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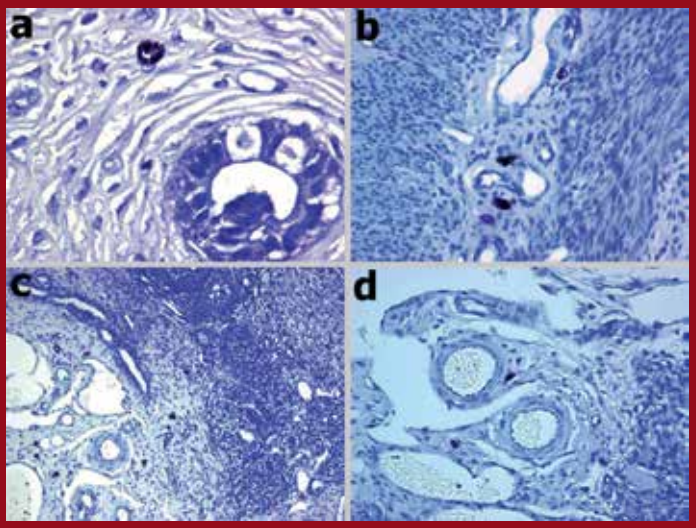

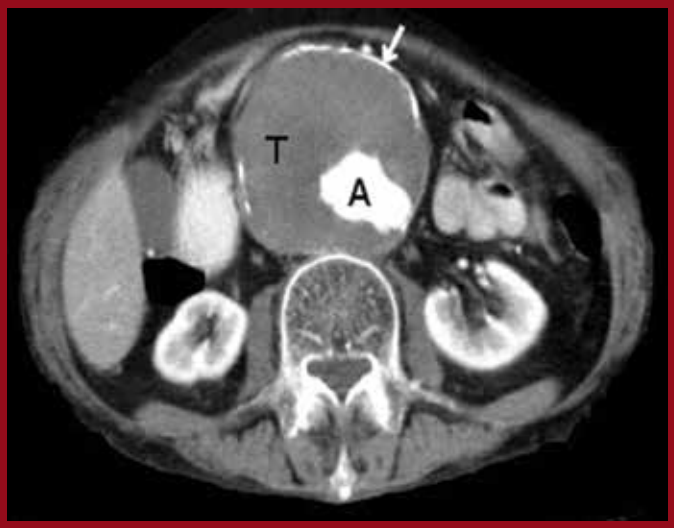

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ARAŞTIRMA YAZISI / ORIGINAL ARTICLE

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Propofol ile Deksmedetomidin Sedasyonunun Aksiller Blok Uygulaması Üzerine Olan Etkilerinin Karşılaştırılması

Comparison of the Effects of Propofol and Dexmedetomidine Sedation on Axillary Block

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ABSTRACT

AIM: *We aimed to compare the effects of propofol and dexmedetomidine on intra-operative sedation, hemodynamic parameters and post-operative analgesia during fore-arm surgery with axillary block.*

METHODS: *Forty patients scheduled for elective hand and forearm surgery with axillary brachial plexus block (ASA I-II) were randomized into two groups. Group D patients received a loading and continuous infusion dose of intravenous dexmedetomidine 1 µg kg-1 in ten minutes before the axillary block and 0.2–0.7 µg kg-1 h-1, respectively. Group P patients received a loading and continuous infusion dose of intravenous propofol 1 mg kg-1 in ten minutes before the axillary block and 50–100 µg kg-1 min-1, respectively. Upon reaching a target sedation score of 3–4 (assessed with Ramsey sedation scale), axillary block was performed. At the end of surgery, intravenous infusions were stopped. Groups were compared in terms of sedation scores, hemodynamic and respiratory parameters, sensory and motor block levels (with Pin-prick test and Bromage scores), time to regression of sensory and motor blocks, time to first analgesic requirement, and adverse events.*

RESULTS: *Demographic data, hemodynamic and respiratory parameters, sedation scores, sensory and motor block levels, and adverse events did not significantly differ between groups. Dexmedetomidine significantly delayed regression of sensory block and first analgesic requirement compared with propofol (p<0.05).*

CONCLUSION: *Dexmedetomidine as a sedative agent is as effective and safe as propofol. If surgery is expected to last longer, dexmedetomidine may be better suited because it prolongs sensory block regression time and time to first analgesic requirement.*

Key words: *axillary block; dexmedetomidine; propofol; sedation*

ÖZET

AMAÇ: *Önkol cerrahisinde propofol ve deksmedetomidinin intraoperatif sedasyon, hemodinamik parametreler ve postoperatif analjezi üzerine etkilerini karşılaştırmayı amaçladık.*

YÖNTEM: *Aksiller yaklaşım ile brakial pleksus bloğu uygulanacak, elektif el ve ön kol cerrahisi geçirecek, ASA I-II, 40 olgu 2 gruba randomize ayrıldı. Grup D'deki (n=20) olgulara aksiller blok uygulamasından önce deksmedetomidin 1 µg kg-1 yükleme dozu 10 dakika uygulandıktan sonra 0.2–0.7 µg kg-1 sa-1 dozunda infüzyon, Grup P'deki (n=20) olgulara ise propofol 1 mg kg-1 yükleme dozu 10 dakika uygulandıktan sonra 50–100 µg kg-1 dk-1 dozunda propofol infüzyonu başlandı. Grupların sedasyonu Ramsay Sedasyon Skoru'na göre 3–4 olarak hedeflendi. Hedef sedasyon düzeyine erişildiğinde aksiller blok uygulandı. Deksmedetomidin veya propofol infüzyonu cerrahi girişim bittiğinde sonlandırıldı. Gruplar; sedasyon skorları, hemodinamik parametreler, periferik oksijen satürasyonu, solunum sayısı, Pin-prick testi ve Bromage skorları ile duyusal ve motor blok seviyeleri, postoperatif dönemde duyusal ve motor blok gerileme zamanı, ilk analjezik gereksinim zamanı ve yan etkiler açısından karşılaştırıldı.*

BULGULAR: *İki grup arasında demografik veriler, hemodinamik parametreler, sedasyon skorları, duyusal ve motor blok seviyeleri ve yan etkiler açısından fark bulunmadı. Deksmedetomidin grubunda postoperatif duyusal blok geri dönüş zamanı ve ilk analjezik gereksinim zamanı propofol grubuna göre anlamlı olarak daha uzun bulundu (p<0.05).*

SONUÇ: *Deksmedetomidinin propofol kadar etkili ve güvenli sedatif bir ilaçtır. Aksiller blok sonrasında duyusal blok süresi ve ilk analjezik gereksinim zamanını uzatması nedeniyle, operasyon süresinde uzama beklenen olgularda daha iyi bir seçenek olabilir.*

Anahtar kelimeler: *aksiller blok; deksmedetomidin; propofol; sedasyon*

Giriş

Brakiyal pleksusa aksiller yaklaşım; el ve ön kol cerrahi girişimlerinde daha etkili olup, özellikle günübirlik cerrahilerde yaygın olarak kullanılan bir periferik sinir bloğu tekniğidir[1,2]. Sinir hasarı, hematom, intravenöz enjeksiyon gibi komplikasyonlar diğer periferik sinir blok yaklaşımlarına göre oldukça nadir görülür[2,3].

Rejyonal anestezi tekniklerinin ponksiyon alanında ağrı, iğne korkusu ve işlemin hatırlanması gibi bazı

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dezavantajları mevcuttur. Bilinçli sedasyon; bilincin minimal deprese olması, hastanın koruyucu reflekslerinin ve solunum fonksiyonlarının normal olarak devam etmesidir. Periferik sinir bloklarında hasta ajitasyonunu azaltmak, cerrahi işleme uyumu arttırmak, analjezi, anksiyoliz ve amnezi sağlamak için intravenöz bilinçli sedasyon tercih edilmektedir[4].

Propofol, intravenöz infüzyonla sedasyonda kolay titre edilebilmesi, anksiyoliz ve amnezi yapması, bulantı-kusma insidansının düşük olması, hızlı ve tam uyanma sağlaması nedeni ile sık olarak tercih edilmektedir[5–8]. Ancak propofol analjezi sağlamadığı gibi enjeksiyonları da ağrılı olabilmektedir[9]. Sedatif-hipnotik ve sempatolitik özellikleri olan alfa$_2$ (α_2) adrenerjik reseptör agonisti deksmedetomidin analjezik özelliğe de sahip bir ajandır[10–15]. Diğer sedatif ajanlara göre hasta kooperasyonunun daha fazla olduğu ve derin sedasyon dozlarında bile solunum depresyonu yapmadığı bildirilmiştir[16–21].

Bu çalışmada; el ve ön kol cerrahisi yapılacak hastalarda uygulanacak intravenöz deksmedetomidin sedasyonunun, aksiller blok üzerine etkisini intravenöz propofol sedasyonu ile karşılaştırmayı amaçladık.

Yöntem

Onsekiz-altmış yaş arası, ASA I-II grubu, aksiller yaklaşımla brakiyal pleksus bloğu uygulanarak el ve ön kol cerrahisi planlanan 40 olgu etik kurul onayı alındıktan sonra çalışmaya dahil edildi. Her olguya çalışma hakkında bilgi verilerek yazılı onamları preoperatif dönemde alındı.

Kooperasyon kurulamayan, alkol alışkanlığı olan, ilaç alerjisi hikayesi olan, böbrek veya karaciğer yetmezliği olan, α_2 reseptör agonisti veya antagonisti tedavisi alan, rezerpin kullanan, psikiyatrik bozukluğu olan, rejyonal anestezi uygulamasının kontrendike olduğu olgular (girişim yerinde lokal enfeksiyon, sepsis, koagülasyon bozukluğu gibi) çalışma dışı bırakıldı.

Olgular kapalı zarf yöntemine göre randomize olarak iki gruba ayrıldılar. Grup D (n=20) olgulara aksiller blok uygulamasından önce intravenöz (iv) olarak 1 $\mu g\ kg^{-1}$ deksmedetomidin yükleme dozu 10 dakikada uygulandıktan sonra 0.2–0.7 $\mu g\ kg^{-1}\ sa^{-1}$ dozunda deksmedetomidin infüzyonu, Grup P (n=20)'ye iv olarak 10 dakika 1 $mg\ kg^{-1}$ propofol yükleme dozunu takiben 3–6 $mg\ kg^{-1}\ sa^{-1}$ (50–100 $\mu g\ kg^{-1}\ dk^{-1}$) propofol infüzyonu başlandı. Her iki gruptaki olgularda Ramsay Sedasyon Skoru (RSS) ile sedasyon değerlendirildi ve hedef sedasyon seviyesine (RSS=3–4) ulaşıldığında aksiller blok uygulandı (Tablo 1) [22].

Tüm olgulara elektrokardiyografi, non-invaziv kan basıncı, soluk sonu karbondioksit basıncı ($EtCO_2$) ve periferik oksijen satürasyonu (SpO_2) monitörizasyonu standart olarak uygulandı. Olgulara cerrahi işlem uygulanmayacak koldan damar yolu açılarak izotonik sodyum klorür infüzyonu verilmeye başlandı. Sedasyon uygulaması ile birlikte tüm olgulara oksijen maskesi ile oksijen verildi.

Periferik sinir stimülatörü (Stimuplex® HNS 11, B. Braun, Germany) ile sinir stimülasyonu eşliğinde Stimuplex® A kanül (B. Braun, Melsulgen AG) ile arterin hemen üstünden cilt geçilerek perinöral alana yaklaşıldı. Her iki grupta aksiller blok için 100 mg %0.5 Bupivakain, 200 mg %2 Lidokain, 10 ml Serum Fizyolojik ile toplam hacmi 40 ml olan solüsyon uygulandı.

Sistolik arter basıncı (SAB), diastolik arter basıncı (DAB), kalp atım hızı (KAH), SpO_2, dakika solunum

Tablo 1. *Çalışmada kullanılan bazı test ve ölçeklerin özeti*

Puan	Ramsay Sedasyon Skoru	Pin-prick testi	Bromage Skalası
0	-	Duyu bloğu yok	Blok yok
1	Ajite, anksiyöz	Dokunma hissi +, ağrı -	Motor güç azalmış, ancak kol hareketli
2	Koopere	Dokunma hissi -, ağrı -	Kol hareketsiz, ancak parmaklar hareketli
3	Sadece emirlere yanıt	-	Tam blok
4	Glabellaya vuru veya yüksek sesli uyarana canlı yanıt	-	-
5	Glabellaya vuru veya yüksek sesli uyarana tembel yanıt	-	-
6	Yanıt yok	-	-

sayısı (SS), $EtCO_2$ ve RSS sedasyon başlamadan önce ve sedasyonun 5,10,15,20 ve 30. dakikalarında ve sedasyon süreci boyunca her 10 dakikada bir kaydedildi. Aksiller blok işlemi sonrasında Pin-prick testi ile duyusal blok ve Bromage skalasıyla motor blok derecesi değerlendirildi (Tablo 1).

Derlenme odasında ve ameliyat sonrası ilk 24 saatlik dönemde SAB, DAB, KAH, SpO_2, SS, motor ve duyusal blok gerileme zamanı, Visüel Ağrı Skoru (VAS; 0=Ağrı yok, 10=Olası en büyük ağrı) ve ilk analjezik gereksinim zamanı (VAS≥4) kaydedildi**.**

Hipotansiyon (ortalama arter basıncının başlangıç değerine göre %20 düşmesi) olduğunda iv 10 mg efedrin ve iv sıvı replasmanı; hipertansiyon (başlangıç değerine göre %20 yükselmesi) olduğunda sedatif ilaç dozu arttırılması ve analjezik olarak iv 1 $\mu g\ kg^{-1}$ fentanil uygulanması planlandı. Bradikardi (başlangıç KAH değerine göre %20 azalması) olduğunda atropin 0.5 mg dozunda iv uygulanması, taşikardi (başlangıç KAH değerine göre %20 artması) olduğunda uygulanan sedatif ilaç dozunun arttırılması ve analjezik olarak iv 1 $\mu g\ kg^{-1}$ fentanil uygulanması planlandı. SpO_2'nin %90'ın altına düşmesi durumunda pozitif basınçlı ventilasyon uygulanması planlandı. Bulantı veya kusma olduğunda 20 mg metaklopramid, alerji ve ürtiker durumlarında 20 mg difenhidramin iv uygulanması planlandı.

Çalışmanın istatistiksel analizleri SPSS 21 istatistik paket programı kullanılarak yapıldı. İstatistiksel analizinde Ki-kare testi ve Mann-Whitney U testi kullanılarak gruplar karşılaştırıldı. Veriler ortalama ± standart sapma veya olgu sayısı olarak sunuldu. İstatistiksel olarak $p<0.05$ değeri anlamlı kabul edildi.

Bulgular

Her iki grup arasında demografik veriler, blok başlama süresi, operasyon ve anestezi süreleri açısından istatistiksel olarak fark bulunmadı (Tablo 2).

Gruplar arasında hemodinamik değişiklikler, SpO_2, SS ve RSS değerleri açısından istatistiksel olarak anlamlı fark saptanmadı (Şekil 1). Benzer olarak, duyusal blok seviyesi ve başlama zamanı, motor blok seviyesi ve süresi açısından da anlamlı fark saptanmadı (Şekil 2).

Postoperatif dönemde ilk analjezik gereksinim zamanları Grup D'de, Grup P'ye göre anlamlı olarak daha uzun bulundu ($p<0.05$). Her iki grup arasında duyusal ve motor blok gerileme zamanı karşılaştırıldığında; duyusal blok gerileme zamanı Grup D'de Grup P'ye göre anlamlı olarak daha uzun ($p<0.05$) bulunurken; motor blok gerileme zamanı açısından istatistiksel olarak anlamlı fark tespit edilmedi (Şekil 2).

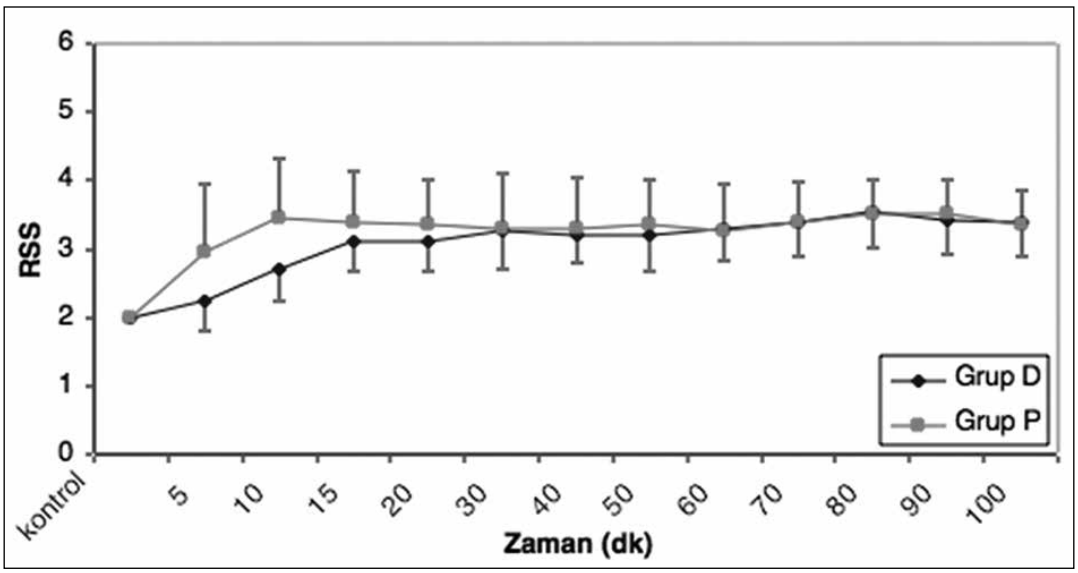
Grup D'de bir olguda yükleme dozu sonunda 10. dakikada, bir olguda ise 12. dakikada bradikardi saptandı. Her iki olguda da atropin 0,5 mg iv uygulanması ve deksmedetomidin infüzyon hızının 0.2 $\mu g\ kg^{-1}\ sa^{-1}$ dozuna geçilmesi ile bradikardi tedavi edildi. Grup D'de bir olguda da tedavi gerektirmeyen ağız kuruluğu gözlendi.

Grup P'de bir olguda yükleme dozu sonrası solunum depresyonu gözlendi. Sedasyon infüzyonu durduruldu, %100 oksijen ile pozitif basınçlı ventilasyon iki dakika uygulandı. Spontan solunumun sağlanması ve RSS'nun 3 olması üzerine sedasyona 1 $mg\ kg^{-1}\ sa^{-1}$ dozunda devam edildi. Başka bir olguda infüzyonun 5. dakikasında RSS artması üzerine kısa süreli solunum

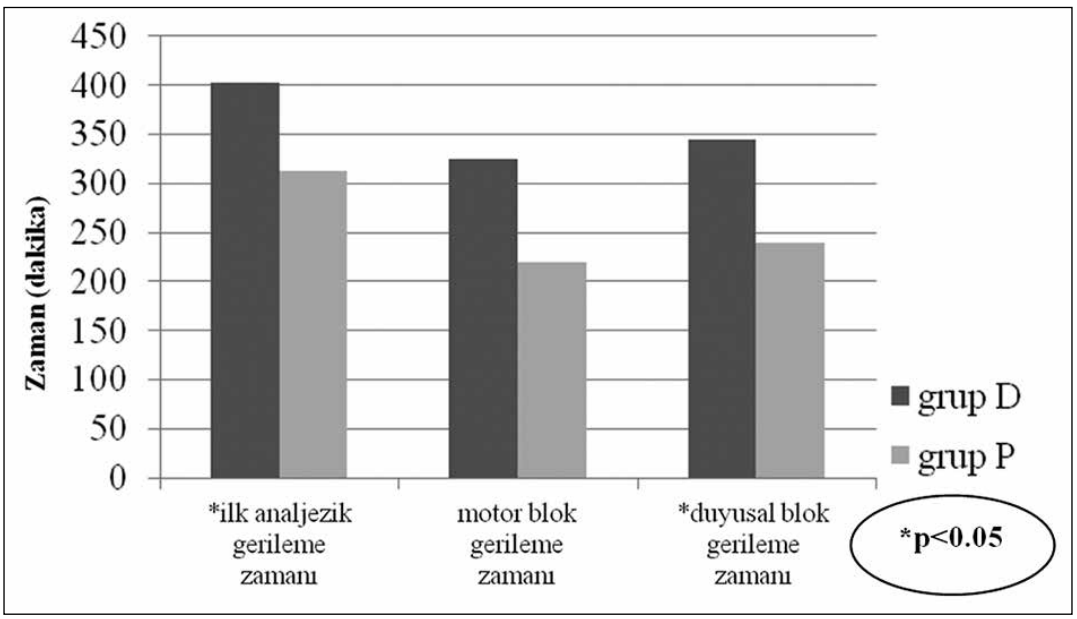
Tablo 2. *Brakial pleksus bloğu sırasında deksmedetomidin (D) ve propofol (P) sedasyonu uygulanan olguların karşılaştırılması (ortalama ± standart sapma)**

	Grup D (n=20)	Grup P (n=20)
Yaş (yıl)	35,3±13,5	41,7±14,2
Cinsiyet (K/E)	7/13	6/14
Boy (cm)	170,0±6,2	173,3±8,5
Vücut ağırlığı (kg)	74,2±10,6	70,5±9,2
ASA sınıflaması (1/2)	19/1	19/1
Operasyon tipi (el/ön kol cerrahisi)	16/4	14/6
Blok başlama süresi (dk)	9,5±3,4	10,2±4,0
Operasyon süresi (dk)	73,5±31,6	84,0±32,7
Anestezi süresi (dk)	103,0±30,9	120,2±34,4

*Karşılaştırılan parametreler açısından gruplar arası anlamlı fark saptanmadı ($p>0.05$)



Şekil 1.



Şekil 2 .

depresyonu gözlendi. İnfüzyon durduruldu ve sözel uyarı ile solunum sayısı artırıldı. RSS'u 3 olduğunda sedasyona devam edildi. Bir olguda da sedasyon süresi içinde 20. dakikada hipotansiyon görüldü.10 mg efedrin iv uygulandı ve infüzyon hızı 3 mg kg^{-1} sa^{-1} olacak şekilde sedasyon uygulamasına devam edildi.

Her iki grupta da ilk analjezik ihtiyacında non-steroid antiinflamatuar ajan intramusküler uygulanarak analjezi sağlandı.

Tartışma

Çalışmamızda; aksiller blok ile el ve ön kol cerrahisi geçiren olgularda deksmedetomidinin ve propofolün benzer hemodinamik stabilite ve sedasyon sağladığını; deksmedetomidinin duyusal blok geri dönüş zamanını ve ilk analjezik gereksinim zamanını propofole göre anlamlı olarak uzattığını saptadık.

Rejyonal anestezi ile cerrahi girişim uygulanacak olgularda operasyon dönemindeki stresin azaltılması,

hastanın konforunun ve ortama uyumunun arttırılması amacıyla sıklıkla sedasyon uygulanmaktadır. Deksmedetomidinin klinikte kullanımı sırasında bradikardi, hipotansiyon veya hipertansiyon ile seyreden kardiyovasküler yan etkiler bildirilmiştir[12,13,23,24]. Alfa$_2$ adrenerjik agonistler düşük dozlarda α_2A adrenerjik reseptör subtipi ile sempatolizis yaparak nöroefektör bileşkede norepinefrin salınımını ve beyindeki "locus ceruleus" çekirdeğini inhibe ederler ve klinik kullanımda hipotansiyona neden olurlar[25]. Deksmedetomidinin neden olduğu hipotansiyon ve bradikardi, cerrahi stres yanıtın kontrolünde avantaj oluştururken hipovolemik veya kalp bloğu olan hastalarda ise dezavantajdır[26]. Yüksek dozlarda ise damarlardaki düz kas hücrelerinde bulunan α_2B adrenerjik reseptörlerinin aktive olması ile hipertansif etki oluştururlar[13,25]. Ebert ve arkadaşları sağlıklı bireylerde yaptıkları çalışmada deksmedetomidinin, yüksek plazma konsantrasyonlarında bile kalp hızını azalttığını, kan basıncı, sistemik ve pulmoner vasküler rezistansı artırdığını ve buna bağlı olarak kardiyak debiyi azalttığını saptamışlardır[10].

Hall ve arkadaşları 10 dakika yükleme dozunu takiben 50 dakika süresince 0.2 μg kg^{-1} sa^{-1} ve 0.6 μg kg^{-1} sa^{-1} dozlarında deksmedetomidin infüzyonu uygulamışlar ve infüzyonun 60. dakikasında, derlenme döneminde 1. ve 2. saatlerde ortalama arter basıncı ve kalp hızının anlamlı olarak azaldığını bildirmişlerdir[12]. Özellikle 10 dakikalık yükleme döneminde kalp hızının başlangıç değerine göre 0.2 μg kg^{-1} sa^{-1} dozunda uygulandığında %10,0.6 μg kg^{-1} sa^{-1} dozunda uygulandığında ise %16 oranında düştüğünü saptamışlardır. Bizim çalışmamızda deksmedetomidin grubunda iki olguda bradikardi saptanmış, atropin 0.5 mg iv uygulanması ve deksmedetomidin infüzyon hızının 0.2 μg kg^{-1} sa^{-1} dozuna geçilmesi ile tedavi edilmiştir.

İntraoperatif sedasyonda propofol ve deksmedetomidin sedasyonunun karşılaştırıldığı bir çalışmada ortalama arter basınçları, intraoperatif dönemde propofol grubunda, postoperatif dönemde ise deksmedetomidin grubunda anlamlı olarak daha düşük bulunmuş ve bu sonucun propofolün güçlü sempatik sistemi deprese edici etkisinden dolayı olabileceği ileri sürülmüştür[13]. Turan ve arkadaşları monitörize anestezi bakımında deksmedetomidin ve propofol sedasyonunu karşılaştırdıkları çalışmalarında, intraoperatif ve postoperatif dönemde kalp hızı, ortalama kan basıncı ve SpO_2 değerlerinde gruplar arasında fark olmadığını saptamışlardır[27]. Balcı ve arkadaşları propofol ve deksmedetomidin infüzyonunun hemodinamik ve bispektral indeks (BİS) değerlerine etkisini karşılaştırdıkları çalışmada, deksmedetomidin grubunda kan basıncı ve kalp hızının daha düşük, sedasyon başlama ve sonlanmasının daha yavaş olduğunu bulmuşlardır[15]. Çalışmamızda Balcı ve arkadaşlarının uygulamasına göre deksmedetomidin ortalama infüzyon dozunun daha düşük olmasına bağlı olarak hemodinamik parametrelerde propofol ve deksmedetomidin grupları arasında anlamlı fark saptamadık.

Turan ve arkadaşları ise endoskopik sinüs ameliyatlarında propofol ve deksmedetomidin infüzyonu ile monitörize anestezi bakımı uygulamışlar ve deksmedetomidin grubunda intraoperatif sedasyon skorlarının anlamlı olarak daha yüksek olduğunu saptamışlardır[27]. Ancak uygulanan propofol dozu bu çalışmada çalışmamıza göre daha düşük olduğundan biz peroperatif dönemde istediğimiz hedef sedasyon düzeyine ulaşmada zorlukla karşılaşmadığımız gibi propofol ve deksmedetomidin grupları arasında sedasyon düzeylerinde de farklılık saptamadık. Ayrıca çalışmamızda propofol grubunda iki olguda daha derin sedasyon ve solunum depresyonu tespit ettik.

Arain ve arkadaşları intraoperatif sedasyonda propofol ve deksmedetomidinin etkinliğini, yan etkilerini ve uyanma özelliklerini karşılaştırmış, deksmedetomidin grubunda sedasyonun daha yavaş başladığını ve daha yavaş sonlandığını saptamışlardır[13]. Bu çalışmada uygulanan propofol yükleme dozu ise çalışmamıza göre oldukça yüksekti (75 μg kg^{-1} sa^{-1}). Rejyonel anestezi veya monitörize anestezi bakımı ile cerrahi girişim uygulanan olgulara çalışmamızdaki gibi propofol ve deksmedetomidin ile sedasyon uygulanmış ve deksmedetomidin uygulanan olgularda postoperatif ağrı skorlarının ve analjezik tüketiminin daha az olduğu saptanmıştır[13,27]. Araştırmacılar bu sonucu deksmedetomidinin analjezik özelliklerinin uyanma döneminde devam etmesine bağlamışlardır. Çalışmamızda da, postoperatif analjezi süresi, deksmedetomidin grubunda anlamlı olarak daha uzun bulundu.

Balcı ve arkadaşları da çalışmamıza benzer olarak el cerrahisi ameliyatlarında propofol ve deksmedetomidin infüzyonu uygulamışlar, sedasyon skorlarının ve BİS değerlerinin intraoperatif dönemde propofol grubunda, postoperatif dönemde ise deksmedetomidin grubunda daha düşük olduğunu bulmuşlardır[15]. Bizim çalışmamızda ise gruplar arasında sedasyon skoru açısından anlamlı fark saptanmadı. Bu bulgu; çalışmamızda sedasyon düzeyinin daha önceden belirlenen sedasyon düzeyinde sabit tutulmaya çalışılmasına,

farklı sedasyon skorlamasının kullanılmasına ve deksmedetomidin dozunun düşük olmasına bağlı olabilir. Çalışmamızda blok başlama süreleri arasında fark olmamasına rağmen, deksmedetomidin grubunda propofol grubuna göre duyusal blok geri dönüş zamanı anlamlı olarak uzun saptandı. Motor blok zamanı değerlendirildiğinde ise deksmedetomidin grubunda klinik olarak daha uzun olmasına rağmen gruplar arasındaki fark anlamlı düzeyde bulunmadı.

Kaya ve arkadaşları spinal anestezide duyusal blok süresi üzerine deksmedetomidin, midazolam ve serum fizyolojik solüsyonunun etkilerini karşılaştırmışlar ve çalışmamıza benzer olarak deksmedetomidinin spinal anestezi duyusal blok süresini arttırdığını belirtmişlerdir[28]. Alfa$_2$ adrenerjik agonistlerin lokal anesteziklerin motor ve duysal blok zamanlarını uzatma mekanizmaları tam olarak açıklanamamaktadır. Bu etkinin, α_2 adrenerjik agonistlerin lokal anesteziklerin sistemik absorbsiyonunu azaltmasına bağlı olamayacağı çünkü intratekal klonidinin bupivakain ile beraber uygulandığında bupivakainin plazma seviyelerini azaltmadığı bildirilmiştir[29,20]. Motor ve duyusal blok zamanlarının uzamasının, lokal anestezik ve α_2 adrenerjik agonistlerin farklı etki mekanizmalarının sinerjistik veya additif etkilerine bağlı olabileceği düşünülmektedir.

Sonuç olarak; deksmedetomidin sedasyonu, aksiller blok sırasında sağlanan duyusal bloğun geri dönüş süresini uzatır ve propofole benzer sedasyon sağlar. Aksiller blok sırasında duyusal blok süresini ve ilk analjezik gereksinim zamanını uzatması nedeniyle özellikle operasyon süresinde uzama beklenen olgularda deksmedetomidin ile sağlanan sedasyon, propofolün iyi bir alternatifidir. Deksmedetomidin, el ve ön kol cerrahisi için aksiller blok uygulanan hastalarda ciddi yan etki olmadan yeterli sedasyon seviyesi ile ek analjezi sağlar.

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Comparative Evaluation of the Lighted Intubation Stylet, Storz DCI Videolaryngoscope, and Macintosh Laryngoscope in Adult Patients

Erişkin Hastalarda Işıklı Entübasyon Stilesi, Storz DCI Videolaringoskop ve Macintosh Laringoskopun Karşılaştırılması

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ABSTRACT

AIM: *To compare a lighted intubation stylet (LIS), Storz DCI videolaryngoscope, and Macintosh laryngoscope regarding endotracheal intubation (ETI) times, the number of intubation attempts required, hemodynamic findings, and complications related to intubation-extubation.*

METHODS: *A total of 60 patients age 18–65 with American Society of Anesthesiologists score I-II and Mallampati score I-II, who were scheduled for elective surgery, were randomized into 3 groups: Group I, on which ETI was performed using the LIS; Group V, on which ETI was performed using the Storz DCI videolaryngoscope; and Group L, on which ETI was performed using the Macintosh laryngoscope. For each study group, ETI was applied by an operator who had previously performed at least 15 successful endotracheal intubations. Heart rates (HRs), mean arterial pressure (MAP), and peripheral oxygen saturation (SpO2) were recorded before and after induction, immediately, and 1, 2, 3, 4, and 5 minutes after ETI. However, ETCO2 was recorded immediately, and 1, 2, 3, 4, and 5 minutes after ETI. In addition, the number of attempts required to achieve ETI, ETI-related complications, and ETI times were noted. Potential complications were recorded immediately, and also 2 and 6 hours after extubation.*

RESULTS: *The demographic characteristics of the patients, ETI times, HR, MAP, ETCO2, and SpO2 did not differ between groups. Immediately after extubation, complications (stridor, coughing) were seen in 2 (10%) patients in Group L; however, they weren't observed in other groups (p=0.362). Sore throat was seen in Groups I (n=2; 10%), V (n=1; 5) and L (n=2; 10%) (p=0.804). Two hours after extubation, sore throat was observed in one (5%) patient in both Group I and L (p=0.596).*

CONCLUSION: *There wasn't difference between the LIS, Storz-DCI videolaryngoscope and Macintosh laryngoscope with respect to hemodynamic parameters, the number of ETI trials, ETI times, and related complications.*

Key words: *lighted intubation stylet; Storz DCI videolaryngoscope; Macintosh laryngoscope; intubation*

ÖZET

AMAÇ: *Erişkin hastalarda, lighted intubation stylet, Storz DCI videolaringoskop ve Machintosh laringoskop arasında endotrakeal entübasyon (ETI) süresi, entübasyon için girişim sayısı, entübasyon-ekstübasyon ilişkili komplikasyonlar, hemodinamik bulguların karşılaştırılması.*

YÖNTEM: *Çalışmaya, yaşları 18–65 arasında değişen, American Society of Anesthesiologists skoru I-II, Mallampati skoru I-II, elektif cerrahi uygulanacak 60 hasta dahil edildi. Hastalar rastgele üç gruba ayrıldı; Grup I: LIS ile ETI, Grup V: Storz DCI video laringoskop ile ETI, Grup L: Machintosh laringoskop ile ETI yapılan grup. ETI her çalışma grubu için en az 15 başarılı deneme yapan uygulayıcı tarafından yapıldı. Grupların kalp atım hızı (KAH), ortalama arter basıncı (OAB), periferik oksijen satürasyonu (SpO2), indüksiyondan önce, indüksiyondan sonra, ETI'dan hemen sonra, ETI'dan sonraki 1., 2., 3., 4. ve 5. dakikalarda kaydedildi. ETCO2 ise ETI'dan hemen sonra, ETI'dan sonraki 1., 2., 3., 4. ve 5. dakikalarda kaydedildi. Ayrıca ETI'nin kaçıncı denemede gerçekleştiği, ETI esnasında oluşan komplikasyonlar ve ETI süresi de tespit edildi. Ekstübasyon sonrası komplikasyonlar ise ekstübasyondan hemen sonra, 2. saatte ve 6. saatte kaydedildi.*

BULGULAR: *Gruplar arasında demografik özellikler, ETI süreleri, KAH, OAB, ETCO2 ve SpO2 açısından farklılık saptanmamıştır. Ekstübasyon sonrası komplikasyonlara bakıldığında ise ekstübasyondan hemen sonraki komplikasyonlar (stridor, öksürük) Grup L'de iki (%10) hastada görülürken diğer gruplarda görülmedi (p=0.362). Boğaz ağrısı ise Grup I'da 2 (%10), Grup V'de 1 (%5), Grup L'de 2 (%10) hastada görüldü (p=0.804). Ekstübasyon sonrası 2. saatte boğaz ağrısı komplikasyonu Grup I ve L'de birer (%5) hastada görüldü (p=0.596).*

SONUÇ: *Çalışmamızda, LIS, Storz-DCI Videolaringoskop ve Machintosh laringoskop karşılaştırıldığında hemodinamik parametreler, ETI deneme sayısı, ETI süresi ve komplikasyonlar açısından fark yoktu.*

Anahtar kelimeler: *ışıklı entübasyon stilesi; Storz DCI videolaringoskop; Macintosh laringoskop; entübasyon*

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Introduction

Endotracheal intubation (ETI) is the placement of a tube within the trachea in order to secure the respiratory tract and/or control respiration[1]. ETI was first performed by Curry in 1792 using a tactile method [1]. Later on, in 1895, Kirstein used a laryngoscope to achieve ETI, while in 1920, Magill used ETI with the intent to institute anesthesia[1].

ETI is routinely performed under general anesthesia, preferably following muscular relaxation. Under direct laryngoscopic visualization of the glottis, an endotracheal tube is inserted into the oral cavity and engaged in the trachea[1,2]. The development of digital technology has enabled the fabrication of video laryngoscopes for better visualization of the glottis[3]. Video laryngoscopes combine a standard laryngoscope blade with an endoscopic system[4]. In this system, the camera is mounted on an ergonomically designed laryngoscope handle to obtain a larger (king-size) view of the airway structures[4].

A lighted intubation stylet (LIS) is a long, flexible instrument with a battery in its handle and a light source mounted on its tip[5,6]. When LIS is placed within the trachea, a pretracheal glow can be easily seen, whereas when the laryngoscope is slipped into the esophagus, the pretracheal glow cannot be seen. Because of this advantageous characteristic of LIS, this stylet has been included in this algorithm for the management of difficult airways, as formulated by the American Society of Anesthesiologists (ASA)[7]. During insertion of the LIS, manipulation of the head and neck is rarely required, and a large mouth opening is not a must[8].

During ETI, stimulation of the laryngeal and tracheal tissues induces reflexive increases in sympathoadrenal activity, leading to the emergence of physiopathological changes such as tachycardia, and increases in blood, intracranial, and intraorbital pressure[1,9]. In healthy individuals, these reactive responses are generally well tolerated, while in patients with limited coronary or myocardial reserves, they can lead to myocardial ischemia or failure[9].

In our study, we aimed to compare the effects of these technological devices on the duration of ETI performed using a standard laryngoscope, the number of failed ETI attempts, hemodynamic responses, complications that might develop following intubation, and extubation procedures.

Material and Methods

In our double-blind, randomized, positive-controlled study, we compared the advantages and disadvantages of the LIS, Storz DCI videolaryngoscope, and Macintosh laryngoscope in patients who would undergo ETI procedures (Figure 1). Our study was performed in the Department of Anesthesiology and Reanimation after the approval of the Ethics Committee of Ondokuz Mayıs University, Faculty of Medicine was obtained in compliance with the directives of the Declaration of Helsinki.

A total of 60 patients age 18–65 with American Society of Anesthesiologists score (ASA) I-II and Mallampati score I-II who were scheduled for elective surgery were included in the study. Patients with a higher ASA risk (>II) and Mallampati (>II) scores, pregnant women, hypertensives, β-blocker users, obese (body mass index ≥ 30 kg/m^2) individuals, patients with complaints, and symptoms of coughing, stridor, foreign substance,

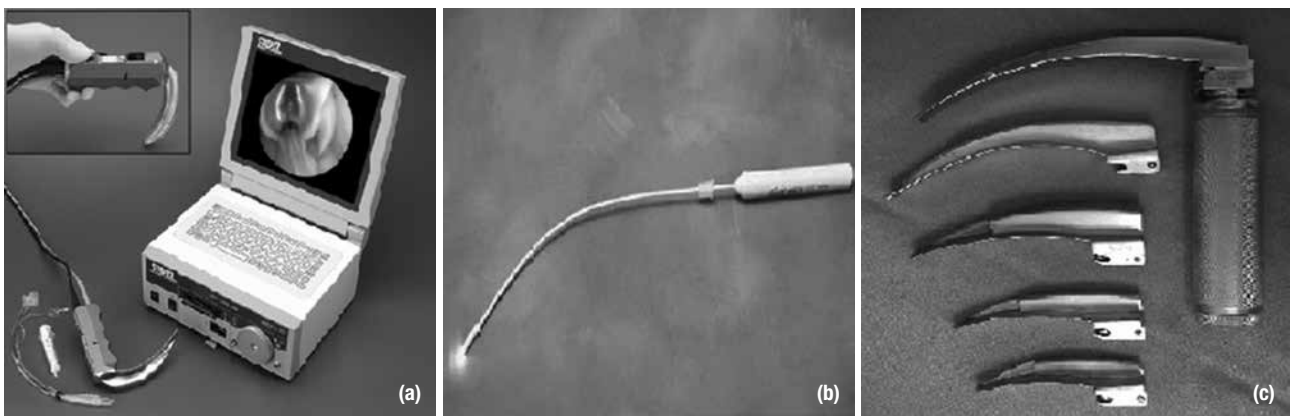

Figure 1. a–c. *Storz DCI Video Laryngoscope[19]* ***(a)****; Lighted Intubation Stylet[20]* ***(b)****; Macintosh Laryngoscope[21]* ***(c)****.*

tumour, polyp, and abscess in the upper respiratory tract were excluded from the study. Besides, patients for whom three ETI attempts failed were excluded from the study.

Signed informed consent forms were obtained from all study participants and then the patients were randomized into 3 groups based on random number tables. Each group consisted of 20 patients as follows:

Group I: ETI was performed using the LIS;

Group V: ETI was performed using the Storz DCI video laryngoscope;

Group L: ETI was performed using the Macintosh laryngoscope.

After positioning the patient on the operating table, monitorizations of the patients were performed based on electrocardiographic (ECG) examination results, noninvasive blood pressure, and peripheral oxygen saturation (SpO_2) measurements. For the induction of anesthesia, 2.5 mg/kg propofol IV, 0.5 mg/kg aritmal, and 1 μg/kg fentanyl were administered through an intravenous route. Muscle relaxation was achieved with IV 0.6 mg/kg rocuronium. All ETIs were performed by operators who had used the LIS, Storz DCI video laryngoscope, and Macintosh laryngoscope at least 15 times.

In Group I, all lights in the operating room were turned off and the mouth of the patient lying in a neutral position was opened. Then the patient's lower jaw was held and lifted up with the anesthetist's non-dominant (usually left) hand. With his/her dominant hand, the anesthetist held the LIS already placed in the tube and slid it over the midline of the tongue until the pretracheal glow was seen at the level of the cricothyroid cartilage. Then the stylet was withdrawn delicately with simultaneous insertion of the tube into the trachea.

In Group V, the Storz DCI video laryngoscope was held with the non-dominant hand and the patient's mouth was opened slightly. The patient's tongue was deviated to the left and a laryngoscope blade was inserted at the midline towards the oropharynx, then the tip of the blade was engaged in the vallecula. An endotracheal tube with its stylet was inserted from the right side of the mouth and its tip was advanced through the vocal cords, and the stylet was withdrawn.

In Group L, the Macintosh laryngoscope was held with the non-dominant hand of the anesthetist and the patient's mouth was slightly opened with his/her dominant hand. The tongue was placed to the left side of the blade and the tip of the blade was advanced towards the oropharynx, and engaged in the vallecula. When the rima glottis was visualized, an endotracheal tube was inserted from the right side of the mouth and advanced between the vocal cords.

In all groups, when auscultation of the lungs revealed equivalent pulmonary ventilation, the cuff of the endotracheal tube was inflated until the air-leak sound ceased. The position of the endotracheal tube was confirmed by an end-tidal carbon dioxide ($ETCO_2$) monitor, then the patient was connected to the ventilation system.

The heart rate (HR), mean arterial pressure (MAP), and SpO_2 of the patients were recorded before and after the induction of anesthesia, immediately, and 1,2,3,4, and 5 minutes after ETI. However, $ETCO_2$ was recorded immediately, and 1,2,3,4, and 5 minutes after ETI. Besides the number of interventions attempted to achieve ETI, complications occurred during the ETI procedure (bleeding, laceration, etc.) and procedural times were determined. Post-extubation complications (coughing, stridor, hoarseness, sore throat, and laryngospasm, etc.) were recorded immediately, and 2 and 6 hours after extubation.

The time that elapsed from opening the mouth to placing the endotracheal tube in the oral cavity up to the detection of the $ETCO_2$ was termed ETI time in Group I. However, in the other groups, the time from the placement of the laryngoscope blade into the oral cavity up to the detection of the $ETCO_2$ value was considered the procedural time. A 20% increase from baseline systolic arterial pressure was recorded and intervened with IV perlinganit at a dose of 1 μcg/kg.

Statistical Analyses

Data were analyzed using the statistical package for social sciences (SPSS) V.15. Assuming a statistical power of 80%and an alpha of 5%, 20 patients in each group were required to reach a statistical significance. The compatibilty of continuous data with normal distribution was evaluated using the Shapiro-Wilk test. Since SpO_2 values did not fit to the normal distribution curve, but medians, and other continuous variables demonstrated normal distribution, they were expressed as means ± standard deviation. For intergroup comparisons of continuous data which displayed normal distribution One-Way Analysis of Variance (ANOVA) and

Tukey HSD tests; for those incompatible with normal distribution Kruskal- Wallis Analysis of Variance were used. For pairwise comparisons of distinctly different parameters, the Mann-Whitney U test was employed. For intergroup comparisons of quantitative data, a multi-level *chi*-square test was used. $P<0.05$ was considered to signify a level of significance.

Results

No statistically significant intergroup difference was found for demographic characteristics, anesthesia, operative and ETI times, HR, MAP, $ETCO_2$, and SpO_2 (p>0.05) (Table 1 and 2) (Figure 2).

In all three groups, patients were intubated on the first attempt and no complications were observed following the ETI procedures.

As far as immediate post-extubation complications are concerned, stridor and coughing were only seen in 2 (10%) patients in Group L (p=0.362). Sore throat was observed in Groups I (n=2; 10%) and V (n=1; 5%) (p=0.804). Sore throat was also seen at the 2-hour mark following extubation (one patient in Groups I and L, respectively) (p=0.596).

Discussion

The achievement and maintenance of airway patency are among the essential responsibilities of an anesthesiologist[10]. A delay in the achievement of airway patency may cause hypoxia and subsequently anoxia, irreversible brain damage, or even death[10]. The perpetuation of vital functions depends on the achievement and maintenance of airway patency[10]. Therefore, making necessary preparations, taking required measurements, and ensuring the maintenance of the airway evaluation and the achievement of its patency are among the responsibilities of an anesthesiologist[10].

In failed cases of ETI, other alternatives to standard ETI have been applied. Among them, ETI procedures performed using a Storz DCI Video Laryngoscope and LIS can be enumerated[10].

Table 1. *Demographic distribution of the groups (mean ± standard deviation; n, %)*

	Group I (n=20)	Group V (n=20)	Group L (n=20)	*p*
Gender	10 (50%)			
Female	10 (50%)	10 (50%)	10 (50%)	0.500
Male		10 (50%)	10 (50%)	
*ASA				
I	16 (80%)	14 (70%)	12 (60%)	0.386
II	4 (20%)	6 (30%)	8 (40%)	
Age (years)	42.35±14.98	41.65±14.45	42.40±11.84	0.982
Mallampati Score				
I	10 (50%)	11 (55%)	12 (60%)	0.817
II	10 (50%)	9 (45%)	8 (40%)	

*ASA: American Society of Anesthesiologists.

Table 2. *Anesthesia, ETI, and operative times in all groups (mean ± standard deviation)*

	Group I (n=20)	Group V (n=20)	Group L (n=20)	*p*
Anesthesia time (min)	119.75±39.35	107.75±46.46	115.25±41.62	0.669
*ETI time (sec)	17.25±5.32	20.30±3.79	19.65±4.34	0.090
Operative time (min)	105.00±38.14	94.50±39.89	97.25±38.84	0.679

*ETI: Endotracheal Intubation.

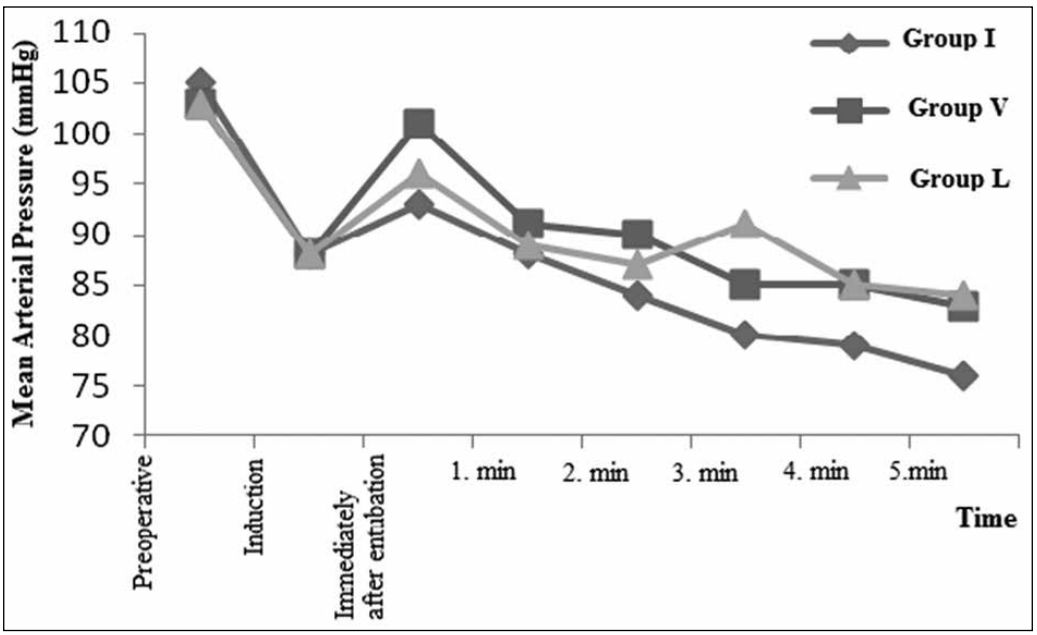

Figure 2. *Mean arterial pressure measurements of the groups.*

In their study, Sui et al. compared the Bonfils fiberscope and the LIS (Trachlight-TM), and detected shorter operative times for ETI procedures performed with the LIS[11]. However, Cavus et al. compared operative times for ETI performed using the C-MAC Video Laryngoscope or Macintosh laryngoscope[12]. Despite relatively longer operative times for ETI performed with the C-MAC Video Laryngoscope, they recommended the potential use of the C-MAC Video Laryngoscope as a standard ETI method for both management of airway patency and training purposes[12]. However, Healy et al. compared the use of a GlideScope, C-MAC, Storz-DCI Video Laryngoscopes, and Macintosh laryngoscope in a simulation mannequin, and obtained improved glottis visualization with the GlideScope, C-MAC, and Storz-DCI Video Laryngoscopes compared with the Macintosh laryngoscopes [13]. However, they observed longer ETI times with the GlideScope and Storz-DCI Video Laryngoscopes, relative to the Macintosh and C-MAC video laryngoscopes[13]. However, in our study, ETI times were similar in all groups. We think that these controversial outcomes cited in the literature might be associated with differences in the amount of experience the operators had with these laryngoscopes.

Park et al. compared the Airtraq video laryngoscope and LIS in the routine management of the respiratory airway and, as is seen in our study, no intergroup difference was found regarding ETI attempts, procedural time, and hemodynamic responses[14]. Turkstra et al. evaluated and compared the required mobility of cervical vertebra for the LIS, GlideScope Video Laryngoscope, and Macintosh laryngoscopy[15]. In conclusion, they observed minimal mobility of cervical vertebra during LIS when compared with other laryngoscopic procedures. This phenomenon may explain the lesser impact of ETI performed with the LIS on hemodynamic responses.

Montes et al. analyzed the effects of LIS and Macintosh laryngoscopy on hemodynamic response rates in patients with coronary artery disease and, as in our case, they couldn't find any difference between the two procedures (Montes et al., 2003). Still, similar to our study, in patients who had undergone LIS, somewhat lower hemodynamic values were detected. In other studies, also similar to our study, LIS affected hemodynamic values to a lesser extent than Macintosh laryngoscopy without any statistically significant difference between these procedures[16–18].

Friedman et al. compared the use of the LIS and Macintosh laryngoscopes, and detected relatively fewer complication rates with the use of the LIS[18]. Sue et al. compared the Bonfils fiberscope and LIS, and noted relatively lower complication rates with the use of the LIS[11]. Kihara et al. evaluated the Macintosh

laryngoscope, LIS, and Fastrach LMA for their relevant complication rates, and revealed higher complication rates with the use of Fastrach LMA, while they couldn't detect any difference in complication rates between the Macintosh laryngoscopy and LIS[17]. However, in our study, no difference was found between groups regarding complication rates.

In conclusion, in our study, no statistically significant difference was found among the LIS, Storz-DCI Video Laryngoscope, and Macintosh laryngoscope with respect to hemodynamic parametres, the number of ETI attempts, ETI procedural time, and related complications.

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Blefaropitoz Tedavisinde Frontal Askı Materyalleri: Klinik Sonuçlar*

Frontalis Suspension Materials for the Treatment of Blepharoptosis: Clinical Results

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ABSTRACT

AIM: *Assessment of frontalis suspension surgery with three different sling materials in patients with poor levator palpebrae function.*

METHODS: *Fourty one eyes of 31 blepharoptosis patients who underwent frontalis suspension surgery between 2005 and 2013 were evaluated retrospectively. Age, gender, levator function, and sling materials were recorded.*

RESULTS: *The mean age of the patients was 15,4 years (range: 2 months – 80 years). The male/female ratio was 3.42 (24/7). Bilateral surgery was performed in 10 patients, right side in 10 and left side in 11 patients. While 26 patients had congenital blepharoptosis, the duration for the others were changing 2 to 10 years. The mean levator function was 2.25 mm (range: 0–6 mm). The most used materials were silicone rod in 29, poliamide suture in 9, and autogenous fascia lata in 3 patients. The mean follow up was 19.8 months (range: 4 months – 8 years). The recurrence rates were 20.6% in silicone rod group, 11% in poliamide suture group, and 0% in autogenous fascia lata group.*

CONCLUSION: *Successfull results could be obtained in frontalis sling surgery with three different materials as silicone rod, poliamide suture, and autologus fascia lata.*

Key words: *blepharoptosis; surgery; frontalis suspension*

ÖZET

AMAÇ: *Levator fonksiyonu zayıf olan hastalarda uyguladığımız üç farklı frontal askı materyali ile yapılan cerrahileri değerlendirmek.*

YÖNTEM: *Kliniğimizde 2005–2014 yılları arasında blefaropitoz nedeniyle frontal askılama cerrahisi geçiren hastaların dosyaları retrospektif olarak tarandı. 31 hastanın 41 gözü çalışmaya dahil edildi. Hastalar yaş, cinsiyet, levator fonksiyonu ve cerrahide kullanılan askılama materyali açısından değerlendirildi.*

BULGULAR: *Hastaların yaş ortalaması 15,4 yıl (2 ay – 80 yıl) idi. Otuz bir hastanın 24'ü erkek, 7'si bayan idi. On hasta her iki gözden, 10'u sağ gözden, 11'i ise sol gözden cerrahi geçirmişti. Yirmi altı hastanın doğuştan beri blefaropitozu mevcuttu. Diğer hastaların 2-10 yıl arasında değişen kapak düşüklüğü şikayetleri mevcuttu. Ölçülebilen levator fonksiyonları 0 mm ile 6 mm (ort. 2,25 mm) arasında değişmekte idi. Materyal olarak 29 gözde silikon çubuk, 9 gözde polyamid sütür, 3 gözde otojen fasya lata kullanılmıştı. Hastaların takip süreleri 4 ay ile 8 yıl (ortalama 19,8 ay) arasında değişmekte idi. Fasya lata grubundaki 3 gözün hiçbirinde nüks görülmezken, polyamid sütür grubunda 1 gözde (%11) cerrahiden 1 ay sonra nüks gelişti ve hastaya tekrar frontal askılama yapıldı. Silikon materyal grubunda 6 gözde (%20.6) nüks gelişti.*

SONUÇ: *Blefaropitoz cerrahisinde kullanılan fasya lata, silikon çubuk ve polyamid sütür materyallerinin üçü ile de başarılı sonuçlar elde edilmektedir.*

Anahtar kelimeler: *blefaropitoz; cerrahi; frontal askılama*

Giriş

Frontal askılama tekniği, levator palpebra kasının fonksiyonunun yetersiz olduğu blefaropitoz olgularında kullanılan bir cerrahi yöntemdir. Bu cerrahi konjenital miyojenik blefaropitozda, blefarofimozis sendromunda, okülomotor sinir felçlerinde, Marcus-Gunn blefaropitozunda, kronik progresif oftalmopleji gibi birçok durumda tercih edilmektedir.

Frontal askılama cerrahisi için birçok materyaller denenmiştir. Bu materyallerden greft olarak hastanın kendisinden alınan fasya lata, başka bir hastadan alınıp saklanmış fasya lata, palmaris longus tendonu, sklera, temporal kas fasyası gibi greftler kullanılmıştır. Sentetik materyal olarak da polyamid sütür (Supramid), polipropilen sütür, ipek sütür, genişletilmiş politetrafloroetilen (ePTFE, Gore-Tex), silikon çubuk ve mersilen mesh gibi materyaller kullanılmıştır[1,2]. Otojen fasya latanın birçok çalışmada etkili bir materyal olduğu gösterilmesine rağmen, ek cerrrahi işlem gerekmesi, bacağın oftalmologlar için alışılmadık bir bölge olması,

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3 yaş altı çocuklarda fasya latanın yeterli büyüklüğe ulaşmamış olması gibi dezavantajları cerrahları farklı materyaller kullanmaya yönlendirmiştir[3–5].

Bu çalışmada, kliniğimizde blefaropitoz nedeniyle frontal askı cerrahisi uygulanan hastalarda kullanılan askılama materyallerinin etkinliğini, komplikasyonlarını ve nüks oranlarını araştırmayı amaçladık.

Gereç ve Yöntem

Kliniğimize 2005–2013 yılları arasında blefaropitoz nedeniyle başvuran levator fonksiyonu zayıf olan hastaların dosyaları geriye dönük olarak tarandı. Otuz bir hastanın 41 gözü çalışmaya dahil edildi. Çalışma, Helsinki Deklerasyonu 2008 prensiplerine uygun olarak yapıldı ve tüm hastalardan/velilerden aydınlatılmış onam alındı. Hastalar yaş, cinsiyet, blefaropitozun etiyolojisi, levator fonksiyonu ve cerrahide kullanılan askılama materyali açısından değerlendirildi. Hastaların muayenelerinde levator fonksiyonu, kapak aralığı, kapak refleks mesafesi ölçüldü.

Çocuklarda operasyona karar verilirken blefaropitozun görme aksını kapatması, ambliyopi riski, baş pozisyonu olması göz önünde bulunduruldu. Görme aksını kapatmayan hafif olgularda cerrahi önerilmedi (17 olgu). Yetişkin hastalarda operasyona karar verilirken görme aksını kapatmasının yanında, hastanın kozmetik isteği de değerlendirildi. Frontal askılama materyali olarak silikon çubuk, polyamid sütür ve otojen fasya lata kullanıldı. Çocuklarda genel anestezi altında frontal askılama yapılırken, erişkinlerde ise lokal anestezi tercih edildi.

Cerrahi yöntem olarak silikon çubuk kullanılan grupta, 11 no'lu bistüri ile kaş bölgesinin lateral ve medialine 1'er adet, alın bölgesine 1 adet yaklaşık 4–5 mm'lik kesiler yapıldı. Üst kapak cilt kesisi yapılarak tarsa ulaşıldı.5/0 polyester sütür ile silikon çubuk, 3 adet sütür ile tars yüzeyine sütüre edildi. Cerrahide Wright iğnesi yerine Karslioglu ve ark.' nın[6] tanımladığı alternatif bir yöntem olan içerisinden sütür geçirilmiş iğne ile önce kaş üzerindeki insizyonlardan sonra alındaki insizyondan geçilerek iki taraftan gelen materyal pitozis düzeltilecek şekilde düğümlendi.

Otolog fasya lata grubunda, diz fleksiyona getirilerek tensor fasya lata'nın gerginliği hissedildi. Dize yakın bölümden 1,5–2 cm'lik cilt kesisi yapılarak fasya lata bulundu. Fasya latanın bir kısmı fasya soyucu aletin içine yerleştirilerek cilt altından iliak kanada doğru yönelinerek alınabilecek en fazla fasya lata alındı. Alınan parça dikey uzun bir kesi ile iki kısma ayrıldı. Bir parça, tars üzerine gelecek şekilde santral-lateralden, diğeri yine tars üzerine gelecek şekilde santral-medialden geçecek şekilde Wright iğnesi ile yerleştirildi. Lateral kısma denk gelen parçanın her iki ucu yine lateral kaş bölgesinden olacak şekilde cilt altından aynı iğne ile çekildi. Medial parça için de aynı işlem yapıldı. Hem medial hem de lateraldeki greftler düğümlenerek, düğümlerin üstünde kalan kısımlar alın bölgesinde yapılan kesiden yine aynı iğne ile çıkarılarak birbirlerine düğümlendi. Cilt kesisi yapılan yerler 5/0 prolen sütür ile kapatıldı.

Polyamid sütür grubunda, sütürün kendi iğneleri olduğundan, materyali ilerletmek için herhangi ek bir alete ihtiyaç duyulmadı. Sütür önce tars bölgesinden ardından kaş bölgesinden geçilerek alın kısmında birbirine bağlandı.

Tüm vakalarda, alt kapak 5/0 ipek veya prolen sütür ile ile korneayı örtecek şekilde yukarı çekilerek alına sabitlendi (Frost sütürü). Cerrahiden sonraki birinci gün Frost sütürü açıldı. Hastaların cerrahi sonrası 1. gün, 2. hafta, 2. ay, 6. ay ve yıllık kontrol muayeneleri yapıldı.

Hastalara antibiyotikli pomad günde 3 kez 10 gün boyunca kullandırıldı. Çocuklarda sistemik antibiyotik ve analjezik önerildi.

Bulgular

Otuz bir olgunun 24'ü (%77,4) erkek, 7'si (%22,6) bayan hastadan oluşmaktaydı. Hastaların yaş ortalaması 15,4 yıl (2 ay – 80 yıl) idi. On hastaya her iki gözden, 10 hastaya sağ gözden, 11 hastaya ise sol gözden cerrahi uygulandı. Yirmi altı hastanın (%83,9) doğuştan beri blefaropitozu mevcuttu. Diğer hastaların 2–10 yıl arasında değişen kapak düşüklüğü şikayetleri mevcuttu.

Hastaların ölçülebilen levator fonksiyonları 0 mm ile 6 mm (ort. 2,25 mm) arasında değişmekte idi. Yedi hastada baş pozisyonu mevcuttu ve bu hastaların hepsi doğuştan blefaropitozu olan hastalardı. Blefaropitoz etyolojisi olarak 21 hastada konjenital blefaropitoz, 3 hastada blefarofimozis sendromu, 2 hastada Marcus-Gunn blefaropitozu, 1 hastada 3. kraniyal sinir paralizisine bağlı blefaropitoz, diğer 4 hastada ise involüsyonel blefaropitoz mevcuttu (Tablo 1).

Materyal olarak 29 gözde silikon materyal, 9 gözde polyamid sütür, 3 gözde otojen fasya lata kullanılmıştı (Tablo 2). Gruplar arasında sayısal uygunluk olmadığından dolayı gruplar arası istatistiksel çalışmalar

Tablo 1. *Blefaropitoz etiyolojisi*

Blefaropitoz etiyolojisi	Hasta sayısı	%
Konjenital	21 (26 göz)	67,7
Blefarofimozis sendromu	3 (6 göz)	9,7
Okülomotor sinir felci	1 (1 göz)	3,2
Marcus-Gunn blefaropitozu	2 (2 göz)	6,5
İnvolüsyonel blefaropitoz	4 (6 göz)	12,9
TOPLAM	31	100

Tablo 2. *Frontal askılama materyallerinde nüks oranları*

MATERYAL	Başarılı	Nüks
Silikon çubuk (29 göz)	23 göz (%79,4)	6 göz (%20,6)
Polyamid sütür (9 göz)	8 göz (%89)	1 göz (%11)
Otojen fasya lata (3 göz)	3 göz (%100)	0 göz (%0)

yapılamamıştır. Hastaların takip süreleri 4 ay ile 8 yıl (ortalama 19,2 ay) arasında değişmekte idi.

Silikon materyal grubunda 6 gözde (%20,6) nüks gelişti. Bu vakaların dışında 2 vakada cerrahi sonrası ilk haftada silikon materyalin kopmuş olduğu görüldü ve bu hastalara tekrar silikon materyal ile frontal askılama yapıldı. Postoperatif takiplerinde komplikasyon gelişmedi. Silikon materyal grubunda 2 hasta gözünü tam kapatamıyordu fakat bell fenomeni mevcut olduğundan herhangi ek bir müdahalede bulunulmadı. Polyamid sütür grubunda 1 gözde (%11) cerrahiden 1 ay sonra nüks gelişti ve hastaya tekrar frontal askılama yapıldı. Fasya lata grubunda nüks görülmedi.

Tartışma

Frontal askılama, levator fonksiyonun zayıf olduğu blefaropitoz hastalarında kullanılan bir cerrahidir. Frontal askılama materyali olarak birçok materyal denenmiş ancak görüş birliği sağlanamamıştır. Bunun yanında otojen fasya lata kozmetik sonucu en iyi, en az nüks blefaropitoz gelişen, en az komplikasyon olan materyaldir. Fakat, ek cerrrahi işlem gerekmesi, bacakta skar oluşması, 3 yaş altı çocuklarda fasya latanın yeterli büyüklüğe ulaşmamış olması gibi dezavantajları cerrahları farklı materyaller kullanmaya yönlendirmiştir[3–5,7].

Frontal askılama cerrahisinde amaç her ne kadar düşük olan göz kapağını kaldırmak olsa da, kaldırılan göz kapağının uzun dönemde tekrar inmemesi yani nüks olmaması daha öncelikli bir amaç haline gelmiştir. Nüks oranları çeşitli çalışmalarda farklı oranlarda çıkmaktadır. Wasserman ve ark.'nın yaptıkları çalışmada nüks oranı; otojen fasya lata ile %4,2, rezerve fasya lata %51,4, örgü polyester ile %27,3, poliprolen ile %12,5, monoflament naylon ile %69 olarak bulunmuştur. Enfeksiyon ve granülom oranı en düşük olarak fasya lata grubunda bulunmuştur.[2]

Ülkemizden Ünal ve ark.'nın 100 hastanın 141 gözünü değerlendirdikleri çalışmalarında, 72 gözde otojen fasya lata kullanılmış ve %94,4 (68 göz) oranında başarılı, %2,8 (2 göz) oranında tatminkar, %2,8 (2 göz) oranında başarısız olarak bulunmuştur. Gore-Tex ile askılama yapılanların %53,7'si başarılı, %31,7'si başarısız bulunmuş. Silikon çubukla askılama yapılanların %61.9'u başarılı, %14,3'ü tatminkar, %23,8'i başarısız bulunmuş. Mersilen mesh kullanılan 3 gözün 2'si başarılı, 1'i tatminkar, prolen sütür kullanılan 4 gözün 3'ü başarılı, 1'i tatminkar bulunmuştur[8].

Çalışmamızda en sık yöntem olarak silikon çubukla askılama yapılmıştır. Frontal askılamada kullanılan silikon çubuk ilk olarak 1966'da Tillett tarafından tanımlanmıştır[9].

Hazır olarak satın alınabilmesi, kolay bulunması, basit bir girişimle kapak seviyesinin tekrar ayarlanmasına izin vermesi, herhangi bir komplikasyon durumunda etraf dokulara entegre olmadığı için kolaylıkla çıkarılabilmesi gibi avantajlarından dolayı tercih edilmektedir[8,10]. Elastik yapısından dolayı silikon çubuk uygulanan hastalarda korneanın açıkta kalma riski daha az

olmaktadır. Carter ve ark. silikon materyalle yaptıkları çalışmada %7 oranında nüks olduğunu bildirmişlerdir[11]. Ünal ve ark. yaptığı çalışmada silikon çubuk kullanılan grupta %23,8 oranında nüks blefaropitoz rapor etmişlerdir[8]. Bizim çalışmamızda da literatüre yakın olarak nüks oranı %20.6 olarak görülmüştür.

Çalışmamızda polyamid sütür grubunda 9 gözün 1'inde (%11) cerrahiden 1 ay sonra nüks gelişti ve hastaya tekrar frontal askılama yapıldı. Takipler sırasında enfeksiyon veya granülom gibi herhangi bir komplikasyon görülmedi. Bu iki materyalle de olgu sayılarımız az olmakla birlikte literatürle uyumlu görülmektedir. Bu materyal ile yapılan cerrahilerin başarısı yüksek olmakla birlikte, maliyetinin yüksek olması dezavantajları arasında görülmektedir.

En etkili frontal askılama materyalinin otojen fasya lata olduğu oftalmoloji literatüründe sıkça vurgulanmaktadır. Bunun sebebini araştırmak için yapılan bir çalışmada fasya latanın fibroblast ve makrofajlar için bir köprü oluşturduğu, bu hücresel reaksiyonların zamanla kalıcı bir bağ dokusu meydana getirdiği, buna bağlı olarak da geç dönem sonuçlarının daha iyi olduğu belirtilmiştir[10]. Bizim çalışmamızda otojen fasya lata ile frontal askılama cerrahisi çok az bir rakam olarak 3 göze uygulanmıştı ve bu gözlerin hiçbirinde nüks görülmedi. Otojen fasya lata ve silikon çubuk ile yapılan frontal askılama sonuçlarının karşılaştırıldığı geniş serili iki çalışmada, Tök ve ark.[12], kozmetik başarı açısından iki grup arasında istatistiksel olarak anlamlı bir fark bulunmadığını bildirirken, Yüksel ve ark.[13], otojen fasya lata grubunda sonuçların anlamlı olarak daha iyi olduğunu bildirmişlerdir.

Sonuç

Blefaropitoz cerrahisinde kullanılan fasya lata, silikon çubuk ve polyamid sütür materyallerinin üçü ile de başarılı sonuçlar elde edilmektedir. Silikon çubuk, ek cerrahi gerektirmemesi ve diğer yöntemlere göre daha ucuz olması ile, polyamid sütür yüksek maliyeti, fasya lata ise yüksek başarısı ile ön plana çıkmaktadır.

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The Determination of the Antibacterial Activities of Rose, Thyme, Centaury and Ozone Oils Against Some Pathogenic Microorganisms

Ozon, Kantaron, Kekik ve Gül Yağlarının Bazı Patojenik Mikroorganizmalara Karşı Antimikrobiyal Aktivitelerinin Belirlenmesi

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ABSTRACT

AIM: *The increase in antibiotic-resistant bacteria has dramatically revived the interest in plant products as alternative antimicrobial agents to prevent the efficiency of pathogenic microorganisms. Our aim in this study is to show the antimicrobial activities of commercially obtained thyme, rose, centaury and ozone oils against the clinically important bacteria and yeasts.*

METHODS: *The antimicrobial activity of the thyme, rose, ozone and centaury oils were tested against Escherichia coli, Proteus vulgaris, Proteus mirabilis, Stenotrophomonas maltophilia, Enterococcus spp., Acinetobacter baumannii, Streptococcus spp., Citrobacter freundii, Staphylococcus aureus and Candida albicans strains. Disc diffusion method (Kirby-Bauer) was used to show the antimicrobial activity by measuring the zone diameters.*

RESULTS: *Most bacteria including Stenotrophomonas maltophilia (which is only sensitive to a few antibiotics) are found sensitive to the thyme oil. Gram positive bacteria and yeasts found more resistant than the Gram negative bacteria to the thyme oil. Escherichia coli and Staphylococcus aureus found sensitive to the rose oil. The anti-microbial activities of some herbal oils and ozone oil and rose oil were tried to be shown.*

CONCLUSION: *The thyme oil has a stronger antimicrobial activity than the rose, ozone and centaury oils. Herbal essential oils, especially thyme oil, are candidates to be alternatives in medical applications due to their anti-microbial effects.*

Key words: *bacteria; antimicrobial activity; disc diffusion method; herbal oils*

ÖZET

AMAÇ: *Antibiyotiklere dirençli bakterilerin sayısındaki artış, tedavi basamağında alternatif bitkisel ürünlerin kullanılmasına olan ilginin dramatik bir şekilde artışına da sebep olmuştur. Bu çalışmadaki amacımız, ticari olarak elde ettiğimiz ozon, gül, kantaron ve kekik yağlarının klinik olarak önemli bakteri ve mantarlara karşı olan antimikrobiyal etkilerinin gösterilmesidir.*

YÖNTEM: *Ozon, gül, kantaron ve kekik yağlarının Escherichia coli, Proteusvulgaris, Proteusmirabilis, Stenotrophomonas maltophilia, Enterococcus spp., Acinetobacter baumannii, Streptococcus spp., Citrobacter freundii, Staphylococcus aureus ve Candida albicans isimli mikroorganizmalara karşı antimikrobiyal aktiviteleri test edilmiştir; Disk difüzyon metodu (Kirby-Bauer) kullanılmış ve oluşan zon çapları ölçülerek anti-mikrobiyal etki ortaya konulmuştur.*

BULGULAR: *Sadece birkaç antibiyotiğe karşı duyarlı olan Stenotrophomonas maltophilia başta olmak üzere birçok bakteri, kekik yağına karşı duyarlı olarak tespit edilmiştir. Gram pozitif bakterilerin ve Kandida suşlarının kekik yağına, Gram negatif bakterilerden daha dirençli oldukları görülmüştür. Bunun yanı sıra Escherichia coli ve Staphylococcus aureus suşlarının ise gül yağına karşı duyarlı oldukları tespit edilmiştir. Bazı herbal yağların ve ozon yağının muhtemel antimikrobiyal etkileri bu çalışma ile ortaya koyulmaya çalışılmıştır.*

SONUÇ: *Kekik yağının antimikrobiyal etkinliği ozon, gül ve kantaron yağından oldukça yüksek düzeyde tespit edilmiştir. Sonuç olarak başta kekik yağı olmak üzere bitkisel uçucu yağlar, antimikrobiyal aktivitelerinden dolayı tıbbi ilaç uygulamalarına iyi bir alternatif olabilme potansiyeli taşımaktadır.*

Anahtar kelimeler: *bakteriler; anti-mikrobiyal aktivite; disk difüzyon testi; bitkisel yağlar*

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Introduction

A big percentage of the population uses herbal products for preventative and therapeutic purposes. The increase in antibiotic-resistant bacteria has dramatically revived the interest in plant products as alternative antimicrobial agents to prevent the efficiency of pathogenic microorganisms. A major group of plant antimicrobial compounds is represented by essential oils, which are complex mixtures of volatile secondary metabolites. They are mostly used in the food industry because of their preservative activity against food-borne pathogens, thanks to their antimicrobial, antibacterial, and antifungal properties[1,2].

Plant essential oils are generally isolated from non-woody plant material by distillation methods, usually by evaporation or hydro-distillation. These oils contains variable mixtures such as terpenoids, specifically monoterpenes [C10] and sesquiterpenes [C15] although diterpenes [C20] is also present, and a variety of low molecular weight aliphatic hydrocarbons acids (linear, ramified, saturated and unsaturated), alcohols, aldehydes, acyclic esters or lactones, nitrogen- and sulphur-containing compounds and homologues of phenyl-propanoids in their ingredients. Terpenes are one of the important chemicals responsible for the medicinal, culinary and fragrant uses of aromatic and medicinal plants[3].

Hypericumperforatum (centaury oil) is one of the best-studied medicinal plants all over the world and its chemical ingredients are well-characterized. The phytopharmaceuticals based on standardized extracts have been approved against mild to moderate depression and for the short-term treatment of symptoms in mild depressive disorders. Moreover, *Hypericumperforatum* can be effective in the treatment of somatoform disorders, anxiety disorder, sleep disorders, obsessive compulsive disorder and seasonal affective disorder[4–7].

In recent years, interest in natural products has increased, and medicinal plants have been investigated for various biological activities and therapeutic potentials[8]. Oil of thyme is derived from thyme, also known as *Thymus vulgaris*. Thyme also has a number of medicinal properties, which is due to the herb's essential oils. The health benefits of thyme essential oil can be attributed to its properties as an antispasmodic, antirheumatic, antiseptic, bactericidal, cardiac, carminative, cicatrisant, diuretic, expectorant, hypertensive, insecticide, stimulant and tonic substance. Oil of *Thymus vulgaris* has been shown to exhibit antimicrobial activities against pathogenic microorganisms[9,10].

Rosa damascena is popular in the world for its perfume[11]. This plant has several therapeutic effects such as treatment of menstrual bleeding, digestive problems, anti-inflammatory, the analgesic, anticonvulsant, antitussive, and bronchodilatory effects[12,13]. Addition to these activities, rose oil (*Rosa damascena*), has an antimicrobial performance against some microorganisms[14].

And the final oil which is used in this study is ozone oil. The biocidal activity of ozone reveals by a combination of its high oxidation potential, reacting with organic-material up to 3,000 times faster than chlorine, and its ability to diffuse through biological cell membranes[15].

Our aim in this study is to show the antimicrobial activities of these herbal oils and compare the possible antimicrobial effects.

Method

The essential oils of thymus, rose, centaury and ozone were screened for antimicrobial activity using an agar diffusion technique (Kirby-Bauer Disc Diffusion Method) against the following pathogenic microorganisms; *Escherichiacoli, Proteus vulgaris, Proteus mirabilis, Stenotrophomonasmaltophilia, Enterococcus faecalis, Acinetobacter baumannii, Streptococcus spp, Citrobacterfreundii, Staphylococcusaureus and Candidaalbicans.*

At first, *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 25923) and *Candida albicans* (ATCC 10231) were standard bacterial strains which provided from American Type Culture Collection (ATCC). Then, other microorganisms were isolated from the samples by using Automatic Bacteria Identification Machine (VITEK-2 Compact System, BioMerieux, France). Then identified bacteria were cultured with stock medium and stored at -80°C till the experiment day.

The fresh passages were performed before the study and for the inoculum, colonies were selected from 18-24 h old plates. Turbidity was visually adjusted to that of a 0.5 McFarland turbidity standard (1.5×10 ~ CFU/ml) using sterile Mueller-Hinton broth. Sterile filter paper disks were prepared to a diameter of 6.35 mm and sterilized in a Pasteur-oven, (at 170 ~ for 2 hour). On the other hand, essential oils and extracts were sterilized by passing through 0.22 mm pore-size membrane filters and then 20 HI (0.02 ml)

of the solution of essential oils was pipetted (0.1 ml) into the center of each disk to achieve the desired potency. By the way, the herbal oils were commercially provided. The manufacturer extraction protocol is seen in the following sentence: "It is extracted from the fresh or partly dried flowering tops and leaves of the plant by water or steam distillation and the yield is 0.7–1.0%". Also, the concentration of herbal oils were 100%.

To compare the antimicrobial activity of these oils, we used some standard commercial antibiotics onto these microorganisms such as Ampicillin 25μg (Oxoid, USA), Imipenem 10μg (Oxoid, USA), Gentamycin30μg (Oxoid, USA), Cefoxitine 30μg (Oxoid, USA) and Flucanozole 25μg (Oxoid, USA).

Disks were air-dried in a contamination free environment. *E.coli, P.vulgaris, P.mirabilis, S.maltophilia, E. faecalis, A.baumannii, Streptococcus spp, C.freundii, S.aureus and C.albicans* were swabbed onto the surface of Mueller-Hinton agar plates by rotating the plates approximately with a sterile cotton swab. Inoculated plates were allowed to stand for at least 3 minutes before applying antimicrobial disks.Disks were not placed closer to each other than 24 mm, measured from center to center. Plates were incubated at 37°C for 18–24 h. After overnight incubation, the diameter of the zone of inhibition around each disk was measured in mm. The measurement was performed by a scale and evaluated by 2 different microbiologists. The obtained data were compared with the standard antibiotics zone diameters which were evaluated according to The Clinical and Laboratory Standards Institute (CLSI) criteria.

Results

Antimicrobial activities of rose, thyme, centaury and ozone oils were determined by agar diffusion against nine pathogenic bacteria and yeasts. On the other hand, standard commercial antibiotics were also applied to the same pathogens. Rose oil was only effective on *E.coli* and *S.aureus* while centaury oil and ozonized oil have no antimicrobial effects of all microorganisms. However, rose oil zone diameters were quite low when compared with standard commercial antibiotics. Additionally, the thyme oil has a stronger antimicrobial activity than other oils, when the data were evaluated. It has no antimicrobial effects only on *A.baumannii* and *Candida albicans.* The biggest effect of thyme oil was detected on *Citrobacter* and *Streptococcus* strains. The zone diameters were 24 and 21 mm respectively. On the other hand, thyme oil had higher zone diameters from Gentamycin and nearly same diameters for cefoxitin (Table 1).

Table 1. *The data about the antimicrobial activity of oils*

	Bacteria									
Oils	E.coli	Proteus vulgaris	Proteus mirabilis	S.maltophilia	E.faecalis	Acinetobacter baumannii	Streptococcus spp.	Citrobacter freundii	S.aureus	Candida albicans
Rose	Zone ≥5 mm	No zone	No zone	No zone	No zone	No zone	No zone	No zone	Zone ≥3 mm	No zone
Thyme	Zone ≥19 mm	Zone ≥17 mm	Zone ≥17 mm	Zone ≥20 mm	Zone ≥19 mm	No zone	Zone ≥21 mm	Zone ≥24 mm	Zone ≥17 mm	No zone
Centaury	No zone	No zone	No zone	No zone	No zone	No zone	No zone	No zone	No zone	No zone
Ozone	No zone	No zone	No zone	No zone	No zone	No zone	No zone	No zone	No zone	No zone
Ampicilin	≥28 mm	≥21 mm	≥20 mm	Not applied	≥18 mm	Not applied	≥24 mm	≥26 mm	≥33 mm	Not applied
Imipenem	≥23 mm	≥21 mm	≥19 mm	Not applied	Not applied	≥16 mm	≥22 mm	≥20 mm	≥18 mm	Not applied
Gentamycin	≥18 mm	≥17 mm	≥15 mm	Not applied	Not applied	≥14 mm	Not applied	≥19 mm	≥15 mm	Not applied
Cefoxitin	≥19 mm	≥20 mm	≥22 mm	Not applied	Not applied	Not applied	Not applied	≥23 mm	≥25 mm	Not applied
Flucanozole	Not applied	Not applied	Not applied	Not applied	Not applied	Not applied	Not applied	Not applied	Not applied	≥18 mm

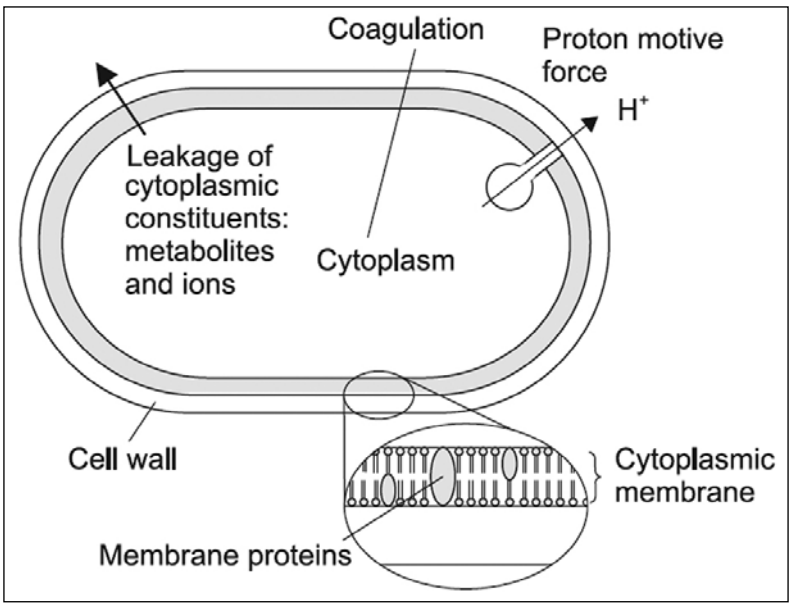

Figure 1. *Essential oils components effects: degradation of the cell wall, damage tocytoplasmic membrane, damage to membrane proteins, leakage of cell contents, coagulation of cytoplasm,and depletion of the proton motive force*[25].

Some antimicrobial agents which are routinely used in Microbiology Laboratories were used for this study to compare the antimicrobial activities. Ampicillin was the antimicrobial agent which had the largest diameter zones. Also imipenem had larger zones after ampicillin. At that point, it was seen that thyme oil had close diameter zones with these two important antibiotics. In addition, thyme oil was effective to all bacteria except *Acinetobacter baumannii*.

Discussion

One of the alternative strategies to eliminate antibiotic-resistant bacteria is the use of natural antimicrobial substances such as plant essential oils and their components[16]. On the other hand comparing the antibacterial effect of these plants is important for choosing the most appropriate ones. In this study, the effects of rose, thyme, centaury and ozone oils were determined and compared against 9 different pathogenic and resistant microorganisms.

The results of the present study indicate that the thyme oil has important antimicrobial effects on some pathogenic microorganisms. In our country, thyme was traditionally used to treat medical symptoms such as coughing, upper respiratory congestion, gastritis, bronchitis, spasm, sprains, stomach cramps, dysmenorrhea, dyspepsia, and urinary tract infection (Figure 1)[17]. Because of the ingredient of *Thymus vulgaris* (Thymol 10–64%, Carvacrol 2–11%, g-Terpinene 2–31%, p-Cymene 10–56%), it may has a strong antimicrobial activity as seen in this study[18,19]. It seems reasonable that mechanism of action of thyme oil would therefore be similar to other phenolic; this is generally considered to be the disturbance of the cytoplasmic membrane, disrupting the proton motive force (PMF), electron flow, active transport and coagulation of cell contents[20].

Other herbal oils were also evaluated and it was seen that rose oil has an antimicrobial activity. However, this activity was limited with 2 microorganisms. In the current literature, antibacterial effect of major components of rose oil (citronellal, geraniol and nerol) was reported previously[21–24]. Rose oil is a volatile oil obtained by distillation of the fresh flowers of *R.damascena*. The chief producing countries are Bulgaria, Turkey and Morocco[11]. The identified compounds from rose oils were; β-citronellal (14.5–47.5%), nonadecane (10.5–40.5%), geraniol (5.5–18%), and nerol and kaempferol were the major components of the oil[25]. The in vitro antibacterial activities of essential oil from R.damascene were also shown by disk diffusion testing against *E.coli, S.aureus and P.aeruginosa*. R.damascene showed antimicrobial activity against S.aureus in some studies[21]. Our results suggest that essential oils have potential use as

antimicrobials especially thyme and rose oils. Essential oils and main components of some of these oils, such as carvacrol, citronellal, geraniol, and nerol have been previously reported to have antibacterial effects[26].

On the other hand, there were no antimicrobial effects for centaury and ozone oils .n this study. No zone diameters were detected for these 2 oils. However, there must be 2 reasons to explain this issue. First one; the bacteria used in this study were selected from the most resistant to the most antibiotics and Extended spectrum beta-lactamase (ESBL) positives. And the second reason is that the oil dose might be inadequate. So, new doses experiments should be performed to put out the real data about the antimicrobial activities of ozone and centaury oils.

In conclusion, our study showed that because of strong antibacterial effects of the thymus and rose oil (Table 1). These oils can be used in treatment process as an alternative application structures. The intensive use of antibiotics has often resulted in the development of resistant strains.As found in this study,plant essential oils may be an alternative treatment options and may be used for elimination of some bacteria.

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Biatrial Volume Reduction Surgery in Management of Atrial Fibrillation

Atriyal Fibrilasyon Tedavisinde Biatriyal Hacim Küçültme Cerrahisi

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ABSTRACT

AIM: *In this study, we aimed to demonstrate the efficiency of biatrial volume reduction surgery and investigate the outcomes of the atrial mass decrease in the treatment of atrial fibrillation (AF) among the patients with a significant increase in atrial diameter. It is performed together with mitral and tricuspid valve surgery together with the ablation procedure in patients with AF.*

METHODS: *Between March 2012 and January 2015, twenty-three cases with mitral valvular pathology with coexisting AF and biatrial dilatation treated with biatrial volume reduction operation along with the mitral and tricuspid valve surgery were included the study. Preoperative and postoperative data were retrospectively evaluated.*

RESULTS: *Out of twenty-three patients, twelve patients were applied tricuspid ring annuloplasty and eleven patients were treated with DeVega annuloplasty. Mitral valve replacement (MVR) process was performed in all 23 patients. Biatrial volume reduction was done in all patients. While the preoperative left and right atrial diameters were 70±20 mm and 65±21 mm, the average of postoperative left atrial and right atrial diameters were measured 50±14 mm and 45±8 mm respectively. Sinus rhythm was achieved in all patients at the end of the operations.*

CONCLUSION: *One of the important factors affecting the success of the treatment of AF is the atrium diameter. The sizes of both atria in the electrophysiological studies are seen as the most important factor for the development of permanent AF. Atrial volume reduction operations are thought to be necessary for the achievement of sinus rhythm.*

Key words: *atrial fibrillation; biatrial volume reduction; ablation; surgery*

ÖZET

AMAÇ: *Bu çalışmada, atriyum çapları ileri derecede artmış atriyal fibrilasyon (AF) hastalarında, biatriyal hacim küçültme ameliyatlarının etkinliğinin gösterilmesi ve atriyum kütlesindeki azalmanın AF tedavisi üzerindeki etkilerinin araştırılması amaçlanmıştır. Atriyum küçültmesi, AF hastalarında mitral ve triküspid kapak cerrahisine ek olarak ablasyon işlemi ile birlikte uygulanmıştır.*

YÖNTEM: *Mart 2012 ile Ocak 2015 tarihleri arasında mitral ve triküspid kapak patolojisi ile birlikte biatriyal dilatasyonu olan ve tedavisinde mitral ve triküspid kapak cerrahisi ile birlikte biatriyal hacim küçültme operasyonu uygulanan yirmiüç AF hastası çalışmaya dahil edildi. Preoperative ve postoperative veriler retrospektif olarak incelendi.*

BULGULAR: *Yirmi üç hastanın, onikisinde triküspid ring annuloplasti, onbir hastada ise DeVega annuloplasti uygulandı. Hastaların tümünde mitral kapak replasmanı (MVR) yapıldı. Biatriyal hacim küçültme tüm hastalara uygulandı. Ortalama preoperatif atrium çapları sol ve sağ sırasıyla 70±20 mm ve 65±21 mm iken, postoperatif sol ve sağ atrial çaplar, sırasıyla 50±14 mm ve 45±8 mm olarak ölçüldü. Postoperatif atriyal çaplarda belirgin azalma sağlandı. Tüm hastalar operasyon sonunda sinüs ritmine döndü.*

SONUÇ: *AF tedavisinin başarısını etkileyen önemli faktörlerden biri de atrium çapıdır. Elektrofizyolojik çalışmalarda, atriyum boyutlarının kalıcı AF gelişmesinde en önemli faktörlerden biri olduğu gösterilmiştir. Sinüs ritminin yakalanmasında atriyum hacim küçültme ameliyatlarının gerekli olduğunu düşünmekteyiz.*

Anahtar kelimeler: *atriyal fibrilasyon; biatriyal hacim küçültme; ablasyon; cerrahi*

Introduction

Atrial fibrillation (AF) is a cardiac rhythm anomaly affecting 0.4–1% of all population. It is demonstrated in 40–60% of the patients with mitral valvular disease and 5–10% of the patients scheduled for coronary artery bypass grafting (CABG) operation[1]. Additionally, 2% of all patients with AF demonstrates no cardiopulmonary pathology[2]. Prevalence is higher in older age, male gender, and in the presence of impaired left ventricular function. Failure rates of medical treatment are 50% at the end of the first year and 84% at the end of the second year[3]. The success rates of the radiofrequency

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ablation (RFA) during mitral valve surgery are still unsatisfactory regarding the treatment of AF. Atrium diameter directly affects the success of the treatment[4].

The arrhythmia surgery for the treatment of AF has a significant role in valvular pathologies with the developments in heart surgery. Various surgical methods were performed for the AF treatment so far. In 1914, Garrey reported that the mass size of the atrium is important in the formation and the continuation of AF. Surgical remodelling of the atria was considered as an important factor for the treatment of AF via preventing the macro-waves due to the increased atrial mass[5]. As soon as the macro-waves were blocked, a normal sinus activation could be achieved with the Maze procedure or RFA. In most studies, a direct relationship between the surgical correction of AF and the reduction of atrial size was demonstrated. Regarding the conversion to the sinus rhythm, left atrium (LA) diameters below 45 mm reveals a nearly 100% success with the Maze procedure[6]. Left atrial isolation procedure was initially applied in 1980 by Cox and his colleagues. Atrioventricular (AV) node catheter ablation was performed in 1982 by Scheinman, and the corridor method was used by Guiraudon in 1985. Then the atrial transaction procedure has been developed. None of these methods had a provision of sinus rhythm, AV synchronization or eliminating the risk of thromboembolism. However, Maze (cut and sew) operation that was introduced in 1980 by James Cox and his colleagues achieved significant progression in this area. High success was obtained with Cox-Maze III method in patients with AF, which was refractory to medical treatment[7].

Regarding the atrial remodeling, weight, area, maximum and minimum dimensions of the atria are considered equally for the permanent treatment of AF. The size of both atria in the electrophysiological studies are seen as the most important factor for the formation of permanent AF[8]. For this reason, the success of RFA treatment for AF during mitral valve surgery mostly depends on the atrial volume reduction surgery. Additionally, growth of atrium in mitral valve disease accompanies the respiratory system dysfunction due to mechanical compression. Especially, in case of a giant left atrium, complications related to the bronchial compression of the lungs have reported[9].

In this article, we report a series of atrial volume reduction surgery in 23 cases presented with a simultaneous AF and mitral and tricuspid valve disease requiring mitral and tricuspid valve surgery.

Patient and Methods

The study was performed multicentrically by the cardiovascular surgery departments of Ahi Evren Thoracic and Cardiovascular Surgery, Trabzon, Turkey and Private Sevgi Hospital, Kayseri, Turkey. Twenty-three cases with mitral valvular pathology with coexisting AF and biatrial dilatation were included in the study between March 2012 and January 2015. Biatrial volume reduction operation was performed in all cases along with the mitral and tricuspid valve surgery. Right and left atrial diameters were measured preoperatively and postoperatively by using Transthoracic echocardiography (TTE) and trans-esophageal echocardiography (TEE). Data were collected retrospectively. Patient demographics and cardiac parameters were demonstrated in Table 1. Accompanying comorbidity and cross-clemp time were given in Table 2.

Table 1. *Patient demographics and cardiac parameters*

The average age	47±12
Gender (F/M)	14 / 9
Mitral Stenosis (Moderate & Severe)	10
Mitral Insufficiency (Moderate & Severe)	8
Mitral Stenosis + Mitral Insufficiency	5
Additional tricuspid Insufficiency	23
Preoperative. Left and right atrial diameter	70±20 mm / 65±21 mm
Postoperative. Left and right atrial diameter	50±14 mm / 45±8 mm
Percentage of patients with atrial fibrillation	% 100
NYHA Classification	Class 3 (%91); Class 4 (%9)
The average LVEF	% 50±5
Average arterial blood pressure	80±6 mmHg
Average pulmonary artery pressure	41±9 mmHg
Pulmonary vascular resistance	3.2±1.4 mmHg
Cardiac index (L/min/m^2)	2.6±0.7
Stroke volume index (ml/m^2)	36±6

mm: milimeter, LVEF: Left Ventricular Ejection Fraction, NYHA: New York Heat Association.

Table 2. *Comorbidity and cross-clemp time*

Diabetes	3
Hypertension	8
COPD	2
Preoperative antiarrhythmic	20
Patients over 60 years	0
Cross-clamp time (min)	73.43±14.21

COPD: Chronic Obstructive Pulmonary Disease

Surgical Technique

Mediastinum was reached under general anesthesia with median sternotomy. Extracorporeal circulation was established with a standard aortic and venous bicaval canulation. Cardiac arrest was achieved with moderate hypothermia (28–32 C°). Antegrade cardioplegic solution with a dose of 10ml/kg was given after the aortic x-clemp was placed. Intermittant cardioplegia was administered via retrograde cannula through the coronary sinus in every twenty minutes. Standard mitral valve replacement (MVR) with mechanical prosthetic heart valve was performed in all patients. DeVega or ring annuloplasty was performed in all patients as they all had additional tricuspid insufficiency. RFA was applied to all patients. Transseptal biatrial volume reduction was achieved by the superior transeptal approach to all patients (Fig. 1). Patients were followed for one-year postoperatively in terms of the AF recurrence.

Results

Nine of the cases were females, and 14 were men. The average age was 47±12 years. Average preoperative left and right atrial diameters were measured at 70±20 mm and 65±21 mm respectively (Fig 2). MVR operation was performed in all 23 patients. Tricuspid ring annuloplasty was performed in 12 patients. Eleven patients were treated with DeVega annuloplasty. Tricuspid annuloplasties were performed following MVR procedures. Biatrial volume reduction was achieved in all patients. No revision operation was needed postoperatively due to bleeding or any other reasons. None of the patients required pacing. The average of postoperative left atrial and right atrial diameters were measured 50±14 mm and 45±8 mm respectively. Amiodarone was started to all patients postoperatively as an antiarrhythmic. After being followed two days in intensive care and 5–6 days in service they were discharged. Patients were followed one year after their operation. No mortality was occurred in one year. After one-year follow-up, 14 patients (60.86%) were in sinus rhythm, 6 patients (26.08%) were in paroxysmal AF and 3 patients (13.06%) were in permanent AF.

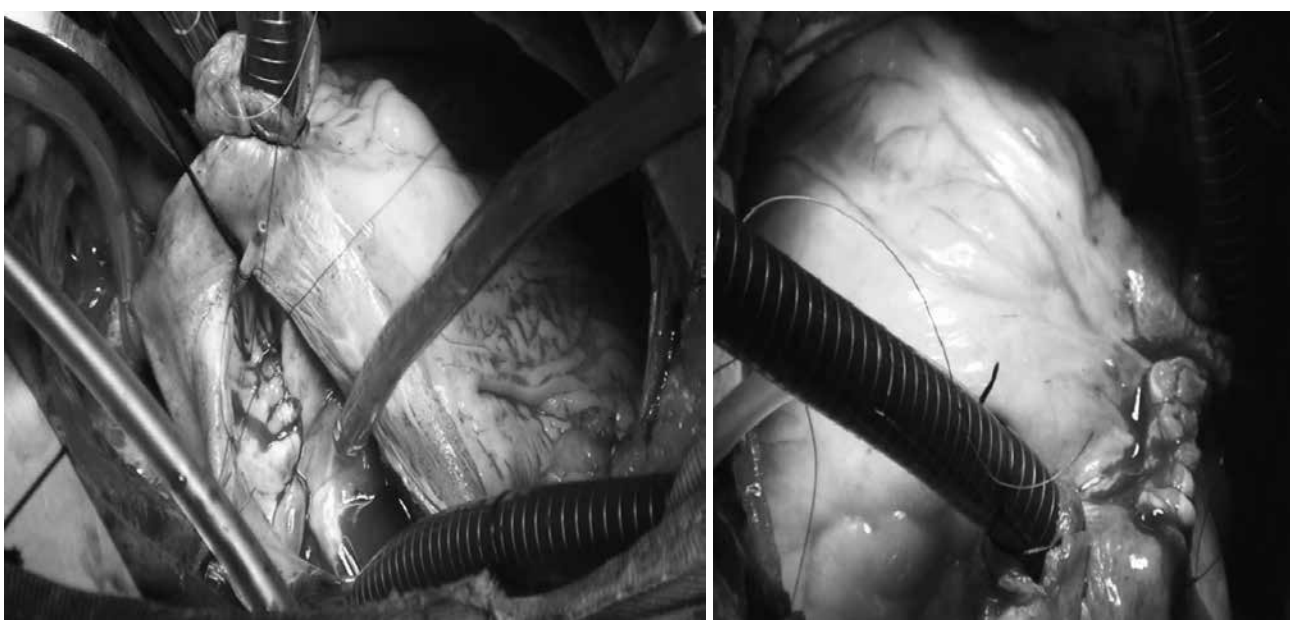

Figure 1. a, b. *Intraoperative pictures of left (**a**) and right (**b**) atrial remodelling.*

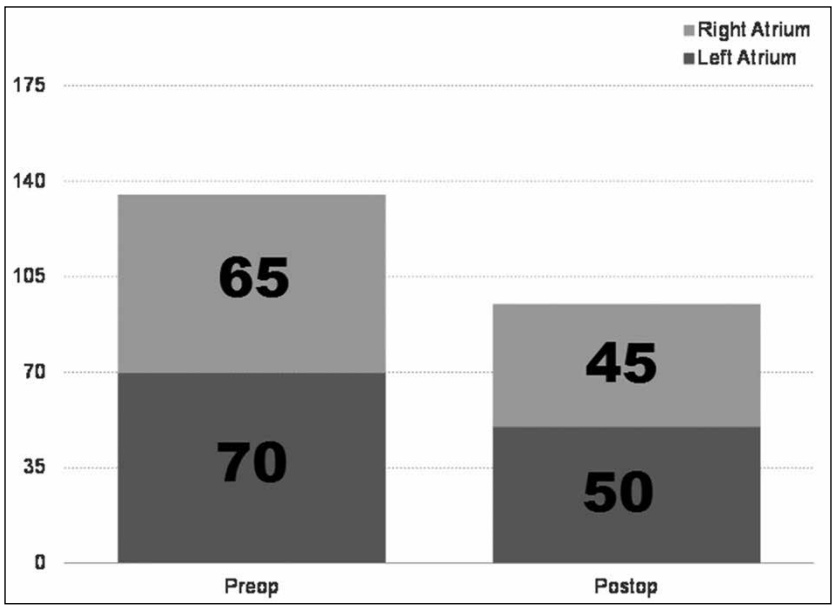

Figure 2. *Preoperative and postoperative atrium diameters.*

Discussion

Regarding the mitral valve surgery, AF becomes determinant as a permanent risk factor for the mortality[1]. The potential ventricular proarrhythmic effects of antiarrhythmic drugs were also demonstrated in various studies[10]. For this reason, consideration of the arrhythmia surgery along with mitral valve surgery should be evaluated as a treatment of choice in AF patients[3]. In our study, we performed AF operation with valvular correction as well as atrial resizing. In most studies, electrical activations in the right atrium proved to be more complicated than the left atrium and associated with the presence of permanent AF. It was also revealed that the left atrium isolation would not only be sufficient, but insulation in the right atrium was also necessary[2]. For this reason, re-entry activations in the right atrium necessitate biatrial incision and the pulmonary isolation as a complete treatment. Surgical blocking of the activation of both atria achieved an 89% success in providing the sinus rhythm[4]. In addition, the recurrence of AF is greater in a large atrium[5]. Prevention of postoperative thromboembolic complications and restoration of the impaired hemodynamic status are considered as the supplementary objectives of the atrium reduction operation. Left ventricular pressure is decreased by the left atrial de-sizing as the posterobazal wall of the heart would no longer be compressed by the atrial mass. It is known that large atrium tissue and its extent causes paroxysmal arryythmia in patients with a chronic AF[3]. In order to prevent these complications, resection and plication techniques during mitral valve surgery have been reported for the left atrial volume reduction[5].

In this study, the valvular pathologies were surgically corrected as well as the atrial sizes were reduced. The mean preoperative left and right atrium diameters were 70±20 mm and 65±21. However, the postoperative diameters were reduced to 50±14 mm and 45±8 mm respectively (Fig. 2). This data indicates 20±6 mm volume reduction in left atrium (40% of reduction) and 25±12 mm in right atrium (35.7% of reduction). These measurements indicates the efficiency of our surgical method in reduction of the atrial diameters. The atrial diameters are not only enough in maintaining the sinus rhythm. Regarding the surgical treatment of AF, left atrial ablation including mitral annulus is also essential for the maintenance of the sinus rhythm[7]. However, the size of the mass of atrial tissue is also known to be important for macro-waves. Biatrial reduction is an ideal method of treatment to restore the normal atrial geometry. Isolation of the left atrium appendix alone cuts leading AF foci and restricts re-entry fields[11].

Out of twenty-three of patients, 14 of them (60.86%) maintained their sinus rhythm after one year following the surgery. Nine patients were lost the sinus rhythm. Out of these nine patients, six patients were in paroxysmal atrial tachycardia and three patients were turned

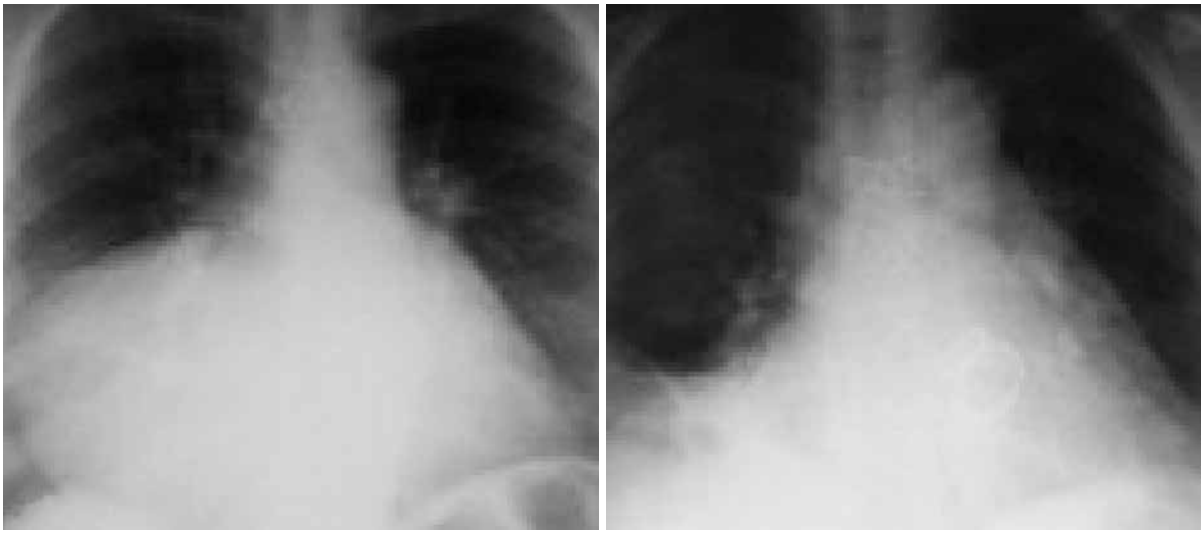

Figure 3. a, b. *Preoperative (**a**) and postoperative (**b**) demonstration of biatrial size in direct roentenogram.*

into AF permanently. What was the reason for them to regain the AF? Should atrial reduction or the Maze procedure be blamed? The reason of this may be due to the ineffectively performed Maze procedure. It may also be related to the reccurrent progressive re-enlargement after the surgery[11]. The atria may reach the initial size by re-enlargement even after an volume reduction surgery[1]. In our study the postoperative measurements of the both atria were observed unchanged even in patients with reccurrent AF occurred after one year following the surgery. This may be due to the increased pressures inside the atria[11]. However, the exact mechanism can't be strictly identified due to the lack of enough information.

Biatrial reduction is an ideal method of treatment to restore the normal atrial geometry. Isolation of the left atrium appendix alone cuts leading AF foci and restricts re-entry fields[12]. On the other hand, remaining unoperated large left atrium may further cause respiratory failure and low postoperative cardiac output that are frequently seen after mitral valve surgery[4]. In our study, RFA was also applied to all cases together with an aggressive volume reduction and suggested to be useful in establishing the sinus rhythm along with respiratory function improvements (Fig. 3).

Conclusion

Consideration of the surgical treatment in mitral and tricuspid valvular diseases should accompany with the antiarrythmic surgical options, if the patient is suffering AF. The atrial volume reduction method and the Maze procedure are the two options regarding the antiarrythmic surgical treatment. In this study, both options were used together in AF patients. The usage of these two surgical procedures together in cases with AF undergoing a valvular correction surgery may improve postoperative AF incidence in these patients. However, investigations with a limited number of cases need to be supported by larger study populations in the future.

Conflict of Interest

No conflict of interest was declared.

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Streptozotosin ile Deneysel Diyabet Oluşturulan Sıçanlarda Östrus Siklusunun Değişik Evrelerinde Ovaryum ve Uterus Dokularında Mast Hücrelerinin Dağılımının Histokimyasal ve İmmünohistokimyasal Olarak İncelenmesi

Streptozotocin-Induced Diabetic that Histochemical and Immunohistochemical Examination of Mast Cells Distribution in Ovary and Uterus During Different Stages of Estrous Cycle in Rats

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ABSTRACT

AIM: *The objective of this study was to evaluate in the ovary and uterus distribution of mast cells at histochemical and immunohistochemical in the diabetic rats.*

METHODS: *In the present study 64 adult female wistar albino rats were used. Subjects have been randomly separated into 8 different groups, four of which constituted the control group while the remaining four were the actual experimental group. Diabetes was induced by intraperitoneal injection of 60 mg/kg streptozotocin; the control group received physiological saline (5 mL kg–1). At the end of this period, both groups were processed for every cycle after detecting their menstrual cycles according to the vaginal smear findings.*

RESULTS: *Higher mast cell (MC) numbers were observed by toluidine blue staining in ovary of experimental groups, and the least dioestrous phase of the oestrous cycle compared with other diabetic groups. However, the highest mast cells were observed in metoestrous phase, and the least cells pre-oestrous phase of the oestrous cycle. Tryptase and chymase immune staining control and diabetic rats, tryptase and chymase-positive mast cells were the most intense phase of met-oestrous.*

CONCLUSION: *As a result, depending on the estrous cycle, it has changed and that the change in the distribution of mast cells in the ovary and the uterus was found to be a significant impact of diabetes.*

Key words: *oestrus cycles; mast cells; diabetes mellitus; ovary; uterus*

ÖZET

AMAÇ: *Bu çalışmada, diyabetik sıçanların ovaryum ve uteruslarında mast hücrelerinin dağılımının histokimyasal ve immunohistokimyasal olarak incelenmesi amaçlandı.*

YÖNTEM: *Çalışmada, 64 dişi Wistar Albino sıçan kullanıldı. Denekler, rastgele 4'ü kontrol, 4'ü ise deney grubu olmak üzere toplam 8 gruba ayrıldı (n=8). Deney grubunda diyabet oluşturmak için deneklere 60 mg/kg oranında streptozotosin (STZ) uygulandı. Deney sonunda vajinal smear bulgularına göre menstural siklus evreleri saptanarak her evre için deney ve kontrol gruplarında 8 sıçan işleme alındı.*

BULGULAR: *Toluidine mavisi ile yapılan boyamada, deney grubu ovaryumlarında mast hücreleri en yoğun östrüs, en az ise diöstrüs evresinde tespit edildi. Bununla birlikte diyabetik endometriyumda mast hücresi en fazla metöstrüs, en az ise proöstrüs evresinde gözlemlendi. Triptaz ve kimaz immun boyamasında, kontrol ve diyabetik sıçanlarda, triptaz ve kimaz pozitif mast hücresi en yoğun metöstrüs evresinde tespit edildi.*

SONUÇ: *Sonuç olarak, östrüs siklüsüne bağlı olarak ovaryum ve uterusda mast hücre dağılımının değiştiği ve bu değişimde diyabetin önemli etkisi olduğu tespit edildi.*

Anahtar kelimeler: *östrus siklusu; mast hücreleri; diabetes mellitus; over; uterus*

Giriş

Diyabet, özellikle son yıllarda gelişmiş ülkelerde artmakta ve Dünya Sağlık Örgütü (DSÖ) tarafından "salgın" olarak nitelenmekte olup karbonhidrat, yağ ve protein metabolizması bozukluğu ile seyreden kronik bir metabolizma hastalığıdır[1]. Diyabet ve etkileri ülke ekonomilerine ciddi bir yük getirmektedir. Bu yükün Türkiye için yıllık maliyeti yaklaşık 3 milyar doların üzerinde olduğu tahmin edilmektedir[2].

Diyabet, hastalarda çeşitli komplikasyonlara neden olmaktadır. Kardiyovasküler rahatsızlık riskini arttırmakta[3], retinopati ile körlük meydana getirebilmekte[4],

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hamileliği olumsuz etkileyebilmektedir[5]. Bu etkilerinden dolayı birçok deneysel hayvan modeli oluşturularak diyabet incelenmektedir[3].

Memeli canlılarda, erişkin dönemde hayvan türüne göre değişen sürelere sahip genital siklus (östrüs) izlenmektedir[6]. Bu siklus; insan, fare ve sıçan gibi canlılarda proöstrus, östrus, metöstrus ve diöstrus olmak üzere birbirini takip eden dört evreden meydana gelmektedir[7]. Menstrüel siklüsdeki hormonal değişikliklerden başta vajina olmak üzere tüm genital kanal organları etkilenmektedir.

Mast hücreleri sitoplazmik granüllerinde histamin, heparin, triptaz, kimaz, eozinofil kemotaktik faktör-A (ECF-A) gibi serin proteinler bulunduran bağ dokusunun immünolojik hücrelerindendir. Mast hücreleri organizmada özellikle dış ortam ile bağlantılı doku ve organ kompartmanlarında ve özellikle kan damarları yakınlarında lokalize olma eğilimi gösteren hücrelerdir[8,9]. Mast hücreleri, granüllerinde bulunan sülfatlanmış glikozaminoglikanların (heparin) varlığı nedeniyle bazik (TB, metilen mavisi, tiyonin vb.) boyalar ile boyandığında metakromazi gösterirler[10]. Yapılan çalışmalarda, genital siklusa bağlı olarak ovaryum ve uterusta mast hücresi dağılımının değiştiği rapor edilmiştir[9].

Yapılan literatür taramalarında, ovaryum ve uterus dokularında deneysel diyabete bağlı olarak mast hücresi dağılımını immunohistokimyasal metotlarla gösterir çalışmaya rastlanılamadı. Mast hücreleri doku içi hemostazisin ayarlanmasında önemli roller oynayarak, ovaryumlarda folikülogenezis ve uterusda ise endometriyum yenilenmesinde önemli görevler almaktadır. Diyabette görülen folikül gelişim kusurları ve endometriyumundaki immun yanıtta mast hücrelerinin fonksiyonları tam olarak aydınlatılamamıştır. Planlanan bu çalışmada, deneysel diyabet oluşturulmuş sıçanların ovaryum ve uterus dokularında östrus siklusuna bağlı olarak mast hücrelerinin dağılımındaki değişimlerin histokimyasal ve immünohistokimyasal metotlarla ortaya konularak literatüre katkı sağlanması amaçlandı.

Gereç ve Yöntemler

Çalışmada, ağırlıkları 250–300 g arasında değişen, Trakya Üniversitesi Tıp Fakültesi Deney Hayvanları Birimi'nde üretilmiş, 64 adet erişkin Wistar albino dişi sıçan kullanıldı. Denekler deney süresi boyunca, optimum laboratuvar koşulları altında (22±10C, 12 saat karanlık/aydınlık), günlük içme suyu ve %21 ham protein içeren pelet yemlerle (Purina) beslendi. Çalışma için Trakya Üniversitesi deney hayvanları etik kurulundan TÜHDYEK-2012/45 protokol no.lu izin alınarak çalışma başlatıldı.

Çalışma başlangıcında, hayvanların tartımları yapılarak tamamı bir gece aç bırakıldı. Ertesi sabah bütün hayvanların açlık kan şekerleri (IME-DC, Almanya) ölçüldü. Ölçüm sonunda elde edilen kan değerleri ile (en düşük 52 mg/dl; en yüksek 136 mg/dl) hayvanların sağlıklı oldukları tespit edildi. Çalışmamızda hayvanlar rastgele Kontrol grupları ve Diyabetik gruplar olarak ikiye ayrıldı. Otuz iki sıçan kontrol gruplarını oluşturmak için ayrıldı ve herhangi bir uygulama yapılmadı. Diyabet gruplarının oluşturulması için 32 sıçana 60 mg/kg tek doz intraperitoneal streptozotosin (STZ) uygulanarak 48 saat beklendi. İkinci günün gecesinde STZ uygulanan hayvanlar aç bırakılıp sabah tekrar kan değerleri ölçüldü. Ölçümde elde edilen değerler ile (en düşük 320 mg/dl, en yüksek 541 mg/dl) hayvanların diyabet olduklarına karar verildi. Ölçüm sonunda 18 gün (ilk STZ uygulamasının ardından 21 gün) beklendi. Yirmibir (21) gün sonra vajinal smear yöntemiyle deneklerin östrus siklusu tayini yapıldı.

Deney grupları;

1- Kontrol Proöstrus,
2- Kontrol Östrus,
3- Kontrol Metöstrus,
4- Kontrol Diöstrus,
5- Diyabet Proöstrus,
6- Diyabet Östrus,
7- Diyabet Metöstrus ve
8- Diyabet Diöstrus, şeklinde oluşturuldu.

Vajinal Smear Yöntemi

Deney sonunda 21. günden başlanarak 24 saatte bir defa deneklerin vulva bölgesi 70'lik etil alkolle (Merck, Almanya) silindikten sonra, steril tahta çubukların pamukla kaplanmış uç kısımları nemlendirildi ve vajina içerisinden, nazikçe sürüntü alınıp, lam üzerine yayıldı. Yayma lamların oda sıcaklığında kuruması beklendi. Kuruyan yaymalar %70'lik metanole (Merk, Almanya) daldırılıp bekletilmeden çıkarıldı ve oda sıcaklığında kurutularak yaymanın fiksasyonu sağlandı. %1'lik toluidine blue (TB, Fluka, 89640) ile 5 dakika boyanan preparatlar distile su ile yıkanıp kurutuldu ve kapatma uygulamaksızın incelendi. Fazların fotoğraflanması (Olympus CX31-Japan) ile sağlandı.

Işık Mikroskobik İnceleme

Işık mikroskobik incelemeler için ovaryumlardan biri ve uterusdan alınan uygun büyüklükteki örneklerin, Carnoy fiksatörü (60 ml absolut alkol, 30 ml kloroform, 10 ml glasiyal asetik asit) ile 12 saat fiksasyonu sağlandı. Rutin histolojik takiplerin ardından doku örnekleri parafinde bloklandılar. Parafin bloklardan elde edilen 5µm kalınlığındaki kesitlere, mast hücrelerinin dağılımlarını göstermek için %1'lik TB boyaması uygulandı.

Mast Hücre Sayımları ve İstatistiksel Analizler

TB ile boyanan preparatlarda mast hücrelerinin dağılımını belirlemek için yapılan hücre sayımlarında 100 kare oküler mikrometre (eyepiece graticule) kullanıldı. Kırklık objektif büyütmesinde okuler mikrometrenin 100 kare birim alanındaki mast hücreleri sayıldı ve milimetre kare (mm^2)'deki hücre sayısı hesaplandı[11].

Her uterus kesitinin endometriyum ve miyometriyum katmalarından rastgele seçilen her bir bölgeden 6'şar (toplam 12) büyütülmüş alanda hücre sayımı yapıldı. Ovaryum kesitlerinde (korteks + medulla) rastgele seçilen her bir bölgeden 12 büyütülmüş alanda mast hücre sayımları yapıldı. Seri kesitlerin sayılması ile elde edilen mast hücre sayılarının aritmetik ortalaması alındı.

Her iki organda da mast hücre sayılarının SAS v.12.0 paket programı kullanılarak variyans analizleri yapıldı. Gruplar arası ve içindeki farklılıklar Duncan testi ile belirlendi.

İmmünohistokimyasal İnceleme

Bu amaçla ovaryumlardan biri (sağ veya sol rastlantısal biçimde) ve uterus doku örneğinin %10'luk tamponlu formaldehit solüsyonu (100 ml %37'lik formaldehit solüsyonu 900 ml distile su, 6,5 gram Na_2HPO_4,4 gram $NaH_2PO_4H_2O$) ile 48 saat fiksasyonu sağlandı. Rutin histolojik takiplerden sonra parafin bloklardan alınan kesitler anti-triptaz (Abcam, ab2378) ve anti-kimaz (Biorbyt, orb4912) ile 2 saat süreyle inkübe edildi (1:250). Kromojen olarak anti-triptaz boyamasında 3-Amino-9-Ethylcarbazole AEC (Abcam, ab64257) ve anti-kimaz için ise 3,3'-diaminobenzidine (DAB) 10 dk. süre ile uygulandı ve Weigert'ın demirli hematoksilen'de 5 dakika zemin boyaması yapıldı.

İmmünohistokimyasal İnceleme ve Hücre Sayımları

İmmünohistokimyasal boyama yapılan preparatlarda kimaz pozitif ve triptaz pozitif mast hücre dağılımı semikantitatif olarak değerlendirildi. Semikantitatif değerlendirme; taranan alanda pozitif hücre yok (-), 1–2 hücre (±), 3–4 hücre (+), 5–6 hücre (++), 7 ve daha fazla sayıda hücrede (+++), şeklinde yapıldı.

Bulgular

Kontrol ve diyabet gruplarına ait deney başlangıç ve deney sonu kan glikoz ve vücut ağırlık değişim değerleri Tablo 1 ve 2'de verilmiştir.

Table 1. *Kontrol ve diyabet gruplarına ait kan glikoz değişimleri*

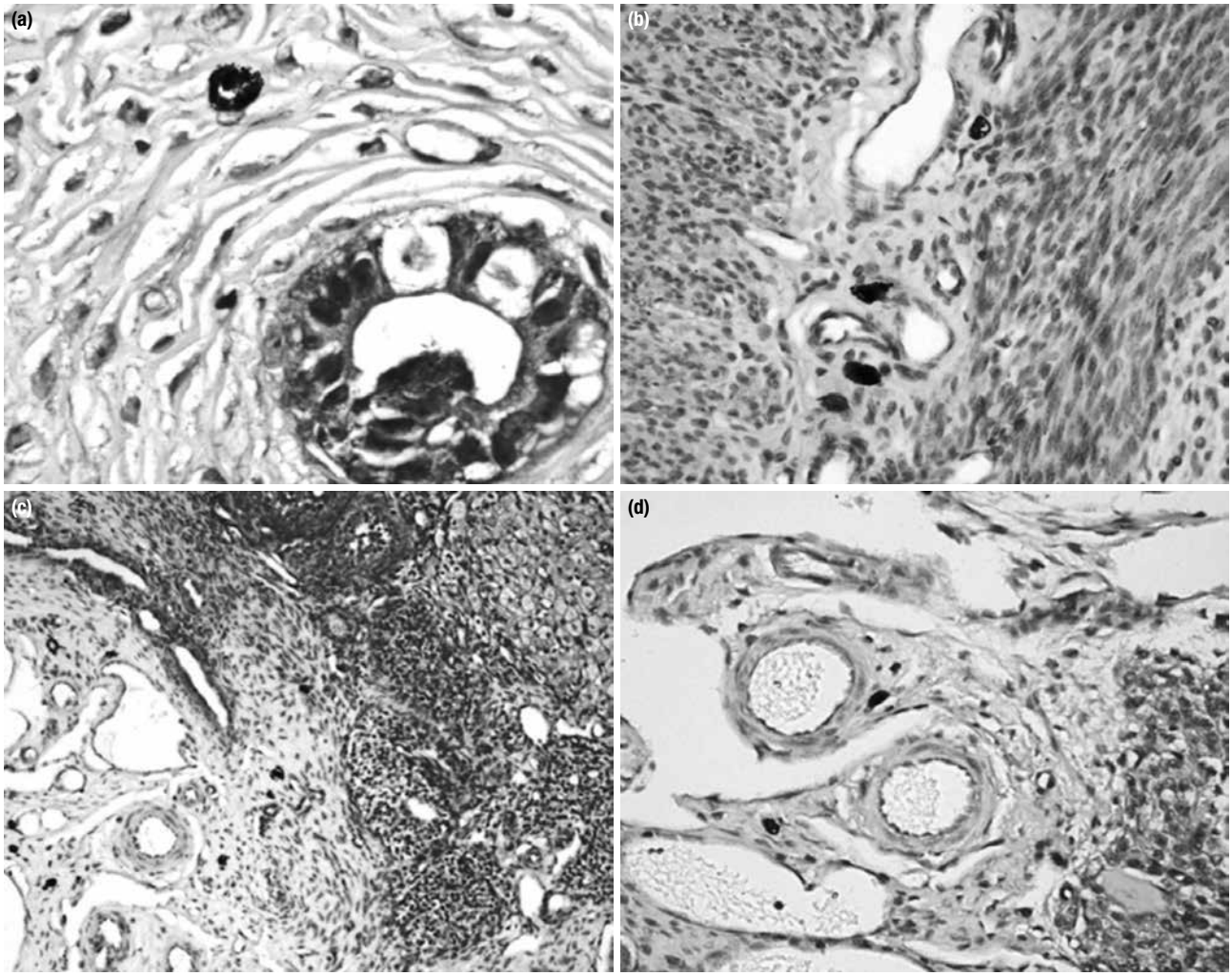
	Kontrol		Diyabet	
Siklus Fazı	Deney başlangıcı kan glikoz seviyesi (mg/dl)	Deney son kan glikoz seviyesi (mg/dl)	Deney başlangıcı kan glikoz seviyesi (mg/dl)	Deney son kan glikoz seviyesi (mg/dl)
Proöstrus	89,63	88,00	80,40	443,40*
Östrus	76,25	75,50	78,20	411,60*
Metöstrus	75,86	77,43	81,83	401,83*
Diöstrus	90,38	88,38	74,67	452,33*

*: Başlangıç değerine göre istatistiksel olarak anlamlı; P<0.05

Tablo 2. *Kontrol ve diyabet gruplarına ait vücut ağırlık değişimleri*

	Kontrol		Diyabet	
Siklus Fazı	Deney başlangıcı vücut ağırlığı (gr)	Deney sonu vücut ağırlığı (gr)	Deney başlangıcı vücut ağırlığı (gr)	Deney sonu vücut ağırlığı (gr)
Proöstrus	176,25	191,75*	189,40	147,60*
Östrus	169,88	180,75	185,80	141,60*
Metöstrus	167,86	185,86*	179,50	139,17*
Diöstrus	170,38	188,25*	174,00	143,67*

*: Başlangıç değerine göre istatistiksel olarak anlamlı; P<0.05



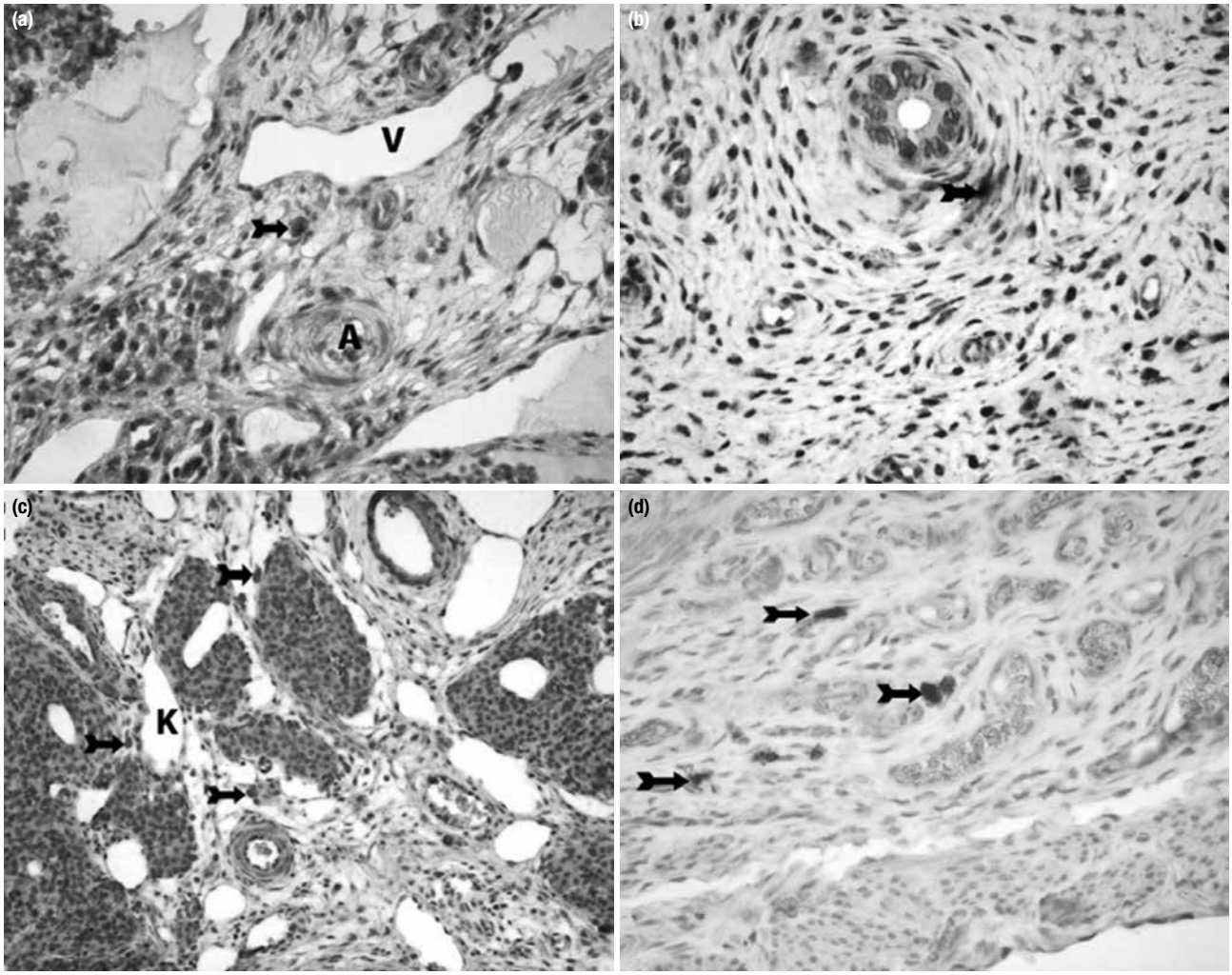
Şekil 1. a–d. *Toluidine blue boyaması ile mast hücrelerinin görünümü. Kontrol grubu östrus evresi endometriyum dokusu (1000×) (**a**); diyabetik grup metöstrüs evresi myometriyum dokusu (400×) (**b**); diyabetik grup östrüs evresi ovaryum dokusu (200×) (**c**); kontrol grubu metöstrüs evresi ovaryum (400×) (**d**).*

Uterus ve Ovaryumda Toluidine Blue Pozitif Mast Hücre Dağılımı

Uterus endometriyum katmanı incelendiğinde, mast hücrelerinin lamina propriya tabakasında bulunduğu gözlemlendi (Şekil 1a). Uterusun endometriyum katmanında diyabet ve kontrol gruplarından elde edilen mast hücresi sayıları incelendiğinde diyabetik sıçanlarda, kontrol grubuna göre istatistiksel olarak anlamlı bir artışın olduğu gözlendi ($P<0.05$).

Uterus miyometriyum katmanı incelendiğinde mast hücrelerinin stratum vaskulare bölgesinde damarlara yakın konumda yerleştikleri gözlemlendi. Yine bu katman değerlendirildiğinde, kontrol ile diyabet gruplarını karşılaştırılmasında östrus ve diöstrus evrelerinde istatistiksel olarak anlamlı bir değişim gözlenmezken ($P>0.05$), proöstrus ve metöstrus evrelerinde diyabet grubu ile kontrol grubu arasında istastiksel olarak anlamlı bir değişim gözlemlendi ($P<0.05$; Şekil 1b).

Ovaryum dokusunda TB ile boyamada, metakromatik boyanan mast hücrelerinin genellikle ovaryumun medulla kısmında ve bu alanda da genellikle kan damarı yakınlarında yerleşik oldukları saptandı (Şekil 1c). Kortikal alanlarda TB (+) mast hücreleri daha azınlıktaydı ve germinal epitel katmanında, follikül içinde ve korpus luteumda bu hücrelere rastlanmadı. Proöstrus, östrus, diöstrus sikluslarının kontrol ve diyabet grupları karşılaştırıldığında, diyabet gruplarında mast hücresi sayısında istatistiksel olarak anlamlı bir artış görülürken ($P<0.05$), metöstrus evresindeki kontrol ve diyabetik sıçanların ovaryumlarındaki mast hücresi sayısındaki değişimin istatistiksel olarak anlamlı olmadığı tespit edildi ($P>0.05$; Şekil 1d).



***Şekil 2. a–d**. Anti-triptaz immunreaktivitesi. Kontrol grubu proöstrüs evresi ovaryum dokusu, (400×) (**a**); kontrol grubu diöstrüs evresi uterus dokusu (400×) (**b**); kontrol grubu östrüs evresi ovaryum dokusu (200×) (**c**); diyabetik grup östrüs evresi myometriyum dokusu (400×) (**d**) (ok, triptaz pozitif mast hücresi; A, arter; V, ven).*

İmmünohistokimyasal Bulguları

Triptaz Pozitif Mast Hücresi Dağılımı

Ovaryum ve uterusun dokularında yapılan immünohistokimyasal triptaz boyamasından elde edilen triptaz pozitif mast hücre dağılımı Tablo 3'te verilmiştir.

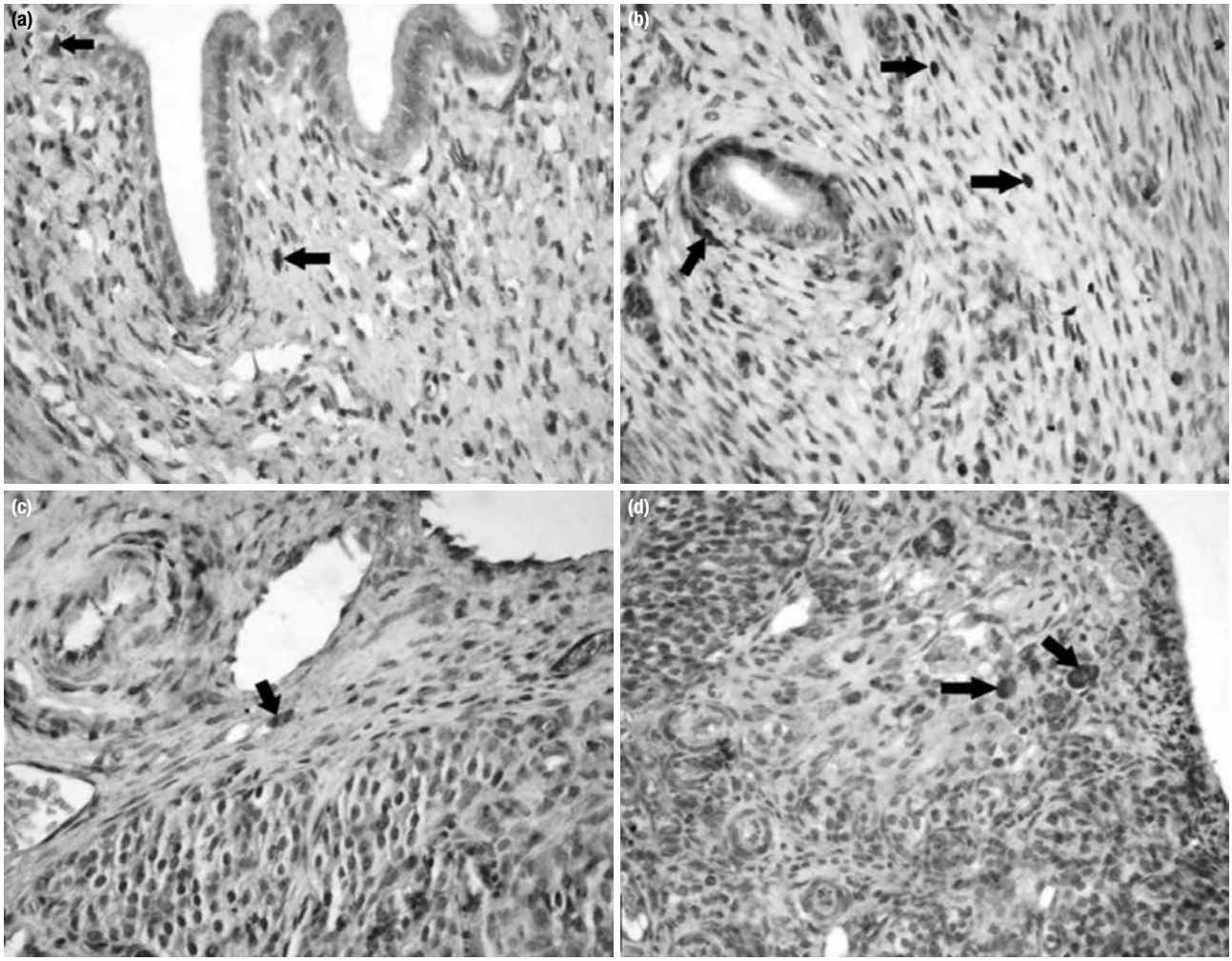
Triptaz boyaması sonucunda siklus fazlarına göre ovaryum dokusu incelendiğinde proöstrus ve metöstrus fazlarında deney grubu ile kontrol grupları arasında triptaz pozitif hücre sayısında bir değişim gözlenmemiştir. Östrus siklusu incelendiğinde deney grubu sıçanlarının ovaryumlarında, kontrol grubu sıçanların ovaryumlarına göre bir artış olduğu gözlendi. Diöstrus evresinde ise diyabet grubu sıçanların ovaryumlarında, kontrol grubu sıçanlarının ovaryumlarına göre bir azalmanın olduğu tespit edildi (Şekil 2a, c).

***Tablo 3.** Ovaryum ve uterus dokularında farklı siklus evrelerinde triptaz pozitif mast hücrelerinin semikantitatif dağılımı*

	Kontrol		Diyabetik	
Siklus Evresi	Ovaryum	Uterus	Ovaryum	Uterus
Proöstrus	±	-	±	-
Östrus	±	±	+	+
Metöstrus	++	++	++	+
Diöstrus	+	+	±	±

Yok (-), 1–2 hücre (±), 3–4 hücre (+), 5–6 hücre (++), 7 ve daha fazla sayıda hücrede (+++)

Yapılan triptaz boyamasında diyabet ve kontrol gruplarının uteruslarında, proöstrus evreside triptaz pozitif mast hücresine rastlanılmadı. Östrus evreside triptaz pozitif mast hücre sayısının diyabet grubu sıçanların uteruslarında,



***Şekil 3. a–d**. Anti-kimaz immunreaktivitesi. Kontrol proöstrüs endometriyum dokusu (400×) (**a**); diyabetik grubu metöstrüs evresi endometriyum dokusu (400×) (**b**); kontrol grubu metöstrüs evresi ovaryum dokusu (400×) (**c**); diyabetik grup diöstrüs evresi ovaryum dokusu (400×) (**d**) (ok, kimaz pozitif mast hücresi).*

kontrol grubu sıçanların uteruslarına göre bir artış gösterdiği tespit edildi. Metöstrus ve diöstrus evrelerinin kontrol ve diyabet grupları kendi içlerinde karşılaştırıldığında triptaz pozitif mast hücre sayısının diyabet grubu sıçanların uteruslarında, kontrol grubu sıçanların uteruslarına göre bir azalma gösterdiği saptandı (Şekil 2b, d).

Kimaz Pozitif Mast Hücresi Dağılımı

Ovaryum ve uterus dokularında kimaz pozitif boyanan mast hücre dağılımı Tablo 4'te verilmiştir.

Proöstrus evresi uterus örneklerinde, kimaz pozitif mast hücresi yoğunluğunun diyabetik ve kontrol grupları arasında yapılan karşılaştırmasında bir değişiklik göstermediği tespit edildi (Tablo 4; Şekil 3a, b). Metöstrus grubu sıçan, uterus dokularında kimaz pozitif mast hücre yoğunluğunda diyabetik grupta kontrol grubuna göre bir artışın olduğu gözlenmiştir. Östrus ve diostrus gruplarına ait uteruslarda ise diyabetik gruplarda, kimaz pozitif mast hücre yoğunluğunun kontrollere göre azalma gösterdiği belirlenmiştir (Tablo 4).

***Tablo 4.** Ovaryum ve uterus dokularında farklı siklus evrelerinde kimaz pozitif mast hücre semikantitatif dağılımı*

	Kontrol		Diyabetik	
Siklus Evresi	Ovaryum	Uterus	Ovaryum	Uterus
Proöstrus	±	±	+	±
Östrus	+	++	+	±
Metöstrus	++	++	++	+++
Diöstrus	±	+	±	±

Yok (-), 1–2 hücre (±), 3–4 hücre (+), 5–6 hücre (++), 7 ve daha fazla sayıda hücrede (+++)

Kimaz boyamasında, genel olarak kimaz pozitif mast hücrelerinin ovaryum medullasında lokalize oldukları gözlemlenirken, çok seyrek olarak da korteks alanında görüldü. Kimaz pozitif mast hücre dağılımı incelendiğinde ovaryumda östrus, metöstrus ve diöstrus fazlarında kontrol ve deney grupları arasında bir farklılığın olmadığı tespit edildi. Proöstrus grubunda ise, diyabet grubu ovaryumlarında kontrol grubuna göre bir artış gösterdiği gözlemlendi (Tablo 4; Şekil 3c, d).

Tartışma

Diabetes mellitus (DM), kan glikoz düzeyinde artışa, bireylerin kilo kayıplarına sebebiyet veren, karbonhidrat, protein ve lipid metabolizmasını etkiliyen oldukça kompleks bir metabolik hastalıktır. STZ ile yapılan deneysel diyabet modeli çalışmalarında, deneklerde kilo kayıpları, kan glikoz düzeyinde artış, endokrin pankreasta hasar ve buna bağlı olarak insülin hormon seviyesinde azalma meydana gelmektedir[12,13].

Östrus siklusu sırasında dişi genital organlarda birçok fizyolojik ve histofizyolojik değişimler meydana gelir. Bu değişimler göz önünde bulundurularak, vajinal smear metodu ile tüm memeli canlılarda östrus siklusu belirlenebilmektedir[7]. Sunulan çalışmada da, bu bilgilere paralel smear görüntüleri elde edilmiş ve sıçanların östrus fazları belirlenmiştir.

Mast hücrelerinin fare, sıçan, inek, hamster gibi türlerin ovaryum ve uteruslarında östrüs siklüsüne bağlı değişim gösterdiği bildirilmiştir[9]. Yapılan araştırmalarda, sıçan ovaryum ve uterus dokularında östrus siklusunun farklı evrelerinde mast hücreleri sayısal dağılımlarında farklılıklar olduğu görülmektedir[9,14]. Aynı çalışmalarda ovaryum medulla ve korteksinde mast hücresinin var olduğu, ama medullanın kortekse göre daha fazla mast hücresi içerdiği rapor edilmektedir[9]. Yapılan bu çalışmada da, buna paralel olarak mast hücreleri ovaryumda tespit edilmiş ve medullada kortekse göre daha fazla mast hücresinin yerleştiği gözlenmiştir.

Mast hücrelerinin, östrus siklusunun farklı evrelerinde uterustaki dağılımının değiştiği farklı hayvan türlerinde çeşitli çalışmalarla ortaya konmuştur. Eren ve ark. fare uterusunda yaptıkları çalışmada, östrus ve diöstrus dönemi uteruslar kıyaslanmış, hem endometriyum hem de miyometriyumda östrus dönemindeki dağılımın diöstrus dönemindeki farelere göre fazla olduğu tespit edilmiştir[15]. Aynı çalışmada, miyometriyumda endometriyuma göre daha fazla mast hücresi yerleştiği tespit edilmiştir. Sıçan uterusu üzerinde yapılan çalışmada[9], endometriyumda en yüksek dağılımın gözlendiği genital siklus fazının östrus, miyometriyumda en fazla mast hücresinin bulunduğu fazın ise metöstrus olduğu gösterilmiştir. Sunulan bu çalışmada, endometriyum ve miyometriyumda TB ile boyanmış en yüksek sayıda mast hücresinin bulunduğu fazın metöstrus olduğu tespit edilmiştir.

Deneysel diyabet çalışmalarında, diyabete bağlı olarak farklı doku ve organlarda yerleşik olan mast hücre dağılımının değiştiği ve degranülasyonun olduğu bildirilmiştir. Kalp, karaciğer ve mesane gibi farklı organ ve organ katmanlarında diyabete bağlı olarak mast hücresi dağılımının değiştiği gösterilmiştir. STZ ile deneysel diyabet oluşturulmuş sıçanlar üzerinde Çetin ve ark. tarafından yapılan çalışmada, diyabetik sıçanların kalp dokularında kontrol grubuna göre mast hücrelerinde bir artışın olduğu tespit edilmiştir[16]. Vardı ve ark. sıçanlar üzerine yaptıkları çalışmada, deneysel diyabetin karaciğer dokularında mast hücresi sayısını azalttığını göstermiştir[17]. Deneysel diyabet oluşturulan sıçanların mesanelerinde yapılan incelemede, kontrol grubu hayvanların mesanelerinde intraepiteliyal mast hücrelerine rastlanmaz iken, diyabet oluşturulan gruplarda diyabete bağlı intraepiteliyal mast hücrelerine rastlanmıştır[18].

Sunulan bu araştırmada, ovaryum dokusunda proöstrüs, östrüs ve diöstrüs grubu diyabetik sıçanlarda, kontrole göre mast hücre sayılarının anlamlı olarak yükseldiği tespit edilmiştir ($P<0.05$). Metöstrüs evresinde mast hücreleri diyabetik grupta artmasına rağmen istatistiksel olarak anlamlı düzeyde olmadığı gösterilmiştir. Karaca ve ark. yaptıkları bir çalışmada, sıçan ovaryumunda mast hücresi medulla östrüs evresinde; korteksde ise metöstrüs evresinde en yüksek sayıda olduğu bildirilmiştir[9].

Aydın ve ark. (1998) yaptıkları çalışmada, ovaryum dokusunda proöstrüs grubu sıçanlarda kortekste mast hücresine rastlanmadığı bildirilmiş, kortekste en yüksek mast hücre sayısının metöstrüs evresinde olduğu ileri sürülmüştür. Bununla birlikte, ovaryum medullasında en yüksek mast hücre sayısı östrüs fazında, en düşük değerin ise proöstrüs evresinde olduğu bildirilmiştir[14].

Sunulan bu araştırmada, kontrol grubu sıçanlarda, ovaryum dokusunda mast hücre sayısı mm^2'de en yüksek metöstrüs, en düşük ise diöstrüs evresinde tespit edilmiştir. Bu bulgular metöstrüs fazındaki mast hücresi sayısı açısından Karaca ve ark. (2007) ve Aydın ve ark. (1998)'in çalışmaları ile benzerken, en düşük sayıdaki mast hücresi sayısı açısından ise adı geçen çalışmalarla farklılıklar göstermektedir[9,14]. Jones ve ark. (1980) ovaryum medullasında en yüksek sayıda mast hücre sayısının östrüs, en

az ise proöstrüs evresinde olduğunu bildirmişlerdir[19] Krishna ve ark. (1989) yaptıkları çalışmada, hamster ovaryum medullasında en az mast hücresinin benzer olarak proöstrüs evresinde olduğunu göstermişlerdir[20]. Bununla birlikte Jones ve ark. ovaryum korteksinde mast hücrelerine rastlamadıklarını iddia etmişlerdir[19]. Bu sonuçlarla, yapılan bu çalışmanın sonuçları karşılaştırıldığında korteksde mast hücrelerin az da olsa varlığının tespiti adı geçen çalışma ile farklılıklar göstermektedir.

Shinohara ve ark. (1987) yaptıkları araştırmada, ovaryan bursada östrüs siklusunun 4. gününde mast hücre sayısı 1, 2, ve 3. östrüs günlerine göre önemli derecede azalmaların olduğu tespit edilmiştir[21]. Gaytan ve ark. (1991) yaptıkları çalışmada, siklüsa bağlı olarak ovaryum medulla ve korteksinde önemli değişimler olmasına rağmen, ovaryan bursada ise önemli bir değişimin olmadığı tespit edilmiştir[22].

Uterusta mast hücrelerinin östrüs fazına bağlı dağılımı üzerine yapılan çalışmalarda, endometriyum ve miyometriyum katmanlarında bu hücrelerin sayısının östrus fazına bağlı olarak değişiklik gösterdiği bildirilmiştir[9,14,23]. Sunulan bu çalışmada, kontrol grubu sıçanlarda endometriyumda en fazla sayıda mast hücresi metöstrüsde; en az ise proöstrüs evresinde olduğu tespit edilmiştir. Bununla birlikte, diyabetik sıçanların endometriyumunda mast hücre sayısının tüm östrüs siklüs evrelerinde kontrole göre anlamlı olarak artmış olduğu tespit edilirken ($P<0.05$); diyabetik sıçanların endometriyum dokusunda en yüksek sayıda mast hücresine metöstrüsde, en az ise östrüs evresinde olduğu tespit edilmiştir. Endometriyum katmanında, hem kontrol hem de diyabetik sıçanlarda bez epitelinde ve lumen epitelde mast hücresi gözlenmemiştir.

Sunulan bu çalışmada, uterus miyometriyumunda mast hücre dağılımı incelendiğinde en yüksek sayıda hücre kontrol grubunda metöstrüs, en az proöstrüs; diyabetik sıçanlarda ise aksine en yüksek proöstrüs en azda östrüs evresinde tespit edilmiştir. Miyometriyumda mast hücrelerinin yoğun olarak kas katmanları arasında yer alan stratum vaskulare katmanında yerleşik oldukları gözlemlenirken, az sayıda da kas lifleri arası bağdokusu içine lokalize oldukları tespit edilmiştir. Miyometriyum mast hücreleri dağılımları Karaca ve ark.'nın çalışması ile paralellik göstermesine rağmen, Aydın ve ark. çalışması ile farklılık göstermektedir[9,14].

Yapılan literatür taramalarında sıçanların dişi genital organlarında mast hücrelerinin immünohistokimyasal olarak incelendiği (triptaz ve kimaz) bir çalışmaya rastlanılamadı. Bu nedenle, triptaz ve kimaz pozitif mast hücrelerindeki dağılım az sayıda rastlanılan farklı doku ve organ sonuçları ile tartışılmıştır.

Kedilerde yapılan bir çalışmada, triptaz ve kimaz pozitif mast hücresinin deri, dil, kalp, karaciğer, dalak, böbrek ve gastrointestinal kanal organlarında değişik oranlarda bulunduğu rapor edilmiştir[24]. İnsanlarda, mast hücrelerinin immünohistokimyasal metotlarla içerdikleri proteazların varlığına göre yalnızca triptaz içeren mast hücreleri (MC_T), yalnızca kimaz içeren mast hücreleri (MC_C) ve hem triptaz ham de kimaz içeren mast hücreler (MC_{TC}) olarak sınıflandırılmıştır[25,26].

Sunulan çalışmada yapılan immunohistokimyasal boyamada, triptaz pozitif mast hücrelerinin yapılan semikantitatif değerlendirilmesinde, kontrol ve diyabetik sıçan ovaryumlarında en yoğun mast hücresine metöstrüs evresinde rastlanılmıştır. Uterus incelendiğinde ise, kontrol ve diyabetik sıçanlarda, immun boyama sonucunda proöstrüs fazında triptaz pozitif mast hücresine rastlanılmazken, kontrol gruplarına benzer olarak en yoğun metöstrüs fazında olduğu tespit edilmiştir.

Triptaz proteazı, gastrointestinal ve bronşial mukoza gibi alanlarda yerleşik olan atipik mast hücrelerinde (mukozal mast hücreleri-MMC) lokalize oldukları tespit edilmiştir[27]. Bunun yanında triptazın, insan akciğer mast hücrelerinde de varlığı yapılan araştırmalarla ortaya konmuştur[28,29]. Sunulan bu araştırmada, triptaz pozitif mast hücrelerin sıçan ovaryum ve uteruslarında varlığı tespit edilerek, östrüs siklusuna göre de değişim gösterdiği ilk kez ortaya konmuştur.

Yapılan araştırmalarda kimazın; sıçan deri[30], kas[31], akciğer parenşimi[31], serozal kavite[31,32] ve karaciğer[33] mast hücrelerinde varlığı tespit edilmiştir[34]. Mitani ve ark. (2002), kimaz pozitif mast hücrelerine normal gebelik miyometriyumunda ve plasenta dokularında değişik oranlarda rastladıklarını bildirmişlerdir[35] Bu hücrelerin preeklampsi durumunda miyometriyumunda artarken, plasentada ise anlamlı derecede azaldığı bildirilmiştir. Sıçanlarda yapılan bir araştırmada, endometriyumda rat mast hücresi proteaz II (RMCP-II)'nin bulmadığı, oysa miyometriyumda az da olsa bu enzimi içeren mast hücrelerine rastlandığı bildirilmiştir. Buna karşın uterus dokusunda RMCP-I içeren mast hücrelerinin bulunduğu bildirilmiştir[36].

Sonuç olarak, yapılan bu çalışma ile diyabetik sıçanlarda östrüs siklusunun farklı günlerinde meydana gelen hormonal değişime paralel olarak, triptaz ve kimaz immun reaktif mast hücre dağılımlarının değiştiği ortaya konmuştur.

Bununla birlikte, bu hücrelerin dağılımlarındaki değişiklerin biyokimyasal ve ileri tekniklerle desteklenerek araştırılmasına gereksinim bulunduğu kanaatindeyiz.

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Agonist and Antagonist Effects of ATP-Dependent Potassium Channel on Penicillin Induced Epilepsy in Rats

Sıçanlarda ATP-Bağımlı Potasyum Kanal Agonist ve Antagonistlerinin Penisilin ile Oluşturulmuş Epilepsi Üzerine Etkileri

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ABSTRACT

AIM: *Epileptic seizures occur when the balance between stimulating and inhibiting systems in the brain tends to deterioration in the direction of stimulating systems dominancy. Antiepileptic effect of potassium (K) channel openers has been shown in in vitro and in vivo studies. The purpose of this study is to investigate K ATP channel agonist (pinacidil) and antagonists (glibenclamide) acute effects on experimental epilepsy models.*

METHODS: *In this study 32 adult male Wistar rats weighing 200–250 g were used, and these rats were divided into 4 groups as control (saline), glibenclamide, pinacidil and DMSO (dimethylsulfoxide). All rats were anesthetized with the dose of 1.25 g/kg urethane, and it was administered to the rats intraperitoneally. After rats were anesthetized, the left part of the cortex was opened and the electrodes were placed on somatomotor area. Epileptiform activity was induced by intracortical (ic) administration of penicillin (500 IU, 2.5 µl). At the 30th minutes of penicillin application, all substances (glibenclamide, pinacidil, DMSO, saline) was injected intraperitoneally (i.p). Obtained electrocorticographic (ECoG) data from recordings were analyzed by software. Spike-wave frequency and spike-wave amplitude of epileptiform activity were analyzed statistically.*

RESULTS: *Results of the study was showed that pinacidil decreases spike-wave frequency in epilepsy model which induced by penicillin ($p<0.05$), however it does not have any significant effect on spike-wave amplitude of epileptiform activity ($p>0.05$). Similarly, glibenclamide which is a blocker of KATP channel does not have any significant effect on both spike-wave frequency and spike-wave amplitude of epileptiform activity ($p>0.05$).*

CONCLUSION: *The results of the present study showed that administration of pinacidil has antiepileptic effect in penicillin induced epilepsy model in rats. Pinacidil may be a potential antiepileptogenic drug in future.*

Key words: *epilepsy; pinacidil; glibenclamide; KATP channels; penicillin*

ÖZET

AMAÇ: *Epileptik nöbetler, beyindeki uyarıcı ve duraklatıcı sistemler arasındaki dengenin, uyarıcı sistemlerin aktivitelerinin artışı yönünde bozulması sonucunda meydana gelir. İn vitro ve in vivo çalışmalarında, birçok K+ kanal açıcılarının antiepileptik etkisi gösterilmiştir. Bu çalışmada, çeşitli deneysel epilepsi modellerinde etkisi araştırılan KATP kanal agonist (pinacidil) ve antogonistlerinin (glibenclamide) penisilinle oluşturulan deneysel epilepsi modeli üzerindeki akut etkisi araştırıldı.*

YÖNTEM: *Çalışmada 200–250 gr ağırlığında 32 adet erkek Wistar-Albino sıçan kullanıldı. Deney 10 hayvanları, kontrol, DMSO (dimetilsülfosit), pinasidil ve glibenklamid olarak dört gruba ayrıldı. Sıçanlar 1,25 gr/kg üretan dozunun intraperitoneal olarak uygulanmasıyla anestezi altına alındı. Sıçanlar anestezi altına alındıktan sonra sol korteks açıldı ve somatomotor alana elektrotlar yerleştirildi. Epileptiform aktivite intrakortikal (i.c.) penisilin (500 IU, 2,5 µl) uygulanmasıyla oluşturuldu. Penisilin uygulamasının 30. dakikasında tüm maddeler (salin, DMSO, pinasidil ve glibenklamid) intraperitoneal 15 (i.p.) olarak uygulandı. Kayıtlardan elde edilen elektrokortikografik (ECoG) veriler yazılım programı ile analiz edildi. Epileptiform aktivitenin diken dalga sıklığı ve diken dalga genliği istatistiksel olarak analiz edildi.*

BULGULAR: *Penisilin ile oluşturulan deneysel epilepsi modelinde pinasidilin diken dalga sıklığını azalttığı ($p<0,05$), fakat diken dalga genliği üzerinde anlamlı bir etkisinin olmadığı görüldü ($p>0,05$). Benzer şekilde KATP kanal kapatıcısı olan glibenclamidenin ise hem diken dalga sıklığı hem diken dalga genliği üzerine anlamlı bir etkisinin olmadığını bulundu ($p>0,05$).*

SONUÇ: *Yapılan çalışmada pinasidil uygulamasının sıçanlarda penisilinle oluşturulmuş deneysel epilepsi modeli üzerinde antiepileptik etkiye sahip olduğu gösterildi. Pinasidil gelecekte potansiyel bir antiepileptik ilaç olabilir.*

Anahtar kelimeler: *epilepsi; pinasidil; glibenklamid; KATP kanalları; penisilin*

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Introduction

There are 50 million patients around the world who suffer from epilepsy. Therefore, many significant studies are made for the prevention and treatment of epilepsy. The incidence of the epilepsy in children and elderly people are at the highest level, but its frequency in young people is at low level[1].

Although the incidence of epilepsy is approximately 1% and it is one of the neurological disorders, many studies do not fully explain the cause of epilepsy in half of the patients[2]. Epileptic seizure is a clinical condition caused by excessive discharge of a group of neurons in the brain. This clinical situation contains sudden and temporary abnormal changes in level of consciousness, motor, sensory, autonomic or psychic. Epilepsy may occur without primarily damage or risk factor in the brain, and it may occur another underlying neurological, metabolic, toxic, or traumatic depending on secondary reasons[3]. Epileptic seizures may happen in many ways as loss of consciousness in which tonic, clonic muscle contraction or emotional and thought disorder[4].

In epileptic seizures recorded during electrophysiological recordings both the abnormal discharge of spikes waves occur and it is quite significant changes in the frequency and amplitude of normal brain wave have been known for many years, and these changes are called epileptiform activity. However due to ethical and scientific rules the difficulty of studies on humans as in many fields of medical science, which requires the use of animal experiments in this regard. A substance should be tested in a variety of experimental models and effectiveness of this substance must be demonstrated before further researches and being a drug. For this purpose many epilepsy models have been developed[5–8].

In recent studies, as an opinion that adenosine triphosphate-dependent potassium channels (K_{ATP}) to be effective on the formation process of epilepsy has prevailed. K_{ATP} channels are therapeutic targets, and both activators and inhibitors of K_{ATP} channels used in clinics. Although secretion of insulin in pancreatic β-cell of K_{ATP} channels' classical role well understood, neuronal function is still unclear. In the study, which used dead mice, neuronal K_{ATP} channels are important to prevent the seizure induction and extension, and the numbers of active neuronal K_{ATP} channels were found to be effective in controlling the seizure threshold[9].

Pinacidil, a K_{ATP} channel activator, effective on K_{ATP} channels in vascular smooth muscle and sarcolemma of cardiac muscle cells and mitochondria[10]. Genetic, molecular, physiological and pharmacological findings support that some K^+ channels have roles on the control of epileptogenesis and neuronal excitability. Therefore, there have been many studies on K^+ channel openers[11,12]. In the models of in vitro and in vivo, K^+ channel openers like diazoxide have been shown antiepileptic effects. Hence, this information suggests that K_{ATP} channel may be a potential target of novel drugs[13].

The purpose of this study is to investigate K_{ATP} channel agonist (pinacidil) and antagonist (glibenclamide) acute effects on penicillin induced epilepsy model by using electrocorticogram in anesthetized rats.

Materials and Methods

Animals

Male Wistar rats (200–250 g, aged of 12 weeks) were provided from the Duzce University, Experimental Animals Research Center (Duzce, Turkey) and housed in groups of six under the standard laboratory conditions. They were kept at constant room temperature (21±2°C) under a 12/12 h light/dark cycle. Commercial food pellets and tap water were given freely available. The experiments were performed during the light portion of the cycle, between 08:00–12:00 a.m., to avoid circadian influences. All animal experiments were carried out in accordance with the regulations of the Ethics Committee of the Duzce University.

Drugs and Doses

As purchased chemicals, pinacidil (Sigma-Aldrich, St Louis, MO, USA) administered i.p. in 0.01 mg/kg and glibenclamide (Santa Cruz Biotechnology, Santa Cruz, CA) administered 1.0 mg/kg were used in the study. Pinacidil and glibenclamide were dissolved in dimethylsulfoxide (DMSO, Loba Chemie, India) following diluted with saline (99% DMSO; 0.2 ml final solution DMSO/saline 1:4, v/v, respectively). Urethane (Sigma-Aldrich, St Louis, MO, USA) in 1.25 g/kg i.p. dose was used as anesthetic. Epileptic activity was stimulated by injecting 500 IU/ 2 μl penicillin i.c. in 2 mm lateral, 1 mm anterior and 1.2 mm depth of Bregma line with Hamilton microenjector (701N, Hamilton Co., Reno, NV, USA). All drugs were prepared daily.

Surgical Procedure

Each of the animals in all groups, was anesthetized with urethane, and fixed onto stereotaxic frame (Harvard Instruments, South Natick, MA, USA). After shaving the head area, the scalp was incised through midline, from front to back with scalpel. Then, the bone part above the left cerebral cortex was slenderized with tour motor (Proxxon Minimot 40/E), and carefully removed.

Experimental Groups

Group 1, "control group", which injected penicillin + saline (500 IU/2 µl, i.c.), [n=8].

Group 2, "DMSO (solvent) group", which injected penicillin + DMSO (1 ml/kg i.p.), [n=8].

Group 3, "0.01 mg/kg pinacidil group", which injected penicillin + pinacidil, [n=8].

Group 4, "1.0 mg/kg glibenclamide group", which injected penicillin + glibenclamide, [n=8].

Electrophysiological Records

Two Ag-AgCl top electrodes were placed on the somatomotor cortex area, which was opened on left hemisphere in the lateral of Bregma line. After the electrodes were placed, electrocortigography (ECoG) records (PowerLab/8SP, AD Instruments Pty Ltd, Castle Hill, NSW, and Australia) were taken throughout the experiment. Before application of penicillin, five minutes basal activity recording was taken. Thereafter epileptiform activity was induced by intracortical administration of penicillin. At the 30th minutes of penicillin application, substances (saline, DMSO, pinacidil and glibenclamide) were injected. The analyses of the obtained records were performed with the Power Lab Chart v.6.0 software package. The epileptiform activity, which was occurring in bipolar spike and spike-wave complexes, were examined. Additionally, the values of spike wave frequency and amplitudes per 5 minute-periods of ECoG recordings of each animal were measured and used as data.

Statistical Analysis

Spike wave frequency and amplitude of epileptiform activities data were digitized and computed from the records of each animal by using Chart software. In the evaluation of received data, each group changes from baseline in their various periods were evaluated by paired t-test, the difference between the four groups in terms of periodic changes were evaluated with one-way analysis of variance, and the significant differences were evaluated with Tukey post hoc test, $p < 0.05$ was considered as significant. PASW 18.0 software was used for statistical calculations. The resulting data descriptor values ± standard deviation (SD) were presented in graphs.

Results

Basal ECoG activity of each rats were recorded before the administration of substances. Spontaneous spike was not detected in any animals. Epileptiform activities that characterized with bilateral spikes began within 3–8 min after penicillin application and lasted for 3–4 h. Frequency and amplitude of spikes reached a constant level about 30 min after penicillin application. Including from five minutes before the injection of pinacidil and glibenclamide 125 minutes was divided into 5 minutes periods. Consequently, 25 different measurements values were obtained.

The Effect of Pinacidil and Glibenclamide on Spike-Wave Frequency of Epileptiform Activity

After penicillin injection, the mean of spike wave frequency of epileptiform activity was between 136.38 spike/min and 82.00 spike/min in the control group. Decreasing in the frequency of epileptiform activity continued for 125 minutes (except for some periods) (Fig. 1, Table 1). The mean of spike wave frequency of epileptiform activity in DMSO group was between 134.38 spike/min and 64.38 spike/min after DMSO injection and there was no statistically significant difference according to the control group ($p>0.05$) (Fig. 1, Table 1).

The mean of spike wave frequency of epileptiform activity of 1.0 mg/kg glibenclamide group was between 56.00 spike/min and 127.00 spike/min after injection and there was no statistically significant difference comparing to the control group ($p>0.05$) (Fig. 1, Table 1).

After 0.01 mg/kg pinacidil injection, spike wave frequency of epileptiform activity mean was between 4.38 spike/min and 106 spike/min in the pinacidil group. After the injection of pinacidil at 0.01 mg/kg dose reduced the mean spike wave frequency in the time periods of 1–5, 11–55, 61–65, 76–80 and 81–85, but these decreasing were not statistically significant when it is compared with the other groups ($p>0.05$) (Table 1). However, decreasing effects of 0.01 mg/kg

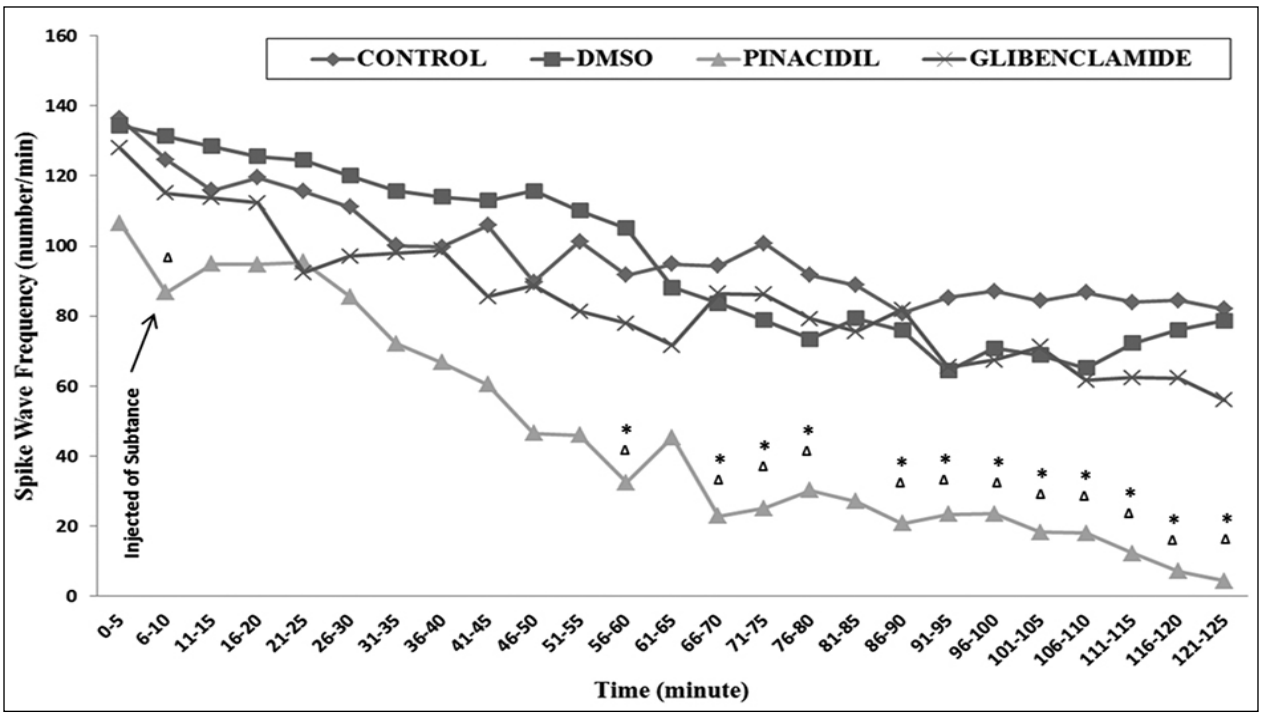

Figure 1. *Mean values of spike-wave frequency (number/min) obtained from recording after penicillin. (*: Significance compared to control group [p<0,05]; Δ: Significance compared to DMSO group).*

Table 1. *The effects of control, DMSO, pinacidil and glibenclamide on frequency of penicillin-induced epileptiform activity*

Time		Control		DMSO		Pinacidil		Glibenclamide		
(min)	N	Mean±SEM	Median	Mean±SEM	Median	Mean±SEM	Median	Mean±SEM	Median	P
1–5	8	136,38±54,047	121,50	134,38±30,085	133,00	106,50±34,013	98,00	127,88±38,27	110,50	0,473
6–10	8	124,63±35,290	119,50	131,38±25,427	130,00	86,75±27,732$^{\Delta}$	90,50	115,00±48,59	105,50	**0,048**
11–15	8	115,88±41,495	111,00	128,50±32,628	128,50	94,88±17,291	100,00	113,75±62,47	107,00	0,272
16–20	8	119,50±25,518	119,50	125,50±36,095	121,00	94,75±19,631	97,50	112,25±59,17	135,00	0,224
21–25	8	115,63±24,477	107,50	124,50±40,118	119,00	95,38±30,194	105,00	92,38±57,56	98,50	0,478
26–30	8	111,13±22,643	106,00	120,00±37,401	110,00	85,50±32,036	95,50	97,13±65,53	110,50	0,568
31–35	8	100,13±29,464	100,50	115,75±40,461	99,50	72,13±43,943	68,50	98,00±53,65	101,50	0,507
36–40	8	99,63±26,295	93,00	114,00±36,426	102,50	66,75±57,708	68,00	98,75±57,87	97,50	0,497
41–45	8	105,88±30,694	98,50	113,00±43,612	95,50	60,50±55,379	61,50	85,50±50,87	81,50	0,267
46–50	8	89,75±24,064	85,50	115,75±49,352	95,50	46,50±46,347	38,50	88,63±54,59	90,50	0,116
51–55	8	101,25±38,340	87,00	110,13±47,221	85,00	46,00±41,463	50,50	81,38±52,89	78,50	0,090
56–60	8	91,75±30,775	90,00	105,13±38,765	83,00	32,50±33,037$^{*\Delta}$	25,50	77,88±55,31	77,50	**0,004**
61–65	8	94,88±33,336	85,50	88,13±13,442	86,00	45,38±52,877	29,50	71,63±55,47	76,00	0,200
66–70	8	94,25±40,372	79,50	83,63±35,018	78,50	22,88±29,897$^{*\Delta}$	4,00	86,38±90,79	70,00	**0,009**
71–75	8	100,75±44,506	80,00	78,88±27,772	78,00	25,13±31,133$^{*\Delta}$	7,50	86,13±92,96	72,00	**0,010**
76–80	8	91,63±50,560	74,00	73,50±25,840	80,00	30,25±41,018	1,50	79,25±90,45	65,00	0,161
81–85	8	88,75±38,291	79,00	79,38±14,937	80,00	27,13±37,104	1,50	75,50±82,45	69,00	0,067
86–90	8	80,75^{a}±38,243	72,00	75,88^{a}±12,552	77,50	20,75^{b}±30,886$^{*\Delta}$	1,50	81,88^{a} ±86,37	73,00	**0,035**
91–95	8	85,25±32,208	82,00	64,38±23,250	70,00	23,38±34,924$^{*\Delta}$	0,50	65,38±70,51	58,50	**0,032**
96–100	8	87,13±36,385	77,50	70,88±26,205	78,00	23,50±35,881$^{*\Delta}$	2,00	67,38±70,41	63,00	**0,031**
101–105	8	84,38±40,659	72,00	68,88±22,731	75,50	18,25±34,204$^{*\Delta}$	0,00	71,25±69,42	70,50	**0,036**
106–110	8	86,75±36,507	86,00	65,13±14,377	65,50	18,00±27,198$^{*\Delta}$	2,50	61,63±66,09	54,00	**0,009**
111–115	8	84,00±48,146	83,00	72,25±16,140	70,50	12,25±22,657$^{*\Delta}$	1,00	62,38±65,95	56,50	**0,012**
116–120	8	84,50±35,984	81,00	76,13±19,172	73,50	7,13±18,954$^{*\Delta}$	0,00	62,25±62,96	49,50	**0,004**
121–125	8	82,00±40,178	88,50	78,75±20,408	76,00	4,38±11,173$^{*\Delta}$	0,50	56,00±59,14	38,50	**0,003**

All values are number/minute. p≤0.05 was considered statistically significant. *: Statistically significant differences compared to control group. Δ: Statistically significant differences compared DMSO group.

dose pinacidil in the spike wave frequencies were statistically significant in the time periods of 56–60, 66–70, 71–75 and 86–125. The mean spike-wave frequency of 0.01 mg/kg dose pinacidil group were observed to be significantly lower comparing to the control and DMSO groups in most of periods ($p<0.05$) (Table 1). Moreover administration of 0.01 mg/kg dose pinacidil decreased spike-wave frequency as compared with other group which was DMSO group in 6–10 time period ($p=0.048$) (Fig. 1, Table 1).

The Effect of Pinacidil and Glibenclamide on Spike-Wave Amplitude of Epileptiform Activity

Considering the data obtained from the control group, the mean spike wave amplitude of epileptiform activity reached a maximum value (3,444 mV) at 21–25 time period after penicillin and gradually decreasing continued for 125 min (Fig. 2). In DMSO group the mean spike wave amplitude of epileptiform activity were between 3,915 mV (46–50 min) and 2.462 mV (121–125 min) (Fig. 2, Table 2). At the same time, effect of DMSO on epileptiform activity was investigated. Although, DMSO administration increased the spike-wave amplitude as compared with the control group, there was no statistically significance ($p>0.05$) (Fig. 2).

There was no significant difference in the spike-wave amplitude of epileptiform activity of 0.01 mg/kg pinacidil group compared to the other groups in all time periods ($p>0.05$) (Fig. 2, Table 2). There was no significant difference in the spike-wave amplitude of epileptiform activity of 1.00 mg/kg glibenclamide group compared to the other groups in all time periods ($p>0.05$).

Discussion

In the present study, administered intraperitoneally in the doses of 0.01 mg/kg pinacidil and 1.0 mg/kg glibenclamide effects on epileptiform activity in rats which induced by penicillin have been researched. When epileptiform activity spike-wave frequency mean value analyzed which belongs to pinacidil 0.01 mg/kg dose in the records, except for some period, was determined that in the 125 minutes time interval 0.01 mg/kg dose pinacidil is significantly lower compared to the control and DMSO group. Thus, pinacidil decreased the frequency of epileptiform activity and this effect lasted for at least 2 hours after penicillin injection was observed. This finding is important due to pinacidil effects on epilepsy did not previously studied electrophysiologically. However, effect of pinacidil on the epileptiform activity spike-wave amplitude was not observed. Similarly, glibenclamide, which is a selective and strong blocker on K_{ATP} channels, intraperitoneal administration in the dose of 1.0 mg/kg has no effect on epileptic discharges in experimental epilepsy model which induced by penicillin.

An epileptic seizure occurs when the balance between stimulating and inhibiting systems in the brain tends to deterioration in the direction of stimulating systems dominancy[14]. Nowadays, there have been many studies on both causes and treatment of epilepsy[15–17]. Several experimental models have been used for explanation of mechanisms underlying epilepsy, testing of new antiepileptic, the development of appropriate diagnostic approaches and treatment modalities or determination of new approaches in order to eliminate the problems caused by epilepsy. In recent studies have been dominated by the view that the ATP-dependent potassium channel effective on the formation process of epilepsy. Many proconvulsant and anticonvulsant agents have been studied in experimental epilepsy models. We conducted our study by using pinacidil, which is an ATP-dependent potassium channel agonist, and glibenclamide, which is an ATP-dependent potassium channel antagonist.

K_{ATP} channel openers such as diazoxide in appropriate concentration, which used in the treatment of hypertension in accordance with the clinical purpose, or K_{ATP} channel blockers like sulfonylureas, which used in the treatment of type II diabetes may be effective on control of ischemic tolerance and seizure threshold are considered[18]. In a conducted study showed that subunit of K_{ATP} channels in substantia nigra pars reticulata (SNr) has special effect on the formation of epilepsy[19]. Obtained results from studies on transgenic rats support that K_{ATP} channels has role in the spread of seizures. Made with ATP-sensitive K^+ channel openers like diazoxide and cromakalim in vivo and in vitro experiments antiepileptic effects of these substances are shown[13,20]. Similar results were obtained from some performed studies [21,22].

Potassium channel openers, as a result of membrane hyperpolarization, reduce neuronal excitability. Moreover, potassium channel openers have an antinociceptive effect mediated by the activation of endorphins, free encephalin and opioid receptors. There are studies on pinacidil and cromakalim both have been shown analgesic effect via nitric oxide, which is affected by the opening of sarcolemmal K_{ATP} channels [25-27].

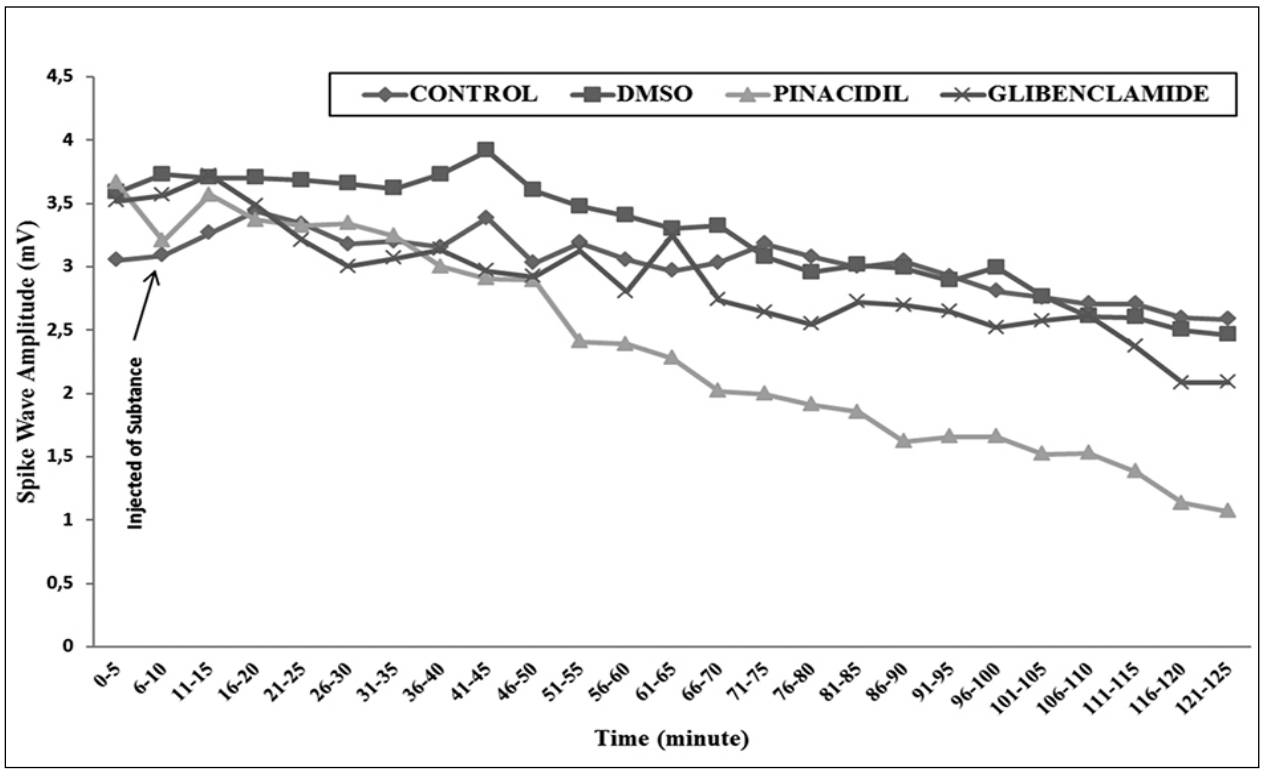

Figure 2. *Spike-wave amplitude (mV) mean values obtained from recording after penicillin.*

Table 2. *The effects of control, DMSO, pinacidil and glibenclamide on amplitude of penicillin-induced epileptiform activity*

Time (min)	Control			DMSO		Pinacidil		Glibenclamide		
	N	Mean±SEM	Median	Mean±SEM	Median	Mean±SEM	Median	Mean±SEM	Median	P
1–5	8	3,050±1,197	3,294	3,587±1,200	3,674	3,666±1,486	4,030	3,518±1,08	3,778	0,421
6–10	8	3,090±1,176	3,306	3,731±1,246	3,798	3,207±2,057	3,127	3,566±1,057	4,004	0,948
11–15	8	3,268±1,330	3,350	3,703±1,271	3,841	3,568±1,667	3,108	3,723±1,304	3,977	0,474
16–20	8	3,444±1,426	3,355	3,702±1,247	3,945	3,369±1,639	2,677	3,486±1,158	3,915	0,995
21–25	8	3,340±1,192	3,400	3,682±1,218	3,725	3,323±1,649	2,806	3,208±1,315	3,328	0,416
26–30	8	3,179±1,010	3,388	3,657±1,128	3,744	3,341±1,588	3,406	3,004±1,116	3,071	0,970
31–35	8	3,200±0,975	3,345	3,617±1,111	3,668	3,244±1,628	3,379	3,069±1,478	2,728	0,958
36–40	8	3,157±1,019	3,398	3,729±1,089	3,680	3,001±1,843	3,110	3,137±1,588	2,350	0,502
41–45	8	3,384±0,625	3,376	3,915±0,655	3,719	2,905±1,714	3,106	2,970±1,532	2,332	0,361
46–50	8	3,028±0,800	3,308	3,602±0,891	3,562	2,894±1,488	2,853	2,922±1,494	2,328	0,870
51–55	8	3,192±0,980	3,566	3,477±1,000	3,408	2,411±1,521	2,489	3,129±1,749	3,017	0,672
56–60	8	3,057±0,745	3,308	3,403±0,862	3,290	2,389±1,417	2,367	2,802±1,593	2,258	0,504
61–65	8	2,970±0,778	3,139	3,300±1,056	3,132	2,280±1,541	2,379	3,247±1,842	3,171	0,222
66–70	8	3,032±0,933	3,447	3,323±1,126	3,161	2,019±1,417	2,105	2,740±1,446	2,253	0,695
71–75	8	3,183±0,914	3,558	3,080±1,038	3,098	1,995±1,300	2,162	2,642±1,429	2,283	0,505
76–80	8	3,080±0,871	3,423	2,956±1,015	2,960	1,914±1,352	1,932	2,548±1,434	2,155	0,658
81–85	8	3,000±0,718	3,256	3,013±1,016	2,916	1,853±1,221	1,832	2,725±1,513	2,968	0,158
86–90	8	3,045±0,832	3,281	2,993±1,048	2,860	1,619±0,958	1,448	2,696±1,460	2,751	0,579
91–95	8	2,926±0,796	3,049	2,892±1,081	2,668	1,661±1,034	1,744	2,647±1,550	2,683	0,625
96–100	8	2,806±0,763	2,775	2,995±1,095	2,904	1,661±1,027	1,754	2,520±1,409	2,663	0,742
101–105	8	2,756±0,739	2,754	2,766±0,984	2,637	1,520±0,953	1,409	2,574±1,549	2,530	0,362
106–110	8	2,706±0,870	2,701	2,609±0,891	2,537	1,529±0,890	1,602	2,616±1,821	2,320	0,899
111–115	8	2,709±0,855	2,699	2,600±1,040	2,494	1,382±0,678	1,586	2,370±1,502	2,230	0,918
116–120	8	2,597±0,844	2,686	2,501±0,924	2,411	1,136±0,472	1,182	2,083±1,390	1,939	0,775
121–125	8	2,585±0,907	2,671	2,462±1,004	2,350	1,069±0,460	,989	2,089±1,610	1,947	0,258

Shafaroodi-et al (2007), investigated using the specific K_{ATP} channel blocker glibenclamide, the specific K_{ATP} channel opener cromakalim, and the possible involvement of K_{ATP} channels in the effects of morphine on pentylenetetrazole (PTZ)-induced seizure threshold in mice. K_{ATP} channel blockade depolarizes neurons. K_{ATP} channels have regulatory effects in the formation of epileptic seizures induced by PTZ. Their data indicated that the non-effective dose of glibenclamide was able to antagonize the proconvulsant effects of morphine and this effect of glibenclamide was inhibited by co-administration of cromakalim [26]. Pharmacological studies support that K_{ATP} channels have important role on control of seizure threshold [27].

Almost everything that interferes the normal functioning of nerve cells in the brain can cause epilepsy. Head traumas, genetic factors, infection and congenital disorders are among those reasons. The treatment of epilepsy is based on control seizures with drugs. Complete recovery is possible in some types of epilepsy (primary type). Spontaneous-abnormal electrical discharges during epileptic seizures cause to increase K^+ ions in intracellular area. Inducing of seizure by penicillin, which applied directly to the cerebral cortex, is occurred by blocking of inhibitory postsynaptic potential (IPSP). Reduction of inhibition in a cortical region has a very important effect on the behavior of neuron groups. Therefore, the administration of the convulsant drug may cause an acute focal epilepsy without causing morphological changes in cells[20,28]. Sullivan and Osorio (1991) induced epileptiform activity with administered penicillin intraperitoneally in rats[29]. Walden et al (1992) applied local penicillin to cortex surface, and they reported that epileptiform potentials seen in ECoG recordings after 4–5 minutes administration of penicillin[30]. In recent study, epileptiform activities began within 3–8 minutes after penicillin application and lasted for 3–4 hours.

In conclusion, in this study showed that acute using of 0.01 mg/kg pinacidil decreases the spike-wave frequency of epileptiform activity. We did not perform molecular and biochemical analyses in this study, but only investigated the effect on epileptiform activity electrophysiologically. Conducting multidisciplinary studies involving biochemical and histological studies, about this issue will help to enlighten this matter. In epilepsy treatment for understanding the K_{ATP} channel agonist efficacy and mechanism of action must be made many basic and clinical researches.

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Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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The Skin Findings of Pregnant Women and Our Treatment Choices. A Turkish Experience: A 5-year Survey

Gebelerde Görülen Dermatolojik Hastalıklar ve Bu Hastalarda Tedavi Tercihlerimiz. Türkiye'den Bir Deneyim: 5 Yıllık Bir İnceleme

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ABSTRACT

AIM: *The number of pregnant women applying to dermatology outpatient clinics has increased. This has brought to notice the need for a specialized approach. In order to deal with pregnant women and their diseases, one must have a good knowledge of the skin disorders of pregnancy. Pregnant women and women who are considering pregnancy should be treated exclusively.*

METHODS: *Our aim was to evaluate the skin disorders of the pregnant women and to establish the treatment choices of dermatologists in our city when their patients were pregnant women.*

RESULTS: *Six hundred and ninety seven pregnant women who applied to the outpatient clinics were included in the study. Their diagnoses and the medications which are prescribed to them are retrospectively analyzed.*

Results: Pruritus, urticaria, acne and contact dermatitis were the most common diagnoses. Mostly topical medications were prescribed by the dermatologists. Among the systemic therapies antihistamines, steroids and antibacterials were prescribed 195, 148 and 87 times respectively which account for almost 95.98% of all systemic medications.

CONCLUSION: *Pregnancy is a unique period with a different range of dermatological diseases. It is also a vulnerable stage in terms of both the mother and the fetus. That's why the physicians generally choose topical therapies. Our study is an instructive one, showing the therapy preferences of dermatologists in our city when their patients are pregnant women.*

Key words: *dermatologic therapy; pregnancy; skin disorders*

ÖZET

AMAÇ: *Son yıllarda dermatoloji polikliniğine başvuran gebe sayısı artmıştır. Bu da beraberinde bu hastalara özel bir yaklaşım zorunluluğunu getirmiştir. Gebe bir hastaya dermatolojik olarak yaklaşabilmek için klinisyenlerin gebelikte görülen dermatolojik hastalıkları iyi bilmesi gerekmektedir. Gebeler ve gebelik düşüncesi olanlar ayrıcalıklı olarak gözden geçirilmelidir. Bu çalışmadaki amacımız gebelerde görülen deri hastalıklarını incelemek ve şehrimizdeki dermatologların bu hasta grubunda tercih ettiği tedavileri belirlemekti.*

YÖNTEM: *Kliniğimize başvuran 697 hasta retrospektif olarak değerlendirmeye alındı. Bu hastalara verilen tanılar ve reçetelendirilen ilaçlar analiz edildi.*

BULGULAR: *Gebe hastalarda en sık görülen hastalıklar kaşıntı, ürtiker, akne ve kontakt dermatit olarak bulundu. Bu hastalara çoğunlukla topikal tedaviler reçete edilmişti. Sistemik tedavilerden en sık tercih edilenler antihistaminikler, steroidler ve antibakteriyellerdi. Bu sistemik tedaviler sırası ile 195, 148 ve 87'şer defa reçete edilmişti ve gebe hastalarda yazılan sistemik tedavilerin yaklaşık % 96'sını oluşturuyorlardı.*

SONUÇ: *Gebelik çok sayıda dermatolojik hastalığın görülmesi ile kendine özgü bir dönemdir. Aynı zamanda gerek anne gerek de fetüs açısından çok hassas bir dönemdir. Bu nedenlerden dolayı doktorlar bu hasta grubunda genellikle topikal tedavileri tercih etmektedirler. Bu çalışma bölgemizdeki dermatologlarının gebe hastalarda tedavi tercihlerini göstermesi açısından yol göstericidir.*

Anahtar kelimeler: *deri hastalıkları; gebelik; dermatolojik tedavi*

Introduction

Pregnancy is a complex period due to hormonal, vascular, metabolic and immunological changes. Ninety percent of pregnant women experience a skin change of some kind or another[1]. These changes can be physiological or improval or worsening of existing dermatological conditions during pregnancy and dermatoses which are specific to pregnancy.

During pregnancy, the placenta acts like an endocrine organ and synthesizes estriol and progesterone.

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Hypertrophy of the parathyroid glands causes decreased serum calcium levels. Such hormonal changes may play a part in the pathogenesis of certain skin diseases of the pregnancy[2].

Immunological changes also occur during pregnancy. The T helper 1 (Th1): T helper 2 (Th2) cytokine ratio is shifted to the right, favoring the production of Th2 cytokines[3]. This tendency to the production of IL-4, IL-5, IL-10 and IL-13 seems to be necessary for the fetal survival. This shift is vital for the acceptance of foreign paternal antigens for the growth and development of the semi-allogeneic fetus[4]. Diseases like psoriasis that are mediated by Th1 cytokines tend to improve, while those mediated by Th2 cytokines, such as atopic dermatitis, may worsen. IL-4 also has an important role in the production of immunoglobulin E (IgE) by B lymphocytes and this is why atopic eruption of pregnancy develops[5].

In recent years, the number of pregnant women applying to dermatology outpatient clinics has increased. This is due to health services being more readily available and socio-cultural improvement. This increase in the number of pregnant patients has brought to notice the need for a specialized approach. In order to deal with pregnant women and their diseases, one must have a good knowledge of the skin disorders of pregnancy. Pregnant women and women who are considering pregnancy should be treated exclusively.

One study reported that 68% of the 2752 pregnant women included, received at least one prescribed or non-prescribed medication during pregnancy[6]. Considering that both the mother and the fetus are vulnerable to the hazardous effects of medications, physicians must be familiar with the potential effects of certain drugs on the developing fetus and the mother. Because of their not having a good command of the subject, many physicians prefer not to prescribe any drugs during the pregnancy period. Another explanation for their not prescribing drugs is that they think that the most common dermatologic problems do not require urgent treatment.

After the catastrophic effects of thalidomide and diethylstilbestrol use in the Fifties and Sixties, international pregnancy risk classifications for medications were established. The United States Food and Drug Administration (FDA), the Swedish Catalogue of Approved Drugs (FASS) and the Australian Drug Evaluation Committee (ADEC) are just a few of these. Although FDA classifications are the most widely used, other sources like Teratogen Information Service and Reproductive Toxicology Service data may be more up to date[7].

Based on all this information, epidemiological research focusing on skin diseases in pregnancy would be a suitable approach to pregnant women and their dermatologic problems.

Material and Method

Pregnant women who applied to our hospital's Dermatology and Venereology Outpatient Clinic between February 2010 and February 2015 were included in the study. The ages and dermatological diagnosis of the patients were recorded using the hospital's automation system. In order to ensure a proper diagnosis, dermatological inspection, laboratory tests, and if necessary, skin biopsies were performed. In case of multiple diagnoses in a single pregnant woman each diagnosis was evaluated separately. Any individual who visited the hospital a few times with the same diagnosis was counted once. The patients were evaluated under certain dermatological disease groups. These disease groups were as follows: pigmentary disorders, vascular disorders, hair disorders, nail disorders, striae distensae, scabies, urticaria, drug eruptions, psoriasis, contact dermatitis, atopic dermatitis, seborrheic dermatitis, acne, rosacea, systemic lupus erythematosus, bacterial infections, fungal infections, viral infections, intertrigo, recurrent aphthous stomatitis/Behçet's disease, unguis incarnatus, vasculitis, pruritus, xerosis, specific pregnancy dermatoses and others. Subgroups of specific pregnancy dermatoses were also separately evaluated.

As the second part of the study, we analyzed the medications that were prescribed by dermatologists in our region to pregnant patients. For this purpose, our hospital's data management system and the Ministry of Health's Pharmacy Data Management System (Medulla®) were used.

Results

Six hundred and ninety seven pregnant women who were hospitalized or visited our outpatient clinics were included in the study. Their ages varied between 17 and 38, with a mean of 24.63. The total number of diagnoses given to these 697 patients (after omitting

repetitive diagnosis for the same individual) was 937. Eighteen patients were given three diagnoses and 204 patients were given two different diagnoses. Four hundred and seventy five patients were given only one diagnosis.

The dermatological diseases, number of patients with each diagnosis and ratios are listed in Table 1. Pruritus was the most frequent diagnosis with a ratio of 8.86% followed by urticaria (72 patients, 7.68%). Acne and contact dermatitis were the most frequent third and fourth diseases with ratios of 6.51% and 6.30% respectively. Other forms of dermatitis such as atopic dermatitis, seborrheic dermatitis and unspecified dermatitis make up a group of 107 patients, which is nonignorable.

The total number of drugs prescribed to these 697 pregnant women that we were able to have access to was 3184, including moisturizers and magistral drugs. The most frequently prescribed topical and systemic drugs are listed in Table 2 and Table 3. Not surprisingly, mostly topical medications were preferred. Moisturizers and topical steroids were, by far, the most frequently prescribed topical drugs. Magistral drugs were prescribed 397 times. Topical antifungals and antibacterials followed these three, at 193 and 179 times respectively.

Antihistamines were the most frequently prescribed systemic drugs followed by systemic steroids and antibacterials. These three groups were prescribed 195, 148 and 87 times respectively which accounts for almost 95.98% of all systemic medications.

Table 1. *Dermatological diseases and their frequencies*

Dermatological diseases	Number of patients / ratio
Pigmentary disorders	48 / 5.12%
Vascular disorders	16 / 1.71%
Hair disorders	45 / 4.80%
Nail disorders	21 / 2.24%
Striae distensae	37 / 3.95%
Scabies	9 / 0.96%
Urticaria	72 / 7.68%
Drug eruptions	14 / 1.49%
Contact dermatitis	59 / 6.30%
Atopic dermatitis	30 / 3.20%
Seborrheic dermatitis	34 / 3.63%
Psoriasis	30 / 3.20%
Systemic lupus erythematosus	9 / 0.96%
Acne	61 / 6.51%
Rosacea	27 / 2.88%
Bacterial infections	29 / 3.10%
Fungal infections	32 / 3.42%
Viral infections	15 / 1.60%
Unguis incarnatus	14 / 1.49%
RAS/Behçet's disease	30 / 3.20%
Intertrigo	29 / 3.10%
Vasculitis	12 / 1.28%
Pruritus	83 / 8.86%
Xerosis	54 / 5.76%
Spesific pregnancy dermatoses	18 / 1.92%
Dermatitis nonspecified	43 / 4.59%
Others	66 / 7.05%
Total	937 / 100%

Discussion

Pregnancy is a critical period with a lot of physiological changes and vulnerability to various dermatoses. Due to various hormonal, vascular, metabolic and immunological changes, some diseases are more frequently observed whereas the others are less observed. Similarly some preexisting dermatoses heal whereas others worsen during the pregnancy period. The course of many other diseases is unpredictable.

In our study 8.86% of the pregnant women had nonspecific pruritus. Wong et al. reported that this ratio could rise to 20%[8]. In another study by Shanmugam et al. this ratio was 4.6%[9]. Pruritus is mostly caused by dry skin but it can also be an early sign of nonspecific and specific pregnancy dermatoses. Since pruritus can be a forerunner of some dermatoses, pregnancy specific or nonspecific, a detailed history taking, proper physical examination and necessary laboratory studies are obligatory.

Inflammatory skin disorders, including contact dermatitis, atopic dermatitis, seborrheic dermatitis and psoriasis, affected 153 pregnant women. Pregnancy is a period of reduced cellular immunity and reduced production of Th1 cytokines such as IL-2, IFN-γ and IL-12[10]. For this reason one would normally expect to see

Table 2. *Topical agents prescribed to pregnant women*

Topical agent	Total number prescribed
Topical steroids	673
- Weak potent	210
- Medium potent	258
- Potent	121
- Superpotent	84
Antifungals	193
- Azoles	90
- Terbinafin/butenafin	92
- Other antifungals	11
Antibacterials	179
- Mupirocin	74
- Fucidic acid	61
- Other antibacterials	44
Antivirals	57
Topical antihistamines	89
- Diphenhydramine	47
- Mepyramine	42
Moisturizer	813
- Urea	612
- Other moisturizers	201
Calcineurin inhibitors	93
- Tacrolimus	52
- Pimecrolimus	41
Calcipotriol	138
Permethrin	9
Benzoyl peroxide	57
Azelaic acid	38
Magistral drugs	397

Table 3. *Systemic agents prescribed to pregnant women*

Systemic Drug	Number of prescriptions
Systemic steroids	148
- Prednisolone	87
- Fluocortolone	48
- Betametasone	13
Antihistamines	195
- Diphenhydramine	7
- Chlorpheniramine	0
- Hydroxyzine	19
- Cetirizine	32
- Loratadine	11
- Levocetirizine	33
- Desloratadine	29
- Ebastine	5
- Pheniramine	42
- Rupatadine	17
Antibacterials	87
- Penicillin	59
- Cephalosporines	18
- Azithromycin	10
Antifungals	0
Antivirals	0
Lidocaine	8
Biologic agents	5
- Infliximab	5
Cyclosporine	5

contact dermatitis and psoriasis less than atopic dermatitis due to the fact that Th2 cytokines such as IL-4 and IL-10 dominate in the pregnancy period. IL-4 increases IgE generation by the B lymphocytes causing atopic eruption. However in our study 59 patients had contact dermatitis, which was almost double the incidence of atopic dermatitis which affected 30 individuals. This was an unexpected finding.

Vulvovaginal candidiasis is a common pathology in the pregnancy period. It is also caused by suppressed cellular immunity. Another reason for this is that high levels of estrogen cause an increase in the vaginal glycogen level which creates a suitable media for candidal growth[11]. Briggs et al. reported that vulvovaginal candidiasis is seen in almost 15% of all pregnant women[12]. However in our study this ratio was only 3%. This might be due to the fact that vulvovaginal candidiasis was, possibly, treated by gynecologists.

The incidence of all infections throughout pregnancy is 25%[12]. In our experience this was almost 8% including vulvovaginal candidiasis. Herpes simplex virus (HSV) was seen in 2% of pregnant women[13]. Only three of our

patients had HSV infection. This discordance came to our attention. Again, we thought that some pregnant women could have been treated by gynecologists, internal diseases specialists or family doctors.

Hyperpigmentation is a common problem in many pregnant women. It is due to increased levels of estrogen, progesterone and melanocyte stimulating hormone (MSH). Estrogen and progesterone increase melanin secretion from the melanocytes[14]. Melasma is the most common form of hyperpigmentation, especially in women with darker skin. In our experience 40 pregnant women had melasma (4.27%). Barankin et al. reported that 45% of pregnant women had had melasma[15]. Pregnant women in Turkey are exposed to sunlight in almost every season of the year and melasma is a common skin condition. For this reason, pregnant women might have accepted melasma as normal. This may explain the low ratio.

Estrogen prolongs the anagen phase of the hair cycle and decreases the transition from anagen to telogen[4]. Its clinical manifestation is hypertrichosis which was observed in 3.6% of our patients. One should remember that, in contrast, in the postpartum period compensatory telogen effluvium is observed and can continue from six to twelve months[2].

Striae are one of the most disturbing changes seen in pregnancy. They are seen in approximately 90% of pregnant women. They can be seen because of physical stretch or intradermal tears of collagen[2]. Only 3.95% of our patients complained about striae, which was much less when compared with the literature. Based on this, it can be said that, striae are not accepted as troubling by Turkish women or seen as a worthwhile reason for applying to a hospital.

Pemphigoid gestationis, polymorphic eruption of pregnancy, intrahepatic cholestasis of pregnancy and atopic eruption of pregnancy make up a group of diseases which are specific to the pregnancy period and are called the specific dermatoses of pregnancy. These were seen in 5% of 1430 patients in one study[16]. Only 1.92% of our patients were given one of these diagnoses. Possibly some patients who were given the diagnosis of pruritus and atopic dermatitis must have been categorized in this group, as many of the specific pregnancy dermatoses may start with nonspecific pruritus.

When we reviewed the prescriptions given to these pregnant women, as expected, we encountered mostly topical choices. As pregnancy has many mysteries, it seems to be rational to be protective and minimalist when prescribing a medication. Therefore many physicians are unwilling to prescribe medications to pregnant women. However, a multinational survey indicated that 86% of pregnant women took an average of 2.9 medications throughout their pregnancy[17].

Apart from moisturizers, steroids were the most commonly prescribed topical agents. Generally weak potent and medium potent ones were chosen. Topical steroids are accepted as safe during pregnancy, with a few exceptions. Chi et al. indicated that the use of more than 300 grams of potent and ultra-potent topical steroids throughout pregnancy can cause low birth weight in infants[18]. Furthermore, they proposed a guideline for topical steroid use in pregnancy in 2011[19].

Topical antifungals and antibacterials were prescribed to 193 and 179 pregnant women respectively. Terbinafine and imidazoles were equally chosen. Considering that terbinafine is a category B drug and imidazoles are category C[20], one would have expected to see terbinafine prescribed more. As topical antibacterials, mupirocin and fusidic acid, both category C[20], were most commonly chosen.

Generally topical antihistamines are not chosen by dermatologists because of their potential to cause irritation[2]. However, in our study we observed that topical diphenhydramine and mepyramine were prescribed 47 and 42 times respectively. This may be a reflection of the fear to prescribe systemic agents.

For the treatment of acne, mostly azelaic acid (B), benzoyl peroxide (C) and magistral drugs were chosen (Table 2).

Among the systemic drugs, antihistamines, steroids and antibacterials were prescribed 195, 148 and 87 times respectively. Antihistamines are among the most commonly used drugs in pregnancy. Older, first generation ones are better studied with more data. There are contradictory reports about antihistamine use in pregnancy. A large number of pregnancies exposed to first generation antihistamines have been studied, and no definitive increased teratogenic risk was observed[20]. However, there are reports indicating fetal hypoxia with diphenhydramine, fetal eye and ear defects with chlorpheniramine[21], and hypospadias with loratadine use[22]. Zierler, in 1986, reported that the use of antihistamines within two weeks of delivery caused a twofold increase in retrolental fibroplasias[23]. One recent study indicates that maternal antihistamine use increases the

risk of congenital heart defects[24]. Chlorpheniramine and hydroxyzine are the best two choices[2]. From the second generation antihistamines, cetirizine and loratadine can be safely used after the first trimester[2]. In our study more than half of the antihistamines prescribed to pregnant women were second generation ones. Although these new antihistamines seem to be safe, there are insufficient data about them being used in pregnancy.

In the placenta, prednisone and prednisolone are enzymatically inactivated. For this reason, they are the first choices in case of systemic steroid necessity[20]. In our study prednisolone and fluocortolone, both category C drugs, were the most commonly prescribed systemic steroids. Although widely used during pregnancy, systemic steroids are thought to have the potential to cause orofacial clefts, premature delivery, intrauterine growth retardation, gestational diabetes, hypertension and preeclampsia[25]. For this reason, physicians must be careful when prescribing them.

Penicillins, cephalosporins and azithromycin were the systemic antibiotics prescribed to pregnant women in our study. All are considered compatible with pregnancy[25].

We realized that neither antifungals nor antivirals were prescribed systemically to our patients. Considering that terbinafine and acyclovir are category B drugs[20], this attitude can be accepted as overprotective. Another possible explanation is "lack of knowledge"

Among the biologic agents, only infliximab was given to five pregnant women. As these agents are new, there is a lack of data at present. There are reports about etanercept causing spontaneous abortion, vertebral anomalies, anal atresia, cardiac anomalies, skeletal anomalies and cardiac anomalies in animal models when used in pregnancy[26]. Thus, physicians should avoid prescribing these agents to pregnant women if there is an alternative.

Cyclosporine is a category C immunosuppressive agent. It has been used and studied in pregnant organ transplant recipients for a long time[27]. No birth defects have been attributed to it. Therefore it can be used in cases of resistant psoriasis and atopic dermatitis[6]. Despite this fact only five of our patients were prescribed systemic cyclosporine.

As a limitation, the number of patients included in the study can be considered as insufficient. Another limitation is that, as a diagnostic tool for epidemiology, health management and clinical purposes, The International Classification of Diseases version 10 (ICD-10) is used in our country. Whether or not patients' records are accurately and fully documented using the ICD-10 system is also uncertain. Furthermore, there are still diseases which are not categorized in the ICD-10 system.

Conclusion

When we review the literature about pregnancy and dermatological diseases, we generally come across the specific dermatoses of pregnancy. There are only a few reports about the dermatological diseases seen in pregnant women that are not specific to pregnancy. In this respect our study seems to be an illustrative one. Although limited to a certain region of the country, this study is also instructive, showing the therapy preferences of dermatologists in our region when their patients are pregnant women.

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DERLEME / *REVIEW*

A Contemporary Perspective on Therapeutic Measures and Approaches to Pain Management in Lung Cancer

Akciğer Kanserindeki Ağrıyı, Tedavi Edici Önlem ve Yaklaşımlara Güncel bir Bakış Açısı

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ABSTRACT

Lung cancer is the commonest malignancy worldwide, and 80–90% of patients die within one year of diagnosis. Since it is usually very difficult and sometimes impossible to cure lung cancer radically, the precautions and therapy modalities chosen as palliative measures for the improvement of quality of life of the cancer patient become more important than the curative treatments. Lung cancer also commonly induces moderate to severe pain, but little is known of the extent of this complex problem. The aim of this review is to highlight current treatment modalities for the pain associated with lung cancer and to suggest a broader perspective in its study and management.

Key words: *cancer pain; lung cancer; neuropathic pain*

ÖZET

Akciğer kanseri dünyadaki en yaygın kanser türüdür ve hastaların %80-90'ı tanıda bir yıl sonra ölmektedir. Akciğer kanserinin kesin tanısı genellikle zordur ve bazende imkansızdır. Kanser hastalarının yaşam kalitesinin iyileştirilmesi için palyatif tedbirler olarak seçilen önlemler ve tedavi yöntemleri kesin tedavi kadar önemlidir. Ayrıca akciğer kanseri orta ve şiddetli ağrıya neden olur, ama bu karmaşık sorun ufak ölçüde bilinmektedir. Bu derlemenin amacı, akciğer kanseri ile ilişkili ağrı için mevcut tedavi yöntemlerini vurgulamak ve tedavinin çalışma ve yönetimi daha geniş bir bakış açısı ile önermektir.

Anahtar kelimeler: *kanser ağrısı; akciğer kanseri; nöropatik ağrı*

Introduction

According to a study by Hauser et al, prognostic factors in patients with advanced cancer can be conceptualised as attributes of the host, tumour and treatment, and interactions among the three reflected in symptoms, quality of life performance status and laboratory tests[1]. Pain is a major problem that has a great impact in the quality of life of cancer patients.

In spite of the continuing study of the physiology and biochemistry of pain, it remains true that cancer pain is only partially understood. Pain is often experienced as several different types, with combined somatic and neuropathic types the most frequent[2].

Neuropathic pain results from damage to or dysfunction of the peripheral or central nervous system, rather than stimulation of pain receptors. Diagnosis is suggested by pain out of proportion to tissue injury, dysesthesia (e.g. burning, tingling), and signs of nerve injury detected during neurologic examination[3].

Nociceptive pain may be somatic or visceral. Somatic pain receptors are located in skin, subcutaneous tissues, fascia, other connective tissues, periosteum, endosteum, and joint capsules. Stimulation of these receptors usually produces sharp or dull localized pain, but burning is not uncommon if the skin or subcutaneous tissues are involved. Visceral pain receptors are located in most viscera and the surrounding connective tissue. Visceral pain due to obstruction of a hollow organ is poorly localized, deep, and cramping and may be referred to remote cutaneous sites. Visceral pain due to injury of organ capsules or other deep connective tissues may be more localized and sharp[3].

The prevalence of cancer pain varies from 5%[4] to 100%[5,6] among studies. The type and stage of cancer accounts for some of this variability. Lung cancer, head and neck cancer and genito-urinary cancer cause particularly high levels of pain[7,8,9], and in general, those with advanced cancer are more likely to experience pain than those with early disease[10,11].

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A survey by IASP (International Association for the Study of Pain)[12] reported that pain interpreted by the clinician to be nociceptive and due to somatic injury occurred in 71.6% of patients. Pain labeled nociceptive was noted in 34.7% of subjects and pain attributable to neuropathic mechanisms occurred in 39.7% of subjects. In a broad classification, the major pain syndromes comprised bone or joint lesions (41.7%), visceral lesions (28.1%), soft tissue infiltration (28.3%), and peripheral nerve injuries (27.8%). Twenty-two types of pain syndrome were most prevalent. This wide IASP survey of 1,095 patients confirmed that cancer pain characteristics, syndromes and pathophysiologies are very heterogeneous.

In a study designed by a group of Japanese cancer researchers, nociceptive pain was the most common, occurring in 85% of patients, and neuropathic pain in 33%[13]. For these reasons, pain control in cancer is centered on opioid therapy, and therefore adequate use of opioids becomes important[14,15].

In a study by Mercadante et al, sixty consecutive lung cancer patients referred to a palliative care service were followed until death to obtain detailed information about the prevalence, characteristics and location of pain. Satisfactory relief of somatic incident pain was not achieved, while patients with neuropathic pain were not disadvantaged compared to those exhibiting somatic or visceral pain[16].

Lung cancer causes a very high frequency of distressing symptoms and survival in the majority of patients is measured in months, not years[17]. Pain is one of the most common symptoms causing distress in the final months and weeks of life.

Somatic Pain in Lung Cancer

Specifically, lung cancer can cause pain locally by invading the parietal pleura, ribs, thoracic spinal cord or brachial plexus or elsewhere in the body by metastasis. In addition, the short and long term consequences of radiotherapy and chemotherapy treatments can be painful[7,18].

The skeleton is one of the most common sites of metastasis in patients with lung cancer. The incidence of bone metastases in lung cancer patients is approximately 30–40%, and the median survival time of patients with such metastases is 6–7 months[7]. Metastatic bone disease leads to various complications or skeletally related events, including pain.

The prevention and treatment of bone metastases is mainly dependent on effective treatment against lung cancer itself. Radiation therapy, surgery and bisphosphonates are the principle direct treatments for bone metastases[19]. However, pain is not always adequately controlled by high doses of specific medication, radiation therapy or chemotherapy. When these therapies do not provide adequate pain relief, percutaneous vertebroplasty, cementoplasty, radiofrequency ablation and internal radiotherapy appear to be efficient complementary pain control methods[20]. In considering bisphosphonates, they inhibit osteoclast-mediated bone resorption by binding to bone minerals, interfering with osteoclast activation. These agents also promote repair by stimulating osteoblast differentiation and bone formation. As a result, these agents are playing an increasing role in the treatment of painful bone metastases[21].

Pancoast's syndrome is produced by apical lung tumor, with a local extension to the inferior brachial plexus, paravertebral sympathetic chain, vertebral bodies and first, second and third ribs. Its major cause is non-small cell lung cancer, and it may produce shoulder pain and Horner's syndrome. The best diagnostic method is transthoracic needle aspiration, because of its peripheral location. Neoadjuvant chemo-radiotherapy followed by complete surgical excision is the preferred approach to these tumors[22].

Pain is especially a problem when there is chest wall involvement or bony metastases. Careful use of appropriate analgesics based on the 'WHO analgesic ladder' is the mainstay of treatment, but it is important to recognize opioid-resistant pain. Occasionally nerve root block or even cordotomy are required for intractable symptoms. Palliative radiotherapy is also an important component of pain management in some patients[23].

In the late 1980's, a pain-free state for most patients with advanced cancer seemed unattainable[23]. Since then many studies have been undertaken to assess the prevalence and nature of cancer pain and they have helped reduce the level of pain experienced by most lung cancer patients by offering a broader suite of complementary treatments[2,23].

The most common pain sites reported by persons with lung cancer are the chest and lumbar spine. Nociceptive and somatic pains are the major subtypes of pain, but neuropathic pain accounts for 30%[24]. Silvestri et al reported that the three main causes of malignancy-related pain in lung cancer are skeletal metastases (34%), Pancoast tumor (31%) and chest wall disease (21%)[25].

Skeletal metastases usually present with localized pain. Palliative radiotherapy is the mainstay of treatment for painful skeletal metastases, complemented with optimal oral, transdermal or parenteral analgesia[24]. According to a review on teletherapy and radiopharmaceutical therapy of painful bone metastasis, many questions remain as to the optimal use of radiopharmaceuticals, including whether combinations of radiopharmaceuticals with each other, with bisphosphonates or with chemotherapy can further improve therapeutic outcomes[26].

The pain in Pancoast tumors may be severe and unrelenting, worsened by movement of the affected arm, and often develops months before diagnosis[27]. Treatment includes vigorous efforts to achieve local control. Radiotherapy alone at a dose of 6,000 cGy is the usual treatment; however, complete surgical excision, when possible, achieves the most appreciable pain control[28]. Pre- and postoperative radiotherapy is also considered appropriate. Pharmacological management of superior sulcus pain syndrome is very challenging and includes the use of opioids, neuropathic agents, and interventional pain therapy[24]. Chest wall pain may be due to direct chest wall extension by the tumor which can cause radicular pain. Chest wall pain can also be treatment-related, such as post-thoracotomy pain, or pain subsequent to pleural drainage and pleurodesis[24].

Neuropathic Pain in Lung Cancer

The identification of a neuropathic pain syndrome in a cancer patient requires a focused clinical evaluation based on knowledge of common neuropathic pain syndromes. If a tumor is directly involved in the etiology of the pain, oncologic treatment is an initial consideration and may include surgery, radiation, or chemotherapy. There is no single accepted algorithm for the analgesic treatment of neuropathic pain and a systematic approach utilizing therapeutic trials of specific agents at gradually increasing doses is warranted[29].

Neuropathic pain is a common syndrome in cancer patients. Its pathophysiology is not fully understood, often leading to poor management and needless suffering. Knowledge of the potential mechanisms of neuropathic pain, skill in both interpreting the case history and physical-assessment techniques, and awareness of the more common neuropathic pain syndromes and their etiologies, as well as familiarity with the role of new pharmacologic interventions, should allow healthcare professionals to provide better relief of neuropathic pain. At present, a variety of agents are used to treat neuropathic pain situations. Rehabilitation of persons with neuropathic pain should both be part of overall management and specifically address functional impairment and safety factors to prevent accidents resulting from sensory loss[30].

Increases in our understanding of the function of the neurologic system over the last few years have led to new insights into the mechanisms underlying pain symptoms, especially chronic and neuropathic pain[31]. At present, therapeutic options for the traetment of neuropathic pain are largely limited to drugs approved for other conditions, including anticonvulsants, antidepressants, antiarrhythmics, and opioids. Therefore, treatment based on the underlying disease state (eg, postherpetic neuralgia, diabetic neuropathy) may be less than optimal, in that two patients with the same neuropathic pain syndrome may have different symptomatology and thus respond differently to the same treatment.

Cancer pain syndromes may arise from the interruption of bone, viscera, and neural structures by malignant spread of the disease[32]. However, not only malignant spread, but paraneoplastic effects of cancer may cause neuropathies leading to neuropathic pain[33].

The shoulder-hand syndrome is a paraneoplastic syndrome that can cause neuropathic pain in lung cancer and is described by many authors as a sequela of myocardial infarction, hemiplegia and cancer of the lungs. The syndrome evolves in a form that resembles the post-traumatic algodystrophies. Pain, stiffness and tenderness of the shoulder, coupled with limited movement indistinguishable from capsulitis, are usually the first symptoms and these sometimes progress to swelling, pain, stiffness and discoloration of the hand[33].

According to a study by Potter and Higginson, pain experienced by lung cancer patients is usually of mixed pathophysiology and a relatively high proportion is attributable to neuropathic mechanisms[7].

Neuropathic pain may be a consequence of malignant invasion of neurological structures (including Pancoast tumours) or neurological damage resulting from antineoplastic treatment. Neuropatic pain may also contribute disproportionately to the duration and intensity of pain because it is difficult to identify and is relatively resistant to conventional analgesic treatment[34,35]. Despite this, early diagnosis and treatment are critical to the prevention of irreversible neurological damage and chronic neuropathic pain in cancer patients[36].

Chemotherapy-induced peripheral neuropathy (CIPN) is a major dose-limiting side effect of many commonly used chemotherapeutic agents, including platinum drugs, taxanes, epothilones and vinca alkaloids, and also newer agents such as bortezomib and lenolidamide[37]. Taxanes produce asymmetric, axonal, predominantly sensory distal neuropathy, with less prominent motor involvement[38]. Regrettably, there are currently no effective symptomatic treatments for paclitaxel-associated pain, myalgias and arthralgias. However, tricyclic antidepressants and anticonvulsants have been used with some success to treat the symptoms of neurotoxicity[38].

The current authors earlier reported a lung cancer patient suffering from severe pain and concluded from his therapy follow-ups that gabapentin seemed to be reliable even at high doses, and may become the first choice treatment in the taxane-induced arthralgias and myalgias which usually accompany neuropathic pain[39].

The disabling condition of metastatic plexopathy often accompanies advanced systemic cancer and may involve any of the peripheral nerve plexuses. Brachial plexopathy most commonly occurs in carcinoma of the breast and lung, and lumbosacral plexopathy is most commonly associated with colorectal and gynecologic tumors, sarcomas, and lymphomas. Regardless of the location, neoplastic plexopathy is often characterized by severe, unrelenting pain[40].

Facial pain can, on rare occasions, be the presenting symptom of lung cancer[16]. The pain is frequently described as severe and aching, and may be continuous or intermittent and is typically neuropathic. In the literature, there are only a few case reports on this subject[41–43].

To our knowledge, treatment of neuropathic pain in cancer patients does not have any specifically stated guidelines. However, the EFNS (European Federation of Neurological Societies) Task Force published guidelines in 2006 and advised the use of gabapentin, pregabalin and tricyclic antidepressants (TCA) as the first line of drugs in painful neuropathy, whereas lamotrigine, opioids, serotonin-noradrenalin reuptake inhibitors (SNRIs) and tramadol were recommended as second line drugs[44]. Seven of the patients had lung cancer and all patients had high scores of LANSS (The Leeds Assessment of Neuropathic Symptoms and Signs) which indicated that their pain was neuropathic rather than nociseptive[45].

Our clinical observations generally correspond with a recent review on neuropathic cancer pain, according to which, drugs used in non-cancer neuropathy appear to be effective in cancer-induced pain states[46].

Very recently, alpha-lipoic acid has been shown to be neuroprotective against chemotherapy-induced neurotoxicity. Mitochondrial toxicity is an early, common event both in paclitaxel and cisplatin induced neurotoxicity[47]. Paclitaxel and cisplatin are used very commonly in lung cancer treatment. Alpha-lipoic acid protects sensory neurons through its anti-oxidant and mitochondrial regulatory functions, possibly by inducing the expression of frataxin. These findings suggest that alpha-lipoic acid might reduce the risk of the development of peripheral nerve toxicity in patients undergoing chemotherapy and encourage further confirmatory clinical trials[47].

Because pain is a common cause of distress in lung cancer, pain control is a high priority in the supportive care of this population[23]. However, it is usually underdiagnosed and its management needs further consideration.

The current authors believe that a detailed history of pain should be obtained from both patients and care givers. Frequent visits to patients or at least seeing them regularly in the outpatient clinic may help achieve better understanding of the pain these patients suffer from.

We currently have many different treatment modalities for lung cancer induced pain when compared to the past. Patients with advanced disease often experience multiple symptoms, including fatigue, pain, dyspnea, coughing, hemoptysis and anorexia[48]. Unfortunately, survival rates have not improved in the past 30 years, despite considerable research in diagnostics and therapeutics. The sharing of interdisciplinary knowledge must become a higher priority to help improve the therapy and outcomes of these patients.

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DERLEME / *REVIEW*

Malnutrition in Long-Term Hospitalized Patients

Uzun Süre Hastanede Yatan Hastalarda Malnütrisyon

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ABSTRACT

Malnutrition is a very serious problem in long term hospitalized patients. Malnutrition is associated with negative outcomes for patients, including higher infection and complication rates, increased muscle loss,impaired wound healing, longer hospital stays, and increased morbidity and mortality. Despite the seriousness of malnutrition, there is not enough emphasis on its diagnosis, prevention and treatment. In this context, increasing the awareness of malnutrition would have positive clinical results.

Key words: *malnutrition; nutrition; nursing care*

ÖZET

Uzun süre hastanede yatan bireylerde malnütrisyon önemli bir sorundur. Enfeksiyon, kas kaybı, yara iyileşmesinde gecikme, hastane kalış süresinde uzama, morbidite ve mortalite oranlarında artışa neden olmaktadır. Malnütrisyon bu kadar ciddi bir sorun olmakla birlikte uygulamaya bakıldığında tanılanması, önlenmesi ve tedavisine yeterince önem verilmediği görülmektedir. Bu bağlamda sağlık ekibi içerisinde malnütrisyona ilişkin farkındalığın arttırılması klinik önem göstermektedir.

Anahtar kelimeler: *malnütrisyon; beslenme; hemşirelik bakımı*

Introduction

Malnutrition is a comprehensive term that is used to define an individual's status of being inadequately nourished. Malnutrition may occur during illness when the need for nourishment increases but the intake of nutrients is inadequate or when there is a failure to absorb nutrients or in the case of an extreme loss of nutrients due to underlying diseases. When these factors are combined, malnutrition presents as a serious complication that affects multiple organs and systems in the body. Infection, muscle loss, delays in wound healing and extensions of hospital stays may increase morbidity and mortality rates[1,2].

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The European Society of Parenteral and Enteral Nutrition (ESPEN) makes important distinctions in the definition of malnutrition, to differentiate the terms "cachexia","sarcopenia" and "malnutrition". Cachexia which is a multi-factor syndrome chacracterized by severe loss of body weight, fat and muscle is mostly displayed as increased protein catabolism. The malnutrition is in hospitalized patients may be accompanied by cachexia (illness-associated) but also be unaccompanied[3].

The risk of developing malnutrition increases as the stay in the hospital is extended. For this reason, patients hospitalized for long periods of time pose a serious issue that must be addressed. Although malnutrition is a serious problem, a closer look at practices reveals that not enough importance is placed on diagnosing, preventing and treating this condition. In this context, it is of clinical significance that awareness about malnutrition should be raised among healthcare professionals.

The literature shows that the high risk of malnutrition as a result of receiving inadequate nourishment is known and attention is called to the many factors involved. These factors can be considered in two groups: factors stemming from the patient and those stemming from the healthcare team. Patient-related factors include age, apathy and depression, illness (cancer, diabetes, cardiac, gastrointestinal conditions), drug treatment, problems with chewing and swallowing, motor restrictions, impaired smell and taste, and treatment methods (ventilation, surgery, drains). Factors related to the healthcare team are described as the failure of health professionals to recognize malnutrition, deficiencies in the systems of screening and evaluation, uncertainties in nutrition education and responsibilities related to nutrition, missing height and weight records, gaps in medical records related to the patient's oral intake, and a general inability to grasp the importance of nutrition[2,4,5].

Malnutrition Screening and Evaluation

Diagnosing malnutrition or assessing the risk of malnutrition forms the foundation of treatment. The use of tools can aid the health team in identifying nutritional risks, evaluating nutrition, correctly identifying patients at risk of malnutrition and in increasing the effectiveness of the treatment a patient is receiving. Nutritional support is generally provided to patients by their doctors, nurses and dieticians but the time allotted for this purpose is inadequate[2]. Because of this, many hospitals are unable to identify the development of malnutrition and consequently, the process of evaluation and treatment of malnutrition is ultimately neglected.

Identifying nutritional status not only reveals the existence, risk and degree of malnutrition, but it also sheds light on the effectiveness of nourishment. The diagnosis is based on the patient's medical history, physical examination (muscle mass, muscle loss, fat storage, edema, acids), anthropometric measurements (body weight, height, body mass index, triceps' size), laboratory tests (creatinine, serum transferrin, serum albumin, prealbumin), and functional tests (hand dynamometer, direct muscle stimulation, respiratory and immune function tests). Furthermore, doctors and nurses may also use identifying tools for which validity and reliability tests have been carried out to identify a patient's nutritional status. As known, the various screening and evaluation instruments available, with respect to nutrition, facilitate the identification of risk and the process of diagnosis (Table 1)[6–8].

Table 1. *Methods of assessing the nutritional status with various parameters*

Nutritional Status Evaluation Tools
Prognostic Nutritional Risk Index (PNI)
Nutritional Risk Index (NRI)
Geriatric Nutritional Risk Index (GNRI)
Maastrict Index (MI)
Instant Nutritional Assessment (INA)
Determining a Nutritional Health Check List (DETERMINE)
Simplified Nutrition and Appetite Questionnaire (US - SNAQ)
Short Nutritional Assessment Questionnaire (Dutch - SNAQ)
Nutritional Risk Screening 2002 (NRS - 2002)
Subjective Global Assessment (SGA)
Malnutrition Universal Screening Test (MUST)
Protein Energy Malnutrition Scale (PEMS)
Malnutrition Risk Scale (SCALES)
Mini Nutritional Assessment (MNA)
Mini Nutritional Assessment-Short Form (MNA - SF)

Hospital and Illness-Related Prevalence of Malnutrition

The main cause of malnutrition in developed countries is generally illness. Many studies conducted over the last 30 years have emphasized the seriousness of illness-related malnutrition in hospitalized patients. Whether it is acute or chronic, malnutrition is triggered by more than one factor. Malnutrition is commonly observed in patients with chronic liver disease, chronic cardiac disease, kidney failure, acquired immune deficiency syndrome (AIDS), chronic obstructive pulmonary disease (COPD), inflammatory intestinal conditions, neurodegenerative diseases and other chronic conditions, as well as in patients hospitalized for malignant diseases[9]. The assessment of malnutrition prevalence in studies varies between 20%-60%[10,11]. In a screening of 9336 persons at a hospital in the UK, it was found that 28% of the patients were at risk of malnutrition, 43% of those who had developed malnutrition were suffering from digestive system ailments, 33% had neurological conditions, 21% cardiovascular disease and 18% had musculoskeletal disorders[11]. In Turkey, Korfalı et al. (2009) reported in a study they conducted in 62 hospitals that 15% of the 29,139 persons they assessed had developed malnutrition. It was found that 52% of intensive care unit patients, 43.4% of medical oncology patients, 23.9% of neurology patients, 24% of hematology patients, 19.1% of gastroenterology patients, 18.3% of gastrointestinal surgery patients, 18.2% of thoracic surgery patients, 16.4% of internal medicine patients, 10.3% of cardiology patients, and 10.9% of cardiac surgery patients had developed malnutrition[12]. In a study conducted by Sungurtekin et al. (2004) using two different nutritional screening tools, it was observed that 36% of patients at a hospital were suffering from malnutrition[13]. In Bayır's study (2012) on malnutrition rates in cases undergoing open-heart surgery and determining related risk factors, it was revealed that 20% of patients suffered from malnutrition and that hospital stay durations for these patients was longer than for other patients. The study also reported that patients with longer hospital stays were more likely to develop malnutrition than patients who were present for shorter stays[14].

Treatment and Care in Malnutrition

Patients who are screened, evaluated and found to be at risk of malnutrition are started on nutritional support. This treatment involves oral intake of nutrients, the type of which varies according to the preferences of

the individual, and in patients with no capacity for oral intake, the patient is fed parenterally[15]. Enteral nutrition (EN) is indicated in patients with adequate digestive and absorptive capacity of the gastrointestinal tract but who cannot eat enough. Enteral nutrition offers many advantages when compared to parenteral nutrition. These are the normalization of enteral nutrition intestinal functions in a shorter time, having lower risk of infection, being more suitable for human physiology, its easier application, being cheaper than parenteral nutrition, less occurrence of metabolic and septic complications, lower mortality and morbidity rates, applicable with fewer personnel and being ready to use[16-18]. However, nutrition tolerance of the patient (e.g. nausea, vomiting), nursing practices (e.g. the change of body position and nutrition arrest), other medical procedures and nutrition programs that are not prepared according to the individual are among the major factors adversely affecting enteral nutrition[19.]

Parenteral nutrition (PN) is another form of nutrition that enables nutrition for patients with gastrointestinal limited absorption capacity who cannot be nourished functionally or enterally. Although it positively affects the patient's course of recovery when properly applied to the correct patient, its use causes the increase of infectious complications, the formation of metabolic complications and cost increase when preferred wrongfully. Therefore, it is essential to apply PN in case of failure to meet the nutritional requirements enterally and in patients who are unable to take oral implementing at least 7 days. Parenteral nutrition is applied in two ways as peripheral parenteral nutrition and central parenteral nutrition. The decision to implement PN requires a multidisciplinary approach[20].

The beneficial effect of parenteral nutrition (PN) in improving the nutritional status of hospitalized patients who are malnourished is well established[21]. However, several retrospective and prospective studies have shown that the use of PN is an independent risk factor developing the other health problems[22]. PN is a costly technology and can also be associated with complications such as electrolyte disturbances, hyperglycaemia, hypertriglyceridaemia, as well as hepatobiliary, infectious and mechanical complications[23]. Considering these complications caused by it, individual nutritional solution should be selected considering the condition of the patient while deciding on PN support.

After deciding upon the route to be taken in feeding the patient, the daily calorie need is then calculated. Depending upon the clinical condition of the patient, the choice between enteral and parenteral nutrition is an important factor in achieving tolerance and preventing complications. Products that need to be used in tube feeding should not be administered orally and the patient should be monitored in terms of complications such as nausea, vomiting, diarrhea, pulmonary aspiration, fluid overload, electrolyte imbalance, dehydration, hyperglycemia or the development of an infection. Bodoky& Smith (2009) state that diarrhea is a complication that can be prevented with enteral nutrition and that nausea and vomiting must be prevented because of the risk of aspiration[24]. The speed, amount and level of tolerance to products administered via the enteral route (gastric residue, distension) must be strictly controlled. Studies have shown that nurses are not adequately equipped to identify the nutritional needs of tube-fed patients, that they do not adequately consult the guides and display a general lack of knowledge, being therefore unable to provide suitable care[25,26]. In another study conducted by Uysal et al. (2011), it was reported that nurses were precise about following up on the administration of the feeding, the nutrients, the speed the products were administered, their amounts and the gastric residue status at 4-6 hour intervals[27].

Patients who receive nutritional support need to be monitored in terms of their vital signs and weight as well as through a weekly evaluation of anthropometric measurements and laboratory tests (albumin, etc.). In a follow-up study on the nutritional status and development of malnutrition in in-patients at a hospital, Güngör (2009) found that 77% of hospitalized patients displayed an average weight loss of 3.9 kg despite their nutritional support. These patients' body mass index values fell as the duration of the hospital stay increased[5]. In situations where enteral feeding is not possible, the nutritional needs are met with parenteral feeding. Products to be administered via the parenteral route may be applied peripherally or centrally. In PN status, it is important to watch the patient for infection symptoms and findings and monitor for air embolisms, hyperglycemia, hypoglycemia and circulatory overload[27–29]. A study by Küçük et al. reports that 17% of patients developed infections and 52.1% experienced hyperglycemia[30].

Conclusion and Recommendations

To prevent malnutrition, it is important to evaluate the nutritional status of hospitalized patients and to closely

monitor their consumption of nutrients, anthropometric measurements and blood-test results. The first stage in treating malnutrition is the identification and assessment of the condition. For this reason, doctors and nurses need to complete a comprehensive evaluation of patients from the moment they are admitted to the hospital, working in cooperation with the rest of the professional healthcare team. The European Society of Parenteral and Enteral Nutrition (ESPEN) and other international associations have issued guidelines to follow when using screening tools but these are not enough by themselves. Acting upon the results of screening will play an important role in finding solutions to the problems presented by malnutrition.

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OLGU SUNUMU / *CASE REPORT*

Occupational Exposure to the Nitrogen Based Fertilizer: A Severe Case of Irritant Contact Dermatitis

Nitrojen Bazlı Gübreye Mesleki Maruziyet: Ağır Bir İrritant Kontakt Dermatit Olgusu

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ABSTRACT

Nitrogen is a chemical substance used in cryobiology, cryotherapy and agriculture. Here, we have reported a case of 19-years-old male farmer that developed severe bullous lesions on both of his legs after occupational exposure of nitrogen based liquid fertilizer through the strawberry leaves. Fertilizer induced contact dermatitis has extremely rare been reported in the literature. We have highlighted the importance of protection from occupational exposure to the fertilizers in this case.

Key words: *contact dermatitis; nitrogen fertilizer; strawberry leaves*

ÖZET

Nitrojen kriyobiyoloji, kriyoterapi ve tarımda kullanılan kimyasal bir maddedir. Burada, çilek yapraklarına kullanılan nitrojen bazlı gübreye maruz kalınması sonrası her iki bacağında ciddi büllöz lezyonları gelişen, 19 yaşında erkek çiftçi olgusunu sunduk. Literatürde gübrenin tetiklediği kontakt dermatitler çok nadirdir. Bu olguda mesleki gübreye temasın önlenmesinin önemini vurgulamak istedik.

Anahtar kelimeler: *kontakt dermatit; nitrojen gübre; çilek yaprakları*

Introduction

Nitrogen is a chemical substance that used in cryobiology and cryotherapy, especially in dermatology. It is also an essential element required for successful plant growth that the most used variety of fertilizer in agriculture[1]. Direct skin contact with liquid nitrogen causes severe skin irritation called cryogenic burns.

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Case History

A 19-years-old strawberry picker man was admitted to our clinic with severe vesicular and bullous lesions accompanied with complaints of intensely itching and burning. Lesions were on erythematous base and localized on his both legs (Fig. 1). He had worked in strawberry field approximately 12 hours before onset of lesions. The lesions were limited to uncovered contact area with the leaves. He had applied a nitrogen based liquid fertilizer to the strawberry leaves and shortly after had begun to work in the field. He had a continuously contact with the leaves while he was working. Patient has no history of any allergy, medication or disease include contact or food allergy to the strawberry and strawberry leaves. Patch test was not performed because patient denied. Laboratory investigations were completely with in normal limits. No any microorganism detected in cultures obtained from blisters fluid. Histological examination of biopsy specimen showed lack of epidermis and mixed inflammatory infiltrate of lymphocytes in superficial dermis (Fig. 2). Direct immunofluorescence staining was negative. Based on these findings, we made a diagnosis of irritant contact dermatitis due to nitrogen based fertilizer. Patient treated with a short tapering course of systemic methylprednisolone (40 mg/day, tapered by 5 mg/day), topical wed dressing and topical antibiotic. The lesions resolved completely in 25 days without any complication.

Discussion

Farmers are exposed to many skin damaging factors. In a study that include 132 farmers of diagnosed with contact dermatitis, causes of 13 percent were found to be chemical irritants such as fertilizers, pesticides etc.

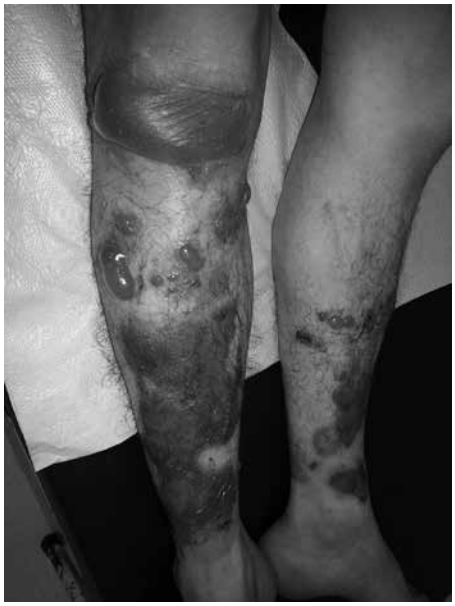

Figure 1. *Lesions on erythematous base and localized on his both legs.*

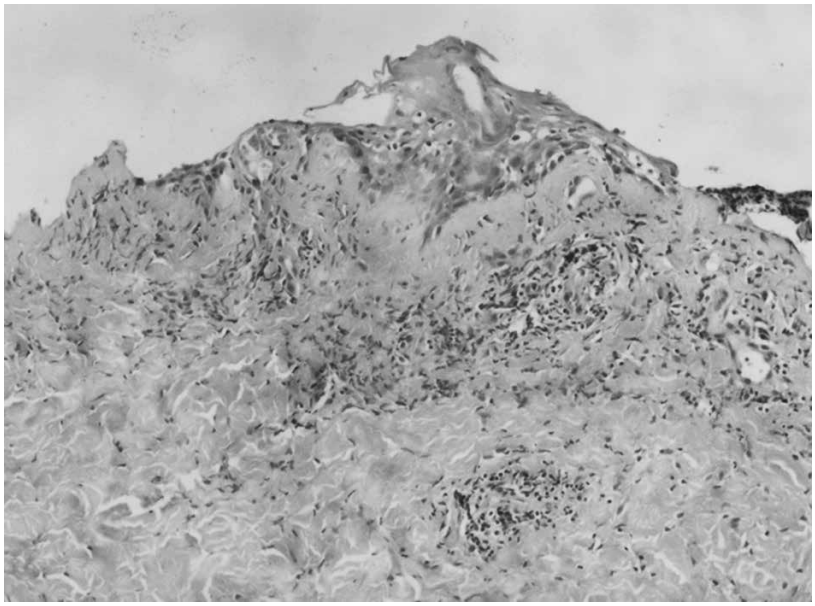

Figure 2. *Histological examination of biopsy specimen showed lack of epidermis and mixed inflammatory infiltrate of lymphocytes in superficial dermis.*

These chemical irritants cause an extent and severe dermatitis according to the other contact factors[2]. Despite the widespread use, there are a few reports about contact injuries caused by nitrogen[3,4]. Moreover, fertilizer induced contact dermatitis has extremely rare been reported in the literature[5,6]. Foti et al. reported a case of allergic contact dermatitis due to a fertilizer containing cyanamid that can transform ammonium carbonate, a source of nitrogen[5]. In the case, patient presented with severe and itchy vesicular and bullous lesions like our case.

Conclusion

We would like to emphasize that the nitrogen based fertilizers exposure causes more severe and wider skin reaction than other variety of fertilizers. For this reason, protection from contact exposure to the fertilizers, especially from nitrogen fertilizers is very important issue of occupational safety and health in agriculture.

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OLGU SUNUMU / *CASE REPORT*

Inheritance of Factor VII and Protein S Deficiency Together with Factor V Leiden Mutation

Faktör VII ve Protein S Eksikliğinin Faktör V Leiden Mutasyonu ile Birlikte Kalıtımı

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ABSTRACT

Homozygous or heterozygous mutations of factor V Leiden (FV Leiden) and the thrombophilic factors like protein S deficiency are associated with venous or arterial thrombosis. In these patients, thrombosis may be seen even in the presence of coexistent congenital disorders of bleeding. Factor VII (FVII) deficiency is a rare autosomal recessive disorder of blood coagulation. When FVII deficiency occurs in combination with thrombophilic mutations, the symptoms of hemorrhagic diathesis are alleviated, like in other inherited hemorrhagic disorders. Herein, a 5-year-old and a 7-year-old, an asymptomatic sister and brother who respectively had 2 (FV Leiden mutation and protein S deficiency) and 1 (FV Leiden mutation) thrombophilic factors coexistent with FVII deficiency, are presented. The levels of FVII were 36% (N: 55%-116%) in the sister and 38% (N: 52%-120%) in the brother. FV Leiden mutation was homozygous and heterozygous in the sister and the brother, respectively. The protein S activity was 47% (N: 54%-118%) in the sister and normal in the brother. Familial work-up revealed FV Leiden mutation (heterozygous) in both parents and protein S deficiency in the mother [51% (N: 55%-160%)].

The paternal grandmother, who had died due to myocardial infarction, was learned to have had FVII deficiency. Neither of the siblings nor the grandmother had hemorrhagic diathesis. Even children with moderately decreased FVII levels may present with bleeding symptoms. Therefore, we think that the absence of hemorrhagic diathesis in our patients can be attributed to coinheritance of thrombophilic factors (protein S deficiency and/or FV Leiden mutation).

Key words: *factor V Leiden mutation; factor VII deficiency; protein S deficiency*

ÖZET

Faktör V Leiden (FV Leiden) mutasyonu ve protein S eksikliği gibi trombofilik faktörler, venöz ve arteriyel tromboz ile ilişkilidir. Bu hastalarda tromboz, eşlik eden bir kongenital kanama hastalığının varlığında bile görülebilir. Faktör VII (FVII) eksikliği, nadir rastlanan, otozomal resesif geçişli bir pıhtılaşma bozukluğudur. Faktör VII eksikliği trombofilik mutasyonlarla birlikte olduğunda, hemorajik diyatez belirtileri, diğer kalıtsal hemorajik hastalıklarda olduğu gibi hafifler. Burada, beş ve yedi yaşlarında olup, FVII eksikliği ile birlikte sırasıyla iki (FV Leiden mutasyonu ve protein S eksikliği) ve bir (FV Leiden mutasyonu) trombofilik faktör taşıyan semptomsuz bir kız ve erkek kardeş sunulmaktadır. Faktör VII düzeyleri kız kardeşte % 36 (N: 55–116) ve erkek kardeşte % 38 (N: 52–120) idi. FV Leiden mutasyonu sırasıyla kız ve erkek kardeşte homozigot ve heterozigottu. Protein S aktivitesi kız kardeşte % 47 (N: 54–118), erkek kardeşte normal idi. Aile çalışmasında, her iki ebeveynde FV Leiden mutasyonu (heterozigot) ve annede protein S eksikliği [% 51 (N: 55–160)] vardı.

Miyokard infarktüsünden ölen babaannede FVII eksikliği olduğu öğrenildi. Kardeşlerin hiçbirinde ve babaannede kanama diyatezi yoktu. FVII düzeyi orta derecede azalmış olan çocuklar bile kanama belirtileri gösterebilirler. Bu nedenle, hastalarımızda hemorajik diyatez olmamasının, bu hastalarda, trombofilik faktörlerin (FV Leiden mutasyonu ve protein S eksikliği) birlikte kalıtılmış olmasına bağlanabileceği düşüncesindeyiz.

Anahtar kelimeler: *Faktör V Leiden mutasyonu; Faktör VII eksikliği; Protein S eksikliği*

Introduction

Factor VII (FVII), a glycoprotein dependent on vitamin K, is an important factor in initiating the coagulation cascade. Following vascular injury, the tissue factor (TF) binds to the membrane and forms a calcium-dependent complex with either FVII (it is converted to FVIIa after a proteolytic degradation) or FVIIa (its serum level is extremely low) throughout the circulation. FVIIa, which binds to TF, activates factor X (FX) and accelerates the production of FXa. FXa and factor Va (FVa), its cofactor, convert prothrombin to thrombin. Additionally, the TF/FVIIa complex can also activate factor IX (FIX) to FIXa, which, after forming a complex with factor VIIIa (FVIIIa), contributes to FXa generation and thereby to thrombin formation via the intrinsic pathway. The activity of

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the TF/FVIIa complex in the plasma is inhibited by tissue factor pathway inhibitors (TFPIs). TFPIs form complexes with FXa, FVIIa, and TF to express their activity. Finally, thrombin production is stopped by activated protein C (APC). APC, in turn, proteolytically inactivates FVa and FVIIIa, the basic cofactors of prothrombin-activating complexes[1].

FVII (a proconverting, stable factor) deficiency is a rare autosomal recessive disorder of blood coagulation. The FVII gene has been mapped on chromosome 13(13q34)[1].

The factor V Leiden (FV Leiden) mutation delays the inactivation of activated FV and thus leads to hypercoagulation[2]. Both heterozygous and homozygous forms of this disease are known to be associated with a high risk of recurrent thrombosis. Venous and arterial thrombosis may even be seen in the presence of coexistent congenital disorders of coagulation[2].

FVII deficiency in combination with thrombophilic mutations may lead to milder symptoms of bleeding diathesis, as in hemophilic disorders. Furthermore, mild to moderately low FVII levels do not always require bleeding symptoms to be absent or minor. Here, coinheritance of FV Leiden mutation and deficiencies of both FVII and protein S in a 5-year-old girl and coinheritance of FV Leiden mutation and deficiency of FVII in her 7-year-old brother are presented.

Case Report

A 5-year-old girl who presented for tonsillectomy was referred to our department since her *prothrombin time* was found to be prolonged in the preoperative evaluation and the prolongation persisted after intravenous vitamin K administration (3 mg). She had no history of prolonged bleeding from venipuncture sites and no history of easy bruising, spontaneous ecchymosis, pink-colored cutaneous eruption, gingival bleeding, epistaxis, hematuria, or hematochezia. She had no history of operative intervention. Her parents were second-degree relatives. Her mother (age: 35) had protein S deficiency [51% (N: 55%-160%)] and surprisingly had experienced prolonged bleeding only once, a few years ago after cardiac catheterization, while she had no history of menorrhagia or prolonged postpartum bleeding. She had not used oral contraceptives. The patient's brother, father, and other family members reported no history of prolonged bleeding. Her paternal grandmother had FVII deficiency without a history of prolonged bleeding and she had died of myocardial infarction at the age of 73. The lipid profile of the grandmother was not known.

The work-up of all family members revealed that the patient and her mother had protein S deficiency and her brother also had FVII deficiency (FVII level: 38%). The patient had homozygous FV Leiden mutation while her father, mother, and brother were heterozygous for the same mutation (Fig 1). Physical examination, complete blood count, blood smear, liver and renal function tests, and other laboratory results of both the patient and her brother were within normal limits. The laboratory results of hemostatic parameters of the patients and their parents, which were all tested at least twice, are presented in Table 1.

Discussion

It is well documented that FV Leiden or other thrombophilic factors like PT20210 G>A mutation or protein C deficiency coexisting with factor deficiencies like FVIII, FIX, or FVII may delay the onset of hemorrhagic symptoms and decrease the severity of clinical findings [2,3,4,5,6]. In vitro production of thrombin has been demonstrated to increase in these patients[2-7].

This report summarizes our evaluation of an asymptomatic girl with FVII deficiency and her family. That the family history displayed an FVII-deficient paternal grandmother who had no bleeding symptoms and developed myocardial infarction (arterial thrombosis) prompted us to evaluate the patient and her family for the main thrombophilic factors. Our work-up revealed that her brother was also FVII deficient and that the patient and her brother respectively had 2 (FV Leiden mutation and protein S deficiency) and 1 (FV Leiden mutation) thrombophilic factors coexistent with FVII deficiency; protein S deficiency with/without FV Leiden mutation prevailed in the family members. Although the literature contains no solid evidence to support a relationship between FV Leiden mutation and the risk of arterial thrombosis[8], there are a few exceptional cases with[9-12] or without[13,14] coexistent thrombophilic factors or disorders. However, we do not know if the paternal grandmother developed myocardial infarction as a rare manifestation of arterial thrombosis due to a possible FV Leiden mutation[13] or due to atherothrombosis, since she was learned not to have undergone replacement therapy or surgical operation before myocardial infarction.

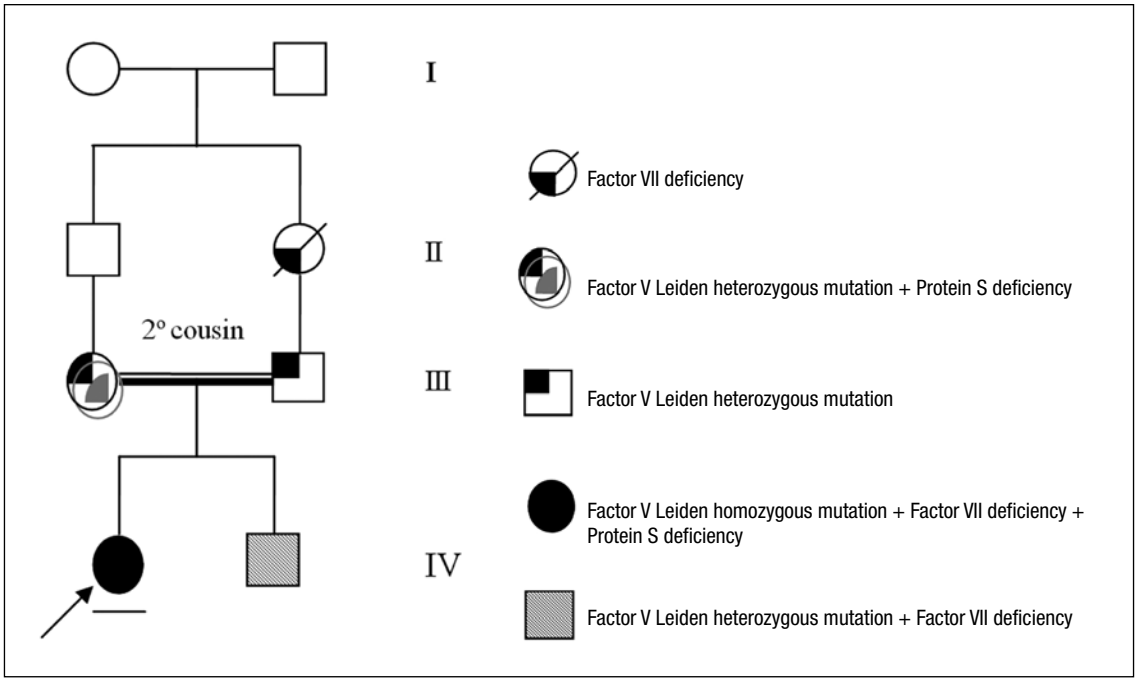

Figure 1. *The pedigree of the patient.*

Table 1. *Laboratory results of the patients and other family members*

	PT (11.1–13.2) sec	PTT (25–40) sec	INR (0.8–1.3)	Bleeding time (1–3')	ATIII (adult: 70–125%) (5 years: 82–139%)[24] (7 years: 90–131%)[24]	Protein C activity (adult:70–140%) (5 years: N 40–92%)[24] (7 years: N 45–93%)[24]	Protein S activity (adult:55–160%) (5 years: N 54–118%) (7 years: N:41–114 %)	FVII* (adults: 50–150%) (5 years: 55–116%) (7 years: 52–120%)	Factor V Leiden (1691 G>A)	Prothrombin gene mutation (20210G>A)
Father (age: 40 years)	12	28,3	1,179	147"	106,0	84,0	70,0	68,0	Heterozygous mutant	No mutation
Mother (age: 35 years)	11,7	27,9	1,145	150"	102,0	76,0	51,0	60,0	Heterozygous mutant	No mutation
Daughter (age: 5 years)	13.8	28.6	1.16	1'30"	120.0	70.0	47.0	36.0	Homozygous Mutant	No mutation
Son (age: 7 years)	14.8	25.6	1.25	1'45"	118.0	70.0	58.0	38.0	Heterozygous mutant	No mutation

As to the serum FVII level (10 to 50 IU/dL), both siblings were in the mild to moderate and heterozygous group, usually expected to be asymptomatic[15]. However, a characteristic of FVII deficiency is that a weak correlation exists between the degree of deficiency and the risk of bleeding[16,17]. Hence, FVII level did not differ between symptomatic and asymptomatic heterozygous FVII A294V subjects (FVII: 44+15%)[7]. Bhavnini et al.[18] reported 7 children with heterozygous FVII deficiency (FVII: 25%-56%), 6 of whom had spontaneous ecchymosis, 4 postoperative bleeding, and 1 epistaxis. FVII genotypes failed to explain the discrepancy between clinical severity groups[16]. In light of these findings, we can neither conclude that presence of FV Leiden mutation in both siblings and protein S deficiency in the sister alleviated the symptoms of bleeding nor that it affected the bleeding symptoms.

Eleven FVII-deficient patients out of 539 were reported to have developed thromboembolism [19,20]. All the tested patients with thromboembolism revealed normal

protein C, protein S, and ATIII levels and negative antiphospholipid antibodies and lupus anticoagulant[19,20]. Only one revealed an elevated homocysteine level[19]. On the other hand, a comparison of the prevalence of FV Leiden mutation, PT G20210A, FV HR2, and MTHFR C677T polymorphism and triggering risk factors for thrombosis (surgery and replacement therapy) between FVII-deficient cases with and without thrombotic events did not reveal any significant difference[19]. This shows that presence of FVII deficiency does not attenuate or change the effect of prothrombotic genes on the development of thromboembolism and does not offer protection when triggering factors for thrombosis like surgery and replacement therapy are present[18,21]. However, none of the 7 patients with FV Leiden mutation out of 25 FVII-deficient patients of Astermark et al.[20] experienced thrombosis. On the other hand, the overall protein C activity was found to be significantly lower in the FVII-deficient subjects than the normal controls[20]. In the literature, protein S deficiency in FVII deficiency is a new finding, showing that protein S may have a complementary role in the defect of the protein C pathway as a cofactor of protein C.

The protein C and S deficiencies may be compensatory hemostatic mechanisms alleviating the bleeding tendency. In the literature, we could not encounter any case with FVII deficiency carrying both thrombophilic factors of FV Leiden mutation and protein S deficiency together. In our patients, we could not evaluate antiphospholipid antibodies. Both siblings are being followed for possible bleeding diathesis and thromboembolism.

Coexistent FV Leiden mutation was found at frequencies ranging from normal (8.8%)[19,20] to elevated (14.2%) in patients with FVII deficiency (normal carriage incidence: 1%-8.5%; in Turkey: 7.9%)[2,22,23]. The frequency of the FV HR2 allele was very high in asymptomatic patients with FVII A294V mutation, unlike in the symptomatic ones (30% vs. 5.5%; normal population: 7.4%)[7]. PT G20210A mutation was reported at 4.4%, 0%, and 0% in FVII-deficient patients[19], in a subgroup of FVII-deficient patients with FVII Lazio mutation[2], and in a subgroup of FVII-deficient patients with FVII A294V mutation[7], respectively. Depending on the literature, we can state that the characteristic genotype/phenotype discrepancy in FVII deficiency may be due to compensatory hemostatic regulatory mechanisms such as increased frequency in FV Leiden mutation, although there are exceptions[20], FV HR2 allele[7], or decreased protein C level[20], which seem to differ as to the type of mutation.

The parents were accepted as heterozygous and the children as probably homozygous (less probably heterozygous) for FVII deficiency, and the daughter as protein S-deficient.

We think that protein S deficiency and other gene products or environmental factors to influence the activity or the turnover of the FVII molecule[7] should also be verified in greater numbers of FVII-deficient patients to establish the reasons for genotype/phenotype discrepancy.

Conflict of Interest Statement

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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OLGU SUNUMU / *CASE REPORT*

Epidural Anesthesia and Endovascular Repair of Abdominal Aortic Aneurysm Case Presenting with Severe Pulmonary Disease

Ağır Akciğer hastalığının Eşlik Ettiği Abdominal Aorta Anevrizması Olgusunda Epidural Anesteziyle Endovasküler Tedavi

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ABSTRACT

Endovascular surgery simplifies repair of abdominal aortic aneurysms. As a result, many patients with comorbidities are being operated. Anaesthetic plan of such patients should be planned according to their specific conditions. We aimed to describe the anesthetic management of a patient with severe obstructive pulmonary disease scheduled for endovascular abdominal aortic aneurysm repair.

Key words: *endovascular abdominal aneurysm repair; epidural anesthesia; perioperative complications*

ÖZET

Endovasküler cerrahi, abdominal aort anevrizmalarının tedavisini kolaylaştırmaktadır. Bunun sonucunda, ek hastalıkları olan pek çok hasta ameliyat edilmektedir. Bu tür hastaların anestezileri, kendilerine özgü sorunlara yönelik planlanmalıdır. Endovasküler abdominal aortik anevrizma onarımı planlanan, ağır obstrüktif akciğer hastalığı olan bir olguda anestezi yönetimimizi sunmayı amaçladık.

Anahtar kelimeler: *endovasküler abdominal aort anevrizması onarımı; epidural anestezi; perioperatif komplikasyonlar*

Introduction

Aortic aneurysm is common in elderly. There is no effective treatment, so palliation and regular checkups are important[1]. Vascular prosthesis replacement via open surgery was the main treatment option until recently however invasive endovascular techniques are increasingly used[2]. Endovascular abdominal aortic aneurysm repair has a decreased complication rate compared to major surgery requiring general anesthesia. Major advantages are reduced blood loss, hospital stay and no need for general anesthesia. All these advantages contribute to decreased mortality and morbidity[3]. This paper describes the anaesthetic management of an old patient presenting with severe obstructive pulmonary disease scheduled for endovascular abdominal aortic aneurysm repair.

Case Report

A 71 year old male presented to our emergency department with abdominal pain and nausea. Medical history consisted of chronic obstructive pulmonary disease, pneumonia, hypertension, previous history of smoking and tuberculosis, which was successfully treated. Physical examination was unremarkable except for rales in the right lung, prolonged expirium and arterial hypoxia (Peripheral oxygen saturation: 87–90% despite six l/min oygen therapy). Respiratory function tests showed severe obstruction (Forced expiratory volume in one second: 38%, forced expiratory volume in one second/forced vital capacity: 0.56). Computerised tomography revealed bilateral apical fibrotic sequels, traction bronchiectasis, peribronchovascular thickenings and emphysematous regions in the lungs, 40 mm wide ascending aorta with 13 mm wide patchy hypodense lesions, 58 mm wide aortic aneurysm located between the iliac artery and distal end of the superior mesenteric artery with 22 mm wide patchy hypodense regions (Fig. 1). These hypodense areas were initially thought of as thrombosis. As laboratory values were consistent with pneumonia (CRP: 25,3 mg/dl, WBC: 11.5 K/uL, sedimentation rate: 84), empirical antibiotherapy, oral and inhaler bronchodilator therapy, and prophylactic anticoagulant

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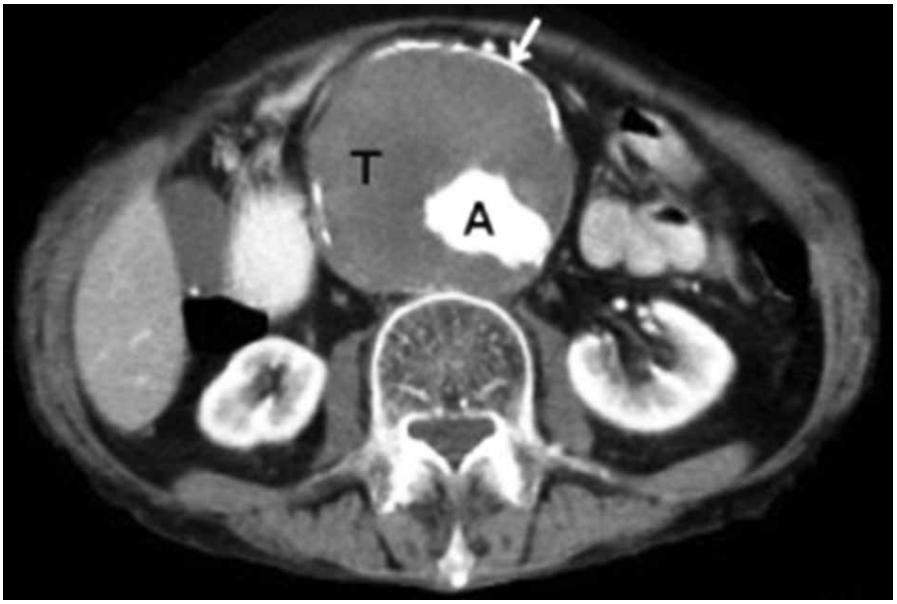

Figure 1. *Seventy-one-year-old male presenting with abdominal pain and nausea was subsequently diagnosed with thrombosed abdominal aortic aneurysm. Contrast enhanced preoperative tomography. Axial plane at the first lumbar vertebra shows thrombosed abdominal aortic aneurysm (T), the shaggy aorta (A) and calcified borders (white arrow).*

therapy with 100 IU/kg enoxaparin once a day was initiated. At the tenth day, infection signs regressed, pulmonary function was slightly better (Peripheral oxygen saturation: 92% with two l/min nasal oxygen therapy, forced expiratory volume in one second: 45%, forced expiratory volume in one second/forced vital capacity: 0.68). Cardiovascular surgeons planned endovascular abdominal aortic aneurysm repair.

Following routine monitorization and iv infusion of %0.9 NaCl, we catheterized the radial artery, the right internal jugular vein and the epidural space through L1-2 intervertebral space. We achieved sensorial block at T8 (confirmed with pin prick test at anterior axillary line) with bolus doses of 0,025% levobupivacaine (a total of 20 ml within 20 min) and sedation with 0.02 mg/kg dormicum. The initial blood pressure of 100/55 mmHg dropped to 84/43 mmHg. Therefore, we started an infusion of dopamine at a rate of five mcg/kg/min, to prevent fluid overload. The surgeons cannulated right femoral artery, placed an infrarenal graft and an iliac artery graft to the contralateral side (Fig. 2). Surgery ended in one hour without any complications or further need for analgesics. The patient was followed-up in the cardiovascular surgery ward for three days anticipating complications such as hemodynamic disturbances or pleural effusion. At third postoperative day, the patient was transferred to the infection ward to be discharged with oral antibiotic therapy.

Discussion

Abdominal aortic aneurysms are usually seen in elderly men with co-morbid diseases such as hypertension, chronic obstructive pulmonary disease, coronary artery and cerebrovascular disease, diabetes mellitus renal disease[4]. Until now, surgery was the main form of treatment. Recently minimally invasive endovascular techniques are becoming popular as they are easier to perform and are associated with decreased rate of morbidity and mortality, mainly because they do not require general anesthesia[5]. Preoperative evaluation of this case showed severe obstructive respiratory disease, which is associated with high perioperative complication rates due to arterial hypoxia and postoperative respiratory insufficiency. Therefore, endovascular abdominal aortic aneurysm repair via regional anesthesia was the most appropriate choice in this patient. Although endovascular technique costs much more compared to open surgery, it compensates for the difference with shorter hospital stay and fewer complications. This difference is especially notable in elderly patients presenting with co-morbid diseases and complications due to analgesic therapies[6].

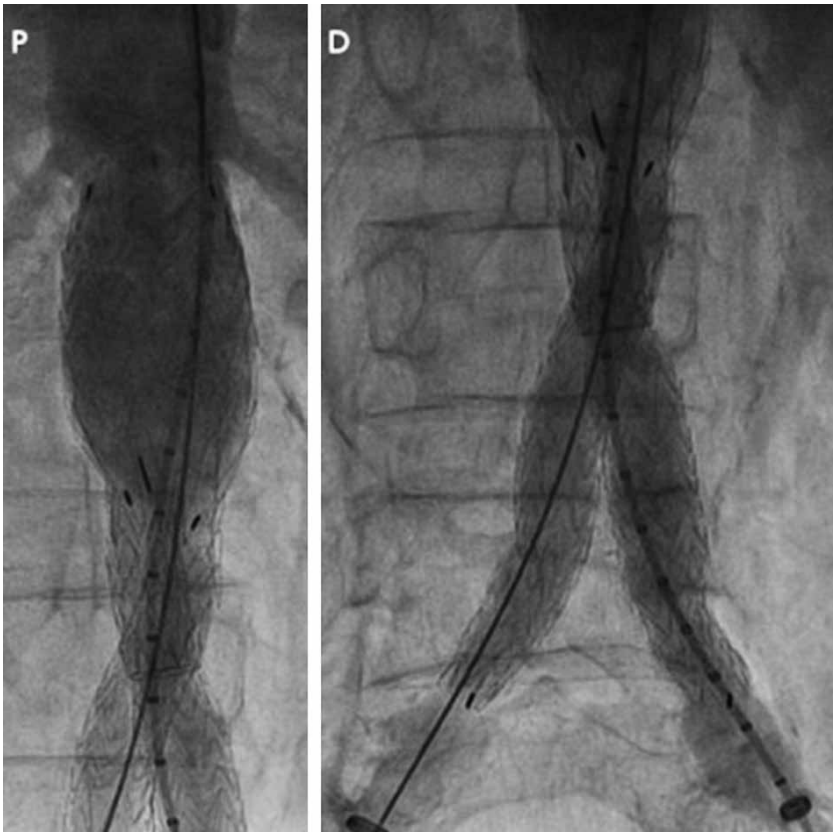

Figure 2. *Seventy-one-year-old male was operated using endovascular surgical technique with the diagnosis of abdominal aortic aneurysm. Postoperative angiogram extending from third lumbar to second sacral vertebra shows infrarenal (P) and iliac (D) grafts.*

Epidural anesthesia in endovascular abdominal aortic aneurysm repair is advantegous because it totally eliminates postoperative pain and provides hemodynamic stability during the procedure. In this case, epidural anesthesia prevented complications associated with intubation like laryngospasm, bronchospasm and hypertension, and also perioperative pulmonary complications like increased secretions and atelectasis. We experienced hypotension due to high level of anesthesia, which was easily treated with low dose of dopamine infusion.

Conclusion

Elderly abdominal aortic aneurysm patients complicated with pulmonary comorbidities can be efficiently treated with endovascular technique and regional anesthesia. The authors think that endovascular surgical technique and regional anesthesia shortens hospital stay and minimizes perioperative pulmonary complications associated with general anesthesia.

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OLGU SUNUMU / *CASE REPORT*

Treatment Selection for a Vesicoureteral Reflux Case Following Renal Transplantation

Böbrek Nakli Sonrası Gelişen Vezikoüreteral Reflü Olgusunda Tedavi Seçimi

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ABSTRACT

The vast majority of renal transplant patients suffer from urological complications. These urological complications account for the most important causes of morbidity and mortality cases such as delay in graft functions and graft loss following transplantation.57-year-old male patient contracted vesicoureteral reflux (VUR) following cadaveric renal transplantation. Initially subureteric injection was tried because of recurrent urinary tract infection and impairment of graft functions but open procedure ureteroneocystostomy was repeated since the injection failed to produce results. The patient is currently in his post-op month 10 and his follow-ups revealed no problems thus far.While less invasive methods such as endoscopic procedures can primarily be selected for the treatment of VUR, which leads to urinary tract infections and impairment in graft functions subsequently, open surgical procedures are considered to be an appropriate approach for failed injection or advanced stage cases.

Key words: *renal transplantation; subureteric injection; vesicoureteral reflux*

ÖZET

Böbrek nakli yapılmış hastaların önemli bir kısmında ürolojik komplikasyonlar gelişmektedir. Gelişen bu ürolojik komplikasyonlar nakil sonrası greft fonksiyonunda gecikme, greft kaybı gibi morbiditelerin ve mortalitenin en önemli sebeplerindendir. Elli yedi yaşında erkek hastada kadaverik böbrek nakli sonrasında vezikoüreteral reflü gelişti. Tekrarlayan idrar yolu enfeksiyonu ve greft fonksiyonlarında bozulmaya yol açması nedeni ile öncelikle subüreterik enjeksiyon denedi; fakat başarılı olmaması üzerine açık prosedürle üreteroneosistostomi işlemi tekrarlandı. Hasta ameliyat sonrası 10. ayında ve takipleri problemsiz olarak devam ediyor. Sonuçta idrar yolu enfeksiyonu ve greft fonksiyonlarında bozulmaya yol açan VUR sonrasında öncelikle daha az invazif bir yöntem olan endoskopik yöntemler tercih edilebilirken, başarısız enjeksiyon; ya da ileri evre vakalarda açık cerrahi prosedürün tercih edilmesi uygun bir yaklaşım olarak görülmektedir.

Anahtar kelimeler: *böbrek nakli, subüreterik enjeksiyon, vezikoüreteral reflü*

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Introduction

The 5-year survival rate for renal transplant patients is significantly higher than that of dialysis patients (85.5% and 35.8% respectively)[1]. Although renal transplantation has such positive sides as cost-efficiency and high survival rates, a vast majority of renal transplant patients contract urological complications. These urological complications account for the most important causes of morbidity and mortality cases such as delay in graft functions and graft loss following transplantation[2]. The most significant of these complications are urinary leakage, narrowness, and vesicoureteral reflux.

Our aim in this case report is to present the case of a patient that received endoscopic subureteral injection for the treatment of vesicoureteral reflux following renal transplantation but had to go through ureteroneocystostomy again since the injection failed to produce results in the light of literature on the subject.

Case Report

Fifty-seven-year-old male patient, who had been in hemodialysis for the last 8 years because of chronic renal failure brought about by diabetes and hypertension, underwent cadaveric renal transplantation. Lich-Gregoir method was performed for ureterovesical anastomosis during the surgery. Urinary output was enabled following surgery. A drop in urea and creatinine values was seen. Early examinations revealed no pathologies in the transplanted kidney's blood build-up, excretion, and concentration functions. The patient was discharged on day 15 without any problems.

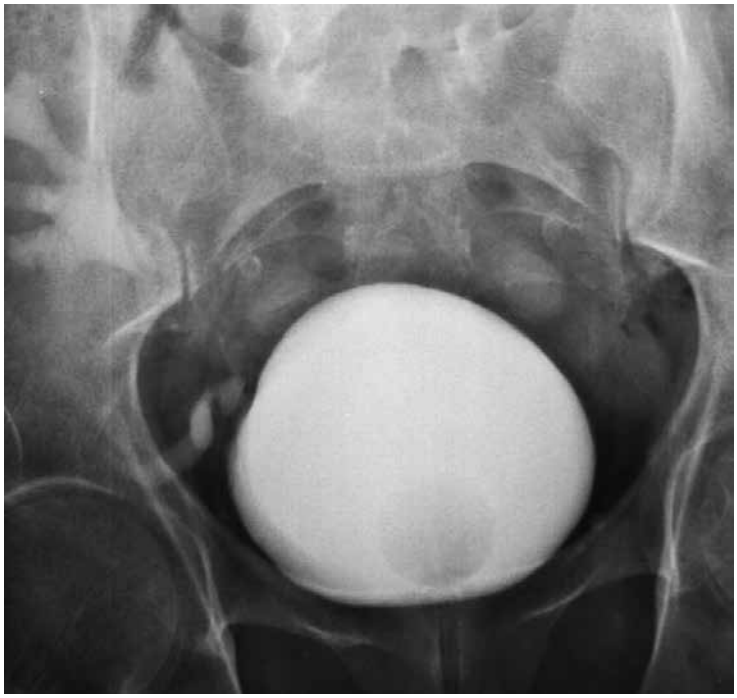

Figure 1. *Voiding cystourethrographic view of recurrent reflux after subureteral injections.*

The patient, who had burning sensation when urinating, was seen to have urinary tract infection in the first post-op month during the follow-ups. Escherichia and klebsiella pneumonia as seen in the urine culture. The patient's problem frequently recurred and he had secondary renal function impairment brought about by urinary tract infection. In his laboratory, creatinin value was 2,2 mg/dL, üre 98: mg/dL, white blood cell:3400. Upon the patient's voiding cystourethrography revealed that there was vesicoureteral reflux (VUR) in the transplanted kidney, the urology clinic administrated subureteric Dextranomer / hyaluronic acid copolymer (Deflux) injection to the patient. Patient's complaints continued and no progress was seen in his current pathology as revealed by his laboratory and radiological results at the end of the first month following this procedure (Fig. 1). Reoperation was planned and during operation ureter of transplanted kidney was seen as dilated and tortuous. Open procedure ureteroneocystostomy was repeated accorrding to the Lich-Gregoir technique. The patient's routine follow-ups continue to be performed and his examinations and analyses revealed neither urinary tract infection nor any finding that would be suggestive of VUR in the post-op month 10 and his renal functions were within normal on bounds. As there were no evidence of a urinary tract infection or renal failure due to laboratory results, urine culture and ultrasonograph, voiding cystourethrography was not repeated after second operation to avoid contrast nephropathy.

Discussion

Although renal transplantation plays a positive role in maintaining cost-efficiency and survival, a significant portion of renal transplant patients develop urological complications. These complications give way to an increase in morbidity rates and subsequently an increase in graft loss in patients[2]. According to the data presented in literature, the rate of post-renal transplantation complications like leakage, narrowness, and VUR varies between 2.5% and 14.1%[3]. In our case, the patient, who had recurrent urinary tract infection following renal transplantation, we determined VUR as revealed by examinations and analyses.

One of the most significant reasons for these problems relies both on organ removal and technical problems faced during preparation and ureteral anastomosis[4]. In a study by Gürkan et al. the authors compared two ureteral anastomoses techniques and stated that VUR was seen in 3 out of 34 cases in which the Lich Gregoir technique was used, while no VUR cases were seen

in 41 cases that had undergone ureteroureterostomy[5]. The results of this study suggest that ureteroureterostomy should be performed as the type of anastomosis in patients with no VUR in the native kidney[5]. The initial operation for our patient was also the Lich Gregoir technique used in ureteral anastomosis. We think that VUR, which was developed in our patient, related with technical problems faced during first operation.

Post-transplantation VUR rate varies between 50% and 86% depending on the technique of ureteroneocystostomy[6]. In most of the studies the cases with VUR are mostly early stage, while stages 4 and 5 are not seen. There are many studies which have shown that in early stage VUR cases, or even in advanced stage VUR as presented in some studies, the rate of urinary tract infection and the rate of related urosepsis did not change in comparison to control groups[7]. In spite of the presence of these data, most of the clinicians are in consensus that advanced stage VUR cases with urosepsis based on recurrent urinary tract infection or urinary tract infection should be surgically treated[8]. Intervention was planned for our case upon frequent urinary tract infection and related impairment in graft functions.

Endoscopic treatment methods came to the fore since a second open surgical procedure would be an invasive method and the risk of ureteral necrosis, urinary leakage, and narrowness at the anastomosis. It is preferred over subureteric injection open surgery because it has a low rate of post-op morbidity, shorter period of procedure and hospitalization, and it does not give way to any problems in dissection during a possible operation following failed injection[9]. Materials like teflon, dextranomer in sodium hyaluronate, calcium hydroxyapatite, pyrolytic carbon coated xirconium oxide were used in suburetic injection[9]. Although the results of suburetic injection are similar to those of open surgery in low-grade VUR cases, success rates go down with advanced stage cases and after repeated injections[9]. We initially administered suburetic injection in our patient because it was a method with less morbidity but since it failed we performed open surgical procedure.

Consequently, ureteral anastomosis technique used during renal transplantation proves to be an important factor for VUR alongside with other post-operative urological complications. While endoscopic methods that are less invasive can be primarily selected to treat VUR cases, which causes urinary tract infection and impairment in graft functions, to prefer open surgical procedures after failed injection or in advanced cases is considered to be an appropriate approach.

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AMAÇ VE KAPSAM

Kafkas Tıp Bilimleri Dergisi (Dergi) Türkçe ve İngilizce yazılmış makaleleri kabul eden, hakemli bir genel tıp dergisidir. Dergi tıbbi bilimleri geliştiren ve aydınlatan ya da okuyucularını eğiten orijinal biyomedikal makaleleri (Tıp bilimleri ile ilgili araştırma, kısa bildiri, derleme, editöryal, editöre mektup, çeviri, tıbbi yayın tanıtma vb türlerden yazılar) yayımlar. Yılda 3 sayı halinde (Nisan, Ağustos, Aralık) tek cilt olarak, matbu ve elektronik ortamlarda basılır. Dünyanın her yerinden makaleler kabul edilir.

MAKALE GÖNDERME

Makale toplama ve değerlendirme işlemleri http://meddergi.kafkas.edu.tr web adresinden online yapılır. Web adresinden giriş yapılmasını takiben "online makale gönder, takip et, değerlendir" butonunun tıklanması ile çıkacak direktiflerin takip edilmesi gereklidir.

ETİK

Dergi, Yayın Etikleri Komitesi'nin (COPE) rehberlerindeki iyi yayın uygulamaları ilkelerine sıkı bir şekilde bağlıdır (http://publicationethics.org/resources/guidelines). Makale başvurusunda bulunan yazarlar; çalışmalarının etik, hukuki ve bilimsel kurallara uygun olduğunu, daha önce yayınlanmamış ve başvuru sırasında başka bir yerde yayınlanmak için değerlendirme aşamasında olmadığını kabul ederler. Daha önce yayınlanmış tablo, şekil ve yazı makalede açıkça belirtilmeli ve yayın haklarını elinde tutanlardan izin alınmalıdır. Dergi, uygun etik kurul başvurularının yapılmış olmasını, bilgilendirilmiş onamların alınmasını ve bunların makalede bildirilmesini zorunlu tutar. İnsan öğesini içeren tıbbi çalışmalarda, Helsinki Deklarasyonu ilkelerine sıkıca bağlıdır (http://www.wma.net/e/policy/pdf/17c.pdf). Yazarlar, laboratuvar hayvanlarının kullanımında ve bakımında kurumsal ya da ulusal rehberlere uygun davrandıklarını bildirmek zorundadır.

BAŞVURU SIRASINDA İSTENEN MAKALE NİTELİKLERİ

Dergi, Uluslararası Tıp Dergileri Editörleri Komitesi'nin (ICMJE) rehberlerine sıkıca bağlıdır (http://www.icmje.org/index.html). Türkçe makaleler için, Türkçe özete ek olarak İngilizce özet; İngilizce makaleler için, İngilizce özete ek olarak Türkçe özet istenmektedir.

MAKALE HAZIRLANMASI

Tercihen Times New Romans yazı karakteri, 12 punto ve çift aralıklı yazılması önerilir. Makaleler açık, kısa ve akıcı bir Türkçe veya İngilizce ile yazılmalı, imla kurallarına uyulmalıdır. Dergi, özellikle giriş ve tartışma kısmı olmak üzere, makale uzunluğunu içerdikleri bilgiyle orantılı ölçüde kısa tutulmasını önerir. Bütün yazarlara bir istatistik uzmanı ile görüşmeleri önerilir.

Başlangıç Sayfası: Makale başlığı kısa ve devamlı nitelikte olmalıdır. Başlık indeksleme ve bilgi toplama açısından yararlı olacak biçimde tanımlayıcı ve bilgi verici olmalıdır. Bütün yazarların ad ve soyadları yazılmalıdır. Her yazar için çalıştığı bölüm, kurum belirtilmeli, iletişim yazarının şehir, ülke ve posta kodunu da içeren tam yazışma adresi, fax, telefon ve Email adresi sunulmalıdır.

Özet: Özetler anlaşılır olmalı ve yazının amaç ve belirgin sonuçlarını gösterebilmelidir. Yalnızca temel bulgu ve sonuçları belirterek, uyarlanmaya gerek duymadan özetleme servislerince kullanılabilmelidir. Araştırma makalelerinde özet bölümü yazısını şu alt başlıklara (Giriş, yöntem, bulgular, sonuç) göre sıralamak gerekir. Derlemeler,olgu sunumlarında alt başlık gerekmez. Editöryal, editöre mektup gibi türlerde özetleme yapılmaz. Özetlemede yalnızca standart kısaltmalar kullanılmalıdır.

Anahtar Kelimeler: Yazıyla ilgili "Index Medicus: Medical Subject Headings ve Türkiye Bilim Terimleri" standartlarına uygun üç ile altı arası anahtar kelime özet altına yazılmalıdır.

Giriş: Anlaşılır ve kısa olmalı, son paragrafında çalışmanın amacı açıkça belirtilmelidir. Literatürün gözden geçirilmesi çalışmanın nedenselliğine yönelik olmalı ve önemli bilgileri içermelidir.

Yöntem: Gözlemsel ya da deneysel çalışma katılımcılarının neye göre seçildiği (hastalar, kontroller ya da laboratuvar hayvanları) açıkça tanımlanmalıdır. Katılımcıların yaş, cinsiyet ve diğer önemli özellikleri belirlenmelidir. İnsan ve hayvanlar üzerinde yapılan çalışmalarda etik standartlar açıkça tanımlanmalıdır. Yazarlar, diğer araştırmacılar tarafından da bulguların tekrarlanabilmesi için yöntem, cihaz ve işlemleri yeterli açıklıkta tanımlamalıdırlar. İstatistiksel yöntemler de dahil, daha önceden kabul görmüş yöntemler için referanslar sağlanmalıdır. Yeni ya da uyarlanmış eski yöntemler tanımlanmalı, neden kullanıldıkları ve sınırları açıklanmalıdır. Bütün ilaç ve kimyasallar jenerik isimleri, dozları ve uygulanma yolları sunulmalıdırlar. Randomize kontrollü klinik çalışmalarda, çalışmanın ana öğeleriyle ilgili, çalışma protokolü (çalışma populasyonu, müdahaleler ya da maruziyetler, beklenen sonuçlar ve istatistik analizin nedenselliği), müdahalelerin belirlenmesi (randomizasyon yöntemi, gruplara ayırmada gizlilik) ve grupların maskelenmesini (körleme) içeren özellikler sunulmalıdır. Yapılan istatistiksel analiz yöntemi belirtilmelidir. Makalenin anlaşılması için özellikle gerekli değilse, istatistiksel testlerin ayrıntılarla anlatılması gerekmez. Ancak, özellik arz eden yöntemler kullanıldığında ve makale istatistik ağırlıklı olduğunda ayrıntılı tanımlar gereklidir.

Bulgular: Tablo, şekil ve yazıda sunulan bilgilerin gereksiz tekrarlanmasından kaçınılmalıdır. Yalnızca tartışma ve ana sonucun anlaşılması için gerekli olan önemli bilgiler sunulmalıdır. Veriler bütünlük içinde ve tutarlı olarak sunulmalı, raporun açık ve mantıksal ilerlemesi sağlanmalıdır. Tablo ve şekillerdeki veriler yazıda tekrarlanmamalıdır. Yalnızca önemli gözlemler vurgulanmalı ya da özetlenmelidir. Aynı veriler hem tablo hem de grafiklerde sunulmamalıdır. Verilerin yorumlanması tartışma bölümüne saklanmalıdır.

Tartışma ve Sonuç: Tartışma asıl bulguları anlatan kısa ve özlü bir cümle ile başlamalı, çalışmanın güçlü ve zayıf yönlerini tanımlamalı, bulguları diğer çalışmalarla ilişkilendirerek tartışmalı, olası açıklamalar sağlamalı ve gelecekte yanıtlanabilecek sorulara işaret etmelidir. Tartışma, bulgular bölümünde zaten sunulmuş bulguların tekrarıyla değil, bunların yorumlanmasını ile ilgilenmelidir. Yeni bulgularla, zaten bilinenlerin ilişkisini kurmalı ve mantıksal çıkarsamalar yapmalıdır. Sonuç çalışmanın amacıyla ilişkilendirilebilir ama niteliksiz önermelerden ve verilerle desteklenmeyen sonuçlardan kaçınmak gerekir. Çalışmanın üstünlüğü konusunda iddialarda bulunmaktan kaçınmak gerekir. Öneriler kesinlikle gerekli ve konuyla ilintiliyse tartışma bölümünde belirtilmelidir.

Teşekkürler: Teşekkürler kısa ve net olmalı, yalnızca bilimsel/teknik destek ve finansal kaynak için yapılmalıdır. Rutin kurum olanaklarının kullanılması, makale hazırlanmasındaki destek ya da yardımlar (yazma işi ya da sekreterlik işleri) gibi durumları içermemelidir.

Kaynaklar: Normalde toplam kaynak 30 adet ile sınırlandırılmalıdır. Literatüre atıfta bulunan kaynaklar ardışık olarak sıralanmalı ve makalenin sonunda yer almalıdır. Yazının bütününde atıflar üst karakterle cümle bitiminde yer almalıdır. Olabildiğince yazı içinde yazar isimleri kullanmaktan kaçınmak gerekir. Kafkas Tıp Bilimleri Dergisi aynı zamanda ulusal dergilerin kaynak gösterilmesini teşvik eder. Kaynaklar; Index Medicus stiline uygun yapılmalıdır. *Üç yazarlıya kadar makale:* Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med 2002; 347:284-7. *Üçten fazla yazarlı makale:* Rose ME, Huerbin MB, Melick J, et al. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res 2002; 935:40-6. *Kitap:* Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002:93-113.

Tablolar: Tablolar ayrı olarak yazılmalı ve verilen rakamlar ile sıralanmalıdır. Her tablo kendisi ile ilgili tanımları içermeli ve kısa tanımlayıcı başlık içermelidir. Tablo içindeki kısaltmalar, tablo altında açıklanmalıdır. Tablo (ilgili başlık, tanımlayıcı ve açıklayıcı bilgiler) ayrı bir sayfada sunulmalıdır.

Şekiller: Şekiller (ilgili başlık, tanımlayıcı ve açıklayıcı bilgiler) ayrı bir sayfada sunulmalıdır.

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Dergiye sunulan bütün yazılar en az iki hakem tarafından değerlendirme işlemine alınır. Karar hakem değerlendirme raporlarına göre verilir. Bütün kabul görmüş makaleler dergi kural ve formatına uygun olarak redaksiyon işlemine tabi tutulur.

SON KONTROL

Yazının kabulünü takiben yapılacak editöryal işlemlerden sonra, yazının mizanpajlı şekli yazarların onayına sunulacak ve üç gün içinde telif hakkı devir formu ile birlikte geri istenecektir.

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