5	*>4+4 (n,%)*	6 (5.2%)
pT	*T2a*	*(n,%)*	27 (23.5%)
	T2b	*(n,%)*	14 (12.2%)
	T2c	*(n,%)*	52 (45.1%)
	T3a	*(n,%)*	14 (12.2%)
	T3b	*(n,%)*	8 (7%)
PNI	*Negative*	*(n,%)*	51 (44.3%)
	Positive	*(n,%)*	64 (55.7%)
LVI	*Negative*	*(n,%)*	109 (94.8%)
	Positive	*(n,%)*	6 (5.2%)
Lymph Node	*Nx*	*(n,%)*	94 (81.7%)
	N0	*(n,%)*	20 (17.4%)
	N1.	*(n,%)*	1 (0.9%)
Surgical Margin	*Negative*	*(n,%)*	73 (63.5%)
	Positive	*(n,%)*	42 (36.5%)

min: Minimum, max: Maximum. kg: Kilogram, Preop: Preoperative,
PSA: prostate-specific antigen, ng: Nanogram, ml: Milliliter,
ISUP: International Society of Urological Pathology, min: minutes
pT: pathological T stage, PNI: Perineural invasion,
LVI: Lymphovascular invasion

At the end of the third-year follow-up status, the patients were categorized into two groups based on the presence of BCR. The 3-year BRFS rate was 61.8%. Group 1 (n=71) included patients without BCR, while Group 2 (n=44) included those with BCR. The comparison between these groups indicated that patients with BCR had a higher incidence of positive surgical margins (54.5% vs. 25.4%, p= 0.003), significantly elevated PSA density (0.38 vs. 0.15, p=0.033), and a significantly greater proportion of patients with higher ISUP grade groups (p=0.048). (Table II)

Table II: Comparative analysis of clinicopathological characteristics of the groups

			Group 1 (n=71)	Group 2 (n=44)	p-value
Age (median, min&max; years)			64.6 (51.9-75.3)	63.9 (47.5-71.9)	0.629
Body weight (median, min&max; kg)			77 (67-102)	87.5 (65-105)	0.388
Prostate volume (median, min&max; ml)			45 (20-120)	36 (25-62)	0,247
Preop PSA level (median, min&max; ng/ml)			8.1 (3.1-27.3)	9.3 (4.1-27.5)	0.629
PSA density (median, min&max; ng/ml^2)			0.15 (0.11-1.16)	0.38 (0.09-1.17)	**0.033**
ISUP Grade Group	*1*	*(n,%)*	47 (66.2%)	19 (43.2%)	**0.048**
	2,3	*(n,%)*	19 (26.8%)	21 (47.7%)	
	4,5	*(n,%)*	5 (7%)	4 (9.1%)	
pT	*pT2*	*(n,%)*	58 (81.7%)	35 (79.5%)	0.968(cc)
	pT3	*(n,%)*	13 (18.3%)	9 (20.5%)	
PNI	*Negative*	*(n,%)*	34 (47.9%)	17 (38.6%)	0.437(cc)
	Positive	*(n,%)*	37 (52.1%)	27 (61.4%)	
LVI	*Negative*	*(n,%)*	69 (97.2%)	40 (90.9%)	0.201(fe)
	Positive	*(n,%)*	2 (2.8%)	4 (9.1%)	
Surgical Margin	*Negative*	*(n,%)*	53 (74.6%)	20 (45.5%)	**0.003**cc
	Positive	*(n,%)*	18 (25.4%)	24 (54.5%)	

min: Minimum, max: Maximum. kg: Kilogram, Preop: Preoperative, PSA: prostate-specific antigen, ng: Nanogram, ml: Milliliter, ISUP: International Society of Urological Pathology, pT: pathological T stage, PNI: Perineural invasion, LVI: Lymphovascular invasion

Cox regression analysis performed to identify parameters influencing BRFS indicated that only positive surgical margins had a significant impact (HR: 2.388, p=0.004 CI: 1.319-4.322). (Table III) Survival analysis further demonstrated that patients with positive surgical margins had a statistically significantly shorter BRFS (the log-rank test, p=0.000). (Figure 1)

Table III: Cox regression analysis for predictors of biochemical recurrence free survival.

Factor		Cox regression Analysis			
				%95 CI	
		OR	p-value	Lower	Upper
Preop. PSA level	*(ng/ml)*	1.007	0.687	0.973	1.043
Age	*years*	0.961	0.142	0.910	1.014
ISUP Grade Group	*1*		0.853		
	2, 3	1.850	0.074	0.943	3.629
	4, 5	1.685	0.433	0.457	6.208
pT	pT2 (R) vs pT3	0.981	0.965	0.422	2.281
PNI	*Negative (R) vs positive*	0.836	0.601	0.428	1.635
LVI	*Negative (R) vs positive*	1.243	0.692	0.424	3.645
Surgical Margin	*Negative (R) vs positive*	**2.388**	**0.004**	**1.319**	**4.322**

OR: Odss ratio, Preop: Preoperative, PSA: Prostate-specific antigen, ng: Nanogram, ml: Milliliter, R: Reference category,
ISUP: International Society of Urological Pathology, pT: Pathological T stage, PNI: Perineural invasion,
LVI: Lymphovascular invasion.

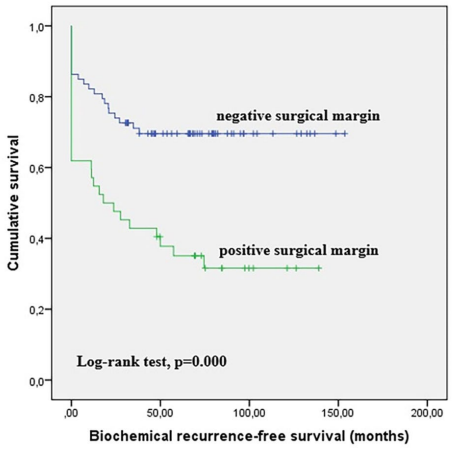

Figure 1:
Kaplan-Meier survival curves according to surgical margin status

Patients were classified into three groups to assess the impact of positive apical surgical margins on BRFS: negative surgical margins, positive margins confined to the apex, and positive margins outside the apex. The BRFS of patients with positive apical surgical margins did not differ significantly from those with positive margins outside the apex (p=540, median BRFS 23.7 [0-84.5] vs. 18 [0-139] respectively). However, the BRFS of patients with positive apical surgical margins was significantly shorter than those with negative surgical margins (p=0.033, median BRFS 23.7 [0-84.5] vs. 56.3 [0-153.6] respectively).

Discussion and Conclusion

This study found that RRP is an effective treatment for PCA, and a positive surgical margin is the most influential factor in BRFS. Furthermore, we observed that patients with BCR tended to have higher PSA density and ISUP grade group. A high-volume study with long-term follow-up of patients with localized prostate cancer identified positive surgical margins, pT3b staging, and pT3a combined with an ISUP grade group >2 as factors associated with a high risk of BCR[11]. In our study, positive surgical margins were the only factor found to be significant. The relatively low number of patients with pT3b (n:8. 7%) and pT3a combined with an ISUP grade group >2 (n:3, 2.6%) in the entire cohort may explain why these two factors did not achieve statistical significance in our analysis. Although the number of pT3 patients in our study was limited, the relatively higher proportion of patients with higher ISUP grade groups among those who developed BCR within three years is consistent with findings reported in the literature[12].

In a review conducted by Ho MD et al. on the stratification of prostate cancer, PSA density was suggested to be associated with high-grade disease[13]. Similarly, Sasaki et al. found that patients with a familial history of prostate cancer exhibited higher PSA density and that these individuals demonstrated poorer clinicopathological outcomes and an association with disease progression following radical prostatectomy[14]. These findings align with our cohort results, where patients defined as BCR within three years exhibited higher PSA density. Furthermore, Greco et al. suggested that PSA density could predict biochemical and local failure in radiotherapy patients[15]. When evaluated alongside these findings and other studies, PSA density emerges as an essential biomarker indicative of tumor burden. However, there is a need for well-designed, advanced studies to investigate this subject further.

A long-standing debate persists regarding which surgical approach, RARP, LRP, or RRP, is superior for the treatment of patients diagnosed with localized PCA. Urology associations have not endorsed any method superior to the others[2,16]. The consensus is that all three approaches demonstrate comparable effectiveness regarding oncological outcomes[2,9,17–20]. Systematic reviews and meta-analyses have indicated that RARP offers advantages in reduced blood loss, lower transfusion requirements, shorter hospital stays, and fewer complications[17,20,21]. Wang et al. reported that RARP results in lower rates of positive surgical margins and BCR compared to RRP[21]. Similarly, Ramsay et al. reviewed studies comparing RARP and LRP and found no significant differences in BCR rates, although they highlighted the superiority of RARP in reducing positive surgical margins[17]. Haglind et al. found no significant differences between RARP and RRP regarding incontinence or positive surgical margins in a prospective, controlled, non-randomized study. Still, they noted that erectile dysfunction outcomes were modestly better in RARP patients[22]. In contrast, Du et al. argued that RARP is superior to both LRP and RRP in terms of nerve-sparing, erectile function, and urinary continence outcomes in a systematic review and meta-analysis[23].

An often-overlooked issue in RARP studies is cost-effectiveness. RARP imposes a substantial financial burden on patients and healthcare systems, with reports suggesting that centers performing RARP must maintain a high annual case volume of approximately 150 to mitigate these costs. LRP, another minimally invasive approach, is less expensive than RARP and has been shown to offer benefits such as reduced blood loss and shorter hospital stays compared to RRP[17]. However, its extended learning curve and reports from particular series indicating disadvantages compared to RRP, such as higher rates of anastomotic leakage, organ injury, and ileus, represent notable disadvantages for LRP[2,17]. Additionally, the fact that surgeons performing RARP and LRP are often more experienced and operate in higher-volume settings compared to those performing RRP raise concerns that functional, and some oncological outcomes may be influenced by surgical experience rather than solely by the surgical method itself[20]. Furthermore, it has been observed that the RRP series typically involve a more significant number of surgeons per study and have longer follow-up durations[20]. Based on this information, RRP remains positioned in treating localized prostate cancer due to its comparable oncological and functional outcomes, relatively shorter learning curve, and cost-effectiveness[9,24].

Our findings regarding estimated blood loss, operative time, and length of hospital stay are consistent with the literature[17,18,25]. Prudhomme et al. presented the case series of a single experienced surgeon, noting that the estimated blood loss was nearly as low as in the RARP series[26]. This low blood loss may be attributed to the surgeon's experience. Our estimated blood loss result is comparable to that reported in other studies[18,25]. However, our surgical margin positivity rate was somewhat higher than those described in the literature. Notably, these studies primarily reported the outcomes of a single experienced surgeon[18,25,26]. Given that our center is a teaching hospital that trains urology residents and allows them to perform RRP, we suggest that this factor contributes to our study's higher surgical margin positivity rate. Grabbert et al. conducted their study in a tertiary health care center and did not specify the operations were exclusively performed by a single experienced surgeon. Their study reported a surgical margin positivity rate of 29%[27]. Consequently, our surgical margin positivity rate is within an acceptable range based on teaching hospitals that train residents.

Previous studies have reported that positive apical surgical margins are not associated with poor prognostic outcomes compared to positive surgical margins outside the apex[28]. Some of these studies have even suggested that patients with positive apical surgical margins exhibit BRFS durations comparable to those with negative surgical margins[29]. In contrast, our study demonstrated that patients with positive apical surgical margins experienced BCR significantly earlier than those with negative surgical margins. Furthermore, there was no significant difference in BRFS between patients with positive apical surgical margins and those with positive margins outside the apex. Consistent with our findings, Pettus et al. reported that positive apical surgical margins do not indicate a better prognosis than positive margins outside the apex and that such patients experience BCR more frequently than those with negative surgical margins[30]. To resolve this dilemma., there is a need for well-designed, high-quality studies.

The primary limitation of our study is the retrospective nature of the study. The secondary one is the lack of post-RRP functionality data (urinary incontinence and erectile dysfunction rates), a limitation stemming from the challenges inherent in standard data collection processes due to the study's retrospective design. Additionally, our study primarily focuses on the oncological outcomes of RRP. Given the low overall and PCA-specific mortality rates, data on overall and cancer-specific survival could not be presented. Nonetheless, due to the growing preference for minimally invasive surgical techniques and the decreasing volume of recent publications on RRP, our study seeks to contribute to the reappraisal of this surgical approach by presenting a contemporary series on RRP.

This study highlights the effectiveness of RRP in the surgical management of localized PCA. Positive surgical margins emerged as the primary predictor of BRFS. PSA density may be a promising parameter in predicting BCR, but further studies are needed. Although minimally invasive techniques are gaining prominence, RRP is a viable alternative, especially in settings with limited resources. A positive apical surgical margin is not associated with a better prognosis.

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ÖZGÜN ARAŞTIRMA

Acil Servise El Yaralanması ile Başvuran İş Kazalarında Konsültan Hekim ve Acil Servis Hekiminin Tanısal Yaklaşımlarının Karşılaştırılması*

Çağrı AKCA[1], Şule AKKÖSE AYDIN[2], Vahide Aslıhan DURAK[2], Gökay EKEN[3], Süleyman ÇEÇEN[4], Göksel AYDOĞAN[2], Sümeyye Tuğba SARKI CANDER[5]

[1] Hakkari Devlet Hastanesi Acil Servisi, Hakkari, Türkiye.
[2] Bursa Uludağ Üniversitesi Tıp Fakültesi, Acil Tıp Anabilim Dalı, Bursa, Türkiye.
[3] Bursa Uludağ Üniversitesi Tıp Fakültesi, Ortopedi ve Travmatoloji Anabilim Dalı, Bursa, Türkiye.
[4] Bursa Uludağ Üniversitesi Tıp Fakültesi, Plastik ve Rekonstrüktif Cerrahi Anabilim Dalı, Bursa, Türkiye.
[5] Çekirge Devlet Hastanesi Acil Servisi, Bursa, Türkiye.

ÖZET

Bu çalışmanın amacı acil servise el ve el bilek travması ile başvuran hastaların klinik özelliklerinin değerlendirilmesi ve acil servis hekimleri ile el cerrahisi hekimleri arasında yaklaşım farklılıklarının ortaya konmasıdır. Çalışmamız 1 Ocak 2023 - 31 Mayıs 2023 tarihleri arasında acil servise el veya el bileği yaralanması nedeniyle başvuran 333 iş kazası olgusunun prospektif olarak çalışmaya dahil edilmesi ile çalışma gerçekleştirilmiştir. Olguların %88,3'ü erkekti ve yaş ortalaması 36,98±12,51'di. Acil serviste yapılan değerlendirme ve konsültan hekim tarafından yapılan değerlendirme sonucunda en sık saptanan patolojiler fraktür (%68,5 vs %64,0), tendon yaralanması (%35,7 vs %26,7), sinir yaralanması (%15,6 vs %18,6) ve damar yaralanmasıydı (%9,3 vs %9,3). Olguların %24,0'ına primer onarım, %55,6'sına cerrahi onarım, %4,8'ine redüksiyon ve %3,0'ına yabancı cisim çıkarılması uygulanırken, olguların %12,3'ü tedaviyi reddetti. Olguların %72,4'ü taburcu edilirken %13,5'i kliniğe yatırıldı. Acil serviste saptanan damar yaralanmaları (κ = 0,822) ve fraktür olgularının (κ = 0,859) konsültan hekimle yüksek düzeyde tutarlı olduğu, sinir (κ = 0,620) ve tendon yaralanmalarının ise (κ = 0,653) orta düzeyde tutarlı olduğu görüldü. Acil hekimlerinin el ve el bileği yaralanması olgularında bu patolojilere dair daha detaylı değerlendirme yapması, klinik pratikte bu olguların atlanmasını engelleyebilir. Bu konuda yapılacak çok merkezli çalışmalarla daha net ve bütün el ve el bileği yaralanmalarına genellenebilir sonuçlar elde edilebileceği düşünülmektedir.

Anahtar Kelimeler: Acil servis. İş kazası. El yaralanması.

Comparison of Diagnostic Approaches of Consultant Physicians and Emergency Department Physicians in Occupational Accidents Who Present to the Emergency Department with Hand Injuries

ABSTRACT

The aim of this study is to evaluate the clinical characteristics of patients presenting to the emergency department with hand and wrist trauma and to reveal the differences in approach between emergency room physicians and hand surgeons. The study was conducted prospectively by including 333 work accident cases who applied to the emergency department due to hand or wrist injury between January 1, 2023 and May 31, 2023. 88.3% of the cases were male and the average age was 36.98±12.51. As a result of the evaluation made in the emergency room and the evaluation made by the consultant physician, the most frequently detected pathologies were fracture (68.5% vs 64.0%), tendon injury (35.7% vs 26.7%), nerve injury (15.6% vs. 18.6%) and vascular injury (9.3% vs 9.3%). Primary repair was performed in 24.0% of the cases, surgical repair in 55.6%, reduction in 4.8% and foreign body removal in 3.0%, while 12.3% of the cases refused treatment. While 72.4% of the cases were discharged, 13.5% were admitted to the clinic. It was observed that vascular injuries (κ = 0.822) and fracture cases (κ = 0.859) detected in the emergency department were highly consistent with the consultant physician, while nerve (κ = 0.620) and tendon injuries (κ = 0.653) were moderately consistent. Emergency physicians' more detailed evaluation of these pathologies in cases of hand and wrist injuries may prevent these cases from being overlooked in clinical practice. It is thought that more clear and generalizable results for all hand and wrist injuries can be obtained with multi-center studies on this subject.

Key Words: Emergency department. Hand injury. Occupational accidents.

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Dr. Vahide Aslıhan DURAK
Bursa Uludağ Üniversitesi Tıp Fakültesi Acil Tıp Anabilim Dalı, Görükle, BURSA
Tel.: 0532 446 25 12
E-posta:aslidurakis@hotmail.com
Yazarların ORCID Bilgileri:
Çağrı Akca: 0009-0000-7391-1428
Şule Akköse: 0000-0002-5336-8621
Vahide Aslıhan Durak: 0000-0003-0836-7862
Gökay Eken: 0000-0001-9447-4749
Süleyman Çeçen: 0000-0003-2430-727X
Göksel Aydoğan: 0009-0006-2750-207X
Sümeyye Tuğba Sarkı Cander: 0000-0002-4161-5381

El; insanın çevresiyle doğrudan etkileşimini sağlayan vücudun hayati bir parçasıdır. Üst ekstremitenin en aktif, aynı zamanda korunması en az ve en sık yaralanan bölümüdür[1].

El yaralanmaları genellikle kesikler, kırıklar, ezilmeler ve amputasyonlar gibi çeşitli türlerde olabilir. Bu tür yaralanmalar, hastaların günlük yaşam aktivitelerini ve iş performanslarını ciddi şekilde etkileyebilir[2].

İş kazaları sonucu el yaralanmaları, acil servislerde sıkça karşılaşılan durumlardan biridir ve genellikle acil müdahale gerektirir. Bu yaralanmalar, hem hasta hem de sağlık hizmeti sunucuları için ciddi zorluklar doğurabilir. El yaralanmaları iş gücü kaybına, uzun iyileşme sürelerine ve bazen kalıcı sakatlıklara yol açabilmektedir[3].

Acil servislerde, el yaralanmalarıyla başvuran hastaların ilk değerlendirmesi ve tedavisi büyük önem taşır. Acil servis hekimlerinin hızlı ve etkili bir müdahale yapması gerekmektedir. Ancak, bu hızlı müdahaleler sırasında bazı detayların gözden kaçma riski vardır. Bu nedenle, konsültan hekimlerin daha spesifik bir değerlendirme yapması gerekebilir[4].

Acil servis hekimleri ve konsültan hekimler arasında tanısal ve tedavi yaklaşımlarında belirgin farklılıklar olabilir. Acil servis hekimleri genellikle hızlı karar almak zorunda olduklarından, tanısal süreçte bazı detayları atlayabilirler. Buna karşın, konsültan hekimler daha detaylı bir değerlendirme yaparak, spesifik tedavi planları oluşturabilirler[5].

Bu farklılıklar, tedavi sonuçları üzerinde önemli etkiler yaratabilir. Literatürde yer alan bir çalışmada, konsültan hekimlerin müdahalelerinin daha düşük komplikasyon oranları ve daha iyi fonksiyonel sonuçlar sağladığı görülmüştür[6].

Bu çalışmanın amacı acil servise el ve el bilek travması ile başvuran hastaların klinik özelliklerinin değerlendirilmesi ve acil servis hekimleri ile el cerrahisi hekimleri arasında yaklaşım farklılıklarının ortaya konması olup işbirliği ve koordine çalışma ile hasta bakım kalitesinin yükseltilmesi ve komplikasyonların azaltılması hedeflenmektedir.

Gereç ve Yöntem

Çalışmaya başlamadan önce Klinik Araştırmalar Etik Kurulu'ndan izin alınmıştır (karar no: 2023-1/39).

Kesitsel tipte olan bu çalışma, 1 Ocak 2023 – 31 Mayıs 2023 tarihleri arasında acil servise el veya el bileği yaralanması nedeniyle başvuran iş kazası olgularının prospektif olarak çalışmaya dahil edilmesi ile gerçekleştirilmiştir.

Acil servise ilgili tarihler arasında başvuran, iş kazası olan, el veya el bileği yaralanması saptanan, konsülte edilen hastalar çalışmaya dahil edilirken acil servisi izinsiz terk ettiği tespit edilen 8 hastaya ek olarak ısırık ve yanık/ donma sebebi ile başvuran hastalar çalışmaya dahil edilmemiştir.

Hastaların yaş ve cinsiyetleri, yaralanma şekli (sıkışma, delici kesici yaralanma, spiral ile kesi), yaralanan el, yaralanan bölge, yaralanan parmak, acil hekiminin değerlendirmesi, konsültan hekimin değerlendirmesi, ilk ve ikinci basamak tedavileri ve klinik sonlanımları kayıt altına alınmıştır.

Acil servisin travma alanında hastaları değerlendiren acil servis araştırma görevlileri ve konsültan araştırma görevlileri için asistanlık sürelerinin 2 yılını tamamlamış olması gerekmekte olup konsültan hekimler ortopedi ve plastik cerrahi branşlarından oluşmaktadır.

İstatiksel Analiz

Çalışmanın analizleri SPSS 25.0 paket programı ile gerçekleştirilmiştir. Kategorik değişkenler sayı ve yüzde, sürekli sayısal değişkenler ortalama, standart sapma, ortanca değerleri ile özetlenmiştir.

Hekimlerin verdiği kararlar arası uyum Kappa (κ) istatistiği kullanılarak değerlendirilmiş olup tutarlılık derecelendirilmesinde Douglas G. Altman sınıflaması (κ<0.20 zayıf, κ:0.21-0.40 az oranda, κ:0.41-0.60 orta düzeyde, κ:0.61-0.80 iyi, κ:0.81-1.00 çok iyi) kullanılmıştır.

Bulgular

Acil servise başvuran 333 el ve el bileği travmalı olgunun %88,3'ü erkekti ve yaş ortalaması 36,98 ± 12,51 (medyan: 37) idi. En sık yaralanma şekli %48,6 sıkışma ve %46,5 delici-kesici alet yaralanması olup olguların %56,5'inde sol el, %43,2'sinde sağ el ve %0,3'ünde ise her iki el birlikte yaralanmıştı (Tablo I).

Tablo I. Olguların cinsiyet, yaralanma şekli ve yaralanan el özelliklerinin dağılımı

Değişkenler	n	%
Cinsiyet		
Erkek	294	88,3
Kadın	39	11,7
Yaralanma şekli		
Sıkışma	162	48,6
Delici-kesici alet	155	46,5
Spiral	5	1,5
Diğer	11	3,3
Yaralanan el		
Sol el	188	56,5
Sağ el	144	43,2
Bilateral el	1	0,3

Sıklık sırasına göre yaralanan yer %90,1 oranı ile parmaklar, %6,6 oranı ile el ve %3,3 oran ile el bileğiydi. En sık yaralanan parmaklar ise %33,3 oranında 2. parmak ve %31,8 oranı ile 3. parmaktı.

Acil serviste yapılan değerlendirme ve konsültan hekim tarafından yapılan değerlendirme sonucunda en sık saptanan yaralanmalar fraktür (%68,5 vs %64,0), tendon yaralanması (%35,7 vs %26,7), sinir yaralanması (%15,6 vs %18,6) ve damar yaralanmasıydı (%9,3 vs %9,3) (Tablo II).

Tablo II. Acil hekimi ve konsültan hekimin saptadığı yaralanmaların dağılımı

Değişkenler	n	%
Acil hekimi tarafından saptanan yaralanma		
Fraktür	228	68,5
Tendon yaralanması	119	35,7
Sinir yaralanması	52	15,6
Damar yaralanması	31	9,3
Konsültan hekim tarafından saptanan yaralanma		
Fraktür	213	64,0
Tendon yaralanması	89	26,7
Sinir yaralanması	62	18,6
Damar yaralanması	31	9,3

Olguların %24,0'ına primer onarım, %55,6'sına cerrahi onarım, %4,8'ine redüksiyon ve %3,0'ına yabancı cisim çıkarılması uygulanırken, olguların %12,3'ü tedaviyi reddetti. En sık uygulanan cerrahi onarımlar %24,6 açık fiksasyon onarımı, %16,5 amputasyon onarımı ve %9,3 tendon onarımıydı (Tablo III).

Tablo III. Olguların tedavi özelliklerinin dağılımı

Değişkenler	n	%
Tedavi		
Cerrahi onarım	185	55,6
Primer onarım	80	24,0
Redüksiyon	16	4,8
Yabancı cisim çıkarılması	10	3,0
Pansuman	1	0,3
Tedavi olmadan red	41	12,3
Cerrahi onarım		
Açık fiksasyon onarımı	82	24,6
Amputasyon onarımı	55	16,5
Tendon onarımı	31	9,3
Tırnak yatağı onarımı	5	1,5
Tendon + sinir onarımı	2	0,6
Sinir onarımı	2	0,6
Damar onarımı	2	0,6
Tendon + sinir + damar + açık fiksasyon onarımı	1	0,3
Tendon + sinir + açık fiksasyon onarımı	1	0,3
Tendon + açık fiksasyon onarımı	1	0,3
Tırnak yatağı onarımı + redüksiyon	1	0,3
Tendon + amputasyon onarımı	1	0,3
V-Y flep uygulanması	1	0,3

Klinik sonlanım açısından bakıldığında olguların %72,4'ü taburcu edilirken %13,5'i kliniğe yatırıldı. Olguların %17,1'i ise taburculuktan sonraki 1 hafta içerisinde yatırılarak opere edildi (Tablo IV).

Tablo IV. Olguların sonlanım özelliklerinin dağılımı

Değişkenler	n	%
Klinik sonlanım		
Taburcu	241	72,4
Klinik yatış	45	13,5
Tedavi red	47	14,1
Taburcu sonrası 1 hafta içinde yatırılıp opere edilen (2. işlem)		
Evet	57	17,1
Hayır	276	82,9

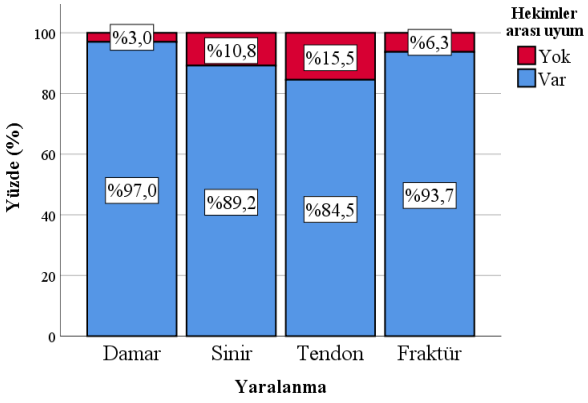
Acil serviste saptanan damar yaralanmalarının konsültan hekim tarafından saptanan damar yaralanmaları ile yüksek düzeyde tutarlı olduğu (κ = 0,822, p<0,001) ve %97,0 uyumlu olduğu; sinir yaralanmalarının konsültan hekim tarafından saptanan sinir yaralanmaları ile orta düzeyde tutarlı olduğu (κ = 0,620, p<0,001) ve %89,2 uyumlu olduğu; tendon yaralanmalarının konsültan hekim tarafından saptanan tendon yaralanmaları ile orta düzeyde tutarlı olduğu (κ = 0,653, p<0,001) ve %84,5 uyumlu olduğu ve fraktür olgularının konsültan hekim tarafından saptanan fraktür olguları ile yüksek düzeyde tutarlı olduğu (κ = 0,859, p<0,001) ve %93,7 uyumlu olduğu belirlendi (Tablo V).

Tablo V. Acil hekimi ve konsültan hekimin saptadığı yaralanmaların karşılaştırılması

			Konsültan hekim					
			Yok		Var			
			n	%	n	%	Kappa	Uyumluluk (%)
Acil tıp hekimi	Damar yaralanması	Yok	297	98,3	5	1,7	0,822	97,0
		Var	5	16,1	26	83,9		
		Toplam	302	6,9	31	93,1		
	Sinir yaralanması	Yok	258	91,8	23	8,2	0,620	89,2
		Var	13	25,0	39	75,0		
		Toplam	271	81,4	62	18,6		
	Tendon yaralanması	Yok	204	95,3	10	4,7	0,653	84,5
		Var	40	33,6	79	66,4		
		Toplam	244	73,3	89	26,7		
	Fraktür	Yok	102	97,1	3	2,9	0,859	93,7
		Var	18	7,9	210	92,1		
		Toplam	120	36,0	213	64,0		

Acil hekimi ve konsültan hekim arasında yaralanma saptama açısından uyumluluk sıklığı Şekil 1'de görülmekte olup; uyumsuzluk açısından sıklık sıralaması %15,5 tendon yaralanması, %10,8 sinir

yaralanması, %6,3 fraktür ve %3,0 damar yaralanması olarak belirlendi.



Şekil 1.
Acil hekimi ve konsültan hekim arasında yaralanma saptama açısından uyumluluk sıklığının grafiksel gösterimi

Tartışma ve Sonuç

Çalışmamızda acil servise başvuran 333 el ve el bileği travmalı olgunun demografik ve klinik özellikleri incelenmiş olup olguların %88,3'ü erkekti ve yaş ortalaması 36,98 ± 12,51 idi. Wu ve ark. 2112 iş kazasına bağlı el yaralanmasını değerlendirdikleri çalışmalarında da olguların %81'inin erkeklerden oluştuğu ve yaş ortalamasının 31,33 ± 11,00 olduğu belirlenmiştir[7] Aynı şekilde Serinken ve ark. tarafından yapılan ve iş kazalarına bağlı el yaralanması geçiren 244 hastanın değerlendirildiği çalışmada olguların %87'sinin erkek olduğu, yaş ortalamasının 27,8 ± 6,1 olduğu belirtilmiştir[8].

Erkek cinsiyetin; el ve el bileği yaralanmalarına daha sık neden olan inşaat, imalat, madencilik ve ağır sanayi gibi yüksek riskli ve fiziksel güç gerektiren iş kollarında daha fazla çalışmakta olduğu ve bu durumun da el ve el bileği yaralanmaları riskini arttırdığı bilinmektedir. Buna ek olarak erkeklerin iş yerinde daha fazla risk alma eğiliminde oldukları ve bu durumun da daha fazla yaralanma olasılığını beraberinde getirebildiği görülmektedir. Bu bakımdan çalışmamıza ait bulguların literatürde yayınlanan benzer çalışmalar ile uyumlu olduğu ifade edilebilmektedir.

Çalışmamızda en sık yaralanma şekli %48,6 sıkışma ve %46,5 delici-kesici alet yaralanmasıydı. Yiğit çalışmasında AS'ye iş kazasına bağlı el travması ile başvuran olgularda en sık yaralanma çeşidini %36 sıkışma ve %29 delici-kesici yaralanma olarak belirtmiştir[9]. Şakrak ve ark. çalışmasında ise el yaralanmasının %32,6 delici-kesici aletle ve %7 sıkışma ile meydana geldiği gösterilmiş olup çalışmamızın literatür ile uyumlu olduğu söylenebilmektedir[10].

Endüstriyel ortamlarda ve imalat sektöründe çalışanlar, sık sık pres makineleri, kesme makineleri, torna makineleri ve benzeri ağır makinelerle çalışmakta olup bu tür makineler, dikkatsizlik veya güvenlik önlemlerinin yetersizliği durumunda elde sıkışma tarzı yaralanmaya neden olabilmektedir. Aynı şekilde çekiç, tornavida, bıçak, testere gibi el aletleri, özellikle bakım, tamirat ve montaj işlerinde yaygın olarak kullanılmakta olup dikkatsiz kullanım veya aletin kontrolünün kaybedilmesi durumunda delici ve kesici yaralanmalara yol açabilmektedir.

Çalışmamızda olguların %56,5'inde sol el, %43,2'sinde sağ el yaralanmıştı. Wu ve ark. çalışmasında ise sağ el yaralanma oranı %53'tür[7]. Aslan ve ark.'ın çalışmasında ise olguların %54,6'sının sağ eli yaralanmıştır ve bu durum sağ elin daha sık dominant el olmasına bağlanmıştır[11]. Bu çalışmalardan farklı olarak Karakurt ve ark. ise AS'ye başvuran iş yeri kazası yaralanmalarında %53 ile sol tarafın daha çok etkilendiği belirtilmiştir[12]. Çalışmamızda da bu çalışma ile uyumlu olarak sol tarafın daha çok etkilendiği görülmüştür.

Çalışmamızda sıklık sırasına göre yaralanan yerler %90,1 parmak, %6,6 el ve %3,3 el bileği olup en sık yaralanan parmaklar ise %33,3 2. parmak ve %31,8 3. parmaktı. Wu ve ark. yaptığı çalışmada da %81 ile en sık parmakların yaralandığı rapor edilirken en sık yaralanan parmaklar %27 ile 2. ve aynı oranla 3. parmaklar olarak bildirilmiştir[7]. De Jong ve ark. çalışmasında ise %33 2. parmak, %22 1. parmak ve %20 3. parmağın yaralandığı belirlenmiştir[13]. El anatomisinde, özellikle 2. ve 3. parmaklar diğer parmaklara göre daha uzun ve daha dışta yer alır. Bu durum, bu parmakların daha fazla dış etkilere maruz kalmasına ve dolayısıyla yaralanma riskinin artmasına neden olabilir. Buna ek olarak 2. ve 3. parmaklar, günlük yaşamda ve iş yerinde sıkça kullanılan parmaklardır. Bu parmaklar, el işlerinde, alet kullanımında ve objeleri tutmada daha fazla aktif rol oynarlar. Bu nedenle, iş kazalarında bu parmakların yaralanma olasılığı diğer parmaklara göre daha yüksek olabilmektedir. Mevcut bilgilerin ışığında çalışmamızın literatür ile uyumlu olduğu söylenebilmektedir.

Çalışmamızda hem acil servis hekimi hem de konsültan hekim tarafından yapılan değerlendirme sonucunda en sık saptanan yaralanmalar fraktür (%68,5 vs %64,0), tendon yaralanması (%35,7 vs %26,7), sinir yaralanması (%15,6 vs %18,6) ve damar yaralanması idi (%9,3 vs %9,3). Angermann ve ark. tarafından yapılan bir çalışmada[14] olguların %35'inde yumuşak doku yaralanması, %19'unda fraktür, %19'unda kontüzyon ve %5'inde tendon yaralanması, %2 yanık, %1 amputasyon ve %1 sinir yaralanması tespit edilirken, Aslan ve ark. çalışmasında ise[11]

%32,7 tendon yaralanması, %31,1 fraktür ve %18,4 yumuşak doku yaralanması gözlenmiştir. Çalışmamızla uyumlu olarak literatürde yer alan diğer çalışmalarda da, fraktür ve tendon yaralanmalarının ön planda olduğu görülmektedir. Çalışmalara dahil edilen iş kollarının farklı olması ve yaralanma tiplerinin farklı şekilde sınıflandırılması nedeniyle bu farklı sıklıkların ortaya çıktığı düşünülmüştür.

Çalışmamızda olguların %16,5'ine amputasyon onarımı yapılmıştır. Yiğit ve ark. tarafından yapılan çalışmada[9] iş kazasına bağlı el yaralanmalarında %15 amputasyon uygulandığı gösterilirken, Wu ve ark. tarafından yapılan çalışmada bu oran %7 olarak kaydedilmiştir[7].

El yaralanmalarında ampütasyon kararını belirleyen faktörler arasında el yaralanmasının şiddeti, etkilediği alan, tedavinin gecikmiş veya yetersiz olması ve hastanın genel durumu sayılabilmektedir. Bu açıdan çalışma bulgularımızın literatür ile farklılık göstermesi kabul edilebilir bir durum olmaktadır.

Çalışmamızda acil servis hekimi ve konsültan hekimin saptadığı yaralanmaların karşılaştırılması yapılmış olup literatürde bu kapsamda sınırlı sayıda çalışma olup. Hartley ve ark. tarafından yürütülen bir çalışmada deplase fraktür, açık fraktür ve angulasyonlarda en az tutarlılık görülürken kondillerin dahil olduğu fraktürler, malrotasyon ve dislokasyonlarda daha yüksek tutarlılık rapor edilmiştir[15].

Çalışmamızda saptanan el cerrahisi konsültan hekimi ile acil servis hekimi arasındaki ilk ve son muayene farklılıklarının, dış merkezden el cerrahisi konsültasyon istemi nedeniyle yönlendirilen, ancak bizim kontrollerimizde tendon, arter ya da sinir kesisi düşünülmeyen hastaların, ilgili klinik hekimlerine konsülte edilmesinden kaynaklanmış olabileceği düşünülmektedir.

Sonuç olarak iş kazası sonucunda el ve el bileği yaralanması gelişen olguların çoğunluğunun erkeklerden oluştuğu ve en sık fraktür ve tendon yaralanması geliştiği saptandı. Acil hekimi ve konsültan hekim değerlendirmeleri arasında en fazla tutarsız olan yaralanmalar tendon ve sinir yaralanmalarıydı. Acil hekimlerinin el ve el bileği yaralanması olgularında bu patolojilere dair daha detaylı değerlendirme yapması, klinik pratikte bu olguların atlanmasını engelleyebilir. Bu konuda yapılacak çok merkezli çalışmalarla daha net ve bütün el ve el bileği yaralanmalarına genellenebilir sonuçlar elde edilebilir.

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ÖZGÜN ARAŞTIRMA

Kardiyopulmoner Resüsitasyon Başarısını Etkileyen Faktörlerin Retrospektif Olarak İncelenmesi*

Nuh KUMRU[1], Selcan YEREBAKAN AKESEN[2], Suna GÖREN[2]

[1] Karaman Eğitim ve Araştırma Hastanesi, Karaman, Türkiye.
[2] Bursa Uludağ Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, Bursa, Türkiye.

ÖZET

Kardiyopulmoner resüsitasyon (KPR) uygulanan hastalarda sağkalımı etkileyen faktörleri belirlemek amacıyla yapılan çalışmamızda, bir yıl içinde hastanemizde KPR uygulanan 1576 hastaya ait 1995 KPR kayıt formu incelendi. Çalışmaya 18 yaş altı hastalar ve birden fazla KPR uygulananların ilk resüsitasyonları dışındaki veriler alınmadı. Geriye kalan 1228 hastanın dosya ve KPR formlarındaki hasta özellikleri, KPR ile ilgili bilgiler ve laboratuvar parametreleri kaydedildi. Spontan dolaşımın geri dönüşü (SDGD), ilk 24 ve 48 saatlik sağkalım üzerine etkileri araştırıldı. İstatistiksel analizde tek ve çok değişkenli lojistik regresyon analizi kullanıldı. Hastaların %37,9'u kadın, %62,1'i erkek olup, yaş ortalaması 64,0±14,1 yıl idi. SDGD oranı %32,41, ilk 24 ve 48. saat sağkalım oranları sırasıyla %8,15 ve %7,46 olarak bulundu. SDGD'yi etkileyen bağımsız risk faktörleri arasında yatış süresi, yoğun bakım ve acil serviste arrest, sepsis, metastaz, karaciğer yetmezliği, solunum depresyonu ve ventriküler fibrilasyon/nabızsız ventriküler taşikardi ilk ritmi yer aldı. İlk 24 ve 48 saatte mortalite oranları yoğun bakımda arrest (OR=3,01 ve 4,57), yüksek SAPS II (Simplified Acute Physiology Score II) skoru, yüksek GOFAR (Good Outcome Following Attempted Resuscitation) ve PAR (Prognosis After Resuscitation) skorlarıyla ilişkilendirildi. Sonuç olarak, hastane içi KPR'de sağkalım tahmininde SAPS II, GOFAR ve PAR skorlarının kullanılabileceği, yoğun bakımda arrestin sağkalımı olumsuz etkilediği saptandı.

Anahtar Kelimeler: Kardiyak arrest. Kardiyopulmoner resüsitasyon. Prognostik faktörler. Skorlama sistemleri. Sağkalım.

A Retrospective Analysis of Factors Affecting the Success of Cardiopulmonary Resuscitation

ABSTRACT

In our study conducted to determine the factors affecting survival in patients undergoing cardiopulmonary resuscitation (CPR), 1995 CPR record forms belonging to 1576 patients who underwent CPR in our hospital within one year were examined. Patients under the age of 18 were excluded from the study, as were resuscitation data of patients who underwent more than one CPR, except for their first resuscitation. Patient characteristics, characteristics related to CPR implementation, and laboratory parameters were recorded from the files and CPR registration forms of the remaining 1,228 patients. The effects of all these data on return of spontaneous circulation (ROSC) and survival in the first 24 and 48 hours after CPR were investigated. Univariate and multivariate logistic regression analyses were used for statistical evaluation. It was determined that 37.9% of the patients were female and 62.1% were male, with a mean age of 64.0±14.1 years. The ROSC rate was found to be 32.41%, while survival rates at the first 24 and 48 hours were 8.15% and 7.46%, respectively. In determining the ROSC rate, length of stay, arrest in the intensive care unit (ICU) and emergency room, sepsis, metastasis, liver failure, presence of respiratory depression, ventricular fibrillation/pulseless ventricular tachycardia in the first rhythm were determined as independent risk factors. Mortality rates in the first 24 and 48 hours were associated with arrest in the ICU (OR=3.01 and 4.57), high Simplified Acute Physiology Score II (SAPS II) score, high Good Outcome Following Attempted Resuscitation (GOFAR) and Prognosis After Resuscitation (PAR) scores. In conclusion, it was determined that SAPS II, GOFAR and PAR scores could be used to predict survival in in-hospital CPR, and that, the occurrence of arrest in the intensive care unit has an adverse effect on survival.

Keywords: Cardiac arrest. Cardiopulmonary resuscitation. Prognostic factors. Scoring systems. Survival.

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Dr. Nuh KUMRU
Karaman Eğitim ve Araştırma Hastanesi /
Üniversite Mh., 1984. Sk. No:1,
70200 Merkez/Karaman Merkez/Karaman
Tel.: 0534 829 54 69
E-posta :nuhkumru@hotmail.com

* Yenilenen Resüsitasyon Kılavuzları- 4. Resüsitasyon Derneği E- Sempozyumu (9 Nisan 2021, Çevrimiçi) sözlü bildiri olarak sunulmuştur.

Yazarların ORCID Bilgileri:
Nuh KUMRU: 0000-0001-6571-5224
Selcan YEREBAKAN AKESEN: 0000-0002-9518-541X
Suna GÖREN: 0000-0002-1190-6831

Kardiyopulmoner resüsitasyon (KPR) uygulanan hastalarda amaç, spontan dolaşımın geri dönüşüne (SDGD) kadar geçen sürede miyokard, beyin ve diğer yaşamsal organların metabolik gereksinimlerini karşılamak üzere bu organlara gerekli kanın ve oksijenin ulaştırılmasını sağlamaktır[1]. Bu hastalarda sağ kalım şansını arttıran en önemli faktörlerden biri erken dönemde yapılan etkili ve kaliteli KPR'dir[2,3].

Günümüzde KPR uygulaması ile SDGD sağlanan hastalarda, nörolojik açıdan iyi bir klinik tablo ile sonuçlanan sağ kalım için önemli olabilecek faktörleri belirleyebilmek amacıyla çalışmalar devam etmektedir. Bu çalışma ile hastanemizde, bir yılda gerçekleştirilen KPR olgularını retrospektif olarak inceleyerek KPR'a yanıt alınan hastalardaki sağkalımı etkileyebilecek faktörleri belirlemeye amaçladık. Ayrıca, hem kritik hastalar için tanımlanmış, hem de KPR için tanımlanmış farklı skorlama sistemlerini kullanarak, elde ettiğimiz veriler ile KPR uygulanan hastaların sağkalımını tahmin etmedeki başarılarını değerlendirdik.

Gereç ve Yöntem

Bu çalışmada Bursa Uludağ Üniversitesi Tıbbi Araştırmalar Etik Kurulu'nun 10/04/2018 tarih ve 2018-7/20 nolu kararı ile etik kurul onayı alındıktan sonra, 1 Ocak 2016 - 31 Aralık 2016 tarihleri arasında Bursa Uludağ Üniversitesi Sağlık Uygulamaları Araştırma Merkezi Hastanesi'nde KPR uygulanan hastalar retrospektif olarak değerlendirilmiştir. Bu döneme ait 1998 adet KPR hasta kayıt formu incelenmiştir. Çalışmamızda, dışlama kriterleri olarak belirlediğimiz 18 yaş altı hastalar ve birden fazla KPR uygulanan hastaların ilk resüsitasyonları dışındaki 2. ve daha sonraki resüsitasyonları ile ilgili veriler çalışma dışı bırakıldıktan sonra geriye kalan, 1228 hastanın verileri irdelenmiştir.

Hastaların altta yatan hastalıkları (malignite, metastaz, hematolojik hastalık, evde bakım hastası olma, geçirilmiş serebrovasküler olay, renal yetmezlik, karaciğer yetmezliği, kalp yetmezliği, iskemik kalp hastalığı) ve hastane yatış tanıları (sepsis, majör travma) değerlendirmeye alınmıştır. KPR uygulaması ile ilgili özelliklerden arrest yeri [acil servis, ameliyathane, yoğun bakım, cerrahi veya dahili klinik, diğer (radyoloji birimleri, günübirlik gastroenteroljik girişimlerin yapıldığı alanlar gibi)], kardiyak arrestin gerçekleşmesine neden olan durumlar (aritmi, hipotansiyon, solunum depresyonu, miyokard infarktüsü, koroner iskemi, hipoksi, diğer), monitörde görülen ilk ritim [Ventriküler Fibrilasyon (VF), Nabızsız Ventriküler Taşikardi (VT), Nabızsız Elektriksel Aktivite (NEA), asistol] kaydedilmiştir. Laboratuvar parametreleri [Beyaz kan hücresi (WBC), Hematokrit (HTC), Trombosit sayısı (PLT), Retikülosit dağılım genişliği (RDW), kreatinin, üre, albümin, sodyum, potasyum, kalsiyum] ve monitörize edilen oksijen saturasyonları (SpO_2) kayıt altına alınmıştır. Çeşitli skorlama sistemlerinin [Glasgow Koma Skoru (GKS), Good Outcome Following Attempted Resuscitation Score (GOFAR), Pre-arrest Morbidity Score (PAM), Prognosis After Resuscitation Score (PAR), Acute Physiology and Chronic Health Evaluation Score II (APACHE II), Sequential Organ Failure Assessment Score (SOFA), Simplified Acute Physiology Score II (SAPS II), Multiple Organ Dysfunction Score (MODS), Logistic Organ Dysfunction Score (LODS)] değerleri bu bilgilerden yararlanılarak hesaplandı. Tüm bu verilerin; SDGD, KPR sonrası ilk 24 ve 48 saatlik dönemdeki sağkalımlar üzerine etkileri araştırıldı.

İstatistiksel Analiz

Verilerin tanımlayıcı istatistiklerinde ortalama, standart sapma, medyan, en düşük, en yüksek, frekans ve oran değerleri kullanılmıştır. Değişkenlerin dağılımı Kolmogorov Smirnov testi ile ölçüldü. Nicel bağımsız verilerin analizinde Mann-Whitney U testi kullanıldı. Nitel bağımsız verilerin analizinde Ki-Kare testi, Ki-Kare test koşulları sağlanmadığında Fischer testi kullanıldı. Sağ kalım üzerine etkili olan faktörlerin analizi amacıyla tek değişkenli ve çok değişkenli lojistik regresyon analizleri yapıldı. Tek değişkenli lojistik regresyon analizi sonucu anlamlı bulunan faktörlerden bağımsız risk faktörlerinin tespiti için çok değişkenli lojistik regresyon analizi yapıldı. Çok değişkenli lojistik regresyon analizinde Forward Likehood Ratio yöntemi ile indirgeme yapılmıştır. Analizlerde SPSS 22.0 programı kullanılmış, $p<0.05$ istatistiksel olarak anlamlı olarak kabul edilmiştir.

Bulgular

KPR uygulanan hastaların %37,9'u (n=465) kadın, %62,1'i (n=763) erkek olup, yaş ortalamasının 64,0±14,1 yıl olduğu tespit edildi. Hastaların %9,4'ünün (n=116) 18-44 yaşları arasında, %38'inin (n=467) 45-64 yaşları arasında, %29,4'ünün (n=361) 65-74 yaşları arasında, %18,7'sinin (n:230) 75-84 yaşları arasında, %4.4'ünün (n:54) 85 yaş ve üzeri olduğu görüldü. Kardiyak arrest gelişmesi sonucu mavi kodun aranması ile mavi kod ekibinin arrest haldeki hastaya ulaşma süresi ortalama 1,4±0,5 dakika olarak tespit edildi. Bu hastalara uygulanan KPR süresi 1- 74 dakika (34,1±16,9) arasında değişmekteydi (Tablo I).

Hastalarımızda SDGD oranı %32,41 (n=398), ilk 24 ve 48. saatteki sağ kalım oranları sırasıyla %8,15 (n=95) ve %7,46 (n=87) ve taburculuk oranı %1.54 (n=18) olarak bulundu. Hastaların yaş ve cinsiyetleri ile SDGD, 24 saatlik sağkalım, 48 saatlik sağkalım arasında anlamlı bir fark saptanmadı ($p>0,05$).

Tablo I. Hastaların yaş, cinsiyet, yatış süresi, ulaşma süresi, KPR süresi ve resüsitasyon saatine göre dağılımları

		Min-Mak	Medyan	n	Ort.	± S.s.	%
Yaş		18,0 - 93,0	65,0		64,0	14,1	
Yaş (yıl)	18-44			116			9,4
	45-64			467			38
	65-74			361			29,4
	75-84			230			18,7
	≥ 85			54			4,4
Cinsiyet	Kadın			465			37,9
	Erkek			763			62,1
Yatış Süresi (Gün)		1,0 - 258,0	9,0		15,7	22,0	
Ulaşma Süresi (Dk)		1,0 - 4,0	1,0		1,4	0,5	
KPR Süresi (Dk)		1,0 - 74,0	45,0		34,1	16,9	
Resüsitasyon Saati	08-16			383			31,2
	16-08			845			68,8

Arrest öncesi hastanede yatış süresi ve KPR süresi SDGD sağlanan hastalarda anlamlı olarak daha düşük saptandı (p<0,001; p<0,001). Ulaşma süresi, resüsitasyon saati ile SDGD arasında istatistiksel anlamlı bir fark saptanmadı (p=0,149; p=0,153). 24 saatlik sağkalım ve 48 saatlik sağ kalım açısından değerlendirildiğinde; yatış süresi, KPR süresi, ulaşma süresi, resüsitasyon saatinin istatistiksel açıdan anlamlı olmadığı gözlendi (p>0,05).

Hastaların altta yatan hastalıkları ve hastane yatış tanıları incelendiğinde; sepsis, renal yetmezlik, karaciğer yetmezliği olan hastaların SDGD, 24 saatlik sağkalım, 48 saatlik sağkalım açısından daha kötü prognozlu olduğu bulundu (p<0,05). İskemik kalp hastalığı tanılı hastaların ise SDGD oranı yüksek bulundu (p=0,004).

KPR uygulamasının gerçekleştirilme alanı olarak yoğun bakımdaki arrestlerde SDGD oranı, tüm diğer yerlere göre daha yüksek bulunmasına karşın, 24 saatlik ve 48 saatlik sağkalım oranı daha düşük saptandı (sırasıyla p=0,002, p=0,000, p=0,000).

Arrest ritmi VF, nabızsız VT olan hastaların SDGD oranı anlamlı olarak yüksek, arrest ritmi asistoli olanların ise daha düşük olduğu saptandı (sırasıyla p=0,000, p=0,000, p=0,000). NEA ile anlamlı ilişki saptanmadı (p=0,217). Arrest ritimleri ile 24 saatlik ve 48 saatlik sağkalım arasında istatistiksel olarak anlamlı bir ilişki bulunmadı (p>0,05).

Laboratuvar değerlerinden sodyum, potasyum, kalsiyum ve HTC değerinin çalışmamızdaki herhangi bir sağkalım sonucunu etkilemediği görüldü (p>0,05). Diğer laboratuvar değerleri SDGD açısından değerlendirildiğinde WBC, üre, albümin değerlerinin düşüklüğü ve PLT, RDW yüksekliği anlamlı olarak daha iyi prognoz ile ilişkili bulundu (p<0,05). 24 saatlik ve 48 saatlik sağkalım açısından üre değerinin düşüklüğü ve kreatinin değerinin yüksekliği iyi prognoz ile ilişkili bulundu (p<0,05).

Hesapladığımız skorlama sistemlerine ait değerler ile çalışmamızdaki tüm sağ kalım sonuçları anlamlı bir şekilde ilişkili saptandı (p<0,05). Bu değerlerden, yaşayan hastalarda GOFAR, PAM, PAR, APACHE II, SOFA, SAPS II, LODS ve MODS skorları daha düşük, GKS skoru ise daha yüksek bulundu.

SDGD açısından tek ve çok değişkenli lojistik regresyon analiz sonuçları Tablo II'de özetlenmiştir. Tek değişkenli analizde KPR'ye yanıtı olan ve olmayan hastaların ayrımında; yatış süresi, KPR süresi, WBC, PLT, RDW, üre, SpO2, GKS, GOFAR, PAM, PAR, APACHE II, SOFA, SAPS II, MODS, LODS değerinin anlamlı etkinliği gözlendi. Altta yatan hastalıkları ve mevcut hospitalizasyon esnasındaki tanıları açısından ele alındığında; KPR'ye yanıtı olan ve olmayan hastaların ayrımında sepsis, metastaz, evde bakım hastalığı, renal yetmezlik, karaciğer yetmezliği, iskemik kalp hastalığı varlığının anlamlı (p<0,05) etkinliği olduğu gözlendi. Arrest yeri ile ilgili olarak acil servis, yoğun bakım, dahili klinik, cerrahi klinikte arrest oluşun anlamlı (p<0.05) etkinliği gözlendi. Arrest nedenleri ve ritmileri olarak aritmi, hipotansiyon, solunum depresyonu, VF, nabızsız VT, asistol, varlığının anlamlı etkinliği gözlendi. Çok değişkenli indirgenmiş modelde ise, KPR yanıtı olan ve olmayan hastaların ayrımında yatış süresinin, üre değerinin, SPO_2 değerinin, sepsis varlığının, metastaz varlığının, evde bakım hastası olmanın, karaciğer yetmezliği varlığının, acilde veya yoğun bakımda arrest olmanın, solunum depresyonu varlığının, VF veya nabızsız VT varlığının, anlamlı-bağımsız etkinliği gözlendi.

Tablo II. SDGD'ye etki eden faktörlerin lojistik regresyon analizlerine ait sonuçları

KPR Yanıt	Tek Değişkenli Model			Çok Değişkenli Model		
	OR	% 95 GA	p	OR	% 95 GA	p
Yatış Süresi	0,99	0,98 - 1,00	***0,001***	0,99	0,98 - 1,00	***0,013***
KPR Süresi	0,53	0,42 - 0,66	***0,000***			
WBC	1,03	1,01 - 1,03	***0,035***			
Plt	1,00	1,00 - 1,00	***0,002***			
RDW	1,00	1,00 - 1,02	***0,045***			
Üre	1,00	0,99 - 1,00	***0,000***	1,00	1,00 - 1,00	***0,015***
ALB	1,00	0,97 - 1,02	0,925			
SPO	1,14	1,11 - 1,18	***0,000***	1,13	1,09 - 1,18	***0,000***
GKS	1,29	1,23 - 1,36	***0,000***			
GOFAR	0,92	0,91 - 0,93	***0,000***			
PAM	0,77	0,73 - 0,80	***0,000***			
PAR	0,84	0,82 - 0,86	***0,000***			
APACHE II	0,86	0,83 - 0,88	***0,000***			
SOFA	0,70	0,66 - 0,75	***0,000***			
SAPS II	0,92	0,91 - 0,94	***0,000***			
MODS	0,68	0,64 - 0,73	***0,000***			
LODS	0,84	0,82 - 0,88	***0,000***			
Sepsis	0,30	0,23 - 0,38	***0,000***	0,19	0,13 - 0,28	***0,000***
Metastaz	0,19	0,14 - 0,27	***0,000***	0,16	0,11 - 0,24	***0,000***
Evde Bakım Hastası	0,31	0,20 - 0,47	***0,000***	0,41	0,25 - 0,66	***0,000***
Renal Yetmezlik	0,70	0,55 - 0,89	***0,003***			
KC Yetmezliği	0,49	0,33 - 0,73	***0,001***	0,52	0,32 - 0,83	***0,006***
İskemik Kalp Hastalığı	1,88	1,22 - 2,89	***0,004***			
Acil	0,19	0,07 - 0,47	***0,000***	0,09	***0,03*** - 0,28	***0,000***
Yoğun Bakım	1,48	1,16 - 1,88	***0,002***	0,64	0,47 - 0,88	***0,007***
Dahili Klinik	0,64	0,50 - 0,81	***0,000***			
Cerrahi Klinik	1,68	1,02 - 2,78	***0,042***			
Aritmi	1,97	1,18 - 3,28	***0,009***			
Hipotansiyon	0,68	0,53 - 0,87	***0,002***			
Solunum depresyonu	1,46	1,06 - 2,02	***0,022***	1,79	1,21 - 2,67	***0,004***
VF	6,83	4,28 - 10,89	***0,000***	8,13	4,32 - 15,28	***0,000***
Nabızsız VT	8,57	4,68 - 15,68	***0,000***	23,04	8,73 - 60,80	***0,000***
Asistol	0,22	0,16 - 0,29	***0,000***			

Lojistik Regresyon

KPR: Kardiyopulmoner resüsitasyon, **WBC:** Beyaz kan hücresi, **PLT:**Trombosit sayısı, **RDW:**Retikülosit dağılım genişliği, **ALB:**Albumin, **SPO_2:** Oksijen Satürasyonu, **GKS:** Glasgow Coma Score, **GOFAR:**Good Outcome Following Attempted Resuscitation *Score*, **PAM:** Pre-arrest Morbidity Score, **PAR:**Prognosis After Resuscitation Score, **APACHE II:** Acute Physiology and Chronic Health Evaluation Score II, **SOFA:** Sequential Organ Failure Assessment *Score*, **SAPS II**: Simplified Acute Physiology Score II, **MODS:** Multiple Organ Dysfunction Score, **LODS:** Logistic Organ Dysfunction Score, **KC**: Karaciğer, **VF:** Ventriküler fibrilasyon, **VT:** Ventriküler taşikardi

24 saatlik sağkalım açısından tek değişkenli modelde ilk 24 saatte eksitus olan ve olmayan hastaların ayrımında üre, GKS, GOFAR, PAM, PAR, APACHE II, SOFA, SAPS II, MODS, LODS değerlerinin; sepsis, metastaz, renal yetmezlik, karaciğer yetmezliği varlığının; yoğun bakım, dahili klinikte arrest oluşun; solunum depresyonu varlığının anlamlı ($p<0.05$) etkinliği gözlendi. Çok değişkenli indirgenmiş modelde ilk 24 saat eksitus olan ve olmayan hastaların ayrımında SAPS II skorunun, yoğun bakımda arrest olmasının varlığının anlamlı-bağımsız ($p< 0.05$) etkinliği gözlendi (Tablo III).

Tablo III. İlk 24 ve 48 saatlik mortaliteye etki eden faktörlerin lojistik regresyon analizlerine ait sonuçları

İlk 24 Saat Mortalite	Tek Değişkenli Model			Çok Değişkenli Model		
	OR	% 95 GA	p	OR	% 95 GA	p
Üre	1,01	1,00 - 1,01	***0,000***			
GKS	0,88	0,80 - 0,96	***0,005***			
GOFAR	1,03	1,01 - 1,06	***0,006***			
PAM	1,21	1,12 - 1,31	***0,000***			
PAR	1,08	1,03 - 1,13	***0,002***			
APACHE II	1,08	1,03 - 1,13	***0,002***			
SOFA	1,22	1,10 - 1,36	***0,000***			
SAPS II	1,06	1,04 - 1,09	***0,000***	1,06	1,03 - 1,09	***0,000***
MODS	1,21	1,08 - 1,34	***0,001***			
LODS	1,10	1,02 - 1,17	***0,008***			
Sepsis	2,57	1,58 - 4,17	***0,000***			
Metastaz	2,66	1,02 - 6,95	***0,046***			
Renal Yetmezlik	2,47	1,50 - 4,07	***0,000***			
KC Yetmezliği	3,37	1,00 - 11,30	***0,049***			
Dahili Klinik	0,42	0,26 - 0,67	***0,000***			
Yoğun Bakım	2,86	1,73 - 4,71	***0,000***	3,01	1,37 - 6,62	***0,006***
Solunum Depresyonu	0,48	0,27 - 0,82	***0,008***			

İlk 48 Saat Mortalite	Tek Değişkenli Model			Çok Değişkenli Model		
	OR	% 95 GA	p	OR	% 95 GA	p
Plt	1,00	1,00 - 1,00	***0,019***			
Üre	1,01	1,00 - 1,01	***0,001***			
GKS	0,84	0,75 - 0,94	***0,002***			
GOFAR	1,04	1,01 - 1,06	***0,002***	0,95	0,91 - 0,99	***0,025***
PAM	1,23	1,13 - 1,33	***0,000***			
PAR	1,08	1,03 - 1,13	***0,001***	1,17	1,06 - 1,30	***0,003***
APACHE II	1,11	1,05 - 1,17	***0,000***			
SOFA	1,29	1,14 - 1,45	***0,000***			
SAPS II	1,08	1,05 - 1,12	***0,000***	1,09	1,04 - 1,13	***0,000***
MODS	1,26	1,12 - 1,42	***0,000***			
LODS	1,15	1,06 - 1,24	***0,001***			
Sepsis	2,57	1,56 - 4,25	***0,000***			
Renal Yetmezlik	2,54	1,51 - 4,28	***0,000***			
KC Yetmezliği	4,71	1,10 - 20,07	***0,036***			
Dahili Klinik	0,42	0,26 - 0,68	***0,000***			
Yoğun Bakım	2,93	1,74 - 4,93	***0,000***	4,57	1,75 - 11,96	***0,002***
Solunum Depresyonu	0,48	0,27 - 0,84	***0,010***			

Lojistik Regresyon

KPR: Kardiyopulmoner resüsitasyon, **WBC:** Beyaz kan hücresi, **PLT:**Trombosit sayısı, **RDW:**Retikülosit dağılım genişliği, **ALB:**Albumin, **SPO_2:** Oksijen Satürasyonu, **GKS:** Glasgow ComaScore, **GOFAR:** Good Outcome Following Attempted Resuscitation *Score*, **PAM:**Pre-arrest Morbidity Score, **PAR:** Prognosis After Resuscitation Score, **APACHE II:**Acute Physiology and Chronic Health Evaluation Score II, **SOFA:** Sequential Organ Failure Assessment *Score*, **SAPS II**: Simplified Acute Physiology Score II, **MODS:** Multiple Organ Dysfunction Score , **LODS:** Logistic Organ Dysfunction Score, **KC**: Karaciğer, **VF:** Ventriküler fibrilasyon, **VT:** Ventriküler taşikardi

48 saatlik sağkalım açısından tek değişkenli modelde ilk 48 saatte eksitus olan ve olmayan hastaların ayrımında PLT, üre, GKS, GOFAR, PAM, PAR, APACHE II, SOFA, SAPS II, MODS, LODS skorları değerlerinin, eşlik eden hastalıklardan sepsis, renal yetmezlik, karaciğer yetmezliği varlığının, yoğun bakım ve dahili klinikte arrest oluşun, solunum depresyonu varlığının anlamlı ($p<0.05$) olarak etkilediği gözlendi. Çok değişkenli indirgenmiş modelde ilk 48 saatte eksitus olan ve olmayan hastaların ayrımında GOFAR, PAR ve SAPS II skorlarının, yoğun bakımda arrest olmanın anlamlı-bağımsız ($p<0.05$) etkinliği gözlendi (Tablo III).

Tartışma ve Sonuç

Çalışmamızın amacı hastane içi KPR uygulanan hastalarda sağ kalım üzerine etkili olan faktörlerin önceden belirlenebilmesidir. KPR başarısı üzerine etkili olan faktörlerin bilinmesi KPR başarısının tahmin edilmesine olanak sağlayacaktır ve bu sayede yaşam beklentisi daha az olan hastalar önceden belirlenebilecektir.

Bir yıl içerisinde hastanemizde KPR uygulanan 1228 hastanın verilerinin değerlendirildiği çalışmamızda SDGD oranı %32,41, 24 saatlik sağ kalım oranı %8,15, 48 saatlik sağ kalım oranı %7,46, taburculuk oranı ise %1.54 bulundu. Sağ kalım oranları ile literatürde yapılmış olan çalışmalardan Xue ve ark.'nın[4] yaptıkları çalışmada SDGD oranını %25,8, 24 saatlik sağ kalım oranını %13,8 ve taburculuk oranını %6,6 olarak bulmuşlardır. Başka bir çalışmada da SDGD oranı %45, taburculuk oranı %18.4 saptanmıştır[5]. Çalışmamızdaki sağkalım oranları literatür ile kıyaslandığında daha düşük bulunmuştur. Bu durum; ülkemizde kanunlar gereği 'resusite etme' (DNAR - do not attempt resuscitation) kararı alınamaması sebebiyle arrest olan her hastaya KPR uygulanması ve her türlü tıbbi müdahalenin yapılmasının gerekmesi ile açıklanabilir. Hastanemizin de, üçüncü düzey üniversite hastanesi olması nedeniyle, son dönem kronik hastalıkları olan ya da terminal dönem kanser tanılı hasta sayısının yüksek olması ve DNAR kararının uygulanamaması sonucu sağ kalım oranlarının düşük bulunmasını açıklamaktadır.

Çalışmamızda KPR uygulanan hastaların yaşları ve cinsiyetleri ile incelediğimiz sonuçlarımız dikkate alındığında anlamlı farklılık gözlemlenmemiştir. Literatürde çalışmamıza benzer şekilde yaş ve cinsiyetin KPR başarısı üzerine etkisi olmadığını belirten çalışmalar olduğu gibi[6]; yaşlı hastalarda KPR başarısının daha az olduğunu saptayan çalışmalara da rastlanmaktadır[7,8].

Hastaların hastaneye yatışı ile KPR tarihi arasındaki ortalama yatış süresi 15,7±22 gün olup, yatış süresi kısa olan hastalar SDGD sağlanması açısından daha şanslı bulundu. Yatış süresi ile ilgili çok değişkenli lojistik regresyon analizi sonucu yatış süresi ile SDGD arasında anlamlı ilişki saptandı. Literatürde çalışmamızla uyumlu olarak yatış süresinin artışı ile sağkalım azalmasının ilişkilendirilmektedir[9].

Mavi kod çağrısı ile hastaya ulaşma süresi çalışmamızda ortalama 1,4±0,5 dakika bulundu ve ulaşma süresi ile incelediğimiz sonuçlarımız arasında anlamlı farklılık gözlemlenmedi. Sandorini ve ark.'nın[10] 114 kardiyak arrest hastasını aldıkları çalışmada SDGD ve taburculuk açısından yaşayan hastalardaki ortalama ulaşma süresi1.30±1.70 dakika, eksitus olanlarda ise 2.51±2.37 dakika bulunmuş ve bu farkın istatistiksel olarak anlamlı olduğu belirtilmiştir. Çalışmamızda incelediğimiz sonuçlar açısından ulaşma süresinin anlamsız bulunmasının sebebinin arrest haldeki tüm hastalara mavi kod ekibinin oldukça kısa bir süre içinde (ortalama 1,4±0,5 dakika) ulaşması olduğunun kanısındayız.

Arrest haldeki hastalara uygulanan KPR süresi çalışmamızda ortalama 31,4±16,9 dakika olarak saptandı. KPR süresi SDGD sağlanan hastalarda anlamlı olarak daha düşük saptandı ve bu sonuç literatür ile uyumlu bulundu[11,12]. Bu durumla ilgili ülkemizde hastane içi kardiyak arrestlerin incelendiği bir çalışmada özellikle KPR süresi 20 dakika altı olan hastaların SDGD oranlarının daha fazla olduğu ve 6 aylık sağkalım oranlarının daha yüksek olarak bulunduğu saptanmıştır[13].

Resüsitasyon saati çalışmamızda: 8-16 ve 16-08 olmak üzere iki kısımda incelendi ve resüsitasyon saati ile incelediğimiz sonuçlar arasında anlamlı fark saptanmadı. Literatürde resüsitasyon saati ile ilgili yapılmış olan çalışmalardan Wallace ve ark.'nın[14] 2008-2012 yılları arasında 4789 hasta üzerinden yaptığı çalışmada SDGD açısından ve Khan ve ark.'nın[15] 383 hastada yaptıkları çalışmalarında 24 saat sağ kalım açısından resüsitasyon saatinin anlamlı olmadığını belirtmişlerdir. Çalışmamızda da KPR saatinin alınan yanıtı etkilememesinin nedeni olarak, hastanemizde günün her saatinde "Mavi kod" sisteminin aynı etkinlikte çalışması ve KPR uygulamasını gerçekleştiren ekibin aynı özellikleri taşımasına bağlı olduğunu düşünmekteyiz.

Sonuçlarımızı arrest yeri ile ilgili olarak değerlendirdiğimizde yoğun bakımlarda gerçekleşen arrestlerde SDGD oranının daha fazla olduğu, ancak sağkalımın düşük olduğu saptandı. Yoğun bakım hastalarının monitörize olarak yakın takibi ve kliniklere kıyasla eğitimli personel sayısının daha fazla olması ile gerçekleşen arrest durumu daha erken fark edilmekte ve uygun müdahaleye daha erken başlanmaktadır. Bu sayede SDGD oranları artmakta, buna karşın yoğun bakım hastalarının ciddi hastalıklara sahip olması nedeniyle de sağ kalım oranlarının daha düşük olduğu kanısındayız. Arrest yerleri ile ilgili literatür taramamızda sağkalımı yoğun bakımda gerçekleşen arrestlerde[16] ve kliniklerde gerçekleşen arrestlerde[17] daha yüksek bulunduğunu bildiren çalışmalara rastlamak mümkündür.

Günümüzde kardiyak arrestlerde ilk ritmin şoklanabilir ritim olmasının sağ kalım oranlarını yükselttiği bilinmektedir[4,5,18]. Çalışmamızda da arrest esnasında mönitörde ilk tespit edilen ritmi şoklanabilir ritim olan hastalar SDGD açısından daha şanslı bulundu. SDGD oranlarının, ilk ritmi şoklanamaz ritimlerden asistol olan hastalarda daha az olduğu, ancak diğer şoklanamaz ritim olan NEA için farklılık göstermediği saptandı.

Çalışmamızda tüm sonuçlarımız açısından sepsis, renal yetmezlik, karaciğer yetmezliği birlikteliğinin sağ kalım azalması ile ilişkili olduğu saptandı. Metastazı olan malignite hastalarında ise SDGD ve 24 saat sağ kalım oranlarının daha düşük olduğu tespit edildi. Literatür taramamızda KPR uygulanan hastalarda metastazı olan maligniteler[17], böbrek yetmezliği[6,9], karaciğer yetmezliği[19], sepsis[20] gibi hastalıkların birlikteliğinin sağkalım ile ilişkilendirildiğini gördük. Çalışmamızda istatistiksel olarak sağ kalım artışı saptanan tek hastalığın iskemik kalp hastalığı olduğu ve iskemik kalp hastalığı olan hastaların SDGD oranları anlamlı olarak daha yüksek saptandığını tespit ettik. Benzer şekilde literatürde sonuçlarımızı destekler biçimde İskemik Kalp Hastalığı nedeni ile arrest olan hastalarda daha iyi sağkalım bildiren çalışmalar mevcuttur[21,22].

Laboratuvar değerleri ile sağ kalım sonuçlarımız arasında SDGD açısından WBC, üre, albümin değerlerinin düşüklüğü ve PLT, RDW yüksekliği anlamlı olarak daha iyi prognoz ile ilişkili bulundu. 24 saatlik ve 48 saatlik sağkalım açısından üre değerinin düşüklüğü, kreatinin değerinin yüksekliği anlamlı olarak iyi prognoz ile ilişkili bulundu. Laboratuvar değerleri ile ilgili literatürde yapılmış olan çalışmalardan Isenschmid ve ark.'nın[23] prospektif olarak erişkin kardiyak arrest olguları ile ilgili çalışmalarında resüsitasyon sonrası taburculuk oranları daha az olan hastaların WBC değeri, üre değeri, kreatinin değerleri anlamlı olarak daha yüksek bulunmuştur. Aynı zamanda bu çalışmada WBC değeri SDGD açısından anlamlı bulunmamıştır. Fontana ve ark.[24] yoğun bakımdaki kardiyak arrest hastaları üzerinden yaptıkları çalışmasında yüksek RDW değerinin KPR sonrası 30 günlük yaşam azalması ile ilişkili olduğunu bulmuşlardır. Kim ve ark.[25] çalışmalarında RDW değeri, BUN değeri, kreatinin değerleri yüksekliği olan hastaların ve albümin değeri, hematokrit değeri, trombosit sayısı değerleri düşüklüğü olan hastaların KPR sonrası 30 günlük mortalite oranlarını daha düşük bulmuşlardır. Bu verilerin tümünü birlikte ele aldığımızda PLT, RDW, üre ve albumin değerlerinin KPR'ye yanıtı ve daha sonraki dönemde sağkalımı göstermede katkı sağlayabileceklerini, ancak bu iki safhadaki etkilerinin farklı olabileceğini göstermektedir.

Skorlama sistemleri ile ilgili yapılmış olan çalışmaları irdelediğimizde özellikle kritik hastalıklar veya KPR uygulanan hastalar için tanımlanmış çok sayıda ve farklı skorların kullanıldığı görülmektedir[26-29].

Prognostik açıdan en sık kullanılanlar arasında APACHE, SOFA ve GKS skorları yer almaktadır. Liu ve ark.'nın[27] çalışmasında GKS skoru yüksek ve APACHE II skoru düşük olan hastaların SDGD oranları anlamlı olarak daha yüksek bulunmuş olup, aynı çalışmada 24 saat sağ kalım sağlanan hastaların APACHE II skorları anlamlı olarak daha düşük bulunmuştur. Ohlsson ve ark.[28] ise 287 hastada yaptıkları çalışmalarında GOFAR skoru yüksek olan hastaların KPR sonrası taburculuk oranlarını anlamlı olarak daha düşük saptamışlardır. Ülkemizde yapılan bir çalışmada yoğun bakımda uygulanan KPR'lerde PAM skoru KPR sonrası beklenen mortalite ile uyumlu bulunmuştur[30]. Mısır'da 380 hastane içi kardiyak arrest hastasını içeren bir diğer çalışmada PAM skoru düşük olan hastaların 24 saat sağ kalım oranları daha az saptanmıştır[31]. İngiltere'de yapılmış 264 kardiyak arrest hastasının yer aldığı bir diğer çalışmada PAM ve PAR skoru yüksek olan hastaların KPR sonrası taburculuk oranları daha düşük bulunmuştur[29]. Organ fonksiyon bozukluğu hakkında öngörü sağlayan MODS, LODS ve SOFA skorları ile hastane içi kardiyak arrest hastaları arasındaki sağkalım ilişkisini araştıran çalışmalardan; Hagiwara ve ark.[32] çalışmalarında APACHE II ve SOFA skoru yüksekliği olan hastalarda SDGD oranının anlamlı olarak daha düşük olduğunu göstermişlerdir. SAPS II skoru ile ilgili Kore'de bir diğer çalışmada SAPS II skoru yüksekliği olan hastaların SDGD ve resüsitasyon sonrası taburculuk açısından daha şanssız olduğu bildirilmiştir[33]. Benzer şekilde SAPS II skorunun sağ kalım tahmini üzerine etkisinin incelendiği çalışmalar bulunmaktadır[34,35]. Hastalarımızı bu farklı özelliklere sahip skorlama sistemleri ile değerlendirdiğimizde GOFAR, PAM, PAR, APACHE II, SOFA, SAPS II, LODS ve MODS skorları KPR'ye yanıtı olan hastalarda anlamlı olarak daha düşük; GKS skoru ise anlamlı olarak daha yüksek saptandı. Ayrıca GOFAR ve PAR skoru SDGD sonrası hospitalizasyon süresince ve ilk 48 saatte mortalite; SAPS II skoru ise her üç dönemdeki mortalite ile ilişkili bulundu.

Sonuç olarak KPR uygulamasının başarı ile sonuçlanması üzerine etkili olan faktörlerin bilinmesi ve özellikle uygun skorlama sistemlerinin kullanımı ile bu hastalarda KPR'nin başarısını arrest öncesi öngörmede ve KPR uygulaması sonrasında sağkalımlarının tahmin edilebilmesinde yol gösterici olacağı kanısına varılmıştır.

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ÖZGÜN ARAŞTIRMA

Dapagliflozin, Empagliflozin ve Eksenatid Kullanan Tip 2 Diyabetli Hastalarda Kardiyovasküler Olay Oranlarının Retrospektif Olarak Değerlendirilmesi

Bahriye GÜLTAŞ[1], Özen ÖZ GÜL[2], Soner CANDER[2]

[1] Bursa Uludağ Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Bursa, Türkiye.
[2] Bursa Uludağ Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Endokrinoloji ve Metabolizma Hastalıkları Bilim Dalı, Bursa. Türkiye.

ÖZET

Tip 2 diyabet hastalarında kardiyovasküler hastalıklar diyabeti olmayanlara göre daha yüksektir. SGLT-2 inhibitörlerinin (empagliflozin, dapagliflozin vb.) ve GLP-1 analoglarının (exenatid vb.) kardiyak etkilerine ilişkin olumlu sonuçlar veren geniş çaplı çalışmalar mevcuttur. Bu çalışmayla empagliflozin, dapagliflozin veya eksenatid kullanan hastalarda kardiyovasküler sonuçları değerlendirmek ve karşılaştırmak amaçlanmıştır. Kontrol grubu olarak kardiyak açıdan nötr olduğu bilinen DPP-4 inhibitörü (linagliptin) kullanan hastalar seçilmiştir. Bu çalışma her tedavi grubundan (linagliptin, eksenatid, dapagliflozin, empagliflozin) en az on iki aydır tedavi gören 100 hasta olmak üzere toplam 400 hasta ile gerçekleştirilmiştir. Miyokard enfarktüsü (MI), serebrovasküler olay (SVO), kardiyak nedenlere bağlı ölüm, majör kardiyovasküler olay (MACE: MI, SVO ve kardiyak ölüm), kalp yetmezliği nedeniyle hastaneye yatış, kararsız angina/akut koroner sendrom (AKS), periferik arter hastalığı ve tüm nedenlere bağlı ölümler değerlendirilmiştir. Tüm kardiyovasküler patolojilerin toplam oranları incelendiğinde linagliptin grubunda %10, eksenatid grubunda %6, dapagliflozin grubunda %4 ve empagliflozin grubunda %6 olarak tespit edilmiştir. Kardiyak hastalık öyküsü olmayan hastalar karşılaştırıldığında eksenatid, dapagliflozin ve empagliflozin grubunda toplam kardiyovasküler patoloji oranlarının linagliptin grubuna göre istatistiksel olarak anlamlı derecede azaldığı saptanmıştır. Kardiyak öyküsü olan hastalarda ise dapagliflozin ve empagliflozin grubunda angina/AKS tablosunun anlamlı derecede azaldığı ortaya konmuştur. Bu sonuçlar diyabet hastalarının kardiyak patolojilerden birincil korunmasında eksenatid, dapagliflozin ve empagliflozin moleküllerinin faydalı olduğunu göstermektedir. Dapagliflozin ve empagliflozin molekülleirinin hastaların kardiyovasküler patolojilerden sekonder korunmasında da tekili olabileceğini düşündürmektedir.

Anahtar Kelimeler: Linagliptin. Eksenatid. Dapagliflozin. Empagliflozin. SGLT-2 inhibitörleri. Kardiyovasküler Olay.

Retrospective Evaluation of The Rate of Cardiovascular Events in Type 2 Diabetic Patients Using Dapagliflozin, Empagliflozin and Exenatide

ABSTRACT

Cardiovascular diseases are more common in patients with type 2 diabetes than in those without diabetes. Large-scale studies have shown positive results regarding the cardiac effects of SGLT-2 inhibitors (empagliflozin, dapagliflozin, etc.) and GLP-1 analogs (exenatide, etc.). This study aimed to evaluate and compare cardiovascular outcomes in patients using empagliflozin, dapagliflozin, or exenatide. Patients using a DPP-4 inhibitor (linagliptin), known as cardiac neutral, were selected as the control group. This study was conducted with 400 patients, 100 of whom received treatment for at least twelve months from each treatment group (linagliptin, exenatide, dapagliflozin, and empagliflozin). Myocardial infarction (MI), cerebrovascular accident (CVA), death due to cardiac causes, major cardiovascular event (MACE: MI, CVA, and cardiac death), hospitalization due to heart failure, unstable angina/acute coronary syndrome (ACS), peripheral artery disease and all-cause deaths were evaluated. When the total rates of all cardiovascular pathologies were examined, it was determined that they were 10% in the linagliptin group, 6% in the exenatide group, 4% in the dapagliflozin group and 6% in the empagliflozin group. When patients without a history of cardiac disease were compared, it was determined that the total cardiovascular pathology rates in the exenatide, dapagliflozin, and empagliflozin groups were statistically significantly reduced compared to the linagliptin group. In patients with a cardiac history, it was revealed that angina/ACS was significantly reduced in the dapagliflozin and empagliflozin groups. These results show that exenatide, dapagliflozin, and empagliflozin molecules are helpful in the primary prevention of cardiac pathologies in our diabetic patients. Dapagliflozin and empagliflozin molecules may also be unique in the secondary protection of patients from cardiovascular pathologies.

Keywords: Linagliptin. Exenatide. Dapagliflozin. Empagliflozin. SGLT-2 inhibitors. Cardiovascular event.

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Dr. Bahriye GÜLTAŞ
Bursa Uludağ Üniversitesi Tıp Fakültesi
Tel.: 0543 431 01 03
E-posta: bahrys91@gmail.com

Yazarların Orcid Bilgileri:
Bahriye GÜLTAŞ: 0000-0001-5699-7813
Soner CANDER: 0000-0001-6303-7896
Özen ÖZ GÜL: 0000-0002-1332-4165

Dünya genelinde 18-99 yaş arası erişkinlerde diyabetes mellitus (DM) prevalansının 2017 yılında %8.4 olduğu ve 2045 yılında %9.9'a çıkacağı tahmin edilmektedir. Güncel verilere göre dünya genelinde yaklaşık 415 milyon diyabet hastası olduğu bilinmektedir[1]. Diyabetik hastalarda glisemik kontrolün sağlanamaması uzun dönemde çeşitli komplikasyonlara neden olmaktadır. Bu komplikasyonlar arasında kardiyovasküler hastalıklar, serebrovasküler hastalıklar, periferik arter hastalıkları ve böbrek yetmezliği gibi hayati hastalıklar yer almaktadır. Diyet, kilo kontrolü ve günlük fiziksel aktivitenin arttırılması gibi yaşam tarzı değişiklikleri, glisemik kontrol için ilk basamak tedaviyi oluşturur. Tip 2 DM hastalarında kardiyovasküler hastalık riski diyabetik olmayanlara göre 2-4 kat daha fazladır. Bu hastaların %65-70'i makrovasküler komplikasyonlar (koroner arter hastalığı, periferik arter hastalığı, serebrovasküler hastalık) nedeniyle ölmektedir[2]. Tip 2 DM'nin artan prevalansına rağmen, hastaların çoğunda yeterli glisemik kontrol sağlanamamaktadır. Öte yandan diyabet tedavisindeki gelişmeler özellikle milenyumdan itibaren hız kazanmış ve birçok yeni ilaç kullanıma girmiştir. Bazıları sodyum-glukoz ko-transporter-2 (SGLT-2) molekülünü inhibe eden ilaçlardır. Bu ilaçlar proksimal tübüldeki sodyum-glukoz kanallarını inhibe ederek böbrekten glukoz atılımını sağlar. Son yıllarda SGLT-2 inhibitörlerinin ve glukagon-like peptid-1 (GLP-1) analoglarının kardiyovasküler koruyucu etkileri üzerine birçok çalışma ve meta-analiz yapılmaktadır. Randomize kontrollü çalışmalar her iki sınıfın da glisemik kontrolü iyileştirdiğini ve aynı zamanda kardiyoprotektif ve renoprotektif etkiler sağladığını göstermektedir[3,4].

Özellikle SGLT-2 inhibitörleri (empaglifilozin, dapaglifilozin vb.) ile ilgili hem kalp hem de böbrek açısından etkileyici sonuçlar tespit edilmiştir. Bazı çalışmalarda SGLT-2 inhibitörü grubundan empagliflozinin sekonder kardiyak korumada daha etkili bir ajan olduğu bulunmuştur. Ancak primer korumadaki rolü açısından daha fazla çalışmaya ihtiyaç olduğu belirtilmektedir[5,6].

Bu çalışmada SGLT-2 inhibitörü (empaglifilozin, dapaglifilozin) veya GLP-1 reseptör agonisti (eksenatid) kullanmakta olan tip 2 DM tanılı hastalarda ilaca başladıktan sonra gelişen kardiyovasküler olayların oranını belirlemek ve prospektif çalışmaların gerçek yaşam projeksiyonunu retrospektif olarak ortaya koymak amaçlandı.

Gereç ve Yöntem

Etik kurul onayı, Uludağ Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu'ndan 2019-7/18 numaralı karar ile alındı. Mart 2017-Şubat 2019 tarihleri arasında çalışmanın yapıldığı merkeze başvuran veya kliniğe yatışı yapılan erişkin (>18 yaş) tip 2 diyabet hastaları arasından linagliptin (DPP-4 inhibitörü), eksenatid (GLP-1 analogu), dapagliflozin (SGLT-2 inhibitörü) veya empagliflozin (SGLT-2 inhibitörü) ilaçlarını en az 12 aydır kullanmakta olan, bu ilaçlar haricinde başka bir oral antidiyabetik kullanmayan ve elektronik kayıtlarında yeterli veri bulunan hastalar tarandı. Bu ilaçlara başlanmadan önce, başladıktan 6 ay ve 1 yıl sonra izlenen hastalar çalışmaya dahil edildi. İlaç yazıldıktan sonra takip edilemeyen ve/veya verileri eksik olan hastalar, tip 1 DM hastaları, çocuk yaş grubunda olanlar, gebelik ve emzirme dönemindeki kadın hastalar, ilaç yazıldıktan sonra başka bir hastanede takip edilen hastalar dışlama kriteri olarak belirlendi.

Daha önceki çalışmalarda dipeptidil peptidaz-4 (DPP-4) inhibitörlerinin kardiyovasküler hastalık riski üzerine nötr etkileri olduğu tespit edildiğinden bu grup kontrol grubu olarak kabul edildi[7-9].

Çalışma Tasarımı ve Örneklem

Bu çalışmada 4 ilaç grubu (linagliptin, eksenatid, dapagliflozin, empagliflozin) arasında empagliflozin en yeni tedavi olduğu ve çalışma tek merkezde yürütüldüğü için her tedavi grubundaki hasta sayısı empagliflozin kullanan hasta sayısına eşit olarak belirlendi. Empagliflozin verilen ve düzenli takipleri yapılan maksimum 100 hastaya ulaşıldı ve bu nedenle diğer tedavi gruplarından da çalışmaya dahil edilme kriterlerini karşılayan 100 hasta seçildi ve değerlendirildi. Toplam 818 hasta dosyası retrospektif olarak tarandı (229 linagliptin, 140 eksenatid, 272 dapagliflozin ve 177 empagliflozin kullanan hasta dosyası tarandı) ve toplamda 400 hasta çalışmaya dahil edildi.

Hastalara ait elektronik dosyalar detaylı olarak incelendi. Yaş, cinsiyet, sigara içme durumu, hipertansiyon, hiperlipidemi ve kalp hastalığı veya ortaya çıkan kardiyovasküler patolojilerin varlığı (birincil sonuç: miyokard enfarktüsü, inme ve ölümcül kardiyovasküler olay - ikincil sonuç: anjina/akut koroner sendrom, periferik arter hastalığı ve kalp yetmezliği) ve tüm nedenlere bağlı ölümler kaydedildi. ACEI/ARB, betabloker, lipid düşürücüler (statinler), spiranolakton gibi ilaç kullanımları analiz edildi. Yeterli kardiyak verisi olmayan hastalar telefonla aranarak bilgi alındı. Ancak kiloyla ilgili hastane kayıtlarının yetersizliği ve hastaların geçmişe yönelik kilolarını hatırlamamaları sebebiyle değerlendirmeye dahil edilmedi. Glisemik açıdan hastaların 0. (0 ay: tedavi başlamadan hemen önce), 6. ve 12. aylarda glikozile hemoglobin A1c (HbA1c) değerleri kaydedildi. Hastaların DPP-4 inhibitörü, GLP-1 agonisti veya SGLT-2 inhibitörü kullanmaya başlamadan hemen önce aldıkları tüm ilaçlar ile tedavi başlangıcından 1 yıl sonra aldıkları tüm ilaçlar not edilerek karşılaştırıldı.

İstatistiksel Analiz

Sürekli değişkenlerin normal dağılıma uygunluğu Shapiro Wilk testi ile incelenmiştir. Değişkenler ortalama ± standart sapma, medyan (minimum: maksimum) ya da n(%) değerleriyle ifade edilmiştir. Normallik testi sonucuna göre tedavi grupları arasında yapılan karşılaştırmalarda Kruskal Wallis testi kullanılmıştır. Kruskal Wallis testi sonrasında anlamlılık bulunması durumunda gruplar arasındaki ikili karşılaştırmalar Dunn testi kullanılarak yapılmıştır. Tedavi gruplarında 6. ay ve 12. ayda elde edilen ölçümlerin başlangıç değerleriyle karşılaştırılması için yapılan analizlerde ise Wilcoxon İşaretli Sıra Testi ya da eşleştirilmiş örneklemler için t-testi kullanılmıştır. Kategorik değişkenlerin gruplar arası karşılaştırmaları ise Pearson ki-kare testi, Fisher-Freeman-Halton Testi ya da Fisher'in kesin ki-kare testi kullanılarak gerçekleştirilmiştir. İstatistiksel analizler için SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) programı kullanılmış ve istatistiksel karşılaştırmalarda tip I hata düzeyi α=0.05 olarak kabul edilmiştir.

Bulgular

Bu çalışmada 143 erkek (%35.8) ve 257 kadın (%64.3) olmak üzere toplam 400 hastanın verileri bulunmaktadır. Her ilaç grubunda yaş, cinsiyet dağılımı ve sigara kullanımı, hipertansiyon tanısı, geçirilmiş kalp hastalığı, anjiotensin dönüştürücü enzim inhibitörü (ACEİ) veya anjijotensin reseptör blokeri (ARB) kullanımı, beta bloker kullanımı, spiranolakton kullanımı, lipid düşürücü ilaç kullanımı, insülin kullanım oranları Tablo I'de yer almaktadır.

Linagliptin grubunda ortalama HbA1c seviyesi tedavi başlangıcında %8.10, tedavinin 6. ayında %7.45, 1 yılın sonunda ise %7.10 olarak tespit edilmiştir. Eksenatid grubunda ortalama HbA1c seviyesi tedavi başlangıcında %8, tedavinin 6. ayında %7.5, 1 yılın sonunda ise %7.2 olarak tespit edilmiştir. Dapagliflozin grubunda ortalama HbA1c seviyesi tedavi başlangıcında %8.45, tedavinin 6. ayında %7.25, 1 yılın sonunda ise %7.20 olarak tespit edilmiştir. Empagliflozin grubunda ortalama HbA1c seviyesi tedavi başlangıcında %8.20, tedavinin 6. ayında %7.80, 1 yılın sonunda ise %7.30 olarak tespit edilmiştir. Gruplar arasında 1 yıl içindeki HbA1c değişimleri açısından istatiksel olarak anlamlı bir fark görülmemiştir.

Linagliptin grubunda yaş ortalaması diğer gruplara göre daha yüksek saptanmıştır. Eksenatid ve dapagliflozin gruplarındaki kadın oranı, linagliptin ve empagliflozin gruplarına göre daha yüksek bulunmuştur.

Tablo I. Tedavi grupları arasında bazal karakteristiklerin karşılaştırılması

	Linagliptin (n=100)	Eksenatid (n=100)	Dapagliflozin (n=100)	Empagliflozin (n=100)	p-değeri
Yaş	64(22:90) 62.19±12.02	57(29:77) 56.23±10.76	59(25:82) 58.10±9.78	59(28:79) 58.20±10.31	**<0.001[a]** *
Cinsiyet					
Kadın	49(%49)	81(%81)	70(%70)	57(%57)	**<0.001[b]** **
Erkek	51(%51)	19(%19)	30(%30)	43(%43)	
Sigara	17(%17)	20(%20)	16(%16)	17(%17)	0.891[b]
HT	60(%60)	60(%60)	54(%54)	46(%46)	0.149[b]
Eski KVS	19(%19)	15(%15)	22(%22)	34(%34)	**0.009[b]** ***
ACEI/ARB	44(%44)	40(%40)	45(%45)	42(%42)	0.896[b]
Betabloker	27(%27)	14(%14)	19(%19)	20(%20)	0.146[b]
Spiranolakton	3(%3)	1(%1)	3(%3)	1(%1)	0.647[c]
Lipid düşürücü	33(%33)	15(%15)	27(%27)	37(%37)	**0.003[b]** ****
İnsulin	50(%50)	33(%33)	38(%38)	47(%47)	**0.047[b]**

Veriler n (%), medyan (minimum: maksimum) ve ortalama ± sapma olarak verilmiştir.
HT:Hipertansiyon, KVS: Kardiyovasküler hastalık, ACEI: Anjiotensin dönüştürücü enzim inhibitörü, ARB: Aldosteron-renin sistem blokeri
[a]: Kruskal Wallis Testi, [b]: Pearson Chi-Square Testi, [c]: Fisher-Freeman-Halton Testi, [d]: Dunn Testi
* Yaş, ikili karşılaştırmada anlamlı p değerleri: Lin&Exena: <0.001, Lin&Empa: 0.015, Lin&Dapa: 0.026
** İkili karşılaştırmada cinsiyet oranında anlamlı p değerleri: Lin&Exena: <0.001, Lin&Empa: 0.002, Exena&Empa: <0.001
*** Eski KVS, ikili karşılaştırmalarda anlamlı p değerleri: Lin&Empa: 0.016, Exena&Empa: 0.002
**** Lipit düşürücü ilaç, ikili karşılaştırmalarda anlamlı p değerleri: Lin&Empa: 0.003, Exena&Dapa: 0.037, Exena&Empa: <0.001.

Daha önce kardiyovasküler olayı veya bilinen kalp hastalığı olan hasta oranının linagliptin grubunda %19, eksenatid grubunda %15, dapagliflozin grubunda %22 ve empagliflozin grubunda %34 olduğu tespit edilmiştir. Empagliflozin grubunda geçirilmiş kardiyak patoloji oranının diğer gruplara göre daha yüksek olduğu saptanmıştır.

Bu çalışmanın temeli SGLT-2 inhibitörü veya GLP-1 analogu kullanan hastalarda kardiyak patoloji prevalansının değerlendirilmesidir. Her ilaç grubunda meydana gelen kardiyak patolojiler Tablo II'de verilmiştir. Linagliptin ve empagliflozin gruplarında miyokard infarktüsü (MI) geçiren 1 hasta varken, diğer iki grupta MI olmadığı görülmüştür. Grupların hiçbirinde ölümcül kardiyovasküler olay tespit edilmemiştir. Linagliptin ve empagliflozin gruplarında serebrovasküler olay (SVO) gelişen bir hasta varken, diğer iki grupta SVO olmadığı görülmüştür. MI, SVO ve ölümle sonuçlanan patolojiler majör advers kardiyovasküler olaylar (MACE) olarak kabul edilmiştir ve bu patolojilerin toplam insidansı açısından ilaç grupları kendi aralarında karşılaştırıldığında istatistiksel olarak anlamlı fark bulunmamıştır.

Tablo II. Tedavi grupları arasında karşılaştırmalar

	Linagliptin (n=100)	Eksenatid (n=100)	Dapagliflozin (n=100)	Empagliflozin (n=100)	p-değeri[c]
MI	1(%1)	0	0	1(%1)	>0.999[g]
SVO	1(%1)	0	0	1(%1)	0.727[b]
Fatal KVS	0	0	0	0	>0.999[g]
Primer sonlanım					
MI	1(%1)	0	0	1(%1)	0.528[g]
SVO	1(%1)	0	0	1(%1)	
Yok	98(%98)	100(%100)	100(%100)	98(%98)	
Angina/AKS	2(%2)	5(%5)	0	2(%2)	0.148[g]
PAH	0	0	1(%1)	0	>0.999[g]
KY nedenli yatış	2(%2)	1(%1)	2(%2)	1(%1)	>0.999[g]
Ex	4(%4)	0	1(%1)	1(%1)	0.174[g]
Toplam Olay	10(%10)	6(%6)	4(%4)	6(%6)	0.373[b]

Veriler n(%) olarak verilmiştir.
MI:miyokard infarktüsü, SVO: serebrovasküler olay, KVS: kardiyovasküler, AKS: akut koroner sendrom, PAH: periferik arter hastalığı, KY: kalp yetmezliği, Ex: exitus (ölüm), Primer sonlanım (MI, SVO ve ölümle sonuçlanan kardiyovasküler olaylar), Toplam olay (tabloda bahsi geçen tüm patolojiler)
[c]: Fisher Freeman-Halton Testi

Kararsız angina/akut koroner sendromlu linagliptin ve empagliflozin grubunda 2 hasta varken, eksenatid grubunda 5 hasta tespit edilmiştir, dapagliflozin grubunda ise hiç olmadığı görülmüştü. Dapagliflozin grubunda sadece 1 hastada periferik arter hastalığı tespit edilmiştir. Linagliptin grubunda 4, dapagliflozin ve empagliflozin gruplarında 1'er hastada tüm nedenlere bağlı ölüm olduğu ve eksenatid grubunda ölüm olmadığı saptanmıştır.

Toplamda tüm kardiyovasküler patolojilere bakıldığında linagliptin alan 10 hastada, eksenatid kullanan 6 hastada, dapagliflozin alan 4 hastada ve empagliflozin alan 6 hastada yeni kardiyovasküler olay tespit edilmiştir. Ancak analiz sonucunda yeni gelişen kardiyovasküler patolojiler açısından tedavi grupları arasında istatistiksel olarak anlamlı bir fark olmadığı görülmüştür (p> 0.05).

Kardiyak patoloji öyküsü olan hastalarda yeni kardiyak patolojiler değerlendirildiğinde angina/akut koroner sendrom (AKS) insidansı açısından tedavi grupları arasında anlamlı fark olduğu saptanmıştır. Alt grup analizlerinde eksenatid tedavi grubunda anjina/AKS insidansının dapagliflozin ve empagliflozin gruplarına göre daha yüksek olduğu görülmüştür (sırasıyla p=0.021 ve p=0.026). Tablo III'teki diğer değişkenler açısından tedavi grupları arasında anlamlı bir fark saptanmamıştır (p> 0.05).

Kardiyak patoloji öyküsü olmayan hastalarda yeni gelişen kardiyak patolojiler değerlendirildiğinde toplam olay yüzdesi açısından tedavi grupları arasında anlamlı bir fark tespit edilmemiştir. Alt grup analizlerinde linagliptin tedavi grubundaki toplam olay yüzdesinin eksenatid, dapagliflozin ve empagliflozin tedavi gruplarına göre daha yüksek olduğu görülmüştür (sırasıyla p = 0.016, p = 0.034, p = 0.042). Diğer değişkenler açısından tedavi grupları arasında anlamlı fark saptanmamıştır. (Tablo IV)

Tablo III. Daha önceden bilinen kardiyak patoloji öyküsü olan hastalarda (n=90) yeni gelişen kardiyak patolojiler açısıdan tedavi grupları arasındaki karşılaştırmalar

	Linagliptin (n=100)	Eksenatid (n=100)	Dapagliflozin (n=100)	Empagliflozin (n=100)	p-değeri[c]
MI	0	0	0	1(%2.94)	>0.999
SVO	0	0	0	1(%2.94)	>0.999
Fatal AKS	0	0	0	0	-
Angina/AKS	1(%5.26)	4(%26.67)	0	1(%2.94)	**0.011** *
PAH	0	0	1(%4.55)	0	0.622
KY nedenli yatış	1(%5.26)	1(%6.67)	1(%4.55)	1(%2.94)	0.908
Ex	0	0	1(%4.55)	1(%2.94)	>0.999
Toplam Olay	2(%10.50)	5(%33.3)	3(%13.60)	5(%14.70)	0.367

Veriler n(%) olarak verilmiştir.
MI: miyokard infarktüsü, SVO: serebrovasküler olay, KVS: kardiyovasküler, AKS:akut koroner sendrom, PAH: periferik arter hastalığı, KY: kalp yetmezliği, Ex: exitus (ölüm), Primer sonlanım (MI, SVO ve ölümle sonuçlanan kardiyovasküler olaylar), Toplam olay (tabloda bahsi geçen tüm patolojiler)
[c:] Fisher Freeman-Halton Testi, [g]:Fisher'in Kesin Ki-Kare Testi
* İkili karşılaştırmada anlamlı p değerleri: Exena&Dapa: 0.021, Exena&Empa: 0.026

Tablo IV. Daha önce kardiyak patoloji öyküsü olmayan hastalarda yeni gelişen kardiyak patolojiler açısından tedavi grupları arasındaki karşılaştırmalar (n = 310)

	Linagliptin (n=100)	Eksenatid (n=100)	Dapagliflozin (n=100)	Empagliflozin (n=100)	p-değeri[c]
MI	1(%1.23)	0	0	0	-
SVO	1(%1.23)	0	0	0	-
Fatal AKS	0	0	0	0	-
Angina/AKS	1(%1.23)	1(%1.17)	0	1(%1.52)	0.891
PAH	0	0	0	0	-
KY nedenli yatış	1(%1.23)	0	1(%1.28)	0	0.718
Ex	4(%4.94)	0	0	0	-
Toplam Olay	8(%9.90)	1(%1.20)	1(%1.30)	1(%1.50)	**0.009***

Veriler n(%) olarak verilmiştir.
MI: miyokard infarktüsü, SVO: serebrovasküler olay, KVS: kardiyovasküler, AKS: akut koroner sendrom, PAH: periferik arter hastalığı, KY: kalp yetmezliği, Ex: exitus (ölüm), Primer sonlanım (MI, SVO ve ölümle sonuçlanan kardiyovasküler olaylar), Toplam olay (tabloda bahsi geçen tüm patolojiler)
[c:] Fisher Freeman-Halton Testi, [g]: Fisher'in Kesin Ki-Kare Testi
* İkili karşılaştırmada anlamlı p değerleri: Lin&Exena: 0.016, Lin&Dapa: 0.034, Lina&Empa: 0.042

Tartışma ve Sonuç

Bu çalışma ile dapagliflozin, empagliflozin ve eksenatid tedavilerinin kardiyak öyküsü olmayan diyabet hastalarını kardiyovasküler patolojilerden primer korumada etkili olduğu saptanmıştır. Ayrıca daha önce kardiyak patoloji öyküsü olan hastalarda yeni kardiyak patolojiler düşünüldüğünde angina/akut koroner sendrom (AKS) insidansının dapagliflozin ve

empagliflozin gruplarında, eksenatid grubuna göre düşük olduğu ortaya konulmuştur.

Hastaların yaş istatistikleri linagliptin, eksenatid, dapagliflozin ve empagliflozin moleküllerinin kardiyovasküler etkilerine ilişkin daha önce yapılan çalışmalardaki görülen yaş istatistikleri ile uyumlu bulunmuştur[4-6,10-16].

Bu çalışmada eksenatid alan hastalarda kadın hasta oranının diğer gruplara ve çalışmalara göre daha yüksek olduğu tespit edilmiştir. Bunun durumun ülkemizde sosyal güvenlik politikaları nedeniyle vücut kitle indeksi >35 olan diyabetik hastalarda eksenatid tedavisinin reçetelenebilmesi ve obezitenin kadınlarda daha sık görülmesinden kaynaklandığı düşünülmüştür[17].

İncelenen her dört tedavi grubunda sigara içen hasta oranının %17-20 arasında olduğu ve bu oranın literatürle benzerlik gösterdiği tespit edilmiştir[10,11,18-21]. Her tedavi grubundaki hastaların yaklaşık yarısında hipertansiyon saptanmıştır. Bilinen kardiyovasküler patolojisi olan hasta oranının linagliptin grubunda %19, eksenatid grubunda %15, dapagliflozin grubunda %22 ve empagliflozin grubunda %34 olduğu görülmüştür. Bilinen kardiyovasküler patolojisi olan hasta oranı CANVAS (kanagliflozin) çalışmasında %65, EMPAREG (empagliflozin) çalışmasında %100, DECLARE (dapagliflozin) çalışmasında %40 ve REWIND (dulaglutid) çalışmasında %31'dir[4-6,16,21].

Empagliflozin grubunda kardiyak patoloji öyküsü olan hasta oranının daha yüksek olmasının kardiyovasküler hastalık öyküsü olan hastalarda EMPAREG çalışmasından sonra kılavuzlara empagliflozinin daha erken girmesiyle ilişkili olduğu düşünülmüştür.

GLP-1 analoglarının kardiyovasküler etkileri üzerine HARMONY (albiglutid) ve REWIND çalışmalarında ACEI/ARB kullanımı %81-82, betabloker kullanımı %66 ve %45.2, statin kullanımı %84 ve %66.3, insülin kullanımı %60 ve %24 idi. Bu çalışmada ise GLP-1 analogu kullanan hastalarda ACEI/ARB kullanımı, betabloker ve lipid düşürücü ilaç kullanımı daha düşük oranda tespit edilmiştir (sırasıyla %40, %14, %15). Yaşam süresini uzatan ilaçların literatüre göre daha düşük oranda kullanılmasının eksenatid grubunda görülen kardiyak patoloji oranlarını olumsuz yönde etkilemiş olabileceği düşünülmüştür. Hastaların insülin kullanımının ise literatürle benzer olduğu görülmüştür.

SGLT-2 inhibitörleri daha yeni bir ilaç grubu olduğu için kardiyak etkileri açısından yapılan çalışmalar daha yeni ve sayıca azdır. DECLARE (dapagliflozin) ve EMPAREG (empagliflozin) çalışmasında ACEI/ARB kullanım oranı %80-81, betabloker kullanım oranı %52 ve %65, statin kullanımı %52 ve %78, insülin kullanımı %41.6 ve sırasıyla %47'dir. Bu çalışmada ise SGLT-2 inhibitörü kullanan hastalarda ACEI/ARB kullanımı, betabloker ve lipid düşürücü ilaç kullanımı daha düşük oranda tespit edilmiştir (%42-45, %19-20, %27-37). Bu oranların literatüre göre daha düşük olmasının dapagliflozin ve empagliflozin grubunda görülen kardiyak patoloji oranlarını olumsuz yönde etkilemiş olabileceği düşünülmüştür. Hastaların insülin kullanımının literatüre benzer olduğu görülmüştür.

CARMELINA (2018) çalışmasında ortalama 2.2 yıl süreyle linagliptin alan 6979 hasta izlemiş ve 1 yıl içinde MACE oranını %5.77 olduğu bulunmuştur. Çalışmaya dahil edilen ve linagliptin verilen grupta 1 yıl içinde tüm nedenlere bağlı mortalite %4.69, MI %2.06, SVO %0.22, kararsız angina/AKS %0.55 ve kalp yetmezliğine bağlı yatış %2.77 olarak tespit edilmiştir. Plasebo grubu ile linagliptin grubu arasında bu oranlar açısından anlamlı fark olmadığı için linagliptin kullanımının kardiyak nötral olduğu sonucuna varılmıştır[9]. Bu çalışmada 1 yıl içinde linagliptin alan hastalarda MI oranı %1, SVO %1, MACE oranı %2, kararsız angina/AKS oranı %2, kalp yetmezliğine bağlı yatış oranı %2 ve tüm nedenlere bağlı ölüm oranı %4 saptanmıştır. Bu bulgular gerçek yaşam analizindeki sonuçların CARMELINA çalışmasına yakın olduğunu göstermiştir.

Eksenatid

EXSCEL (2017) çalışmasında medyan 3.2 yıl boyunca eksenatid alan 14752 hasta izlemiş ve 1 yıl içinde MACE oranı %3.7, MI oranı %2.1, SVO %0.8, kalp yetmezliği nedeniyle hastaneye yatış %0.9, kararsız angina/AKS %2.6 ve tüm nedenlere bağlı ölüm %2.6 olarak belirlenmiştir. Plasebo grubu ile eksenatid grubu arasında bu oranlar açısından anlamlı bir fark olmadığı için eksenatid kullanımının kardiyak-nötr olduğu sonucuna varılmıştır[12]. Bu çalışmada 1 yıl içinde eksenatid alan hastaların MACE oranının %0, kalp yetmezliği nedeniyle hastaneye yatış oranının %1, kararsız angina/AKS oranının %5, SVO oranının %0 ve tüm nedenlere bağlı ölüm oranının %0 olduğu gözlenmiştir. EXSCEL çalışmasında kadın hasta oranı %38 ve yaş ortalaması 62 iken, bu çalışmada kadın hasta oranı %81 ve yaş ortalaması 57 olarak tespit edilmiştir. Kardiyovasküler patolojilerin EXSCEL çalışmasına göre daha düşük oranda görülmesinin bu faktörlerden kaynaklanabileceği düşünülmüştür.

Eksenatid kullanan tüm hastalar linagliptin kullanan hastalarla karşılaştırıldığında MACE, MI, SVO ve tüm nedenlere bağlı mortalite açısından anlamlı bir fark görülmemiştir. Ancak eksenatid kullanan hastalardan kardiyak öyküsü olmayanlar incelendiğinde yeni gelişen kardiyovasküler patolojilerin linagliptin grubuna göre anlamlı oranda düşük olduğu tespit edilmiştir. Kardiyak öyküsü olan hastalar incelendiğinde ise yeni gelişen kardiyovasküler patolojiler açısından anlamlı bir fark olmadığı

görülmüştür. Bu durum eksenatid molekülünün diyabet hastalarını kardiyovasküler patolojilerden primer korumada etkili olabileceğini düşündürmüştür.

Dapagliflozin

DECLARE (2019) çalışmasında medyan 4.2 yıl boyunca dapagliflozin kullanan 17160 hasta izlenmiş ve 1 yıl içinde MACE oranı %2.26, MI oranı %1.17, SVO oranı %0.69, kalp yetmezliği nedeniyle hastaneye yatış oranı %0.62 ve tüm nedenlere bağlı ölüm oranı %1.15 olarak tespit edilmiştir. DECLARE çalışmasında kardiyovasküler ölüm ve kalp yetmezliği nedeniyle hastaneye yatış oranlarının plasebo grubuna göre daha az olduğu bulunmuştur ve diğer parametreler açısından anlamlı bir fark olmadığı görülmüştür[22]. Ancak EMPAREG çalışmasından farklı olarak daha önce kalp hastalığı öyküsü olan hastaların oranının %40 olduğu unutulmamalıdır (EMPAREG çalışmasında bu oran %100'dür). Dolayısıyla dapagliflozinin kardiyovasküler riski yüksek olan ancak henüz kalp hastalığı geçirmemiş diyabetli hastaları olası kardiyak patolojilerden koruduğu söylenebilir. Literatürde dapagliflozinin kardiyovasküler öyküsü olan veya olmayan hastalarda kardiyovasküler patolojileri azalttığını gösteren başka çalışmalar da mevcuttur[23-26]. Bu çalışmalar dapagliflozinin hastaları hem primer hem de sekonder korumada etkili olduğunu düşündürmektedir.

Bu çalışmada dapagliflozin kullanan hastaların 1 yılda MACE oranı %0, kalp yetmezliği nedeniyle hastaneye yatış oranı %2, kararsız angina/AKS oranı %0, SVO oranı %0 ve tüm nedenlere bağlı ölüm oranı %1 olarak tespit edilmiştir.

Dapagliflozin kullanan tüm hastalar linagliptin kullanan hastalarla karşılaştırıldığında MACE, MI, SVO ve tüm nedenlere bağlı mortalite açısından anlamlı bir fark görülmemiştir. Ancak dapagliflozin kullanan hastalardan kardiyak öyküsü olmayanlarda yeni gelişen kardiyovasküler patolojilerin ve kardiyak öyküsü olanlarda angina/AKS tablosunun linagliptin grubuna göre anlamlı oranda düşük olduğu tespit edilmiştir. Bu durum bize dapagliflozin molekülünün diyabet hastalarını kardiyovasküler patolojilerden primer ve sekonder korumada etkili olabileceğini düşündürmüştür.

Empagliflozin

EMPAREG (2015) çalışmasında medyan 3.1 yıl boyunca empagliflozin kullanan 7020 hasta (bu hastaların %100'ünün önceden bilinen kardiyak patolojisi vardı) izlenmiş ve 1 yıl içinde MACE oranı %3.74, MI oranı %1.68, SVO oranı %1.23, kalp yetmezliğine bağlı hastaneye yatış oranı %0.94 ve tüm nedenlere bağlı ölüm %1.94 olarak tespit edilmiştir (5). Kardiyovasküler olay açısından yüksek risk altındaki hastalarla yapılan bu çalışmada MACE oranı plasebo grubuna göre anlamlı olarak düşük bulunmuştur (MI, SVO açısından fark olmadığı fakat kardiyak nedenlere bağlı ölüm açısından fark olduğu görülmüştür). Literatürde empagliflozinin kardiyovasküler öyküsü olan veya olmayan hastalarda kardiyovasküler patolojileri azalttığını gösteren başka çalışmalar da mevcuttur. Bu çalışmalar empagliflozinin hastaları kardiyovasküler patolojilerden primer ve sekonder korumada etkili olduğunu düşündürmektedir[27-30].

Bu çalışmada 1 yıl içinde empagliflozin kullanan hastaların MACE oranının %2, MI oranının %1, kararsız angina/AKS oranının %2, SVO oranının %1, kalp yetmezliği nedeniyle hastaneye yatış oranının %1 ve tüm nedenlere bağlı ölüm oranının %1 olduğu görülmüştür.

Empagliflozin kullanan tüm hastalar linagliptin kullanan hastalarla karşılaştırıldığında MACE, MI, SVO ve tüm nedenlere bağlı mortalite açısından anlamlı bir fark görülmemiştir. Ancak empagliflozin kullanan hastalardan kardiyak öyküsü olmayanlarda yeni gelişen kardiyovasküler patolojilerin ve kardiyak öyküsü olanlarda angina/AKS tablosunun linagliptin grubuna göre anlamlı oranda düşük olduğu tespit edilmiştir. Bu durum bize empagliflozin molekülünün diyabet hastalarını kardiyovasküler patolojilerden primer ve sekonder korumada etkili olabileceğini düşündürmüştür.

Bu çalışmanın kısıtlılığı tek merkezde yürütülmesidir. Dört farklı molekülün karşılaştırılması ve gerçek yaşam verilerini ortaya koyması ise çalışmanın güçlü yanlarıdır.

Sonuç olarak tüm gruplarda daha önce kardiyovasküler patoloji öyküsü olmayan hastalar linagliptin grubu ile ayrı ayrı karşılaştırıldığında MACE açısından aralarında anlamlı fark olmadığı ancak eksenatid, dapagliflozin ve empagliflozin kullanan hastalarda total kardiyovasküler patoloji oranlarının linagliptin alanlara göre istatistiksel olarak anlamlı derecede düşük olduğu saptanmıştır. Kardiyovasküler patolojisi olan hastalarda ise yalnızca dapagliflozin ve empagliflozin grubunda angina/AKS tablosunun anlamlı şekilde azaldığı görülmüştür. Bu çalışma dapagliflozin, empagliflozin ve eksenatid tedavilerinin diyabet hastalarını kardiyovasküler patolojilerden primer korumada etkili olduğunu düşündürmüştür. Dapagliflozin ve empagliflozin tedavilerinin diyabet hastalarını angina/AKS açısından sekonder korumada da etkili olduğunu göstermiştir. Bu konuda yeni çalışmalara ihtiyaç olmakla birlikte tespit edilen sonuçlar hayati önem taşıyan kardiyovasküler patolojilerden diyabet hastalarının korunması açısından önem arz etmektedir.

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ÖZGÜN ARAŞTIRMA

Klasik Tedaviye Dirençli Romatoid Artrit ve Ankilozan Spondilit Hastalarında Tümör Nekroz Faktör Alfa Blokeri Kullanımının Böbrek Fonksiyonları Üzerine Etkisi

Oğuzhan ÖZTÜRK[1], Mehmet SEZEN[2], Tuncay DAĞEL[2]

[1] Biruni Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, İstanbul, Türkiye.
[2] Bursa Şehir Hastanesi, Nefroloji Kliniği, Bursa, Türkiye.

ÖZET

Romatoid Artrit (RA) ve Ankilozan Spondilit (AS) kronik, inflamatuar, sistemik hastalıklardır. Bu hastalıklar kontrol altına alınmadığında hastalarda morbidite ve mortalitede artışa neden olmaktadır. Genellikle eklem tutulumu görülmesine rağmen inflamatuar süreçten vücudun diğer organları da olumsuz etkilenebilmektedir. RA ve AS'nin patogenezinde proinflamatuar sitokin olan tümör nekrozis faktör-α'nın (TNF-α) rolü olduğu anlaşılmıştır. Bu nedenle tedavi amaçlı anti- TNF-α ajanlar geliştirilmiştir. Özellikle de hastalığı modifiye edici antiromatizmal ilaçlara (DMARD) dirençli hastalarda etkin oldukları gösterilmiştir. . Biz bu çalışmamızda DMARD'a dirençli RA ve AS hastalarında etanersept tedavisinin böbrek fonksiyonları ve hasar markırları üzerine olan etkisini araştırmayı amaçladık. Çalışmaya Kasım 2005-Ağustos 2006 tarihleri arasında Uludağ Üniversitesi İç Hastalıkları Ana Bilim Dalı Romatoloji Bilim Dalı polikliniğine başvuran 11 RA ve 8 AS hastası alındı. Hastalara haftada iki kez subkutan 25 mg dozunda etanersept tedavisi başlandı. Tedavi öncesi, tedaviden sonra 4. hafta ve 16. haftalarda, kreatinin klirensi, serum sistatin-c, serum β-2 mikroglobulin, 24 saatlik idrarda N asetil β-D glukozaminidaz (NAG) ve mikroalbuminüri düzeyleri araştırıldı. Tedavi sonunda hem serum ve hem de idrarda bakılan parametrelerde tedavi öncesine göre istatiksel açıdan anlamlı olmayan değişiklikler gözlendi. Sonuç olarak; çalışmamızda, DMARD tedavisi alan RA ve AS hastalarında etanersept tedavisinin böbreğin glomerüler ve proksimal tübül fonksiyonları üzerine olumlu ya da olumsuz bir etkisinin olmadığını saptadık.

Anahtar Kelimeler: Romatoid Artrit. Ankilozan Spondilit. Etanersept. N asetil β-D glukozaminidaz. Sistatin-c.

Rheumatoid Arthritis Resistant to Conventional Treatment The Effect of Tumor Necrosis Factor Alpha Blocker Use on Renal Functions in Patients with Ankylosing Spondylitis

SUMMARY

Rheumatoid Arthritis (RA) and Ankylosing Spondylitis (AS) are chronic, inflammatory, systemic diseases. When these diseases are not controlled, they cause an increase in morbidity and mortality in patients. Although joint involvement is usually seen, other organs of the body can also be negatively affected by the inflammatory process. Tumor necrosis factor-α (TNF-α), a proinflammatory cytokine, has been implicated in the pathogenesis of RA and AS. Therefore, anti-TNF-α agents have been developed for therapeutic purposes. They have been shown to be especially effective in patients resistant to disease-modifying antirheumatic drugs (DMARDs). Among these, etanercept, infliximab and adalimumab have been approved by the US National Food and Drug Administration (FDA). There are not enough studies in the literature investigating the effects of these drugs on renal function. In this study, we aimed to investigate the effect of etanercept treatment on renal function in DMARD-resistant RA and AS patients. Between November 2005 and August 2006, 11 RA and 8 AS patients admitted to the outpatient clinic of the Department of Internal Medicine, Division of Rheumatology, Uludag University were included in the study. Patients were started on etanercept at a dose of 25 mg subcutaneously twice a week. Creatinine clearance, serum cystatin-c, serum β-2 microglobulin, N-acetyl β-D glucosaminidase (NAG) in 24-hour urine and microalbuminuria levels were investigated. At the end of treatment, statistically insignificant changes were observed in both serum and urinary parameters compared to pretreatment. In conclusion; in our study, we found that etanercept treatment had no positive or negative effect on glomerular and proximal tubule functions of the kidney in RA and AS patients receiving DMARD treatment.

Keywords; Rheumatoid Arthritis. Ankylosing Spondylitis. Etanercept. N acetyl β-D glucoseaminidase. Cystatin-c.

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Mehmet SEZEN
Bursa Şehir Hastanesi Nefroloji
Tel.: 0506 980 64 81
E-posta:drmehmetsezen@gmail.com

Yazarların Orcid Bilgileri:
Oğuzhan ÖZTÜRK: 0000-0002-7718-8684
Mehmet SEZEN: 0000-0001-5796-6445
Tuncay DAĞEL: 0000-0002-1281-6571

Romatoid artrit (RA) ve ankilozan spondilit (AS), kronik, sistemik ve inflamatuar hastalıklardır. Kontrol altına alınmadıkları takdirde yaşam kalitesinde belirgin düşüşe neden olabilir ve erken ölüme yol açabilirler. Bu hastalıklar yalnızca eklemleri değil, diğer organları da etkileyerek inflamatuar süreç sonucunda fonksiyon kayıplarına neden olabilir[1-3].

RA ve AS, doğrudan böbrekleri etkilemez. Ancak, hastalık sürecinde gelişebilen sekonder AA amiloidoz, başta böbrekler olmak üzere çeşitli organların fonksiyonlarını bozabilir[4-8]. Erken ve etkili tedavi, hastaların morbidite ve mortalitesini belirgin ölçüde azaltabilir.

RA ve AS patogenezinde interlökin-1β ve tümör nekroz faktör-α (TNF-α)'nın önemli bir rol oynadığı gösterilmiştir[9-15]. Bu doğrultuda, TNF-α aktivitesinin bloke edilmesinin hastalık semptomlarını hafifletebileceği ve hastalık progresyonunu yavaşlatabileceği düşünülmüştür. Monomerik TNF reseptörleri (sTNFR'ler) ile karşılaştırıldığında, etanerseptin TNF'ye karşı daha yüksek bir afinitesi olduğu belirlenmiştir[9,16]. Klinik çalışmalar, etanerseptin haftada iki kez 25 mg subkutan uygulanmasının optimum doz olduğunu göstermiştir[9,11].

RA ve ankilozan spondilit AS hastalarında TNF-α blokerlerinin böbrekler üzerindeki etkilerine dair geniş çaplı randomize çalışmalar henüz yapılmamıştır. Ancak vaka raporlarında, özellikle ANCA ilişkili vaskülitler ve diğer glomerüler patolojilere neden olabileceği bildirilmiştir[17-21].

Böbrek hastalıklarının teşhisi ve hasarın belirlenmesi amacıyla idrar enzimlerinin ölçümü klinikte yaygın olarak kullanılmamaktadır. Bu enzimlerden biri olan N-asetil-β-D glukozaminidaz (NAG), renal proksimal tübüllerde baskın olarak bulunan ve geniş çapta dağılan lizozomal bir enzimdir. İdrarda artan NAG aktivitesi, tubüler hasarla ilişkilendirilmiştir[22,23].

Bu retrospektif çalışmada, DMARD tedavisine yanıt vermeyen RA ve AS hastalarında etanersept kullanımının böbrek fonksiyonlarıyla birlikte tubüler ve glomerüler yapılar üzerindeki olası etkilerini araştırmayı amaçladık. Glomerüler patolojileri mikroalbüminüri ile değerlendirirken, böbrek fonksiyonlarını cistatin C ve kreatinin düzeyleri üzerinden inceledik.

Gereç ve Yöntem

Çalışmaya, Uludağ Üniversitesi Tıp Fakültesi İç Hastalıkları Anabilim Dalı Romatoloji Bilim Dalı poliklinik takibinde olan 11 Romatoid Artrit ve 8 Ankilozan Spondilit hastası alındı. Hastaların çalışmaya dahil edilme kriterleri: Klasik Hastalığı Modifiye Edici ilaçlara rağmen hastalık aktivitesi devam eden, ilaca ve içerdiği diğer maddelere karşı alerjisi ya da aşırı hassasiyeti olmayan, kalp yetmezliği olmayan 18- 70 yaş gurubu hastalar olarak belirlendi. Bilinen böbrek hastalığı veya bu hastalıklara bağlı AA amiloidozu olan hastalar, aktif enfeksiyonu olan, tespit edilmiş malignitesi olan, Diyabete bağlı böbrek hastalığı olan hastalar, Anjotensin konverting enzim inhibitörü veya Anjiotensin reseptör blokeri kullanan hastalar çalışmaya dahil edilmedi.

İstatistiksel analiz

Verinin istatistiksel analizi SPSS13.0 istatistik paket programında yapılmıştır. Verinin normal dağılım gösterip göstermediği Shapiro-Wilk testi ile incelenmiştir. Normal dağılmayan veri için iki grup karşılaştırmasında Mann- Whitney U testi kullanılmıştır. Bağımlı grupların karşılaştırılmasında Wilcoxon İşaret Sıra testi kullanılmıştır. Kategorik verinin incelenmesinde Fisher'in Kesin Ki-kare testi kullanılmıştır. Anlamlılık düzeyi $p<0,05$ olarak belirlenmiştir. Çalışmaya bu kriterlere uygun 19 olan hasta alındı. Çalışma öncesi tüm hastalar çalışma hakkında bilgilendirildi ve yazılı olurları alındı. Bu İç Hastalıkları Uzmanlık Tezi'nin yapılabilmesi için Uludağ Üniversitesi Tıp Fakültesi Etik Komitesinden onay alındı.

Bulgular

Çalışmaya, RA tanısı olan 11 ve AS tanısı olan 9 hasta olmak üzere toplam 19 hasta dahil edilmiştir. Hastaların demografik ve klinik özellikleri Tablo I'de sunulmuştur. Hiçbir hastada hipertansiyon saptanmazken, üç hastada tip 2 diyabet tanısı mevcuttur. RA hastalarında kadınlar (E/K: 2/9), AS hastalarında ise erkekler (E/K: 6/2) baskın olarak bulunmuştur. Tüm hastaların DMARD tedavisine klinik ve laboratuvar açısından beklenen yanıtı vermediği belirlenmiştir.

Tablo I. Çalışmaya alınan hastaların genel özellikleri E:Erkek, K: Kadın

	Romatoid Artrit	Ankilozan Spondilit
Hasta sayısı	11	8
Cinsiyet (E/K)	2/9	6/2
Yaş (Yıl)	50,8±1 2	35,1±8,7
Hastalık süresi (yıl)	9,3±5,1	4,2±5

Hastaların kullandığı hastalığı modifiye edici antiromatizmal ilaçlar altı gruba ayrılmaktaydı: NSAİİ, steroid, metotreksat (MTX), hidroksiklorokin (HQ), salazopirin (SLZ) ve leflunomid. NSAİİ ve steroid kullanan hasta sayısı 16, SLZ 12, MTX 10, leflunomid 5 ve HQ 3 idi. Böbrek fonksiyonlarını

değerlendirmek amacıyla ölçülen serum üre, kreatinin, kreatinin klirensi, sistatin-C ve β-2 mikroglobulin düzeyleri tedavi öncesi ve sonrası benzerdi. Aynı zamanda istatistiksel olarak anlamlı bir farklılık saptanmadı. Tablo II'de sunulmuştur.

Tablo II. Hastaların kullandıkları hastalığı modifiye edici antiromatizmal ilaçlar

Hasta	Tanı	Yaş	Cinsiyet	Hastaların Kullandıkları İlaçlar					
				NSAII	Mtx	Steroid	HQ	Slz	Leflunamid
1	RA	51	K	-	-	+	-	+	-
2	RA	68	K	+	-	+	+	-	+
3	RA	71	K	+	+	+	-	-	-
4	RA	38	K	-	+	+	-	+	-
5	RA	44	E	+	-	+	-	+	+
6	RA	50	K	+	-	+	+	+	+
7	RA	39	K	+	-	+	-	+	+
8	RA	34	K	+	-	+	-	+	-
9	RA	63	K	-	+	+	+	-	-
10	RA	53	E	+	+	+	-	-	+
11	RA	48	K	+	+	+	-	+	-
12	AS	36	K	+	+	-	-	+	-
13	AS	38	E	+	-	-	-	+	-
14	AS	43	E	+	+	+	-	-	-
15	AS	18	E	+	+	+	-	+	-
16	AS	42	E	+	-	+	-	+	-
17	AS	31	E	+	-	-	-	+	-
18	AS	42	K	+	+	+	-	-	-
19	AS	28	E	+	+	+	-	-	-
Toplam				16	10	16	3	12	5

K: Kadın, E: Erkek, NSAID: Non Steroid Antiinflamatuar İlaç, Mtx: Metotreksat HQ: Hidroksiklorokin, Slz: Salazopirin

Glomerüler patolojileri değerlendirmek amacıyla ölçülen mikroalbuminüri düzeyi, tedavi öncesine kıyasla tedavinin 4. ve 16. haftalarında daha yüksek izlendi (16,87±14,81 mg/24 saat vs. 30,99±69,81 mg/24 saat**,** 27,36±53,24 mg/24 saat**)**. Ancak bu artış istatistiksel olarak anlamlı değildi **(**p<0,001).

Tubüler hasarı değerlendirmek amacıyla ölçülen 24 saatlik idrarda NAG düzeyi, tedavi öncesi ve sonrası benzer olup, istatistiksel olarak anlamlı bir fark göstermedi.

Tedavi öncesine kıyasla CRP düzeyi, tedavinin 4. ve 16. haftalarında istatistiksel olarak anlamlı bir düşüş gösterdi (p<0,001**).** Benzer şekilde, ESR değeri de tedavi sürecinde anlamlı bir azalma gösterdi p<0,001, Tablo III.

Tablo III. Çalışmaya alınan hastaların tedavi öncesi, tedavinin 4. haftası ve 16. haftasındaki laboratuvar değerleri

	Tedavi Öncesi	4.hafta	16.hafta
Üre (mg/dl)	28±10	30±10	27±8
Kreatinin (mg/dl)	0,84±0,24	0,8±0,14	0,82±0,14
Kreatinin klirensi(ml/dak)	96±31	100±28	93±29
ESR (1.saat)	42±23	19±16*	14±12**
CRP (mg/dl)	6,35±6,4	0,42±0,96*	0,56±1,1**
Sistatin-C(mg/l)	1,03±0,25	1,05±0,24	1,04±0,18
İdrar NAG (U/L)	6,31±4,16	5,42±2,94	7,16±4,01
İdrar NAG (24 saatlik toplam ünite)	12,87±8,45	9,93±4,65	12,57±6,12
Mikroalbuminuri (mg/L)	7,92±6,1	11,4±15,1	13,1±17,7
Mikroalbuminüri(mg/ 24 saat)	16,87±14,81	30,99±69,81	27,36±53,24
β-2 Mikroglobulin(µg/l)	1795±381	1754±461	1889±432

ESR: Eritrosit Sedimentasyon Hızı, CRP: C-Reaktif Protein, NAG: N-asetil β-D glukozaminidaz
* p<0,001 tedavi öncesi ile tedavinin 4.haftası karşılaştırıldığında** p<0,001 tedavi öncesi ile tedavinin 16.haftası karşılaştırıldığında

Tartışma ve Sonuç

TNF-α blokerleri, DMARD tedavisine dirençli RA ve AS hastalarında inflamasyonu baskılamak ve hastalık progresyonunu yavaşlatmak amacıyla yaygın olarak kullanılmaktadır. Ancak, TNF- α inhibitörlerinin uzun vadede organ fonksiyonları üzerindeki etkileri tam olarak aydınlatılamamış olup, özellikle böbrek fonksiyonları üzerindeki potansiyel riskler hala tartışmalıdır. Bu nedenle, TNF-α blokerlerinin renal fonksiyonlar üzerindeki etkilerini değerlendirmek önemli bir araştırma alanı olarak karşımıza çıkmaktadır.

TNF -α blokerlerinin, özellikle DMARD tedavisine dirençli RA ve AS'li hastalarda, hastalık kontrolünde güvenli ve etkili bir seçenek olduğu geniş ölçekli randomize çalışmalarla gösterilmiştir[2-4,9,24,25]. Ayrıca, RA tedavisinde diğer TNF -α blokerlerine kıyasla daha düşük tüberküloz reaktivasyonu riski nedeniyle etanercept tercih edilmekte, bu durum da klinik uygulamalarda desteklenmektedir[26]. John C. Davis ve arkadaşlarının randomize kontrollü çalışmasında AS hastalarında etanerceptin yüksek etkinlik ve güvenilirlik gösterdiği, benzer şekilde J. Brandt ve arkadaşlarının çalışmasında da haftada iki kez uygulanan etanerceptin AS'li hastalarda olumlu klinik yanıtlar sağladığı bildirilmiştir[27,28].

Bununla birlikte, TNF-α blokerlerinin güvenlik profili tam olarak belirlenmiş olmasına rağmen, nadir de olsa renal yan etkilerle ilişkilendirilebileceği bildirilmiştir.

Özellikle RA hastalarında, TNF- α blokerleri sonrasında nefrotik sendrom, lupus nefriti, pANCA ilişkili kresentrik glomerülonefrit ve membranöz glomerülonefrit gibi renal patolojiler vaka bazında rapor edilmiştir[17,19,20,29]. Bu olgular, TNF-α'nın immün yanıt üzerindeki çok yönlü etkileri nedeniyle, bazı hastalarda otoimmün mekanizmalar aracılığıyla böbrek fonksiyonlarının etkilenebileceğini düşündürmektedir. Ancak, bu yan etkilerin oldukça seyrek olduğu ve genel popülasyonda klinik açıdan belirgin bir renal risk oluşturmadığı da vurgulanmaktadır.

Bunların yanında, RA ve Ailevi Akdeniz Ateşi tanıları olan, AA amiloidoz gelişen hastalarda, anti-TNF tedavisinin amiloid birikimini azalttığı ve proteinüriyi belirgin şekilde gerilettiği gösterilmiştir[5,30-32]. Bu veriler, TNF -α blokerlerinin yalnızca güvenli değil, aynı zamanda belirli hasta gruplarında böbrek fonksiyonları üzerinde koruyucu etkilere sahip olabileceğini düşündürmektedir.

Çalışmamızda, etanercept tedavisi sonrası böbrek fonksiyonları üzerinde belirgin bir olumsuz etki görülmemesi, bu tedavinin renal güvenilirliği açısından önemli bir veri sunmaktadır.

Ancak, çalışmamızın bazı kısıtlılıkları bulunmaktadır. Tek bir biyolojik ajan kullanılarak yapılan değerlendirme ve sınırlı hasta sayısı, elde edilen sonuçların genellenebilirliği açısından dikkatle ele alınmalıdır. Daha geniş örneklem gruplarıyla ve uzun süreli takip verileriyle desteklenecek ileri çalışmalar, TNF-α blokerlerinin renal fonksiyonlar üzerindeki uzun vadeli etkilerini daha ayrıntılı olarak ortaya koyacaktır.

Sonuç olarak, DMARD tedavisine dirençli RA ve AS hastalarında etanercept tedavisinin hastalık aktivitesini kontrol etmede etkili olduğu ve böbrek fonksiyonları üzerinde anlamlı bir olumsuz etkiye yol açmadığı görülmüştür. Bununla birlikte, nadir de olsa renal yan etkiler bildirilmiş olduğundan, tedavi sürecinde hastaların dikkatle izlenmesi gerektiği unutulmamalıdır. TNF -α blokerlerini, uzun vadeli güvenlik profilini daha iyi anlamak adına, daha kapsamlı ve uzun süreli takip gerektiren çalışmalara ihtiyaç duyulmaktadır.

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ÖZGÜN ARAŞTIRMA

Meme Cerrahisi Geçiren Hastalarda Uygulanan PECS II (pektoral sinir) Bloğunun İntraoperatif ve Postoperatif Etkileri*

Mustafa Naci BALICA[1], Duygu KARAKÖSE ÇALIŞKAN[1], Selcan YEREBAKAN AKESEN[2], Yunus Gürkan TÜRKER[2]

[1] Bilkent Şehir Hastanesi, Yoğun Bakım Kliniği, Ankara, Türkiye.
[2] Bursa Uludağ Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, Bursa, Türkiye.

ÖZET

Meme cerrahisinde uygulanan PECS II (Pektoral Sinir) bloğun preoperatif ve postoperatif uygulanmasının, intraoperatif anestezik tüketimi ve postoperatif analjezik ihtiyacı ve komplikasyonların sıklığının değerlendirilmesini amaçladık. Meme cerrahisi geçirmiş 75 hastanın anestezi dökümlerinin retrospektif olarak incelenmesiyle ve verilerin analiziyle düzenlenmiştir. Verileri elde edilen hastalar üç gruba kategorize edilmiştir. Grup I (n25:genel anestezi uygulanan kontrol grubu), Grup II (n25:preoperatif PECS II blok ve genel anestezi) ve Grup III (n25: postoperatif PECS II blok ve genel anestezi). Verilerin analizi sonrası preoperatif PECS II blok uygulanan hastalarda intraoperatif desfluran MAC (minimum alveolar konsantrasyon) değerlerinin diğer gruplara göre belirgin olarak düştüğü bulunmuştur. İntraoperatif ve postoperatif PECS II blok uygulanan çalışma gruplarında, kontrol grubuna göre postoperatif analjezik tüketiminde ve ağrı skorlarında (erken dönem, postoperatif 0, 2, 4 ve 8. saat) anlamlı düşüşler görülmüştür. Preoperatif PECS II blok uygulanan grupta postoperatif ilk analjezik uygulama zamanı, sadece genel anestezi uygulanan ve Postoperatif PECS II blok uygulanan gruplardan anlamlı olarak daha geç bulunmuştur. Sadece genel anestezi uygulanan ve Postoperatif PECS II blok uygulanan gruplarda postoperatif ilk analjezik uygulama zamanı benzer bulunmuştur. Meme cerrahisi geçirecek hastalarda PECS II bloğun preoperatif veya postoperatif dönemde genel anesteziye eklenmesi hastalarda daha az ağrı ile seyreden postoperatif analjezi elde edilmesini sağlamaktadır. PECS II bloğun preoperatif uygulanmasının en önemli avantajı ise intraoperatif anestezik tüketimini azaltmasıdır.

Anahtar Kelimeler: Pektoral sinir bloğu. Postoperatif analjezi. Meme cerrahisi. Rejyonal blok.

Effects of PECS II (Pectoral Nerve) Block on Intraoperative Inhaled Anesthetic and Postoperative Analgesic Consumption in Patients Undergoing Breast Surgery

ABSTRACT

We aimed to evaluate the preoperative and postoperative application of PECS II (Pectoral Nerve) block in breast surgery, intraoperative anesthetic consumption, postoperative analgesic requirement and frequency of complications. A retrospective review of the anesthesia records of 75 patients who underwent breast surgery and analysis of the data was performed. The patients whose data were obtained were categorized into three groups. Group I (n25: control group with general anesthesia), Group II (n25: preoperative PECS II block and general anesthesia) and Group III (n25: postoperative PECS II block and general anesthesia). After analysis of the data, it was found that intraoperative desflurane MAC (minimum alveolar concentration) values were significantly lower in patients who underwent preoperative PECS II block compared to the other groups. Significant decreases in postoperative analgesic consumption and pain scores (early period, postoperative 0, 2, 4 and 8 hours) were observed in the study groups who underwent intraoperative and postoperative PECS II block compared to the control group. The first postoperative analgesic administration time was significantly later in the preoperative PECS II block group than in the general anesthesia only and postoperative PECS II block groups. The time to first postoperative analgesic administration was similar in the general anesthesia only and postoperative PECS II block groups. Adding PECS II block to general anesthesia preoperatively or postoperatively in patients undergoing breast surgery provides postoperative analgesia with less pain. The most important advantage of preoperative application of PECS II block is to reduce intraoperative anesthetic consumption.

Keywords: Pectoral nerve block. Postoperative analgesia. Breast surgery. Regional block.

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Dr. Mustafa Naci BALICA
Bilkent Şehir Hastanesi, Üniversiteler, 1604. Cd. No: 9, 06800 Çankaya/Ankara
Tel.: 0506 691 23 84
E-posta: nbalica23@gmail.com

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Yazarların Orcid Bilgileri
Mustafa Naci BALICA: 0000-0002-7712-3872
Duygu KARAKÖSE ÇALIŞKAN: 0000-0003-0025-1478
Selcan YEREBAKAN AKESEN: 0000-0002-9518-541X
Yunus Gürkan TÜRKER: 0000-0002-3019-581X

Akut postoperatif ağrı, kronik postmastektomi ağrısının gelişimi için temel bir risk faktörüdür; kadınların %40'ı meme kanseri cerrahisinden sonra ciddi akut postoperatif ağrı yaşarken %50'si bozulmuş yaşam kalitesiyle beraber kronik postmastektomi ağrısı çekerler[1,2]. Meme cerrahisinde analjezi sağlamak için torakal epidural ve paravertebral bloklar altın standart teknikler haline gelmiştir, ancak anestezistler bu prosedürleri teknik olarak uygulamakta rahat değildir. Bu teknikler için bir alternatif olarak pektoral sinir blokları (PECS I ve PECS II) geliştirilmiştir.

PECS blok tip I, pektoralis major (PMm) ve minor (Pmm) kasları arasında interfasyal düzlemde lateral ve mediyal pektoral sinirleri bloke eden kolay, güvenilir ve yüzeyel bir bloktur. PECS I blok analjezi sağlamak amacıyla farklı meme operasyonları için kullanılabilir, ancak temel olarak meme genişleticilerin ve subpektoral protezlerin yerleştirilmesi için kullanılmaktadır. Diğer potansiyel endikasyonlar; travmatik göğüs yaralanmaları, iyatrojenik pektoral kas disseksiyonları, pacemaker'lar, port kateterler ve göğüs drenlerinin takılmasıdır[3,4].

Blanco ve ark. ilk kez 2011'de pektoralis minor (PECS I) bloğunu uygulamıştır. Yazarlar Meme rekonstrüksiyon cerrahisinin bir parçası olarak meme implantı yerleştirilen 50 hasta üzerinde çalışmışlardır[5]. Daha sonra aynı çalışmacılar 2012 yılında PECS II blok olarak adlandırılan modifiye pektoralis sinir bloğu tekniğini kullanmıştır. Bu yeni teknik ile interkostobrakiyal sinir ve eş zamanlı olarak 3-6. interkostal sinirler, torasikus longus ve pektoral sinirlerin de bloke edilebildiği bildirilmiştir[5].

Meme cerrahisinde ağrı yönetiminde lokal anestezik infiltrasyonu, interkostal sinir bloğu, epidural blok ve paravertebral blok (PVB) gibi çeşitli rejyonel teknikler başarıyla kullanılmıştır[6-8]. PECS bloğun avantajlarını vurgulamak önemlidir. PECS blokta, paravertebral ve epidural bloklarla ilişkili sempatik blok yoktur, opioidler genellikle gerekmez, daha az tümör rekürrensi olur, basit ve hızlı etkili bir bloktur[5]. Rejyonal blokların kullanımı ile daha az riskle etkin analjezi sağlanmış olup, bu sayede hem yüksek riskli girişimsel işlemlerin yerini almıştır hem de sağladığı etkin analjezi ile tüketilen anestezik ve opioid analjeziklerin azalmasına neden olmuştur.

Bu çalışmada Modifiye Radikal Mastektomi (MRM: meme dokusunun alınması + aksiller lenf nodu diseksiyonu) uygulanan PECS II (Pektoral Sinir) bloğun preoperatif ve postoperatif uygulanmasının, intraoperatif anestezik kullanım miktarına etkisi ve postoperatif dönemde kullanılan analjezik ilaçların türü, miktarı ve kullanıma başlama süreleri ile opioid ihtiyacına bağlı gelişebilecek komplikasyonları karşılaştırmayı ve hastane yatış sürelerini belirlemeyi amaçladık.

Gereç ve Yöntem

Çalışmamız, 24 Kasım 2015 tarih ve 2015-20/28 numaralı Uludağ Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu kararı ile onay alındıktan sonra başlamıştır. Haziran 2015-Kasım 2015 tarihleri arasında 18-85 yaş arası, meme kanseri nedeniyle MRM yapılan, ASA I-II olan 75 kadın hasta çalışmaya dahil edildi ve retrospektif olarak incelendi. Hastaların tamamına aynı cerrahi prosedür uygulandı. Hastalara uygulanan MRM cerrahi prosedüründe meme dokusu alındıktan sonra aksiller lenf nodu diseksiyonu yapıldı ve bütün hastalara uygulandı. Aynı cerrahi ekip tarafından yapılan operasyonlar sonrasında hastane yatış takiplerini ve taburculuk kriterlerini cerrahi ekip belirlemiştir. Hastalar Üç grup şeklinde kategorize edildi: Grup I (n:25) sadece genel anestezi uygulanan kontrol grubu, grup II (n:25) genel anestezi + preoperatif PECS II blok ve grup III (n:25) genel anestezi + postoperatif PECS II blok uygulanan hastalar.

İntraoperatif ve Postoperatif Anestezi Yönetimi:

Hastalara, ameliyat odasına alındıktan sonra EKG, pulse oksimetre ve noninvaziv tansiyon arteriyel monitorizasyonu uygulandı. Tüm hastalara ameliyat odasına alındıktan sonra premedikasyon amaçlı 1 mg midazolam intravenöz (IV) verildi. Hastaların anestezi indüksiyonunda; 1-2 mg/kg propofol ve 2-3 mcg/kg fentanil IV verildi. Hava yolu laringeal maske ile sağlandı. Anestezi idamesinde inhalasyon anesteziği olarak %50 hava ile karışık %4-6 volümde desfluran kullanıldı. İntraoperatif kan basıncı ve kalp atım hızında %20 artış olması halinde 50 mcg fentanil IV uygulandı. Anestezi idamesinde nöromusküler bloker ajan kullanılmadı. Hastalara ekstübasyondan önce intraoperatif 1 gr parasetamol IV infüzyon uygulandı.

Hastaların yaş, boy, vücut ağırlığı, VKİ (Vücut Kitle İndeksi), cerrahi süre ve ASA (American Society of Anestesiology, fiziksel risk klasifikasyonu) değerleri kaydedildi. İntraoperatif anestezi kayıt formlarından olguların 15, 30, 45 ve 60. dakikalardaki desfluran MAC (minimum alveolar konsantrasyon) değerleri ile birlikte kan basıncı ve kalp atım hızı değerleri kaydedildi. Postoperatif olarak ilk aneljezik uygulama zamanları, hangi ajan kullanıldığı ve dozları kaydedildi. Klinikte yapılan Vizüel Analog Skala (VAS; 0: ağrı yok, 10: en şiddetli ağrı) takiplerindeki 2, 4, 8, 12. ve 24. saat değerleri kaydedildi. Hastaların postoperatif dönemde ayılma ünitesinde ve servis takiplerinde daha sık ölçümü yapılmasına rağmen biz çalışmamızda hemşire gözlem formlarındaki 2, 4, 8, 12 ve 24. saat VAS değerlerini kayıt altına aldık. Hastaların yatış süreleri boyunca gelişen komplikasyonlar ve taburculuk süreleri kaydedildi.

PECS II blok uygulaması:

Preoperatif olarak yapılan PECS II blok, anestezi indüksiyonu ve hava yolu güvenliği sağlandıktan sonra ultrasound (US) yardımıyla uygulandı. PECS II blok hasta supin pozisyonda cerrahi uygulanacak aynı taraflı omuzunu abduksiyon pozisyonunda tutarken, 8-12 MHz lineer prob kullanılarak US uyumlu 50 mm iğneyle (Stimuplex Ultra, 22 G Braun) gerçekleştirildi. Cilt dezenfekte edildikten sonra US probu ilk olarak infraklavikuler bölgeye saggital düzlemde yerleştirildi. Daha sonra aksiller arter ve ven US ile belirlendi. US probu kaudale doğru kaydırıldı ve torakoakromiyal arter görüldükten sonra prob rotasyon ile horizontal pozisyona getirildi. Fasyal planda pektoral kaslar arasına US eşliğinde probun lateral kenarından in plane teknikle girilerek 10 ml %0,25'lik bupivakain enjekte edildi. Daha sonra, US probu aksillaya doğru serratus anterior kasının görüntülendiği 2, 3 ve 4. kostalar üzerine ilerletildi. Son olarak pektoralis minör ve serratus anterior kaslarının arasına 20 ml %0,25' lik bupivakain enjekte edildi. Postoperatif olarak uyguladığımız PECS II blok ise cerrahi işlem bittikten sonra hasta ekstübe olmadan önce uygulandı. Aynı teknik kullanılarak blok sağlandı.

İstatistiksel yöntem:

Verilerin tanımlayıcı istatistiklerinde, ortalama ± standart sapma, median (minimum-maksimum), frekans ve/veya % oran değerleri kullanılmıştır. Değişkenlerin dağılımı Kolmogorov Simirnov test ile ölçüldü. Nicel verilerin analizinde ANOVA, Kruskal-Wallis ve Mann-Whitney U test kullanıldı. Nitel verilerin analizinde ki-kare test, ki-kare test koşulları sağlanmadığında Fischer test kullanıldı. Analizlerde SPSS 22.0 programı kullanılmıştır.

Bulgular

Grup I, Grup II ve Grup III de olguların demografik verileri (yaş, boy, ağırlık, VKİ, cerrahi süre ve ASA değerleri) Tablo I'de sunulmuştur. Gruplar demografik veriler açısından benzer bulunmuştur ($p > 0,05$) (Tablo I).

İntraoperatif tüm ölçüm zamanlarında desfluran için MAC değerleri Tablo II'de sunulmuştur. Grup II'de intraoperatif desfluran MAC değerleri, Grup I ve Grup III'den anlamlı olarak daha düşük bulunmuştur ($p < 0,05$) (Tablo II). Grup I ve Grup III'de intraoperatif desfluran için MAC değerleri benzer bulunmuştur ($p > 0,05$) (Tablo II).

Tablo I. Olguların demografik verileri

		Grup I (Kontrol, n=25)	Grup II (Preoperatif PECS, n=25)	Grup III (Postoperatif PECS, n=25)	P
Yaş (yıl)	Ort±ss	56,6 ± 13,8	51,5 ± 14,3	50,0 ± 14,1	0,227
	Median Min-Maks	(58 37 - 84)	(49 25 - 80)	(50 27 - 77)	
Boy (cm)	Ort±ss	157,5 ± 7,3	158,4 ± 5,3	158,9 ± 4,3	0,687
	Median Min-Maks	(157 138 - 176)	(159 148 - 168)	(160 150 - 167)	
Ağırlık (kg)	Ort±ss	72,2 ± 12,5	74,2 ± 15,7	70,2 ± 13,4	0,600
	Median Min-Maks	(71 45 - 93)	(72 52 - 113)	(69 50 - 100)	
VKİ (kg/m²)	Ort±ss	29,1 ± 5,1	29,6 ± 5,8	27,9 ± 5,4	0,528
	Median Min-Maks	(29 19 - 41)	(28 21 - 43)	(27 19 - 40)	
Cerrahi Süre (dk)	Ort±ss	75,2 ± 24,6	80,6 ± 22,7	77,8 ± 17,7	0,684
	Median Min-Maks	(75 30 - 120)	(70 50 - 120)	(80 50 - 100)	
ASA I	n (%)	11 (44%)	9 (%36)	8 (%32)	0,372
ASA II	n (%)	14 (%56)	16 (%64)	17 (%68)	0,797

*p<0,05 anlamlı fark var, p>0,05 anlamlı fark yok; ANOVA, KruskallWallis test – ASA:Kikare testi
Ort: Ortalama, SS: Standart Sapma, Min: Minimum, Maks: maksimum, VKİ: Vücut Kitle İndeksi, ASA: American Society of Anestesiology (Amerikan Anestezi Derneği)

Tablo II. Desfluran MAC değerlerinin gruplara göre değişimi

		Grup I (Kontrol, n=25)	Grup II (Preoperatif PECS, n=25)	Grup III (Postoperatif PECS, n=25)	P
İntraoperatif 15. dakika MAC	Ort±ss	1,0 ± 0,1	0,8 ± 0,1	0,9 ± 0,1	**0,000 ***
	Median Min-Maks	(1,0 0,6 –1,0)	(0,8 0,5 – 1,0)	(1,0 0,5 – 1,0)	
İntraoperatif 30. dakika MAC	Ort±ss	0,9 ± 0,2	0,7 ± 0,1	0,9 ± 0,1	**0,000 ***
	Median Min-Maks	(1,0 0,4 –1,0)	(0,7 0,6 – 0,9)	(1,0 0,4 – 1,0)	
İntraoperatif 45. dakika MAC	Ort±ss	0,9 ± 0,2	0,7 ± 0,2	0,9 ± 0,2	**0,001 ***
	Median Min-Maks	(1,0 0,4 –1,0)	(0,7 0,5 – 0,9)	(1,0 0,3 – 1,0)	
İntraoperatif 60. dakika MAC	Ort±ss	0,9 ± 0,2	0,7 ± 0,1	0,9 ± 0,2	**0,000 ***
	Median Min-Maks	(1,0 0,5 –1,0)	(0,65 0,5 – 0,8)	(1,0 0,3 – 1,0)	
İntraoperatif Ortalama MAC	Ort±ss	0,9 ± 0,1	0,7 ± 0,1	0,9 ± 0,1	**0,000 ***
	Median Min-Maks	(1,0 0,5 –1,0)	(0,725 0,5 – 0,9)	(1,0 0,4 – 1,0)	

*p<0,05 anlamlı fark var, p>0,05 anlamlı fark yok; ANOVA, Kruskall Wallis test
MAC: Minimum Alveolar Concentration (Minimum Alveolar Konsantrasyon), Ort: Ortalama, SS: Standart Sapma, Min: Minimum, Maks: Maksimum

Hastaların intraoperatif ortalama arter basınçları (OAB) Tablo III'de sunulmuştur. Gruplar arasında intraoperatif OAB açısından istatiksel anlamlı bir fark gözlenmemiştir ($p > 0,05$) (Tablo III).

Tablo III. İntraoperatif ortalama arter basınçlarının gruplara göre değişimi

		Grup I (Kontrol, n=25)	Grup II (Preoperatif PECS, n=25)	Grup III (Postoperatif PECS, n=25)	P
Preoperatif Ortalama Arter Basıncı (mmHg)	Ort±ss	87,4 ± 12,1	91,2 ± 12,0	90,2 ± 13,5	0,543
	Median Min-Maks	(91 67 - 108)	(92 68 - 124)	(90 68 - 121)	
İntraoperatif 15. dakika (mmHg)	Ort±ss	67,3 ± 13,1	65,0 ± 11,5	67,4 ± 13,6	0,755
	Median Min-Maks	(65 48 - 100)	(60 50 - 100)	(60 40 - 95)	
İntraoperatif 30. dakika (mmHg)	Ort±ss	65,0 ± 14,6	60,6 ± 7,9	67,0 ± 11,3	0,144
	Median Min-Maks	(60 45 - 110)	(60 50 - 80)	(70 40 - 80)	
İntraoperatif 45. dakika (mmHg)	Ort±ss	63,8 ± 11,2	61,0 ± 6,1	65,6 ± 10,2	0,228
	Median Min-Maks	(60 50 - 100)	(60 55 - 80)	(65 45 - 80)	
İntraoperatif 60. dakika (mmHg)	Ort±ss	64,6 ± 10,6	62,3 ± 6,3	63,6 ± 9,8	0,670
	Median Min-Maks	(61 50 - 90)	(60 50 - 80)	(60 45 - 80)	
İntraoperatif Ortalama (mmHg)	Ort±ss	65,4 ± 11,2	62,3 ± 6,9	66,0 ± 10,4	0,355
	Median Min-Maks	(63 51 - 100)	(60 53 - 81)	(66 43 - 83)	

Ort: Ortalama, SS: Standart Sapma, Min: Minimum, Maks: Maksimum

İntraoperatif kalp atım hızları (KAH) Tablo IV'de sunulmuştur. Gruplar arasında intraoperatif KAH açısından 30. dakika değerleri grup II'de anlamlı düşük çıkmıştır ($p < 0,05$) (Tablo IV).

Tablo IV. İntraoperatif kalp atım hızının gruplara göre değişimi

		Grup I (Kontrol, n=25)	Grup II (Preoperatif PECS, n=25)	Grup III (Postoperatif PECS, n=25)	P
Preoperatif Nabız (vuru/dk)	Ort±ss	79,7 ± 10,8	83,2 ± 15,7	80,3 ± 14,9	0,640
	Median Min-Maks	(78 65 - 105)	(85 56 - 122)	(79 52 - 108)	
İntraoperatif 15. Dakika (vuru/dk)	Ort±ss	77,0 ± 11,6	73,2 ± 10,1	80,0 ± 13,8	0,138
	Median Min-Maks	(75 50 - 110)	(75 60 - 95)	(75 55 - 120)	
İntraoperatif 30. Dakika (vuru/dk)	Ort±ss	78,4 ± 14,7	69,4 ± 8,2	75,8 ± 13,0	**0,034 ***
	Median Min-Maks	(75 50 - 105)	(70 60 - 85)	(75 50 - 105)	
İntraoperatif 45. Dakika (vuru/dk)	Ort±ss	73,0 ± 14,2	68,8 ± 7,8	72,4 ± 12,2	0,395
	Median Min-Maks	(70 50 - 100)	(70 60 - 90)	(70 50 - 95)	
İntraoperatif 60. Dakika (vuru/dk)	Ort±ss	73,0 ± 12,3	68,1 ± 7,6	69,5 ± 10,9	0,294
	Median Min-Maks	(75 50 - 95)	(70 60 - 85)	(70 50 - 90)	
İntraoperatif Ortalama (vuru/dk)	Ort±ss	76,3 ± 12,7	70,0 ± 7,4	74,7 ± 11,3	0,104
	Median Min-Maks	(75 50 - 98)	(71 60 - 89)	(74 55 - 98)	

*p<0,05 anlamlı fark var, p>0,05 anlamlı fark yok; ANOVA, KruskallWallis test
Ort: Ortalama, SS: Standart Sapma, Min: Minimum, Maks: Maksimum

Grup II'de postoperatif ilk analjezik uygulama zamanı, grup I ve grup III'den anlamlı olarak daha geç bulunmuştur ($p < 0,05$) (Tablo V). Grup I ve Grup III'de postoperatif ilk analjezik uygulama zamanı benzer bulunmuştur ($p > 0,05$) (Tablo V).

Tablo V. Postoperatif ilk analjezik uygulama zamanının gruplar arasında değişimi

		Grup I (Kontrol, n=25)	Grup II (Preoperatif PECS, n=25)	Grup III (Postoperatif PECS, n=25)	P
Postoperatif İlk Analjezik Uygulama Zamanı (Saat)	Ort±ss	1,3 ± 0,9	2,3 ± ,.8	1,5 ± 0,7	**0,000***
	Median Min-Maks	(1,0 1,0 – 4,0)	(2,0 1,0 – 3,0)	(1,0 1,0 – 3,0)	

*p<0,05 anlamlı fark var, p>0,05 anlamlı fark yok; ANOVA, KruskallWallis test
Ort: Ortalama, SS: Standart Sapma, Min: Minimum, Maks: Maksimum

Postoperatif ağrı skorları (VAS 0-10) Tablo VI'da sunulmuştur. Grup I'de postoperatif 2, 4. ve 8.saatte ölçülen VAS değerleri Grup II ve Grup III'den anlamlı olarak daha yüksek bulunmuştur ($p<0,05$) (Tablo VI). Grup II ve Grup III'de 2, 4 ve 8. saatte ölçülen VAS değerleri benzer bulunmuştur (Tablo VI). Grup III'de postoperatif VAS değerleri nispeten düşük olsada analjezik ihtiyacı erken dönemde olmuştur. Grup I, Grup II ve Grup III'de olguların 12 ve 24.sa'da ölçülen VAS skorları ise hasta sayısı yetersiz olduğu için istatistiksel olarak ölçülememiştir. (Tablo VI).

Tablo VI. Postoperatif VAS değerleri

		Grup I (Kontrol, n=25)	Grup II (Preoperatif PECS, n=25)	Grup III (Postoperatif PECS, n=25)	P
VAS (0-10) - 2. Saat	Ort±ss	2,8 ± 1,7	0,6 ± ,.0	1,4 ± 1,7	**0,000**
	Median Min-Maks	(3 0,0 – 5,0)	(0 0,0 – 3,0)	(0 0,0 – 4,0)	
VAS (0-10) - 4. Saat	Ort±ss	1,7 ± 1,4	0,0 ± 0,2	0,2 ± 0,7	**0,000**
	Median Min-Maks	(2 0,0 – 4,0)	(0 0,0 – 1,0)	(0 0,0 – 3,0)	
VAS (0-10) - 8. Saat	Ort±ss	0,8 ± 1,1	0,0 ± 0,0	0,0 ± ,.0	**0,000**
	Median Min-Maks	(0 0,0 – 4,0)	(0 0,0 – 0,0)	(0 0,0 – 0,0)	
VAS (0-10) - 12. Saat	Ort±ss	0,0 ± 0,2	0,0 ± 0,0	0,0 ± 0,0	x
	Median Min-Maks	(0 0,0 – 1,0)	(0 0,0 – 0,0)	(0 0,0 – 0,0)	
VAS (0-10) - 24. Saat	Ort±ss	0,0 ± 0,0	0,0 ± 0,0	0,0 ± 0,0	x
	Median Min-Maks	(0 0,0 – 0,0)	(0 0,0 – 0,0)	(0 0,0 – 0,0)	
VAS (0-10) Ortalama	Ort±ss	1,36 ± 0,88	0,12 ± 0,24	0,32 ± 0,48	**0,000**
	Median Min-Maks	(0 0,0 - 3)	(0 0,0 - 1)	(0 0,0 - 2)	

*p<0,05 anlamlı fark var, p>0,05 anlamlı fark yok; ANOVA, KruskallWallis test
VAS: Vizüel Analog Skala, Ort: Ortalama, SS: Standart Sapma, Min: Minimum, Maks: Maksimum

Postoperatif analjezik kullanımı ve ilaç çeşitleri Tablo VII'de sunulmuştur. Grup I'de analjezik ajan gereksinimi olan hasta sayısı Grup II ve Grup III'den anlamlı olarak daha fazlaydı ($p < 0,05$) (Tablo VII). Grup I'de hastalara postoperatif dönemde birden fazla analjezik ilaç kullandı. Grup II ve Grup III'de postoperatif analjezik ajan gereksinimi benzer bulunmuştur (Tablo VII). Postoperatif dönemde analjezik olarak kullanılan meperidin, PECS blok

uygulanan hastalarda ihtiyaç duyulmadığı için kullanılmamıştır (Tablo VII).

Tablo VII. Postoperatif analjezik kullanımı ve analjezik ajan dağılımı

		Grup I (Kontrol, n=25)	Grup II (Preoperatif PECS, n=25)	Grup III (Postoperatif PECS, n=25)	P
Analjezik alan	Almadı	n:0 (0,0%)	n:18 (72,0%)	n:14 (56,0%)	0,000*
	Aldı	n:25 (100,0%)	n:7 (28,0%)	n:11 (44,0%)	
Parasetamol		n:25 (100,0%)	n:4 (16,0%)	n:11 (44,0%)	
Tenoksikam		n:11 (44,0%)	n:3 (12,0%)	n:0 (0,0%)	0,000*
Deksketoprofen		n:6 (24,0%)	n:0 (0,0%)	n:0 (0,0%)	
Meperidin		n:11 (44,0%)	n:0 (0,0%)	n:0 (0,0%)	

*p<0,05 anlamlı fark var, p>0,05 anlamlı fark yok; Kikare testi

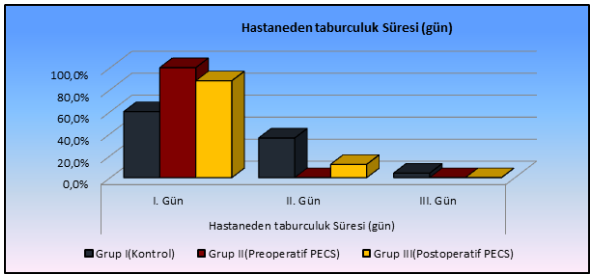
Grup I'de opioide bağlı olarak bulantı ve kusma sıklığı Grup II ve Grup III'den anlamlı olarak daha yüksek bulunmuştur (p < 0,05) (Tablo VIII). Grup II ve Grup III'de bulantı, kusma ve oksijen desaturasyonu gibi postoperatif opioid kullanımına bağlı yan etkiler, opioid gereksinimi olmadığı için hiçbir hastada gelişmemiştir (Tablo VIII). Grup I'de ise bir hastada oksijen desaturasyonu gelişmiştir.

Tablo VIII. Postoperatif opioidlere bağlı yan etkiler

Komplikasyonlar	Grup I (Kontrol, n=25)	Grup II (Preoperatif PECS, n=25)	Grup III (Postoperatif PECS, n=25)	P
Bulantı	n:9 (36,0%)	n:0 (0,0%)	n:0 (0,0%)	**0,006***
Kusma	n:9 (36,0%)	n:0 (0,0%)	n:0 (0,0%)	**0,006***
02 desaturasyonu	n:1 (4,0%)	n:0 (0,0%)	n:1 (4,0%)	0,807

*p<0,05 anlamlı fark var, p>0,05 anlamlı fark yok; Kikare testi

2 gün ve üstü sürede hastaneden taburcu olan hasta sayıları; Grup I için 10 hasta (% 40), Grup II için 0 hasta (% 0) ve Grup III için ise 3 hastaydı (% 12). Grup I'de, Grup II ve Grup III'e göre 2 gün ve üstü hastaneden taburculuk süreleri olan hasta sayısı anlamlı olarak daha fazla bulunmuştur (p < 0,05) (Şekil 1). Grup II ve Grup III'de 2 gün ve üstü hastaneden taburculuk süreleri benzer olarak bulunmuştur (p > 0,05) (Şekil 1).



Şekil 1:
Olguların hastane taburculuk süreleri

Tartışma ve Sonuç

Bu çalışmada preoperatif uygulanan PECS II blok intraoperatif desfluran MAC değerlerini düşürdüğü için diğer gruplara göre daha avantajlı bulundu. Ayrıca PECS II blok uygulanan meme cerrahisi hastalarında, kontrol grubuna göre erken dönem postoperatif ağrı skorlarının düşük olduğu görüldü. Postoperatif dönemdeki analjezik gereksinimi olan hasta sayısı Grup I'de daha fazla bulundu. PECS II Blok uygulanan hastalara opioid analjezik kullanma gereksinimi olmadı. 2 gün ve üstü hastanede yatış yapan hasta sayısı Grup I'de daha fazla bulundu.

Ameliyat sonrası meme kanseri nüksüne üç perioperatif faktör neden olmaktadır. Birincisi; cerrahi operasyon, hücre aracılı bağışıklığı inhibe eder, proanjiyojenik faktör konsantrasyonunu yükseltir, anti-anjiyojenik faktör konsantrasyonunu azaltır ve malign dokuya bağlı büyüme faktörlerinin salınımını teşvik eder[9]. İkinci olarak; inhaler anesteziklerin kullanımı bağışıklık hücrelerinin işlevini etkiler ve doğrudan kanser hücresinin çoğalmasını artırır[10]. Üçüncü olarak; opioid analjezikler hem humoral hem de hücresel bağışıklık fonksiyonunu baskılayacak, anjiyogenezi teşvik edecek ve meme kanserinin büyümesini artıracaktır[11]. Bu çalışmada preoperatif dönemde PECS blok uygulan grupta intraoperatif dönemde kullanılan desfluran MAC değeri diğer gruplara göre daha düşük bulundu. İnhaler anesteziklerin kanser rekürrensine neden olduğunu düşünürsek uygulanan bu bloğun inhaler anestezik tüketimini azaltması nedeniyle rekürrensin önlenmesinde faydalı olacağı düşünülmektedir. Yine aynı şekilde yapılan PECS bloklar, postoperatif dönemde opioid kullanımında azalmaya neden olduğu için kanser rekürrensinin azalmasında olumlu katkı sağlayacağı düşünülmektedir.

48 hasta ile yapılan bir çalışmada 24 hastaya opioid ağırlıklı genel anestezi, diğer 24 hastaya PECS bloğun yapıldığı opioid analjezik ilacın kullanılmadığı genel anestezi uygulanmıştır. İntraoperatif hemodinami her iki grupta da benzer olarak bulunmuştur[12]. Çalışmamızda hastaların intraoperatif dönemdeki ortalama arter basıncı ölçümleri arasında fark bulunmadı. Grup I ve Grup III de inhaler anestezik miktarının fazla olması nedeniyle ortalama arter basınçları Grup II ile benzer olarak bulunduğu düşünülmektedir. Yine aynı şekilde intraoperatif dönemdeki ortalama nabız değerleri gruplar arasında benzer olarak bulundu. Grup I'de 30. dakika nabız değerleri düşük olarak bulunmasını erken dönemde inhaler anestezik miktarının fazla olması ve takiplerde inhaler anestezik miktarının azaltılmasıyla gruplar arasında benzer değerler bulunduğu görüldü. Anestezi idamesinde Grup II'de inhaler anestezik miktarının az olmasına rağmen gruplar arasında ortalama arter basınçları ve nabız değerlerinde anlamlı farklılık

bulunmadı. Preoperatif dönemde uygulanan PECS bloğun anestezi idamesinde ve hastaların vital bulgularının stabilizasyonunda olumlu etkilerinin olduğu görüldü.

PECS II bloğuna karşı analjezik yapılan ve 290 hastayı kapsayan dört çalışmada ilk analjezik talebine kadar geçen süre ölçülmüştür. Bu süre PECS II bloğu uygulanan hastalarda önemli ölçüde uzamıştır[7,13-15]. Bu çalışmada Grup II'de postoperatif dönemde ilk analjezik uygulanma zamanı anlamlı olarak daha geç bulundu. Preoperatif dönemde yapılan PECS II blok etkinliğinin yeterli düzeye ulaşması nedeniyle postoperatif erken dönemde analjezik gereksinimi daha az olarak bulundu. Hastaların servis takiplerinde Grup III'de uygulanan bloğun etkinliği tam oluşana kadar geçen süre içinde intravenöz analjezik uygulandığı düşünülmektedir.

Postoperatif ilk 24 saat boyunca VAS ölçeği kullanılarak ağrı indeksi, opioid tüketimi değerlendirilen bir çalışmada ameliyat sonrası 24 saatlik dönemde toplanan ağrı verileri PECS blok ve PECS blok olmayan gruplar arasında karşılaştırılmıştır. PECS grubunda hastaların %50'sinde ameliyattan 24 saat sonra ağrı olmazken, kontrol grubunda bu oran %42,86'dır. Ameliyat sonrası ağrısı olanların çoğu hafif ağrı grubunda (VAS 1'den 3'e kadar) sınıflandırılmış olup, bu oran PECS grubunda %42,50 ve kontrol grubunda %40,48 olarak bulunmuş (p=0,280)[16]. Bir meta-analizde, PECS bloğu kullanımı VAS ağrı skorlarını postoperatif ayılma ünitesinde 1,90 puan ve postoperatif 1. saatte 2,17 puan azaltmıştır. Ameliyat sonrası 24. saatte VAS ağrı skorlarındaki azalma 1,01 puana düşse de fark anlamlı kalmıştır[17]. Bizim çalışmamızda sadece genel anestezi uygulanan kontrol grubunda postoperatif 2, 4 ve 8. saat VAS değerleri anlamlı olarak daha yüksek bulundu. Gruplar arasında VAS değerleri açısından 12. saat ve sonrasında farklılık görülmedi. Postoperatif hastaların servis takiplerinde VAS değeri 3 üstü olması durumunda VAS değerlerinin daha fazla artışına izin verilmeden rutin olarak analjezikler uygulanmıştır. Postoperatif VAS değerleri Grup III'de Grup I'den düşük olmasına rağmen Grup I ve Grup III'ün ilk analjezik uygulama zamanları benzer olarak bulundu. Bunun nedeninin Grup I'e ilk uygulanan analjeziğin opioid türevi, Grup III'e non-opioid türevi ilaç uygulanması olduğu düşünülmüştür.

Birçok çalışmada PECS blok uygulanan grupta opioid kullanımında azalma görülmüştür. Bu çalışmalarda PECS II bloğu uygulanan veya uygulanmayan hastalarda ameliyattan sonraki ilk 24 saatte opioid tüketimi karşılaştırılmıştır. PECS II bloğu uygulanan hastalarda ameliyattan sonraki ilk 24 saat içinde kontrol gruplarına kıyasla önemli ölçüde daha az opioid tüketilmiştir[7,13,14,18-20]. Wahba ve ark. postoperatif ilk 24 saatteki morfin ihtiyacının PECS grubunda, paravertebral blok (PVB) grubuna kıyasla daha düşük dozda olduğunu bulmuştur. Morfin ihtiyacına kadar geçen süre PECS grupta PVB gruba kıyasla daha uzun olarak saptanmıştır. İstirahat esnasındaki ağrı sayısal değerlendirme skoru (NRS) PECS grupta PVB gruba kıyasla 1, 6 ve 12. saatte daha düşük iken, 18. ve 24. saatte PVB grubunda PECS gruba kıyasla daha düşük bulunmuştur[21]. Opioid tüketiminde ve hasta tarafından bildirilen ağrı skorlarında istatistiksel olarak anlamlı düşüşlerin olduğu çalışmalar daha çok bulunmaktadır[7,9,19,22-31]. Postoperatif dönemde opioid tüketiminde fark görülmeyen[32] çalışmalar bulunduğu gibi, opioid tüketiminde artış görülen[33] çalışmada bulunmaktadır. Çalışmamızda Grup I'de bütün hastalarda postoperatif dönemde analjezik gereksinimi olurken Grup II'de %28 oranında, Grup III'de %44 oranında analjezik gereksinimi oldu. Postoperatif dönemde uygulanan analjeziğin türünü serviste takip eden hekim belirlediği için Grup I'de analjezik olarak meperidin (%44), parasetamol (%100), tenoksikam (%44) ve deksketoprofen (%24) uygulanmıştır. Grup II'de parasetamol (%16) ve tenoksikam (%12) uygulanırken, Grup III'de sadece parasetamol (%44) uygulanmış. PECS blok uygulaması postoperatif dönemde analjezik gereksinimi azaltırken opioid gibi güçlü analjeziklerin gereksinimini ise ortadan kaldırdı.

Genel anestezi altında gerçekleştirilen meme cerrahilerinden sonra bulantı-kusma sıklığı dikkate alınması gereken bir komplikasyondur[34]. Nitröz oksit kullanımından kaçınılması ve propofol kullanılması bulantı ve kusmayı azaltacağı gibi PECS blok yapılan olgularda düşük opioid tüketimi bulantı ve kusmayı azaltan diğer bir etkendir[35,36]. Bashandy ve ark. çalışmasında postanestezi bakım ünitesinde bulantı, kusma ve sedasyon skorlarını değerlendirmiş, bulantı kusma ve sedasyon skorları PECS blok ve genel anestezi uyguladığı grupta tek başına genel anestezi uygulanan gruba göre daha düşük bulmuştur[7]. Yapılan çalışmalarda pektoral sinir bloğu uygulanan hastalarda ameliyat sonrası bulantı ve kusma insidansında istatistiksel olarak anlamlı bir düşüş bildirilmiştir[7,26-28,30]. Bazı çalışmalarda ameliyat sonrası bulantı ve kusma insidansında artış bildirilmişken[32], fark görülmeyen çalışmada bulunmaktadır[23]. Bu çalışmada PECS blok uygulanan olgularda postoperatif dönemde opioid gereksinimi olmadı. Opioid analjezik kullanımına bağlı bulantı kusma sık rastlanılan bir yan etkidir. Hastalarımızda opioid gereksinimi olmadığı için buna bağlı yan etkilerde görülmedi.

Karaca ve ark. yapmış olduğu bir çalışmada pektoral blok uygulanan grupta hastane kalış süreleri daha kısa olarak bulunmuştur[37]. Başka bir çalışmada da PECS blok ve genel anestezi uygulanan grupta tek başına genel anestezi uygulanan gruba kıyasla postanestezi bakım ünitesinde ve hastanede kalış süreleri daha kısa bulunmuştur[7]. Bizim çalışmamızda kontrol grubunda hastane kalış süreleri diğer gruplara göre daha uzun

bulunurken, preoperatif ve postoperatif uygulanan PECS blok sonrasında hastane kalış süreleri arasında farklılık bulunmamıştır. Postoperatif dönemde etkin analjezi sağlanan hastalarda, taburculuk sürelerinin daha kısa olduğu kanısındayız.

PECS bloğun erken dönem postoperatif ağrı skorlarını düşürdüğü görülmüştür. PECS blok aynı zamanda postoperatif opioid ve analjezik gereksinimini azaltıp, opioidlere bağlı bulantı, kusma gibi komplikasyonları azaltmıştır. Preoperatif uygulanan PECS blok, intraoperatif anestezik gereksinimini azaltması nedeniyle postoperatif PECS bloğa göre avantajlı bulunmuştur.

Çalışmamızın limitasyonları ise, hasta yaş aralığının geniş olması nedeniyle ağrı skorlarına etkili olması, postoperatif dönemde yapılan analjezik türlerinin standardize edilmemesi, postoperatif analjezik ajan gereksinimlerini belirlemede hasta kontrollü analjezi (HKA) kullanılmaması olarak değerlendirilebilir.

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ORIGINAL RESEARCH

Use of Eltrombopag in Patients with Chronic Idiopathic Thrombocytopenic Purpura: A Single Center Experience*

Emre HAFIZOĞLU[1], Vildan ÖZKOCAMAN[2], Fahir ÖZKALEMKAŞ[2]

[1] Afyonkarahisar State Hospital, Department of Medical Oncology, Afyonkarahisar, Türkiye.
[2] Bursa Uludağ University Faculty of Medicine, Department of Internal Medicine, Division of Hematology, Bursa, Türkiye.

ABSTRACT

This study aimed to evaluate the efficacy and safety of eltrombopag in the outpatient clinic of the Department of Hematology, Uludag University Faculty of Medicine. Treatment responses and demographic characteristics of 25 patients diagnosed with refractory chronic immune thrombocytopenia (ITP) and receiving eltrombopag between January 2011 and March 2014 were analyzed retrospectively. Both platelet ≥30,000/mm³ and ≥50,000/mm³ values were considered as responses. Prolonged response was defined as the maintenance of platelet 50,000/mm³ values for 12 weeks or longer without the need for any additional treatment, and sustained response was defined as the maintenance of platelet 50,000/mm³ and at least 2 times the baseline values without the need for additional treatment. Twenty-five patients were evaluated. Ten patients (40%) had an initial platelet value of <15,000/mm³, and 15 (60%) had ≥15,000/mm³. The baseline median platelet value increased from 15,700/mm³ to 30,000/mm³ at week 2 and to 51,000/mm³ at week 6, and this level was maintained throughout the 85-week observation period. Thirteen (52%) patients had a sustained response, with a median follow-up of 18 months. In the study, participants were grouped according to splenectomy status, platelet <15,000/mm³, and gender, and there was no statistically significant difference in response. Eltrombopag is an effective and well-tolerated therapeutic agent in patients with chronic ITP refractory to other therapies and at increased bleeding risk. Responsiveness is independent of splenectomy, concomitant therapy, or baseline platelet values.

Keywords: Chronic immune thrombocytopenia. Refractory disease. Treatment. Eltrombopag.

Kronik İdiyopatik Trombositopenik Purpura Tanılı Hastalarda Eltrombopag Kullanımı: Tek Merkez Deneyimi

ÖZET

Bu çalışmada, Bursa Uludağ Üniversitesi Tıp Fakültesi Hematoloji Bilim Dalı polikliniğine başvuran hastalarda eltrombopag tedavisinin etkinliği ve güvenilirliğini değerlendirmeyi amaçladık. Ocak 2011 ile Mart 2014 tarihleri arasında refrakter kronik immün trombositopeni (ITP) tanısı konan ve eltrombopag alan toplam 25 hastanın tedavi yanıtları ve demografik özellikleri retrospektif olarak analiz edildi. Hem trombosit ≥30.000/mm^3 hem de ≥50.000/mm^3 değerleri yanıt olarak kabul edilmiştir. Uzamış yanıt, trombosit 50.000/mm^3 değerlerinin herhangi bir ek tedaviye ihtiyaç duyulmadan 12 hafta veya daha uzun süre korunması ve sürekli yanıt, trombosit 50.000/mm^3 ve başlangıç değerlerinin en az 2 katının ek tedaviye ihtiyaç duyulmadan korunması olarak tanımlandı. Yirmi beş hasta değerlendirildi. Başlangıç median trombosit değerinin 15,700 /mm^3'den 2. haftada 30,000/mm^3'e, 6. haftada 51,000/mm^3'e yükseldiği ve 85 haftalık gözlem periyodu süresince bu düzeyin korunduğu görüldü. Hastaların 13'ünün (%52) devam eden yanıta sahip olduğu; median izlem sürelerinin 18 ay, eltrombopag kullanım sürelerinin ise 11 ay olduğu görüldü. Çalışmada katılımcılar splenektomi durumuna, trombosit <15,000/mm^3 olup olmamasına ve cinsiyete göre gruplandırıldı ve yanıt açısından istatistiksel olarak anlamlı fark olmadığı görüldü. İlaç genel olarak iyi tolere edildi. Eltrombopag, diğer tedavilere dirençli ve artmış kanama riski olan kronik ITP hastalarında etkili ve iyi tolere edilen bir terapötik ajandır. Çalışmamızın sonuçları, yanıt durumunun splenektomi, eşzamanlı tedavi alma veya başlangıç trombosit değerlerinden bağımsız olduğunu ortaya koymuştur.

Anahtar Kelimeler: Kronik immun trombositopeni. Refrakter hastalık. Tedavi. Eltrombopag.

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Dr. Emre HAFIZOĞLU
Afyonkarahisar State Hospital, Department of Medical Oncology, Afyonkarahisar, Türkiye
Phone: 0532 525 21 45
E-mail: emrehafizoglu@gmail.com

Authors' ORCID Information:
Emre HAFIZOĞLU: 0000-0001-6291-851X
Vildan OZKOCAMAN: 0000-0003-0014-7398
Fahir ÖZKALEMKAŞ: 0000-0001-9710-134X

Chronic immune thrombocytopenia (ITP) is characterized by increased platelet destruction and impaired production caused by autoantibodies directed against platelets and megakaryocytes.[1] The objective of treatment in chronic ITP is to elevate platelet levels and sustain them within a safe range to prevent bleeding; Moreover, improving health-related quality of life (HRQOL) is an important goal for most patients. The American Society of Hematology (ASH) recommends a platelet count of 30,000 to 50,000/mm³ for people who don't have any other risk factors so that they don't have intracerebral hemorrhage or major gastrointestinal bleeding, which are the worst complications associated with ITP.[2,3]

In adults with newly diagnosed ITP, platelet counts <30,000, and asymptomatic or minor mucocutaneous hemorrhage, the ASH guideline panel recommends corticosteroid therapy over follow-up. Additionally, it strongly advocates for follow-up in adults with newly diagnosed ITP, platelet counts of 30,000 or higher, and asymptomatic or minor mucocutaneous hemorrhage. The panel suggests that prednisone (0.5-2.0 mg/kg per day) or dexamethasone (40 mg per day for four days) be used as the initial corticosteroid.[2,3]

The ASH guideline panel recommends splenectomy, rituximab, or a thrombopoietin (TPO) receptor agonist (RA) for adults with ITP lasting ≥3 months who are corticosteroid-dependent or unresponsive to corticosteroids. Nevertheless, it suggests a TPO-RA (eltrombopag or romiplostim) rather than rituximab. The panel observed that there was no singular optimal second-line treatment for adult patients with ITP. The selection of treatment should be individualized based on the following factors: the duration of ITP, the frequency of bleeding episodes necessitating hospitalization, comorbidities, patient age, drug compliance, patient values and preferences, cost, and availability. Each of these therapies is an effective option. The choice of treatment should be decided together with the patient in line with patient expectations. Splenectomy should be postponed for a minimum of one year following diagnosis to account for the possibility of spontaneous remission within the first year, if feasible. Nevertheless, in cases where patients are not amenable to long-term drug therapy, splenectomy or rituximab may be considered a preferable alternative.[2,3]

Although the ASH clinical guidelines are the most prominent, other guidelines also inform the treatment of ITP. The following treatment options are included in these guidelines and are used in subsequent steps: fostamatinib, avatrombopag, intravenous immune-globulin (IVIg), azathioprine, cyclophosphamide, cyclosporine, danazol, dapsone, mycophenolate mofetil, and vinca alkaloids.[4-7]

Eltrombopag is a non-peptide TPO-R agonist that has been approved for use in patients who have demonstrated an inadequate response to at least one other form of treatment. The substance is ingested orally, and it has been demonstrated to increase platelet production by binding to the transmembrane domain of TPO-R. In vitro studies have shown that it does not compete with endogenous TPO, and it has been observed to induce proliferation and differentiation of progenitor cells in the megakaryocytic series. Following a period of up to six months of eltrombopag treatment, eighty percent of patients have shown that their platelet levels are ≥50,000/mm^3. Still, more research on the safety and effectiveness of ITP treatments is required since patients could be subjected to these treatments for years or perhaps longer.[8-11]

This study aimed to contribute to existing literature by evaluating the demographic features, therapeutic response, and side effect profile in refractory cases of chronic immune thrombocytopenia undergoing eltrombopag treatment.

Material and Method

A total of 25 patients diagnosed with chronic immune thrombocytopenia and using eltrombopag at the outpatient clinic of the Division of Hematology, Department of Internal Medicine, Bursa Uludag University Faculty of Medicine from January 2011 to March 2014 were included in the study.

The inclusion criteria were being older than 18 years, a diagnosis of ITP, previous use of methylprednisolone, a history of splenectomy, or the absence of splenectomy due to contraindications, and refractory disease. We excluded pregnant and breastfeeding patients, and patients with severe liver disease.

Treatment responses and demographic characteristics (e.g., age, gender, date of diagnosis, other treatments received, baseline platelet value, eltrombopag initiation date, treatment response status) were analyzed.

Both platelet ≥30,000/mm³ and platelet ≥50,000/mm³ values were considered as responses. Statistical analyses were performed according to both values. A prolonged response was defined as the continuous maintenance of platelet levels of 50,000/mm³ or more for 12 weeks or more without the need for additional treatment. A continuous (sustained) response was defined as the maintenance of platelet levels of 50,000/mm³ or more and at least twice the baseline levels without the need for further treatment.

The therapeutic objective of eltrombopag treatment was not to raise platelet levels to normal levels, but rather to maintain them at a level that prevents bleeding. The treatment was initiated with a daily dose of 50 mg of eltrombopag. Concomitant use of methylprednisolone with eltrombopag was not

permitted. Patients were evaluated at two-week intervals for the purpose of dose adjustment. After four weeks of treatment with 75 mg of eltrombopag, the drug was stopped if platelet levels did not rise to a level high enough to stop bleeding, to a clinically significant level.

The statistical analysis of the data was conducted utilizing the SPSS 22.0 statistical package program. The data from our study was subjected to descriptive statistics (mean, median, standard deviation) and frequency distributions. We examined the normality assumptions of continuous variables by implementing the Shapiro-Wilk test. For the purpose of comparison between two groups with non-normal data, the Mann-Whitney U test was employed. We analyzed categorical data using both Pearson's chi-square test and Fisher's exact chi-square test.

Results

The study included nine male patients (36%) and 16 female patients (64%), with a mean age of 41 years (range 20-61). The baseline platelet value was found to be less than 15,000/mm³ in 10 patients (40%) and greater than or equal to 15,000/mm³ in 15 patients (60%). The median platelet value at the time of diagnosis was calculated to be 15,700/mm³. The demographic characteristics of the patients are shown in Table I.

Table I. Demographic characteristics of the 25 patients

	Median (range) or n (%)
Median Age	41 (20-61)
Gender	
Female	16 (64)
Male	9 (36)
Initial Platelet Value	
< 15,000/mm³	10 (40)
≥ 15,000/mm³	15 (60)
Previous Treatments	
1	1 (4)
2	7 (28)
3	8 (32)
≥4	9 (36)
Splenectomy	
Yes	19 (76)
Previous Treatments	
Steroid	25 (100)
IVIg	21 (84)
Colchicine	15 (60)
Danazol	8 (32)
Azathioprine	3(12)
Vincristine	1 (4)
Rituximab	5 (20)

The median duration of eltrombopag treatment was six months (min: 1.5, max: 22), and the median follow-up period was nine months (min: 1.5, max: 22). The baseline median platelet value increased from 15,700/mm³ to 30,000/mm³ at week 2 and to 51,000/mm³ at week 6, and this level was maintained during the 85-week observation period (see Figure I).

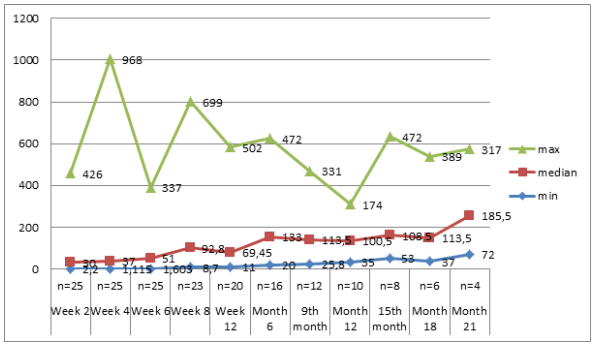

Figure 1.
Median, minimum, and maximum platelet values during eltrombopag treatment

In the course of the study, 21 (84%) patients with platelets ≥30,000/mm³ and 18 (72%) patients with platelets ≥50,000/mm³ were identified. The response status according to platelet ≥30,000/mm³ and ≥50,000/mm³ values during follow-up is shown in Figure II. The investigation revealed no statistically significant differences in response rates between the male and female demographics (see Table II).

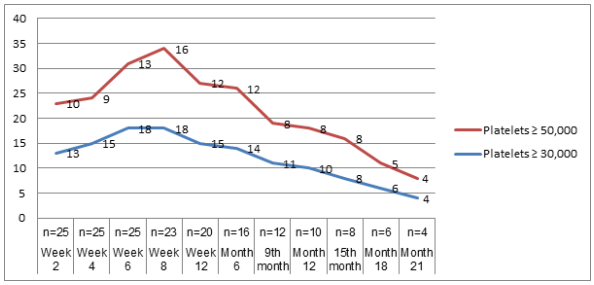

Figure 2.
Response status according to platelet ≥30,000/mm³ and ≥50,000/mm³ values

Table II. Response status by gender

	Woman	Male	P
Ongoing response	10	3	0.226
Platelets ≥ 30,000/mm³	13	8	1.0
Platelets ≥ 50,000/mm³	12	6	0.673

Thirteen patients (52%) demonstrated a continuous (sustained) response, with a median follow-up period of 18 months and a duration of eltrombopag use of 11 months. The number of patients exhibiting a prolonged response was five, who maintained reliable platelet values without the need for treatment during a median follow-up period of 10 months (3-19). This constituted 20% of all patients and 38.5% of those demonstrating prolonged responsiveness.

Tables III and IV show that platelet counts of 30,000/mm³ and above are thought to mean that there has been a response. The response status is shown based on the splenectomy status.

Table III. Response according to splenectomy status-1

		Platelets ≥ 30,000/mm³ at any time		
		No	There is	P
Splenectomy	No	2	4	0.234
	Yes	2	17	

Table IV. Response according to splenectomy status-2

		Platelets ≥ 50,000/mm³ at any time		
		No	There is	P
Splenectomy	No	2	4	1.0
	Yes	5	14	

If platelet counts of 30,000/mm³ and 50,000/mm³ are taken as signs of a response, Tables V and VI show the response status based on the initial platelet level.

Table V. Response according to baseline platelet value-1

	Platelets ≥ 30,000/ mm³ at any time		
	No	There is	P
Baseline platelets ≥15,000/mm³	1	14	0.267
<15,000/mm³	3	7	

Table VI. Response according to baseline platelet value-2

	Platelets ≥ 50,000/ mm³ at any time		
	No	There is	P
Baseline platelets ≥15,000/mm³	2	13	0.075
<15,000/mm³	5	5	

In the present study, subjects were categorized according to splenectomy status, platelet count (platelet count of <15,000/mm³), and gender. The study revealed no statistically significant differences in response.

The prevalence of adverse effects was as follows: headaches (60%), weakness (40%), diarrhea and nausea (16%), upper respiratory tract infection (12%), motor weakness (4%), pain (8%), epistaxis (8%), and dizziness (4%). Bleeding of grade 1 occurred in 28% of patients during treatment. The bleeding manifested as gingival bleeding. Thromboembolic events occurred in two patients (8%), presenting as deep vein thrombosis. In one of these patients, the platelet count exceeded 1,000,000 and was successfully managed with Hydrea. Severe bleeding (grade 3-4) during treatment and post-treatment bleeding were not observed. The occurrence of hepatobiliary events, cataracts, and malignancies was not observed in the study. The study found no significant differences in the side effect profile between the sexes.

Discussion and Conclusion

Eltrombopag is an oral, non-peptide, thrombopoietin receptor agonist that increases platelet production by stimulating megakaryocyte differentiation and proliferation. It was approved by the United States Food and Drug Administration (FDA) in 2008 for the treatment of chronic ITP and by the European Medicines Agency (EMA) in 2010 for the treatment of chronic ITP after splenectomy. In view of the fact that it does not have as long a history as other drugs used in the treatment of ITP, a significant number of international studies are currently underway to elucidate the clinical implications of the drug.

In our study conducted with twenty-five patients, the mean age of the patients was 41 years, and the mean age of starting eltrombopag was 39±15.4 years. The mean age of the patients was 47 years in the RAISE study[10], 50 years in the EXTEND study[11], and 50.5 years in the REPEAT study[12]. The female sex ratio was found to be 57%, 66%, and 69% in the same studies, respectively.[10-12] In our study, this rate was found to be 64%, compatible with the literature.

The 'Delphi-based Consensus Recommendations' panel reported from Turkey recommends the use of thrombopoietin receptor antagonists (TPO-RAs) or rituximab in patients with persistent or chronic pITP who are refractory or dependent on corticosteroids or who relapse after corticosteroids. There is a recommendation that TPO-RAs (eltrombopag or romiplostim) should be used as second-line treatment before splenectomy in these patients. Splenectomy should be performed for patients with chronic pITP (>12 months) who are refractory to current treatments and who relapse.[4] Nevertheless, the present study revealed that 76% of patients underwent splenectomy prior to TPO-RA. This is attributable to the fact that the guidelines at the time of the study differed from those in effect at present.

In this study, 40% of patients had a baseline platelet value of <15,000/mm^3. We observed an increase in the initial median platelet value from 15,700/mm³ to 30,000/mm³ at week 2, to 51,000/mm³ at week 6. This level was maintained during the 85-week observation period. A review of the literature indicates that platelet levels of ≥50,000/mm³ are typically attained by week 2.[10-12] However, in our study, this level was achieved by week 6. This discrepancy can be attributed to the heterogeneous distribution of patients in the studies and the exclusion of platelet levels >30,000/mm³ from our study.

In the present study, it was observed that 21 (84%) patients responded when platelet levels ≥30,000/mm^3 were taken at any time, and 18 (72%) patients responded when platelet levels ≥50,000/mm^3 were taken. Tomiyama Y et al. conducted a study in Japan with 23 participants, 15 of whom received eltrombopag and eight of whom received a placebo for six weeks. At the end of the sixth week, the response rate in the eltrombopag arm was found to be 60% according to platelet ≥50,000/mm^3.[13] In a subsequent study by Yoshida M et al. in Japan, which involved 22 participants, it was determined that platelet levels should be maintained between 50,000 and 400,000/mm3 for over 75% of the follow-up period. This study also reported a response rate of 65%.[14] Similar results were obtained in a subsequent study by Katsutani S et al. in Japan.[15] Tripathi AK et al. conducted a study with newly diagnosed ITP and inclusion criteria that had not responded to two-week steroid treatment.[16] The study found a response rate of 80% and a median platelet value of 150,000/mm^3 with a platelet ≥50,000/mm^3 value at the first month. 76% and a median platelet value of 126,000/mm^3 at the end of the third month; treatment was not discontinued at the end of the third month against the risk of rebound thrombocytopenia. In a separate study, 94% (17 out of 18) of patients treated with eltrombopag as second-line treatment attained a target platelet count of over 50,000, and their responses remained stable during the entire follow-up period.[17] In another study, a complete response was achieved in 72.1% of patients using eltrombopag as second-line treatment.[18]

If we take a look at the studies done in Turkey, in a study conducted by Eser A. et al., the response rate was found to be 93.5% according to a platelet value ≥50.000/mm³ at any time.[19] Özdemirkıran F. et al. conducted a study with 32 patients in 7 different centers in the Aegean region and found that 75% of the patients had platelet values of ≥100,000/mm^3 and 6.25% had platelet values of 30,000/mm^3 - 100,000/mm^3 at the end of the first month.[20] Another study conducted by Çekdemir D. et al. in 11 different centers with 35 patients found the response rate to be 74% according to the platelet ≥30,000/mm³ value at week 2.[21] In another study, a response rate of 87% was reported.[22] In a study reported from Muğla province with the same response definition, the response rate was found to be above 65%.[23] As a result, the response rate in our study was found to be consistent with the literature.

In the present study, 13 (52%) of the patients demonstrated a sustained response with a median follow-up period of 18 months. The number of patients with a prolonged response was 5 (20%). Gonzalez Lopez TJ. et al. shared the sustained, prolonged response status they obtained in patients using eltrombopag in their follow-up in a report.[24] During a median follow-up period of 7 months (range 6-20 months), 12 patients maintained reliable platelet levels without the need for additional treatment. The median age of the patients was 24 years, the median number of prior treatments was 5, and the median duration of eltrombopag use was 5 months (range 1-13).[24] Mahevas M. et al. similarly reported a sustained, prolonged response. During a median follow-up of 13.5 months (range, 5-27 months), eight patients maintained reliable platelet values without the need for any treatment.[25] It was determined that predicting prolonged response was not feasible. However, it was hypothesized that a significant proportion of patients could maintain response status after discontinuing TPO-R agonists. [25] In a study, the incidence of prolonged response was documented to be 11.3%.[26] In the Phase II TAPER study, the proportion of patients achieving sustained response off-treatment (SRoT) by 12 months following treatment discontinuation was 30.5%, and the median SRoT duration was 8 months.[27] In a further study, 16 patients (17%) were reported to have prolonged response when response was considered as platelet value ≥30,000/mm^3 and 8 patients (8%) were reported to have prolonged response when response was considered as platelet value ≥100,000/mm^3.[28] The higher rates of patients with prolonged response and ongoing responsiveness in our study compared to the literature may be due to individual differences in ITP, the pathogenesis of which has not been clearly elucidated, or to other reasons such as genetic structure, ethnicity, environmental effects, or the relatively small number of patients we evaluated. In our study, participants were divided into groups based on splenectomy status, platelet count (<15,000/mm³) and gender. Our analysis revealed no statistically significant differences in response compared to the findings reported in the literature.

When the side effect profile was analyzed, generally compatible results with the literature were observed, and it was thought that the existing percentage differences may be due to the retrospective nature of the study, inadequacies in our data records, and the lack of an objective method in the evaluation of some side effects.

In conclusion, the objective of treatment with eltrombopag should not be to normalize platelet counts but rather to maintain them above the threshold for hemorrhagic risk. Eltrombopag is an effective treatment for patients with chronic ITP who are refractory to other therapies and have an increased risk of bleeding. It is generally well tolerated in the short and long term, and responsiveness is independent of splenectomy, concomitant treatment, or baseline platelet values. Long-term efficacy and safety studies on eltrombopag with five years of experience and data are needed.

Ethics Committee Approval Information:
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ORIGINAL RESEARCH

Clinical Profile of Schizophrenia in Children and Adolescents: Diagnosis, Symptoms and Prognosis

Hurşit FERAHKAYA[1], Ayşegül Tuğba HIRA SELEN[2]

[1] Necmettin Erbakan University Faculty of Medicine, Department of Child and Adolescent Psychiatry, Konya, Türkiye.
[2] Konya City Hospital, Konya, Türkiye.

ABSTRACT

Schizophrenia is a psychiatric disorder with a wide clinical spectrum that significantly impairs the functionality of the individual. It is less common under 18 years of age and clinical symptoms, diagnosis, treatment and follow-up processes differ from adult schizophrenia in certain aspects. This study aims to evaluate the sociodemographic and clinical characteristics of patients diagnosed with early-onset schizophrenia (EOS) and childhood-onset schizophrenia (COS). In this retrospective study, 83 children and adolescents diagnosed with schizophrenia according to DSM-5 criteria were analyzed. Sociodemographic characteristics, age at first symptom, duration of diagnosis, comorbidities and treatment processes of the patients were analyzed. The mean age at diagnosis of schizophrenia was 14.42 ± 2.46 years. The mean time between the first psychiatric symptom and the diagnosis of schizophrenia was 11.1 ± 1.56 months. The mean age of starting the first psychiatric treatment was 13.26 ± 3.10 years and the mean age of starting the most commonly used drug group, antipsychotic drugs, was 13.93 ± 2.82 years. Comorbid psychiatric disorders were common, with ADHD and intellectual disability being the most frequently observed. In addition, 19% of the patients had a history of psychiatric disorders in their mothers and 20% in their fathers. Our study highlights the delays in the diagnostic process and the prevalence of comorbid disorders by determining the sociodemographic and clinical characteristics of patients diagnosed with EOS and COS. It is emphasized that early diagnosis and intervention processes should be strengthened, individualized treatment approaches should be adopted, and long-term functionality of patients should be increased with multidisciplinary approaches.

Keywords: Childhood-onset schizophrenia. Early-onset schizophrenia. Sociodemographic characteristics. Comorbid psychiatric disorders.

Çocuk ve Ergenlerde Şizofreninin Klinik Profili: Tanı, Belirtiler ve Prognoz

ÖZET

Şizofreni geniş bir klinik yelpazesi olan bireyin işlevselliğini belirgin olarak bozan psikiyatrik bir bozukluktur. 18 yaşın altında daha nadir görülmekte ve klinik belirtiler, tanı, tedavi ve takip süreçleri erişkin dönem şizofrenisinden bazı yönleri ile ayrılmaktadır. Bu çalışma, erken başlangıçlı şizofreni (EOS) ve çocukluk başlangıçlı şizofreni (COS) tanısı almış hastaların sosyodemografik ve klinik özelliklerini değerlendirmeyi amaçlamaktadır. Retrospektif olarak tasarlanan bu çalışmada DSM-5 kriterlerine göre şizofreni tanısı almış 83 çocuk ve ergen hasta incelenmiştir. Hastaların sosyodemografik özellikleri, ilk semptom yaşı, tanı alma süresi, komorbiditeleri ve tedavi süreçleri analiz edilmiştir. Hastaların ortalama şizofreni tanısı alma yaşı 14,42 ± 2,46 yıl olarak belirlenmiştir. İlk psikiyatrik semptomun ortaya çıkışı ile şizofreni tanısı alma arasında geçen süre ortalama 11,1 ± 1,56 ay olarak saptanmıştır. İlk psikiyatrik tedaviye başlama yaşı ortalama 13,26 ± 3,10 yıl ve en sık kullanılan ilaç grubu olan antipsikotik ilaçlara başlama yaşı ortalama 13,93 ± 2,82 yıl olarak saptanmıştır. Komorbid psikiyatrik bozukluklar yaygındı ve en sık DEHB ve entelektüel yetiyitimi gözlendi. Ayrıca, hastaların %19'unun annesinde ve %20'sinin babasında psikiyatrik bozukluk öyküsü saptanmıştır. Çalışmamız, EOS ve COS tanısı alan hastaların sosyodemografik ve klinik özelliklerini belirleyerek, tanı sürecinde yaşanan gecikmelere ve komorbid bozuklukların yaygınlığına dikkat çekmektedir. Erken tanı ve müdahale süreçlerinin güçlendirilmesi, bireyselleştirilmiş tedavi yaklaşımlarının benimsenmesi ve multidisipliner yaklaşımlar ile hastaların uzun vadeli işlevselliğinin artırılması gerektiği vurgulanmaktadır.

Anahtar Kelimeler: Çocukluk çağı başlangıçlı şizofreni. Erken başlangıçlı şizofreni. Sosyodemografik özellikler. Komorbid psikiyatrik bozukluklar.

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Authors' ORCID Information:
Hurşit FERAHKAYA: 0000-0001-8611-0435
Ayşegül Tuğba HIRA SELEN: 0000-0003-1065-5548

Dr. Hurşit FERAHKAYA
Necmettin Erbakan Üniversitesi Tıp Fakültesi, Yunus Emre, Meram Tıp Fakültesi Hst. No:281, 42090, Meram/Konya, Türkiye
Phone: +90 555 524 54 59
E-mail: drhursitferahkaya@gmail.com

Schizophrenia is a complex psychiatric disorder characterized by a broad clinical spectrum of positive and negative symptoms that significantly impair an individual's functionality. While the age of onset varies across studies, the disorder is generally reported to emerge during late adolescence and early adulthood[1]. Research indicates that the peak onset period of schizophrenia is approximately 20.5 years[2]. Schizophrenia is usually diagnosed in the twenties, but the neurodevelopmental processes that cause the disorder are thought to occur during childhood and adolescence[3]. The American Academy of Child and Adolescent Psychiatry classifies cases with onset before the age of 13 as childhood-onset schizophrenia (COS) and cases with onset before the age of 18 as early-onset schizophrenia (EOS)[4]. The prevalence of EOS in the general population is estimated at approximately 0.25%, whereas COS is rarer, with an estimated prevalence of around 0.05%. While COS and EOS fundamentally represent similar disorders and share diagnostic criteria with adult-onset schizophrenia (AOS), they differ in terms of neurobiology, clinical presentation, prognosis, and treatment processes[2,5].

Although EOS and COS are less common than AOS, studies indicate that initial symptoms of schizophrenia appear before the age of 18 in approximately 18% of individuals later diagnosed with schizophrenia in adulthood[2]. Assessments of premorbid symptoms reveal significant deficits in social, motor, and language skills among individuals with EOS and COS. Additionally, these patients frequently present with comorbid neurodevelopmental disorders, such as attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD)[6,7]. EOS and COS exhibit a broad range of initial symptoms and are associated with an insidious onset of psychotic symptoms[8].

In the long term, they are reported to differ from adult cases by demonstrating more severe negative symptoms, pronounced cognitive impairments, and a more treatment-resistant course[6]. The subtle progression of psychotic symptoms in younger patients, along with the predominance of negative symptoms, can contribute to delays in diagnosis and subsequent treatment. A follow-up study found that only 32% of patients initially presenting with symptoms received a schizophrenia diagnosis at the first evaluation, but this figure increased to 40% upon further assessments[9]. Additionally, the duration of untreated psychosis in COS and EOS is reported to be longer than in AOS[9]. Studies suggest that delays in schizophrenia diagnosis and untreated psychosis are associated with increased symptom severity and poorer long-term cognitive and functional outcomes[10,11].

Early diagnosis and intervention are crucial for mitigating symptom severity and improving long-term prognosis[12]. Identifying and monitoring clinical high-risk groups among children and adolescents, as well as recognizing early warning signs of psychotic disorders, provide significant opportunities for timely diagnosis and intervention.

Since schizophrenia is a rare disorder, studies examining the diagnostic process and the progress of schizophrenia in children and adolescents are very limited in Türkiye. This study aims to evaluate the sociodemographic and clinical characteristics of individuals diagnosed with EOS and COS who were admitted to our clinic. By analyzing the management and treatment processes of this patient group, we seek to contribute to a more comprehensive understanding of schizophrenia in children and adolescents and to emphasize the importance of early intervention programs in clinical practice.

Material and Method

This retrospective study was designed using data from the Child and Adolescent Psychiatry outpatient clinic database at Necmettin Erbakan University, Faculty of Medicine. The study sample comprised patients diagnosed with schizophrenia over the past 10 years. Psychiatric diagnoses were made by child psychiatrists based on the DSM-5 diagnostic criteria. In addition to psychiatric diagnoses, sociodemographic characteristics (age, gender, parental age and education level, socioeconomic status), the onset of symptoms, the timing of schizophrenia diagnosis, family history, treatment, and follow-up processes were recorded. The study was approved by the Non-Interventional Clinical Research Ethics Committee of Necmettin Erbakan University (06.09.2024-2024/5165) and conducted in accordance with the principles of the Helsinki Declaration.

Statistical Analysis

The data were analyzed using SPSS (Statistical Package for the Social Sciences) version 25.0. Descriptive statistics (mean, standard deviation, frequency, and percentage) were used to summarize the data. Relationships between categorical variables were assessed using the chi-square test. A significance level of $p<0.05$ was considered statistically significant.

Results

97 patients diagnosed with schizophrenia were identified in our database. However, 14 individuals were excluded due to missing data, resulting in a final

study group consisting of 83 participants (46 males, 37 females). The participants' ages ranged from 6 to 18 years, with a mean age of 13.86 ± 3.13 years. Among the participants, 37 were continuing their high school education, while 10 had discontinued formal schooling. Approximately 20% of participants belonged to single-parent households, 33% had three siblings, and 45% were the firstborn child in their family. The sociodemographic data of the participants are summarized in Table I.

Table I. Sociodemographic and clinical characteristics of the participants

	Mean	SD
Age	13.86	3.13
Mother's age	41.42	4.29
Father's age	43.72	3.61
	n	%
Gender, Male/Female	46/37	55.4/44.6
Education level		
Illiterate	10	12.0
Primary school	36	43.4
Secondary school	37	44.6
Comorbidity		
Organic comorbidity, Yes/No	18 / 65	21.7 / 78.3
Psychiatric comorbidity	54 / 29	65.1 / 34.9
ADHD	16	19.3
ID	15	18.1
OCD	8	9.6
MDD	3	3.6
AD	3	3.6
ASD	2	2.4
CD	2	2.4
BPD	2	2.4
Diğer	3	3.6
Mother's education level	n	%
Illiterate	20	24.1
Primary school	54	65.1
Secondary school	7	8.4
University	2	2.4
Father's education level		
Illiterate	17	20.5
Primary school	50	60.2
Secondary school	14	16.9
University	2	2.4
Economic Level		
Low	49	59.0
Middle	24	29.0
High	10	12.0
Family Structure		
Nuclear	57	68.7
Extended	10	12.0
Fragmanted	16	19.3

SD = standard deviation, n= number of cases
ADHD: attention deficit/hyperactivity disorder, ID: intellectual disability, OCD: obsessive compulsive disorder, MDD: major depressive disorder, AD: anxiety disorder, ASD: autism spectrum disorder, CD: conduct disorder, BPD: bipolar disorder

43 patients initially presented with internalizing problems (depression, anxiety disorders etc.), while 40 patients sought consultation due to externalizing issues (ADHD, conduct disorder, etc.). No statistically significant gender differences were found regarding internalizing and externalizing problems (χ^2=0.91, p=0.338). Negative symptoms were the first psychotic symptoms in 43% of patients, while delusions were the most frequently observed positive psychotic symptom, present in 25% of cases. Additionally, 65% of participants had comorbid psychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD) and intellectual disability. Eighteen participants had a history of organic medical conditions, primarily epilepsy.

The mean age at the onset of initial psychiatric symptoms was 13.53 ± 2.89 years, whereas the onset age of the first psychotic symptom was 14.43 ± 2.78 years. The mean duration between the first psychiatric symptom and the first psychotic symptom was 10.8 ± 1.43 months, while the mean interval between the first psychiatric symptom and the diagnosis of schizophrenia was 11.1 ± 1.56 months. The mean age at schizophrenia diagnosis was 14.42 ± 2.46 years, with initial psychiatric treatment being initiated at 13.26 ± 3.10 years and antipsychotic treatment commencing at 13.93 ± 2.82 years. Antipsychotic medications were the most commonly prescribed first-line treatment (65%), followed by selective serotonin reuptake inhibitors (SSRIs) (14%). 22 patients required hospitalization for treatment and follow-up. Furthermore, five participants had a history of suicide attempts, while nine had a history of substance use. The clinical characteristics of the patients are presented in Table II and Figure 1.

Table II. Clinical characteristics of patients and diagnosis/treatment processes

First Psychiatric Symptom	**n**	**%**
Symptoms of Externalisation	43	51.8
Symptoms of Internalisation	40	48.2
First Psychotic Symptom	**n**	**%**
Negative Symptoms	36	43.4
Hallucination	21	25.3
Delusion	14	16.9
Dysorganised Behaviour	7	8.4
Dysorganised Speech	5	6.0
Variables	**Mean**	**SD**
First Psychiatric Symptom (Year)	13.53	2.80
First Psychiatry Admission (Year)	13.86	3.13
First Psychotic Symptom (Year)	14.43	2.75
Diagnosis (Year)	14.46	2.34
First Psychiatric Symptom - First Psychotic Symptom Interval (Month)	10.8	1.43
First Psychiatric Symptom – Diagnosis Interval (Month)	11.1	1.56
Psychiatric Treatment Initiation (Year)	13.26	3.20
Antipsychotic Treatment Initiation (Year)	13.93	2.82

SD = standard deviation, n= number of cases

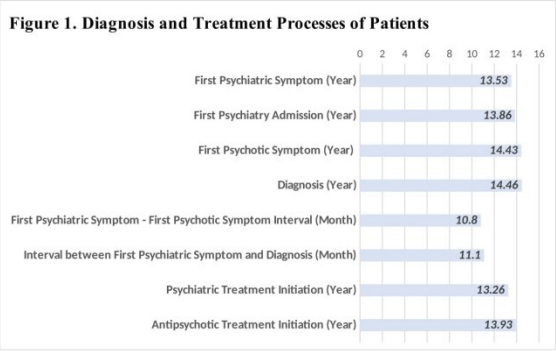

Figure 1:
Diagnosis and Treatment Processes of Patients

Examination of family history revealed that the participants' mothers (mean age: 41.42 ± 4.29 years) and fathers (mean age: 43.72 ± 3.61 years) had an educational level of primary school in approximately 50% of cases, and 59% of families had a low socioeconomic status. Additionally, psychiatric disorders were identified in 19% of mothers and 20% of fathers.

Discussion and Conclusion

In this study, we conducted a detailed evaluation of the sociodemographic and clinical characteristics of children and adolescents diagnosed with schizophrenia. The mean age of the participants was 13.86 ± 3.13 years. The majority of the patients had negative first psychotic symptoms. The mean age of the first psychotic symptoms was 13.53 ± 2.89 years, and the mean age of the first psychotic symptoms was 14.43 ± 2.78 years. The mean time between the first psychiatric symptom and the diagnosis of schizophrenia was 11.1 ± 1.56 months, and the mean age of the diagnosis was 14.42 ± 2.46 years.

In line with previous studies, one of the key findings of our research is that schizophrenia was found to be more prevalent among males[4]. Additionally, more than 10% of participants had discontinued their education. Individuals diagnosed with EOS and COS are reported to experience significant impairments in academic functioning, with frequent disruptions in their educational trajectories[7]. Schizophrenia adversely affects cognitive capacity and social skills, while also leading to motivational deficits, which can contribute to increased dropout rates from school[8]. Therefore, in addition to symptom management through pharmacological treatment, providing educational support and implementing individualized educational programs for individuals with schizophrenia may help mitigate academic functional impairments.

In our study, about 20 per cent of the participants came from broken families. This finding suggests a bidirectional relationship. Family structure has been identified as a significant factor in the development of psychiatric disorders in children and adolescents, and studies indicate that children from single-parent families have a higher risk of developing EOS[13]. Family conflicts, limited social support, and economic difficulties observed in fragmented families may increase the risk of psychopathology[14]. Furthermore, children raised in unstable family environments are more likely to be exposed to stressors, which could exacerbate neurodevelopmental vulnerabilities[15]. Additionally, the burden of having a family member with a chronic psychiatric disorder, along with the challenges of diagnosis, treatment, and follow-up, may further contribute to family stress and disrupt family integrity. This finding suggests a bidirectional relationship. Therefore, strengthening family support systems and providing mental health support to caregivers could play a crucial role in improving the prognosis of children and adolescents diagnosed with schizophrenia.

Participants in our study presented with externalizing symptoms (e.g., hostility, aggression, impulsivity) and internalizing symptoms (e.g., depression, anxiety, social withdrawal) at similar rates. Our findings support the notion that schizophrenia in children and adolescents presents with a heterogeneous clinical profile[18]. Some studies suggest that internalizing symptoms are more common in the prodromal phase, particularly anxiety and depressive symptoms in EOS cases[9]. However, externalizing symptoms are also noteworthy clinical indicators, particularly in the presence of comorbid ADHD and conduct disorder, where they tend to be more pronounced[16]. Thus, a comprehensive clinical assessment that evaluates both internalizing and externalizing symptoms simultaneously is essential for developing effective early intervention strategies. Another key finding of our study was that there were no significant gender differences in the prevalence of internalizing or externalizing symptoms. This suggests that schizophrenia in childhood and adolescence manifests across a broad spectrum of psychopathology, independent of gender. Although previous research has reported that males exhibit more externalizing symptoms while females present with more internalizing symptoms, our study did not observe this distinction[17]. The fact that externalization and internalization problems did not differ between genders in our study can be explained by several factors. Firstly, although it is traditionally accepted that men are more externalized (aggression, anger outbursts) and women are more internalized (depression, anxiety), modern social dynamics may have reduced these differences. In addition, the fact that women participate more in business life and

social life and men receive more psychosocial support may eliminate the difference between the sexes in terms of the expression of symptoms.

Regarding psychotic symptoms, 43% of participants initially exhibited negative symptoms, while delusions were the most commonly reported positive symptom (25%). Our findings align with previous literature indicating that negative symptoms predominate in EOS[18]. The early predominance of negative symptoms may prevent families and social circles from recognizing the disorder, contributing to diagnostic delays[19]. Therefore, early identification and appropriate management of negative symptoms in children and adolescents is of paramount importance. The presence of comorbid psychiatric disorders, including ADHD and intellectual disability in 65% of participants, underscores the strong association between EOS/COS and neurodevelopmental disorders. Neurodevelopmental impairments are considered significant risk factors for schizophrenia and further complicate patients' academic and social functioning [20]. Moreover, the presence of organic medical conditions, particularly epilepsy, in 18 participants highlights the neurobiological and neurological underpinnings of schizophrenia. The relationship between epilepsy and schizophrenia has been extensively studied, with research suggesting shared neurobiological mechanisms underlying both conditions[21].

In our study, the mean age at onset of initial psychiatric symptoms was 13.53 years, while the mean age at onset of psychotic symptoms was 14.43 years. Literature suggests that EOS typically has an insidious onset, which can delay diagnosis[9]. The average interval between the first psychiatric symptom (whether internalizing or externalizing) and the onset of psychotic symptoms was 10.8 months, while the mean duration from the first psychiatric symptom to schizophrenia diagnosis was 11.1 months. In other words, non-psychotic psychiatric symptoms often precede psychotic symptoms, and schizophrenia is diagnosed approximately one year after the initial symptoms emerge. This finding highlights that diagnostic delays in EOS and COS remain a significant concern. Various factors may contribute to these delays. Firstly, psychotic symptoms in childhood and adolescence may be misattributed to neurodevelopmental disorders (e.g., ADHD or ASD) or mood disorders[7]. Additionally, the early predominance of negative symptoms may obscure the clinical detection of psychotic processes[22]. Conducting detailed family history assessments and carefully evaluating symptom progression may help reduce diagnostic delays. Our study also found that the mean age at initiation of psychiatric treatment was 13.26 years, while the mean age at initiation of antipsychotic treatment was 13.93 years. Many children and adolescents exhibiting early psychiatric symptoms initially receive treatment for anxiety, depression, or behavioral problems, with antipsychotic treatment introduced only when psychotic symptoms become more apparent[23]. This could explain the gap between clinical diagnosis and the commencement of antipsychotic treatment. Our findings emphasize the need for improved early intervention strategies in EOS and COS. These findings underscore the importance of early recognition and careful monitoring of psychiatric symptoms in children and adolescents at risk for schizophrenia. Implementing structured screening protocols and increasing awareness among clinicians could help minimize diagnostic delays and ensure timely initiation of appropriate treatment strategies.

Our study also found that 22 patients required hospitalization. Hospitalization rates in EOS and COS are generally high, likely due to the severity of symptoms and greater treatment resistance in this patient group[24]. Additionally, five participants had a history of suicide attempts, while nine had a history of substance use. Previous research has corroborated the high prevalence of suicide risk and substance use among children and adolescents with schizophrenia[20]. Suicide attempts and social withdrawal are particularly common in patients with predominant negative symptoms[22]. Therefore, early identification of suicide risk and a multidisciplinary approach to managing EOS and COS patients are essential.

An examination of family history revealed that 50% of participants' parents had only a primary school education, and 59% were classified as having low socioeconomic status. Low socioeconomic status and lower parental education levels have been identified as major risk factors for the development of psychiatric disorders in children[7]. Additionally, psychiatric disorders were identified in 19% of mothers and 20% of fathers, with schizophrenia specifically diagnosed in 10% of both mothers and fathers. Genetic predisposition is a well-established risk factor for schizophrenia and other psychotic disorders, with individuals having a parent diagnosed with schizophrenia being at significantly greater risk than the general population[16]. These findings underscore the interplay between biological and environmental factors in schizophrenia development. Early identification and intervention strategies for high-risk groups may help improve disease outcomes.

Our study has several limitations. First, as a retrospective study, we were unable to track long-term functional outcomes or treatment responses, limiting our ability to draw definitive conclusions about disease progression and treatment efficacy. Second, our sample size was relatively small and drawn from a single center, which may restrict the generalizability of our findings. Future studies should replicate our

findings across diverse geographical and cultural settings. Lastly, our study did not use a scale to assess positive and negative symptoms in more detail, which may have limited the comprehensive assessment of negative symptoms and cognitive impairments. Future research should incorporate long-term follow-up data and evaluate the effectiveness of early intervention programs for managing EOS and COS.

This study provides valuable insights into the sociodemographic and clinical characteristics of individuals diagnosed with EOS and COS, highlighting critical findings regarding diagnosis and management. Enhancing early screening programs, adopting multidisciplinary approaches, and implementing individualized treatment strategies are essential for optimizing the care and long-term functionality of affected individuals. Future prospective and large-scale studies may further refine our understanding of EOS and COS and contribute to the development of more effective intervention strategies.

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ÖZGÜN ARAŞTIRMA

Metastatik Renal Hücreli Kanser Tedavisinde Tirozin Kinaz İnhibitörlerinin Etki ve Yan Etkisinin Değerlendirilmesi

Abdülkadir ŞAHİN[1], Erdem ÇUBUKÇU[2]

[1] Sağlık Bilimleri Üniversitesi, Ankara Dr. Abdurrahman Yurtaslan Onkoloji Sağlık Uygulama ve Araştırma Merkezi, Dahili Tıp Bilimleri Bölümü, İç Hastalıkları Anabilim Dalı, Hematoloji Bilim Dalı, Ankara, Türkiye.
[2] Bursa Uludağ Üniversitesi Tıp Fakültesi, Tıbbi Onkoloji Bilim Dalı, Bursa, Türkiye.

ÖZET

Bu çalışma, metastatik renal hücreli karsinom (mRHK) tedavisinde tirozin kinaz inhibitörlerinin (TKİ) etkinlik ve yan etkilerini retrospektif olarak değerlendirmeyi amaçlamaktadır. mRHK, ileri evrede tanı konulan ve yaşam süresi beklentilerini sınırlayan bir kanser türüdür. Türkiye'de interferon alfa tedavisi geleneksel olarak birinci basamak tedavi olarak uygulanmasına rağmen, progresyon gösteren hastalarda TKİ'ler gibi hedefe yönelik tedaviler öncelikli hale gelmiştir. Çalışmada, 2010-2018 yılları arasında mRHK tanısı almış ve TKİ tedavisi görmüş 65 hasta incelenmiştir. Bu retrospektif analizde, hastaların demografik ve klinik verileri ile tedaviye verilen yanıtlar değerlendirilmiştir. Ana bulgular arasında sunitinib ve pazopanib tedavilerinin sağkalım sonuçlarının literatürle uyumlu olduğu ve yan etkiler arasında halsizlik, hipertansiyon, dermatit gibi etkilerin öne çıktığı belirlenmiştir. Ortalama sağkalım süresi 26 ay olarak hesaplanmıştır. Çalışmanın sonuçları, TKİ'lerin mRHK tedavisindeki etkisini destekler nitelikte olup, gelecekte yapılacak daha geniş hasta gruplarını içeren prospektif çalışmalarla bu etkinliğin daha iyi anlaşılabileceği öne sürülmüştür.

Anahtar Kelimeler: Metastatik renal hücreli kanser (mRHK). Tirozin kinaz inhibitörleri. VEGF inhibitörleri. Retrospektif analiz.

Evaluation of the Effect and Side Effect of Tyrosine Kinase Inhibitors on the Treatment of Metastatic Renal Cell Carcinomas

ABSTRACT

This study aims to retrospectively evaluate the efficacy and side effects of tyrosine kinase inhibitors (TKIs) in the treatment of metastatic renal cell carcinoma (mRCC). mRCC is a type of cancer diagnosed at advanced stages and significantly limits life expectancy. In Turkey, interferon-alpha has traditionally been used as a first-line treatment; however, targeted therapies such as TKIs have become a priority for patients showing progression. In the study, 65 patients who were diagnosed with mRCC and treated with TKI between 2010 and 2018 were examined. This retrospective analysis evaluated the demographic and clinical data of patients and their response to treatment. Key findings indicated that the survival outcomes of sunitinib and pazopanib treatments were consistent with the literature, with fatigue, hypertension, and dermatitis being prominent side effects. The average survival duration was calculated as 26 months. The results of the study support the effectiveness of TKIs in the treatment of mRCC and suggest that their impact could be better understood through prospective studies involving larger patient cohorts in the future.

Keywords: Metastatic renal cell carcinoma. Tyrosine kinase inhibitors. VEGF inhibitors. Prognostic factors. Retrospective analysis.

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Dr. Abdülkadir ŞAHİN
Sağlık Bilimleri Üniversitesi, Ankara Dr. Abdurrahman Yurtaslan Onkoloji Sağlık Uygulama Ve Araştırma Merkezi, Dahili Tıp Bilimleri Bölümü, İç Hastalıkları Anabilim Dalı, Hematoloji Bilim Dalı, Ankara.
Tel.: 0506 330 56 43
E-posta: draksca@gmail.com

Yazarların Orcid Bilgileri
Abdülkadir ŞAHİN: 0000-0003-4256-3437
Erdem ÇUBUKÇU: 0000-0002-0070-0889

Renal Hücreli Karsinom (RHK), böbrek kanserlerinin büyük bir kısmını oluşturmakta ve ileri evrede tanı alması nedeniyle yaşam süresi üzerinde ciddi olumsuz etkiler yaratmaktadır[1-3]. Lokalize hastalıkta cerrahi genellikle küratif sonuçlar verirken, metastatik olgularda tedavi seçenekleri sınırlıdır[4]. Bu durum, mRHK tedavisinde etkili ve yönetilebilir yan etki profiline sahip yeni tedavi yaklaşımlarına olan ihtiyacı artırmıştır[5,6].

Son yıllarda, tirozin kinaz inhibitörleri (TKİ), mRHK yönetiminde önemli bir ilerleme sağlamış ve interferon-alfa (IFN-α) gibi geleneksel tedavilerin yerini almaya başlamıştır. TKİ'lerin, tümör büyümesini baskılayan vasküler endotelyal büyüme

faktörü (VEGF) yolu gibi spesifik moleküler hedeflere yönelmesi, bu ilaçların önemini daha da artırmıştır[7-9].

Bu çalışmanın amacı, mRHK tedavisinde TKİ'lerin etkinliğini ve yan etki profillerini retrospektif olarak değerlendirmektir. Çalışmada, klinik uygulamada TKİ kullanımının gerçek yaşam verileri ile literatürdeki çalışmalar arasındaki benzerlik veya farklılıkların ortaya konması amaçlanmıştır.

Gereç ve Yöntem

Bu çalışma, Tıp Fakültesi Etik Kurulu tarafından 15 Mayıs 2018 tarihli ve 2018-9/16 numaralı karar ile onaylanmıştır. Çalışma, 2010-2018 yılları arasında xxxx Üniversitesi Tıp Fakültesi Hastanesi Tıbbi Onkoloji Polikliniği'nde metastatik renal hücreli karsinom (mRHK) tanısı almış 18 yaş üzeri hastaların retrospektif incelemesini kapsamaktadır.

Çalışmaya dahil edilme kriterleri: (1) Renal hücreli kanser (RHK) tanısı almış olmak, (2) TKİ kullanımı, (3) Hasta tanı ve takibinin Uludağ Üniversitesi'nde gerçekleştirilmiş olmasıdır. Çalışma dışı bırakılma kriterleri ise (1) Böbrek dışında bir primer tümörün varlığı ve (2) TKİ kullanım süresinin 2 aydan az olması olarak belirlenmiştir.

Yerleşmiş yöntemler kaynaklarla desteklenmiştir (Kaplan-Meier sağkalım analizi, log-rank testi) ve SPSS 23.0 yazılımı kullanılarak istatistiksel analiz yapılmıştır. Yeni bir yöntem kullanılmadığı için ek açıklama gerekmemektedir. Tüm hastaların klinik ve demografik bilgileri ile sağkalım oranları değerlendirilmiş; tedaviye bağlı yan etkiler yan etki yönetim kılavuzlarına göre sınıflandırılmıştır.

Hastaların ölüm tarihleri, Türkiye Cumhuriyeti Sağlık Bakanlığı Halk Sağlığı Kurumu Ölüm Bildirim Sistemi veritabanından elde edilmiştir. Bulguların geçerliliği için veri analizi dikkatli şekilde kontrol edilmiştir.

Biyoistatistiksel Analiz: Sağkalım ve progresyon verileri Kaplan-Meier yöntemi ile analiz edilmiş ve gruplar arasındaki farklılıklar log-rank testi ile değerlendirilmiştir. Kategorik değişkenlerin analizi için ki-kare testi kullanılmıştır. Sürekli değişkenlerin karşılaştırılmasında t-testi veya Mann-Whitney U testi uygulanmıştır. Tüm analizler SPSS 23.0 yazılımı kullanılarak gerçekleştirilmiş olup, $p<0,05$ değeri istatistiksel olarak anlamlı kabul edilmiştir.

Bulgular

Çalışmaya mRHK tanısı almış, IFN tedavisini tolere edemeyen ya da sonrasında progresyon gelişen 65 hasta dahil edildi. Hastaların 44'ü (%67,7) erkek, 21'i (%32,3) kadındı. Tanı anı median yaş kadın ve erkek hastalarda aynı bulundu (erkek=57, kadın= 57,7). 51 hasta <65 yaş, 14 hasta ise ≥65 yaş olarak bulundu. ECOG 0-1 olan hasta sayısı 51'di.

34 hastada berrak hücreli (% 52,3), 8 hastada papiller tip (%12,3), 2 hastada eozinofilik tip (%3,1) ve 5 hastada kombine (%7,7) görülürken, 16 hastanın histolojik tipi bilinmiyordu (%24,6). Hastaların metastaz yerleri incelendiğinde 31 hastada akciğere (%47,6), 4 hastada karaciğere (%6,1), 23 hastada kemiğe (%35,1) ve 5 hastada beyine (%7,6) metastaz saptandı. 51 hastada tek odağa metastaz saptanırken (%78,4) diğer 14 hastada iki ve daha fazla odağa metastaz (%21,5) saptandı. (Tablo I)

Tablo I. Hastaların demografik, klinik ve patolojik özellikleri

Cinsiyet (Sayı/%)	Kadın	21/32,3
	Erkek	43/67,7
Yaş (median)	Kadın	57,7619
	Erkek	57,0227
Yaş (yıl)	≥65	14/21,53
	<65	51/78,46
ECOG (Sayı/%)	0-1	51/78,46
	≥2	14/21,53
Histoloji (Sayı/%)	Berrak hücreli	34/52,3
	Papiller	8/12,3
	Eozinofilik	2/3,1
	Kombine	5/7,7
	Bİlinmeyen	16/24,6
Metastaz (Sayı/%) yeri	Akciğer	31/47,69
	Karaciğer	4/6,15
	Kemik	23/35,18
	Beyin	5/7,69
Metastaz (Sayı/%) sayısı	<2	51/78,46
	≥2	14/21,54

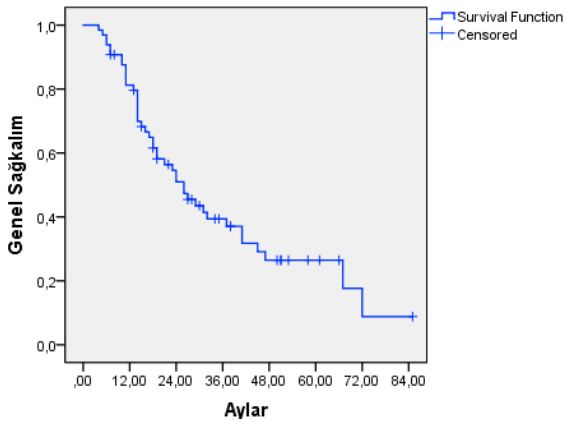
ECOG: Eastern cooperative oncology group

Çalışmamızdaki hastaların tamamı interferon tedavisi aldı. İnterferon tedavisini tolere edemeyen ya da sonrasında progrese olmuş hastalar TKİ'den sunitinib veya pazopanip tedavisi tercih edilmişti. TKİ tedavisi sonrasında hastalar axitinib (n=14), everolimus (n=22), nivolumab (n=2) aldılar. Çalışmadaki hastaların tedavi seçim oranları tablo II'de yer almaktadır.

Tablo II. Tedavi seçimleri

Tedavi ajanı		
IFN		65/100
IFN sonrası seçim	Sunitinib	45/69,23
	Pazopanib	20/30,77
TKİ sonrası seçim	Everolimus	22/55
	Axitinib	14/35
	Nivolumab	2/5

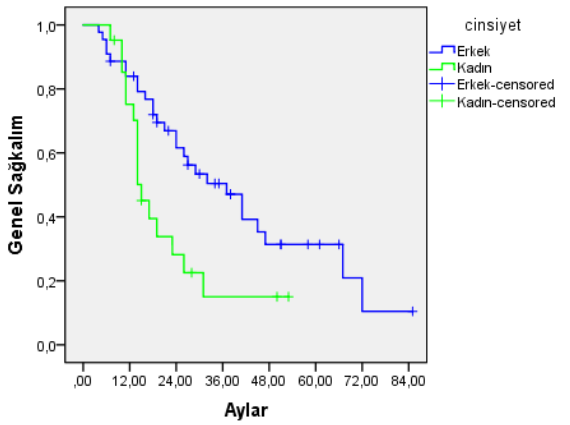
Çalışmamızda verileri ele alınan mRHK hastalarının tanı anından itibaren hesaplanan tüm sağkalım oranları 26 ± 4,029 ay olarak hesaplandı.(Şekil 1)



Şekil 1:
Tüm hastaların genel sağkalımı (GS)

Tamamı TKİ kullanan hastaların genel özelliklerine göre sağkalımları değerlendirildi.

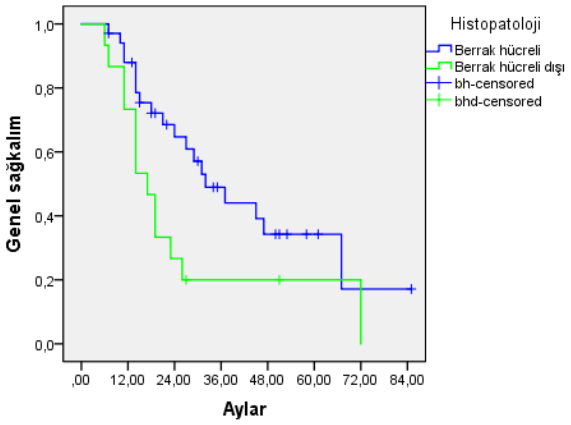
PS kadınlarda 9 ayken erkek hastalarda 15 ay olarak saptandı fakat bu fark istatiksel anlamlı değildi (p=0,149). Hastalar GS üzerinden değerlendirildiğinde kadın hastaların GS 15 ayken erkek hastaların GS 37 ay olarak bulundu ve bu fark istatiksel olarak anlamlı bulundu (p=0,015). (Şekil 2)



Şekil 2:
Cinsiyete göre GS

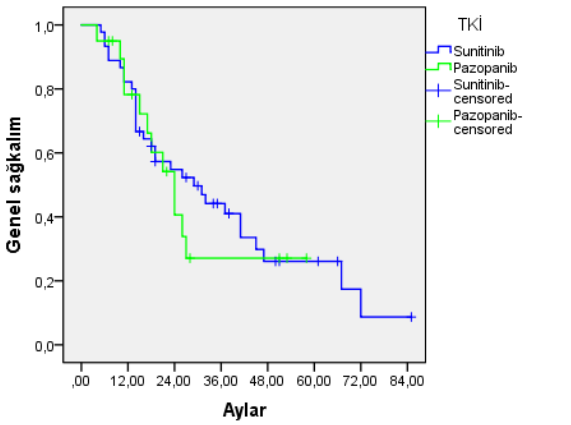
Tanı yaşı ≥65 ve <65 olarak değerlendirildiğinde progresyonsuz sağkalım(PS) ≥65 yaş grubunda 14 ay <65 yaş grubunda 15 ay olarak bulundu. GS her iki grupta da 26 ay olarak bulundu.

Hastalar histopatolojik olarak berrak hücreli RHK (bhRHK) ve berrak hücreli dışı RHK (bhdRHK) olarak gruplara ayrıldığında PS bhRHK'de 15 ayken bhdRHK'de 5 ay olarak bulundu. GS'lerine bakıldığında bhRHK'de 32 ay bhdRHK 17 ay olarak bulundu. Her iki sağkalımdaki fark istatiksel olarak anlamlıydı (p=0,033).(Şekil 3)



Şekil 3:
Histopatolojik tipe göre GS

Çalışmamızda sunitinib ve pazopanib alan hastalar PS üzerinde karşılaştırıldığında her iki hasta grubunda da PS 15 ay olarak bulundu. GS ise sunitinib grubunda 29 ayken pazopanib grubunda 24 ay olarak bulundu fakat bu fark istatiksel olarak anlamlı değildi (p=0,647). (şekil 4)



Şekil 4:
Sunitinib ve pazopanib'in GS karşılaştırması

Çalışmamızda TKİ kullanımına bağlı yan etkiler incelendiğinde;

19 hastada hipotiroidi (%29,2), 7 hastada halsizlik (%15), 17 hastada hipertansiyon (%26,2), 14 hastada cilt bulguları (%21,5), 5 hastada mukozit (%7,7), 9 hastada bulantı (%13,8), 3 hastada diyare (%4,6), 30 hastada lökopeni (%46,2), 20 hastada nötropeni (%30,8), 20 hastada lenfopeni (%30,8), 18 hastada anemi (%27,7), 18 hastada trombositopeni (%27,7), 14 hastada transaminaz artışı (%21,5), 3 hastada da (%4,6) biluribin artışı saptandı. Hastalardan sadece bir tanesinde farklı bir tedavi seçeneğine geçildi.

Saptanan yan etkiler üzerinden sunitinib ve pazopanib karşılaştırıldı. Saptanan sonuçlar tablo III'de yer almaktadır.

Tablo III. Sunitinib ve pazopanib'in yan etki oranlarının karşılaştırılması.

Yan etki	Sunitinib(%)	Pazopanib(%)
Halsizlik	8,9	15
Hipertansiyon	22,2	35
Dermatit	28,9	5
Mukozit	11,1	..
Bulantı	15,6	10
Diyare	4,4	5
Hipotiroidi	28,9	30
Anemi	28,9	25
Lökopeni	53,3	30
Nötropeni	35,6	20
Lenfopeni	31,1	30
Trombositopeni	14	20
Hiperbilirubinemi	2,2	10
Transaminaz artışı	22,2	20

Tartışma ve Sonuç

Erişkin kanserlerin %2-3'ünü RHK oluşturmaktadır. Kadınlarda dokuzuncu, erkeklerde ise yedinci en sık görülen kanserdir[1]. Renal hücreli karsinom, sitotoksik tedaviye, radyoterapi ve hormon tedavisi ile yanıt oranları düşüktür[10-12]. Anjiyogenez inhibitörlerinin yakın zaman önce, interferon-α (IFN-α) ve / veya interlökin-2 (IL-2) dahil olmak üzere sitokin bazlı tedavi, sınırlı klinik aktiviteye ve anlamlı olmasına rağmen, ilerleyen RHK için tedavinin temel dayanağıydı[11,12]. VEGF rolü ve rapamisin yollarının memeli hedefini içeren RHK tümör biyolojisinin anlaşılmasındaki ilerlemeler, sorafenib, sunitinib, bevacizumab dahil olmak üzere birçok ajanın başarılı klinik gelişimine yol açmıştır.

Çalışmamızda mRHK görülme sıklığı erkek hastalarda kadın hastalardan 2 kat daha fazlaydı. Hastaların median tanı yaşı ise 57 olarak bulundu. Siegel ve ark.'ın yapmış oldukları çalışmada ise hastalığın görülme sıklığı erkek hastalarda kadın hastalardan 1,6 kat daha fazla olarak belirtilmiştir ve median tanı yaşı 65 saptanmış olup daha yaşlı hastalar mevcuttur. Görülme sıklığı benzerdir[2].

Çalışmamızdaki hastalarda histopatolojik olarak berrak hücreli, papiller tip, eozinofilik tip ve kombine tip görüldü, Patard ve ark.'ın yapmış oldukları çalışmada berrak hücreli (%60-70), papiller (%5-15), kromofobik (%5-10), onkositik (%5-10) ve toplayıcı kanal (<%1) olarak belirtilmiş olup bizim çalışmamız ile benzer özellik taşımaktadır[13].

Çalışmamızda hastaların metastaz yerleri incelendiğinde akciğere, karaciğere, kemiğe ve beyine metastaz saptandı. 51 hastada tek organda metastaz varken diğer 14 tanesinde iki ve daha fazla organda metastaz saptandı. M.Bianchi ve ark.'ın yapmış olduğu çalışma ile karşılaştırıldığında çalışmamızda akciğer, kemik ve beyin metastazı daha fazla oranda saptanırken, karaciğer metastazı daha az oranda saptanmıştır. Yine aynı çalışmayla karşılaştırıldığında çalışmamızda tek organda metastazı daha fazla görülürken, iki ve daha fazla organa metastaz daha az saptanmıştır[14].

Eski çalışmalarda mRHK'lu hastalarda GS düşük oranda saptanırken Heng DY. ve ark.'ın çalışmasında GS hedefe yönelik tedavilerle artmış ve 28,4 ay saptanmıştır. Bizim çalışmamızda da GS benzer bulunmuştur.

Çalışmamızda kadın hastaların PS erkek hastalarla karşılaştırıldığında 9 aya 15 ay olarak bulundu fakat istatiksel olarak anlamlı değildi (p=0,149). Ancak hastalar GS üzerinden değerlendirildiğinde kadın hastaların genel sağkalımları 15 ayken erkek hastaların genel sağkalımları 37 ay olarak bulundu ve bu fark istatiksel olarak anlamlı bulundu (p=0,015). Literatür incelendiğinde Monish ve ark.'ın yapmış olduğu SEER veri tabanı analizinde kadınlarda GS daha üstün olmakla birlikte, evre ve dereceye göre ayarlandığında kansere özgü sağkalım, erkeklerle benzer bulunmuştur. Genel sağkalımın erkek hastalarda daha kısa olması erkeklerde bhRHK daha az görülmesi, büyük tümör boyutu, yüksek grade ve ileri evre ile ilişkilendirilmiştir. Bizim çalışmamızdaki erkek hastalar incelendiğinde ise bhRHK oranının daha fazla olduğu görüldü ve bu anlamlı istatiksel fark bu durumla ilişkilendirildi[15].

Hastalar histopatolojik olarak bhRHK ve bhdRHK olarak gruplara ayrıldığında PS bhRHK'de 15 ayken bhdRHK grupta 5 ay olarak bulundu. Genel sağkalımlarına bakıldığında bhRHK'de 32 ay bhdRHK 17 ay olarak bulundu. Her iki sağkalımdaki fark istatiksel olarak anlamlıydı (p=0,033)[16].

mRHK hastalarında yapılan faz I, faz II çalışmalar sunitinibin etkili tedavi seçeneği olduğunu göstermiştir. Tümör boyutunda etkin küçülme olmasa da sunitinibin hastalıkta stabilizasyon sağladığı görülmüştür[17]. Motzer ve ark.'ın tedavi almamış 750 bhRHK hastasının olduğu bir faz III çalışması sunitinib ile IFN kullanımı karşılaştırmış ve PS sırası ile 11 ay, 5 ay bulunmuştur (p<0,0001). Objektif yanıt oranı ise %31'e %6 (p<0,001) olarak bulunmuştur. Ortanca sağkalımlar sırası ile 26,4 ay, 21,8 ay olarak gerçekleşmiş ve istatistiksel anlamlı fark (p=0,051) görülememiştir[18]. Bu durum IFN sonrası progresyon gelişen hastaların da TKİ kullanmasına bağlı olabileceği öne sürülmüştür.

Çalışmanın 2009'da güncel verileri açıklandığında IFN grubundaki hastaların diğer tedavileri (sunitinib

%33, diğer anti-VEGF %32) aldığı saptanmıştır. Başka tedavi almamış sadece sunitinib almış 193 hasta ve sadece IFN almış 162 hasta tespit edilmiş ve karşılaştırma yapılmıştır. Sadece sunitinib almış grubun genel sağkalımı 28,1 ay iken IFN almış grupta 14,1 ay bulunmuştur (p=0,003) [6]. Bizim çalışmamızda mRHK olup sunitinib alan hastaların sağ kalımları incelendiğinde PS 15 ay olarak bulundu. Hastaların genel sağkalımları ise Motzer ve ark.'ın çalışmasıyla benzer olarak bulundu.

Sternberg ve ark.'ı tedavi almayan 233 hasta ya da sitokin almış 435 metastatik bhRHK hastasını dahil ettikleri çalışmalarında pazopanib ile plasebo karşılaştırılmıştır. Çalışmadaki hastaların hepsi değerlendirildiğinde pazopanib alan grupta PS 9,2 ay iken plasebo grubunda 4,2 ay bulunmuştur (p<0,0001). Çalışmadaki daha önceden tedavi almamış 233 hasta ayrıca değerlendirildiğinde pazopanib grubunun PS 11,1 ay, plasebo grubunun ise 2,8 ay olarak bulunmuştur (p<0,0001) (137). Ayrıca sitokin almış olan pazopanib grubunda PS 7,4 ayken plasebo grubunda PS 4,2 ay (p<0,001) saptanmıştır [19]. Sunitinib ile karşılaştırıldığı (COMPARZ) çalışmada benzer sağkalım oranları (pazopanib: 8,4 ay, sunitinib: 9,5 ay) saptanırken pazopanibde daha iyi hayat kalitesi elde edilmiştir[20]. Diğer çalışmada (PISCES) ise hastaların yan etkiler nedeniyle pazopanibi sunitinibe tercih etttikleri görülmüştür[21]. Bizim yapmış olduğumuz çalışmada ise pazopanib alan hastaların PS 15 ay olarak bulundu. Genel sağkalımları değerlendirildiğinde 24 ay olarak bulundu.

Sonuç olarak çalışmamızda 01.12.2010-30.04.2018 arasında mRHK tanısı almış ve TKİ kullanmış olan 65 hastanın demografik, histopatolojik özellikleri ve tedavilerinin retrospektif olarak değerlendirmesi yapıldı. Hastalar birinci basamakta IFN-α tedavisi aldı ve sonraki basamakta TKİ tercihleri değerlendirildi. Tedavi cevaplarında, IFN-α sonrası tedavi seçeneklerinden sunitinib ve pazopanip kullanan hastalar karşılaştırıldı. Literatürde TKİ kullanımı plasebo ve IFN-α ile karşılaştırılmış GS ve PS üzerinde daha etkin olduğu görülmüştür. Bizim çalışmamızda da literatüre benzer sağkalım sonuçlarına ve genel yan etki profilleri de rastlandı.

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ORIGINAL RESEARCH

Prediction of Proximal Humerus Morphometric Characteristics for Patient-Specific Humerus Prosthesis Design

Alper VATANSEVER, Serdar BABACAN, Kemal GÜLŞEN, Gizem ÇETIN, Mahinur Rabia KARAKILIÇ

Bursa Uludag University Faculty of Medicine, Department of Anatomy, Bursa, Türkiye.

ABSTRACT

The human arm and shoulder joint depend on the humerus, which is the bone that bears the most weight in the upper limb. An individual's quality of life could be affected by a humeral fracture; the rigid geometry of current prosthetic systems complicates the process of obtaining anatomical restoration after arthroplasty. This study aimed to generate hypotheses about the morphometric properties of the proximal end of the humerus, derived from the morphometric characteristics of the distal end of the individual's humerus, to enable the construction of a personalized humeral prosthesis. There were 33 dry humerus bones used in the study; IBM SPSS Statistics was used for statistical analysis. This paper developed predictive linear regression models using 33 dry humeral bones in order to determine proximal humerus morphometric features. The approach showed developments in patient-specific humeral prosthetic design and offers a solution to problems related with current standardized prosthetic systems. The thorough approach, clinically relevant approach, and clear presentation of results of the study make it a major source for building patient-specific humeral prosthesis. The developed equations might improve surgical results and patient quality of life. Validating these equations in vivo using CT imaging and clinical data should be given priority in future studies.

Keywords: Anatomy. Morphometry. Prosthesis. Humerus. Fracture.

Kişiye Özgü Humerus Protezi Dizaynı için Humerus'un Proksimal Bölümünün Morfometrik Özelliklerinin Tahmin Edilmesi

ÖZET

İnsan kolu ve omuz eklemi, üst ekstremitedeki en fazla ağırlık taşıyan kemik olan humerus'a bağlıdır. Bir bireyin yaşam kalitesi, bir humerus kırığı tarafından etkilenebilir; mevcut protez sistemlerinin kalıp geometrisi, artroplasti sonrası anatomik restorasyon elde etme sürecini karmaşıklaştırır. Bu çalışmada, bireyin humerus'unun distal ucunun morfometrik özelliklerinden türetilen, humerus'un proksimal ucunun morfometrik özellikleri hakkında hipotezler oluşturmak amaçlandı ve böylece kişiselleştirilmiş bir humeral protez dizaynı geliştirme yönünde yeni formüller ortaya kondu. Çalışmada 33 kuru humerus kemiği kullanıldı; istatistiksel analiz için IBM SPSS Statistics v28.0 kullanıldı. Bu makale, proksimal humerus morfometrik özelliklerini belirlemek amacıyla 33 kuru humerus kemiği kullanarak öngörücü doğrusal regresyon modelleri geliştirmiştir. Yaklaşım, hasta spesifik humeral protez tasarımında gelişmeler gösterdi ve mevcut standartlaştırılmış protez sistemleriyle ilgili sorunlara bir çözüm sundu. Kapsamlı yaklaşım, klinik olarak ilgili yaklaşım ve çalışmanın sonuçlarının net sunumu, hasta spesifik humeral protezlerin oluşturulmasında önemli bir kaynak haline getiriyor. Geliştirilen denklemler, cerrahi sonuçları ve hasta yaşam kalitesini artırabilir. Bu denklemlerin in vivo olarak CT görüntüleme ve klinik veriler kullanılarak doğrulanması, sonraki çalışmalarda ön planda olmalıdır.

Anahtar Kelimeler: Anatomi. Morfometri. Protez. Humerus. Kırık.

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Alper VATANSEVER,
Bursa Uludag University Faculty of Medicine,
Department of Anatomy,
Bursa, Türkiye
Phone: +902242953815
E-mail: avatansever@uludag.edu.tr

Authors' ORCID Information
Alper VATANSEVER: 0000-0002-3632-1020
Serdar BABACAN: 0000-0002-7410-7738
Kemal GÜLŞEN: 0000-0002-4944-1451
Gizem ÇETIN: 0009-0002-0390-2942
Mahinur Rabia KARAKILIÇ: 0009-0008-4701-9522

The humerus is the largest bone of the upper extremity and defines the human brachium. The humeral and cubital joints are two important joints that are used in daily lives. Proximally, the shoulder joint is formed by the humeral head articulating with the glenoid cavity, and distally, it articulates with the radius and ulna through the cubital joint. The most proximal part of the humerus is the caput humeri, and it forms a ball-and-socket joint with the shallow cavity called the glenoid cavity on the scapula. Because it combines the structure of two important joints, any pathology in this bone affects the individual's life quality[1-4]. About 5% of the fractures showing up to the emergency room are proximal humerus fractures. Patients with poor bone

quality, those unsuitable for osteosynthesis, those in poor health, and those with low rehabilitation potential, as well as those with poor fracture dislocation and multiple anatomical neck fractures are advised hemiarthroplasty, a shoulder replacement whereby the humerus is replaced with a metal implant and the other part of the shoulder joint belonging to the scapula is left intact[4,5]. However, it was shown that restoring normal anatomy during arthroplasty could be challenging due to the relatively fixed geometry of current prosthetic systems[2]. Therefore, the dimensional data of the proximal end of the humerus are important for the optimal design of prosthetic components[3]. Recent designs for the replacement of the proximal end of the humerus with a prosthesis have emphasized the importance of accurately reconstructing the normal three-dimensional anatomy. For replacing the proximal part of the humerus with a prosthesis is to recreate normal anatomy, it is important to understand the normal humeral morphology in three dimensions[6]. The gold standard for determining the premorbid anatomy of a fractured bone is to mirror the contralateral side and use it as a template for reconstruction. However, this approach has its limitations; it requires a computed tomography (CT) scan of both arms, the contralateral humerus must be healthy, and there may be differences in the morphology of the dominant and non-dominant humerus[7].

This could also cause the approach to be suboptimal[7]. The aim of the study is to develop formulas that predict the morphometric characteristics of the proximal end of the humerus based on the morphometric features of the distal end of the individual's humerus to design a personalized humerus prosthesis.

Material and Method

This study commenced after receiving ethical approval from Institutional Ethical Board (Degree No. 2025/4-11).

The study was performed on 33 dry humeri of unknown age and sex and without distinction between right and left sides, in the Anatomy Laboratory of the authors' institution. Bones with anatomical variations, pathology, erosion and fractures that would affect the measurement and statistical results were not included in the study. As a result of the power analysis test performed to determine the number of humeri to be used in the study, using a two-sided test, 5% significance level test (α=0.05) and 80% power (β=0.2) for an effect size of 0.75, the required sample size was approximately 33 (n=33) humerus.

Morphometric measurements were performed by the same researcher using a manual caliper with sensitivity of 0.1 millimeter (mm) in the standard position in the morphometry laboratory. Three researchers observed the measurements to ensure standardization. Standardization. The researchers observed the researcher who made the main measurement and checked whether the measurement was between the correct landmarks, whether the measurement on the caliper was read correctly, and whether the measurement added to the data set was added correctly. Maximum length of the humerus (MLH), humeral shaft diameter (HSD) (Figure 1), eleven perimeters of the proximal part (Figure 2) and sixteen perimeters (Figure 3) of the distal part of the humerus were measured.

Figure 1.
Maximum length of the humerus (MLH), Humeral shaft diameter (HSD)

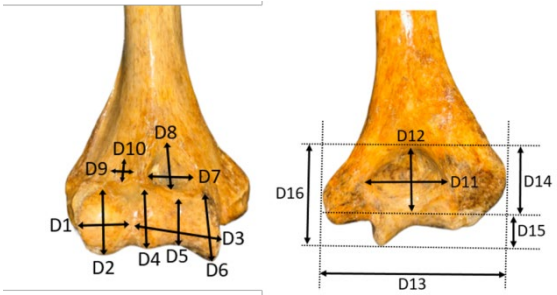

Figure 2.
Variables measured on the proximal part of the humerus. P1- Humeral head transverse diameter; P2- Humeral head vertical diameter; P3- Anatomical neck diameter; P4- Surgical neck diameter; P5- Intertubercular sulcus length; P6- Intertubercular sulcus width; P7- Intertubercular sulcus depth; P8- Humeral head height; P9- Angle between humeral head and humeral shaft; P-10 Vertical distance between the top of the greater tubercle and the top of the humeral head; P11- Distance between the lower border of the humeral head and the upper point of the greater tubercle

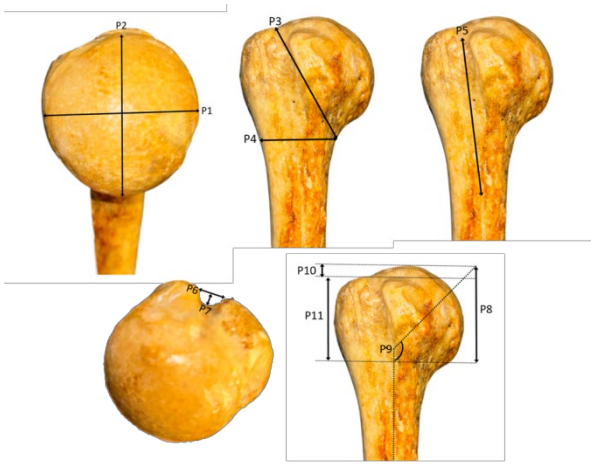

Figure 3.
Variables measured on the distal part of the humerus. D1- Capitulum humeri width; D2- Capitulum humeri height; D3- Trochlea humeri width; D4- Lateral height of humeral trochlea; D5- Medial height of humeral trochlea; D6- Median height of humeral trochlea; D7- Width of coronoid fossa; D8- Height of coronoid fossa; D9- Radial fossa width; D10- Radial fossa height; D11- Olecranon fossa width; D12- Olecranon fossa height; D13- Epicondylar width; D14- Distance between the upper and lower borders of the olecranon fossa; D15- Distance between the lower border of the olecranon fossa and the lower border of the trochlea humeri; D16- Distance between the distal end of the humerus and the upper border line of the olecranon fossa

Statistical data analyses were performed in IBM SPSS 29.0.2.0 (IBM Corp. Released 2023. IBM SPSS Statistics for Windows, Version 29.0.2.0 Armonk, NY: IBM Corp.). The descriptive statistical analysis was performed for Median (Med) ((Minimum (Min) – Maximum (Max)) and Mean ± Standard Deviation (SD) values of the data. We performed the stepwise multiple linear regression analysis to develop equations to estimate the dimensions of the proximal part of the humerus using the morphometric characteristics of the distal part of the humerus, which were correlated. Statistically, the significance level was accepted as α=0.05.

Results

In the study, 33 dry humeri of unknown gender and age were used without any distinction between right and left. Statistical findings of the measurements taken from the bones are given in Median (Minimum-Maximum) and Mean ± Standard Deviation in Table I.

Table I. Descriptive statistics of measured variables on the humerus (mm)

Variables	Med (Min-Max)	Mean ± SD
MLH- Maximum length of the humerus	323.00 (280.00 – 354.00)	324.09 ± 17.02
P1- Humeral head transverse diameter	44.00 (37.00 – 49.00)	43.63 ± 2.56
P2- Humeral head vertical diameter	47.00 (39.00 – 52.00)	46.72 ± 3.13
P3- Anatomical neck diameter	47.00 (39.00 – 53.00)	46.84 ± 3.28
P4- Surgical neck diameter	31.00 (24.00 -36.00)	30.63 ± 3.43
P5- Intertubercular sulcus length	71.00 (50.00 – 115.00)	71.45 ± 11.84
P6- Intertubercular sulcus width	9.00 (7.00 – 10.00)	8.63 ± 1.08
P7- Intertubercular sulcus depth	5.00 (3.00 -7.00)	4.83 ± 0.69
P8- Humeral head height	38.00 (32.00 -45.00)	38.24 ± 3.24
P9- Angle between humeral head and humeral shaft	125.00 (112.00 - 136.00)	124.69 ± 5.36
P-10 Vertical distance between the top of the greater tubercle and the top of the humeral head	6.00 (3.00 -7.00)	5.48 ± 1.17
P11- Distance between the lower border of the humeral head and the upper point of the greater tubercle	32.00 (24.00 -39.00)	31.96 ± 3.54
HSD- Humeral shaft diameter	21.00 (17.00 -26.00)	21.27 ± 1.95
D1- Capitulum humeri width	17.00 (11.00 -21.00)	17.27 ± 1.79
D2- Capitulum humeri height	21.00 (17.00 – 25.00)	20.84 ± 1.84
D3- Trochlea humeri width	27.00 (24.00 – 33.00)	27.27 ± 2.06
D4- Lateral height of humeral trochlea	19.00 (15.00 – 22.00)	19.12 ± 1.89
D5- Medial height of humeral trochlea	25.00 (20.00 – 30.00)	24.93 ± 2.30
D6- Median height of humeral trochlea	17.00 (14.00 -21.00)	16.96 ± 1.89
D7- Width of coronoid fossa	14.00 (11.00 – 18.00)	14.15 ± 1.97
D8- Height of coronoid fossa	11.00 (7.00 -16.00)	10.87 ± 1.69
D9- Radial fossa width	11.00 (8.00 – 13.00)	10.45 ± 1.17
D10- Radial fossa height	9.00 (6.00 – 11.00)	8.60 ± 1.14
D11- Olecranon fossa width	25.00 (19.00 – 29.00)	24.96 ± 2.43
D12- Olecranon fossa height	17.00 (14.00 -21.00)	17.78 ± 1.74
D13- Epicondylar width	63.00 (53.00 – 72.00)	62.60 ± 4.32
D14- Distance between the upper and lower borders of the olecranon fossa	19.00 (16.00 -22.00)	19.57 ± 1.87
D15- Distance between the lower border of the olecranon fossa and the lower border of the trochlea humeri	18.00 (13.00 -21.00)	17.39 ± 2.01
D16- Distance between the distal end of the humerus and the upper border line of the olecranon fossa	37.00 (31.00 – 40.00)	36.30 ± 2.55)

The stepwise multiple linear regression equations were developed to estimate the dimensions of the proximal part of the humerus from the morphometric measurements taken from the distal part of the humerus using the values correlated between the proximal part and the distal part of the humerus, the adjusted R squared and the standard error of the estimate values was given in Table II.

Table II. The Stepwise multiple linear regression equations estimating the dimensions of the proximal part of the humerus from morphometric characteristics of the distal part (mm)

Equations	Model Significance Test statistics	P value	Adjusted R^2	Standard Error of the Estimation
MLH- Maximum length of the humerus (mm)=70.128 + (1.987 x HSD) + (2.021 x D1) – (2.004 x D2) + (1.576 x D3) + (2.964 x D5) + (2.540 x D7) + (1.810 x D16)	F(7;25)=7.755	<0.001	0.596	10.817
P1- Humeral head transverse diameter (mm)= 8.405 + (0.256 x HSD) + (0.309 x D1) + (0.347 x D3) + (0.313 x D5) – (0.310 x D10) + (0.503 x D14)	F(6;26)=8.430	<0.001	0.582	1.655
P2- Humeral head vertical diameter=1.507 + (0.354 x HSD) + (0.508 x D1) + (0.581 x D3) + (0.368 x D5) – (0.308 x D6) + (0.693 x D7) + (0.294 x D16) – 0.344 x D2) – (0.402 x D9)	F(8;24)=8.655	<0.001	0.667	1.810
P3- Anatomical neck diameter= -9.119 + (0.617 x HSD) + (0.489 x D1) + (0.510 x D3) – (0.522 x D9) – (0.456 x D12) + (0.212 x D13) + (0.562 x D14) + (0.269 x D16)	F(8;24)=7.757	<0.001	0.628	2.006
P4- Surgical neck diameter=-16.0908 + (0.829 x HSD) – (0.433 x D2) + (0.317 x D3) – (0.422 x D4) + (0.752 x D12) + (178 x D13) + (0.796 x D15)	F(7;25)=8.724	<0.001	0.628	2.095
P5- Intertubercular sulcus length=43.336 + (1.575 x HSD) + (1.858 x D6) + (2.292 x D7) – (5.027 x D9) + (5.374 x D10) – (1.528 x D11) – (1.271 x D14)	F(7;25)=3.069	<0.001	0.312	9.824
P6- Intertubercular sulcus width= -1.422 + (0.105 x HSD) + (0.143 x D3) – (0.252 x D7) + (2.16 x D11) + (0.118 x D12)	F(5;27)=7.520	<0.001	0.505	0.763
P7- Intertubercular sulcus depth= 4.960 – (0.092 x HSD) + (0.075 x D2) – (0.094 x D8) – (0.156 x D10) + (0.148 x D12)	F(5;27)=2.556	0.051	0.196	0.621
P8- Humeral head height=17.852 + (0.436 x HSD) + (0.580 x D3) – (0.658 x D4) – (1.026 x D5) + (1.051 x D6) – (0.442 x D7) + (0.450 x D14) + (0.754 x D15)	F(8;24)=2.448	0.043	0.266	2.735
P9- Angle between humeral head and humeral shaft= 137.892 + (0.881 x D1) + (1.136 x D3) – (0.937 x D6) – (1.170 x D8) – (2.124 x D10) – (0.287 x D13) – (1.327 x D15) + (0.786 x D16)	F(8;24)=1.787	0.129	0.181	4.856
P10- Vertical distance between the top of the greater tubercle and the top of the humeral head= 1.237 + (0.192 x HSD) 0.176 x D1) – (0.205 x D3) + (0.217 x D5) – (0.235 x D6) + (0.311 x D7) – (0.224 x D10) + (0.151 x D14) – (0.236 x D15)	F(9;23)=1.885	0.129	0.199	1.052
P11- Distance between the lower border of the humeral head and the upper point of the greater tubercle= 3.212 + (0.651 x HSD) + (0.631 x D2) + (0.653 x D3) – (1.472 x D4) – (1.037 x D5) + (1.461 x D6) – (0.538 x D8) + (0.545 x D11) – (0.497 x D12) + (0.818 x D15)	F(10;22)=4.204	0.002	0.500	2.502

The equation with an adjusted R^2 value of 0.667 has the highest prediction percentage among the developed equations and the standard error of the estimation of the equation was 1.810.

Discussion and Conclusion

From distal humerus measurements, this study efficiently built predictive linear regression equations to determine proximal humerus morphometric characteristics. This approach offers a reasonable solution to the problems connected with current standardized prosthetic systems and shows a clear development in the field of patient-specific humerus prosthetic design.

The main strength of this study was its practically appropriate and clinically relevant method. Using easily measured morphometric variables of distal humeri, the study provides a basis for estimating proximal anatomy. When contralateral imaging is unavailable or inaccurate, such as in bilateral fractures or when the other humerus exhibits disease, this method could be very helpful[8]. The established equations provide surgeons and prosthetic designers with a useful tool to personalize implants, hence potentially improving functional results and reducing issues.

The rigorous approach adopted in this study increases its validity. One researcher applying a specific measuring technique under validation by three observers decreases inter-observer variability and ensures data consistency[9]. Based on a clinically appropriate effect size, the estimation of sample size by means of power analysis shows a commitment to statistical accuracy. Moreover, a clear and understandable model for estimating proximal humerus dimensions is provided by linear regression analysis, appropriate for discriminating linear correlations among variables[8,10].

This study could help to create prediction equations. The equations shown in Table II offer a straightforward, quantitative method for evaluating proximal humerus form. Reflecting the variance in the dependent variable explained by the independent variables, the modified R-squared values show a strong predictive power of the produced models. The standard error of the estimate would help physicians to understand the likely range of variability by quantifying the accuracy of projections[11].

Especially relevant to prosthetic design was the focus on morphometric characteristics. Restoring suitable joint kinematics and stability depends on exact repair of the humeral head and other proximal features. This work presented equations that satisfy this demand by providing a means to estimate these fundamental dimensions using distal observations. This approach

could increase the precision of implant choice and placement, therefore producing better patient results[12].

Using dry bone specimens offers a controlled environment for data collection, even though it limits the research to anatomical measurements. This approach would help to assess bone shape assess bone shape more precisely by eliminating the confusing factors linked to soft tissue and image artefacts. This controlled environment ensures the highest data accuracy acquired.

The clear and concise presentation of data, including descriptive statistics and regression analysis, would help physicians to understand and apply the results. Tables I and II provided a complete overview of the data, therefore allowing readers to quickly acquire and use the knowledge. The credibility of the study was enhanced and its application in clinical practice would be facilitated by the clarity in data presentation.

By means of measurements of the distal humerus, this work efficiently generated prediction equations for ascertaining the morphometric features of the proximal humerus. The virtues of this study were highlighted by the strict methodology, therapeutically relevant approach, and clear presentation of results. The developed equations offer a great tool for the design of patient-specific humeral prosthesis, thereby improving patient quality of life and maybe leading to improved surgical results. Future studies should focus on verifying these equations in vivo using CT imaging and clinical data and investigate the likely impact of these forecasts on prosthesis design and patient outcomes.

Orthopedic studies conducted on dry bones can indeed be beneficial for in vivo clinical trials, as they provide foundational insights into bone morphology and material properties that are crucial for developing and testing new orthopedic materials and treatments. These studies allow researchers to understand the structural and functional aspects of bones without the ethical and practical challenges associated with in vivo studies. This foundational knowledge can then be applied to in vivo settings to enhance the development and evaluation of orthopedic interventions. Dry bone studies, such as those using CT scans, provide detailed information on trabecular bone morphology, which is essential for understanding bone strength and adaptation. This information can be used to infer functional adaptations and compare them with in vivo data, as demonstrated by the Bone Ratio Predictor method, which links dry and fresh bone data[13]. Dry bones serve as a platform for testing new biomaterials, such as the 3D bioactive scaffolds designed for bone regeneration. These scaffolds are evaluated for their mechanical properties and biocompatibility before being tested in vivo, ensuring that only promising materials proceed to clinical trials[14].

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ORIGINAL RESEARCH

Real-World Experience with Canakinumab in Familial Mediterranean Fever: A Single-Center Study

Tuğba OCAK[1], Ayşe BULUR[2], Burcu YAĞIZ[3], Belkıs Nihan COŞKUN[3], Hüseyin Ediz DALKILIÇ[3], Yavuz PEHLİVAN[3]

[1] Bursa City Hospital, Department of Rheumatology, Bursa, Türkiye.
[2] Bursa Uludag University Faculty of Medicine, Department of Internal Medicine, Bursa, Türkiye.
[3] Bursa Uludag University Faculty of Medicine, Department of Rheumatology, Bursa, Türkiye.

ABSTRACT

Familial Mediterranean fever (FMF) is an autoinflammatory disorder caused by mutations in the Mediterranean fever gene (MEFV), leading to excessive interleukin-1 beta (IL-1β) production. While colchicine is the primary treatment for FMF, a subset of patients exhibits resistance or intolerance, necessitating alternative therapeutic strategies. Canakinumab, a selective IL-1β inhibitor, has emerged as a potential treatment option. This study aims to evaluate canakinumab's real-world efficacy and safety in colchicine-resistant or colchicine-intolerant FMF patients. A retrospective, single-center study was conducted on FMF patients aged over 18 who initiated canakinumab treatment between January 2013 and October 2023. A total of 34 patients experiencing colchicine resistance or intolerance criteria were analyzed. Clinical and laboratory parameters, including Pras scores, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum amyloid A (SAA), were assessed before and after canakinumab treatment. Statistical analyses were performed using the Wilcoxon test and paired sample t-test. Canakinumab treatment significantly reduced Pras scores ($p<0.001$), ESR ($p<0.001$), CRP ($p<0.001$), and SAA levels ($p<0.001$). A decrease was observed post-treatment among patients with proteinuria, though not statistically significant ($p=0.140$). Treatment was discontinued in three patients due to active disease or adverse effects. No serious infections were reported. In conclusion, canakinumab could be a promising treatment option in colchicine-resistant or colchicine-intolerant FMF patients.

Keywords: Canakinumab. Colchicine. Familial Mediterranean fever.

Ailevi Akdeniz Ateşinde Kanakinumab ile Gerçek Yaşam Deneyimi: Tek Merkezli Bir Çalışma

ÖZET

Ailesel Akdeniz ateşi (AAA), Mediterranean Fever (MEFV) geninde mutasyonların neden olduğu ve aşırı interlökin-1 beta (IL-1β) üretimine yol açan otoinflamatuar bir hastalıktır. Kolşisin AAA için ana tedavi olsa da, hastaların bir alt grubu direnç veya intolerans göstererek alternatif tedavi stratejilerine ihtiyaç duymaktadır. Selektif bir IL-1β inhibitörü olan kanakinumab, potansiyel bir tedavi seçeneği olarak ortaya çıkmıştır. Bu çalışma, kolşisine dirençli veya kolşisine intoleransı olan AAA hastalarında kanakinumabın gerçek yaşamdaki etkinliğini ve güvenliğini değerlendirmeyi amaçlamaktadır. Ocak 2013 ve Ekim 2023 tarihleri arasında kanakinumab tedavisine başlayan 18 yaş üstü AAA hastalarında retrospektif, tek merkezli bir çalışmadır. Kolşisin direnci veya intoleransı kriterlerini karşılayan toplam 34 hasta analiz edildi. Pras skorları, eritrosit sedimantasyon hızı (ESR), C-reaktif protein (CRP) ve serum amiloid A (SAA) dahil olmak üzere klinik ve laboratuvar parametreleri kanakinumab tedavisinden önce ve sonra değerlendirilmiştir. İstatistiksel analizler Wilcoxon testi ve eşleştirilmiş örneklem t-testi kullanılarak gerçekleştirilmiştir. Kanakinumab tedavisi Pras skorlarını ($p<0,001$), ESR ($p<0,001$), CRP ($p<0,001$) ve SAA düzeylerini ($p<0,001$) anlamlı ölçüde azaltmıştır. Proteinürisi olan hastalarda tedavi sonrasında istatistiksel olarak anlamlı olmasa da bir düşüş gözlenmiştir ($p=0,140$). Aktif hastalık veya yan etkiler nedeniyle üç hastada tedavi kesilmiştir. Hiçbir ciddi enfeksiyon bildirilmemiştir. Sonuç olarak, kanakinumab kolşisine dirençli veya kolşisine intoleranslı AAA hastalarında umut verici bir tedavi seçeneği olabilir.

Anahtar Kelimeler: Kanakinumab. Kolşisin. Ailevi Akdeniz Ateşi.

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Dr. Tuğba OCAK
Department of Rheumatology, Bursa City Hospital, Bursa, Türkiye
Phone: 0507 011 89 08
E-mail: tugba@uludag.edu.tr

Authors' ORCID Information:
Tuğba OCAK: 0000-0002-4560-1569
Ayşe BULUR: 0009-0007-7962-8472
Burcu YAĞIZ: 0000-0002-0624-1986
Belkis Nihan COŞKUN: 0000-0003-0298-4157
Hüseyin Ediz DALKILIÇ: 0000-0001-8645-2670
Yavuz PEHLİVAN: 0000-0002-7054-5351

Familial Mediterranean fever (FMF) is an autoinflammatory disease with autosomal recessive inheritance.[1] It is characterized by fever and recurrent episodes of serositis, usually lasting 12-72 hours.[2] FMF treatment aims to reduce the frequency of clinical attacks and suppress subclinical inflammation.[3] Inadequate treatment can lead to secondary amyloidosis, which is associated with high morbidity and mortality.[4,5] The Mediterranean fever gene (MEFV) responsible for the disease is localized in the 16p13.3 region. The MEFV gene, which consists of ten exons and 781 amino acids, encodes the pyrin protein. Mutations in the MEFV gene disrupt pyrin function and, thus, lead to uncontrolled production of interleukin-1 beta (IL-1β).[6] IL-1β is the triggering cytokine for the onset of an FMF attack.

Colchicine, the primary treatment for FMF, is highly effective in controlling attacks and preventing the development of amyloidosis.[7] However, 5–10% of patients do not respond to or resist colchicine.[8] In addition, colchicine cannot be used at adequate doses in some patients due to side effects or intolerance.[9] IL-1 inhibition is a safe and effective treatment for FMF patients who do not respond to or are intolerant to colchicine.[10,11] The IL-1 inhibitors used in Türkiye are anakinra and canakinumab. Canakinumab is a human monoclonal antibody that selectively targets IL-1β.[12] The first case report of a colchicine-resistant FMF patient who responded to treatment with canakinumab was published in 2011.[13] Later, case series with short follow-ups and small sample sizes were reported on the use of canakinumab in FMF patients.[14-17] There is limited real-life data on canakinumab's long-term efficacy and safety in FMF patients.[18-21] Our study aimed to present our experience using canakinumab in FMF patients who are colchicine-resistant or colchicine-intolerant at a single center.

Material and Method

Study Population

In our center, patients over 18 years of age who initiated canakinumab treatment between January 2013 and October 2023 with a diagnosis of FMF according to the Tel-Hashomer[22] and New Eurofever/PRINTO classification criteria[23] were evaluated using the hospital's electronic system. There were 46 patients for whom canakinumab treatment was initiated with a diagnosis of FMF. Of these patients, 12 patients who had a follow-up time of fewer than 3 months, were not regularly followed up at our center, and had missing clinical data in the hospital's electronic system were excluded from the study. The number of patients enrolled in the study was 34; all enrolled patients were either colchicine-resistant or colchicine-intolerant. Colchicine resistance was defined as having at least one attack per month despite taking the maximum tolerated dose of colchicine.[23] Colchicine intolerance was defined as the inability to increase the effective colchicine dose due to gastrointestinal side effects, especially diarrhea, nausea, and abdominal pain.[24]

Study Design and Data Collection

Patient demographics, attack characteristics at diagnosis, presence of the MEFV gene, presence of amyloidosis, family history of FMF, colchicine doses before canakinumab treatment, anakinra status prior to canakinumab treatment, the duration of disease at the start of canakinumab treatment, the follow-up period under canakinumab treatment, the duration of canakinumab treatment interval extending and the reasons for treatment discontinuation were recorded retrospectively using the hospital's electronic system. The diagnosis of patients with amyloidosis was verified by tissue biopsy. The Pras score, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum amyloid A (SAA) levels at the last visit before treatment with canakinumab and at the last visit with canakinumab were used to assess the response to treatment with canakinumab. The proteinuria values of patients with proteinuria were evaluated before and after treatment. The Pras score includes age at disease onset, frequency of attacks, dose of colchicine administered to control attacks, joint involvement, erysipelas-like erythema, and presence of amyloidosis.[25] Remission was accepted as the absence of attacks in the last 6 months and normal acute phase reactant levels during the attack-free period.

Statistical Analysis

Statistical analysis was conducted using SPSS (Statistical Package for Social Sciences) version 26.0. Descriptive statistics measured the patient's sociodemographic, clinical, and laboratory parameters. The normality of variables was assessed using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Quantitative data are expressed as mean ± standard deviation for normal distribution and median (minimum-maximum) for non-normal distribution. The Wilcoxon test was used to evaluate treatment response and determine whether there was a relationship between the data Pras score, ESR, CRP, and SAA levels before and after canakinumab. A paired sample T-test was used to compare the proteinuria levels of patients with proteinuria before and after canakinumab.

Results

The demographic and clinical characteristics of 34 patients with FMF treated with canakinumab are shown in Table I. The mean FMF diagnosis age of the

patients was 19.7±11.1 years, and 19 (55.8%) were male. The median time between diagnosis and initiation of treatment with canakinumab was 15 (1.8-50.6) years. The most common symptom at diagnosis was abdominal pain (n=30, 80.2%). MEFV mutation was analyzed in 29 patients. Of these patients, 10 were M694V homozygous, 6 M680I heterozygous, 3 M694V heterozygous, 3 M694V/V726A positive, 2 M680I homozygous and 1 E148Q heterozygous. The MEFV mutation was negative in 4 patients. Amyloidosis was present in 4 patients. A kidney biopsy was performed in two patients, a rectal biopsy in one patient, and a colon biopsy in one patient to determine the presence of amyloidosis. The most common comorbidity was hypertension (n=6, 17.6%). All patients had been treated with colchicine before treatment with canakinumab, and the median colchicine dose was 1.5 (1-2) mg. Twenty-one (61.8%) patients had received anakinra before treatment with canakinumab. Among patients receiving anakinra treatment, 14 had active disease with anakinra, and 7 had side effects with anakinra.

The mean follow-up time under canakinumab treatment was 49.1±35.1 months. Treatment with canakinumab was started at 150 mg once a month in all patients. A complete remission was achieved in 23 patients (67.6 %) and a partial response in 8 patients (23.5 %). The dosing interval for canakinumab was extended in 5 patients in remission during treatment. The median duration of the extending of the canakinumab dosing interval was 14.1 (7.9-104.2) months. The canakinumab doses of the patients in whom the dosing interval was extended were initially adjusted to 150 mg every 6 weeks. No activation was observed in the patients with extended dosing intervals during a follow-up period of 51.4±26.5 months. In two patients with extended dose intervals, the canakinumab dose was adjusted to 150 mg every 8 weeks.

Efficacy and Side Effects

Pras score, ESR, CRP, and SAA values were analyzed before and after treatment with canakinumab to evaluate the efficacy of canakinumab treatment. Statistically significant differences in Pras score, ESR, CRP, and SAA values were found after treatment with canakinumab compared to before treatment ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, respectively). The creatinine value before canakinumab was 0.78 (0.55-5.85), the creatinine value after canakinumab was 0.76 (0.52-5.92) and there was no statistically significant difference ($p=0.092$). In 7 patients with proteinuria, proteinuria was 4698±4691 mg/day before treatment with canakinumab and decreased to 2084±1390 mg/day after treatment with canakinumab. However, no statistically significant difference was found between the proteinuria values before and after treatment with canakinumab ($p=0.140$). Treatment was discontinued in 3 patients. In 2 patients, treatment with canakinumab was discontinued after 4.3 and 8.4 months due to active disease during canakinumab treatment. In one patient, treatment with canakinumab was discontinued after 4.2 months due to dizziness.

Table I. Demographic and clinical features of FMF patients treated with canakinumab (n=34)

Age, years, median (min.-max.)	37.6 (25.4-74.9)
Gender (F/M)	15/19
FMF diagnosis age, years, mean ± std deviation	19.7±11.1
Age at onset of canakinumab therapy, years, median (min.-max.)	33.4 (21.8-72.4)
Time between diagnosis and canakinumab therapy, years, median (min.-max.)	15 (1.8-50.6)
Family history FMF n (%)	14 (41.2)
Fever n (%)	24 (70.6)
Abdominal pain n (%)	30 (80.2)
Chest pain n (%)	7 (20.6)
Arthralgia/Arthritis n (%)	15 (44.1)
Myalgia n (%)	9 (26.5)
Erysipelas-like erythema n (%)	2 (5.9)
Hepatomegaly n (%)	3 (8.8)
Splenomegaly n (%)	6 (17.6)
Amyloidosis n (%)	4 (11.8)
Comorbidities n (%)	16 (47.1)
Hypertension n (%)	6 (17.6)
Chronic renal failure n (%)	5 (14.7)
Spondyloarthropathies n (%)	4 (11.8)
Coronary artery disease n (%)	3 (8.8)
Hyperlipidemia n (%)	2 (5.9)
Pulmonary disease n (%)	2 (5.9)
Diabetes mellitus n (%)	1 (2.9)
Anakinra treatment before canakinumab n (%)	21 (61.8)
Colchicine dose before canakinumab, mg, median (min.-max.)	1.5 (1-2)
Colchicine dose after canakinumab, mg, median (min.-max.)	1.5 (1-2)
Duration of canakinumab, months, mean ± std deviation	49.1±35.1

Min: Minimum, Max: Maximum, F: Female, M: Male. Std: Standard, FMF: Familial Mediterranean Fever

Table II. Comparison of treatment responses before and after canakinumab

	Before canakinumab	After canakinumab	p
PRAS, median (min.-max.)	6 (3-12)	2 (0-5)	<0.001
ESR, mm/h, median (min.-max.)	10.5 (2-80)	4.5 (2-32)	<0.001
CRP, mg/L, median (min.-max.)	10 (2-289)	2 (2-82)	<0.001
SAA mg/L, median (min.-max.)	43.5 (2-1370)	9.5 (2-60)	<0.001

PRAS: Disease Severity Score, Min: Minimum, Max: Maximum, ESR: Erythrocyte Sedimentation Rate, CRP: C-reactive protein, SAA: Serum Amyloid A.

Discussion and Conclusion

In this study, we evaluated the real-life efficacy and safety of canakinumab in FMF patients who were colchicine-resistant or colchicine-intolerant. Treatment with canakinumab resulted in a statistically significant reduction in Pras score, ESR, CRP, and SAA levels.

In FMF patients, colchicine is a treatment that prevents attacks and suppresses subclinical inflammation.[26,27] However, a group of patients do not respond to colchicine or develop intolerance to colchicine.[28] Several studies have shown the efficacy of canakinumab in colchicine-resistant FMF patients.[29-32] In a systematic review of eight studies, including 40 colchicine-resistant FMF patients, the complete and partial response rates to canakinumab were 68% and 32%, respectively.[31] In the study conducted by Ataş et al. with 27 FMF patients receiving canakinumab, disease activity was improved.[33] Similar to other studies, our study observed a significant decrease in disease activity scores and inflammatory markers with canakinumab treatment.

The aim of treatment in FMF patients is to prevent attacks and suppress inflammation. The most serious complication in FMF patients is amyloidosis. Controlling inflammation can prevent the development and progression of amyloidosis. Colchicine, the primary treatment for FMF, can reduce proteinuria. Sevillano et al. showed that IL-1 inhibitors reduce proteinuria.[34] In the study conducted by Ataş et al., 8 patients treated with canakinumab had proteinuria.[33] No decrease in proteinuria was observed in 6 of the patients. A decrease in proteinuria was observed in 2 patients previously treated with anakinra and in whom anakinra was discontinued due to side effects.[33] In our study, a decrease in proteinuria was observed after treatment with canakinumab in patients who had proteinuria at the start of treatment with canakinumab. However, this decrease was not statistically significant. This may be due to the small number of patients. Canakinumab could have a positive effect on renal involvement in FMF. However, more extensive studies with extended follow-up periods are needed to reduce proteinuria and prevent complications associated with amyloidosis. Data on the use of IL-1 inhibitors as monotherapy in amyloidosis are limited.[35-37] The standard approach is to use IL-1 inhibitors in combination with colchicine. In our study, treatment with colchicine was continued in all patients, along with treatment with canakinumab.

Canakinumab is administered at 150 mg every 4 weeks. There is no clear consensus on the optimal dose, the extension of the dosing interval, and the duration of treatment with canakinumab; in the study conducted by Akarcan et al., a standard tapering protocol was used in 9 pediatric FMF patients.[38] Four of the patients experienced a seizure 9.0±2.9 (6-12) months after discontinuation of treatment.[38] However, in practice, factors such as concomitant diseases and varying numbers and types of attacks during treatment may complicate the application of standard protocols for dose reduction or discontinuation of therapy. In our study, treatment with canakinumab was started every 4 weeks in all patients. In 5 patients in remission during treatment, the dose interval was extended. In the patients with prolonged dose intervals, no activation was observed during the 51.4±26.5-month follow-up period after prolongation of the dose interval. It may be appropriate to extend the canakinumab dosing intervals and duration of tapering depending on patient characteristics.

In terms of safety, canakinumab was generally well tolerated. However, two patients experienced active disease during treatment with canakinumab, and therapy was discontinued. No severe infection was observed during the follow-up. In a review of 40 colchicine-resistant FMF patients, no side effects related to canakinumab were observed in any patient. Two patients reported serious infections in a randomized controlled trial of 63 colchicine-resistant FMF patients.[32] In our study, no severe infection was observed during follow-up. Treatment with canakinumab was discontinued after 4.23 months in only one patient because he felt dizzy after the injection and did not want to continue treatment. In a 3-year interim analysis postmarketing of canakinumab in cryopyrin-associated periodic syndromes, dizziness was also reported among the side effects.[39] The rare occurrence of dizziness during treatment with canakinumab should be considered in patients' follow-ups.

The main limitations of our study are that it is a retrospective study involving a limited number of patients and evaluating the clinical characteristics of patients using data stored in the hospital's electronic system.

In conclusion, our study provides real-world data demonstrating the efficacy and safety of canakinumab in FMF patients. Canakinumab has been shown to reduce disease activity and inflammatory markers. Canakinumab could be a good treatment option for this patient group.

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ORIGINAL RESEARCH

Biomarker Profiling for Discrimination of High-Risk Asymptomatic Carotid Artery Stenosis Patients with Ulcerated Plaques: A Pilot Study

Atif YOLGOSTEREN[1*], Ceyda COLAKOGLU BERGEL[2*], Isil Ezgi ERYILMAZ[3], Unal EGELI[3], Basak ERDEMLI GURSEL[4], Murat BICER[1], Gulsah CECENER[3], Mustafa TOK[1]

[1] Bursa Uludag University Faculty of Medicine, Cardiovascular Surgery Department, Bursa, Turkiye.
[2] Bursa Uludag University Graduate School of Medical Sciences, Medical Biology Department, Bursa, Turkiye.
[3] Bursa Uludag University Faculty of Medicine, Medical Biology Department, Bursa, Turkiye.
[4] Bursa Uludag University Faculty of Medicine, Radiology Department, Bursa, Turkiye.

ABSTRACT

Although various methods are used to treat patients with asymptomatic carotid artery stenosis (ACAS), approaches are controversial, and combining imaging of carotid plaque features with biomarkers to identify plaques prone to rupture may be crucial in identifying high-risk ACAS patients. This study aimed to investigate a blood-based biomarker for discriminating ulceration in ACAS patients by analyzing plaque surface morphology through RNA sequencing of blood samples. Peripheral blood samples were collected from ACAS patients with plaque morphology determined by Doppler ultrasonography. Then, total RNA was isolated, and RNA-Seq was performed to analyze differentially expressed genes (DEGs). The KEGG, Reactome, and Gene Ontology (GO) terms pathway enrichment analyses were performed to investigate the molecular functions and biological processes involved in plaque formation. The pilot study included 7 ACAS patients, 57.1 % exhibiting ulcerated plaques. RNA-Seq results revealed significant upregulation of genes related to immune response, cell cycle regulation, and oxidative stress in ulcerated plaques. Especially, *TP73*, *CCL3L3*, and *PXDNL* genes showed the highest fold changes, indicating their role in endothelial damage, immune activation, and oxidative stress. KEGG and Reactome analyses identified TNF and chemokine signaling pathways as key regulators in ulcerated plaque formation. Our findings indicate that *TP73*, *CCL3L3*, and *PXDNL* may be potential biomarkers for identifying high-risk ACAS patients with ulcerated plaques due to their involvement in immune system regulation and oxidative stress-related processes. Thus, these genes and the pathways may be candidate biomarkers for early diagnosis and risk stratification, improving treatment approaches for ACAS.

Keywords: Carotid stenosis. Carotid artery plaque. Biomarker. RNA-Seq. Ulcerated plaque.

Ülsere Plaklı Yüksek Riskli Asemptomatik Karotis Arter Stenozu Hastalarının Ayırımı İçin Biyobelirteç Profillemesi: Pilot Çalışma

ÖZET

Asemptomatik karotis arter stenozu (ACAS) olan hastaların tedavisinde çeşitli yöntemler kullanılsa da yaklaşımlar tartışmalıdır ve plak rüptürü eğilimli olan hastaları belirlemek için karotis plak görüntülerinin biyobelirteçlerle birleştirilmesinin, yüksek riskli ACAS hastalarının belirlenmesinde önemli olduğu düşünülmektedir. Mevcut çalışmada, plak yüzey morfolojisini analiz ederek ACAS hastalarında ülserasyonu ayırt etmek için RNA sekanslama yoluyla kan bazlı biyobelirteç araştırılması amaçlanmıştır. Bu doğrultuda, Doppler ultrasonografi ile plak morfolojisi belirlenen ACAS hastalarından periferik kan örnekleri toplandı. Daha sonra, total RNA izole edildi ve farklı şekilde ifade edilen genleri (DEG'ler) analiz etmek için RNA-Seq gerçekleştirildi. Plak oluşumunda yer alan moleküler işlevleri ve biyolojik süreçleri araştırmak için KEGG, Reactome ve Gen Ontolojisi (GO) ile yolak zenginleştirme analizleri gerçekleştirildi. Pilot çalışmaya 7 ACAS hastası dahil edildi ve %57,1'inde ülsere plaklar olduğu görüldü. RNA-Seq sonuçları ülsere plaklarda bağışıklık tepkisi, hücre döngüsü düzenlemesi ve oksidatif stresle ilgili genlerde önemli bir artış olduğunu ortaya koydu. Özellikle *TP73, CCL3L3* ve *PXDNL* genlerinin bu süreçlerde rol aldığı ve bu genlerin endotel hasarı, bağışıklık aktivasyonu ve oksidatif streste rolleri olduğu gösterildi. KEGG ve Reactome analizleri, ülserli plak oluşumunda anahtar düzenleyiciler olarak TNF ve kemokin sinyal yollarını tanımladı. Bulgularımız, *TP73, CCL3L3* ve *PXDNL*'nin bağışıklık sistemi düzenlemesi ve oksidatif stresle ilişkili süreçlerdeki katılımları nedeniyle ülserli plakları olan yüksek riskli ACAS hastalarını tanımlamak için potansiyel biyobelirteçler olabileceğini göstermektedir. Bu nedenle, ilişkili genlerin ve yolakların erken tanı ve risk sınıflandırması için aday biyobelirteçler olabileceği ve ACAS için tedavi yaklaşımlarını iyileştirebileceğini düşündürmektedir.

Anahtar Kelimeler: Karotis stenozu. Karotis arter plağı. Biyobelirteç. RNA-Seq. Ülsere plak.

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* Atif YOLGOSTEREN and Ceyda COLAKOGLU BERGEL have shared the first authorship.

Dr. Unal EGELI
Bursa Uludag University, Faculty of Medicine,
Medical Biology Department, Bursa, Turkiye,
Phone:
E-mail: egeli@uludag.edu.tr

Authors' ORCID Information:
Atif YOLGÖSTEREN: 0000-0002-4467-3915
Ceyda ÇOLAKOĞLU BERGEL: 0000-0002-7471-5071
Işıl Ezgi ERYILMAZ: 0000-0002-3316-316X
Ünal EGELİ: 0000-0001-7904-883X
Başak ERDEMLİ GÜRSEL: 0000-0002-0047-1780
Murat BİÇER: 0000-0002-9280-086X
Gülşah ÇEÇENER: 0000-0002-3820-424X
Mustafa TOK: 0000-0001-9656-537X

Atherosclerosis is a chronic and progressive vascular disorder that constitutes the primary pathophysiological basis of a significant proportion of cardiovascular diseases, which remain the leading cause of mortality and morbidity globally[1]. The disease is characterized by the accumulation of lipids within the arterial wall, chronic inflammation, fibrotic remodeling, and the progressive narrowing of the vascular lumen[2]. When this narrowing, or stenosis, occurs in the carotid arteries, it is referred to as carotid artery stenosis (CAS), a condition that significantly elevates the risk of ischemic stroke[3].

CAS patients are clinically categorized into two groups: (i) symptomatic (SCAS) and (ii) asymptomatic (ACAS). The distinction between these groups is pivotal for tailoring appropriate treatment strategies and minimizing the risk of cerebrovascular events[4]. ACAS is defined as 50% or greater stenosis in the proximal internal carotid artery at the bifurcation in individuals without a history of ischemic stroke in the ipsilateral carotid region within the last six months. Various treatment modalities are available for ACAS, including carotid endarterectomy (CEA), carotid artery stenting (CAS), and medical treatment. However, the optimal approach remains controversial. Moreover, ACAS patients often remain clinically stable for extended periods. Thus, the unpredictable progression from an asymptomatic to a symptomatic state represents a substantial clinical challenge[5,6]. Consequently, accurate clinical differentiation of high-risk ACAS patients is essential to optimize treatment approaches, balance the risks and benefits of invasive procedures, and avoid unnecessary interventions in low-risk individuals.

The surface morphology of atherosclerotic plaques plays a crucial role in the clinical outcomes of CAS. Plaque rupture is closely associated with various cerebrovascular events and is categorized into two groups based on their biological characteristics: (i) stable and (ii) vulnerable plaques[7]. Unlike stable plaques, vulnerable plaques, considered high-risk, are characterized by a thin, inflammatory fibrous cap that is particularly prone to rupture[8]. These plaques are further classified according to their surface morphology into (i) smooth, (ii) irregular, and (iii) ulcerated types. Ulceration, commonly observed in vulnerable plaques, is considered a predictive feature of plaque instability[9]. Surface characteristics, including ulceration, rupture, and erosion, are critical determinants of plaque stability and significantly influence the risk of thromboembolic events. Even when the degree of luminal stenosis is similar, variations in plaque morphology can substantially affect the patient's risk profile[10]. Therefore, the accurate assessment of plaque surface morphology is essential for effective risk stratification, treatment decisions, and optimizing clinical outcomes in patients with CAS.

The current study identified RNA-based biomarkers by performing transcriptome sequencing on blood samples obtained from ACAS patients, whose plaque surface morphologies -ulcerated or smooth- were determined through Doppler imaging. While previous research has focused on evaluating plaque biology using various biomarkers[11-14], this is the first study to utilize blood-based biomarkers to differentiate between ulcerated and smooth plaques in ACAS patients.

Material and Method

Study cohort

In the current study, peripheral blood samples were collected before CEA from ACAS patients, whose plaque surface morphologies -ulcerated or smooth- were determined using Doppler ultrasonography, and total RNA was isolated from blood materials. For the pilot group, 7 ACAS patients, of whom 57.1% had ulcerated plaques, were selected for RNA-Seq analysis.

All participants provided written informed consent for using their RNA samples in the RNA-Seq analysis conducted at the Department of Medical Biology, Bursa Uludag University. The study received ethical approval from the Bursa Uludag University Medical Ethics Committee (2021-6/38) and adhered to the Helsinki Declaration's ethical standards.

The inclusion criteria for this study were as follows: patients aged over 60 years with stenosis greater than 70%, as determined by the North American Carotid Endarterectomy Trial (NASCET) criteria, who were diagnosed with ACAS based on Doppler ultrasonography findings. Carotid plaque ulceration was assessed using Color Doppler ultrasonography (US), one of the most commonly used methods, and was defined by an expert (B.E.G.) of the carotid

arteries. The plaque surface was defined as smooth, slightly irregular, or ulcerated if there was more than a 2 mm height difference on the plaque surface. The reverse filling in the plaque was also determined. Plaques were classified as either ulcerated or smooth according to imaging results, and patients had no history of ischemic stroke in the ipsilateral carotid region within the last six months. Exclusion criteria included patients under 60, those with less than 70% stenosis according to NASCET criteria, and individuals with additional peripheral vascular diseases. Patients with a history of ischemic stroke within the last six months, systemic inflammatory or autoimmune diseases, malignancies, or other chronic illnesses that could influence gene expression profiles were also excluded.

RNA-Seq analysis

Total RNA was extracted from blood samples of ACAS patients, classified by plaque morphology (ulcerated or smooth), using the RNeasy Lipid Tissue Mini Kit (Hilden, Germany). RNA quality and concentration were evaluated using the Agilent Technologies 2100 (Santa Clara, CA, USA), and samples with DV200 scores greater than 70% were selected for RNA-Seq analysis. mRNA libraries were generated with the Ion AmpliSeq™ Chef-Ready Kit (Thermo Fisher Scientific, MA, USA) and the Ion AmpliSeq Transcriptome Human Gene Expression Panel. cDNA conversion (10 ng RNA per sample) and library preparation were performed using the Ion Chef Instrument, and sequencing was conducted on the Ion GeneStudio™ S5 System using Ion 540™ Chips at Bursa Uludag University, Medical Biology Department NGS Lab.

Determination of differentially expressed genes (DEGs)

The Kyoto Encyclopedia of Genes and Genomes (KEGG), Reactome, and Gene Ontology (GO) terms pathway enrichment analyses were used for the functional analysis of mRNA sets after correction of the enrichment results by the Benjamini-Hochberg FDR method, biological processes, and molecular pathways were considered significant with adjusted *p*-values of less than 0.05 for the genes. RPKM-normalized count data from RNA-Seq were used to identify DEGs. Significant genes were analyzed using the Web Gestalt toolkit to explore biological processes and molecular pathways. GO terms were used for biological processes, while KEGG and Reactome databases were utilized for pathway analysis.

Statistical Analysis

A *p*-value correction was performed using the false discovery rate (FDR) correction method to eliminate false positive genes, and adjusted *p*-values were determined for each gene. The cut-off value for the adjusted *p*-value for statistically significant genes was set at 0.05, and genes below this value were considered statistically significant. Down-regulated and up-regulated genes were determined by the fold changes calculated.

Results

The clinical characteristics of ACAS patients

For the pilot group, 7 patients with ACAS were included in this study. Of these, 57.2% (n=4) were male and 42.8% (n=3) were female. According to the anamnesis, 57.1% (n=4) of the patients had ulcerated plaque. The mean age was 72.4 ± 6.9 years. Additionally, 85.7% (n=6) of the patients had hypertension, 57.1% (n=4) had diabetes, and 14.3% (n=1) had hyperlipidemia. Moreover, 28.5% (n=2) of the patients had peripheral artery, and 14.3% (n=1) had coronary artery disease ($p>0.05$). The clinical characteristics of the patients are shown in Table I.

Table I. Clinical characteristics of ACAS patients.

Pilot Group (n=7)	Ulcerated (n=4)	Smooth (n=3)	*p* value
Gender (n, %)			
Female (n=3)	33.3% (n=1)	66.7% (n=2)	*0.486*
Male (n=4)	75% (n=3)	25% (n=1)	
Age (Mean ± SD)	71.25 ± 4.7	74.0 ± 10.0	*0.721*
Diabetes Mellitus	75% (n=3)	33.3% (n=1)	*0.486*
Hyperlipidemia	-	33.3% (n=1)	*0.429*
Hypertension	100% (n=4)	66.6% (n=2)	*0.429*
Coronary Artery Disease	25% (n=1)	-	*1*
Peripheral artery Disease	50% (n=2)	-	*0.429*

Evaluation of DEGs and pathway analysis for ulcerated and smooth plaques in ACAS patients

RNA-Seq analysis was performed to identify genes with significantly different expression levels among the groups and to identify blood-based biomarkers that could be used to discriminate high-risk ACAS patients. Then, the pilot group's pathway analysis was performed using KEGG, GO terms, and Reactome pathway enrichment analyses in ACAS patients with ulcerated and smooth plaques.

The DEG results indicated that genes involved in the cell cycle, such as *p73*, as well as genes related to chemokine signaling, immune response, and ROS signaling, such as *CCL3L3* and *PXDNL2*, were upregulated in ulcerated plaques ($p<0.001$) (Figure 1). The upregulation of genes associated with the immune system, ROS signaling, and cell proliferation in ulcerated plaques is consistent with endothelial damage and the enhanced immune response observed during ulceration.

Gene	Fold Change	*p* -Value
TP73	23,811	3,70E-03
CCL3L3	21,961	1,40E-03
PXDNL	16,746	3,97E-02
HOXB2	14,024	4,90E-02
BICDL2	9,805	4,30E-02
SHROOM1	9,614	3,29E-03
ABCA13	8,559	4,34E-03
ZNF215	8,540	1,25E-02
JCHAIN	7,814	2,04E-06
ADGRB2	7,470	2,31E-02
FOLR3	6,897	1,99E-07
CITED4	6,646	3,68E-02
CRABP2	5,808	2,87E-02
CDC45	5,805	4,92E-02
SLC22A1	5,092	9,00E-05
G0S2	4,968	9,63E-04
CFAP53	4,092	3,05E-02
FOSB	4,032	8,00E-03
MOB3B	3,891	1,82E-02
PTGS2	3,863	4,75E-03
DEFA3	3,718	7,75E-04
KLHL14	3,396	8,09E-03
EFCAB12	3,302	3,04E-02
H3C6	3,096	3,75E-02
PGAM4	3,055	2,58E-02
OPLAH	3,037	2,75E-02
CSRNP1	3,028	3,99E-07
LGALS9C	3,012	2,71E-02
TSHZ1	2,966	3,02E-02
TAFA2	2,943	2,34E-02
PANX2	2,907	3,99E-02
CLEC12B	2,830	4,37E-02
HMGB1	2,785	2,50E-02
CHRNE	2,775	5,10E-05
CYP4F12	2,743	1,00E-02
SPATA6	2,666	3,29E-02
PIP5K1A	2,631	2,36E-02

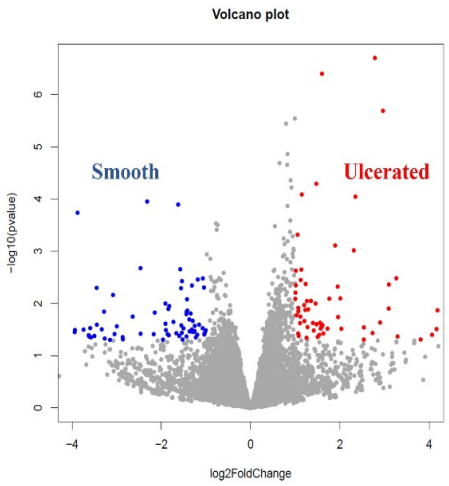

Figure 1.

DEGs and Volcano Plot in ACAS patients with ulcerated and smooth plaques. The left panel shows the table of DEGs between ulcerated and smooth plaques in ACAS patients. Fold change (log2) and corresponding p-values are presented, highlighting significant genes such as TP73, CCL3L3, and PXDNL. The right panel displays the volcano plot, with red points indicating upregulated genes in ulcerated plaques. Gray points represent non-significant genes. The plot emphasizes genes with statistical and biological significance, providing insights into the molecular differences between ulcerated and smooth plaques.

Moreover, GO terms results revealed that genes implicated in forming ulcerated plaques are primarily associated with biological regulation, metabolic processes, and responses to external stimuli. Significantly regulated genes were predominantly localized to the cell membrane, nucleus, and membrane-enclosed lumen. Moreover, these genes exhibit key molecular functions, including protein binding, ion binding, and nucleic acid binding (Figure 2A). In addition to these findings, it was observed explicitly that key immune system-related pathways, such as the cellular response to lipopolysaccharides and the activation pathways of lymphocytes, leukocytes, and T cells, were also significantly regulated.

The analysis of KEGG results also revealed that genes implicated in forming ulcerated plaques are primarily associated with biological regulation, metabolic processes, and responses to external stimuli. Significantly regulated genes were predominantly localized to the cell membrane, nucleus, and membrane-enclosed lumen. Moreover, these genes exhibit key molecular functions, including protein binding, ion binding, and nucleic acid binding. In addition to GO findings, it was observed explicitly that TNF and chemokine signaling were significantly regulated (Figure 2B).

Finally, Reactome analysis revealed that the genes' biological processes, cellular components, and molecular functions were consistent with the results of other studies. Immune system regulation emerged as a common finding across these analyses, with the Toll-like receptor cascade identified as playing a pivotal role in these pathways (Figure 2C).

Discussion and Conclusion

In the current study, RNA-Seq analysis was performed to identify DEGs and potential blood-based biomarkers to distinguish high-risk asymptomatic carotid artery stenosis (ACAS with ulcerated plaques) patients. By comparing ulcerated and smooth plaques, we aimed to uncover the molecular mechanisms underlying plaque destabilization and identify biomarkers that could guide clinical risk assessment. Our findings showed a distinct transcriptional regulation in ulcerated plaques, characterized by upregulation of genes involved in cell cycle, immune response, chemokine signaling, and reactive oxygen species (ROS) pathways. Notable the DEGs, such as *TP73*, *CCL3L3*, and *PXDNL*, were significantly upregulated in ulcerated plaques, highlighting the roles of these genes in endothelial damage, immune

Figure 2.

Functional enrichment analyses of the DEGs in ulcerated and smooth plaques. ***(A)*** *GO Pathway Analysis: Enrichment analysis of DEGs using Gene Ontology (GO) terms includes three categories: (i) Biological Processes, (ii) Cellular Components, and (iii) Molecular Functions. Bar charts on the left display the top enriched terms in each category, while the table on the bottom right lists significant GO terms, such as cellular response to lipopolysaccharide and lymphocyte activation, along with corresponding p-values and false discovery rates (FDR).* ***(B)*** *KEGG Pathway Analysis: Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis highlights enriched pathways among the DEGs. Bar charts display top pathways, such as the TNF and Chemokine signaling pathways, with detailed statistics in the accompanying table, including pathway sizes, p-values, and FDR.* ***(C)*** *Reactome Pathway Analysis: Reactome pathway enrichment analysis reveals significantly enriched pathways such as Immune System, Neutrophil Degranulation, and Cytokine Signaling in the immune system. Bar charts summarize enriched categories, while the table on the right provides details, including pathway sizes, p-values, and FDR. These analyses offer insights into the biological processes, pathways, and molecular mechanisms differentiating ulcerated and smooth plaques.*

activation, and oxidative stress. These results suggest that endothelial damage and an enhanced immune response contribute to plaque vulnerability and ulceration.

Our results revealed significant upregulation of genes involved in cell cycle regulation, immune response, chemokine signaling, and ROS pathways in ulcerated plaques compared to smooth plaques. Notably, *TP73*, a critical regulator of apoptosis and genomic stability, exhibited the highest fold change (23.8-fold, $p<0.001$). *TP73* is known to play a role in cellular proliferation and response to DNA damage, and studies conducted in recent years have highlighted that it is significantly increased in plaque tissue in atherosclerotic human carotid arteries[15,16]. In a different study, p73 was shown to initiate apoptosis in vascular smooth muscle cells (VSMCs) and was found to be highly expressed in human atherosclerotic plaques[17]. Similarly, chemokine-related genes such as *CCL3L3* were highly expressed, emphasizing the role of chemokine signaling in recruiting immune cells to sites of vascular injury. Elevated *CCL3L3* expression has been implicated in monocyte and macrophage activation, which are critical mediators of inflammation in atherosclerosis. It has also been shown that under conditions of acute inflammation, leukocyte-derived CCL3 can induce neutrophil chemotaxis toward atherosclerotic plaque and contribute to progression[18]. These findings suggest that these genes may contribute to pathological processes consistent with their upregulation in the unstable endothelial environment observed in ulcerated plaques by regulating VSMC apoptosis or chemotaxis of immune system cells.

Genes related to ROS signaling, such as *PXDNL*, were also significantly upregulated in ulcerated plaques. ROS production is a hallmark of endothelial dysfunction and contributes to oxidative stress, exacerbating plaque instability[19]. The observed upregulation of ROS-associated genes is consistent with the increased oxidative damage and inflammation reported in studies of vulnerable plaques[20]. PXDN is a peroxidase that modifies the extracellular matrix. *PXDN* expression also influences physiological processes involving redox control[21]. Furthermore, this gene has also been shown to have a pro-angiogenic role that may affect the outcome of atherosclerotic lesions[22]. These findings suggest that PXDN-mediated oxidative stress may play a pivotal role in the pathogenesis of ulcerative plaques, potentially through ROS-induced angiogenic processes.

Functional enrichment analyses provided further insights into the biological processes and pathways driving these transcriptional changes. GO analysis revealed that genes implicated in ulcerated plaques were predominantly associated with biological regulation, metabolic processes, and responses to external stimuli, significantly enriching immune response and cellular signaling pathways. Notably, cellular response to lipopolysaccharides and lymphocyte activation were highlighted, suggesting a robust innate and adaptive immune response in ulcerated plaques. From a pathway perspective, KEGG analysis emphasized the roles of TNF signaling and chemokine signaling pathways, known mediators of inflammation and vascular remodeling. The TNF signaling pathway has been implicated in promoting endothelial cell apoptosis and matrix degradation, contributing to plaque rupture[23,24]. Furthermore, given the critical role of TNF pathways in sustaining the inflammatory microenvironment, it is hypothesized that the recruitment and activation of immune cells, such as monocytes and lymphocytes, may contribute to the inflammatory milieu within ulcerative plaques. This immune cell participation is likely to exacerbate the inflammatory response, further promoting the instability and progression of the plaques.

The Reactome analysis provided complementary findings, reinforcing the role of immune system regulation in plaque ulceration. TLR cascade emerged as a pivotal pathway in ulcerated plaques. TLRs, a type of pattern recognition receptor, are associated with inflammation and the innate immune response. The dysregulation of TLRs has been implicated in developing CAS and various other cardiovascular and metabolic diseases[25]. The activation of these receptors has been identified as triggering an intracellular signaling cascade mediated through MyD88 or TRIF, leading to the production of pro- and anti-inflammatory cytokines[26]. The upregulation of TLR signaling genes in ulcerated plaques suggests their contribution to the heightened inflammatory state observed in these lesions.

Notably, the localization of DEGs to the cell membrane, nucleus, and membrane-enclosed lumen, as identified by GO analysis, highlights their functional relevance in signal transduction and transcriptional regulation. These findings suggest that plaque ulceration is associated with extracellular signaling changes and intracellular transcriptional reprogramming. Molecular functions such as protein binding, ion binding, and nucleic acid binding were also significantly enriched, underscoring the diverse roles of DEGs in modulating cellular responses to stress and injury.

Consequently, although further validation in larger cohorts is required, our preliminary findings suggest that *TP73*, *CCL3L3*, and *PXDNL* may serve as promising biomarkers for ACAS patients with ulcerative plaques. Furthermore, the results suggest that pathways such as TLR and TNF may be key pathways in these processes. Thus, noninvasive, blood-based assays targeting these biomarkers may

provide valuable tools for early detection and risk stratification in ACAS patients with ulcerated plaque. They may offer a more practical approach to personalized ACAS patient care and management.

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ORIGINAL RESEARCH

Epilepsy in Children with Down Syndrome: Case Series

Muhittin BODUR, Rabia TÜTÜNCÜ TOKER

Bursa Uludag University Faculty of Medicine, Pediatric Neurology, Bursa, Türkiye.

ABSTRACT

Epilepsy is more common in children with Down Syndrome than in the normal population. This study examined the clinical and treatment outcomes of children with epilepsy in Down syndrome. This study was conducted retrospectively in children with Down syndrome and epilepsy at the Child Neurology Clinic between January 2020 and August 2024. Medical records were examined in terms of gender, age, age at seizure onset, age at diagnosis, comorbidities, level of intellectual disability, seizure types, previously used antiepileptic drugs, antiepileptic drugs at the last follow-up, interictal electroencephalogram findings, and brain magnetic resonance imaging results. A total of twelve children (five boys and seven girls) with Down syndrome and epilepsy were identified. The median age of the patients was 105.5 months; the median age of seizure onset was twelve months. The seizure types of the patients were as follows: eight patients had focal seizures (focal clonic in six cases, focal tonic/clonic in two cases), three patients had epileptic spasms, and one patient had generalized seizures. When all antiepileptic drugs used by the patients were examined, it was seen that six patients used valproic acid, three patients used ACTH, three patients used phenobarbital, three patients used phenytoin, two patients used topiramate, and one patient used carbamazepine, lamotrigine, and levetiracetam. In this study, the frequency of epilepsy in individuals with Down Syndrome was determined to be 8.76%. Epilepsy in children with Down Syndrome can impede cognitive and motor development and significantly affect their quality of life, especially if diagnosis is delayed or therapeutic management is inadequate. Therefore, early diagnosis and correct treatment are essential for these patients.

Keywords: Down syndrome. Epilepsy. Child.

Down Sendromlu Çocuklarda Epilepsi: Olgu Serisi

ÖZET

Down Sendromlu çocuklarda epilepsi normal popülasyona göre daha yaygındır. Bu çalışmada Down sendromlu ve epilepsili çocukların klinik ve tedavi sonuçları incelendi. Bu çalışma Ocak 2020-Ağustos 2024 tarihleri arasında Çocuk Nöroloji Kliniği'nde Down sendromlu ve epilepsi tanısıyla izlenen çocuklarda retrospektif olarak yapıldı. Tıbbi kayıtlar cinsiyet, yaş, nöbet başlangıç yaşı, tanı yaşı, eşlik eden hastalıklar, zihinsel engellilik düzeyi, nöbet tipleri, daha önce kullanılan antiepileptik ilaçlar, son takipte kullanılan antiepileptik ilaçlar, nöbetler arası elektroensefalogram bulguları ve beyin manyetik rezonans görüntüleme sonuçları açısından incelendi. Down sendromlu ve epilepsili toplam oniki çocuk (beş erkek ve yedi kız) tespit edildi. Hastaların ortanca yaşı 105,5 ay, ortanca nöbet başlangıç yaşı oniki ay olarak bulundu. Hastaların nöbet tipleri şu şekildeydi; sekiz hastada fokal nöbetler (altı olguda fokal klonik, iki olguda fokal tonik/klonik), üç hastada epileptik spazmlar ve bir hastada jeneralize nöbetler mevcuttu. Hastaların kullandıkları tüm antiepileptik ilaçlar incelendiğinde altı hastanın valproik asit, üç hastanın ACTH, üç hastanın fenobarbital, üç hastanın fenitoin, iki hastanın topiramat, bir hastanın karbamazepin, lamotrijin ve levetirasetam kullandığı görüldü. Bu çalışmada Down Sendromlu bireylerde epilepsi sıklığının %8,76 olduğu saptanmıştır. Down Sendromlu çocuklarda epilepsi, bilişsel ve motor gelişimi engelleyebilir ve özellikle tanı gecikirse veya terapötik yönetim yetersizse yaşam kalitelerini önemli ölçüde etkileyebilir. Bu nedenle erken tanı ve doğru tedavi bu hastalar için çok önemlidir.

Anahtar Kelimeler: Down sendromu. Epilepsi. Çocuk.

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Dr. Muhittin BODUR
Bursa Uludag University, Faculty of Medicine,
Department of Pediatrics, Division of
Pediatric Neurology, Bursa, Türkiye
Phone: +90 530 212 71 44
E-mail: mbodur@uludag.edu.tr

Authors' ORCID Information:
Muhittin BODUR: 0000-0002-2588-8195
Rabia TÜTÜNCÜ TOKER: 0000-0002-3129-334X

Down syndrome (DS) occurs in 1 in 700 to 1000 live births worldwide and is the most common cause of genetic intellectual disability.[1] It is caused by trisomy of all or part of chromosome 21 (47+21). Standard trisomy 21 is seen in approximately 95% of cases. Mosaic trisomy is seen in approximately 3–5% of DS cases. Robertsonian translocations are seen in approximately 4% of cases.[2] The mongoloid facial features, multiple congenital disabilities, intellectual disability, immune and endocrine dysfunction associated with DS result from this extra genetic material.[3] The seizure rates reported in DS range from 1 to 13%.[4] These rates are significantly higher than

those reported in the general population (0.35–1%). This highlights the importance of early evaluation and recognition of epilepsy in children with DS.[5] The higher seizure susceptibility in DS has been attributed to associated medical complications such as structural brain abnormalities, cardiovascular abnormalities, or recurrent infections.[4] A three-phase distribution of epilepsy has been described in Down syndrome, including infancy, early adulthood, and patients over 50 years of age. Epileptic spasms, which are late-onset and relatively benign in infancy, are the most common form. In the early adult group, focal seizures are the most common seizure type, while generalized seizures (including tonic-clonic seizures) are evenly distributed throughout life.[6] In this study, we examined the clinical and treatment outcomes of children with Down syndrome and epilepsy.

Material and Method

In this study, we reviewed retrospectively the medical records of patients diagnosed with Down syndrome and epilepsy at the Child Neurology Clinic between January 2020 and August 2024. During this period, a total of 25.612 examinations were performed, and 137 cases of Down syndrome were identified. Among these cases, 12 patients had comorbid epilepsy. In this study, we present data collected from 12 patients. Medical records were reviewed in terms of gender, age, age at seizure onset, age at diagnosis, comorbidities, level of intellectual disability, seizure types, previously used antiepileptic drugs, antiepileptic drugs at the last follow-up, follow-up period, interictal electroencephalogram (EEG) findings and brain magnetic resonance imaging (MRI) results. Seizure classification was based on clinical reports and EEG results. We divided epileptic seizures into the following 4 groups: (1) focal onset, (2) generalized onset, (3) epileptic spasms, and (4) seizures of unknown onset. EEG findings were classified into four groups: normal, hypsarrhythmia, epileptiform activity (spike/sharp waves), and background rhythm irregularity. The Stanford-Binet Intelligence Scales, Fifth Edition (SB-5), or the Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V) were utilized to assess the level of intellectual disability in the patients. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), a diagnosis of intellectual disability necessitates the presence of deficits in both intellectual functioning and adaptive functioning, with symptoms manifesting before the age of 22.[7] The study was conducted according to the Declaration of Helsinki. Since the study was designed retrospectively, written informed consent forms were not obtained from the patients. Data were analyzed using IBM SPSS statistics (version 28), and percentage, median, maximum, and minimum values were used in descriptive statistics.

Results

In this study, epilepsy was found in 12 of 137 cases of Down Syndrome. The frequency of epilepsy among individuals with Down Syndrome was determined to be 8.76%. The clinical and treatment results of twelve patients with DS and epilepsy are shown in of twelve children (five boys and seven girls) with DS and epilepsy were identified. Karyotype analysis revealed standard trisomy 21 in all individuals except one with chromosomal 9/21 translocation. The median age of the patients was 105.5 months (27-209), median age at seizure onset was 12 months (0.33-191), median age at diagnosis was 18 months (0.33-191), and median follow-up was 63 months (18-133). When the patients were examined in terms of comorbidities, nine patients (75%) had hypothyroidism, eight patients (66.7%) had congenital heart disease (six had severe congenital heart disease, two had secundum ASD), three patients (25%) had a history of stroke (one due to Moyamoya disease), and less commonly, one patient each had adrenal insufficiency, hearing loss, CD-19 deficiency, behavioral problems, Hirsprung disease, penoscrotal hypospadias, and Graves disease. Out of the nine patients diagnosed with hypothyroidism, seven were identified during the neonatal period. One patient was diagnosed at 13 months of age. Additionally, one patient developed drug-induced hypothyroidism at 3 years and 4 months. Six of the patients (50%) had moderate intellectual disability, three (25%) had mild intellectual disability, and three (25%) had severe intellectual disability. The seizure types of the patients were as follows: eight patients (66.7%) had focal seizures (six patients had focal clonic, two patients had focal tonic/clonic), three patients (25%) had epileptic spasms, and one patient (8.3%) had generalized seizures. When all antiepileptic drugs used by the patients were examined, six patients (50%) used valproic acid, three patients (25%) used ACTH, three patients (25%) used phenobarbital, three patients (25%) used phenytoin, two patients (16.7%) used topiramate, one patient (8.3%) used carbamazepine, lamotrigine, and levetiracetam. At the time of diagnosis, EEG findings were normal in four patients (33.3%), hypsarrhythmia in three patients (25%), epileptiform activity (two focal, one generalized) in three patients (25%), and background rhythm irregularity in two patients (16.7%). Brain MRI findings of the patients were normal in four patients (33.3%), chronic ischemic findings in three patients (25%), and, less frequently, hypoxic-ischemic encephalopathy findings, cerebral atrophy, mega cisterna magna, corpus callosum hypoplasia and colpocephaly and increased corpus

callosum thickness in one patient each (8.3%). At the last follow-up, all patients were seizure-free, and four patients had stopped their antiepileptic drugs. The drugs used by the patients at their previous follow-up are listed in Table I.

Discussion and Conclusion

This study presents the clinical and treatment results of 12 children with DS and epilepsy. The frequency of epilepsy among individuals with Down Syndrome was determined to be 8.76%. Most of our patients had standard trisomy 21 cases, and only one had a Robertsonian translocation. 58.3% of our patients were female and 41.7% were male. DS is the most common genetic cause of intellectual disability. It is seen in almost all patients. However, the degree of intellectual disability varies along a spectrum of severity.[8] In a study on intelligence scores in DS, 19% had an IQ of 50-69, 30% had an IQ of 35-49, 33% had an IQ of 20-34, and 18% had an IQ of less than 20.[9] Similarly, a study from Norway reported that the degree of intellectual disability in DS was 25% mild, 56% moderate, and 21% severe.[10] Consistent with the literature, 50% of our patients had moderate, 25% mild, and 25% severe intellectual disability.

Although DS has a variable phenotype, there are many common physical findings. These include hypotonia, epicanthic folds, flat nasal bridge, single palmar crease, and sandal toe gap. Children with DS have an increased risk of congenital anomalies, including congenital heart defects and abdominal wall abnormalities.[3] Individuals with DS are associated with both acquired and congenital thyroid disease. The incidence of congenital thyroid disease is significantly increased in infants with DS. One study estimated the incidence to be 26 times higher than the general population.[11] Infants born with DS are frequently diagnosed with congenital heart disease (54–66%) and have significant morbidity and mortality implications.[3] In this study, the most common comorbidities in our patients were hypothyroidism (congenital, acquired, or drug-induced) in 75%, severe congenital heart disease in 50%, and secundum ASD in 16.7%.

The prevalence of epilepsy, especially epileptic spasms, is increased in children with DS compared to the general population, ranging from 1% to 13%.[4] It has been hypothesized that genetic changes in ion channels and neurotransmitter function are secondary to increased susceptibility to seizures.[3] The most common seizure types in patients with DS include focal seizures (47%), epileptic spasms (32%), and generalized tonic-clonic seizures (21%).[8] In our study, seizure onset was before the age of 1 in half of our patients, and the most common seizure type was focal seizures (66.7%), and 25% of the patients had epileptic spasms.

The etiology of epilepsy in DS may be related to structural brain abnormalities, structural/metabolic disorders such as moyamoya disease, stroke, or complications of congenital cardiovascular abnormalities, such as hypoxic-ischemic encephalopathy. However, the underlying cause is unknown in many cases.[1] Normal MRI findings were detected in 33.3% of our cases. Brain MRI findings of the patients showed chronic ischemic findings in three patients and, more rarely, hypoxic-ischemic

Table I. Clinical Data on 12 Patients With Down Syndrome and Epilepsy.

Case	Sex	Age (M)	Karyotype	Comorbidity	Age at seizures onset (M)	Age at diagnosis (M)	Level of intellectual disability	Seizure types	Previously used AEDs	EEG	MRI	Outcomes and last AEDs
1	M	86	47,XY+21	Congenital hypothyroidism, Adrenocortical insufficiency, Behavioral problems	4	25	Moderate	Epileptic spasm	ACTH, VPA, VGB	Hypsarythmia	İncreased corpus callosum thickness	Seizure free, VPA, VGB
2	F	147	47,XX+21	Acquired hypothyroidism, Congenital heart disease, CD-19 deficiency	11	14	Moderate	Generalized myoclonic	VPA, LMT, TPM	Epileptiform activity (G)	Normal	Seizure free, VPA, TPM
3	M	27	47,XY+21	Congenital hypothyroidism, Congenital heart disease, Hearing loss	0.33	0.33	Mild	Focal clonic	FB	Normal	Corpus callosum hypoplasia, colpocephaly	Seizure free, FB
4	F	108	47,XX+21	Drug-induced hypothyroidism	25	25	Mild	Focal clonic	CBZ	Epileptiform activity (F)	Normal	Seizure free, AED-free
5	M	69	46,XY,rob(21;21)(q10,q10)+21	Congenital hypothyroidism, Congenital heart disease, Hirschsprung's disease	4	4	Severe	Focal tonic/clonic	DFH	Focal low frequency	Mega cisterna magna	Seizure free, AED-free
6	F	103	47,XX+21	Congenital hypothyroidism, Secundum ASD	9	10	Moderate	Epileptic spasm	ACTH, VPA	Hypsarythmia	Cerebral atrophy	Seizure free, AED-free
7	F	121	47,XX+21	Congenital hypothyroidism, Congenital heart disease	13	14	Severe	Epileptic spasm	ACTH, VPA, TPM	Hypsarythmia	Normal	Seizure free, VPA,TPM
8	M	50	47,XY+21	Secundum ASD, history of cerebral infarction	22	22	Moderate	Focal clonic	FB	Normal	Chronic ischemic findings	Seizure free,FB
9	F	209	47,XX+21	History of cerebral infarction, Moya moya disease, Graves disease	191	191	Moderate	Focal clonic	DFH	Normal	Chronic ischemic findings	Seizure free,DFH
10	M	33	47,XY+21	Penoscrotal hypospadias, Congenital heart disease, Hypoxic ischemic encephalopathy	6	6	Severe	Focal tonic/clonic	FB, DFH, LEV	Epileptiform activity (F)	Hypoxic ischemic encephalopathy	Seizure free,DFH, LEV
11	F	169	47,XY+21	Congenital hypothyroidism, History of cerebral infarction Tracheoesophageal fistula and esophageal atresia	124	124	Moderate	Focal clonic	VPA	Normal	Chronic ischemic findings	Seizure free,VPA
12	F	183	47,XY+21	Congenital hypothyroidism, Congenital heart disease	70	70	Mild	Focal tonic	VPA	Diffuse low frequency	Normal	Seizure free, AED-free

Abbreviations: M, male; F, female; M, month; AED, antiepileptic drug; ACTH, adrenocorticotropic hormone; VPA, valproic acid; VGB, vigabatrin; TPM, topiramate; FB, phenobarbital; CBZ, carbamazepine; DFH, diphenylhydantoin; LEV, levetriacetam; G, generalized; F, focal.

encephalopathy findings, cerebral atrophy, mega cisterna magna, corpus callosum hypoplasia, colpocephaly, and increased corpus callosum thickness in one patient each.

There are no pathognomonic EEG changes for DS. Most DS patients have normal EEG findings, especially in childhood and early adulthood, in the absence of seizures or severe neurodegeneration. Early pathological EEG changes are usually subtle and may present as a change in background EEG activity. As in individuals without DS, pathological EEG findings depend on the epilepsy and its syndromic classification.[2] EEG of our patients at the time of diagnosis was 33.3% normal, 25% hypsarrhythmia, and 25% epileptiform activity.

The principles of antiepileptic pharmacotherapy in DS patients do not differ significantly from those in diploid patients. There are no scientific studies on the possible superiority of individual antiepileptic drugs in epilepsy in patients with DS.[2] In general, epileptic spasms, when primarily symptomatic, are associated with a poor long-term prognosis. Consistent with a previous report[4], our patients had a better-than-expected response to treatment (mainly ACTH or VPA) and long-term seizure control. In the focal-onset group, seizures were also relatively well controlled (with different antiepileptic drugs). All our patients were seizure-free at the last follow-up, and antiepileptic treatments were discontinued in 33.3%.

The limitations of this study are that it was conducted on a small number of patients and was retrospective.

Epilepsy is a more common comorbidity in children with DS than in the normal population. In this study, the frequency of epilepsy in individuals with Down Syndrome was determined to be 8.76%. There are no pathognomonic EEG changes in DS. Pathological EEG findings depend on the epilepsy and its syndromic classification, as in individuals without DS. In general, epilepsy patients with Down syndrome respond well to traditional antiepileptic drugs. Epilepsy in children with DS can impede cognitive and motor development and significantly affect their quality of life, especially if the diagnosis is delayed or therapeutic management is inadequate. Therefore, early diagnosis and correct treatment are essential for these patients.

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ORIGINAL RESEARCH

Effects of Uridine and Uridine Nucleotides on Proliferation and Migration of L929 Murine Fibroblast Cell Line

Digdem YOYEN-ERMIS[1], Erkan ERMIS[2], Sedef CANSEV[3], Haluk Barbaros ORAL[1], Gökhan GÖKTALAY[2]

[1] Bursa Uludag University, Faculty of Medicine, Department of Immunology, Bursa, Türkiye.
[2] Bursa Uludag University Faculty of Medicine, Department of Medical Pharmacology, Bursa, Türkiye.
[3] TED Bursa College, Bursa, Türkiye.

ABSTRACT

The present study aimed to investigate the effects of uridine and the uridine nucleotides uridine-5'-monophosphate (UMP), uridine-5'-diphosphate (UDP) and uridine-5'-triphosphate (UTP) at different concentrations (1, 10 and 100 µM) on cell viability and migration capacity using the L929 murine fibroblast cell line. To assess cytotoxicity and cellular proliferation, the MTT [(3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide)] assay was performed at 24, 48 and 72 hours of incubation, providing a quantitative evaluation of metabolic activity and cell survival. Additionally, the scratch assay was employed and followed up to 96 hours to analyze fibroblast migration, offering insights into the role of these pyrimidines in wound healing and tissue repair. The MTT assay revealed that the highest concentration (100 µM) of UMP or UDP significantly enhanced proliferation of cells at 72 hours while uridine at 10 and 100 µM and UTP at all concentrations tested provided the same effect. In scratch assay UMP or UDP did not cause any significant cell migration while uridine and UTP, at all concentrations, significantly enhanced migration of fibroblast cells at 96 hours. The results demonstrated distinct effects of uridine and its nucleotides on cell viability and migration, with significant benefit in terms of wound healing provided by uridine and UTP, highlighting their potential biological significance and therapeutic implications in regenerative medicine and tissue engineering.

Keywords: Uridine. L929 murine fibroblast cells. MTT. Proliferation. Migration. Wound healing.

Uridin ve Uridin Nükleotidlerinin L929 Fare Fibroblastik Hücrelerinin Proliferasyonu ve Göçü Üzerindeki Etkileri

ÖZET

Bu çalışmanın amacı, üridin ve üridin nükleotidleri üridin-5'-monofosfat (UMP), üridin-5'-difosfat (UDP) ve üridin-5'-trifosfat (UTP)'ın farklı konsantrasyonlarda (1, 10 ve 100 µM) uygulanmasının L929 kemirgen fibroblast hücre kültüründe hücre canlılığı ve göç etme kapasitesine etkilerini incelemektir. Sitotoksisite ve hücresel proliferasyonu değerlendirmek için 24, 48 ve 72 saatlik inkübasyonların sonunda metabolik aktivite ve hücre canlılığı konusunda kantitatif değerlendirme yapılmasını sağlayan MTT [3-(4,5-dimetiltiazol-2-il)-2,5-difeniltetrazolyum bromür] testi uygulandı. Ayrıca bu pirimidin bileşiklerinin yara iyileşmesi ve doku tamiri konusundaki etkilerini incelemek üzere çizik testi yapılarak fibroblast göçü 96 saate kadar takip edildi. MTT testi ile 72 saat inkübasyon sonunda UMP veya UDP'nin en yüksek (100 µM) konsantrasyonda hücre proliferasyonunu artırırken üridin'in 10 ve 100 µM konsantrasyonlarda ve UTP'nin denenen tüm konsantrasyonlarında aynı etkiyi gösterdiği tespit edildi. Çizik testinde UMP veya UDP anlamlı hücre göçüne neden olmazken 96 saat inkübasyon sonrası üridin ve UTP denenen tüm konsantrasyonlarında hücre göçünü anlamlı olarak artırdı. Bu sonuçlar üridin ve üridin nükleotidlerinin hücre proliferasyonu ve göçü üzerine farklı etkileri olduğunu ve yara iyileşmesi bakımından üridin ve UTP'nin anlamlı faydaları olabileceğini göstermekle birlikte rejeneratif tıp ve doku mühendisliği alanlarındaki potansiyel biyolojik önemlerine ve terapötik kullanımlarına işaret etmektedir.

Anahtar Kelimeler: Üridin. L929 kemirgen fibroblast hücreleri. MTT. Proliferasyon. Migrasyon. Yara iyileşmesi.

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Dr. Digdem, YÖYEN-ERMIŞ
Bursa Uludag University Faculty of Medicine Department of Immunology; 16059, Gorukle, Nilufer, Bursa, Türkiye.
Phone: +90 554 981 85 23
E-mail: dyoyenermis@uludag.edu.tr

Authors' ORCID Information
Diğdem YÖYEN ERMİŞ: 0000-0001-5871-8769
Erkan ERMİŞ: 0000-0001-5359-3477
Sedef CANSEV: 0009-0005-8518-8376
Haluk Barbaros ORAL: 0000-0003-0463-6818
Gökhan GÖKTALAY: 0000-0001-6261-4233

Nucleotides are essential biomolecules that are crucial in various biological processes within living organisms. They are the basic building blocks of nucleic acids that store and transmit genetic information. They also participate in intracellular signaling pathways and contribute to enzymatic reactions. Through these diverse functions, nucleotides support cellular metabolism, communication and genetic regulation, making them indispensable for life[1].

Uridine is the major circulating pyrimidine nucleoside in humans, which is also found in

tissues freely or in phosphorylated forms (nucleotides) such as uridine-5'-monophosphate (UMP), uridine-5'-diphosphate (UDP), and uridine-5'-triphosphate (UTP)[2]. Uridine and uridine nucleotides play a crucial role in RNA synthesis, protein and lipid glycosylation, and membrane biosynthesis by serving as vital components of intracellular metabolic pathways and various biosynthetic processes, highlighting their significance in maintaining overall cellular balance and physiological stability[3]. In addition to their physiological roles, several studies reported anti-apoptotic[4], anti-inflammatory[5] and anti-oxidative[6] effects of uridine as well as extracellular matrix (ECM) modulation[7] on exogenous administration. Moreover, uridine has been recently identified as a conserved pro-regenerative factor by cross-species metabolomic analyses[8].

Fibroblasts, the predominant cells of the connective tissue, are essential for maintaining structural integrity and facilitating key physiological processes such as wound healing, tissue regeneration and regulation of inflammatory responses[9]. Fibroblasts actively synthesize and secrete collagen, along with other ECM components, providing structural support and promoting cellular communication within tissues[10]. Additionally, fibroblasts play a dynamic role in modulating immune responses by interacting with immune cells and releasing cytokines[11]. The L929 murine fibroblast cell line serves as a well-established model for in vitro research, offering valuable insights into cytotoxicity assays, wound healing mechanisms and cellular stress response[12].

Previous studies have shown that pyrimidine nucleotides can influence cell cycle progression to induce cellular proliferation and differentiation. For example, UTP was shown to enhance proliferation of adult multipotent neural stem cells derived from adult rodent subventricular zone[13] and stimulate dopaminergic differentiation in human mesencephalic neural stem/precursor cell line[14]. UTP was also associated with increased migration of rat cardiac fibroblasts as a profibrotic action[15]. fibroblast viability and wound healing, a recent study showed that uridine-loaded polycaprolactone (PCL) nanofiber mats enhanced the viability of L929 fibroblast cells in vitro in MTT assay and accelerated wound healing in vivo on rats[16]. Despite this limited information, little is known about the effects of other pyrimidine compounds such as UMP and UDP on cell proliferation and wound healing.

Therefore, the present study aimed to comprehensively investigate, as well as compare, the effects of uridine and uridine nucleotides on viability and migration of cultured L929 murine fibroblast cells. The effects of pyrimidines on viability and proliferation were analyzed by MTT assay and on migration and wound closure were assessed by scratch assay.

Material and Method

Chemicals

The chemicals that were used in this study and the suppliers that they were purchased are as follows: uridine (Cat. No: U3750), UMP (Cat. No: U6375), UDP (Cat. No: 94330), UTP (Cat. No: U6875), sodium dodecyl sulfate (SDS; Cat. No: 11667289001) and *N,N*-dimethylformamide (DMF; Cat. No: 227056) were purchased from Sigma-Aldrich (St. Louis, MO, USA); Dulbecco's Modified Eagle's Medium (DMEM; Cat. No: 30-2002), fetal bovine serum (FBS; Cat. No: 30-2021), L-Glutamine solution (Cat. No: 30-2214) and penicillin-streptomycin solution (Cat. No: 30-2300) were purchased from the American Type Culture Collection (ATCC; Bethesda, MD, USA); and MTT [(3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide)] assay kit (Cat. No: M6494) was purchased from Thermo Fisher Scientific (Waltham, MA, USA).

Cell Culture

L929 murine fibroblast cell line (American Type Culture Collection, LGC Promochem, Rockville, MD, USA) was used throughout the study. They were cultured in a high-glucose DMEM medium (containing 4 mM L-glutamine, 1% penicillin-streptomycin and 10% FBS) at 37°C in a humidified incubator with 5% CO_2. The cells were passaged every two days and experiments were conducted when they reached 80-90% confluency.

MTT Cell Viability Assay

The MTT assay was performed to investigate the effect of uridine and uridine nucleotides on cell viability. L929 murine fibroblast cells were seeded into 96-well plates at a density of $30x10^3$ cells/100 µL and incubated for 24 hours. Uridine, UMP, UDP and UTP were dissolved with the culture medium at different amounts and then administered at 1, 10 and 100 µM concentrations onto cells in the culture. Control group only received the culture medium. Cells were incubated with the culture medium either not containing (control) or containing the pyrimidines for 24, 48 and 72 hours.

On completion of incubation, cells were incubated for an additional 4 hours with the addition of 25 µL of MTT solution (5 mg/ml) to each well to allow for the formation of formazan crystals within the

cell. Formazan was then solubilized by adding 80 µL of a solubilizing solution containing 23% SDS and 45% DMF followed by overnight incubation. Next day, optical density (OD) in each well was detected using a microplate reader (µQuant, Biotek, Winooski, VT, USA) at 570 nm. Cell viability was expressed as percentage change in OD compared to control values.

Scratch Assay

Scratch assay was performed to evaluate the effect of pyrimidines on the migratory ability of L929 cells. The cells were seeded into 6-well plates and cultivated until they reached 100% confluence. A vertical scratch was made on the monolayer cell surface using a P1000 pipette tip. Then 2 ml of the culture medium without (as control) or with 1, 10 and 100 µM uridine, UMP, UDP or UTP was added onto cells and the cells were incubated for 24 hours. Scratch areas were visualized by an inverted light microscope and images were taken at 0, 24, 48, 72 and 96 hours. Images were analyzed using Image J software and percentage of wound closure was calculated. The image taken from the light microscope was uploaded to the ImageJ program and processed. After threshold resetting, the FFT and bandpass filter were selected. FFT Analysis (Fast Fourier Transform) transforms signals from the time domain to the frequency domain. This step can lead to investigating numerous signal characteristics, much more than when inspecting the time domain data. Adjusting the threshold, the most apparent contrast was obtained for the cell and the space (distance). The distance value was obtained in pixels by selecting the wand (tracing) tool. Different time points data normalized to day 0 data (initial day distance).

Wound closure % formula=

$$100 - \left(\frac{end\ time\ points\ pixel\ x\ 100}{initial\ day\ pixel}\right).$$

Statistical Analysis

Statistical analyses were performed using GraphPad Prism software. Data were expressed as mean ± standard error of means (SEM). All experiments were repeated at least three times at separate times (biological replication). In addition, cells were seeded in at least two wells from each condition, and technical replication was performed. Shapiro-Wilk test was used to evaluate whether the data are normally distributed or not. One-Way ANOVA followed by post-hoc Tukey test was used to compare the groups if the data were normally distributed. If not, Kruskal-Wallis followed by post-hoc Dunn's test was applied with Bonferroni's correction. Level of significance was set at $p<0.05$.

Results

Cell Viability

Cell viability was assessed by MTT assay at 24, 48 and 72 hours of incubation and expressed as percentage of proliferation in comparison to control group at each time point (Figure 1). At 24 hours, significantly increased cell viability was observed with uridine at 10 and 100 µM concentrations ($p<0.01$), UMP at 10 µM ($p<0.05$) and 100 µM ($p<0.001$) concentrations, UDP at 10 µM ($p<0.01$) and 100 µM ($p<0.001$) concentrations and with UTP at all concentrations tested ($p<0.01$ for 1 and 10 µM and $p<0.001$ for 100 µM). At 48 hours, significantly increased cell viability was observed with uridine at 10 µM ($p<0.01$) and 100 µM ($p<0.001$) concentrations and UTP at 10 and 100 µM concentrations ($p<0.001$). UMP or UDP had no significant effect on cell viability at 48 hours incubation. At 72 hours, significantly increased cell viability was observed with uridine at 10 µM ($p<0.01$) and 100 µM ($p<0.001$) concentrations, UMP at 100 µM concentration ($p<0.01$), UDP at 100 µM concentration ($p<0.001$) and with UTP at all concentrations tested ($p<0.001$ for 1 and 100 µM and $p<0.01$ for 10 µM).

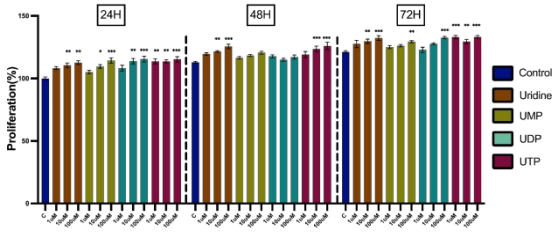

Figure 1:
*Results of MTT assay performed to assess the effect of uridine, UMP, UDP and UTP administered at 1, 10 and 100 µM concentrations on cell viability at 24, 48 and 72 hours of incubation. Data were expressed as mean ± SEM of three independent experiments and presented as % proliferation. *p<0.05, **p<0.01 and p<0.001 compared to control group within each time point.*

Cellular Migration

Cellular migration was assessed by scratch assay at 24, 48, 72 and 96 hours of incubation and expressed as percentage of wound closure compared to control group at each time point (Figure 2). Percentage of wound closure was similar and did not differ significantly in all groups at around 25%, 50% and 70% at 24-, 48- and 72-hours incubation, respectively. At 96 hours however, percentage of

wound closure was significantly greater at all uridine concentrations ($p<0.05$ for 1 and 10 μM and $p<0.01$ for 100 μM) as well as in UTP groups at all concentrations ($p<0.01$) compared to the control group. UMP or UDP had no significant effect on wound closure at any period of incubation. Figure 3 shows a representative image of scratch assay for each group at each time point.

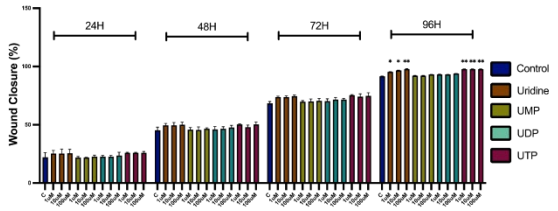

Figure 2:
*Results of scratch assay performed to assess the effect of uridine, UMP, UDP and UTP administered at 1, 10 and 100 μM concentrations at 24, 48, 72 and 96 hours of incubation on cellular migration. Data were expressed as mean ± SEM of three independent experiments and presented as % wound closure. *p<0.05, **p<0.01 and p<0.001 compared to control group within 96 hours.*

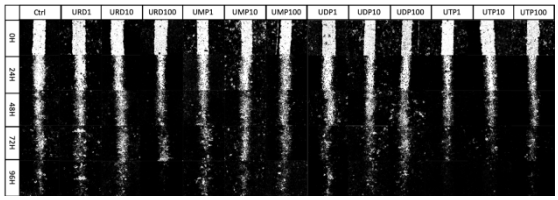

Figure 3:
Representative images of scratch assay containing wound closure effects of uridine, UMP, UDP and UTP administered at 1, 10 and 100 μM concentrations from day 0 to day 4 (96 hours).

Discussion and Conclusion

These data show that exogenous administration of the pyrimidine nucleoside uridine and its nucleotides UMP, UDP and UTP all enhances cell viability in cultured L929 murine fibroblast cells while only uridine or UTP significantly increases cellular migration, suggesting their beneficial effect on wound closure. To the best of our knowledge, our study is the first to investigate these pyrimidine compounds on viability and migration of fibroblast cells.

Uridine is the major circulating pyrimidine nucleoside in humans which is also found in breast milk and tissues freely or as a constituent of pyrimidine nucleotides[2]. Uridine and uridine nucleotides play a crucial role in RNA synthesis, protein and lipid glycosylation and membrane biosynthesis by serving as vital components of intracellular metabolic pathways and various biosynthetic processes[3]. Exogenous administration of uridine has been shown to confer benefit in experimental models of hypoxic-ischemic[4] or hyperoxic[6] brain damage and peripheral nerve injury[17] through mechanisms involving inhibition or alleviation of apoptosis[4,18], inflammation[5], oxidative stress[6,18] and modulation of epigenetic mechanisms[4,19] or the ECM composition[7].

Cell proliferation and migration are essential components of wound healing which also involves hemostasis and maturation[20]. Along with thrombocytes, macrophages are critical to the hemostasis stage which are involved in fibroblast proliferation and migration. Fibroblasts are key to this proliferative stage since they actively participate in collagen production[21]. Additionally, fibroblasts provide structural support and promote cellular communication within tissues[10] by also playing a dynamic role in modulating immune responses by interacting with immune cells and releasing cytokines[11]. Hence, fibroblasts represent a valuable tool for studies of wound healing[9]. The L929 murine fibroblast cell line has been widely recognized as a good candidate for such studies due to its reproducibility and responsiveness to various stimuli which offers valuable insights into cytotoxicity (proliferation) assays and wound closure (cellular migration) studies[12].

Not much is known about the effect of pyrimidines on cell proliferation or wound healing. Available data showed that uridine-loaded polycaprolactone (PCL) nanofiber mats enhanced the viability of L929 fibroblast cells in vitro in MTT assay and accelerated wound healing in vivo on rats[16]. UTP was shown to enhance proliferation of adult multipotent neural stem cells[13] and stimulate dopaminergic differentiation in human mesencephalic neural stem/precursor cell[14]. UTP was also reported to increase migration of rat cardiac fibroblasts as a profibrotic response[15]. Besides, the involvement or effects of UMP or UDP in these processes have not yet been evaluated. Therefore, the present study investigated the effects of uridine and uridine nucleotides on proliferation and migration of cultured L929 murine fibroblast cells to gain further insight into the potential contribution of pyrimidines in wound healing.

The results of the present study showed that uridine and uridine nucleotides all enhanced cell proliferation especially at high doses after 72 hours of incubation. The effect of uridine or UTP was

stronger compared to UMP or UDP in terms of fibroblast proliferation. The data also showed that uridine or UTP, but not UMP or UDP, significantly enhanced cellular migration, ensuring a greater recovery and wound closure in the scratch assay.

The reason why uridine or UTP was effective in stimulating wound closure, but UMP or UDP was not, must be further studied. One possible explanation might involve receptor activation by the pyrimidines. While no receptor has been described for uridine or UMP to date, the uridine nucleotides UDP and UTP have been shown to exhibit their effects by stimulating a number of G-protein coupled P2Y receptors. UDP activates P2Y6 and P2Y14 receptors and UTP activates P2Y2 and P2Y4 receptors[22]. Stimulation of P2Y2, P2Y4 and P2Y6 receptors causes phospholipase C activation which is followed by intracellular calcium accumulation while stimulation of P2Y14 receptors inhibits adenylate cyclase to reduce cAMP levels[22]. The expression of any of these receptors on L929 murine fibroblast cells has not been documented, therefore it would only be speculative to discuss the receptor mediation of the effects. Moreover, no receptor has yet been described for uridine while it is involved in several physiological functions and is beneficial in different disease models in vivo. Therefore, investigation of the mechanism of action of pyrimidines in proliferation and migration of fibroblasts remains as a limitation of this study.

In conclusion, the present study investigated the effects of uridine and uridine nucleotides on proliferation and migration of L929 murine fibroblast cells and showed, for the first time, that all tested pyrimidines enhanced fibroblast proliferation, but migration was only enhanced by uridine or UTP. These data enhance our knowledge of the effects of pyrimidines on fibroblast behavior and provide new insights into wound healing and tissue regeneration.

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Researcher Contribution Statement:
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ORIGINAL RESEARCH

Reliability and Agreement of Four Patellar Height Measurement Methods in Knee Radiographs

Mehmet Barıs ERTAN[1], Volkan BUYUKARSLAN[2], Murat YUNCU[2], Emre Mucahit KARTAL[3], Koray Kaya KILIC[4], Ozkan KOSE[2]

[1] Medikum Private Hospital, Orthopedics and Traumatology Clinic, Antalya, Turkiye.
[2] Department of Orthopedics and Traumatology, University of Health Sciences, Antalya Training and Research Hospital, Antalya, Turkiye.
[3] Department of Orthopedics and Traumatology, Antalya City Hospital, Antalya, Turkiye.
[4] Department of Radiology, University of Health Sciences, Antalya Training and Research Hospital, Antalya, Turkiye.

ABSTRACT

This study aimed to evaluate and compare the reliability and agreement of four commonly used methods for patellar height measurement: Insall-Salvati (IS), Modified Insall-Salvati (mIS), Caton-Deschamps (CD), and Blackburne-Peel (BP) indices, using standardized lateral knee radiographs. This prospective study included seventy adult patients with standardized lateral knee radiographs. Radiographs met strict criteria for true-lateral views and appropriate knee flexion angles. Three observers independently measured patellar height using the four methods, each performing two rounds of measurements at a 15-day interval. Intraclass Correlation Coefficients (ICC) were calculated for intra-observer and interobserver reliability. Pairwise agreements between methods were analyzed using Cohen's kappa with 95% confidence intervals (CI). Correlation coefficients (Pearson's r) were computed to assess the relationships between the methods. The BP method exhibited the highest inter-observer reliability (ICC = 0.848, 95% CI: 0.754–0.910) and intra-observer reliability (average ICC = 0.908, 95% CI: 0.829–0.986). This was followed closely by the CD method, while the IS and mIS methods demonstrated moderate reliability. Correlation analysis revealed strong relationships between the BP and CD methods ($r = 0.871$, $p < 0.01$) but weaker correlations between IS and the other methods. Despite high correlation coefficients, agreement in classification was poor, particularly between IS and BP ($\kappa = -0.131$) and IS and mIS ($\kappa = -0.047$).The Blackburne-Peel method is the most reliable and reproducible for patellar height measurement under standardized conditions, making it a robust tool for clinical and research applications. However, the methods were not interchangeable, emphasizing the need for consistent imaging protocols and method selection tailored to clinical objectives.

Keywords: Patellar height. Reliability. Blackburne-Peel index. Caton-Deschamps index. Insall-Salvati ratio. Modified Insall-Salvati ratio.

Diz Radyografilerinde Dört Farklı Patella Yüksekliği Ölçüm Yönteminin Güvenilirliği ve Uyum Analizi

ÖZET

Bu çalışmanın amacı standardize lateral diz radyografileri kullanılarak patellar yükseklik ölçümü için yaygın olarak kullanılan dört yöntemin güvenilirliğini ve uyumunu değerlendirmek ve karşılaştırmaktır: Insall-Salvati (IS), Modifiye Insall-Salvati (mIS), Caton-Deschamps (CD) ve Blackburne-Peel (BP) indeksleri.Bu prospektif çalışmaya standardize lateral diz radyografileri olan yetmiş erişkin hasta dahil edildi. Radyografiler gerçek lateral görünümler ve uygun diz fleksiyon açıları için katı kriterleri karşıladı. Üç gözlemci bağımsız olarak dört yöntemi kullanarak patellar yüksekliği ölçtü ve her biri 15 gün arayla iki tur ölçüm yaptı. Gözlemci içi ve gözlemciler arası güvenilirlik için Sınıf İçi Korelasyon Katsayıları (ICC) hesaplanmıştır. Yöntemler arasındaki ikili anlaşmalar, %95 güven aralıkları (CI) ile Cohen'in kappa'sı kullanılarak analiz edilmiştir. Yöntemler arasındaki ilişkileri değerlendirmek için korelasyon katsayıları (Pearson's r) hesaplanmıştır.BP yöntemi en yüksek gözlemciler arası güvenilirliği (ICC = 0.848, %95 CI: 0.754-0.910) ve gözlemci içi güvenilirliği (ortalama ICC = 0.908, %95 CI: 0.829-0.986) sergilemiştir. CD yöntemi bunu yakından takip ederken, IS ve mIS yöntemleri orta düzeyde güvenilirlik göstermiştir. Korelasyon analizi, BP ve CD yöntemleri arasında güçlü ilişkiler ($r = 0.871$, $p < 0.01$) ancak IS ile diğer yöntemler arasında daha zayıf korelasyonlar ortaya koymuştur. Yüksek korelasyon katsayılarına rağmen, özellikle IS ile BP ($\kappa = -0.131$) ve IS ile mIS ($\kappa = -0.047$) arasında sınıflandırma uyumu zayıftı.Blackburne-Peel yöntemi, standart koşullar altında patellar yükseklik ölçümü için en güvenilir ve tekrarlanabilir yöntemdir, bu da onu klinik ve araştırma uygulamaları için sağlam bir araç haline getirmektedir. Bununla birlikte, yöntemler birbirinin yerine kullanılamaz, bu da tutarlı görüntüleme protokollerine ve klinik hedeflere göre uyarlanmış yöntem seçimine olan ihtiyacı vurgulamaktadır.

Anahtar Kelimeler: Patellar yükseklik. Güvenilirlik. Blackburne-Peel indeksi. Caton-Deschamps indeksi. Insall-Salvati oranı. Modifiye Insall-Salvati oranı.

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Dr. Mehmet Barış ERTAN
Özel Medikum Hastanesi
Kumluca/Antalya

Phone: 0505 116 63 02
E-mail:mehmetbarisertan@gmail.com

Authors' Orcid Information
Mehmet Barış ERTAN: 0000-0002-3783-7109
Volkan BÜYÜKARSLAN: 0009-0005-3926-3419
Murat YÜNCÜ: 0000-0001-8567-6509
Emre Mücahit KARTAL: 0000-0002-8353-1995
Koray Kaya KILIÇ: 0000-0002-2750-8205
Özkan KÖSE: 0000-0002-7679-9635

Patellar height measurement is critical in evaluating disorders affecting the patellofemoral joint, including instability and anterior knee pain. Abnormalities such as patella alta and patella baja have been identified as risk factors for patellofemoral (PF) disorders, including instability, maltracking, and degenerative PF osteoarthritis[1,2]. Such conditions have the potential to alter knee biomechanics, thereby increasing the risk of cartilage damage and accelerating joint degeneration. Consequently, an accurate assessment of patellar height is crucial for both the diagnosis and the guidance of surgical treatment in PF disorders, as it provides surgeons with essential insights into biomechanical abnormalities that may require correction.

While advanced imaging modalities like computerized tomography (CT) and magnetic resonance imaging (MRI) offer detailed assessments of patellar height, they are often expensive, less accessible, and involve higher radiation doses or time requirements. Lateral knee radiographs, in contrast, remain the first-line imaging modality due to their affordability, availability, and relatively low radiation exposure. However, the accuracy of radiographic measurements depends heavily on the method used and the standardization of radiographic techniques, such as achieving a true-lateral view and consistent knee flexion angles.

Over the years, several methods for assessing patellar height have been developed, with the Insall-Salvati (IS) ratio, the modified Insall-Salvati (mIS) ratio, the Caton-Deschamps (CD) index, and the Blackburne-Peel (BP) method being the most widely used. Despite their widespread application, each method has limitations, particularly in their sensitivity to radiographic angles, anatomical variations, and observer reliability. For example, the IS and mIS ratios are highly influenced by variations in the length and attachment of the patellar tendon, whereas the CD and BP methods may offer greater anatomical precision. Although the reliability of these methods has been evaluated in previous studies, significant gaps remain in understanding their relative performance under standardized radiographic conditions. Most studies have focused on single methods or have not rigorously compared intraobserver and interobserver reliability across multiple methods[3]. Furthermore, there is limited data on the correlation between these methods and their practical applicability in clinical decision-making. This study addresses these gaps by comprehensively comparing the reliability and consistency of these four patellar height measurement methods.

Given the critical role of patellar height assessment in managing PF disorders, this study aims to identify the most reliable and consistent method under standardized conditions. The findings are expected to guide clinicians in selecting the most robust method for routine practice, thereby improving diagnostic accuracy and treatment planning. This study hypothesized that the Blackburne-Peel (BP) and Caton-Deschamps (CD) methods would demonstrate superior reliability compared to the Insall-Salvati (IS) and modified Insall-Salvati (mIS) ratios, particularly in terms of interobserver and intra-observer consistency. This study aimed to evaluate and compare the reliability and agreement of four commonly used methods for patellar height measurement.

Material and Method

Patients and study design

The institutional review board approved the study protocol (date/protocol: 24.10.2024, 338-16/11). The study was conducted following the principles of the Declaration of Helsinki. The ethics committee waived the need for patient consent because the study only involved radiographic data. The study was designed as a prospective observational study. Radiographs were obtained by searching the digital image database using the Picture Archiving and Communication System (PACS). Patients were eligible if they were 18 or older and had reached skeletal maturity. Exclusion criteria included any history of acute or healed fractures, previous knee surgery, the presence of implants, a diagnosis of severe knee osteoarthritis (Kellgren-Lawrence Classification, Grade III & IV), and radiographs that did not conform to the specific radiographic acquisition techniques described below.

Standards of the Radiographs

Two primary criteria were applied when selecting radiographs for inclusion in this study. First, the radiographs had to present true-lateral views, ensuring a complete overlap of the posterior condyles (Figure. 1a and 1b). Second, the knee flexion angle had to be between 20° and 30°, measured as the angle between the anatomical axes of the femur and tibia (Figure. 1c). To account for variability and obtain sufficient suitable images, radiographs with knee flexion angles within a 3° tolerance (i.e., 17° to 33°) were also included. A radiologist with over ten years of experience in musculoskeletal radiology evaluated the images for true-lateral view suitability and measured the knee flexion angles. The radiologist carefully selected appropriate patients based on the radiographic standards and the inclusion and exclusion criteria. The radiologist measured the knee flexion angles twice, with a minimum interval of 15 days between the measurements. The intra-observer reliability, assessed using the intraclass correlation coefficient (ICC), was calculated to be excellent, with a value of 0.885 (95%

CI: 0.821–0.927). Following two measurements, the mean knee flexion angle was 28.8 ± 3.8° (18.9–32.9°).

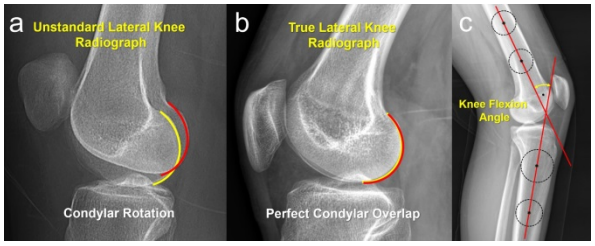

Figure 1.

(a) Example of an unstandardized lateral knee radiograph with visible condylar rotation, demonstrating the lack of complete overlap between the posterior condyles (highlighted with yellow and red arcs). (b) An example of a true lateral knee radiograph showing perfect condylar overlap (highlighted with a single red arc) meets the first inclusion criterion for radiograph selection. ***(c)*** *The knee flexion angle is measured as the angle between the anatomical axes of the femur and tibia, indicating the acceptable range of 20°–30° for inclusion. The yellow arrow highlights the angle, and the red lines illustrate the anatomical axes of the femur and tibia.*

Sample Size Calculation

The sample size was calculated based on the expected inter-rater reliability (Intraclass Correlation Coefficient, ICC) for measuring distances on radiographs by three raters[4] . The expected ICC was set at 0.900, with an acceptable minimum ICC of 0.700, considering a two-way random-effects model for consistency. To achieve 80% power at a significance level of 0.05, a minimum of 68 subjects were required. The calculation was performed using Bonett's method for estimating sample size in reliability studies, considering the number of raters and the difference between the expected and acceptable ICC values. To ensure adequate power, we included 70 randomly selected participants in the study. The study group consisted of 20 females and 50 males with a mean age of 34.6±14.4 years (range 18–76). The mean Body Mass Index (BMI) was 25.5±3.4 (range 19.2–34.5). 27 right knees and 43 left knees were evaluated. Demographic characteristics of patients are presented in Table I.

Measurement methods and normal values

This study used four most frequently used methods to assess patellar height: the Insall-Salvati ratio, the modified Insall-Salvati ratio, the Caton-Deschamps index, and the Blackburne-Peel method (Figure 2). Insall-Salvati Ratio: This method involves measuring the length of the patellar tendon and the greatest diagonal length of the patella. The ratio is calculated by dividing the tendon length by the patellar length[5]. Modified Insall-Salvati Ratio: Similar to the Insall-Salvati ratio, but this method accounts for the patellar tendon attachment by measuring from the lower pole of the patella to the tibial tubercle[6]. Caton-Deschamps Index: This method measures the distance from the inferior edge of the patella to the tibial plateau, divided by the length of the patellar articular surface[7]. Blackburne-Peel Method: The Blackburne-Peel method uses the ratio of the perpendicular height from the tibial plateau to the lower edge of the patellar articular surface divided by the length of the patella's articular surface[8]. Table II summarizes the threshold values for the discrimination of patellar height. Using these thresholds, we have categorized each patient as patella alta, patella norma and patella baja.

Table I. Demographic characteristics of the study population.

Variables	Data
Age (years±SD)	34.6±14.4 (range, 18-76)
Sex (n, %)	
Male	20 (28.6%)
Female	50 (71.4%)
Side (n, %)	
Right	27 (38.6%)
Left	43 (61.4%)
Height (cm±SD)	171.1±7.3 (range, 150-183)
Weight (kg±SD)	74.7±11.0 (range, 55-112)
BMI (kg/m²±SD)	25.5±3.3 (range, 19.2-34.5)

Abbreviations, BMI: Body mass index, SD: Standard deviation

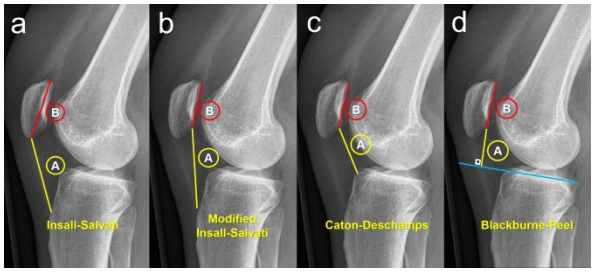

Figure 2.

Illustration of the four methods used to evaluate patellar height. All measurements were calculated as A/B ratios and documented as proportional values. (a) Insall-Salvati ratio, (b) Modified Insall-Salvati ratio. (c) Caton-Deschamps index. (d) Blackburne-Peel method.

Table II. Normal range for patellar height measurements

Method	Patella Alta	Patella Norma	Patella Baja
Insall-Salvati Index	>1.2	0.8-1.2	<0.8
Modified Insall-Salvati Index	>2	≤2	NA
Caton-Deshamphs Index	>1.3	0.6-1.3	<0.6
Blackburne-Peel Index	>1.0	0.5-1.0	<0.5

NA: Not applicable

Reliability Study

Three orthopedic specialists performed the measurements, each conducting two rounds of measurements on the radiographs with at least a 15-day interval between them. All observers were blinded to both their initial measurements and those of the other observers. Any identifying information on the radiographs, such as patient names, ages, and dates, was removed to ensure blinding. Before commencing the study, a meeting was held with all observers to review the measurement methods in detail. A visual aid demonstrating the measurement technique was provided, and the observers were allowed to refer to this image during the measurement process. All measurements were conducted on digital radiographs stored in DICOM format using the RadiAnt DICOM Viewer software (Medixant, Poland).

Statistical Analysis

Descriptive statistics were calculated for demographic and clinical variables, with results presented as means ± standard deviations (SD) or medians with ranges, as appropriate. Intraobserver and interobserver reliability were evaluated using Intraclass Correlation Coefficients (ICC) with 95% confidence intervals (CIs). A two-way random-effects model was used for interobserver reliability, which assessed both absolute agreement and consistency. ICC values were interpreted as poor (< 0.50), moderate (0.50–0.75), good (0.75–0.90), or excellent (> 0.90)[9]. Pairwise agreements between the four methods (IS, mIS, CD, BP) were analyzed using Cohen's Kappa statistic with 95% Cis. Kappa values were interpreted as poor (< 0.00), slight (0.00–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), or almost perfect (0.81–1.00)[10]. Pearson correlation analysis was conducted to evaluate the relationships between the patellar height measurement methods, with correlation coefficients (r) interpreted as very weak (< 0.20), weak (0.20–0.39), moderate (0.40–0.59), strong (0.60–0.79), or very strong (≥ 0.80). The significance level of $p<0.05$ was considered statistically significant[11] .

Results

The study included 70 patients (20 females and 50 males) with a mean age of 34.6 ± 14.4 years (range, 18–76) and a mean BMI of 25.5 ± 3.4 kg/m^2) (range, 19.2–34.5). Of the 70 knees, 27 (38.6%) were right, and 43 (61.4%) were left.

The interobserver reliability analysis demonstrated good levels of agreement (ICC between 0.750-0.900) among the four patellar height measurement methods, with the results summarized in Table III. The Blackburne-Peel (BP) method exhibited the highest interobserver reliability. The intra-observer reliability analysis revealed the highest agreement for the BP method, with an average ICC of 0.908 (95% CI: 0.829–0.986). The other three methods showed good levels of agreement (Table IV) (Figure 3).

Table III. Results of interobserver reliability analysis.

Method	Time 1, ICC 95% CI	Time 2, ICC 95% CI	Average, ICC 95% CI
IS	0.739 (0.612-0.830)	0.835 (0.755-0.892)	0.786 (0.612-0.892)
mIS	0.738 (0.610-0.829)	0.736 (0.608-0.828)	0.737 (0.608-0.829)
CD	0.825 (0.740-0.886)	0.845 (0.769-0.898)	0.835 (0.740-0.898)
BP	0.835 (0.754-0.892)	0.862 (0.795-0.910)	0.848 (0.754-0.910)

Abbreviations, ICC: Interclass correlation coefficient, CI: Confidence interval, IS: Insall-Salvati, mIS: Modified Insall-Salvati, CD: Caton-Deschamps, BP: Blackburne-Peel.

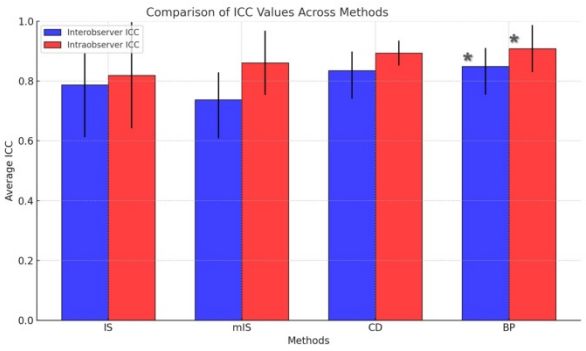

Figure 3.
Comparison of ICC values for interobserver (blue bars) and intraobserver (red bars) reliability across four patellar height measurement methods: Insall-Salvati (IS), modified Insall-Salvati (mIS), Caton-Deschamps (CD), and Blackburne-Peel (BP). Error bars indicate standard deviations. Asterisks (*) denote the methods with significantly higher ICC values compared to others ($p < 0.05$).

Table IV. Results of intra-observer reliability analysis.

Methods	Observer A	Observer B	Observer C	Average
	ICC 95% CI	ICC 95% CI	ICC 95% CI	ICC 95% CI
IS	0.913 (0.863-0.945)	0.638 (0.475-0.758)	0.907 (0.854-0.941)	0.819 (0.641-0.997)
mIS	0.817 (0.721-0.882)	0.795 (0.689-0.867)	0.969 (0.950-0.980)	0.860 (0.753-0.967)
CD	0.904 (0.849-0.939)	0.852 (0.771-0.905)	0.924 (0.880-0.952)	0.893 (0.851-0.935)
BP	0.939 (0.904-0.962)	0.829 (0.738-0.890)	0.957 (0.932-0.973)	0.908 (0.829-0.986)

Abbreviations, ICC: Interclass correlation coefficient, CI: Confidence interval, IS: Insall-Salvati, mIS: Modified Insall-Salvati, CD: Caton-Deschamps, BP: Blackburne-Peel.

Correlation analysis revealed a strong relationship between the CD and BP methods (r = 0.871, p < 0.01) and moderate-to-strong correlations between other methods, such as mIS and BP (r = 0.716, p < 0.01) and IS and CD (r = 0.488, p < 0.01). The IS method showed weaker correlations with mIS (r = 0.348, p < 0.01) and BP (r = 0.344, p < 0.01) (**Figure 4**).

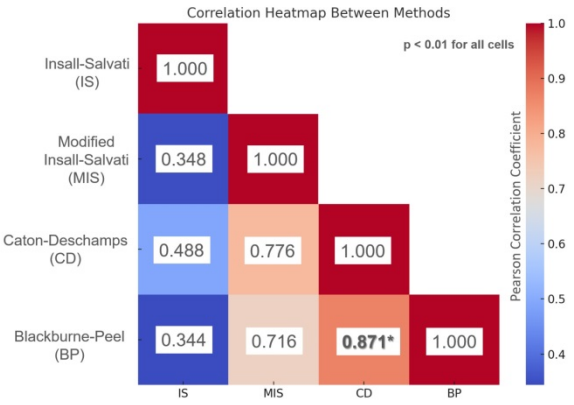

Figure 4.

Correlation heatmap between the patellar height measurement methods. The heatmap displays the Pearson correlation coefficients (r) between the Insall-Salvati (IS), Modified Insall-Salvati (MIS), Caton-Deschamps (CD), and Blackburne-Peel (BP) methods. All correlation coefficients are significant at p<0.01. The strength of the correlations is indicated by the color intensity, ranging from low (blue) to high (red). The highest correlation (r=0.871) is observed between the Caton-Deschamps (CD) and Blackburne-Peel (BP) methods, denoted with an asterisk (*). Diagonal values represent self-correlation (r=1.000).

Despite the high correlation observed between the measured ratios, a notable lack of consistency was evident in the classification results (Table V). The agreement between the Insall-Salvati (IS) and Modified Insall-Salvati (mIS) methods was poor, with a kappa value of -0.047 (95% CI: -0.104 to 0.010). The agreement between IS and Blackburne-Peel (BP) was also poor, with a kappa value of -0.131 (95% CI: -0.200 to -0.062). A moderate agreement was observed between mIS and BP, with a kappa value of 0.419 (95% CI: 0.019 to 0.819). The agreement involving the Caton-Deschamps (CD) method could not be calculated because all classifications under this method were constant, precluding meaningful comparisons. The agreement between the patellar height measurement methods is summarized in Table V. Patient-wise classifications of patellar height based on four methods are presented in Figure 5.

Table V. Pairwise agreement between the methods. Cohen's Kappa and 95% Confidence Interval.

	IS	mIS	CD	BP
IS	1			
mIS	-0.047 (-0.104-0.010)	1		
CD	NA	NA	1	
BP	-0.131 (-0.200-0.062)	0.419 (0.019-0.819	NA	1

Abbreviations, ICC: Interclass correlation coefficient, CI: Confidence interval, IS: Insall-Salvati, mIS: Modified Insall-Salvati, CD: Caton-Deschamps, BP: Blackburne-Peel.NA: Not Applicable. Since all classifications in CD were normal, agreement between methods cannot be calculated.

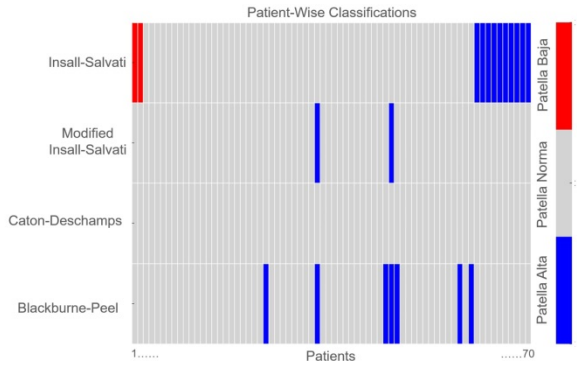

Figure 5.

Patient-wise classifications of patellar height based on four methods: Insall-Salvati, Modified Insall-Salvati, Caton-Deschamps, and Blackburne-Peel. Each row represents one method, and each column corresponds to an individual patient. Colors indicate patellar height categories: red (patella alta), gray (normal), and blue (patella baja). The figure demonstrates variability in classifications across methods, highlighting discrepancies in categorization for some patients.

Discussion and Conclusion

This study sought to evaluate the reliability and agreement of four commonly used patellar height measurement methods, namely Insall-Salvati, Modified Insall-Salvati, Caton-Deschamps, and Blackburne-Peel, using standardized lateral knee radiographs. The findings revealed that the Blackburne-Peel and Caton-Deschamps methods demonstrated superior intra- and inter-observer reliability compared to the Insall-Salvati and Modified Insall-Salvati methods. The BP method demonstrated the highest reliability, with an average ICC exceeding 0.90 for both intra- and inter-observer evaluations, closely followed by the CD method. The results of the correlation analysis demonstrated a strong relationship between the BP and CD methods, while the IS and

mIS methods exhibited weaker correlations with the other methods. Despite the high correlation between the measured ratios, there was poor agreement in the classifications, particularly between the IS and mIS (κ = −0.047, κ = −0.047) and the IS and BP (κ = −0.131, κ = −0.131). These findings underscore the superior reliability and consistency of the BP and CD methods, suggesting their potential as robust tools for clinical and research applications in patellar height assessment. Based on these findings, we recommend choosing the BP method for patellar height measurements. Furthermore, these methods cannot be used interchangeably.

There is currently no consensus in the literature regarding the most appropriate method for measuring patellar height. Different authors have advocated for the superiority of various methods while highlighting the disadvantages of others. This lack of agreement may stem from several factors. One key reason is the variability in imaging modalities used for measurement. For instance, the anatomical landmarks differ between children and adults due to incomplete ossification in pediatric populations. Additionally, the presence of osteoarthritis can alter these landmarks due to osteophyte formation. Beyond modality differences, the standardization of imaging techniques is another critical factor influencing measurement accuracy. Obtaining a true lateral knee radiograph with 30 degrees of knee flexion is essential for standardization and reliable measurements, as studies have shown that rotational misalignment significantly affects results. Similarly, changes in knee flexion angle alter patellar height measurements; reduced flexion leads to patellar tendon relaxation and lower patellar tendon length, while increased flexion results in elongation of the patellar tendon and increase the tendon length. This underscores the importance of maintaining consistent flexion angles during imaging. In MRI, where the knee is often positioned near full extension, the normal and pathological thresholds for patellar height classification differ from those established for radiographs, necessitating the development of adjusted classification ranges. Furthermore, the Insall-Salvati (IS) ratio was modified by Grelsamer to create the Modified Insall-Salvati (mIS) ratio, which focuses on the patella-trochlear engagement, emphasizing the importance of the articulating surface of the patella. However, the Blackburne-Peel (BP) method has been reported to vary with changes in tibial slope, highlighting the influence of anatomical and imaging factors on measurement reliability.

Huddleston et al. and Becher et al. both highlighted critical factors influencing the accuracy of patellar height measurements, emphasizing the need for precise imaging conditions[12,13]. Huddleston et al. demonstrated that aberrant radiographic rotation, particularly in the axial and counterclockwise directions, significantly alters Caton-Deschamps Index (CDI) measurements, with all degrees of rotational error in axial and coronal planes potentially causing clinically significant differences (≥0.1)[12]. This underscores the importance of obtaining true-lateral radiographs to ensure accurate patellar height assessment. Similarly, Becher et al. showed that increasing knee flexion angles significantly affected patellar height indices, including CDI and Patellotrochlear Index (PTI), which decreased progressively with increased flexion, with the most notable reductions observed at 45° flexion[13]. These findings highlight the dynamic nature of patellar positioning with knee flexion and rotation, reinforcing the necessity of controlling both knee angle and radiographic alignment during clinical and imaging evaluations.

The present study builds on the findings of the Berg and Seil studies by reaffirming the reliability of the Blackburne-Peel (BP) method as the most reproducible for patellar height measurement, demonstrating superior inter- and intraobserver reliability across methods[14,15]. Similar to Berg et al., we emphasize the importance of strict radiographic standards and consistent knee flexion angles, with our findings further showing strong correlations between BP and the Caton-Deschamps (CD) index ($r = 0.871$, $p < 0.01$)[14]. Both our study and Seil et al. noted variability among methods, including poor concordance between IS and BP (κ values below zero in our study; 57% in Seil et al.)[15]. While Seil et al. assessed additional methods, such as Labelle-Laurin, both studies strongly advocate for methods that rely on patellar articular surface relationships, like BP and CD[15]. By providing comprehensive correlation data and highlighting poor agreement between IS, Modified Insall-Salvati (MIS), and BP, our study extends these earlier findings and underscores the necessity of standardized imaging conditions to improve reliability.

The present study stands in contrast to the findings of Moon Seok Park et al., Duijvenbode et al., and Verhulst et al., as it advocates for the Blackburne-Peel (BP) method as the most reliable and clinically applicable measure of patellar height, particularly in adults[3,16,17]. While Moon et al. highlighted the limitations of BP in pediatric populations due to indistinct bony landmarks, our results demonstrate its superior reproducibility in adults, where ossification is complete[16]. In contrast to Duijvenbode et al., who recommended the Insall-Salvati (IS) and Modified Insall-Salvati (MIS) methods for their reliability and validity, our findings emphasize BP's resilience in identifying patella alta and baja, especially under standardized radiographic conditions[3]. Similarly, Verhulst et al. favored IS for its inter-method

reliability across imaging modalities. However, we observed that BP outperforms IS in consistency and clinical utility when clear imaging protocols are applied[17]. Our study also addresses some of the criticisms of BP noted in these works, including variability related to landmark identification. We minimised these issues by employing strict radiographic acquisition protocols, further reinforcing BP's practicality and reliability. These differences underscore the importance of considering patient population and imaging conditions, as we argue that BP provides the most accurate and reproducible results in clinical practice, particularly in adults with standardized imaging.

The present study aligns with previous works, including those by Picken et al., Hunter et al., and Kwak et al., in emphasizing the challenges and variability of patellar height measurement methods[2,18,19]. The study also advocates for the Blackburne-Peel (BP) method as the most reliable under standardized conditions. Like Picken et al., we acknowledge the superior reliability of the Insall-Salvati (IS) ratio across observers and modalities but observed higher reliability for BP in our dataset due to stringent radiographic standardization. While Picken et al. highlighted the need for modality-specific normative values, particularly for MRI, our focus on consistent imaging conditions reinforces the importance of clear anatomical landmarks for accurate measurement[18]. Similarly, our findings parallel Hunter et al.'s observations on the variability and poor interchangeability of common indices, but we differ by identifying BP as the most reproducible method when standardization is ensured, contrasting with their findings favoring IS for inter-rater reliability[2]. Kwak et al. further highlighted the importance of age- and modality-specific approaches, demonstrating the Koshino–Sugimoto method's superiority in pediatric populations[19]. In contrast, our study, limited to adult patients, identified BP as the most consistent and clinically applicable method. Collectively, these findings emphasize the critical role of imaging standardization and tailored approaches to improve the accuracy and reliability of patellar height measurements across diverse patient populations.

One important consideration in patellar height measurement is the potential influence of racial and regional differences. While most commonly used methods, such as Insall-Salvati, Modified Insall-Salvati, Caton-Deschamps, and Blackburne-Peel, were originally developed and validated in Western populations, recent studies have shown that these methods may yield different results in non-Western populations. For example, a study conducted in Indonesia reported lower normal values for the Insall-Salvati method (0.78–1.26) compared to the standard Western values (0.8–1.2), suggesting that ethnic differences may influence patellar height measurements[20]. In contrast, a study conducted in Turkey found that patellar height values measured with the same methods were consistent with Western norms, indicating that these standardized methods can be reliably applied to the Turkish population[21]. These findings emphasize the importance of validating measurement techniques across different populations to ensure accurate and reliable clinical assessments.

This study has several limitations. First, the sample consisted solely of adult patients, limiting the generalizability of the findings to pediatric populations or those with incomplete ossification. Additionally, the use of standardized lateral knee radiographs excludes variability seen in routine clinical imaging, which may affect real-world applicability. The study also did not evaluate imaging modalities other than radiographs, such as MRI or CT, which are increasingly utilized in patellar height assessment. Furthermore, the exclusion of patients with severe osteoarthritis or prior surgeries may underestimate the challenges of landmark identification in more complex clinical cases. Despite these limitations, the study has several notable strengths. Its prospective design and rigorous radiographic standardization ensured the collection of high-quality data. Including multiple observers and repeated measurements allowed for a robust assessment of inter- and intra-observer reliability. Additionally, the comparative analysis of four commonly used measurement methods under consistent conditions provided valuable insights into their reliability and applicability, particularly emphasizing the Blackburne-Peel method as a reliable option for both clinical and research settings.

This study highlights the Blackburne-Peel (BP) method as the most reliable and consistent technique for patellar height measurement under standardized conditions, outperforming the Insall-Salvati (IS), Modified Insall-Salvati (mIS), and Caton-Deschamps (CD) methods in terms of both inter- and intra-observer reliability. While the BP method demonstrated superior reproducibility, the variability in classifications across methods underscores the importance of selecting appropriate measurement techniques tailored to specific clinical or research needs. These findings emphasize the necessity of achieving true-lateral radiographs with consistent knee flexion angles to enhance measurement accuracy. Future studies should explore the applicability of the BP method across different imaging modalities, pediatric populations, and in the presence of osteoarthritis to establish a more comprehensive understanding and foster a consensus on patellar height assessment.

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ÖZGÜN ARAŞTIRMA

Acil Servise Başvuran 65 Yaş ve Üzeri İntrakranial Kanaması Olan Hastaların Demografik ve Epidemiyolojik Özelliklerinin Analizi*

Tuğçe YENİ POLAT[1], Özlem KÖKSAL[2], Vahide Aslıhan DURAK[2], Göksel AYDOĞAN[3], Ömer YONTAR[2], Nur Betül COŞKUN[2]

[1] Çekirge Devlet Hastanesi Acil Tıp Anabilim Dalı, Bursa, Türkiye.
[2] Bursa Uludağ Üniversitesi Tıp Fakültesi Acil Tıp Anabilim Dalı, Bursa, Türkiye.
[3] Zonguldak Devrek Devlet Hastanesi Acil Tıp Kliniği, Zonguldak, Türkiye.

ÖZET

Bu çalışmanın amacı acil servise başvuran ≥65 yaş intrakranial kanaması olan hastaların demografik ve epidemiyolojik özelliklerinin incelenmesi ve klinik sonlanımları ile ilişkili faktörlerin belirlenmesidir. Kesitsel tipte olan bu çalışma, 1 Ocak 2018 – 31 Aralık 2022 tarihleri arasında acil serviste intrakranial kanama tanısı alan ≥65 yaş olguların dosyalarının retrospektif olarak değerlendirilmesi ile gerçekleştirilmiştir. Olguların %57,6'sı erkekti ve yaş ortalaması 75,49 ± 7,43 yıldı. Olguların %79,9'unda en az bir ek hastalık, %46,0'ında travma öyküsü vardı. Bilgisayarlı Tomografi sonucunda en sık saptanan kanama türleri %39,1 subdural, %38,6 intraparankimal ve %26,1 subaraknoid kanama idi. Klinik sonlanım açısından bakıldığında; olguların %7,6'sının acil servisten taburcu edildiği %21,2'sinin yoğun bakım ünitesine yatırıldığı, %29,9'unın dış merkez yoğun bakım ünitesine sevk edildiği ve %1,6'sının ise exitus olarak sonlandığı görüldü. Diğer olgularla karşılaştırıldığında, klinik sonlanımı olarak yoğun bakım ünitesi yatış/ sevk/ ölüm olan olgular arasında kadın cinsiyet sıklığı ve subdural kanama sıklığı istatistiksel olarak anlamlı düzeyde daha yüksek iken; Glasgow Koma Skoru ve intraparankimal kanama sıklığı ise anlamlı düzeyde daha düşüktü. Sonuç olarak klinik pratikte özellikle kranial BT'de subdural hematom saptanan ve GKS skoru düşük yaşlı intrakranial kanamalı olgularda kötü sonlanım riskinin daha fazla olduğunu göz önünde bulundurularak, erken dönemde doğru tedavinin uygulanmasının sağ kalımı artıracak çabalar arasında yer alacağı düşünülmektedir.

Anahtar Kelimeler: Acil servis. Glasgow Koma Skoru. İntrakranial kanama.

Analysis of Demographic and Epidemiologic Characteristics of Patients 65 Years and Older with Intracranial Hemorrhage Presenting to the Emergency Department

ABSTRACT

The aim of this study is to examine the demographic and epidemiological characteristics of patients with intracranial hemorrhage aged ≥65 years who applied to the emergency department and to determine the factors associated with their clinical outcomes. This cross-sectional study was conducted by retrospectively evaluating the files of patients aged ≥65 years who were diagnosed with intracranial hemorrhage in the emergency department between January 1, 2018 and December 31, 2022. 57.6% of the cases were male, and the mean age was 75.49 ± 7.43 years. In 79.9% of the cases, there was at least one comorbidity, and 46.0% had a history of trauma. The most frequently identified types of hemorrhage on Computed Tomography were 39.1% subdural, 38.6% intraparenchymal, and 26.1% subarachnoid hemorrhage. In terms of clinical outcomes, 7.6% of the cases were discharged from the emergency department, 21.2% were admitted to the intensive care unit, 29.9% were transferred to an external center's intensive care unit, and 1.6% resulted in death. Compared to other cases, among those with intensive care unit admission/transfer/death, female gender and subdural hemorrhage were statistically significantly higher, while Glasgow Coma Score and intraparenchymal hemorrhage frequency were significantly lower. In conclusion, considering that in clinical practice, the risk of poor outcome is higher in elderly patients with intracranial hemorrhage, especially those with subdural hematoma detected on cranial CT and with low GCS scores, it is thought that the implementation of treatment modalities in the early period will be among the efforts to increase survival rate.

Keywords: Emergency department. Intracranial hemorrhage. Glasgow Coma Scale.

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Dr. Vahide Aslıhan DURAK
Bursa Uludağ Üniversitesi Tıp Fakültesi
Acil Tıp Anabilim Dalı
Tel.: 0532 446 25 12
E-posta: aslidurakis@hotmail.com

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Yazarların Orcid Bilgileri
Tuğçe YENİ: 0000-0002-3742-9797
Özlem KÖKSAL: 0000-0003-2271-5659
Vahide Aslıhan DURAK: 0000-0003-0836-7862
Göksel AYDOĞAN: 0009-0006-2750-207X
Ömer YONTAR: 0009-0007-0239-783X
Nur Betül COŞKUN: 0009-0005-1168-3673

İntrakraniyal kanama (İKK) kraniyum içinde yer alan beyin parankimi ve onu çevreleyen meningeal boşluklar dahil tüm yapılardaki herhangi bir kanamayı tanımlamaktadır[1]. İKK'ların dünya çapındaki insidansı son 20 yılda yaklaşık %47 oranında artmıştır[2]. İKK'ların beş temel alt tipi olup; İntraparankimal (İPH), intraventriküler (IVH), subdural (SDH), epidural (EDH) ve subaraknoid kanama (SAK) şeklindedir. Bunlardan İPH ve İVH intra-aksiyel olarak, SDH, EDH ve SAK ise ekstra-aksiyel olarak sınıflandırılabilir[3]. Hipertansiyon, enfeksiyon, antitrombositer ve antikoagülan ilaç kullanımı, anevrizma, madde kullanımı, cinsiyet, yaş, aile öyküsü, tümöral yapılar, arteriovenöz malformasyonlar ve travma risk faktörleri olarak sayılabilecek başlıca İKK nedenleri olarak sayılabilir[4]. Sun ve ark. 2019 yılında 204 ülke ve bölgedeki yaptıkları çalışmada tahmini 3,4 milyon İKK vakası tanımlamış olup, bu vakaların 2,8 milyonu ölümle sonuçlandığını bildirilmiştir[5]. Yaşlı bireyler, genç hastalara kıyasla İKK için beş kat daha fazla risk taşımaktadır[6]. Erkeklerin, kadınlara göre daha genç yaşta İKK geçirdiği belirlenirken, 80 yaş sonrası kadınlarda kanama eğiliminin arttığı belirlenmiştir. Kadınlar ve erkekler arasında 30 günlük ölüm oranları arasında fark bulunmamıştır[7]. Yaş faktörünün yanında hipertansiyon, diyabet, atriyal fibrilasyon gibi kronik sağlık problemleri ve sistemik koşullar yaşlılarda bu risk oranını arttırırken; gençlerde en sık tütün kullanımı, hipertrigliseridemi, hipertansiyon, travma, alkol kullanımı, vasküler malformasyon önde gelen risk faktörleri olarak kendini göstermektedir[8,9]. Ülkemizde 133 hastanın incelendiği bir çalışmada otuz günlük mortalite ve bir yıllık mortalite oranları sırasıyla %38,3 ve %49,6 olarak rapor edilmiştir. 30 günlük ölüm oranı ve bir yıllık ölüm oranı ise, cinsiyet açısından farklılık göstermemiştir[10]. Travmaya bağlı İKK'lar ise, travmatik bir olaydan sonra hastaların %13-35'inde görülmekte olup; kitle etkisi, refrakter intrakraniyal hipertansiyon ve herniasyona yol açabilmektedir[11,12]. Travma şiddeti, ileri yaş, çoklu lezyonlar, orta hatta şift veya sisternal kompresyon gibi faktörlerle ilişkilidir[11].

İKK tedavi ve yönetiminde intrakraniyal basınç takibi, mannitol, hipertonik salin, antipiretik, cerrahi dekompresyon, antikoagülan tedavinin tersine çevrilmesi gerektiği durumlarda taze dondurulmuş plazma (TDP), protrombin kompleks konsantreleri (PCC), antikonvülsan ilaçlar, kan ürünleri transfüzyonu kullanılan başlıca tedavi yöntemleridir[4]. İKK insidansı ile yaş arasında anlamlı bir ilişki olup bu insidans yaşla birlikte artmaktadır[13].

Yaşlanan bir toplumda, yaşlı insanların oranı arttıkça İKK insidansının arttığına dair kanıtlar var olup bu durum yaşlanma sonuçlu sosyal ve sosyoekonomik zorluklarla, hem hastane içi tedavi ve hem hastane dışı kaynak tahsisindeki zorluklarla başa çıkma yolunda İKK tedavisinde karar verme sürecini kolaylaştırmayı amaçlayan durumları ortaya çıkarmaktadır[14].

Bu çalışmanın amacı acil servis (AS)'e başvuran ≥65 yaş intrakranial kanaması olan hastaların demografik ve epidemiyolojik özelliklerinin incelenmesi ve klinik sonlanımları ile ilişkili faktörlerin belirlenmesidir.

Gereç ve Yöntem

Üniversitemizin Klinik Araştırmalar Etik Kurulu (7 Mart 2023, karar no:2023-5/4) izni ile 1 Ocak 2018 – 31 Aralık 2022 tarihleri arasında Tıp Fakültesi Hastanesi Acil Servisi'nde gerçekleştirilen kesitsel tipte çalışma, İKK nedeniyle başvuran ≥65 yaş olgulara ait 448 hasta dosyasının retrospektif olarak değerlendirilmesi ile gerçekleştirilmiştir.

Çalışmaya; ≥65 yaş olan, intrakraniyal kanama saptanan, verileri ve görüntüleme sonuçları eksiksiz olan hastalar dahil edilmiş olup bu kriterlere uymayan olgular ise çalışma dışı bırakılmıştır.

Hastaların; cinsiyet, yaş, ek hastalıkları, vital bulguları (kan basıncı, vücut sıcaklığı, nabız), Glasgow Koma Skoru (GKS) değeri, trombosit ve International Normalized Ratio (INR) değerleri, travma öyküsü, antikoagülan ilaç kullanımı, yatırılan klinik ve klinik sonlanımları kaydedilmiştir.

İstatistiksel analiz

Çalışmanın analizleri SPSS 27.0 paket programı ile gerçekleştirilmiştir. Kategorik değişkenler sayı ve yüzde, sürekli sayısal değişkenler ortalama, standart sapma, median (min–maks) değerleri ile özetlenmiştir. Sürekli sayısal verilerin normal dağılım durumu Kolmogorov Smirnov testi ile değerlendirilmiş ve normal dağılmadığı görülmüştür. İki grup arasında yapılan sayısal veri karşılaştırmasında Mann Whitney U testi, kategorik veri karşılaştırmasında ki-kare testi ve Fisher'in kesin testi kullanılmıştır. Yoğun Bakım Ünitesi (YBÜ)'ne yatış/ YBÜ'ne sevk/ ölüm açısından bağımsız risk faktörlerinin belirlenmesi amacıyla, tek değişkenli analizlerde anlamlı olduğu belirlenen parametrelerin dahil edildiği çok değişkenli lojistik regresyon analizi gerçekleştirilmiştir. İstatistiksel olarak anlamlılık sınırı olarak p değerinin 0,05 değerinden küçük olması kabul edilmiştir. Verilerin görselleştirilmesinde yığılmış sütun grafiği ve kutu-çizgi grafiği kullanılmıştır.

Bulgular

Acil Servise başvuran 448 İKK olgusunun dahil edildiği bu çalışmada, 258 olgu (%57,6) erkek olup 190 olgu (%42,4) ise kadın olarak saptanmış olup yaş ortalaması ise 75,49 ± 7,43 yıl olarak saptandı. En sık

görülen ek hastalıkların ise %51,6 oranında hipertansiyon, %32,6 oranında kardiyovasküler hastalıklar ve %21,4 oranında diyabetes mellitus olduğu görüldü.

Çalışmaya dahil edilen olguların %46,0'ında travma öyküsü vardı. BT sonucunda en sık saptanan kanamalar %39,1 subdural, %38,6 intraparankimal ve %26,1 subaraknoid kanama şeklinde idi. Hastalara uygulanan antikoagülan ilaçların kullanım sıklığı değerlendirildiğinde en sık %32,6 ile asetilsalisilik asit, %11,6 klopidogrel ve %6,9 yeni nesil oral antikoagülanlar olduğu görüldü (Tablo I).

Tablo I. Travma öyküsü varlığı, bilgisayarlı tomografide saptanan kanama lokalizasyonu ve uygulanan antikoagülan tedavilerin dağılımı.

Değişkenler	Sayı (n)	Yüzde (%)
Travma öyküsü		
Yok	242	54,0
Var	206	46,0
Bilgisayarlı tomografide saptanan kanama lokalizasyonu		
Subdural	175	39,1
İntraparankimal	173	38,6
Subaraknoid kanama	117	26,1
Epidural	15	3,3
İntraventriküler	12	2,7
Antikoagülan ilaç kullanımı		
Yok	229	51,1
Var	219	48,9
Asetil salisilik asit	146	32,6
Klopidogrel	52	11,6
Yeni nesil oral antikoagülan	31	6,9
Varfarin	15	3,3
Düşük molekül ağırlıklı heparin	15	3,3
Tikagrelor	1	0,2
Silostazol	1	0,2

Klinik sonlanımı YBÜ yatış/ sevk/ölüm olan olgular arasında kadın cinsiyet sıklığı istatistiksel olarak anlamlı düzeyde daha yüksek olarak saptandı (p = 0,002).

Diğer olgularla karşılaştırıldığında YBÜ'ne yatırılan, sevk edilen ya da ölen olgular ile bu olguların dışında kalan gruplar karşılaştırıldığında; subdural kanama sıklığının YBÜ'ne yatırılan, sevk edilen ya da ölen olgularda istatistiksel olarak anlamlı düzeyde daha fazla olduğu (%20,8'e karşı %55,5, p<0,001), intraparankimal kanama sıklığının ise YBÜ'ne yatırılan, sevk edilen ya da ölen olgularda anlamlı düzeyde daha düşük olduğu görüldü (%52,8'e karşı %25,9, p<0,001) (Tablo II).

Tablo II. Olguların klinik sonlanımına göre travma varlığı, tomografide saptanan kanama bölgesi ve uygulanan antikoagülan tedavilerin karşılaştırılması.

Değişkenler	YBÜ yatış/ sevk/ ölüm				*p*
	Yok (n = 346)		Var (n = 102)		
	n	%	n	%	
Travma					
Yok	92	43,4	150	63,6	**<0,001**
Var	120	56,6	86	36,4	
Tomografide kanama Bölgesi					
Epidural					
Yok	203	95,8	230	97,5	0,317
Var	9	4,2	6	2,5	
Subdural					
Yok	168	79,2	105	44,5	**<0,001**
Var	44	20,8	131	55,5	
Subaraknoid kanama					
Yok	156	73,6	175	74,2	0,891
Var	56	26,4	61	25,8	
İntraparankimal					
Yok	100	47,2	175	74,2	**<0,001**
Var	112	52,8	61	25,8	
İntraventriküler					
Yok	204	96,2	232	98,3	0,174
Var	8	3,8	4	1,7	
Antikoagülan tedavisi					
Yok	104	49,1	125	53,0	0,409
Var	108	50,9	111	47,0	
Asetil salisilik asit	75	35,4	71	30,1	0,233
Klopidogrel	19	9,0	33	14,0	0,098
Varfarin	7	3,3	8	3,4	0,959
DMAH	7	3,3	8	3,4	0,959
Yeni nesil oral Antikoagülan	17	8,0	14	5,9	0,385
Tikagrelor	1	0,5	0	0,0	-
Silostazol	1	0,5	0	0,0	-

DMAH: Düşük molekül ağırlıklı heparin, YBÜ: Yoğun bakım ünitesi

Klinik sonlanımı YBÜ yatış/ sevk/ ölüm olan olgular diğer olgularla karşılaştırıldığında, sistolik kan basıncı (SKB) (p<0,001) ve diyastolik kan basıncı (DKB) (p = 0,002) değerleri istatistiksel olarak anlamlı düzeyde daha yüksek, GKS değeri ise daha düşüktü (p<0,001) (Tablo III).

Klinik sonlanım açısından bakıldığında; olguların %7,6'sının acil servisten taburcu edildiği %21,2'sinin YBÜ'ne yatırıldığı, %29,9'unın dış merkez YBÜ'ne sevk edildiği ve %1,6'sının ise exitus olarak sonlandığı görüldü. En sık yatış yapılan klinik bölümler ise; %29,9 oranında beyin cerrahisi ve %6,5 nöroloji bölümleri idi.

Tablo III. Olguların klinik sonlanıma göre yaş, vital bulguları, GKS skoru, trombosit sayısı ve INR değerlerinin karşılaştırılması.

Değişkenler	YBÜ yatış/ sevk/ ölüm		*p*
	Yok (n = 346)	Var (n = 102)	
	Ort ± SS (median)	Ort ± SS (median)	
Yaş (yıl)	74,76 ± 6,92 (74)	76,14 ± 7,81 (75)	0,098
SKB (mmHg)	141 ± 26,22 (130)	153,81 ± 39,55 (150)	**<0,001**
DKB (mmHg)	79,19 ± 11,93 (75)	86,56 ± 22,27 (80)	**0,002**
Nabız (atım/dk)	76,3 ± 10,49 (75)	76,92 ± 14,8 (70)	0,272
GKS	14,51 ± 1,1 (15)	9,89 ± 4,13 (11)	**<0,001**
Trombosit (*10^3 mcL)	214,68 ± 66,14 (214,5)	207,67 ± 60,44 (201)	0,251

DKB: Diastolik kan basıncı, GKS: Glasgow koma skalası, INR: International normalised ratio, Ort. Ortalama, SKB: Sistolik Kan basıncı, SS: Standart sapma, YBÜ: Yoğun bakım ünitesi

Tartışma ve Sonuç

Bir üniversite hastanesi AS'inde İKK tanısı alan 65 yaş ve üzeri olguların klinik özelliklerinin değerlendirilmesi amacıyla yapılan bu çalışmaya alınan olguların %57,6'sı erkek ve yaş ortalaması 75,49 ± 7,43 idi. Hsieh ve ark. İKK nedeniyle kabul edilen 1.192 hastanın verileri dört yıllık bir süre boyunca toplandığı çalışmada da erkeklerin oranı %58 ve yaş ortalaması 66,3 ± 15,3 yıl olarak belirlenirken, Xing ve ark. 1325 hasta ile gerçekleştirdikleri çalışmada bu oran %67,7 ve yaş ortalaması 59,14 olarak belirlenmiştir. Her iki çalışmada çalışmamızın literatür uyumluluğunu ortaya koymaktadır[7,15].

Çalışmamızda olguların %79,9'unun en az bir ek hastalığı vardı ve en sık eşlik eden hastalık %51,6 ile hipertansiyon (HT) olarak saptandı. Yine 1003 hasta ile yapılan bir çalışmada HT %70,8 ile en yüksek oranda bulunurken, 364 hastanın prospektif olarak incelendiği çalışmada bu oran %88,7 olarak belirlenmiştir[16,17]. Çalışmamız sonuç olarak literatürdeki diğer çalışmalarla benzerlik gösterirken oransal olarak farklılıklar mevcuttur. Bunun durum çalışmaların tek veya çok merkezli oluşuna bağlı olarak örneklem büyüklüklerinin farklı oluşuna bağlanabilir.

Sonlanım açısından bakıldığında; olguların %7,6'sı taburcu olurken, %21,2'si YBÜ'ne yatırıldı, %29,9'u YBÜ gerekliliği için sevk edildi ve %1,6'sı ise exitus kabul edildi. Faghih ve ark. 100 hastayı incelediği çalışmada ise %43'üne klinik yatış yapılırken, %62 hasta taburcu olmuş, 90 günlük mortalite oranı ise %38 olarak raporlanmıştır[18]. Sonuçlar arasındaki bu farklılıkların çalışmamızın yapıldığı dönemin daha yakın bir dönemi kapsaması, İKK olgularına bakım olanaklarının önceki çalışma dönemlerine kıyasla daha gelişmiş olması ve çalışmamızın bölgesel bir hastanede yapılmış olmasından kaynaklanmış olabileceğini düşündürmüştür.

Çalışmamızda kranial BT sonucunda en sık kanama saptanan alanlar %39,1 ile subdural ve %3,3 ile epidural alan, %38,6 ile intraparankimal ve %26,1 oranıyla SAK olarak saptandı. Literatürde bu duruma travmatik ve travmatik olmayan durumlar olarak yaklaşılmıştır. Yaşlılarda travmatik olmayan kanamalarda etyolojide hipertansiyonun neden olduğunu gösteren çalışmalar mevcuttur[19]. Travmatik yaralanma yönünden Podolsky ve ark. >65 yaş ve üzeri 133 vakayı inceledikleri çalışmada en sık görülen bulgular kronik subdural hematom (%48,1) iken, bunu akut subdural hematom (%37,6) izlemiştir[20].

Çalışmamızda GKS skorunda düşmenin YBÜ yatış/ sevk ve ölüm riskini anlamlı düzeyde arttırdığı görüldü (OR: 0,448 [%95 GA: 0,362- 0,553], p<0,001). Rau ve ark. travmatik beyin yaralanması (TBY) olup 2081 yetişkin hastayı içeren ve 847'i >65 yaş üstü hastadan oluşan çalışmasında da TBY olan yaşlı hastaların yönetiminde daha düşük bir GKS kesme eşiği benimsenmesinin uygun olduğunu belirtmişlerdir[21]. Layrisse ve ark. travma öyküsü olan ≥65 yaş 2905 hastayla gerçekleştirdiği başka bir çalışmada ise travma şiddetinin daha düşük GKS ile ilişkili olduğu raporlanmıştır[22]. Her iki çalışmada çalışmamızın literatür uyumluluğunu ortaya koymaktadır. Çalışmamızda kullanmakta olduğu antikoagülan tedaviler olarak %32,6 asetilsalisilik asit, %11,6 klopidogrel ve %6,9 yeni nesil oral antikoagülan kullanımı öyküsü olduğu; olguların %48,9'unun ise en az bir antikoagülan tedavi aldığı belirlendi. Cloud ve ark. 19.114 yaşlı yetişkinin dahil olduğu randomize çalışmalarında asetilsalisilik asit alan 9525 hastada İKK riskinde artış belirlenirken Shiozawa ve ark. 32.275 hastayı prospektif ve çok merkezli olarak analiz ettikleri başka bir çalışmada antikoagülan kullanımının İKK riskinde artış yaptığı ifade edilmiştir[23,24].

İntrakraniyal kanama nedeniyle acil servise başvuran 65 yaş ve üzeri olgulardan subdural kanama saptananlarda ve GKS skoru daha düşük olanlarda klinik olarak kötü sonlanım riski anlamlı düzeyde daha fazla saptanmıştır. Klinik pratikte özellikle kranial BT'de subdural hematom saptanan ve GKS skoru düşük yaşlı İKK olgularında kötü sonlanım riskinin daha fazla olduğunu göz önünde bulundurularak, erken dönemde doğru tedavinin uygulanması sağ kalımı artıracak çabalar arasında yer alabilir. Gelecek çalışmalarda prospektif olarak birden fazla merkezde ve daha fazla sayıda olgunun dahil edilmesiyle intrakraniyal kanamaların klinik özellikleri daha detaylı olarak ortaya konabilir.

Kısıtlılıklar

Çalışmamızın retrospektif olması sonuçları etkileyebilecek farklı verilerin geriye dönük olarak tekrar sorgulanmasını engellemiştir. Ayrıca tek merkezde gerçekleştirildiği için sonuçların genellenebilirliği sınırlıdır. Çalışmamızda kanama saptanan bölgeler olgu dağılımı nedeniyle bölge özelinde değerlendirilmiş olup, birden fazla bölgede eş zamanlı kanama saptanan olguların sonuçlara olan etkisi çok değişkenli regresyon analizi ile düzeltilmiştir. Daha fazla sayıda olgunun dahil edildiği çalışmalarda, her kanama kombinasyonu ayrı ayrı tek değişkenli analizlerde değerlendirerek, analizlerde ortaya çıkmayan olası etkileri daha detaylı olarak ortaya konabilir. Ayrıca literatürde yapılan çalışmaların çoğunluğu travmatik ya da non-travmatik intrakraniyal kanama olgularının sonuçlarını değerlendirmektedir. Çalışmamızda her iki olgu grubu tek bir havuzda toplanmıştır. Bu nedenle tartışma bölümünde yapılan literatür karşılaştırmaları ve yorumlamaları bazı noktalarda sınırlı düzeyde tutulmuştur. Son olarak çalışmamızın sonuçları sadece 65 yaş ve üzeri bireyleri kapsamaktadır, daha genç İKK olgularının sonuçları farklılık gösterebilir.

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ORIGINAL RESEARCH

The Side Effects of Levetiracetam Monotherapy in Pediatric Epilepsy Patients

Serap BİLGE[1], Nevzat BAŞKAYA[2]

[1] Department of Pediatric Neurology, Ministry of Health, Children Hospital of Diyarbakır, Diyarbakır, Türkiye.

[2] Department of Pediatric Allergy and Immunology, Ministry of Health, Children Hospital of Diyarbakır, Diyarbakır, Türkiye.

ABSTRACT

Levetiracetam is a broad-spectrum second-generation anti-seizure drug. Several side effects can be observed during treatment. In this study, we retrospectively evaluated the side effects of levetiracetam monotherapy in the pediatric epilepsy population and investigated potential indicators that could predict these side effects in the pediatric epilepsy population. The study included pediatric epilepsy patients aged 1-17 who were treated with levetiracetam monotherapy. Data collected included age, gender, body weight, blood pressure, duration of levetiracetam use, dosage, seizure semiology, epilepsy type, EEG and MRI findings, hematological and biochemical laboratory results, and observed side effects. Eighty-five patients were included in the study, with 25 (29%) experiencing side effects. Treatment was discontinued in 11 patients due to these effects. The most common side effects were agitation (9%), headache (6%), and fatigue (5%). No significant relationship was found between side effects and gender, body weight, seizure type, levetiracetam dose, treatment duration, EEG results, or MRI findings. However, vitamin B12 levels were lower in patients with side effects compared to those without. Additionally, side effects were more frequently observed in older age groups. Levetiracetam treatment has been linked to both physical and behavioral side effects, which were more commonly observed in older age groups. The most frequently reported side effects were agitation, headache, and fatigue. Additionally, lower B12 levels may contribute to the onset of certain side effects.

Keywords: Levetiracetam. Anti-seizure medication. Vitamin B12. Side effects. Agitation.

Pediatrik Epilepsi Hastalarında Levetirasetam Monoterapisinin Yan Etkileri

ÖZET

Levetiracetam geniş spektrumlu ikinci nesil anti-nöbet ilacıdır. Tedavi sırasında çeşitli yan etkiler görülebilir. Bu çalışmada, pediatrik epilepsi popülasyonunda levetiracetam monoterapisinin yan etkilerini retrospektif olarak değerlendirdik. Çalışmaya levetiracetam monoterapisi ile tedavi edilen 1-17 yaş arası epilepsili hastalar dahil edildi. Yaş, cinsiyet, vücut ağırlığı, kan basıncı, levetiracetam kullanım süresi, doz, semiyoloji, epilepsi tipi, EEG ve MRI bulguları, hemogram ve biyokimyasal laboratuvar bulguları ve gözlenen yan etkiler kaydedildi. Çalışmaya 85 hasta dahil edildi. Yirmi beş (%29) hastada yan etki görüldü. Yan etkiler nedeniyle 11 hastada tedavi kesildi. En sık görülen üç yan etki ajitasyon (8 hasta, %9), baş ağrısı (5 hasta, %5) ve yorgunluktu (3 hasta, %4). Yan etkiler ile cinsiyet, vücut ağırlığı, nöbet tipi, levetirasetam dozu, süresi, EEG ve MRI bulguları arasında ilişki bulunmamıştır. Yan etki görülen grupta B12 vitamini düzeyleri daha düşük bulunmuştur. Yan etkiler daha yaşlı yaş gruplarında daha sık görülmüştür. Levetirasetam tedavisinde fiziksel-davranışsal yan etkiler gözlenmiştir. Yan etki görülen yaş grubu daha yüksekti. En sık görülen üç yan etki ajitasyon, baş ağrısı ve yorgunluk olmuştur. Düşük B12 düzeyleri bazı yan etkilerin başlamasında rol oynayabilir.

Anahtar Kelimeler: Levetirasetam. Nöbet önleyici ilaç. B12 vitamini. Yan etkiler. Ajitasyon.

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Serap BİLGE
Bursa Yüksek İhtisas Eğitim ve Araştırma Hastanesi,
Bursa, Türkiye
Phone: 0533 497 73 90
E-mail: sarabsmustafa@hotmail.com

Authors' ORCID Information
Serap BILGE: 0000-0002-4265-3363
Nevzat BAŞKAYA: 0000-0002-5587-0041

Levetiracetam (Lev) is a second-generation anti-seizure medication with broad-spectrum efficacy[1,2]. To a great extent, it doesn't interact pharmacodynamically with other drugs and it doesn't induce p450 cytochrome enzymes thus having fewer side effects compared to the other anti-seizure medication (ASM). Lev has a unique mechanism of action compared to other antiepileptic drugs, as it specifically binds to synaptic vesicle protein 2A (SV2A). This protein, located in presynaptic terminals, is thought to mediate its antiepileptic effects

by influencing presynaptic processes that control synaptic vesicle release. However, its precise mechanism of action is not completely understood[2,3]. Lev is rapidly and almost completely absorbed following oral administration, with a bioavailability of nearly 100%, unaffected by food intake. Peak plasma concentrations are reached within 1 hour, and steady-state levels are achieved within 2 days when taken twice daily. Its pharmacokinetics are linear, dose-proportional, and time-independent. The drug undergoes limited metabolism, with 27% excreted as inactive metabolites within 24 hours. Lev is primarily eliminated via the renal route, with 66% excreted unchanged[3]. Dose adjustments are advised only for patients with moderate to severe renal or severe hepatic impairment accompanied by renal insufficiency. In children, the body clearance of Lev is 30–40% higher than in adults[3,4]. One of its noteworthy is that it is an effective drug with a good safety profile and is prescribed as a first-line drug or combination therapy[1]. However, as with all medicines, Lev can cause side effects in some patients[5,6]. Side effects may vary from mild symptoms like drowsiness and dizziness to more serious ones, such as mood changes, irritability, suicidal thoughts, and, in rare cases, allergic reactions. Understanding these potential side effects is vital for both patients and healthcare providers, enabling early recognition and prompt intervention to ensure safe and effective treatment outcomes. Few studies have assessed the tolerability and safety of Lev monotherapy in pediatric epilepsy patients[1,7]. In this study, we retrospectively evaluated the side effects of Lev monotherapy and investigated potential indicators that could predict these side effects in the pediatric epilepsy population.

Material and Method

The medical records of patients aged 1 to 17 years approached Diyarbakır Children's Hospital from December 2021 to March 2023 were retrospectively reviewed to detect the following ICD-10 codes: G40.0 Epilepsy · G40.1 epilepsy G41.2 Complex partial epilepsy · G41.8 Other epilepsy · G41.9 Epilepsy unspecified. The patients with the above ICD codes who adhered to Lev as ASM with reliable seizure records were included in the study. Demographic and clinical variables comprised of age, gender, weight, blood pressure, duration of ASM use, type of seizure, etiology, diet(normal/vegetarian), MRI (normal/with lesion), EEG (normal/epileptic), and hemogram biochemical test results were recorded, either at the end of one year / at the day of cessation Lev due to intolerable side effects. The patients were divided into two groups, a group with no side effects (group 1) and a group with side effects (group 2). The exclusion criteria were changes in the ASM schedule before one year, using other drugs in addition to ASM, history of other systemic or psychiatric diseases. Clinical and demographic data were collected through a questionnaire during follow-up visits and from medical record files. The dose of lev was evaluated as an initial dose (20 mg/kg/day), medium dose (30-50 mg/kg/day), and high dose (> 60mg/kg/day). Epilepsy type and etiology were considered according to the International League Against Epilepsy (ILAE) classification. Our study was approved by the ethics committee of Health Sciences University Gazi Yaşargil Training and Research Hospital, on 17-05-2023 with the approval number 417.

Statistical Analysis

Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and as median and min-max where appropriate. To compare categorical variables between the groups, the Pearson Chi-Square Test or Fisher's Exact Test was used depending on whether the expected value problem arises or not. The normality of distribution for continuous variables was confirmed with the Shapiro-Wilk test. For comparison of continuous variables between the side effect groups, the Student's t-test or Mann-Whitney U test was used depending on whether the statistical hypotheses were fulfilled or not. Logistic regression analysis was performed to determine significant predictors of Side effects. In univariate analysis, variables significant at the $P < 0.25$ level were entered in logistic regression analysis. All analyses were performed using the IBM SPSS Statistics Version 20.0 statistical software package. The statistical level of significance for all tests was considered to be 0.05.

Results

Among the 85 patients included in this study, 42% were male, and 29% of patients experienced side effects. The mean age was 7.5 ± 4.6 years in group 1 (no side effects) and 9.9 ± 5.2 years in group 2 (with side effects) ($p = 0.046$). The duration of levetiracetam use was 18.1 ± 5.5 months in group 1 and 12.7 ± 9.4 months in group 2 (whether the drug was stopped or not). No significant difference was observed in the blood profile between the two groups. Treatment was discontinued in 11 patients due to serious side effects. The three most common side effects were agitation (9%), headache (6%), and fatigue (5%). The average age of patients with side effects was older than those without. There was no correlation between side effects and gender, body weight, seizure type, levetiracetam dose, duration of use, EEG results, or MRI findings. Birth history, family history, and diet type did not

influence the results. Vitamin B12 levels were lower in group 2 (with side effects), although B12 levels were within the normal range for both groups.

Table I presents the clinical and demographic profile of the patients. Table II displays the blood profile of the patients in both groups. Table III illustrates the observed side effects along with their respective percentages. Table IV presents the effect of various variables on levetiracetam side effects. Table V shows the results of the logistic regression analysis for predicting levetiracetam side effects.

Table I. The clinical and demographic profile of the patients.

	Side effect		p
	No-Group 1	Yes-Group 2	
	n=60	n=25	
Age(years), *Mean±SD*	7.5±4.6	9.9±5.2	**0.046**
Gender, *n (%)* Male Female	 31 (52%) 29 (48%)	 11 (44%) 14 (56%)	0.519
Weight (kg), *Mean±SD*	33.1±15.3	38.5±13.6	0.131
Lev use duration, *Mean±SD* *Median (min-max)* *Month*	18.1±5.5 16.5 (12-36)	12.7±9.4 14 (1-34)	**0.031**
Dose, *n (%)* Moderate Low(initial) High	 42 (70%) 14 (23%) 4 (7%)	 15 (60%) 8 (32%) 2 (8%)	0.624
Semiology, *n (%)* Focal Generalized Unknown	 18 (30%) 36 (60%) 6 (10%)	 6 (24%) 16 (64%) 3 (12%)	0.845
EEG, *n (%)* Normal Epileptic	 17 (28%) 43 (72%)	 4 (16%) 21 (84%)	0.230
MRI, *n (%)* Normal Lesion	 49 (82%) 11 (18%)	 22 (88%) 3 (12%)	0.749
Type of Epilepsy, *n (%)* Symptomatic-Cryptogenic Idiopathic Structural	 28 (47%) 24 (40%) 8 (13%)	 16 (64%) 6 (24%) 3 (12%)	0.312

EEG: Electroencephalogram, MRI: Magnetic Resonance Image

Age was determined as an effective measure in terms of the occurrence of side effects. Accordingly, the average age of children with side effects was higher than those with no side effects.

Table II. The blood profiles of the patients in both groups

	Side Effect		P
	NO -Group 1	Yes-Group 2	
	n=60	n=25	
Wbc (×10^3/uL), *Mean±SD*	8.5±3.2	8.1±2.5	0.574
Neutrophile (%), *Mean±SD*	47.9±13.9	52.8±16.4	0.164
Lymphocyte (%), *Mean±SD*	39.6±12.7	35.7±16.2	0.239
Monocyte (%), *Mean±SD*	7.5±2.9	7.8±2.2	0.671
Eosinophils (%), *Mean±SD* *Median (min-max)*	3.4±3.3 2.3 (0.1-14.6)	3.6±3.1 2.9 (0.6-11.9)	0.783
Basophyle (%), *Mean±SD*	0.43±0.28	0.5±0.35	0.393
ANC (×10^3/uL), *Mean±SD*	4.2±2.5	4.2±1.9	0.987
ALC (×10^3/uL), *Mean±SD*	3.3±1.6	2.9±1.6	0.209
RBC (× 10^6/µL), *Mean±SD*	4.7±0.5	4.6±1	0.531
RDW-CV (%), *Mean±SD*	13.9±2.1	14.2±2.3	0.560
PLT (×10^3/uL), *Mean±SD*	325.8±120.6	304.8±121.6	0.466
MPV (fL), *Mean±SD*	9.7±1.7	9.7±1.1	0.890
Hg (g/dl), *Mean±SD*	12.4±1.6	12.6±1.6	0.754
HCT (%), *Mean±SD*	39.2±7.1	38.9±4	0.873
B12 (pmol/l), *Mean±SD*	365.7±147.7	411±126	0.192
Ferritin (ng/ml), *Mean±SD*	42.6±14.0	42±12.9	0.851
Systolic Blood Pressure (mmHg), *Mean±SD*	100.1±14.4	107.2±20.1	0.082
Diastolic Blood Pressure (mmHg), *Mean±SD*	64.1±11.6	61.5±12.3	0.381
Vitamin D (nmol/L), *Mean±SD*	26.5±8.3	25.1±7.3	0.469
CK (IU/L), *Mean±SDMedian (min-max)*	168.4±87.8 165 (54-453)	145.2±80.7 145 (45-324)	0.260
Glucose (mg/dL), *Mean±SD*	80.1±10.9	77±10.1 77 (64-92)	0.233
ALT (IU/L), *Mean±SD* *Median (min-max)*	18.7±7.6 17 (9-44)	20.2±8.6 23 (12-45)	0.399
AST (IU/L), *Mean±SD* *Median (min-max)*	31.4±27.3 27.5 (14-228)	31±8.2 33 (13-45)	0.248
Albumin (g/L), *Mean±SD*	40.6±1.5	40.1±4	0.491
Creatine (mg/dL), *Mean±SD*	0.55±0.12	0.54±0.09	0.814

Wbc: White blood cells, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, Rbc: Red blood cell, RDW-CV: Red cell distribution width - coefficient of variation, PLT: platelet, MPV: Mean platelet volüme, Hg: Hemoglobin, Hct: Hematocrit, CK: Creatine kinase, ALT: Alanine transaminase, AST: Aspartate transferase

Table III. The observed side effects are according to their percentages.

Measurements	Number of patients (%)
Side effect	
No	60 (71%)
Yes	25 (29%)
Agitation	
No	77 (91%)
Yes	8 (9%)
Headache	
No	80 (94%)
Yes	5 (6%)
Fatigue	
No	81(95%)
Yes	4(5%)
Stomach ache	
No	84(99%)
Yes	1(1%)
Allergy	
No	83 (98%)
Yes(Maculopapüler/angiodema)	2 (2%)
Weight loss	
No	84 (99%)
Yes	1 (1%)
Increased frequency of illness	
No	84 (99%)
Yes	1 (1%)
Rhinitis	
No	84 (99%)
Yes	1 (1%)
Sleep habit	
Normal	72 (85%)
Disturbed (which happened secondary due to other side effects)	13 (15%)
Others*	
No	80 (94%)
Yes	5(6%)
Drug discontinuation	14(56%)
No	11(44%)
Yes	

*Somnolence:1 patient, Tremor:1, enuresis:1, insomnia:1, suicide attempt:1
*Some patients experienced more than one side effect

Table IV. The effect of some variables on the side effects of Lev.

	Side effect		P
	No- Group 1	**Yes-** Group 2	
	n=60	n=25	
Birth history, *n (%)*			
Normal	57 (95%)	23 (92%)	0.628
Eventful	3 (5%)	2 (8%)	
Family history, *n (%)*			
No	36 (60%)	20 (80%)	0.076
Yes	24 (40%)	5 (20%)	
Diet type, *n (%)*			
Normal	59 (98%)	25 (100%)	0.999
Vegetarian	1 (2%)	0 (0%)	

Table V. Logistic regression analysis of predicting Lev side effects.

	P	Odds Ratio (OR)	95% CI for OR
B12 level	0.031	1.05	1.01 – 1.09

OR: odds ratio; CI: confidence interval

Discussion and Conclusion

Lev is a broad-spectrum ASM that can be used in all age groups. It can be considered a great choice with a safe profile. But still, some side effects can be seen. Tekgül et al. (2016) conducted a study on 351 pediatric patients, reporting that 17% of them experienced adverse effects, irritability 67%, hyperactivity 8%, somnolence 6%, behavioral disorders 5%, restlessness 5%, increased seizure frequency 3%, enuresis 2%, headache 2% and attempted suicide 2% were the most observed side effects. The same study concluded that there was no relation between the dose, age, and side effects, meanwhile, the adverse effects were seen more frequently in patients with partial focal seizures and who have psychiatric disorders and abnormal EEG patterns. In our study, the three most common side effects were agitation 9%, headache 6% and fatigu 5%. Tremor 4%, somnolence 4%, enuresis 4%, insomnia 4%, and suicide attempt 4% were other observed side effects. In our study, the average age of patients with side effects was higher than those with no side effects, which could be because the younger children could have better body clearance of Lev.

ASMs can cause psychiatric symptoms due to their impact on neurotransmitter systems and neural circuits. They alter the balance of key neurotransmitters such as gamma-aminobutyric acid (GABA), glutamate, and serotonin, which regulate mood, cognition, and behavior, potentially leading to anxiety, irritability, or depression. By modifying electrical activity to prevent seizures, ASMs may also affect brain regions involved in mood regulation and cognition, causing emotional instability or cognitive impairment. Individual susceptibility plays a significant role in this process, as genetic factors and pre-existing mental health conditions can increase vulnerability to these side effects. Additionally, higher doses or drug interactions can intensify psychiatric symptoms by disrupting mood-related pathways. Some ASMs also influence immune activity in the brain, which may contribute to mood disturbances. As a result, individuals taking ASMs, particularly during dosage adjustments, may experience psychiatric symptoms, highlighting the need for careful monitoring and management[8,9]. In our study, psychiatric side effects were observed in 9% of the patients who experienced agitation. Mood changes

can be observed in epilepsy patients and in those who use ASM such as Lev, lamotrigine, phenobarbital, and clonazepam and the cause behind this could be either biological or psychosocial. Researchers have found that people with epilepsy are 5 times at risk of suicide. In addition, the risk is still higher even in surgically treated patients. Other studies suggest that suicide attempt is higher in patients with temporal lobe epilepsy which can be due to abnormal function of the limbic system[10]. A suicide attempt was observed in one patient. She was a conventional school-attending 14-year-old girl. MRI was normal, and there were spike-waves in the left temporal region on EEG. The drug was stopped immediately, and the patient was monitored in the intensive care unit for a few days and switched to another ASM.

Dermatological and non-dermatological changes can be experienced in patients who are treated with Lev. The dermatological side effects mostly appeared on the face, and extremities, characterized by dark-colored skin, and morbilliform macular rash. The non-dermatological side effects experienced were fever, headache, abdominal pain, facial edema, pharyngitis, and periorbital eye swelling[11-13]. Despite these side effects being less likely with Lev compared to other ASMs, still such adverse effects can be seen and immediate withdrawal should be done. In our study, maculopapular rash in one patient and angioedema in another one were observed during Lev treatment. The drug was discontinued.

Drug cessation should be approached for serious side effects. Lev treatment had to be discontinued in 11 patients. The discontinuation of Lev was sometimes immediate, while in other cases, it was delayed until it was confirmed that the side effect was caused by Lev. Lev was stopped in three of the five patients with headaches. Lev was also stopped in patients with allergy (2), stomachache (1), enuresis (1), fatigue (1) suicide tendency (1), weight loss (1), and increased frequency of infection (1) The dose of Lev was adjusted in some patients with tolerable side effects.

Lev may reduce the degranulation of CD8 lymphocytes, leading to an increased incidence of upper respiratory tract infections[14,15]. Drug-induced immunoglobulin decreases have been reported in some patients[15,16]. In our patient group, an increase in the frequency of infection was observed in one patient. Lymphocyte count was low, 1270/uL, but lymphocyte subgroup and immunoglobulin levels could not be analyzed. Lev was stopped in this patient.

Few studies have assessed the hematological effects of Lev in the pediatric population. Dilber et al. conducted a study on 114 children in 2021 and tested the effect of this antiseizure drug on hemogram, liver function, and B12, it was observed after three years of follow-up that there was an increase in hemoglobin and hematocrit, while there was a decrease in absolute neutrophil count (ANC) and absolute lymphocytes count(ALC) while the platelet count was not affected and there was no correlation between gender and hematological changes, and despite the changes there were no clinical complaints by the patients [16,17]. French et al evaluated adult patients who received Lev monotherapy despite the hematological changes at first, all the parameters returned to normal at the end of three years [13]. A decrease in lymphocyte and ALC was observed in studies conducted by Dinopoulos et al and Attilocks et al[17-19]. There are also studies in which antiepileptic treatment decreased vitamin B12 levels[19,20]. In our study, logistic regression analysis showed that lower vitamin B12 levels were associated with more side effects in spite that the B12 levels were with in normal range in both groups. This raises the discussion of whether a cut-off B12 level should be established for patients on Lev monotherapy and monitoring of vitamin B12 levels during treatment with ASM is recommended [21] But further studies are needed.

Urinary and fecal incontinence was reported in patients with Lev monotherapy and the exact mechanism is still unknown[22]. Incecik et al reported an 11-year-old boy patient who experienced fecal and urinary incontinence at a dose of 20 mg/kg[23]. Investigation as MRI, EEG, and infection parameters were normal. The effect was reversible and the patients could gain control after withdrawing the drug. In our study, an 8-year-old boy experienced urinary and fecal incontinence a few days after starting Lev. All the investigations were normal, urine culture and urine analysis showed no infection. The drug stopped immediately and the control was regained.

Fatigue is reported by lots of studies as an adverse effect of Lev monotherapy. Marco Mula et al reported fatigue in 36% of patients with Lev which could be due to an imbalance between excitatory and inhibitory neurotransmission however the exact mechanism of central fatigue is still unclear and this side effect was seen more frequently in females rather than males[3,24]. Recent studies showed that central fatigue could be due to dysfunction in the non-motor area of basal ganglıon and their interaction with the frontal cortex and amygdala but the effect of Lev on these networks is still unknown[24]. In our study fatigue was seen in 5% of the patients while the rest 95% of patients didn't experience such symptoms. Fatigue could be due to multifactorial etiologies.

Lev is associated with higher total sleep duration, and sleep problems are not commonly reported as a side effect[25]. The recent studies' results are very controversial. Some studies showed that Lev increased the N2 stage of sleep [26]. In another study, it was observed that Lev increased wakingness and in a study conducted by yılmaz et al., it was seen that this drug increased daytime napping episodes and total nap

duration while there was a decrease in total activity score at night in monotherapy in adult patients[27]. In our study, sleep disturbances were reported in 15% of patients and occurred secondary to other side effects.

Physical and behavioral side effects were reported during Lev treatment, with affected patients being older on average. The three most common side effects were agitation, headache, and fatigue. No significant associations were found with body weight, gender, epilepsy type, Lev dose, treatment duration, MR, or EEG findings. Larger studies are necessary to identify clinical and laboratory markers that may predict the side effects of Lev monotherapy in pediatric patients.

Our study is retrospective with a small sample size. Sleep disturbances were based on family and patient reports rather than a validated and reliable scale. Additionally, pre-treatment laboratory data was unavailable, preventing a comparative analysis of hematological and biochemical results before, during, and after treatment or its discontinuation.

Abbreviations

Lev: Levetiracetam
ASM: anti-seizure medication
SV2A: synaptic vesicle protein 2A
EEG: Electroencephalogram,
MRI: Magnetic Resonance Image
Wbc: White blood cells,
ANC: Absolute neutrophil count,
ALC: Absolute lymphocyte count,
Rbc: Red blood cell,
RDW-CV: Red cell distribution width coefficient of variation,
PLT: platelet,
MPV: Mean platelet volüme,
Hg: Hemoglobin,
Hct: Hematocrit,
CK: Creatine kinase,
ALT: Alanine transaminase,
AST: Aspartate transferase
GABA: Gamma-Aminobutyric Acid

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ORIGINAL RESEARCH

Evaluation of Capillaroscopy Findings in Patients Presenting with Raynaud's Phenomenon (RP): A Retrospective Study*

Salim MISIRCI, Ali EKIN, Burcu YAĞIZ, Belkıs Nihan COŞKUN, Hüseyin Ediz DALKILIÇ, Yavuz PEHLIVAN

Bursa Uludag University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Bursa, Türkiye.

ABSTRACT

Raynaud's phenomenon (RP) is a discoloration of the fingers due to abnormal vasoconstriction in the digital arteries and cutaneous arterioles in response to cold or emotional stress. The study included patients who presented to a tertiary rheumatology clinic with RP between September 2022 and April 2023 and underwent nailfold capillaroscopy (NFC). Of the included patients, 34 (57.6%) were diagnosed with inflammatory rheumatic disease (IRD) and 25 (42.4%) with primary RP. When analysing antibodies, the most common antibody was antinuclear antibody (ANA) (n=39, 66.1%), and most of them were positive with a low titer (n=22, 37.3%). When comparing patients with and without IRD, the capillary density of ≥7 per 1 millimetre was sufficient in all patients in the group without IRD. There was a decrease in capillary density (<7) in 13 (38.24%) patients in the IRD group. When the sizes of capillaries were evaluated, a significant difference was found between the groups in terms of giant capillaries (>50 µm) (p=0.005). In the IRD group, 14 (41.18%) patients had a scleroderma (SCL) pattern and 20 (58.82%) had a non-SCL pattern. In the non-IRD group, all but two patients had a non-SCL pattern. Age, ANA positivity, high ANA titer, presence of giant capillaries and SCL pattern had a positive significant discriminatory effect (p<0.05) in distinguishing between patients with and without IRD. NFC assessment is an important tool in the diagnosis of IRDs such as systemic sclerosis. Advanced age, SCL pattern, giant capillaries and ANA positivity should be warning signs of secondary RP.

Keywords: İnflammatory rheumatic disease. Capillaroscopy. Raynaud's Phenomenon. Systemic sclerosis.

Raynaud Fenomeni (RF) ile Başvuran Hastaların Kapilleroskopi Bulgularının Değerlendirilmesi: Retrospektif Çalışma Raynaud Fenomeni (RF) ve Kapilleroskopi

ÖZET

Raynaud fenomeni (RF), soğuğa veya duygusal strese karşı dijital arterlerde ve kutanöz arteriyollerdeki anormal vazokonstriksiyona bağlı olarak gelişen parmaklardaki renk değişikliğidir. Çalışmaya Eylül 2022-Nisan 2023 tarihleri arasında üçüncü basamak bir romatoloji polikliniğine RF ile başvurup tırnak kıvrımı kapilleroskopisi (TKK) yapılan hastalar dahil edildi. Dahil edilen hastaların 34 (%57,6)'üne inflamatuvar romatizmal hastalık (İRH) tanısı konulduğu, 25 (%42,4)'inin ise primer RF olarak kabul edildiği belirlendi. Antikorlar değerlendirildiğinde, en sık saptanan anti-nükleer antikor (ANA) (n=39, %66,1) olup, çoğunluğu düşük titrede pozitifti (n=22, %37,3). İRH saptanan ve saptanmayan hastalar karşılaştırıldığında, İRH olmayan gruptaki hastaların tamamında kapiller dansite her 1 milimetrelik alanda ≥7 olup yeterliydi. İRH grubundaki hastaların 13'ünde kapiller dansitede azalma (<7) mevcuttu. Kapillerlerin boyutları değerlendirildiğinde, gruplar arasında dev kapiller (>50 µm) açısından anlamlı farklılık saptandı (p=0,005). İRH grubundaki hastaların 14'ünde SCL paterni, 20 (%58,82)'sinde ise non-SCL paterni saptanmıştı. İRH olmayan gruptaki hastaların sadece ikisi hariç tamamında non-SCL paterni saptanmıştı. Yaş, ANA pozitifliği, yüksek titre ANA pozitifliği, dev kapiller görülmesi ve SCL paterninin İRH olan ve olmayan hastaları ayırmada pozitif anlamlı ayırıcı (p<0,05) etkisi gözlenmiştir. TKK değerlendirmesi, sistemik skleroz gibi İRD'lerin tanısında önemli bir araçtır. İleri yaş, SCL paterni, dev kapiller ve ANA pozitifliği sekonder RF açısından uyarıcı olmalıdır.

Anahtar Kelimeler: İnflamatuvar romatizmal hastalık. Kapilleroskopi. Raynaud fenomeni. Sistemik skleroz.

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Authors' ORCID Information:
Salim MISIRCI: 0000-0002-9362-1855
Ali EKİN: 0000-0003-3692-1293
Burcu YAĞIZ: 0000-0002-0624-1986
Belkis Nihan COŞKUN: 0000-0003-0298-4157
Hüseyin Ediz DALKILIÇ: 0000-0001-8645-2670
Yavuz PEHLİVAN: 0000-0002-7054-5351

Raynaud's phenomenon (RP) is a discoloration of the fingers due to abnormal vasoconstriction of the digital arteries and cutaneous arterioles in response to cold or emotional stress. Initially a white discoloration (vasoconstriction), followed by a blue discoloration (cyanosis due to deposits of deoxygenated blood) and finally a red discoloration (hyperemia after ischemia).[1,2] The overall prevalence of RP is usually between 3 and 5%, although high rates of up to 21% have also been reported.[1,2] A primary RP can be

diagnosed if no underlying cause for the RP can be found. If there is an underlying pathology, in particular connective tissue diseases (CTDs), this is referred to as secondary RP.[3] Primary RP usually occurs at a young age and is 4-20 times more common in women than in men.[4] It presents with symmetric attacks, digital ulcers or trophic lesions are not seen. Capillaroscopic examination shows normal findings. In contrast, secondary RP occurs in middle age, with asymmetric attacks, digital ulcers and gangrene, positive autoantibody formation and abnormal findings on capillaroscopic examination.[4]

In primary RP, there is a functional defect in the arteriovenous anastomoses, which play a role in thermoregulation, whereas in secondary RP, tissue ischemia is observed, which is due to both a disturbance in thermoregulation and structural defects in the nutritional capillaries. Thus, while excessive vasospasm develops after exposure to cold in primary RP, structurally intact feeding capillaries prevent tissue ischemia and thus ischemic damage in primary RP.[5]

Nailfold capillaroscopy (NFC) is a non-invasive, inexpensive and easy-to-use imaging technique that can be used to assess the microcirculation of the nailfold.[6] It is frequently used in rheumatology practice to differentiate between primary and secondary RP and is also included in the ACR/EULAR classification criteria for systemic sclerosis (SSc) published in 2013.[7] It has been used for many years as an auxiliary method in the detection of rheumatic diseases that affect the microcirculation, such as Sjogren's syndrome (SJS), rheumatoid arthritis, systemic lupus erythematosus (SLE) and idiopathic inflammatory myositis, especially SSc among the CTDs.[8]

Structural microvascular abnormalities are one of the main features of SSc related to the pathophysiologic process. With NFC imaging, the column of red blood cells in the capillaries is visualised.[9] In imaging, capillaries consist of an arterial and a venous part and an apical ring that connects the two parts. The arterial part is narrower than the venous part, and the ratio of venous to arterial diameters is about 1.2-1.5/1.[4]

The NFC technique with ×200 magnification, which captures at least two contiguous areas of 1 mm in the nailfold in the middle of the finger, is the gold standard for performing capillaroscopy. The images can be evaluated qualitatively or semi-quantitatively with the NFC. Quantitative assessment includes capillary density (normal, >7/mm per capillary), morphology (normal, capillaries in the shape of a hairpin or once or twice cross-shaped or curved, provided they are convex), width of the apical part (normal, <20 micrometres (μm)) and the presence of haemorrhage areas (normal, absent). In the early phase of the scleroderma (SCL) pattern, the number of capillaries is adequate (>7/mm per capillary), the morphology is normal and there is little or no haemorrhage. The most striking feature of the early SCL pattern is giant capillaries (apical diameter >50 μm). The early SCL pattern is important for the early diagnosis of SSc. In the active phase of the SCL pattern, the number of capillaries is reduced (4-6 per mm) and their morphology is impaired. Areas of haemorrhage are more or absent, and giant capillaries (apical diameter >50 μm) are other detectable findings. In the late phase of the SCL pattern, the capillary density is greatly reduced (< 4 per mm), avascular areas are visible and the morphology is clearly deteriorated. Hemorrhagic areas and giant capillaries are not to be expected.[9]

In secondary RP due to CTDs such as SLE and SJS, which are not part of the scleroderma spectrum, findings in the form of normal patterns or non-specific abnormalities may occur when assessing NFC. Non-specific abnormalities are defined as isolated findings such as enlarged capillaries (apical diameter 20-50 μm), few areas of hemorrhage, partial reduction in the number of capillaries and partial deterioration of morphology. If numerous abnormalities or several different abnormalities occur in a patient, this may indicate an underlying CTD. The fact that non-specific abnormalities can also occur in primary RP can lead to difficulties in the differential diagnosis of primary RP and secondary RP.[9]

In our study, we aimed to evaluate the capillaroscopic findings of patients admitted to our rheumatology outpatient clinic with RP, whether these patients were diagnosed with inflammatory rheumatic disease (IRD) on the basis of clinical, laboratory and imaging procedures and whether the capillaroscopic findings had a significant differential effect with regard to the diagnosis of IRD.

Material and Method

Patients who presented with RP and underwent capillaroscopy at Bursa Uludag University Faculty of Medicine between September 2022 and April 2023 were included in our study. Capillaroscopic findings, clinical and demographic data, laboratory characteristics, autoantibodies (rheumatoid factor, anti-cyclic citrullinated peptide, anti-nuclear antibody (ANA), ANA profile), diagnosis of IRD, diagnosis of primary or secondary RP and presence of lung involvement were recorded. ANA values of 1/320 and below were classified as low positive titers, values above 1/320 titers as high positive titers (Ethics Committee approval date: December 4, 2024; protocol code: 2024-19-18).

A total of 78 patients underwent capillaroscopy during the six-month period; however, 19 of the patients were excluded from the study because clear images could

not be obtained during the capillaroscopic examination for reasons such as the use of nail polish, inappropriate ambient temperature and excessive nailfold skin thickness on the examined fingers. Of the 59 patients included in the study, the third, fourth and fifth toes of both hands were examined at 200x magnification. Cedar oil was used in the examination of all patients to make the capillaries more visible. The examination was carried out after a waiting period of 15-20 minutes in a room with a normal temperature of approx. 20-22°C. The previously acquired images were evaluated by a rheumatologist trained and certified in capillaroscopy, who was blinded to the diagnostic information provided by the patients. Number (per mm), size (apical width) and morphology of capillaries, presence or absence of avascular areas and hemorrhagic areas were determined and recorded as SCL or non-SCL pattern. Patients who were found to have an SCL pattern were categorized into early, active or late phase depending on the findings. Patients classified as non- SCL pattern were categorized as normal or non-specific abnormalities according to the findings of the NFC.

Those who presented with RP and were diagnosed with secondary RP and IRD and those who were diagnosed with primary RP and no IRD were compared as two separate groups with regard to clinical, demographic, laboratory and capillaroscopic findings.

Statistical Analysis

The compatibility of the continuous variables with the normal distribution was tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Normally distributed continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as n (%). When comparing two groups, the Independent Sample t-Test was used for continuous variables with normal distribution. The Chi-square test was used for the comparison of categorical variables. Univariate logistic regression analysis was performed to determine the factors that may be associated with the distinction between patients with IRD and those without IRD. Multivariate logistic regression analysis was performed for the significant variables after the univariate logistic regression analysis. The SPSS (IBM SPSS for Windows, Ver.28) package program was used for the statistical data calculations. $p<0.05$ was accepted as the statistical significance level.

Results

The mean age of the patients (n=59) was 51.17 years (±SD:14.72) and almost all were female (n=56, 94.9%).

It was found that 34 (57.6%) of the patients were diagnosed with IRD during follow-up, while 25 (42.4%) were not diagnosed with IRD and were recognised as primary RP. In the evaluation of the 34 patients diagnosed with IRD, the most common diagnoses were SSc (n=9, 26.5%) and SJS (n=9, 26.5%). Of the patients with a diagnosis other than CTDs (other IRDs), one was diagnosed with ankylosing spondylitis and the other with psoriatic arthritis. When antibodies were evaluated, ANA was the most commonly detected antibody (n=39, 66.1%), and the majority were positive at low titers (n=22, 37.3%). In the ANA profile panel, anti-SSA (n=11, 18.6%) was the most frequently detected antibody (Table I).

Table I. Clinical, Demographic and Laboratory Characteristics of Patients Presenting with Raynaud's Phenomenon

Age (years)	51.17 (±SD:14.72)
Gender, n(%)	
Female	56 (94.9)
Male	3 (5.1)
Diagnosis, n(%)	
No IRD	25 (42.4)
Yes IRD	34 (57.6)
IRD	34 (100)
SSc	9 (26.5)
SJS	9 (26.5)
RA	5 (14.7)
SLE	3 (8.8)
UCTD	5 (14.7)
MCTD	1 (2.9)
Other IRD	2 (5.9)
Lung involvement, n(%)	5 (8.5)
RF positivity, n(%)	7 (11.9)
Anti-CCP positivity, n(%)	5 (8.5)
ANA positivity, n(%)	39 (66.1)
ANA 1/100, n(%)	17 (28.8)
ANA 1/320, n(%)	5 (8.5)
ANA 1/1000, n(%)	12 (20.3)
ANA 1/3200, n(%)	3 (5.1)
ANA 1/10000, n(%)	2 (3.4)
ANA positivity with low titer, n(%)	22 (37.3)
ANA positivity with high titer, n(%)	17 (28.8)
Anti-SSA, n(%)	11 (18.6)
Anti-SSB, n(%)	5 (8.5)
Anti-SCL, n(%)	7 (11.9)
Anti-Centromere, n(%)	10 (16.9)
RNP, n(%)	3 (5.1)
PM-SCL, n(%)	2 (3.4)

ANA, anti-nuclear antibody; ***Anti-CCP,*** anti cyclic citrullinated peptide; ***IRD,*** inflammatory rheumatic disease; ***MCTD,*** mixed connective tissue disease; ***PM-SCL***, Poliomyositis/scleroderma antibody; ***RA,*** *rheumatoid arthritis*; ***RF,*** rheumatoid factor; ***RNP,*** U1-ribonucleoproteins; ***SJS,*** systemic sjogren's syndrome; ***SLE,*** systemic lupus erythematosus; ***SSc,*** systemic sclerosis; ***UCTD,*** undifferentiated connective tissue disease.

When comparing patients with and without IRD, it was found that the patients in the group without IRD were younger (p=0.002). Although ANA positivity was found in almost all patients (n=31, 91.18%) in the IRD group ($p<0.001$), there was no significant difference between the groups in terms of low titer

ANA positivity (p>0.05). High titer ANA positivity was detected in approximately half of the patients in the IRD group (n=16, 47.06%) (p<0.001). When assessing capillary density, capillary density was ≥7 per 1 millimeter (mm) in all patients in the non-IRD group. In 13 patients in the IRD group, capillary density decreased (<7). When assessing the size of the capillaries, there was no significant difference between the two groups with regard to normal capillaries (<20 µm) and enlarged capillaries (20-50 µm) (p>0.05), while a significant difference was found with regard to giant capillaries (>50 µm) (p=0.005). There was no significant difference between the groups in terms of abnormal morphology and hemorrhage (p>0.05). The SCL pattern was detected in 14 patients in the IRD group. In the non-IRD group, all patients had a non-SCL pattern, with the exception of two patients with an SCL pattern. In the IRD group, 20 (58.82%) patients had a non-SCL pattern, of which seven were normal and 13 had non-specific abnormalities. In SSc, one of the most common IRDs, the SCL pattern was found in eight patients (88.88%), while it was found in three (33.33%) of the SJS patients (Table II).

Table II. Comparison of Demographic, Laboratory and Capillaroscopic Characteristics of Patients with and without IRD Presenting with Raynaud's Phenomenon

	No IRD n (%) 25 (42.4)	IRD n (%) 34 (57.6)	p
Age (years)	44.36 (±SD: 13.98)	56.18 (±SD: 13.33)	***0.002*** *t*
Gender			
Female	24 (96.00)	32 (94.11)	>0.05 χ^2
Male	1 (4.00)	2 (5.89)	
Lung involvement	0 (0.00)	5 (14.71)	***0.045*** χ^2
RF positivity, n(%)	0 (0,00)	7 (20.59)	***0.016*** χ^2
Anti-CCP positivity, n(%)	0 (0.00)	5 (14.70)	***0.045*** χ^2
ANA positivity, n(%)	8 (32.00)	31 (91.18)	***<0.001*** χ^2
ANA positivity with low titer, n(%)	7 (28.00)	15 (44.12)	0.206 χ^2
ANA positivity with high titer, n(%)	1 (4.00)	16 (47.06)	***<0.001*** χ^2
Capillary density (/mm)			
≥7	25 (100.00)	21 (61.76)	***<0.001*** χ^2
4-6	0 (0.00)	12 (35.29)	***<0.001*** χ^2
≤3	0 (0.00)	1 (2.95)	>0.05 χ^2
Dimension (µm)			
<20	11 (44.00)	10 (29.41)	0.247 χ^2
20-50	12 (48.00)	10 (29.41)	0.145 χ^2
>50	2 (8.00)	14 (41.18)	***0.005*** χ^2
Abnormal morphology	11 (44.00)	22 (64.70)	0.113 χ^2
Haemorrhage	7 (28.00)	16 (47.06)	0.138 χ^2
Non-SCL pattern	23 (92.00)	20 (58.82)	***0.014*** χ^2
Normal	5 (20.00)	7 (20.59)	0.956 χ^2
Non-specific abnormality	18 (72.00)	13 (38.24)	***0.010*** χ^2
SCL pattern	2 (8.00)	14 (41.18)	***0.005*** χ^2
Early	2 (8.00)	0 (0.00)	0.175 χ^2
Active	0 (0.00)	12 (35.29)	***<0.001*** χ^2
Late	0 (0.00)	2 (5.88)	>0.05 χ^2

ANA, anti-nuclear antibody; ***CCP,*** anti-cyclic citrullinated peptide; ***IRD,*** inflammatory rheumatic disease; ***RF,*** rheumatoid factor; ***SCL,*** scleroderma ***t,*** Independent Samples t Test; ***χ2,*** chi-square test; ***p <0.05***:statistical significance level.

The univariate logistic regression analysis performed to evaluate the factors that might be effective in discriminating between patients with and without IRD showed a positive significant differential effect (p<0.05) for age, ANA positivity, ANA high titer positivity, giant capillary and SCL pattern. On the other hand, the non-SCL pattern had a negative significant differential effect. In the multivariate analysis, only ANA positivity had a positive significant differential effect (p<0.05) (Table III).

Table III. Factors Associated with the Differentiation of Patients with IRD from Patients without IRD

	Univariate Logistic Regression			Multivariate Logistic Regression		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age	1.065	1.020-1.112	**0.004**			
ANA positivity	21.958	5.136-93.871	**<0.001**	21.958	5.136-93.871	**<0.001**
ANA positivity with high titer	21.333	2.585-176.084	**0.004**			
Capillary dimension >50 µm	8.050	1.628-39.800	**0.011**			
Non-SCL pattern	0.195	0.049-0.779	**0.021**			
SCL-pattern	8.050	1.628-39.800	**0.011**			

ANA, anti-nuclear antibody; ***CI,*** *confidence interval*; ***OR,*** Odds ratio*;* ***p <0.05,*** statistical significance level.

Discussion and Conclusion

When evaluating the capillaroscopic findings of patients with RP in our study, SSc and SJS were the most common IRD diagnoses, and SS-A and ANA high titer positivity were important for the diagnosis of IRD. Although the non-SCL pattern is an expected finding, especially in patients with a primary RP diagnosis, it can also be found in patients with IRD (58.82% of our patients with IRD). ANA positivity is an important marker for differentiating between patients with an IRD diagnosis and those without an IRD diagnosis.

Only three of our patients were male, the majority were female. In addition, the patients in the primary RP group without an IRD diagnosis were younger than the patients in the secondary RP group with an IRD diagnosis, and our results are consistent with the literature.[2,4,10]

RP is common in SSc and its prevalence can reach 95%. Therefore, the detection of microvasculopathy by NFC is important for the early diagnosis of CTDs, especially SSc, in patients with RP and is included in the SSc classification criteria.[7,10] When assessing our patients with regard to the diagnosis of CTD, SSc (26.5%) and SJS (26.5%) were the most common diagnoses. The preponderance of patients with SSc is to be expected as the prevalence of RP in patients with

SSc is high. On the other hand, the rate of SJS patients was similar to that of SSc. In the separate evaluation of the capillaroscopic findings of patients with SJS, an SCL pattern was found in 33.3% of these patients. In the study conducted by Corominas et al.[11] the SCL pattern was found in 10.2% of patients with primary SJS. In another study by Capobianco et al.[12] this rate was 11.5%. In the study conducted by Bernardino et al.[10] it was determined that patients who were previously evaluated with NFC were most frequently followed up with the diagnoses of SSc, mixed connective tissue disease (MCTD) and SLE. The small number of patients could be one of the main factors for the difference of our results from those in the literature.

ANA positivity is an important diagnostic marker in CTDs. One study reported that ANA positive patients had significantly longer RP times compared to ANA negative SSc patients. In this study, 90% of SSc patients were also classified as ANA-positive.[13] Another study reported that ANA and SS-A positivity are risk factors for differentiation to a CTD such as SJS and SSc in patients investigated with RP and followed up as undifferentiated connective tissue disease (UCTD)[14]. In our study, ANA positivity, especially ANA high-titer positivity, was found more frequently in the IRD group.

In our study, there was no significant difference between the secondary RP group with IRD and the primary RP group without IRD in terms of haemorrhage, the presence of abnormal morphology and enlarged capillaries. Again, although there was a significant difference between the groups in terms of non-SCL pattern, most patients in the secondary RP group with IRD had a non-SCL pattern, and the majority of these patients had non-specific abnormalities. The SCL pattern, decrease in the number of capillaries and giant capillaries were conspicuous in the patients in the secondary RP group diagnosed with IRD.

The NFC assessment has a high sensitivity and specificity in SSc patients. In addition, similar microvasculopathic changes may occur in other CTDs, and assessment of NFC may become important for early diagnosis.[15] RP is a common finding in patients with SSc, and as there may be a correlation between NFC findings and systemic involvement, monitoring of NFC findings may become important. [10]

In a study conducted in patients with SJS, nonspecific abnormalities were found in 27.2% of patients, while the SCL pattern was found in 10.2%. In other cases, normal capillaroscopic findings were reported.[11] The study by Thomson et al.[16] reported that during follow-up of 86 patients with abnormal capillaroscopic findings, SSc was found in 79 patients, dermatomyositis (DM) in four patients, and antisynthetase syndrome in three patients. Of 71 patients with normal NFC findings at baseline, only four developed SSc during follow-up. For the diagnosis of SSc, the NFC showed a sensitivity of 95% and a specificity of 91%. In our study, SCL pattern and giant capillaries were conspicuous in patients in the secondary RP group who were diagnosed with IRD.

In a study involving 3029 patients with primary RP, the association between NFC findings and the presence of CTD was investigated. Patients were followed up at 6-month intervals for an average of 4.8 years, and NFC findings in the 6 months prior to diagnosis were evaluated. At the end of follow-up, 1123 (37.1%) patients were diagnosed with CTD. The study found that SCL pattern was significantly associated with the development of SSc, DM, SSc overlap and MCTD.[17] In our study, an SCL pattern was present in two of the patients accepted as primary RP. As we had no follow-up data on these patients, it was not possible to determine whether they developed CTD in the future.

In the study by Shenavandeh et al.[14] it was reported that UCTD patients who were ANA positive patients with SCL pattern, enlarged capillaries, giant capillaries and more than five hemorrhage areas on capillaroscopy differentiated into CTD during follow-up. Another study by Szabo et al.[18] found mild avascularity and, in a few cases, enlarged capillaries in patients with primary RP. Another study by Ziegler et al.[3] also reported specific differences in microvascular structure between patients with primary RP and healthy controls. In summary, it was concluded that primary RP may not be entirely benign and may be associated with microcirculatory vasculopathy. In patients with non-rheumatic diseases such as diabetes mellitus, glaucoma, essential hypertension and anorexia nervosa or chronic smokers, findings such as reduced capillary density, haemorrhages, enlarged capillaries and avascular areas may be observed, even if there is no underlying CTD. It has also been reported that COVID-19 infection can cause non-specific changes and hemorrhages.[15] In our study, although no avascular area was found in the capillaroscopic examinations of patients who were not diagnosed with IRD and accepted as primary RP, the rates of hemorrhage and dilated capillaries were similar to those in the secondary RP group, and there was no significant difference between the groups. Since our study was not a prospective study, we could not make a comparison regarding capillaroscopic findings and diagnosis at follow-up of patients in this primary RP group.

The main limitations of our study are the small number of patients and the lack of follow-up data due to the cross-sectional design. We included patients from the first period after the start of recording NFC findings. In later evaluations, however, there were also

patients whose diagnosis was not yet clear. We have therefore chosen this time period to include patients with definitive diagnoses. However, in our study, the findings referred to as nonspecific abnormalities were by no means rare in patients in the primary RP group. In addition, two patients had giant capillaries. Other important limitations were the lack of a healthy control group and the fact that comorbidities such as diabetes mellitus, which can cause capillaroscopic changes, were not recorded.

NFC assessment, in combination with other clinical and laboratory findings, is an important, non-invasive and easily reproducible method for the diagnosis of IRD, especially SSc. A considerable degree of non-specific abnormalities can be detected in patients with primary RP, and it is important to monitor these patients with NFC for future IRD diagnosis. Advanced age, SCL pattern, giant capillaries and ANA positivity should be warning signs of secondary RP.

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REVIEW

Multiple Sclerosis and Cholesterol Metabolism

Furkan SARIDAŞ[1], Filiz MERCAN SARIDAŞ[2], Canan ERSOY[2], Ömer Faruk TURAN[1]

[1] Bursa Uludağ University Faculty of Medicine, Department of Neurology, Bursa, Türkiye.
[2] Bursa Uludağ University Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology and Metabolism, Bursa, Türkiye.

ABSTRACT

Adult lipid metabolism consists of plasma lipids. Triglycerides are the most important sources of energy reserves, while phospholipids and cholesterol are key components of organelles and cell membranes. Lipids, especially cholesterol, are involved in many cellular functions. Various neurodegenerative cellular processes can develop in metabolism disorders. Neurons have significantly different lipid composition compared to other biological membranes. These differences and the role of these lipids in neuronal pathologies are still poorly understood. Studies on lipid molecules in MS date back four decades. Studies on apolipoprotein alterations, plasma lipoproteins and oxysterols have attracted attention. It is thought that impaired cholesterol metabolism may play a role in both the inflammatory and neurodegenerative pathogenesis of the disease and its correction may favorably affect the progression steps in the clinical course of MS, which is still the most limited point for treatment. In this review, the immunopathogenesis and clinical manifestations of Multiple Sclerosis and alterations in cholesterol metabolism are presented.

Keywords: Lipid Metabolism. Multiple Sclerosis. Immunpathogenesis. Neurodegeneration.

Multipl Skleroz ve Kolesterol Metabolizması

ÖZET

Yetişkin lipid metabolizması plazma lipidlerinden oluşur. Trigliseridler enerji rezervlerinin en önemli kaynağı iken fosfolipidler ve kolesterol organellerin ve hücre zarlarının bileşenleridir. Lipidler, özellikle de kolesterol, birçok hücresel fonksiyonda rol oynar. Metabolizma bozukluklarında çeşitli nörodejeneratif hücresel süreçler gelişebilir. Nöronlar, diğer biyolojik membranlara kıyasla önemli ölçüde farklı lipid bileşimine sahiptir. Bu farklılıklar ve bu lipidlerin nöronal patolojilerdeki rolü hala tam olarak anlaşılamamıştır. Multipl Skleroz'da lipid molekülleri üzerine yapılan çalışmalar kırk yıl öncesine dayanmaktadır. Apolipoprotein değişiklikleri, plazma lipoproteinleri ve oksisteroller üzerine yapılan çalışmalar dikkat çekmiştir. Bozulmuş kolesterol metabolizmasının hastalığın hem inflamatuar hem de nörodejeneratif patogenezinde rol oynayabileceği ve düzeltilmesinin tedavi için hala en kısıtlı nokta olan Multipl Skleroz'un klinik seyrindeki ilerleme basamaklarını olumlu yönde etkileyebileceği düşünülmektedir. Bu derlemede, Multipl Skleroz'un immünopatogenezi ve klinik belirtileri ile kolesterol metabolizmasındaki değişiklikler sunulmuştur.

Anahtar Kelimeler: Lipit Metabolizması. Multipl Skleroz. İmmunpatogenez. Nörodejenerasyon.

Lipid Metabolism

Adult lipid metabolism consists of plasma lipids called neutral lipids (triglycerides, phospholipids, and cholesterol). While triglycerides are the primary source of energy reserves, phospholipids and cholesterol are organelle and cell membrane components. Dietary plasma lipids with low water solubility are transported in lipoproteins. Apolipoproteins with enzyme cofactors and receptor-ligand functions ensure that lipid molecules are transported to the correct sites. The composition of dietary calorie intake varies between societies. In Asian societies, 10-15% of dietary calories are from fat, compared to up to 50% in Western societies. The majority of dietary fat intake is from triglycerides. The source of triglycerides may differ between societies; in Western diets, butter with a relatively high oleate content is the source of triglycerides, whereas in the Mediterranean diet, olive oil rich in palmitate is the source. Regardless of the source, excess calories from the diet are converted to triglycerides and stored in adipose tissue. Adipose tissue has functions other than

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Dr. Furkan SARIDAŞ
Bursa Uludağ University Faculty of Medicine,
Department of Neurology, Bursa, Türkiye.
Phone:+90 545 774 16 16
E-mail: furkansaridas@uludag.edu.tr

Authors' ORCID Information:
Furkan SARIDAŞ: 0000-0001-5945-2317
Filiz MERCAN SARIDAŞ: 0000-0002-3135-9388
Canan ERSOY: 0000-0003-4510-6282
Ömer Faruk TURAN: 0000-0002-6752-1519

energy storage. The imbalance in fatty acid flux caused by the release of chemokines and cytokines leads to the formation of adipocytes and the accumulation of macrophages, which play an additional role in inflammatory processes. Energy restriction can effectively control inflammation by reducing inflammatory factors and decreasing lipolysis and energy expenditure.[1]

Lipid Metabolism of the Nervous System

Human cells contain thousands of lipids, such as glycerolipids, glycerophospholipids, sterol lipids, sphingolipids, and free fatty acids[2,3] The function of most lipids depends on their molecular structure. The differences in lipid composition in neurons and the role of these lipids in neuronal pathologies are still poorly understood. To understand this, lipid diversity should be considered specific to myelin and neurons and recognized as units with anatomical and functional properties. Lipids make up just over a third of the dry weight of the neuronal soma. Phospholipids, cholesterol, and galactolipids are the most abundant.

In contrast to the soma, about one-seventh of the neurites are lipids. They contain a similar proportion of phospholipids and a higher proportion of cholesterol and galactolipids. In addition, the sphingomyelin content is higher in neurites[4] Contrary to the well-known assumption that axonal membrane lipids are synthesized in the soma and then transported anterograde to the axons, recent studies have shown that axons can independently carry out some aspects of lipid metabolism.[5]

Axons are surrounded by a lipid-rich myelin sheath. The primary function of myelin is to insulate the axon and cluster sodium channels in Ranvier junctions, effectively ensuring the conduction of action potentials.[6] Myelin is produced by Schwann cells in the peripheral nervous system (PNS) and oligodendrocytes in the central nervous system (CNS). Its lipid composition is well known. It is significantly different in neurons compared to other biological membranes. During active myelination, glial cells rapidly produce excessive amounts of lipids for utilization. The most abundant lipids in myelin are cholesterol and galactosylceramide.[7] Cholesterol regulates the fluidity and permeability of the membrane. It gives stability to myelin. It is necessary for the growth and compression of myelin. Among the different lipid classes, sphingolipids are primarily associated with peripheral neurological disorders. 1-deoxy-SL, which is formed in an alternative reaction during de novo synthesis, has a unique role. Pathology in the formation of 1-deoxy-SL may play a role in disorders such as hereditary sensory and autonomic neuropathy type 1 (HSAN1) and diabetic or chemotherapy-induced neuropathies.

Lipid Metabolism of the Central Nervous System

More than one hundred billion cells in the CNS are rich in lipids and are closely associated with fatty tissue. Approximately 50-60% of their weight is made up of lipids. The highest lipid content of all biological membranes is found in the myelin sheath structure. Lipids play an active role in many cellular processes in the CNS, such as synaptogenesis, neurogenesis, signaling, and energy reserves. Disturbances in the steps of lipid metabolism are involved in the pathogenesis of neurodegenerative diseases by causing changes in the lipid composition of intracellular membrane compartments. In Alzheimer's disease, for example, most of the cholesterol in the neuron is catalyzed by the enzyme cytochrome P46A1 (CYP46A1) to 24-hydroxycholesterol (24-OHC), a cholesterol breakdown product called oxysterol. 24-OHC then crosses the blood-brain barrier (BBB) and enters the plasma, while plasma 27-hydroxycholesterol (27-OHC) travels to the brain. 27-OHC promotes the formation of amyloid beta (Aβ), whereas 24-OHC inhibits the production of Aβ protein.[8] Aβ forms a complex with apolipoprotein E Christchurch (ApoE-CH) particles, which are eliminated by endocytosis, secreted into the peripheral system, or degraded by proteases, leading to amyloid deposition. [9, 10] The implications of this theoretical knowledge can also be seen in the results of trials. It has been reported that the disease is associated with increased low-density lipoprotein (LDL) cholesterol and decreased high-density lipoprotein (HDL) cholesterol levels, independently of ApoE; the risk of developing the disease increases up to twofold in people with total cholesterol (TC) levels above 250 mg/dL, and this association is associated with lipid disorders, especially in middle age (40-60).[11-15]

Lipid Metabolism and Neurodegeneration

The relationship between neurodegeneration and lipid metabolism in Parkinson's disease, the second most common neurodegenerative disease, is not clear. Study results are conflicting, and prospective studies with larger numbers of cases are needed.[16,17] However, the demonstration of a decrease in α-synuclein in Lewy bodies after statin treatment suggests that plasma cholesterol may promote α-synuclein aggregation.[18] In addition, in experimental Parkinson's model studies, it was found that a high-fat diet was associated with increased dopamine depletion in the striatum and substantia nigra and oxidative stress in the subthalamic nucleus in rats.[19,20]

Cholesterol Metabolism and Central Nervous System

Cholesterol in the CNS accounts for a quarter of the total cholesterol in the body and is ten times higher than in the periphery. 70% is found in myelin structures and 30% in cell or organelle membranes (glia 20%, neurons 10%).[21] Clearance of cholesterol metabolism in the CNS is 250-300 times slower.[22] In addition, cholesterol is transported in plasma by several lipoprotein particles because it cannot cross the BBB.[23,24] This suggests that compensation for cholesterol metabolism is more limited in the CNS. Cholesterol synthesis in the CNS is identical to the lanosterol step and is produced de novo. Lanosterol is used for cholesterol synthesis in neurons via the Kandutch-Russel pathway and in astrocytes via the Bloch pathway. The cholesterol produced is highly channeled through ApoE for utilization in cells. Cholesterol, used in glia or neurons, is converted by a cytochromal enzyme, CYP46A1, to 24-OHC, one of the oxysterols oxidized cholesterol forms that can cross the BBB. Increased 24-OHC leads to liver X receptor (LXR) activation, initiating efflux mechanisms from neurons. Thus, toxic accumulation in the cell is prevented. While 1% of 24-OHC circulates in the cerebrospinal fluid, 99% crosses the BBB and enters the peripheral blood circulation. In the liver, it is converted to 27-OHC (the final breakdown product of cholesterol in the whole organism) by a second cytochrome enzyme and excreted in bile acids and feces. However, the formation of 24-OHC as a degradation product far exceeding this clearance rate (e.g., acute demyelinating attack) or the increase in oxysterol resulting from oxidation of LDL with proinflammatory properties after its passage from the circulation to the CNS with impairment of the ENT leads to the accumulation of 24-OHC in neurons. In addition, defects in the synthesis of LXR [e.g., nuclear receptor subfamily 1 group G member 3 (NR1H3) gene mutation], which is involved in maintaining cerebral lipid homeostasis, also accelerate this process.

Consequently, this increased accumulation initiates the process, leading to lipid peroxidation, oligodendrocyte cell death, and neurodegeneration.[25-29] A pre-existing disorder of the lipid profile may facilitate these mechanisms. For example, high LDL levels increase the amount of oxidized LDL in the CNS when the BBB is disrupted, and immune-active cells are more likely to invade the CNS. On the other hand, low HDL and high TC levels accelerate this process by increasing BBB permeability. Studies conducted in this context show a correlation between increased HDL and reduced grey matter volume loss and the number of contrast-enhancing lesions, better BBB integrity, and a reduced risk of developing secondary progressive multiple sclerosis (SPMS). It was found that there was an increase in the number of new or enlarging T2 hyperintense or contrast-enhancing lesions on the Expanded Disability Status Scale (EDSS) with increasing LDL but no change in the frequency of relapse. Therefore, it is suggested that relapse may be associated with disability progression independent of relapse.[14,25,30-39]

Multiple Sclerosis and Lipids

Cholesterol Metabolism and Multiple Sclerosis

Studies of lipid molecules date back forty years. In the early days, studies of apolipoprotein changes in patients with MS were at the forefront. In contrast, studies of plasma lipoproteins and oxysterols have attracted attention in the last two decades. Although the results of many studies on this subject differ, it has been shown that LDL and HDL cholesterol are decreased, and very low-density lipoprotein (VLDL) cholesterol and insulin resistance are increased in MS. Regarding secondary endpoints, the development of new hyperintense or contrasting T2 lesions and cortical atrophy were shown to correlate with decreased HDL or ApoA1 and increased TC/HDL ratio, LDL, 24-OHC, 27-OHC, and ApoB.[31,40,41] In addition, a recent study has shown that dyslipidaemia has a mild negative effect on cognitive performance in people with MS, independent of brain atrophy. [42] It was highlighted that HDL, a mediator of the anti-inflammatory response, has an inhibitory effect on leukocyte migration, has antioxidant properties, and contributes to the improvement of BBB function in MS.[43]

Effects of Anti-Lipids on Multiple Sclerosis

Studies investigating the effect of anti-lipid therapies on MS have been conducted with statin therapies. Initial studies suggested that statins may have a beneficial effect on neurodegenerative processes due to their regulatory effects on cell proliferation, differentiation, migration, and cerebrovascular hemodynamics. With increasing knowledge of the immune pathogenesis of MS, statins have been shown to inhibit major histocompatibility complex (MHC) class II antigen presentation, downregulate T cell activation and proliferation, and induce a switch from a proinflammatory T helper (Th) 1 to a Th2 phenotype in vitro. It was also found to block adhesion molecule expression and inhibit leukocyte migration across the BBB. It was thought to be effective against neurodegeneration and inflammatory processes in MS.[44-50]. Randomized controlled trials of statin therapy date back fifteen years. In patients with clinically isolated syndrome, atorvastatin treatment

did not change the time to definite MS diagnosis or EDSS. However, it had a beneficial effect on radiological activation.[51] Immediately following this study, another multicenter, placebo-controlled, double-blind, randomized, parallel-group, interferon beta-1a (IFNβ-1a, IM) add-on treatment with simvastatin was planned. The patients selected were inflammation-naive (≥ 1 relapse in the previous year). However, the number of relapses, annual relapse rate, relapse-free rate, EDSS scores, radiological activation, no evidence of disease activity (NEDA-3), and no beneficial results on atrophy were not found. In addition, there were no significant results when the in vitro effects of statins were evaluated with serum levels of interleukin 10 (IL10), tumor necrosis factor superfamily member 10 (TNFSF10), MX1, and interferon regulatory factor 7 (IRF7). Simvastatin treatment was found to be ineffective in relapsing-remitting multiple sclerosis (RRMS), with class 1 evidence. However, the inadequate power of this trial (65% instead of 80%) due to the failure to reach the predicted number of relapses, the ineffective results in contrast to in vitro studies on immune markers, and the failure to consider drug tolerance mechanisms have led to criticism.[52] Another small study conducted at a similar time to this trial reported that the use of 80 mg of simvastatin for six months in patients with acute optic neuritis was well tolerated and may have had a beneficial effect on both wave latency and amplitude in visually evoked potential measurements.[53] To evaluate the immunomodulatory and neuroprotective properties of statins, the double-blind, randomized, controlled MS-STAT trial comparing 80 mg of simvastatin with placebo in patients with SPMS with higher disability scores reported a significant 43% reduction in the adjusted mean annual rate of atrophy. This study highlighted that statins may have a neuroprotective effect, and the MS-STAT2 phase 3 trial was initiated (ongoing).[54,55]

Effects of diet on multiple sclerosis

The diet of people with multiple sclerosis (MS) is an important factor that can influence the course of the disease. In particular, foods rich in omega-3 fatty acids, such as fish and flaxseed, can reduce inflammation. In addition, avoiding processed foods, trans fats, and excess sugar can help balance the immune system by maintaining gut health. Drinking enough water and eating a diet rich in fiber can help regulate bowel function and prevent constipation, which is common in people with MS.

There are studies on the amount and variety of dietary fat intake and the development or progression of multiple sclerosis. There is currently no scientifically proven definitive diet for people with MS. However, the Mediterranean diet for MS has been reported to have a preventive effect on the development of the disease. The McDougall diet, a very low-fat, plant-based diet, has been reported to reduce fatigue in people with MS, and the Paleolithic diet, which avoids processed animal foods, wheat products, legumes, refined oils and refined sugars, also has a positive effect on fatigue and improves motor and cognitive function. Calorie restriction and intermittent fasting have been reported to suppress inflammation in experimental models, and a ketogenic diet leads to possible improvements in quality of life and depression. The Swank diet, a diet restricted in saturated fat, has been shown to have a beneficial effect on relapse and progression.[56]

Conclusion

Lipid metabolism is essential for neural function, support structure, signaling, and energy balance. The different lipid composition of the components of the central nervous system results from their different cellular needs. These differences are maintained in a balance that we call lipid homeostasis. Disturbances in homeostasis contribute to neurodegenerative diseases through the formation of cholesterol degradation products, particularly 24- and 27-hydroxycholesterol, lipid peroxidation, oxidative stress, and inflammation.

In multiple sclerosis, abnormalities in lipid metabolism are associated with disease progression and disability. Dysregulation of cholesterol transport and lipid oxidation contributes to blood-brain barrier permeability, neuroinflammation, and neuronal degeneration. The correlation between high LDL cholesterol, low HDL cholesterol, and increased lesion burden highlights the potential of lipid modulation as a therapeutic strategy in the management of MS. Statin therapy, initially investigated for its immunomodulatory and neuroprotective effects, has produced mixed results. While early studies suggested potential benefits in reducing neuroinflammation and brain atrophy, subsequent randomized controlled trials have shown limited efficacy in altering disease progression in relapsing-remitting MS.

Dietary interventions have emerged as a promising avenue for influencing lipid metabolism and modulating disease activity in MS. Although there is no definitive MS-specific diet, research suggests that the Mediterranean diet, which is rich in healthy fats and antioxidants, may have a preventive effect on disease progression.

Given the complex relationship between lipid metabolism, neurodegeneration, and MS pathology, future research should focus on personalized dietary and pharmacological interventions to optimize lipid homeostasis. Understanding how lipid modifications influence neuroinflammation, myelin integrity, and

BBB function may open new therapeutic avenues for neurodegenerative and demyelinating diseases.

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REVIEW

Phacomatosis

Selin BAYKAN, Mevlüt Özgür TAŞKAPILIOĞLU

İstanbul Yeniyüzyıl University, Özel Medicabil Hospital Department of Neurosurgery, İstanbul, Türkiye.

ABSTRACT

Neurocutaneous syndromes are a group of genetically transmitted diseases with skin lesions, of which more than 60 types have been defined and are of ectodermal origin. Except for ataxia-telangiectasia, all are autosomal dominant. These syndromes are significant in neuro-oncology because they create a predisposition to cancer and cause the formation of a wide range of tumors, from hamartomas to malignant tumors. There is no curative treatment in these syndromes; their treatments are symptomatic and surgical treatment is preferred only due to severe neurological deficits and increased mass effect. This article aims to re-summarize the clinical features of common neurocutaneous syndromes in light of current developments.

Keywords: Phakomatosis. Neurofibromatosis. Optic glioma. Von hippel-lindau. Tuberosklerosis.

Fakomatozlar

ÖZET

Nörokütanöz sendromlar ektodermal kökenli 60'ın üzerinde tipi tanımlanmış olan cilt bulguları ile bulunan genetik geçişli bir grup hastalıktır. Ataksi-telenjiektazi hariç hepsi otozomal dominant geçişlidir. Bu sendromlar kanser yatkınlığı oluşturdukları ve hamartomlardan malign tümörlere uzanan geniş bir yelpazede tümörlerin oluşumuna neden oldukları için nöroonkolojide son derece önemlidirler. Bu sendromlarda küratif tedavi bulunmamaktadır, tedavileri semptomatiktir ve cerrahi tedavi ancak ciddi nörolojik defisit ve artmış kitle etkisi sebebi ile tercih edilmektedir. Bu yazının amacı sık görülen nörokütanöz sendromların klinik özelliklerini güncel gelişmeler ışığında yeniden özetlemektir.

Anahtar Kelimeler: Fakomatozlar. Nörofibromatozis. Optik gliom. Von hippel-lindau. Tuberoskleroz.

First introduced by an ophthalmologist named Van Der Hoeve in the early 20th century, phakomatoses were initially divided into three categories: Neurofibromatosis, Tuberous Sclerosis Complex, and Von Hippel-Lindau Disease. The term "phakomatoses," derived from the Greek word meaning "birthmark," refers to hereditary conditions that predominantly follow an autosomal dominant genetic inheritance pattern, with some exceptions[1]. These disorders affect ectodermal tissues such as the skin, eyes, and nervous system. To date, 67 types of phakomatoses have been identified[2]. Phakomatoses are considered highly significant in neuro-oncology due to their predisposition to cancer and tumor formation. In the latest classification by Ruggieri and his team in 2020, phakomatoses were grouped into six main categories: Neurofibromatosis types 1 and 2 (NF), Tuberous Sclerosis (TS), Sturge-Weber Disease (SW), Von Hippel-Lindau Disease (vHL), and Ataxia-Telangiectasia (AT)[2].

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Dr. Mevlüt Özgür TAŞKAPILIOĞLU
Özel Medicabil Hastanesi Beyin ve Sinir Cerrahisi Bölümü,
Mudanya Yolu Fethiye Mh. Küre Sk.No: 1 Nilüfer / Bursa
Phone: 532 447 75 39
E-mail: mozgurt@gmail.com

Authors' ORCID Information:
Selin BAYKAN: 0009-0008-9280-5629
Mevlüt Özgür TAŞKAPILIOĞLU: 0000-0001-5472-9065

Material and Method

We conducted a review of published literature in Turkidh Turkish and English. Ovid Medline, Ovid Embase, CINAHL, and Web of Science were searched for the terms "Neurofibromatosis 1", "Neurofibromatosis 2", "Von Recklinghausen", "Tuberous Sclerosis", "Sturge-Weber Disease", "Von Hippel-Lindau Disease", "Ataxia-Telangiectasia". We included articles that were peer-reviewed in primary studies, reviews, or meta-analyses. We excluded studies with only participants without phacomatosis, case reports, and case studies.

Neurofibromatosis

The term neurofibromatosis first entered the medical literature in 1882, when Friedrich von Recklinghausen coined it from "neurofibroma"[3].

Neurofibromatoses were initially considered a single disorder. Initially considered a single disorder, neurofibromatoses now have eight recognized types in the literature, with NF Type 1 and NF Type 2 being the most common. The term "neurofibromatosis" comes from the Latin for "nerve fibroma." These conditions lead to the formation of tumors along the nerve pathways, including in the brain, spinal cord, and peripheral nerves. Additionally, neurofibromatoses account for about 0.6% of pediatric cancers, specifically related to NF1. They are observed in about 1 in 3,000 people, regardless of gender or race[4].

Neurofibromatoses manifest in two forms: mosaic and segmental[4]. If the mutation occurs after fertilization, the pathogenic variant is present in some cells, meaning the signs of NF are not confined to specific areas; this is known as mosaic neurofibromatosis[3]. In segmental neurofibromatosis, however, the characteristics of NF are usually limited to a specific region.

Neurofibromatosis Type 1

Neurofibromatosis Type 1 (NF1), the most common syndrome accounting for 90% of all neurofibromatoses, is a neurocutaneous syndrome caused by a single gene. The NF1 gene is located on chromosome 17 and contains over 60 exons and more than 300 kilobases of DNA[5]. The prevalence of NF1 in the population is approximately 1-5 per 10,000, with an occurrence rate of about 1 in 3,000-4,000 births[6]. Tumors develop due to a variant in the NF1 gene, which encodes the protein neurofibromin that prevents tumor formation. This condition is observed in approximately half of the patients due to familial inheritance, while the other half arise from sporadic gene variants. In a small but significant portion of patients (about 5%), a microdeletion of the entire NF1 gene, which leads to more severe internal and external manifestations, is observed[7]. Café-au-lait macules (Figure 1), Lisch nodules, gliomas, neurofibromas, and bone dysplasias are some characteristic findings that occur due to NF1[8]. Given the 100% penetrance of the NF1 gene, it is impossible for individuals with the mutation not to display any clinical symptoms.

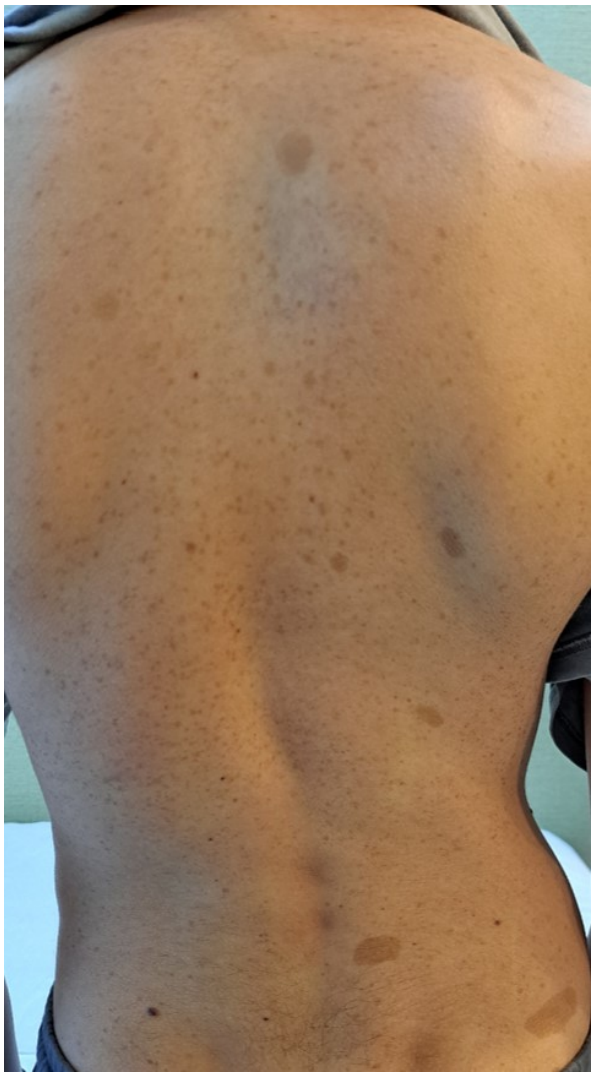

Figure 1.

Multiple café au lait spots are present at birth and increase in number and size over the years. These spots have no malignant potential. They darken in the sun and fade with age. Freckles are usually observed bilaterally (90%) in areas not exposed to the sun, such as the groin and armpits[9].

Neurofibromas can be observed in the peripheral nervous system. These can be cutaneous (85%) in the form of soft nodules on the skin or larger pedunculated and sagging subcutaneous (20%) (Figüre 2). Neurofibromas do not have malignant potential. They affect patients cosmetically. Pinti et al. reported that the probability of developing MPSKT is higher in those with at least two subcutaneous NF[10].

Plexiform NFs are more complex NFs that originate from more than one nerve fascicle or nerve plexus, involve the main nerves, extend along the main nerves, can be internal or external, and can reach giant sizes in large bundles (Figure 3).

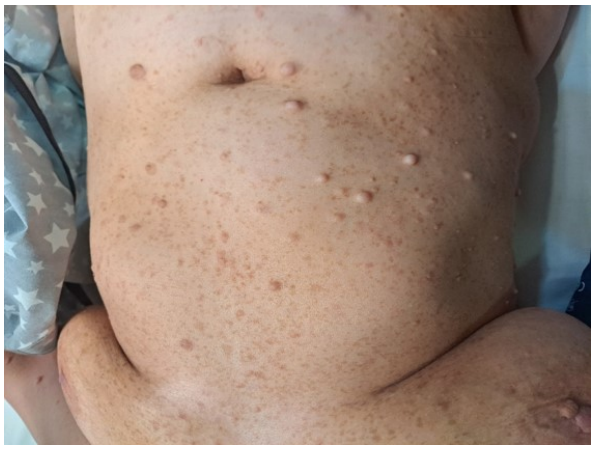

Figure 2.

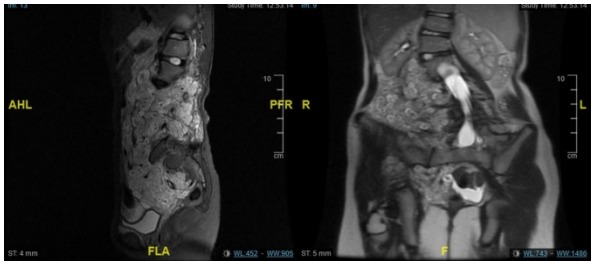

Figure 3.

The onset of pain, the increase in the size of the mass, and the development of malignant change in new neurological findings are signs of malignant transformation. The frequency of malignant peripheral nerve sheath tumor in the general population is 0.001%. 50% of all malignant peripheral nerve sheath tumor cases are NF1

Learning disability (50%), attention deficit, social interaction problems can be observed. Less than 10% of NF1 patients have intellectual disabilities, and 4-13% have epilepsy. Macrocephaly and short stature are standard phenotypic features in these patients.

In 75-90% of patients, hyperintense white matter lesions with well-defined borders called unknown brain objects (UBO) are observed on T2 MRI. These lesions are most commonly seen around the age of 7 and often disappear by puberty[2].

Optic glioma accounts for 2-5% of childhood CNS tumors, 70% of which are NF1. In routine MRI scans of children with NF1, optic glioma is detected in 15% to 20% (Figure 4). Care should also be taken in NF 1 patients in terms of diencephalic syndrome.

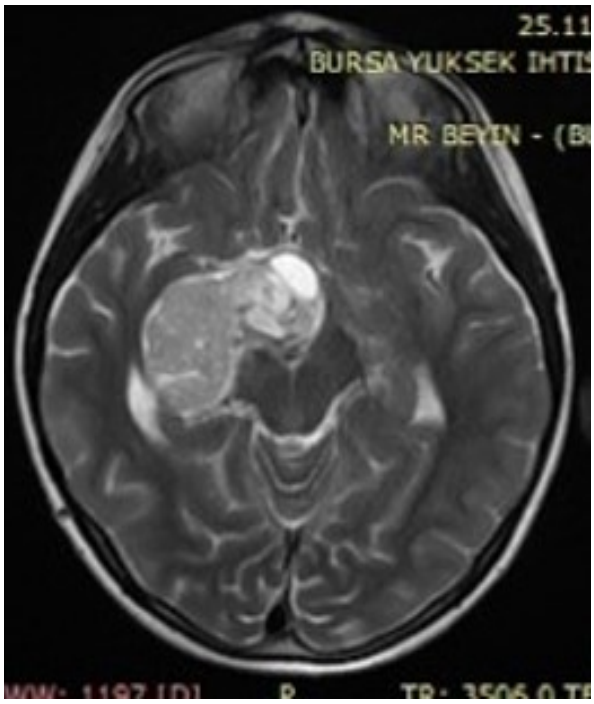

Figure 4.

The standard criteria for diagnosing NF1, established by the National Institutes of Health (NIH) in 1987, were updated in 2021, resulting in the current criteria (Table I)[3]. An NF1 diagnosis is made if two or more of the seven established criteria are present in the patient. While NF1 is known to be a hereditary disease, the criteria met, and the severity of symptoms can vary within a family. challengingGenetic testing may be conducted if diagnosing NF1 is difficult or cannot be clearly distinguished from similar syndromes. If NF1 is identified in a family for the first time, there is a high likelihood that mosaic NF1 may be present in the parents, and this possibility should be investigated. However, if neither parent shows any symptoms, the likelihood of NF1 recurring in the second generation is low.

Table I.

1	Optic glioma
2	Freckling in the ingunial or the axillary regions
3	2 or more Lisch nodules(iris hamartomas)
4	2 or more neurofibromas of any type or one plexiform neurofibroma
5	A distinctive osseous lesion (sphenoid dysplasia or thinning of long bones)
6	Sixx café au lait spots >5 mm in diameter in prepubertal children or >15 mm in postpubertal children
7	A first-degree relative with neurofibromatosis type 1

Neurofibromatosis Type 2

Neurofibromatosis Type 2 (NF2) is observed in approximately 1 in 25,000 to 40,000 individuals and has a prevalence of 1 in 56,000. It was first introduced to the medical literature in 1822 when John H. Wishort encountered it in a deaf patient[3].

NF2 is caused by a variant of the NF2 gene located on chromosome 22, which is responsible for suppressing tumor formation[5]. Like NF1, NF2 is hereditary, but it is rarer compared to NF1. NF2 has important features, such as the production of the Merlin protein, and plays an inhibitory role, particularly in mammalian cells[2]. NF2 is typically characterized by schwannomas, meningiomas, and ependymomas. These lesions usually appear bright on T2-weighted images and may sometimes present in a cystic form.

Hearing loss and tinnitus in the 20s are among the most common symptoms of Neurofibromatosis Type 2. In pediatric cases, juvenile posterior subcapsular cataract and skin tumors are key findings on the path to diagnosis. Additionally, the absence of Lisch nodules combined with the presence of bilateral vestibular schwannomas is one of the most definitive diagnostic features for NF2[3]. The phenotypes observed in individuals with functional loss are generally much more severe than those seen in individuals with large mutations. lower. NF2 is diagnosed when at least two diagnostic criteria from institutions such as the National Institutes of Health and Manchester are present in a patient (Table II)[11].

Table II.

1	A first-degree relative with NF2 AND either • Unilateral vestibular schwannoma OR • Any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities
2	Unilateral vestibular schwannoma AND • Any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities
3	Multiple meningiomas AND • Unilateral vestibular schwannoma OR • Any two of schwannoma, glioma, neurofibroma, cataract
4	Bilateral vestibular schwannomas

There are three types: 1. Congenital (neonatal) type with small bilateral VIIIth nerve schwannomas that progress suddenly in infancy 2. Wishart (severe) (childhood) type with multiple and rapidly progressing CNS tumors other than VS that appear at an early age and may appear years before VS, leading to multiple tumors and death in the 40s 3. Gardner (adult) type with a milder course together with meningiomas

In NF2, the Lisch nodule of NF1 is not seen, and a special type of cataract known as juvenile posterior sublenticular opacity (30-40%) develops. Cataracts under the age of 50 can be considered specific to this disease.

There is no specific lesion on the skin. 65% of patients also have cutaneous nerve sheath tumors[12]. Meningiomas are the second most common tumors in NF2 (20%). Intracranial meningiomas are often multiple, located along the falx cerebri or cerebral convexity (Figure 5). Ependymomas account for over 75% of intramedullary spinal cord tumors associated with NF2[12].

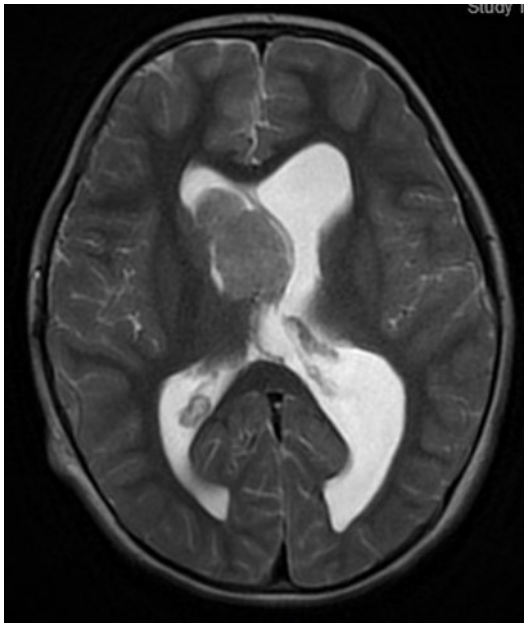

Figure 5.

NF3 Schwannomatosis

It is seen in 1/40,000 frequency. Vestibular Schwannomas and other tumors are not seen, deafness and learning difficulties do not develop. It is usually sporadic, but 10% of cases are familial and often skip generations.

Von Hippel-Lindau Disease

Von Hippel-Lindau (VHL) disease is a rare type of phakomatosis and a neurocutaneous syndrome. It was first described in the medical literature in 1904 by German ophthalmologist Eugen Von Hippel, who observed angiomas in the eye, and in 1927 by Swedish Arvid Lindau, who observed cerebellar hemangio-

blastomas. VHL is observed in approximately 1 in 36,000 births and affects around 200,000 individuals worldwide. The prevalence is 1/53,000, and it is inherited in an autosomal dominant manner[13]. The VHL gene, located on the short arm of chromosome 3 and consisting of 3 exons, has a broad mutation spectrum[5]. As a tumor suppressor gene, VHL is responsible for various tumors in the central nervous system, leading to Von Hippel-Lindau disease. Loss of function of VHL results in the formation of vascular tumors and the activation of hypoxia-inducible genes. About 80% of individuals with VHL have at least one parent with the disease, while in the remaining 20%, the disease is due to a mutation in the gene during fertilization[14]. With modern technology, prenatal detection of VHL can be performed through molecular analysis of chorionic villus cells or preimplantation genetic testing. Patients are observed to have at least one tumoral lesion within the first 65 years of life, as the penetrance of VHL reaches 100% by age 65[2].

In cases of Von Hippel-Lindau (VHL) disease, 50% of the cases involve retinal hemangioblastomas[3]. These tumors can lead to vision loss if they bleed. About 40% of cases consist of central nervous system hemangioblastomas. Although these tumors are generally benign, they can cause problems by compressing nearby nerves. This group is classified into four main categories: simple cysts without macroscopic nodules (5%), cysts with mural nodules (60%), solid tumors (26%), and solid tumors with small cysts (9%)[3].

Melmon and Rosen established the diagnostic criteria for Von Hippel-Lindau (VHL) syndrome and Rosen established the diagnostic criteria for Von Hippel-Lindau (VHL) syndrome in 1964[2]. According to these criteria, if a patient's family history is available, the presence of one hemangioblastoma or a visceral tumor is sufficient to make a diagnosis. However, if the patient's history is unknown, the diagnosis requires at least two hemangioblastomas or one hemangioblastoma along with one visceral tumor[14]. Due to the location of the tumors, surgical intervention is often necessary for treatment.

They are usually located in the posterior fossa (75% cerebellar) and craniocervical junction. 5-30% of cerebellar HB is related to VHLH. The most common (60%) is the mural nodule cystic type. If there is cerebellar HB, the spinal cord should definitely be scanned for lesions. 80% of spinal HB is related to VHLH.

Tuberous sclerosis

Tuberous sclerosis, a neurocutaneous syndrome, was first observed in 1862 by Friedrich Daniel Von Recklinghausen. However, Désiré-Magloire Bourneville identified it as a distinct syndrome, leading to it also being known as Bourneville disease[2]. Tuberous sclerosis (TS) is an autosomal dominant phakomatosis, also referred to as Epiloia, because patients experience epilepsy and developmental delays[3]. Two-thirds of cases arise from spontaneous mutations. It occurs in approximately 1 in 6,000 births, with a prevalence of 3-10 per 100,000, and about 1 million cases worldwide. There is no gender difference, although the phenotype tends to be milder in females[3].

The syndrome is caused by inactivating mutations in the TSC1 and TSC2 genes located on chromosomes 9 and 16, respectively[7]. Inherited paternal TSC1 mutations result in milder phenotypes, whereas sporadic TSC2 mutations lead to more severe phenotypes. TS can affect all organ systems, including the brain, skin, eyes, and kidneys[7]. Symptoms usually present before the age of 5 but can sometimes remain hidden until adolescence[2].

The most significant symptom is seizures, which affect more than 75% of patients and lead to cognitive impairments, behavioral problems, and learning difficulties. The disease often becomes symptomatic before the age of 5. Skin lesions are observed in 95% of patients. Ash-leaf macules (ALM) are hypopigmented macules and are usually present at birth. Adenoma sebaceum (Facial angiofibroma) is observed in 47% of cases[15].

Multiple retinal hamartomas in the eye, depigmented spots on the iris and retina, cataracts, corneal anomalies, vision loss after extensive retinal lesions, and strabismus may be observed.

The most common cause of morbidity is neurological findings. In 75-90% of patients, seizures that begin in infancy are observed. Intellectual disability is seen in less than 50% of patients. Increased cortical tuber size increases the risk of intellectual disabilities. Learning problems, behavioral disorders, autism (25%), autistic spectrum disorder (25%), focal neurological deficits, and ataxia can be seen.

More than 95% of cases have cortical tuberculosis, white matter lesions, SEN or SEGA detected on MRI.

Cortical tuber hamartoma is a cortical dysplasia that can be slightly pale, hard, flat or granular and is seen as a gyrus expansion in the convexity in 95% of cases. It is located mainly located supratentorial and rarely grows. Epilepsy severity and infantile spasms are related to the number, size and location of the KT[16].

Subependymal nodules are hamartomatous lesions located along the ependymal surface of the lateral ventricle, in the striotalamic groove between the caudate nucleus and the thalamus, just posterior to the foramen of Monro. Calcified SEN, especially seen in the vicinity of the foramen of Monro, is typical.

SEGA is often unilateral and develops in the subependymal region of the foramen of Monro (Figure 6). SEGA is at least 10 mm in diameter, SEGAs typically occur in the caudothalamic groove, while SENs occur along the ependyma in the lateral ventricle. SENs may calcify

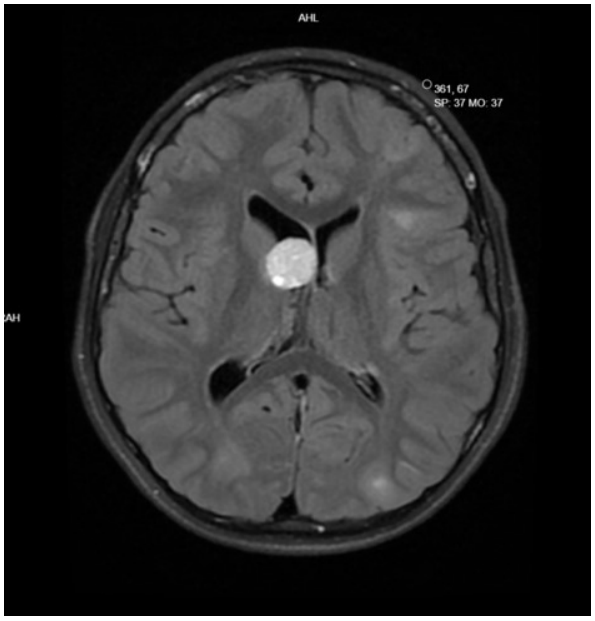

Figure 6.

Although managed with medication, surgical intervention may be needed if lesions are detected. Prenatal diagnosis is possible via MRI during the 20th to 26th weeks of gestation[2]. The International Tuberous Sclerosis Complex Consensus Group updated the clinical criteria in 2021[3].

Sturge-Weber Syndrome

Sturge-Weber syndrome is a rare phakomatosis that is not inherited, unlike similar conditions[8]. Symptoms usually start in childhood and include seizures and skin abnormalities known as "nervus flammeus" or port-wine stains, especially at the V1 dermatome (Figure 7). This syndrome often leads to seizures in 80-90% of those affected, with intellectual disabilities and hemiplegia present in 60% of cases and either of these conditions occurring in 30% of cases[2]. Treatment primarily aims to address the symptoms, using antiepileptic drugs to control seizures. In cases where medication fails to manage epilepsy effectively, lobectomy might be required.

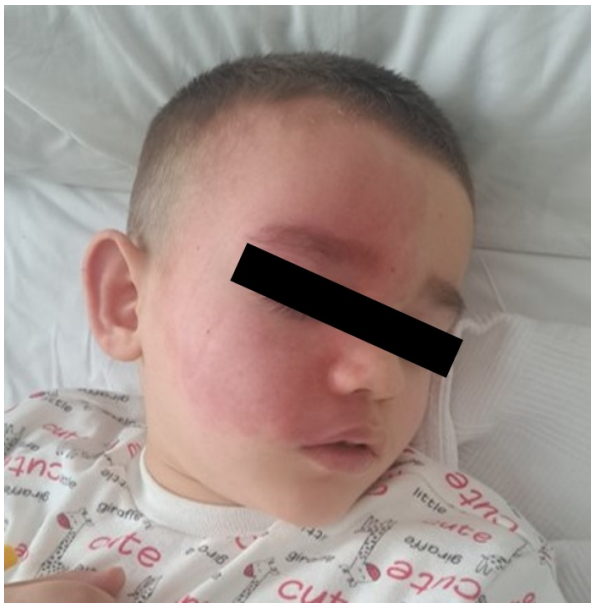

Figure 7.

Ataxia-Telangiectasia

Ataxia-telangiectasia, also known as Louis-Bar syndrome, is a rare genetic disorder that often leads to death due to recurrent infections and developing tumors. It is located on the long arm of chromosome 11 and follows an autosomal recessive inheritance pattern[2]. This condition causes ataxia, which affects coordination, balance, and walking. It also leads to telangiectasia, characterized by red spots on the skin due to dilated blood vessels. Additionally, it causes immune system problems and neurological issues. The first symptom is a delay in walking due to cerebellar ataxia. Death often occurs in the 3rd or 4th decade due to recurrent infections and the development of malignant tumors.

Conclusion

Phakomatosis is a group of hereditary syndromes that show phenotypic overlap with each other and with other genetic syndromes. The presence of characteristic cutaneous features and certain tumor types should raise the possibility of phakomatosis. The clinical manifestations of phakomatosis are highly variable, and treatment and follow-up vary for each phakomatosis patient.

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REVIEW

Effects of Antibiotics on Intestinal Microbiota and Potential Treatment Options

Algül Dilara DOKUMACI

Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Medical Pharmacology, Kahramanmaraş, Türkiye.

ABSTRACT

The gut microbiota is a complex ecosystem that significantly impacts digestion, immunity, and overall health. Although antibiotics are valuable in treating infections, they can cause long-term harmful effects on the host by altering the composition and functions of the microbiota. These effects include reduced microbial diversity, changes in the functional attributes of the microbiota, and the formation of antibiotic-resistant strains. This situation can lead to other complications such as digestive issues, weakened immune system, obesity, diabetes, allergic and autoimmune diseases, neurodevelopmental disorders, and certain cancers. In recent years, the increase in antibiotic use has heightened the likelihood of these problems becoming more acute or prevalent in the future. Antibiotic resistance is a global crisis, and the rising use of antibiotics over time necessitates research into their effects on microbiota and health. This review highlights the adverse effects of antibiotics on gut health and emphasizes various strategies to mitigate these effects, such as probiotics, prebiotics, fecal microbiota transplantation, and phage therapy.

Keywords: Antibiotic. Gut Microbiota. Precision medicine. Fecal Microbiota Transplantation. Probiotics.

Antibiyotiklerin Barsak Mikrobiyotası Üzerindeki Etkileri ve Potansiyel Tedavi Seçenekleri

ÖZET

Barsak mikrobiyotası; sindirim, immünite ve genel sağlık üzerinde önemli bir etkiye sahip karmaşık bir ekosistemdir. Antibiyotikler, enfeksiyonları tedavi etmede önemli olmasına rağmen, mikrobiyota bileşimini ve işlevlerini değiştirerek konakçı için uzun vadeli zararlı etkilere neden olabilmektedir. Bu etkiler arasında mikrobiyal çeşitliliğin azalması, mikrobiyotanın işlevsel özelliklerinde değişiklikler ve antibiyotiğe dirençli suşların oluşması yer almaktadır. Bu durum, sindirim sorunları, immün sistemin zayıflaması, obezite, diyabet, alerjik ve otoimmün hastalıklar, nörogelişimsel bozukluklar ve bazı kanserler gibi diğer komplikasyonlara yol açabilir. Son yıllarda antibiyotik kullanımındaki artış, bu sorunların gelecekte daha akut veya yaygın hale gelme olasılığını artırmaktadır. Antibiyotik direnci küresel bir kriz olup, zamanla artan antibiyotik kullanımının mikrobiyota ve sağlık üzerindeki etkilerinin araştırılmasını gerektirmektedir. Bu derleme, antibiyotiklerin barsak sağlığı üzerindeki olumsuz etkilerini ve bu etkileri azaltmak için probiyotikler, prebiyotikler, fekal mikrobiyota transplantasyonu ve faj tedavisi gibi çeşitli stratejileri vurgulamaktadır.

Anahtar Kelimeler: Antibiyotik. Barsak Mikrobiyotası. Bireyselleştirilmiş Tıp. Fekal Mikrobiyota Transplantasyonu. Probiyotikler.

Antibiotics, the primary drugs used to treat bacterial diseases, have transformed modern medicine by significantly reducing morbidity and mortality associated with bacterial infections[1]. However, the indiscriminate and excessive use of antibiotics has led to serious global health issues, including antibiotic resistance. It has caused unintended consequences, such as alterations in the composition of the gut microbiome[2]. The gut microbiome is a complex system containing 10^{13}–10^{14} microbial cells, including bacteria, fungi, protozoa, and viruses[1]. Dysbiosis refers to an imbalance or disruption in the body's microbial community[3].

Since their discovery, antibiotics have been acknowledged as a key factor in increasing life expectancy during the 20th century, primarily by reducing the mortality caused by infectious diseases[4]. Despite their essential role in treating bacterial infections, antibiotics pose concerns because of their ability to disturb the delicate microbial balance within the gut[5]. Although they are specifically designed to target harmful pathogens, antibiotics often

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Dr. Algül Dilara DOKUMACI
Kahramanmaraş Sütçü İmam Üniversitesi
Tıp Fakültesi Tıbbi Farmakoloji Anabilim Dalı,
Kahramanmaraş, Türkiye.
Phone: 0344 300 26 69 / 0531 651 72 73
E-mail: dilaradokumaci@ksu.edu.tr

Yazarların Orcid Bilgileri
Algül Dilara DOKUMACI: 0000-0002-3703-3952

inadvertently damage the growth and colonization of diverse and beneficial bacterial communities in the gut[1].

The gut microbiome is a highly intricate and dynamic community of nearly 39 trillion microbial cells, including bacteria, viruses, and fungi. These microorganisms inhabit the gut and play a critical role in regulating cellular pathways such as glycolysis, amino acid metabolism, fatty acid metabolism, vitamin synthesis, and host immunity. These are essential for maintaining the ecological balance of the gut[1].

Dysbiosis is characterized as a persistent disruption within the gut microbiota, marked by alterations in its composition and functionality. This imbalance is often driven by host-related or environmental factors that undermine a microbial ecosystem's capacity for resistance and resilience[6]. Research has consistently demonstrated connections between changes in the gut microbiota composition and a range of diseases, including recurrent diarrhea caused by *Clostridium difficile (C. difficile)*, certain bowel disorders such as inflammatory bowel disease (IBD), colorectal cancer, non-alcoholic steatohepatitis, type 2 diabetes, obesity, and advanced chronic liver disease[7,8].

Antibiotic use can cause dysbiosis, leading to digestive problems, weakened immune systems, and an increased risk of certain chronic diseases[9,10]. The primary impact of antibiotics on the gut microbiota is the disruption of microbial balance, often leading to the depletion of beneficial bacteria and the proliferation of opportunistic pathogens[3]. The indiscriminate use of antibiotics throughout an individual's lifetime can contribute to the emergence of antibiotic-resistant microorganisms such as *Vibrio, Acinetobacter, Escherichia, Klebsiella, and Clostridia* within the gut microbiota[1]. Narrow-spectrum antibiotics target specific bacterial groups, limiting their impact on microbiota and minimizing unintended alterations. On the other hand, broad-spectrum antibiotics can act on a wide array of bacterial species, posing a significant threat to microbiota stability[11]. By reducing gut microbial diversity, broad-spectrum antibiotics eliminate the intended pathogen and eradicate beneficial microbes, potentially leading to adverse effects on the host[12,13]. Although these effects may be temporary, there are concerns regarding their potential long-term consequences[13]. Research suggests that prolonged or repeated exposure to antibiotics can induce changes in microbial diversity, contributing to the development of chronic diseases, such as metabolic and autoimmune disorders[5].

This article explores the intricate interplay between antibiotics and the gut microbiota, highlighting short-term and potential long-term effects. Additionally, it investigates novel strategies that could reshape future therapeutic approaches in this field.

The Role and Importance of Gut Microbiota in Human Health

The human gut microbiota encompasses bacteria, archaea, eukaryotes (including fungi and protists), and viruses within the gastrointestinal tract, from the oral cavity to the rectum. It represents the body's largest microbial ecosystem, hosting an estimated 3.9 × 10 bacterial cells[14,15]. Although the domain Bacteria contains 55 recognized phyla, only seven to nine are consistently found in the human gut. *Bacteroidetes* and *Firmicutes* dominate, constituting approximately 90% of gut microbiota[16]. Other commonly identified phyla included *Proteobacteria, Actinobacteria, Fusobacteria*, and *Verrucomicrobia,* whereas archaeal species were relatively sparse[16].

This microbial community evolves in complexity over time and is influenced by numerous factors, including the birth method, age, nutritional habits, geographic location, ethnicity, and migration patterns[17]. Despite significant intra-individual fluctuations, such as those following an acute infectious diarrhea episode or antibiotic treatment, the gut microbiota generally returns to its original state over time, a phenomenon known as persistence[3].

Once thought to play a passive role, the gut microbiome is now recognized as an active and influential participant in human health, contributing to metabolism, immune system regulation, and brain function[1].

Digestion and Nutrient Absorption*:* The gut microbiota aids in breaking down complex carbohydrates and fibers, producing enzymes that facilitate digestion and nutrient absorption. Microorganisms also produce short-chain fatty acids, contributing to energy production and metabolic regulation[18].

Immune System Regulation*:* The gut microbiota helps develop and modulate the immune system from infancy. Microbiota-derived molecules influence immune system development and support the development of a balanced immune response, reducing the risk of allergies and autoimmune disorders[19].

Metabolism and Energy Homeostasis*:* The Gut microbiota influences metabolism by facilitating energy extraction from food and regulating metabolic processes. Metabolites produced by microbiota influence host metabolism and energy expenditure. Imbalances in the microbiota have been linked to pathologies, such as obesity and type 2 diabetes[20].

Gut-Brain Axis and Mental Health*:* The microbiota influences neurotransmitter production, affecting mood and behavior through the gut-brain axis. Changes in the microbiota composition have been

linked to conditions such as anxiety, depression, and neurodegenerative disorders[21,22].

***Protection Against Pathogens**:* A Healthy gut microbiota competes with harmful microorganisms and prevents colonization. Antimicrobial compounds produced by microbiota inhibit pathogen growth, and dysbiosis increases susceptibility to infection[23,24].

***Drug Metabolism and Detoxification**:* Some bacteria in the gut metabolize drugs, affecting their efficacy and side effects. The microbiota also contributes to detoxification by breaking down harmful compounds[25].

***Synthesis of Essential Compounds**:* Certain gut bacteria synthesize essential vitamins (e.g., B vitamins and vitamin K) and bioactive compounds that influence physiological functions[26].

The complex interactions between the gut microbiota and the body extend beyond digestion. A balanced and diverse microbiota is critical for overall health; disruptions caused by factors such as diet, antibiotics, and stress can lead to health problems[27]. Maintaining ~~a~~ healthy gut microbiota through a balanced diet and proactive measures can help prevent pathological conditions[28].

Antibiotics and the Gut Microbiome: A Complex Interaction

In recent years, the impact of antibiotics on gut microbiota has become a significant topic of interest and concern owing to its potential effects on human health[29]. Antibiotics are powerful antimicrobial agents used to treat bacterial infections and to target and kill specific bacteria. Although their primary goal is to eliminate harmful pathogens, antibiotics can also affect unintended bacteria in the gut microbiota. This secondary effect can disrupt the delicate balance between the different microbial species living in the gut[30].

Dysbiosis or dysfunction of the microbiota arises when microbial populations' diversity, biomass, and organization on or within the host are disrupted. These disturbances interfere with the coexistence and communication between bacteria and the host, significantly impairing host physiology, such as digestion and immune responses to pathogens[1].

The misuse of antibiotics, particularly their prolonged or irregular use, significantly reduces beneficial microbes. These adverse effects can be short- or long-term, resulting in microbial imbalances that render the intestinal environment more vulnerable to colonization by opportunistic pathogens usually checked by commensal bacteria[31].

The impact of antibiotics on the microbiome is further influenced by factors such as the type of antibiotic, dosage, and pharmacokinetic properties of the host. For instance, hydrophilic drugs (e.g., β-lactams, cephalosporins, penicillins, and rifampin) and hydrophobic drugs (e.g., macrolides: erythromycin, azithromycin, and clarithromycin) exhibit distinct routes of absorption and excretion, including epidermal, nasal, renal, and gastrointestinal pathways[32].

Both bactericidal and bacteriostatic antibiotics disrupt the balance between microbial populations and the host intestinal metabolism[33]. In comparative studies on mice, antibiotics commonly prescribed for *C. difficile* infections, such as metronidazole and vancomycin, eliminated the infection through different mechanisms. Metronidazole primarily reduces gram-negative bacteria, whereas vancomycin targets gram-positive bacteria, leading to imbalances in microbial density without significantly altering species composition[34].

Unlike vancomycin, antibiotics, such as ampicillin and clindamycin, exhibit long-term effects on the microbiota, increasing bacterial taxa such as *C. difficile* and decreasing others, including *Bacteroides, Subdoligranulum, and Faecalibacterium*[35,36]. Studies indicate that early and later in life, antibiotic usage causes imbalances within microbial communities, disrupting the symbiosis between bacterial species and the host. This imbalance is especially pronounced during the early life stages, from birth to early childhood[37,38].

Reduced Diversity: Antibiotic use is strongly associated with decreased microbial diversity. In children, microbial diversity reportedly recovers within approximately one month after antibiotic treatment[39]. In adults, the use of antibiotic combinations, including meropenem, gentamicin, and vancomycin, is associated with an increase in *Enterobacteriaceae* and other harmful pathogens, coupled with a reduction in beneficial microbes, such as *Bifidobacterium* and butyrate-producing species[40]. Although the overall composition of the microbiota showed significant recovery within approximately six weeks, some common bacterial species may remain absent for a six-month observational period[40].

Altered Metabolism: Low-dose antibiotic exposure in young mice has been shown to increase adiposity and elevate hormone levels associated with carbohydrate, lipid, and cholesterol metabolism[41]. Similarly, administering vancomycin-imipenem increased the arabinitol and sugars (e.g., sucrose) levels in fecal samples[42].

Antibiotic Resistance: Antibiotic resistance has become a pressing global public health concern. Between 2000 and 2015, the antibiotic consumption increased by 65% worldwide[43]. Projections indicate that by 2050, the annual fatalities linked to antibiotic resistance could reach approximately 317,000 in

North America, 390,000 in Europe, 392,000 in Latin America, 4,150,000 in Africa, and 4,730,000 in Asia[44]. The World Health Organization (WHO) estimates that the worldwide death toll due to antibiotic resistance may surpass 10 million annually by mid-century[45].

In summary, the relationship between antibiotics and the gut microbiota is a dynamic and multifaceted interaction with both short- and long-term effects on human health. As our knowledge of this interaction increases, so does the need to balance the benefits of antibiotic therapy with an understanding of its potential impact on the gut microbiota.

Antibiotics, a cornerstone of modern medicine in the fight against bacterial infections, exert their therapeutic effects through various mechanisms by targeting specific components of bacterial cells[46]. Additionally, antibiotics have a spectrum of activities and can effectively combat bacterial species' diversity[47].

The Spectrum of Activity of Antibiotics

Antibiotics are crucial in combating bacterial infections, but their effects extend beyond the target pathogens, influencing the host microbiota. Choosing between narrow-spectrum and broad-spectrum antibiotics significantly affects microbiota composition, resilience, and susceptibility to dysbiosis[48].

Narrow-Spectrum Antibiotics and Microbiota: Narrow-spectrum antibiotics are designed to target specific bacterial species or groups, thereby minimizing collateral damage to the microbiota. These antibiotics are preferred when the causative pathogen is known, as they help to preserve microbial diversity and reduce the risk of antibiotic resistance.

- ***Selective Action*:** Narrow-spectrum antibiotics primarily affect a limited range of bacteria, allowing the microbiota to maintain balance.
- ***Reduced Dysbiosis Risk*:** Since fewer bacterial species are disrupted, the likelihood of dysbiosis, a microbial imbalance associated with conditions such as IBD and metabolic disorders, is lower[49].

Broad-Spectrum Antibiotics and Microbiota: Broad-spectrum antibiotics target many bacterial species, including gram-positive and gram-negative bacteria. Although effective in treating infections of unknown origin, they pose a greater risk to microbiota stability[50].

- ***Widespread Disruption:*** Broad-spectrum antibiotics can significantly reduce microbial diversity, leading to loss of beneficial bacteria[50].
- ***Increased Risk of Opportunistic Infections:*** Depleting protective microbiota can allow opportunistic pathogens, such as *C. difficile*, to proliferate, increasing the risk of infections[51].
- ***Potential Long-Term Effects:*** Prolonged use may lead to persistent alterations in microbiota composition, affecting immune function and metabolic health[3].

The selection of narrow-spectrum and broad-spectrum antibiotics should be guided by infection specificity, patient health status, and concerns regarding antibiotic resistance. While narrow-spectrum antibiotics are preferable for targeted therapy, broad-spectrum antibiotics remain essential in situations that require immediate intervention.

Understanding the differing effects of narrow-spectrum and broad-spectrum antibiotics on microbiota is crucial for optimizing antibiotic therapy while mitigating unintended consequences. The indiscriminate use of broad-spectrum antibiotics can disrupt the balance of gut microbiota and contribute to antibiotic resistance[5]. Therefore, narrow-spectrum antibiotics should be prioritized whenever possible to minimize these risks.

Although antibiotics play a vital role in infection treatment, their rational use, considering mechanisms of action and activity spectra, is essential for preserving their long-term effectiveness and reducing their impact on the microbiota.

Antibiotics: A Double-Edged Sword – Therapeutic Benefits and Secondary Harms

Regarded as life-saving interventions, antibiotics indeed possess a double-edged sword nature. Although their therapeutic benefits in treating bacterial infections are undeniable, the secondary harms they can cause to targeted and non-targeted microorganisms must be carefully considered. This delicate balance between healing and unwanted outcomes underscores the complex nature of antibiotic therapy[47].

Therapeutic Benefits of Antibiotics

- **Elimination of Infection:** Antibiotics are considered the cornerstone agents in the fight against bacterial infections, eliminating pathogens and saving countless lives[46].
- **Transforming Medical Practices:** Antibiotics have transformed medical practices, enabling safer surgical procedures, organ transplants, and cancer treatments by effectively preventing or managing infections[52].
- **Reduced Mortality Rates:** The advent of antibiotics has significantly reduced the mortality rates from infections that were once fatal, marking a monumental achievement in modern medicine[53].

Secondary Harms Caused by Antibiotics

- **Reduction of Beneficial Microorganisms**: Because antibiotics do not distinguish between harmful and beneficial bacteria, their use can reduce diversity within the gut microbiota, affecting its functionality[2,13].
- **Antibiotic Resistance**: Prolonged or inappropriate use of antibiotics can trigger the development of antibiotic-resistant bacteria, making these drugs less effective over time and posing a threat to global health[54].
- **Opportunistic Infections**: Antibiotics can increase the risk of opportunistic infections such as *C. difficile*-associated colitis by eliminating beneficial microorganisms that limit pathogen growth[5].
- **Microbiota Dysbiosis**: Changes in gut microbiota due to antibiotics have been linked to various pathologies, including metabolic disorders, allergies, and immune disorders[55].
- **Long-term Effects**: The effects of antibiotics on the gut microbiota extend beyond the short term. Research has shown that repeated or prolonged antibiotic exposure can lead to deeper and more lasting changes in microbial composition. This raises concerns about potential long-term health effects, including an increased risk of conditions such as obesity, metabolic syndrome, and autoimmune diseases[19,20]. The mechanisms underlying these relationships are complex and multifaceted, involving interactions between the gut microbiota, host physiology, and immune system[56]. There are potential links between early life exposure to antibiotics and the development of chronic diseases such as obesity and asthma[57,58].

Antibiotics truly exhibit the characteristics of a double-edged sword; although they provide vital benefits in the treatment of infections, they can also potentially cause unwanted outcomes[47].

Research has shown that chronic changes in gut microbiota diversity due to antibiotic use are associated with pathologies, such as obesity, IBD, and allergies[55]. Long-term diversity reductions can also impair the microbiome by inhibiting the growth of pathogenic species, leading to an increased susceptibility to infections[59].

Connections between Antibiotics, Microbiota, and Autoimmune Diseases: Metabolic Syndrome, Obesity, and Metabolic Effects

Antibiotics have attracted increasing attention recently because of the complex interplay between them, the gut microbiota, and autoimmune disorders[60].

Antibiotics, microbiota changes, and autoimmunity: Long-term or repeated exposure to antibiotics can change the composition and diversity of gut microbiota. Dysbiosis resulting from such changes has been linked to the dysregulation of immune responses that can promote the development of autoimmune diseases. Impaired immune tolerance and the potential for molecular mimicry between the host and microbial antigens have been reported as mechanisms that drive autoimmune responses[61].

Metabolic syndrome and obesity: Gut microbiota plays a role in developing metabolic syndrome and obesity. Dysbiosis from antibiotic exposure can contribute to low-grade inflammation, insulin resistance, and altered energy metabolism, leading to obesity and its associated metabolic complications[20].

Immunity-metabolism cross-talk: Emerging evidence suggests that gut microbiota-mediated immunity-metabolism cross-talk plays a critical role in maintaining metabolic health. Antibiotic-induced changes in microbial communities can disrupt this interplay, promoting a pro-inflammatory environment and disrupting the metabolic balance. Such changes can create an environment conducive to autoimmune diseases and metabolic dysfunctions[62].

Potential Therapeutic Strategies

Recognition of the connection between antibiotics, gut microbiota, and autoimmune-metabolic interactions has opened new avenues for therapeutic exploration. Probiotics, prebiotics, and dietary interventions to restore gut microbial balance may help reduce the risk of autoimmune diseases and metabolic complications[63]. Precision medicine approaches considering an individual's microbial profile can offer personalized interventions[64].

1. Antibiotic management and long-term health: Balancing the need for antibiotic treatment with ~~the~~ potential long-term consequences on gut microbiota and health is critical. Antibiotic stewardship programs should be designed to minimize gut microbiome disruption while optimizing treatment efficacy[65,66].

Healthcare providers must be equipped with knowledge to balance the necessity of antibiotics with their potential impact on the gut microbiota. Educating patients is pivotal in promoting responsible antibiotic use, emphasizing adherence to prescribed courses, and increasing awareness of dysbiosis symptoms. Antibiotic stewardship programs that address the broader consequences of antimicrobial therapy can guide appropriate prescription practices and mitigate the risk of antimicrobial resistance[53].

Furthermore, reforming or establishing complementary public health measures can significantly reduce the reliance on antibiotics. As

highlighted by Laxminarayan, improving sanitation, expanding vaccine usage, and enhancing hospital infection control are proven strategies for reducing the demand for antibiotic therapies[67]. Additionally, minimizing the unnecessary use of antibiotics in agricultural practices should be prioritized[2].

Given the pivotal role of microbiota in regulating host physiology and the drawbacks of antibiotic use, it is imperative to explore alternative or complementary infection-fighting strategies. Promising avenues for research include antimicrobial peptides, innate defense regulatory peptides, bacteriocins, antisense antimicrobial therapeutics, predatory bacteria, monoclonal antibodies, antimicrobial nanoparticles, and CRISPR-Cas9[53].

2. Future Directions in Treatment: Microbiota-Medicine Interaction: Microbiome research advances have revealed gut microbiota's central role in human health and disease. The dynamic interaction between gut microbiota and human health has expanded our understanding of disease mechanisms and treatment approaches[19]. Microbiota-medicine interactions will enable the emergence of new therapeutic applications that leverage the potential of the gut microbiome to improve the treatment outcomes[68,69].

3. Microbiome applications in personalized medicine: The era of personalized medicine includes microbiome-based applications. A precise microbiome profile allows for individualized interventions that consider individual microbial composition and function differences. Treatments, such as fecal microbiota transplantation (FMT), are being explored for various diseases to restore healthy microbial balance[70].

4. Synthetic microbiota modulation*:* Advances in synthetic biology offer exciting opportunities to engineer microbial communities with health benefits. Engineered probiotics and prebiotics can deliver therapeutic molecules, modulate immune responses, and correct dysbiosis[71]. These innovative approaches hold promise for targeted applications in various pathological conditions, ranging from inflammatory disorders to metabolic diseases[72].

5. Microbiome as a therapeutic target: A changing perspective views the microbiome as a therapeutic target[73]. Small molecules produced by microbiota, known as postbiotics, exhibit various bioactive properties[74]. Developing postbiotics as therapeutic agents offers a new dimension to microbiota-targeted therapies by overcoming the challenges associated with live microbial interventions[75,76].

6. Microbiota-drug interactions**:** Recognizing the impact of the microbiota on drug metabolism and efficacy is critical. Understanding microbiota-mediated drug interactions can guide the optimization of treatment regimens. Developing drugs that interact synergistically with the microbiota can also improve therapeutic outcomes[69].

Advances in Fundamental Treatments

Microbiota-based treatments have gained momentum as innovative strategies to restore microbial balance and improve human health. Various methods such as prebiotics, probiotics, postbiotics, synbiotics, and FMT, are currently used[1].

1. Treatment of microbiome damage following antibiotic use

Antibiotic use is known to alter microbial composition, often with potentially harmful effects on the host. Several strategies can be implemented during or after antibiotic therapy to expedite the recovery of microbial balance. Probiotics are frequently employed for this purpose as they have been shown to boost the population of beneficial microorganisms, stabilize the microbial ecosystem, and mitigate the adverse effects of antibiotics[5]. Additionally, engineered probiotics and prebiotics offer targeted solutions that promote the growth of beneficial bacteria and aid in restoring microbial diversity. Furthermore, probiotics, prebiotics, and fecal microbiota transplantation are being actively investigated to enhance microbial resilience and diversity after antibiotic exposure[77].

2. Probiotics

Probiotics were first identified in the early 1900s and have been shown to transform the gut microbiota, replacing “rotting” bacteria with beneficial ones, thereby improving various disease conditions[5]. Over time, our understanding of probiotics has evolved, recognizing their role beyond regulating the microbiota to include enhancing immunity and improving general physiological functions.

Probiotics exert their effects through several mechanisms, including promoting antimicrobial peptide production, synthesizing bacteriocins, suppressing the growth of non-commensal bacteria by competing for nutrients and receptors on the intestinal mucosa, improving gut barrier function, and modulating immune responses. However, it should be noted that probiotic use may not completely restore the gut microbiota[5].

The therapeutic application of probiotics has shown significant success in balancing microbial configurations. For instance, *Lactobacillus acidophilus* has demonstrated immune modulation in mice via TLR2-dependent IFN-β pathways, enhanced intestinal barrier integrity (maintaining the mucosal layer), and inhibited pathogen colonization[78].

Engineered probiotics represent an innovative advancement in genetically modifying existing

probiotic strains through gene-editing techniques to produce novel microorganisms with desired properties. These modifications allow researchers to directly verify the changes in genetic material, proteins, and functional roles[79]. The progression of gene-editing technologies—from homologous recombination to Zinc Finger Nucleases (ZFNs), Transcription Activator-Like Effector Nucleases (TALENs), and the widely recognized CRISPR-associated systems (CRISPR-Cas)— highlights the rapid advancements in genetic engineering tools in recent years[80].

Emerging gene-editing techniques have shown exceptional promise in developing synthetic engineered probiotics for diagnosing and treating various diseases. Engineered probiotics are being investigated for their application in managing conditions such as cancer, inflammation, and infections. Researchers have aimed to enhance these probiotics' efficacy, safety, and cost-effectiveness compared with conventional therapies or wild-type strains, benefiting a wider range of patients and their families[81].

The advantages of engineered probiotics, including improved stability, specificity, selectivity, affordability, and relative safety, make them promising alternatives for treating various health conditions. However, despite their benefits, several challenges hinder their broader clinical adoption. Addressing concerns related to safety, ethical considerations, and regulatory frameworks is crucial for their successful integration into healthcare practices[82].

3. Prebiotics as microbial growth promoters: Mechanisms and applications

Prebiotics were first introduced in 1995, defining them as non-digestible food components that promote host health by selectively stimulating the growth and activity of specific beneficial bacteria in the colon[83]. This definition has evolved, and according to the International Scientific Association for Probiotics and Prebiotics (ISAPP), prebiotics are now recognized as dietary substances that are selectively utilized by beneficial microorganisms within the host, ultimately contributing to overall health[84].

Prebiotics include various compounds, such as inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS), and lactulose. These beneficial substances are naturally present in foods, such as whole grains, onions, garlic, and bananas[85]. Their primary role is to serve as a nutritional source for the beneficial gut bacteria. Since prebiotics are resistant to digestion by human enzymes, they pass through the digestive system largely intact until they reach the colon, where they undergo fermentation by the gut microbiota[86].

Prebiotic fermentation produces short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, contributing to gut health[87]. Prebiotics support microbiota balance by selectively promoting the proliferation and activity of beneficial bacterial species such as Bifidobacteria and Lactobacilli while suppressing the growth of pathogenic microorganisms[88]. In addition to maintaining gut microbial equilibrium, prebiotic-derived metabolites play essential roles in cellular energy production, immune modulation, reinforcement of gut barrier integrity, and neurological processes through the gut–brain axis[72].

Microencapsulation technology is used to enhance the stability of prebiotics and ensure their delivery to targeted intestinal regions. This method involves encasing prebiotic components in a protective coating, which increases their resistance to stomach acids and enables more effective utilization in the intestines. Advances in biotechnology have made it possible to produce prebiotics more efficiently using genetic engineering and fermentation techniques. Notably, studies focusing on probiotic-prebiotic synergy have aimed to increase the prebiotic content of fermented foods[89].

Synbiotics, which combine prebiotics and probiotics, have shown promising results. For instance, in middle-aged individuals receiving a synbiotic containing *Bifidobacterium animalis lactis* and fructooligosaccharides, improved abdominal discomfort, enhanced intestinal motility, and better bowel movement regularity were observed[90]. Another synbiotic, comprising probiotics (*Lactobacillus acidophilus*, *B. lactis*, *B. longum*, and *B. bifidum*) combined with a prebiotic (galactooligosaccharide mix), demonstrated improvements in blood glucose levels, initially linked to an increase in *Lactobacillus*, and subsequent reductions in BMI and body fat mass, which were associated with a decrease in *Bifidobacterium* levels[91].

5. Fecal Microbiota Transplantation as a Restoration Strategy

FMT involves the transfer of fecal microbiota from a healthy donor to a recipient to restore a diverse and balanced microbial community. Its therapeutic potential extends beyond gastrointestinal disorders, offering promise for autoimmune, metabolic, and neurological diseases—the primary mechanisms underlying FMT microbial reconstitution, immune modulation, and metabolite production[92].

Research has demonstrated that FMT can reduce *C. difficile* infection by inhibiting bacterial overgrowth and regulating bile acid metabolism[93]. A systematic review indicated that FMT has been used in clinical settings worldwide to treat 85 specific diseases between 2011 and 2021[94]. FMT has shown remarkable

efficacy in managing recurrent *C. difficile* infections, with an approximate cure rate of 90%[95].

Four randomized trials assessed fecal transplantation as an induction therapy for achieving remission in active ulcerative colitis, demonstrating statistically significant improvements compared to control treatments. By week 8, remission was achieved in 37% of the participants receiving FMT compared to 18% in the control group[96].

A significant milestone in FMT's advancement is regulatory approval. The prepared fecal microbiota was recognized as a live biotherapeutic product in Australia and the United States in 2022 and 2023, respectively[97]. In addition, the United States Food and Drug Administration (FDA) approved spores isolated from donor feces in 2023[98].

Despite its promise, several factors, such as efficacy, cost, and suitability, make FMT an attractive therapeutic option. However, further research is necessary to optimize its application and explore its potential therapeutic benefits beyond gut-related disorders[100]. Moreover, the success and safety of FMT rely on meticulous donor selection, standardization, and adherence to stringent safety protocols[101].

6. Unveiling the potential of phage therapy for microbiota modulation*:* Phage therapy, using bacteriophages to target bacterial populations selectively, has gained renewed interest as a promising approach to microbiota modulation[101]. Bacteriophages are viruses that infect and lyse specific bacterial species. By selectively eliminating harmful bacteria, phages can restore the microbial balance, enhance gut health, and mitigate inflammatory responses. Recent studies have highlighted their ability to shape the microbiota composition, influence immune function, and reduce antibiotic-resistant bacterial populations[102].

Phage therapy has been investigated for its efficacy in reducing biofilms and addressing lung infections, particularly in mouse models, where its successful application in treating respiratory diseases caused by *Pseudomonas aeruginosa* has been demonstrated[103,104]. Personalized phage therapy has also effectively cleared multidrug-resistant *Acinetobacter baumannii* infections, with documented treatment success in clinical cases[105]. Additionally, case studies have indicated pathogen eradication and symptomatic improvement in patients with bacterial prostatitis, septicemia, and acute kidney injury after undergoing phage therapy[106,107]. In another study, phage therapy was associated with healing in wounds and ulcers of 67 out of 96 patients, demonstrating a significant reduction in pathogenic bacteria[108]. Engineered bacteriophages have shown promise in combating drug-resistant *Mycobacterium abscessus*, leading to clinical improvement in patients with cystic fibrosis[109]. Moreover, phage-derived lytic proteins have emerged as potent antimicrobial agents, positioning phages as compelling alternative antibiotics in the fight against resistant pathogens[5].

Phage therapy offers advantages such as precise targeting and reduced antibiotic use. Phage therapy can particularly benefit patients with antibiotic-resistant infections, dysbiosis-related disorders, and immunocompromised patients. Despite its potential, phage therapy faces challenges like phage stability, immune response interactions, and regulatory hurdles. Advances in genetically engineered phages and personalized phage therapy are expected to enhance their efficacy and broaden their clinical application[101].

In summary, microbiota-based treatments, including FMT, engineered probiotics, prebiotics, and phage therapy, represent exciting avenues for innovations in healthcare. Each approach offers distinct mechanisms and applications for microbiota modulation, reflecting a new era of personalized and precise medicine[75].

Genetic Factors Influencing Antibiotic-Microbiota Interactions: Personalized Therapeutic Approaches

The gut microbiota of each individual comprises numerous unique strains that are absent from others, with inter-individual variations in microbiota composition being significantly greater than intra-individual variations[110]. Factors, such as sex, ethnicity, and geographic location, influence the taxonomic composition of the microbiome[111]. For instance, the fecal microbiota of adults residing in the metropolitan regions of Europe and North America is less diverse than that of adults in rural populations in Africa and South America[112,113].

Individual genetic differences influence responses to antibiotics and their subsequent effects on the gut microbiota. Understanding these interactions is critical for optimizing treatment outcomes while minimizing disruption to microbial communities[59].

1. Genetics Shapes Antibiotic Responses

Genetic polymorphisms, which refer to variations in DNA sequences among individuals, play a significant role in modulating the effects of antibiotics on human microbiota. These genetic differences can influence drug metabolism, efficacy, and extent of microbiota disruption, leading to variability in therapeutic outcomes and susceptibility to dysbiosis-related conditions[114].

Genetic polymorphisms in enzymes, such as cytochrome P450 (CYP) and UDP-glucuronosyltransferases (UGTs), affect the metabolism of antibiotics. For instance, variants in CYP enzymes can alter the breakdown and bioavailability of antibiotics, affecting their

concentration in the gut and, consequently, their effect on the microbiota. Slow metabolizers may experience prolonged exposure to antibiotics, increasing the risk of microbiota imbalance and the development of resistance[115].

Polymorphisms in transporter genes such as ABCB1 (P-glycoprotein) influence the distribution of antibiotics within the body. These variations can affect the concentration of antibiotics in the gut, altering their impact on microbial communities[116]. Genetic differences in immune-related genes, such as those encoding Toll-like receptors (TLRs), can affect the host response to antibiotic-induced microbiota changes. Variations in TLRs may influence inflammation and microbial resilience, shaping the recovery of the microbiota after antibiotic treatment. Variations in genes associated with antibiotic resistance mechanisms, such as efflux pumps and β-lactamases, can contribute to the emergence of resistant strains within the microbiota[114].

Understanding the role of genetic polymorphisms in the effects of antibiotics on microbiota is crucial for personalized medicine. Tailoring antibiotic therapies based on genetic profiles can minimize microbiota disruption, reduce the risk of antibiotic resistance, and enhance therapeutic efficacy. Pharmacogenomics and microbiome research advances are paving the way for personalized approaches to antibiotic therapy. Integrating genetic testing into clinical practice can help predict individual responses to antibiotics and guide the development of microbiota-friendly treatments.

2. Microbiome Profiling for Personalized Therapeutic Strategies

High-throughput sequencing and multi-omics approaches provide microbiome profiles, offering insights into the microbial composition and functional potential. Integrating genetic data with microbiome profiles allows for identifying conditions related to drug response and susceptibility to dysbiosis. Such profiles can inform personalized therapeutic applications, aid~~ing~~ in predicting patient-specific outcomes and guiding antibiotic selection[64,69].

3. Developing Algorithms for Personalized Antibiotic Prescribing

Advances in computational biology and machine learning have enabled the development of algorithms to predict optimal antibiotic regimens based on genetic and microbiome data. These algorithms can assist clinicians in making evidence-based antibiotic choices by considering an individual's genetic makeup and microbial composition. This approach can help minimize the risk of adverse effects and improve the treatment efficacy[117,118].

Integrating genetic and microbiome data into clinical practice poses significant data integration, interpretation, and privacy challenges. To facilitate seamless adoption of personalized therapeutic strategies, collaborative efforts among researchers, clinicians, and bioinformaticians are required to develop standardized protocols and tools. Genetic factors influencing antibiotic-microbiome interactions are critical determinants of individual responses to antibiotics and subsequent outcomes[119].

Ethical Considerations and Regulatory Frameworks

As microbiome-based applications evolve, it is imperative to address the ethical implications. Establishing regulatory frameworks is crucial for ensuring safety, efficacy, and equitable access to these applications. Collaboration among researchers, clinicians, and ethicists is essential for appropriately developing and utilizing microbiota-targeted therapies. Microbiome-medicine interaction represents a transformative paradigm in healthcare. Future directions include personalized applications, synthetic microbiota modulation, and microbiome-centered therapies[120].

Conclusion

In conclusion, the dynamic relationship between antibiotics and gut microbiota highlights the need for precision in prescribing practices and the development of innovative therapies. By considering this complex interplay, healthcare professionals can help preserve both the efficacy of antibiotics and the delicate balance of gut microbiota. This can lead to better health outcomes for individuals and the broader population. Further research in this area will enable the optimization of antibiotic use and the development of new approaches to protect microbiota health.

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