Journal of

BIOTECHNOLOGY & STRATEGIC HEALTH RESEARCH (BSHR)

Cilt / *Vol*: **7**

Sayı / *Issue*: **2**

Ağustos / *August*: **2023**

e-ISSN 2587-1641

jbiosad@gmail.com

e-ISSN 2587-1641

Journal of Biotechnology and Strategic Health Research

http://dergipark.org.tr/tr/pub/bshr

DergiPark tarafından yürürlüğe konulan kurallar çerçevesinde yazarların
"Etik İlkeler ve Yayın Politikası" ile "Yazım Kuralları" na uyulması konusunda ilgili başlıkları
dikkatlice incelemesi tavsiye edilmektedir.

Dergi 2023 yılından itibaren sadece İngilizce yazı kabul etmeye başlayacaktır.

e-ISSN 2587-1641

Journal of Biotechnology and Strategic Health Research

http://dergipark.org.tr/tr/pub/bshr

Değerli Bilim İnsanları,

Biyoteknolojik ve Stratejik Sağlık Araştırmaları Dergisi (JOURNAL OF BIOTECHNOLOGY AND STRATEGIC HEALTH RESEARCH), Deneysel, Biyoteknolojik, Klinik ve Stratejik Sağlık Araştırmaları Derneği'nin uluslararası, bağımsız, önyargısız ve çift-kör hakemlik ilkeleri çerçevesinde yayın yapan açık erişimli, bilimsel yayın organıdır. Dergi, Nisan, Agustos ve Aralık aylarında olmak üzere yılda 3 sayı yayınlanır. Dergi ağırlıklı olarak İngilizce yayın kabul etmektedir.

Derginin amacı; etik kurallara uyumlu hazırlanmış biyoteknolojik, kritik, stratejik sağlık araştırmaları ile ilgili bilimsel makaleleri, klinik ve deneysel çalışmaları, derleme, olgu sunumu, editöre mektup ve editöryel yorum türündeki yazıları yayınlayarak literatüre ve sağlık alanındaki tüm disiplinlerde katkı sağlamaktır.

Derginin hedef kitlesi; sağlık alanındaki tüm disiplinlerde çalışan araştırmacılardır.

Dergimizin 7. Yılı, Nisan 2023 sayımızda da yine birbirinden ilginç derleme ve araştırma yazıları ile karşınızdayız. Makalelerini gönderen değerli yazar arkadaşlarımıza ve zaman ayıran hakemlerimize teşekkür eder, bilginin kullanılarak toplum sağlığına değerli katkılar sağlamasını temenni ederiz.

DergiPark tarafından yürürlüğe konulan kurallar çerçevesinde yazarların "Etik İlkeler ve Yayın Politikası" ile "Yazım Kuralları" na uyulması konusunda ilgili başlıkları dikkatlice incelemesi tavsiye edilmektedir.

Editör
Prof. Dr. Mustafa ALTINDİŞ
Editor in Chief

e-ISSN 2587-1641

Deneysel, Biyoteknolojik, Klinik ve Stratejik Sağlık Araştırmaları Derneği
JOURNAL of BIOTECHNOLOGY and STRATEGIC HEALTH RESEARCH
Nisan, Ağustos ve Aralık aylarında olmak üzere yılda 3 sayı çıkar.
Three issues annually: April, August, December

Yayın dili: Türkçe ve İngilizcedir
Publishing Language: Turkish and English

http://dergipark.gov.tr/bshr

Sahibi (Owner)
Deneysel, Biyoteknoloji, Klinik ve Stratejik Sağlık Araştırmaları Derneği Adına Prof. Dr. Mustafa ALTINDİŞ
Experimental, Biotechnology, Clinical and Strategic Health Research Association on behalf of Mustafa ALTINDIS MD

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Dizin Bilgisi (Indexing)
JOURNAL OF BIOTECHNOLOGY AND STRATEGIC HEALTH RESEARCH(Biyoteknoloji ve Stratejik Sağlık Araştırmaları Dergisi); "Türkiye Atıf Dizini", "Türk Medline", "Google Scholar", "ASOS Index", "SOBIAD"ve "CrossRef" gibi ulusal ve uluslarası dizinlerde taranmaktadır. Makalelere DOİ verilmektedir.

e-ISSN 2587-1641

Journal of Biotechnology and Strategic Health Research

KÜNYE

e-ISSN 2587-1641

Journal of Biotechnology and Strategic Health Research

YAZARLARA BİLGİLER

MAKALE YAZIM KURALLARI

Derginin Kapsamı

JOURNAL OF BIOTECHNOLOGY AND STRATEGIC HEALTH RESEARCH, yılda üç kez Deneysel, Biyoteknolojik, Klinik ve Stratejik Sağlık Araştırmaları Derneği tarafından yayımlanmakta olup tıp alanında ve sağlık bilimlerinin ilgili konularında yazılmış İngilizce veya Türkçe makaleler kabul edilmektedir. Dergiye kabul edilecek yazı türleri deneysel araştırmaları, klinik ve laboratuvar çalışmalarının sunulması amaçlı özgün makaleler, vaka sunumları, derleme makaleleri ve editöre mektuplardır.

A. Genel Bilgiler

➢ Etik Kurallar

Dergiye gönderilen makalelerin daha önce başka bir dergide değerlendirme sürecinde olmaması, yayım için kabul edilmemiş ve de yayınlanmamış, olması, bilimsel ve etik kurallara uygun şekilde hazırlanması gereklidir. Yazarlar, makalelerin bilimsel ve etik kurallara uygunluğundan sorumludur. (http://www.icmje.org/about-icmje/faqs/conflict-of-interest-disclosure-forms/).

Klinik araştırmaların protokolü etik komitesi tarafından onaylanmış olmalıdır. İnsanlar üzerinde yapılan tüm çalışmalarda "Yöntem" bölümünde çalışmanın ilgili komite tarafından onaylandığı veya çalışmanın Helsinki İlkeler Deklarasyonuna (www.wma.net/e/policy/b3.htm) uyularak gerçekleştirildiğine dair bir cümle yer almalıdır. Çalışmaya dahil edilen tüm insanların bilgilendirilmiş onam formunu imzaladığı metin içinde belirtilmelidir. JOURNAL OF BIOTECHNOLOGY AND STRATEGIC HEALTH RESEARCH'ne gönderilen yazıların Helsinki Deklarasyonuna uygun olarak yapıldığını, kurumsal etik ve yasal izinlerin alındığını varsayacak ve bu konuda sorumluluk kabul etmeyecektir. Çalışmada "Hayvan" öğesi kullanılmış ise yazarlar, makalenin "Yöntem" bölümünde Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) prensipleri doğrultusunda çalışmalarında hayvan haklarını koruduklarını ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadır. Sonuç olarak, etik kurul kararı gerektiren klinik ve deneysel insan ve hayvanlar üzerindeki çalışmalar için etik kurul onayı alınmış olmalı, bu onay makalede "Etik Kurul Onay Numarası" ile belirtilmelidir ve belgelendirilmelidir.

Dergide çıkan yazıların tüm hakkı dergiye aittir. Yazılar için yazarlara telif hakkı ödenmez. Makaleye ek olarak yukarıdaki şartları kaşif taramalarına dayalı yazılarda Anabilim Dalı (Bilim Dalı) Başkanlığı, Başhekimlik veya Servis Şefliği tarafından arşivde çalışılmasına izin verdiğine dair bir belgenin çalışmaya eklenmesi zorunludur. Prospektif klinik çalışmalar için resmi gazetenin 29.01.1993 tarih ve 21480 sayılı nüshasında yayımlanan yönetmeliğe uygun bir şekilde Etik Kurulu onayı alınmalıdır. Dergide yer alan makalelerin etik sorumluluğu yazarlarına aittir.

Dergiye gönderilen makalelerden hakeme gönderilmesi uygun görülen makaleler konunun uzmanı hakemlere gönderilir. Makalenin yayımlanabilmesi için iki hakemin de olumlu görüş bildirmesi gerekmektedir. Değişikliğe gerek görüldüğü takdirde, istenilen değişiklikler yazarlarca 15 gün içerisinde yapıldıktan sonra yayın tekrar incelemeye alınır, yazım ve dil bilgisi hataları makalenin içeriğine dokunulmaksızın yayın kurulu tarafından düzeltilir.

Derleme yazılarında, tüm yazarların derleme konusu ile ilgili en az bir SCI/SCI-expanded indekse giren yayınının bulunması gerekmektedir.

Sonucu desteklemek için istatistiksel analiz genellikle gereklidir. İstatistiksel analiz, tıbbi dergilerdeki istatistik verilerini bildirme kurallarına göre yapılmalıdır (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). İstatistiksel analiz ile ilgili bilgi, Yöntemler bölümü içinde ayrı bir alt başlık olarak yazılmalı ve kullanılan yazılım kesinlikle tanımlanmalıdır.

Dergi İntihal İlkesi

JOURNAL OF BIOTECHNOLOGY AND STRATEGIC HEALTH RESEARCH'de makale göndermeden önce uygun intihal yazılım programlarıyla (iThenticate, Turnitin: Tezler için vb.) makalenizdeki benzerlik durumunu belirlemeniz beklenir. Benzerlik oranlarının dergimiz için kaynaklar hariç % 20'un altında olması istenmektedir.

Simgeler, Birimler ve Kısaltmalar

Dergimiz, İngilizce makalelerde Scientific Style and Format, The CSE Manual for Authors, Editors, and Publishers, Council of Science Editors, Reston, VA, USA (7th ed.) uzlaşılarını; Türkçe makalelerde ise TDK Yazım Kılavuzu, Türkiye Bilim Terimleri ve TÜBA Türkçe Bilim Terimleri Sözlüğü'nü esas almaktadır. p, ×, μ, η, or v gibi karakterler, sözcük işlem uygulamasının simge menüsünden seçilerek kullanılmalıdır. Sayılarla birimler arasında bir boşluk bırakılmalı (örn. "3 kg"), sayılarla yüzde simgesi arasında boşluk bırakılmamalıdır (örn. "%45"). Tüm kısaltma ve kısa adlar, ilk kez kullanıldıklarında tanımlanmalıdır. Canlıların ve mikroorganizmaların jenerik isimleri, tür adını değiştirmeden, uygun şekilde kısaltılmalı ve yatık olarak yazılmalıdır.

Makale Hazırlama Şekli ve Biçimi & Gönderim

Makale gönderimi çevrimiçi olarak http://dergipark.gov.tr/bshr adresine Microsoft Word dosyası olarak eklenmelidir. "Öz", "Ana Metin ve Kaynaklar (Çizelgeler dahil)" Microsoft Word dosyası (.doc veya .docx uzantılı) olarak, 12 yazı tipi boyutunda, Times New Roman karakterleriyle, 1,5 satır aralığıyla ve paragraflar iki yana yaslanmış olarak yazılmalıdır. Makalelerin değerlendirilmeye alınabilmesi için, başvuru esnasında 'Telif Hakkı devir formu' doldurulmalıdır. Bu formu içermeyen yazılar değerlendirmeye alınmaz. Makaleler, Ana metnin sayfa numaraları, her sayfanın sağ alt köşesinde belirtilmelidir.

Makaleler, Türkçe veya İngilizce yazılabilir.

B. Yazım Kuralları

Metin içi ve metin sonu kaynak gösterimi için, AMA (Amerikan Tıp Birliği/American Medical Association) Stili kullanılmalıdır (http://library.nymc.edu/informatics/amastyle.cfm; https://drive.google.com/drive/folders/1hzvgxnau1lBPUBYfKN1vTBKbPE31LBXQ) .

Dergide kör hakemlik uygulaması söz konusu olduğundan makale ana metin üstünde yazarlara ilişkin herhangi bir bilgi bulunmamalıdır.

Tüm makale yazarlarının, ORCID iD (Open Researcher and Contributor ID) numaraları başlık sayfasına eklenmelidir.

B. 1. Başlık Sayfası

Yazılar başlık sayfasından başlanarak numaralandırılmalı, sayfa numaraları sağ alt köşeye yazılmalıdır.Başlık sayfasında; yazının başlığı (Türkçe ve İngilizce), başlık altında tüm yazarların ad ve soyadları, kurumları yer almalıdır. Sorumlu yazarın adı ve soyadı, telefon numarası, e-posta ve yazışma adresleri bulunmalıdır. Makale başlığı, 25 kelime ile sınırlı, Türkçe ve İngilizce dillerinde verilmelidir. Kısa başlık (running title, running head) 50 karakterle (boşluk dahil) sınırlı şekilde Türkçe ve İngilizce olmalıdır.

B. 2. Öz Sayfası

Öz (Abstract), Türkçe ve İngilizce olarak en fazla 250 sözcük olacak şekilde; 'Amaç (Objective)', 'Yöntem (Methods)', 'Bulgular (Results)' ve 'Sonuç (Conclusion)' bölümlerinden oluşmalıdır. Derleme ve olgu sunumunda öz sayfası bölümlere ayrılmadan yazılmalıdır.

Öz'ün altına "anahtar kelimeler" (en az 3, en fazla 6) verilmelidir. Anahtar kelimeler Türkçe ve İngilizce yazılmalıdır. İngilizce anahtar kelimeler Index Medicus'da "Medical Subjects Headings" listesine uygun olmalıdır (Bkz: www.nlm.nih.gov/mesh/MBrowser.html). Türkçe anahtar kelimeler Türkiye Bilim Terimleri, uygun olarak verilmelidir (Bkz: www.bilimterimleri.com). Bulunamaması durumunda bire bir Türkçe tercümesi verilmelidir.

B. 3. Ana Metin

B. 3. 1. Özgün Araştırma

Sırasıyla ve kesin sınırlarla ayrılmış "Giriş", "Yöntem", "Sonuç" ve "Tartışma" bölümlerinden oluşmalıdır. Sonuç kısmı, ayrı bir bölüm olarak veya Tartışma'nın son paragrafı olarak yazılabilir. Tartışma kısmının son paragrafında çalışmanın sonuçları ifade edilebilir, ek bir başlık açılmasına gerek yoktur.

En çok 15 sayfa (öz, teşekkür ve kaynaklar hariç) olmalıdır.

Sistematik derleme ve meta-analiz özgün araştırma makalesi kapsamındadır. Yazarlar, taslaklarını gönderirken sistematik derleme ve meta-analiz için, PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) beyanatı (http://www.prisma-statement.org/). yönergesine uyduklarını gösteren standart kontrol listelerini kullanmalı ve istendiğinde sunmalıdır.

Sözcük sayısı öz, teşekkür ve kaynaklar hariç en çok 5 000 olmalıdır. Kaynak sayısı, 50'yi geçmemelidir(derleme hariç). Metin boyunca bilimsel terimler yatık olarak yazılmalıdır.

B.3.2. Derleme

En çok 20 sayfa (öz ve kaynaklar hariç) olmalıdır. Derlemeler, standart yazı şeklinden farklıdırlar. Yazı yazmanın evrensel formatı IMRAD derleme yazılarında uygulanmamaktadır. Ana hatlarıyla "Giriş" bölümü daha geniş olmakta ve derlemenin amacını ve yazı gerekçesini açıklamaktadır.

"Yöntem" ve "Bulgular" kısmı bulunmamaktadır. Tartışma kısmı yine geniş tutulacak ve kişisel deneyimler doğrultusunda aynı konuda yapılmış çalışmalar ve onların sentezi yapılacaktır. Sonuç anlamında bir yorum ve değerlendirme paragrafı bulunmalıdır. Kaynaklar ise tüm yazılara göre daha fazla sayıda olacaktır. Ancak mutlaka yazarın kendi çalışmaları da bulunacaktır.

B.3.3. Olgu Sunumu

En çok 10 sayfa (öz, teşekkür ve kaynaklar hariç) olmalıdırr. Olgu sunumlarında ise sırasıyla giriş, olgu sunumu ve tartışma bölümlerini içermelidir.

B.3.4. Editöre Mektup

En çok 5 sayfa (öz ve kaynaklar hariç) olmalıdır. Çizim ve çizelge içermez. Bir makaleye ithaf olarak yazılmış ise sayı ve tarih verilerek belirtilmeli ve metnin sonunda yazarın ismi, kurumu ve adresi bulunmalıdır.

B.4. Çizim ve Çizelgeler

Metin içerisinde kullanılan fotoğraf, grafik, şekil, resim gibi görsel sunum araçları 'Çizim' olarak tanımlanır. 'Tablo' ise sınıflandırılmış verilerin yer aldığı görsel sunum araçlarıdır. Tablolar kaynaklardan sonra başlıklarıyla birlikte verilmelidir. Tablolar, başlığın alt ve üstünde, ayrıca alt satırın altında yatay kenarlık ve sol sütunun sağ dikey kenarlığı olacak şekilde düzenlenmelidir.

Figür ve Tablolar, numaraları ile metin içinde geçtiği yerlerde ilgili cümlenin sonunda ayıraç içinde belirtilmeli; sırayla numaralandırılmalıdır.

Örnek tablo:

Tablo 1. Araştırmaya katılanların ilk başvurularını birinci basamakta çalışan hekime yapmama nedenleri

e-ISSN 2587-1641

Journal of Biotechnology and Strategic Health Research

YAZARLARA BİLGİLER

Başvurmama Nedeni	*n	%
Sadece psikiyatri uzmanı ruh sağlığı hizmeti sunabilir		
Birinci basamakta çalışan hekimin bu hizmeti sunduğunu bilmemem		
Ebeveyn kararıydı		
Birinci basamakta çalışan hekime güveniyorum ancak tercih etmedim		
	47	53,4
	17	19,3
	12	13,6
	12	13,6

* Toplam hasta sayısı

Tablolar, metne dahil edilmemeli ve sistem üzerinden "Görseller" başlığı seçilerek yüklenmelidir. Görseller; JPG, GIFF, PNG veya TIFF formatında gönderilmelidir. Metine ek olarak sisteme yüklenen tüm çizim başlıkları, "Çizim Başlığı" altında, kaynaklardan sonra listelenmelidir. Kullanılan kısaltmalar çizim ve çizelgelerin altındaki açıklamada 10 yazı boyutunda belirtilmelidir. Ondalıklı sayıların belirtilmesinde Türkçe metinlerde virgül işareti, İngilizce metinlerde nokta işareti kullanılmalıdır. Yüzde ile belirtilen sayılarda Türkçe metinlerde sayı önünde, İngilizce metinlerde ise sayı arkasında % işareti kullanılmalıdır.

B. 5. Açıklamalar

Çalışmada teşekkür, daha önce sunulduğu kongre, çıkar çatışması olmadığı, maddi destek, bağış ya da teknik yardım gibi konular metnin sonunda kaynaklardan önce belirtilmelidir. Çalışmayı maddi olarak destekleyen kişi ve kuruluşlar ve varsa bu kuruluşların yazarlarla olan çıkar ilişkileri belirtilmelidir. (Olmaması durumu da "Çalışmayı maddi olarak destekleyen kişi/kuruluş yoktur ve yazarların herhangi bir çıkar dayalı ilişkisi yoktur" şeklinde yazı yazılmalıdır. Araştırma desteği (Üniversite Bilimsel Araştırma projeleri , TÜBİTAK projeleri ve benzeri kurumlardan) alınmışsa, proje numarası belirtilmelidir.

C. Kaynak Gösterimi

Dergimiz, kaynak gösteriminde AMA stilini kullanılmaktadır ve kaynak yazımında atıf düzenleme programlarının kullanımını tavsiye edilmektedir (EndNote, Mendeley, Zotero vb.).

C. 1. Metin İçinde;

Kaynaklar, metinde geçiş sırasına göre numaralandırılmalıdır ve kaynak numaraları üst simge olarak verilmelidir. Örneğin,"… belirtilmektedir8. , bildirilmiştir8,13,18. , şeklindedir8-10

C. 2. 'Kaynaklar' Başlığı Altında;

Kaynaklar ayrı bir liste olarak metin içindeki sıralamalarına göre numaralandırılarak verilmelidir. Kaynak sayısı özgün araştırmalarda en çok 50, olgu sunumlarında en çok 20, editöre mektuplarda ise en çok 5 olmalıdır.

Kaynaktaki yazar sayısı 3 veya daha az ise tüm yazarlar belirtilmeli; 3'den fazla ise, Türkçe kaynak gösteriminde sadece ilk 3 isim yazılmalı "ve ark." şeklinde, İngilizce kaynak gösteriminde ise ilk 3 isim yazılmalı ve "et al." şeklinde gösterilmelidir.

Dergi isimleri Index Medicus/Medline/PubMed'de yer alan dergi kısaltmaları ile uyumlu olarak kısaltılmalıdır. Index Medicus'ta indekslenmeyen bir dergi kısaltılmadan yazılmalıdır. Çevrimiçi yayınlar için DOİ (digital object identifier) numarası verilmelidir.

Örnek:

1. Gage BF, Fihn SD, White RH. Management and dosing of warfarin therapy. The American Journal of Medicine. 2000; 109(6): 481-488. doi:10.1016/S0002-9343(00)00545-3.

Örnekler:

1. Debes-Marun CS, Dewald GW, Bryant S, et al. Chromosome abnormalities clustering and its implications for pathogenesis and prognosis in myeloma. Leukemia. 2003; 17: 427–436.
2. Ozcelik F, Oztosun M, Gülsün M, ve ark. İdiopatik trombositopenik purpura ön tanılı bir olguda EDTA'ya bağlı psödotrombositopeni. Turk J Biochem. 2012; 37(3): 336–339.

Örnek:

1. Yoldas O, Bulut A, Altindis M. Hepatit A Enfeksiyonlarının Güncel Yaklaşımı. Viral Hepatit J 2012; 18: 81-86.
2. Bir derginin ek sayısı (Supplement) kaynak gösterileceği zaman; İngilizce makalelerde (Suppl.) ve Türkçe makalelerde ise (ES) şeklinde gösterilmelidir.

Çevrimiçi makale ise tam yayın tarihi kullanılır. Genellikle cilt ve dergi sayıları, sayfa numaraları yoktur. Makaleye doğrudan ulaşım adresi ve erişildiği tarih verilmelidir.

Örnek:

5. Frederickson BL (2000, Mart 7). Cultivating positive emotions to optimize health and well-being. Prevention & Treatment 3, Makale 0001a. http://journals.apa.org./prevention/volume3/pre003000-1a.html adresinden 20 Kasım 2000'de erişildi.

Kitabın kaynak gösterimi ise yazarların adı, kitabın adı, birden çok basımı varsa kaçıncı basım olduğu, basımevi, basım yeri, basım tarihi belirtilmelidir

Örnek:

2. Strunk W Jr., White EB. The Elements of Style (4. baskı). Longman, New York, 2000.

Kaynak çok yazarlı bir kitabın bölümü ya da bir makalesi ise bölümün ya da makalenin yazarı, bölümün ya da makalenin adı, kitabın adı, kaçıncı baskı olduğu, cildi, kitabın yayın yönetmenleri, basım yeri, sayfaları, tarih yazılmalıdır.

Örnek:

3. Meltzer HY, Lowy MT. Neuroendocrin function in psychiatric disorders. American Handbook of Psychiatry, 2. Baskı, cilt 8, PA Berger, HKH Brodie (Ed), New York. Basic Books Inc, 1986; s. 110-117.

Çeviri kitaplar aşağıdaki şekilde kaynak olarak gösterilmelidir.

Örnek:

4. Liberman RP. Yetiyitiminden İyileşmeye: Psikiyatrik İyileştirim Elkitabı. American Psychiatric Publishing Inc. Washington DC. 2008. Çev. Mustafa Yıldız, Türkiye Sosyal Psikiyatri Derneği, Ankara, 2011.

Kaynak çevrimiçi (internette yer alıyor) ise erişim tarihi ile birlikte yazılmalıdır.

MAKALE SÜREÇ YÖNETİMİ

A. Çift-Kör Hakemlik

JOURNAL OF BIOTECHNOLOGY AND STRATEGIC HEALTH RESEARCH (J of BSHRS), yılda 3 kez yayınlanan ve çift-kör hakemlik sürecinden geçen bilimsel makalelerin yayınlandığı ulusal/uluslararası ve hakemli bir akademik dergidir. Yayınların incelenmesi için çalışmaların içeriğine ve hakemlerin uzmanlık alanlarına göre en az iki hakem, makale alan editörü/leri tarafından atanır. Bu süreçte hakem değerlendirme raporları elektronik ortamda isimsiz olarak gönderilir. Değerlendirmeyi yapan hakemlerin isimleri çift-kör yöntemi gereği raporlarda ve dergide belirtilmemektedir. Talep edilmesi halinde, hakem olarak dergiye katkı sağladığına ilişkin yazılı bir belge hakemlere verilebilir. Yazarlar, hakemlerle doğrudan iletişime geçemez, değerlendirme ve hakem raporları dergi yönetim sistemi aracılığıyla iletilir. Bu süreçte değerlendirme formları ve hakem raporları editör aracılığıyla sorumlu yazara iletilir.

B. Karar Alma Süreçleri

Yayınlanmak üzere gönderilen tüm çalışmalar, değerlendirme için alanlarında uzman en az iki hakeme gönderilir. İnceleme sürecinin tamamlanmasının ardından editör, söz konusu çalışmanın doğruluğu, araştırmacı ve okuyucular için önemi, hakem raporları, telif hakkı ihlali ve intihal gibi yasal düzenlemeleri de göz önünde bulundurarak hangi çalışmaların yayınlanacağına karar verir. Editör, bu kararı verirken diğer editörlerden veya hakemlerden de tavsiyeler alabilir.

C. İvedilik

Hakem değerlendirmesi yapmak üzere davet alan bir hakem, ilgili çalışma için hakemlik yapıp yapamayacağını yedi gün içinde editöre bildirmelidir. Kabul edilen hakemlik değerlendirme süreci onbeş, sorumlu yazara bildirilen değişikliklerin tamamlanması için, yazarlara verilen süre ortalama onbeş gündür. Sorumlu yazara son okuma için gönderilen metnin değerlendirme süresi ise üç gündür. Değerlendirme için hakemlere gönderilen çalışmalar gizli belge olarak tutulmalıdır. Çalışmalar başkalarına gösterilmemeli, içerikleri tartışılmamalıdır. Gerekli durumlarda editörün izni dahilinde hakemler başka meslektaşlarından tavsiye isteyebilirler. Editör, bu izni ancak istisnai bir koşul olması durumda verebilir. Gizlilik kuralı, hakemlik yapmayı reddeden kişileri de kapsamaktadır.

E. Tarafsızlık İlkesi

Değerlendirme sürecinde yazarlara yönelik kişisel eleştiri yapılmamalıdır. Değerlendirmeler, nesnel ve çalışmaların geliştirilmesine katkı sağlayacak şekilde olmalıdır.

F. Kaynak Belirtme

Hakemler, çalışmada atıf olarak belirtilmeyen alıntılar varsa bunları yazarlara bildirmekle yükümlüdür. Hakemler, alanda atıfta bulunulmayan eserlere ya da benzer eserlerle çakışan alıntılara özellikle dikkat etmelidir. Hakemler, daha önce yayınlanmış herhangi bir çalışma ya da bilgiyle benzerliği olan yayınların farkedilmesi durumunda editörleri bilgilendirmelidir.

G. Bilgilendirme ve Çıkar Çatışması

Hakemler, çalışmasını değerlendirmekle görevlendirildikleri herhangi bir yazar, şirket ya da kurumla işbirliğine dayalı herhangi bir bağlantıları olması durumunda değerlendirme yapmayı kabul etmemeli ve durumdan editörü haberdar etmelidir.

Hakemler, değerlendirme için gönderilmiş, yayınlanmamış eserleri ya da eserlerin bölümlerini yazar(lar)ının yazılı onayı olmadan kendi çalışmalarında kullanamaz. Değerlendirme sırasında elde edilen bilgi ve fikirler hakemler tarafından gizli tutulmalı ve kendi çıkarları için kullanılmamalıdır. Bu kurallar, hakemlik görevini kabul etmeyen kişileri de kapsamaktadır.

YAZI GERİ ÇEKME TÜM YAZARLARIN ONAYI İLE OLMALIDIR.

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Faks: +90.264.295 6629

e-ISSN 2587-1641

Journal of Biotechnology and Strategic Health Research

HEALTH RESEARCH

INSTRUCTIONS FOR AUTHORS

Scope of the Journal

The JOURNAL OF BIOTECHNOLOGY AND STRATEGIC HEALTH RESEARCH is published electronically 3 times a year by the Experimental, Biotechnological, Clinical and Strategic Health Research Association and accepts English or Turkish-language manuscripts in all fields of medicine(Experimental, Biotechnological, Clinical and Strategic Health Research) and other related health sciences. Contribution is open to researchers of all nationalities. The following types of papers are welcome: original articles (for the presentation of clinical and laboratory studies), case reports, review articles, and letters to the editor.

Submission Procedures

All manuscripts must be submitted electronically via the internet to the JOURNAL OF BIOTECHNOLOGY AND STRATEGIC HEALTH RESEARCH through the online system for ULAKBIM dergipark http://dergipark.gov.tr/bshr You will be guided stepwise through the creation and uploading of the various files.

There are no page charges.

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All experimental or clinical researches done in humans or animals should follow the ethical rules. The ethical approval form must be sent and the number of approval must be given in the manuscript. The ethical problems belong only to the author(s).

All copyright of the published papers belong to Experimental, Biotechnological, Clinical and Strategic Health Research Association.

The copyright fee is not paid to all authors.

In manuscripts based on scanning of archieve records, a consent form is needed that shows the permission for retrospective work and signed by Head of the Department, hospital manager or clinic manager.

Preparation of Manuscript Style and format:

Manuscripts should be submitted to http://dergipark.gov.tr/bshr as Microsoft word file in Times New Roman font. All manuscripts including references should be typed in 12 font size,one and a half (1.5) line space and justified. Upon submission, the copyright release form should be filled and downloaded. The manuscript submissions without a copyright release form will not be evaluated.

Each page of main text of the manuscript should be numbered on the right hand side. Manuscripts should be written in Turkish or English. Contributors who are not native English speakers are strongly advised to ensure that a colleague fluent in the English language or a professional language editor has reviewed their manuscript. Repetitive use of long sentences and passive voice should be avoided. It is strongly recommended that the text be run through computer spelling and grammar programs.

Symbols, Units, And Abbreviations:

In general, the journal follows the conventions of Scientific Style and Format, The CSE Manual for Authors, Editors, and Publishers, Council of Science Editors, Reston, VA, USA (7th ed.). Spaces must be inserted between numbers and units (e.g., 3 kg), but not between numbers and mathematical symbols (+, –, ±, ×, =, <, >) and between numbers and percent symbols (e.g., 45%). Please use International System (SI) units. All abbreviations and acronyms should be defined at first mention. Thereafter, generic names should be abbreviated as appropriate without altering the species name.

Typs of Manuscripts Original Article

It should consists of "Introduction", "Methods", "Results" and "Discussion". Conclusion may be written as a last paragraph of discussion, there is no need to add a separate section for conclusion. The whole length of text should be maximum 5 000 words (except abstract, acknowledgements and references). The numbers of references should be maximum 50. Also, scientific names should be spelled italics throughout the text.

Review

It should be maximum 6 000 words (except abstract and references). The author(s) should have at least one published paper in a journal indexed in SCI/SCI-expanded related to the topics of the review. The abstract should be as one paragraph and should be written without a section. The numbers of references should be maximum 100.

Case Report

It should be maximum 1 500 words (except abstract, acknowledgement and references). Case reports should consist of abstract, keywords, introduction, case report and discussion sections. The numbers of references should be maximum 10. Figures or Tables should follow the main text in a separate pages.

Letter to Editor

It should be maximum 1 000 words (except abstract and references). No Tables or Figures are included. If it was written refering to another article, the number and the date should also be added. The name, affiliation(s) and address of author(s) should be written at the end of the text. The numbers of references should be maximum 5.

Manuscript Arrangement

Manuscripts should be arranged as follows: "Title page", "Abstract", "Keywords", "Main text", "Acknowledgements", "References", "Tables",and "Figures".

Title page

All submissions must include a title page, which is to be uploaded as a separate document. The title page should contain the full title in sentence case (e.g., Urothelial cancers: clinical and imaging evaluation). The title should be limited to 25 words or less and should not containabbreviations.The title should be a brief phrase describing the contents of the paper.Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible. It should be written in capital letters both in Turkish and in English. Title in English should be written using italic letters for Turkish manuscripts and vice versa. The first and the family names of the authors should be written in small letters as the first letter being the capital.

The full names and affiliations of all authors should be given clearly and briefly with theirinstitutions, address with zip code and name of country, and the contact details of corresponding author (E-mail address and telephone). In addition, ORCID (Open Researcher and Contributor ID) numbers of all authors should be included into the title page.

Abstract

The abstract should be brief, indicating the purpose/significance of the research, methodology, major findings and the most significant conclusion (s). The abstract shouldnot contain literature citations that refer to the main list of reference attached to the complete article. The abstract should be written as a single paragraph and should be in reported speech format (past tense); complete sentences, active verbs and the third person should be used.

The abstract should be structured to include the study's "Objective", "Methods", "Results", and "Conclusion" under 4 separate headings. Abstracts of review articles should be a brief overview of the main points from the review. In reviews and case reports, abstract should be written without any sections. The abstract (English and Turkish) should not be more than 300 words.

Keywords

The authors must provide 3-6 keywords for indexing purposes and to facilitate the retrieval of articles by search engines. Keywords should be different from the words that make up the title of the article. Keywords should be written below the abstracts both inTurkish andEnglish. Acronyms should be avoided. For English keywords, always try to use terms from the Medical Subjects Headings list from Index Medicus (www.nlm.nih.gov/mesh/MBrowser.html). For Turkish keywords, terms from Turkish Scientific Terms (www.bilimterimleri.com) should be used.

Main text

Introduction

The introduction should be clear and concise, with relevant references on the study subject and the proposed approach or solution. There should be no subheadings. Excessive citation of literature should be avoided. Only necessary and the latest citations of literature that are required to indicate the reason forthe research undertaken and the essential background should be given.

Methods

Explain clearly but concisely your clinical, technical, or experimental procedures. A precise description of the selection of your observational or experimental subjects (for example patients or laboratory animals including controls) must be presented. Experimental research involving human or animals should be approved by ethical committiee.All chemicals and drugs used must be identified correctly, including the generic names, the name of the manufacturer, city and country in parenthesis. The techniques or methodology adopted should be supported with standard references. Briefly describe methods that have been published but are not well known as well as new or substantially modified methods. Description of established procedures are unnecessary. Apparatus should be described only is it is non-standard; commercially available apparatus used should be stated (including manufacturers' name, address in parenthesis). Only SI units should be used for each measurements.

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HEALTH RESEARCH

Results

The result section should provide complete details of the experiment that are required to support the conclusion of the study. The results should be written in the past tense when describing findings in authors experiments. Previously published findings should be written in the present tense. Speculation and the detailed interpretation of the data should not be included in the results but should be put into the discussion section.

Discussion

Statements from the "Introduction" and "Results" sections should not be repeated here. The final paragraph shouldhighlight the main conclusions of the study.

Tables and Figures

The visual presentations like photographs, graphics, picturesetc. must be labelled "Figures". Whereas, the "Tables" shows the classifieddata.Tables should be added after the "References" section. Figure legends should be placed into the end of the main text. Figures should be uploaded as a separate file following the Dergipark System.

All tables and figures must have a caption and/or legend and be numbered (e.g., Table 1., Figure 2.), unless there is only one table or figure, in which case it should be labelled "Table" or "Figure" with no numbering. Captions mustbe written in sentence case (e.g., Figure 1. Macroscopic appearance of the samples.). The font used in the figures should beTimes New Roman. If symbols such as ×, μ, η, or ν are used, they should be added using the Symbols menu of Word.

All tables and figures must be numbered consecutively as they are referred in the text. Please refer to tablesand figures with capitalisation and unabbreviated (e.g., "As shown in Figure 2. …", and not "Fig. 2" or "figure 2").
The resolution of images should not be less than 118 pixels/cm when width is set to 16 cm. Images must bescanned at 300 dpi resolution and submitted in .jpeg, .png or .tif format.

Graphics and diagrams must be drawn with a line weight between 0.5 and 1 point. Scanned or photocopied graphs anddiagrams are not accepted.

Charts must be prepared in 2 dimensions unless required by the data used. Charts unnecessarily prepared in3 dimensions are not accepted.

Figures that are charts, diagrams, or drawings must be submitted in a modifiable format, i.e. our graphicspersonnel should be able to modify them. Therefore, if the program with which the figure is drawn has a "Save as"option, it must be saved as .pdf. If the "Save as" option does not include .pdf extension, the figure must becopied and pasted into a blank Microsoft Word document as an editable object. It must not be pasted as an imagefile (.tiff or.jpeg) unless it is a photograph.

Tables and figures, including caption, title, column heads, and footnotes, must not exceed 16 × 20 cm andshould be no smaller than 8 cm in width. For all tables, please use Word's "Create Table" feature, with no tabbedtext or tables created with spaces and drawn lines. Please do not duplicate information that is already presented inthe figures.
Tables must be clearly typed, each on a separate sheet, and single-spaced. Tables may be continued on anothersheet if necessary, but the dimensions stated above still apply.

Tables should be arranged as a horizontal borderline as well as below the last line. Moreover, there sould be vertical line on the right of first column on the left hand site. Abbreviations used in the tables such as (*) should be explained below the table in 10 font size.

In Tables written in Turkish, decimal numbers should be written with comma, however in English text, decimal numbers should be written with dots. Percentages (%) should be placed in front of the numbers without space and behind the numbers in Turkish and English text, respectively.

Example for a Table:

Table1. The reasons of not applying to general practioner for the first application.

The reasons	*n**	*%*
Only Psychiatrist can do it		
No information about general practioner Parents decision		
Not preferred	*47*	*53.4*
17	*19.3*	
12	*13.6*	
12	*13.6*	

**Total number of patients.*

Acknowledgement

All acknowledgements, poster/oral presentations, financial supports, grants, technical supports and the conflict of interest should be mentioned at the end of the text.

Funding

The type of Project or the financial support such as scientific projects of University, TUBITAK projects etc. should be added at the end of the text including the numbers and the year of the projects.

References

While talking about the source in the text, the first author's surname ın Er and his firends' study12"…… or ın Er et al.12. Both authors should be given the surnames of both authors (similar results were found in the study conducted by Öncü and Ilke13).

Citations in the text should be identified by numbers assuperscript, for example, "The results were as follows: 4
If there are more than one references, separate the numbers with comma, for example, "Several interventions have been successful at increasing compliance.11,14"

In following journals, first and the last numbers should be seperated by "-" , for example: Diabetes mellitus is associated with a high risk of foot ulcers1-3 or "As reported previously,1,3-6"

Do not include personal communications, unpublished data, or other unpublished materials as references, although such material may be inserted (in parentheses) in the text. In the case of publications in languages other than English, the published English title should be provided if one exists, with an annotation such as "(article inTurkish with an abstract in English)". If the publication was not published with an English title, provide the original title only; do not provide a self-translation. A short title for use as a running head (not to exceed 30 characters in length, including spaces between words) is needed. References should be formatted as follows (please note the punctuationand capitalisation):
The list of references at the end of the paper should be given in order of their first appearance in the text. All authors should be included in reference lists unless there are more than 6, in which case only the first 3 should be given, followed by "et al." in English and "ve ark." in Turkish references.

The number of references should not be more than 60 in original articles, not more than 100 in review articles, not more than 20 in case reports and not more than 5 in letter to editor. The journal requires DOI numbers, when available, to be included in all references. Personal experiences and researches without a DOI number should not be used.

In order to arrange the reference list easly, our journal suggest the use of reference arrangement programmes such as EndNote or Mendeley etc.).

For a reference in the reference list, the surname of author, the first letter of author's name, the title of the reference, the name of the journal, the year of the journal, the numbers of its volume, issue and pages should be written. The name of the journal should be abbreviated as in AMA (American Medical Association) ((http://library.nymc.edu/informatics/amastyle.cfm). If the abbreviation is not avalible, whole name of the journal should be written.

Published papers

Yoldas O, Bulut A, Altindis M. Current Approach to Hepatitis A Infections. Viral Hepatit J 2012; 18: 81-86..
Debes-Marun CS, Dewald GW, Bryant S, et al. Chromosome abnormalities clustering and its implications for pathogenesis and prognosis in myeloma. Leukemia. 2003;17:427–436.
Ozcelik F, Oztosun M, Gülsün M, ve ark. Pseudothrombocytopenia due to EDTA in a case with idiopathic thrombocytopenic purpura. Turk J Biochem. 2012;37(3):336–339.

Gage BF, Fihn SD, White RH. Management and dosing of warfarin therapy. Am J Med. 2000;109(6):481- 488. doi:10.1016/S0002-9343(00)00545-3.

If a supplement of a journal is referred, (suppl.) in English and (ES) in Turkish manuscripts should be used.

Electronic journal articles

If a journal from a website is used, the date of publishing is used. Usually, there is no numbers of volume, issue or pages. The web adress and date of download should be given.

Example:

Acetaminophen poisoning. In: DynaMed [database online]. EBSCO Information Services. http://0-search.ebscohost.com.topcat.switchinc.org/login.aspx?direct=true&site=DynaMed&id=113862.

Updated

March 09, 2010. Accessed March 23, 2010.

Book

Harmening D. Modern Blood Banking & Transfusion Practices. 6th ed. Philadelphia, PA: F.A. Davis Company; 2012.
Strunk W Jr., White EB. The Elements of Style. 4th ed. New York, NY: Longman; 2000.
Chapter in a book
Solensky R. Drug allergy: desensitization and treatment of reactions to antibiotics and aspirin. In: Lockey P, ed. Allergens and Allergen Immunotherapy. 3rd ed. New York, NY: Marcel Dekker; 2004:585-606.
McCall RE, Tankersley CM. Phlebotomy and specimen considerations. In: Bishop ML, Fody EP, Schoeff LE, editors. Clinical Chemistry: Techniques, Principles, Correlations. Philadelphia, PA, USA: Lippincott Williams & Williams; 2010:33-73.

Conference proceedings

Weber KJ, Lee J, Decresce R, Subjasis M, Prinz R. Intraoperative PTH monitoring in parathyroid hyperplasia requires stricter criteria for success. Paper presented at: 25th Annual American Association of Endocrine Surgeons Meeting; April 6, 2004; Charlottesville, VA.

Chu H, Rosenthal M. Search engines for the World Wide Web: a comparative study and evaluation met-

e-ISSN 2587-1641

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hodology. Paper presented at: American Society for Information Science Annual Conference; October 19-24, 1996; Baltimore, MD. http://www.asis.org/annual-96/electronicproceedings/chu.html. Accessed February 26, 2004.

Theses

Fenster SD. Cloning and Characterization of Piccolo, a Novel Component of the Presynaptic Cytoskeletal Matrix [master's thesis]. Birmingham: University of Alabama; 2000.

Publication Policy and Manuscript Evaluation Process

A. Double-blinded peer-reviewed method

Biotechnology and Strategic Health Research (J BSHRS) is published 3 times a year (April, August, December) and it is double-blinded peer-reviewed system national journal.

Editorial and publication processes of the BSHRS Derg. are shaped in accordance with the guidelines of the international organizations such as the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE). The journal is in conformity with Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice). Processing and publication is free of charge with the Biyoteknolojik ve Stratejik Sağlık Araştırmaları Dergisi. Authors are not charged a fee at any point during the publication process. All manuscripts should be submitted through the journal's web page at http://dergipark.gov.tr/bshr.

For the evaluation of papers, at least two referees are determined considering the content of the manuscript or the professional scientific area of the referees. In this step, referee assessment form is sent via internet without names. The personal data of the referee is not shown since the double-blind peer-reviewed method is used. Upon request, a written document given to referee as the referee for that contribute to the journal. The authors cannot directly contact with the referees. The referee's evaluation report is sent by the journal management system. The evaluation forms and the referees' reports are sent to the corresponding author(s) by the editor.

B. Decision process

After the referees' evaluation process, the editor decides whether the manuscript will be accepted or not considering the accuracy and the importance of the work, referee's reports, copyright infringement and ethical problems such as plagiarism.

As the editor decides about the manuscript, he or she may require the suggestions of the other member of editorial board or referees.

C. Instancy

A referee invited to the journal for the evaluation of a manuscript should inform the editor about the acceptance in 7 days. The referee should complete the evaluation in 15 days and the corresponding author(s) should download the revised manuscript in 15 days. The requested reading time for the last version of the manuscript by the corresponding author is only 3 days.

D. Confidentiality (Privacy Statement)

Personal information such as names and electronic mail addresses are only used for the scientific purposes of the journal. Other than these purposes this information will not be used and will not be shared with the third parties. The manuscripts sent to referees for assessment are kept as confidential documents. The manuscripts are not shown to other people and the contents of them should not be discussed. If it is necessary, reviewers may need suggestions from their colleagues after editorial permission. The editor may give that permission only in the presence of exceptional condition. The confidentiality rules are also valid for the referees not accepting the assessment of the manuscript.

E. Objectivity principles

In the evaluation process, no personal criticism of the authors should be done. The evaluations should contribute to the development of works and be objective.

F. Citation to reference

The referees should inform the authors if there are any citations that are not referred in the manuscript. The referees should pay particular attention to the citations that do not refer to the subject or to the citations that coincide with similar works. The referees should inform the editors if any publications that have similarity to any previously published work or information are recognized.

G. Information and Conflict of Interest

The referees should not agree to make any evaluation if they have any relation with any author, company or institution in which they are tasked to evaluate their work and inform the editor. The referees may not use the unpublished works or sections of the works submitted for evaluation in their own work without the written consent of the author(s). The information and ideas obtained during the assessment should be kept secret by the referees and should not be used for their own interests. These rules include those who refuse the manuscript assessment.

H. Prevention of Plagiarism

J of Biotechnology and Strategic Health Research(J of BSHR) reports the similarity rates of the articles through the iThenticate and Turnitin programs and shows the care and sensitivity required to prevent plagiarism.

THE WITHDRAW OF THE ARTICLE MUST BE WITH THE APPROVAL OF ALL AUTHORS.

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Journal of Biotechnology and Strategic Health Research

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ARAŞTIRMA MAKALESİ / RESEARCH ARTICLES

DOI:10.34084/bshr.1289441 e-ISSN 2587-1641

Journal of Biotechnology and Strategic Health Research

Araştırma Makalesi /Research Article

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Effect of Propolis on Wound Healing: A Clinical and Histomorphometric Study in Rats

Propolisin Yara İyileşmesindeki Etkisi: Sıçanlarda Klinik ve Histomorfometrik Bir Çalışma

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Geliş Tarihi / Received : 29-04-2023 **Kabul Tarihi / Accepted:** 31-05-2023 **Yayın Tarihi / Online Published:** 30-08-2023

Akpınar A., Özdemir H. Effect of propolis on wound healing: a clinical and histomorphometric study in rats. J Biotechnol and Strategic Health Res. 2023;7(2):81-88

Abstract

Aim Propolis is known to have antioxidant, antiinflammatory, antibacterial, antiviral, immunostimulant and local anesthetic effects. The aim of the present study was to investigate the clinical and histomorphometric effects of propolis on the healing of excisional palatal wounds in rats.

Material and Method Sixty male Wistar rats were used for the study. Six animals were sacrificed at beginning of the study as initial wound (0 day). The rats were divided into three groups: Propolis (P), Chlorhexidine (CHX) and Control (C). Subjects in all three groups were randomly selected to form nine subgroups of six rats each. Under anesthesia, circular excision wounds with a diameter of 3 mm were formed in the middle of the palate of the rats by punching. The mucoperiosteal part was removed with sharp dissection, and the area on the open bone surface was left to heal the secondary wound. Propolis was administered locally at a rate of 1 ml/day. The rats were sacrificed on days 7, 14, and 21, and pictures of the wound area were taken. Each photograph was transferred to a dedicated program to measure the defect area. Histological sections were taken and the presence of inflammatory cells, epithelialization, and degree of healing were assessed.

Results The average wound area between epithelial margins decreased significantly over time in all groups ($p<0.05$). compared to CHX and C groups, significant reduction of wound area was observed after seven, 14 and 21 days by using Propolis at (respectively 5.56±3.77, 3.70±1.76, 1.12±0.83). On day 21st day, the inflammatory cells were still observed in the Control group.

Conclusion The results of the study show that propolis has a positive effect on the healing of soft tissue by accelerating wound healing.

Keywords Chlorhexidine, oral wound healing, propolis

Özet

Amaç *Propolisin antioksidan, antiinflamatuar, antibakteriyel, antiviral, immunostimulant ve lokal anestezik etkileri olduğu bilinmektedir. Bu çalışmanın amacı, sıçanlarda eksizyonel damak yaralarının iyileşmesinde propolisin klinik ve histomorfometrik etkilerinin araştırılmasıdır.*

Gereç ve Yöntem *Çalışmada 60 adet erkek Wistar sıçan kullanıldı. Başlangıçta iyileşme referansı olarak (0 gün) altı hayvan sakrifiye edildi, Sıçanlar 3 gruba ayrıldı: Propolis (P), Klorheksidin (CHX) ve Kontrol (K). Tüm gruptaki denekler rastgele seçilerek altışar sıçandan oluşan dokuz alt grup oluşturuldu. Anestezi altına sıçanların damaklarının tam ortasında punch ile 3 mm çapında sirküler eksizyonel yara yüzeyleri oluşturuldu. Mukoperiosteal kısım keskin diseksiyonla uzaklaştırıldı ve açık kemik yüzeyindeki alan sekonder iyileşmeye bırakıldı. Propolis 1 ml/gün olacak şekilde gavaj yoluyla lokal olarak uygulandı. Sıçanlar yedinci, 14. ve 21. günlerde sakrifiye edildi ve yara bölgesinin fotoğrafları çekildi. Her bir fotoğraf özel bir programa aktarılarak defekt bölgesindeki yara alanı ölçüldü. Histolojik kesitler alınarak enflamatuar hücre varlığı, epitelizasyon ve iyileşme düzeylerine bakıldı.*

Bulgular *Epitelyal marjinler arasındaki ortalama yara alanı, tüm gruplarda zamanla önemli ölçüde azaldı ($p <0,05$). Propolis grubu, Chx ve K grubu ile karşılaştırıldığında yedi, 14 ve 21. günlerde (sırasıyla 5,56±3,77; 3,70±1,76; 1,12±0,83) belirgin bir yara alanı azalması gözlemlenmiştir 21. günde kontrol grubunda inflamatuar hücreler gözlenmeye devam etti.*

Sonuç *Çalışmanın bulguları ışığında propolisin yara iyileşmesini hızlandırarak yumuşak dokunun iyileşmesinde olumlu etkileri gözlenmiştir.*

Anahtar Kelimeler *Klorheksidin, yara iyileşmesi, propolis*

INTRODUCTION

Wound healing is characterised by the union of epithelial cells, endothelial cells, inflammatory cells, platelets, and fibroblasts and the performance of their normal functions in a specific order and sequence. It is well known that many people in the world suffer from chronic wounds.[1]

In the search for an agent that promotes oral wound healing and reduces postoperative complications, many agents have been investigated. Given the difficulty in postoperative plaque control after oral surgery, topical antimicrobial agents are recommended to improve wound healing by reducing plaque accumulation while reducing postoperative pain and swelling.[2,3]

Various plant extracts have been tested for their antimicrobial, analgesic, hemostatic, antibacterial, anti-inflammatory, antifungal, and antiviral effects.[4-7]

Propolis is a resinous product that honey bees collect from living plants and use to build their hives.[8-11] Several components of propolis, such as tannins, flavonoids, and essential oils, have been associated with pharmacological properties. These are thought to act on bacterial cell walls and their specific constituents, such as lipopolysaccharide and reduce the protein content of the oral biofilm.[4,8-10] Propolis extracts effectively inhibit the growth and attachment of Streptococcus mutans, Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium sp, Capnocytophaga sp. and Eikenella sp.[11,12] In addition to the antimicrobial properties of propolis, anti-inflammatory, antipsoriatic and analgesic effects have also been noted.[13]

Jacob et al.[14] studied the effects of Malaysian propolis and Brazilian red propolis on connective tissue fibroblasts and tested their potential for wound healing. Propolis was reported to be an excellent candidate for the treatment of burns as it enhances proliferation, activation and growth capacity of skin cells. The therapeutic efficacy of propolis was verified by quantitative and qualitative analyses of the expression and degradation of collagen type I and III in the wound matrix, suggesting that propolis can create a favourable biochemical environment leading to re-epithelialization. The biological activity of propolis on wound healing and tissue regeneration may be related to its antimicrobial, anti-inflammatory and immunomodulatory properties investigated the effects of topical application of propolis on the healing and closure of diabetic wounds in a streptozotocin-induced type I diabetic mouse model, propolis was shown to accelerate wound closure by promoting TGF-β expression and its downstream signalling, increasing tip I collagen expression and deposition reducing matrix metalloproteinases, and decreasing inflammation.[15-17]

Publication have indicated that Propolis, a naturally occurring resinous substance collected by honey bees to protect the hive from fungal and bacterial infections, can improve tissue healing, especially after pathological injuries such as burns and periodontal disease.[15,16,18-22]

The aim of the present study was to investigate the clinical and histomorphometric effect of propolis on the healing of excisional palatal wounds in rats.

MATERIAL and METHODS

1. Animal and study protocol

The study protocol and experimental design were approved by the Animal Ethics Committee of the Faculty of Medicine, Cumhuriyet University (approval number: B.30.2.CUM.0.01.00.00-50/100). The study group consisted of 60 male Wistar rats that were 3 months old and weighed an average of 280 g.

Rats in each group were fed in different cages under the same conditions in a well-lit and well-ventilated room. All rats were fed ad libitum and maintained on a 12-h/12-h cycle at a temperature of 21 ± 1°C and humidity of 40–60%. The rats were acclimated to their living environment for 10 days prior to the study to avoid stress-induced disruption

of the experimental setup. The experimental phases of this study were performed in the animal laboratory of the Faculty of Medicine, Cumhuriyet University. Six animals were killed immediately and formed the initial group at time 0. The animals were randomly divided into three groups: Propolis, control and chlorhexidine

- (i) Baseline Control (B) group (n=6)
- (ii) Control (0.9% Saline solution.) (C) group (n=18)
- (iii) Chlorhexidine gluconate (0.05%) (CHX) group (n=18)
- (iv) Propolis (P) group (n=18)

Animals were killed by each group after 7, 14 and 21 days.

2. Formation of experimental palatal wound surface

After an adaptation period of 10 days, animals were anesthetized intraperitoneally with xylazine hydrochloride (Rompun; 10 mg/kg, Bayer Animal Health GmbH, Leverkusen, Germany) and ketamine hydrochloride (Ketalar; 40 mg/kg, Eczacibasi Ilac Sanayi, Istanbul, Turkey). A standardized circular wound outline was created on the anterior palate in the mucoperiosteum of the midline of the hard palate using a 3 mm diameter punch biopsy tool. The soft tissue was removed by sharp dissection to expose the underlying bone. Cotton gauze was placed on the wound until hemostasis was achieved. No drugs were administered throughout the experiment.

3. Preparation and administration of propolis extract

Propolis was produced by honey bees (Apis mellifera Linnaeus) in Trabzon, Turkey. Propolis was ground using an ultracentrifugal mill and 10 g of powder was dissolved in 100 ml of dimethyl sulfoxide (100% weight/ volume) by magnetic mixing for 24 hours at 37°C. Coarse particles were removed by filtration through 0.2-mM filters. The clear propolis preparation was diluted in sterile saline to achieve the desired concentrations. Propolis was administered locally at a rate of 1 ml/day.

4. Study process

Six animals were sacrificed immediately to maintain baseline values (BC group). The remaining 54 animals were randomly divided into three experimental groups. 0.5 ml of 0.09% saline (Polifarma İlaç Sanayi ve Ticaret AŞ, Tekirdağ, Türkiye), 0.05% Chlorhexidine Gluconate (Irrisept, Irrimax Corporation, Innovation Technologies, Inc., Lawrenceville, GA), or propolis was applied to each wound site with cotton pellets once daily for 1 minute. Six animals from each group were sacrificed at 7, 14, and 21 days postoperatively. The maxillae were dissected out, and the specimens were assessed photographically and compared with the histologic findings.

5. Photographic assessment

Specimens were photographed with a stereomicroscope (Stemi DV4, Carl Zeiss, Jena, Germany) (25X magnification). The surface of the wound was measured morphometrically using the software "Biowizard –Dwinter, version 3". Photographic evaluation was performed by a single examiner (H.O.) who did not known the identity of the specimens.

6. Histopathological assessment

Histological analysis was performed by a single inverstigator (F.G.) who was also blinded to the identity of the specimens. The specimens were fixed in 10% buffered neutral formalin for 48 hours. They were then dehydrated with alcohol and embedded in paraffin blocks. A microtome was used to make 5 μm serial sections perpendicular to the palatal midline at the largest diameter of the wound. The sections were stained with eosin and hematoxylin. The slides were examined under a light microscopy (Nikon Eclipse, E 600, Tokyo, Japan) for histological changes.

With regard to wound healing stages, specimes taken on the 7^{th}, 14^{th} and 21^{th} were evaluated for wound clearance, scaring re-epithelialization, and inflammatory of infiltration cells.

7. Statistical analysis

Data from the control and experimental groups were compared with each other and with baseline values. IBM Statistical Package for the Social Sciences Statistics for Windows, version 24 (IBM Corp; Armonk, NY, USA) was used for statistical analysis of the data. Mean, standard deviation, median, and frequency were used for descriptive statistics.

Two-way ANOVA or Oneway ANOVA with Tukey's multiple comparisons analysis and Student's t-test were applied. The difference between groups was considered significant when a value of $p< 0.05$.

RESULTS

During the experimental period, the animals did not lose weight, indicating that feeding behaviour was satisfactory in spite of the palatal wound. After surgical operation, photographs of the wound areas were taken with a light microscope (Nikon, DS-Fi1c, Tokyo, Japan), and the images were measured by an observer who was blind to the study groups.

Photographic Observation

On day 0, immediately postoperatively, the wound area was 12.12± 1.28 mm^2. The wound area measurements of all groups at the different time intervals are shown in Table 1, Figure 1. The mean area of circumscribed defects decreased significantly with time ($p<0.05$) in the experimental and control groups.

On the 7^{th}, 14^{th} and 21^{st} days, a statistically significant and faster healing was observed in the mean wound areas in the Propolis and Chx groups compared to the Control group.

On the other hand, in the chlorhexidine group, improvement was observed on the other days, but a significantly less improvement was observed only on the 7^{th} day compared to the propolis group.,

Histological Examination

When comparing the control group and the Chx group on the 7th day, the wound area where epithelization didn't ocur is clearly visible. When compared to the control group and the chlorhexidine group, scab started to form in the C. Spinosa group and it was observed that the inflammatory cells were infiltrated more intensely.

On day 14: Epithelial formation began to be observed in the control group, while more uniform epithelialization was observed in the experimental groups. In the experimental groups, the formation of collagen fibers by fibroblasts begins to migrate into this region in the subepithelial area, while the inflammatory cells are still present in the lower dermis compared to the control group.

Day 21: In the control group, the epithelium is complete and the dermis begins to form. The presence of infiltration of inflammatory cells in the deep region of the dermis compared to the experimental groups indigates that healing isn't yet complete. In the experimental groups, inflammatory cells in the deep dermis were reduced and wound healing was better than in the control group.

Table 1. Wound area measurement of groups (mm^2), mean and standart deviation (SD) (n=6)

Substance/Day	Baseline (means ± SD)	Control (means ± SD)	Chx (means ± SD)	Propolis (means ± SD)
0	12.12± 1.28			
7		10.91 ±0.61569*	9.25±0.96	5.56±3.77#
14		7.81 ±2.15*	4.81±0.62	3.70±1.76
21		4.05 ±3.72*	1.19±0.81	1.12±0.83

*different from control group on 7^{th},14^{th} and 21^{th} days
#different from Propolis group from Clx group on 7^{th} day

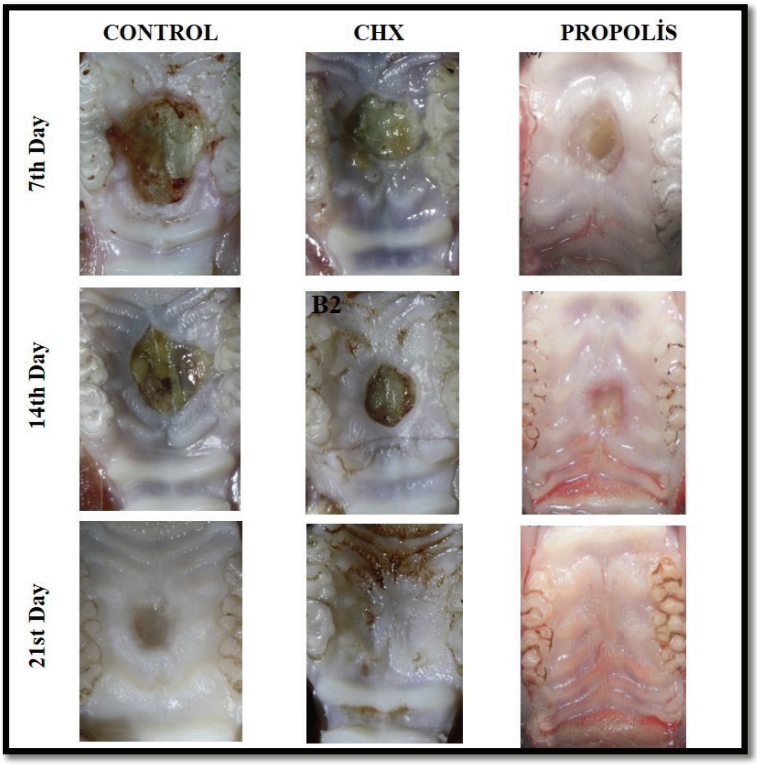

Figure 1. Clinical photographs of the wound area of all groups. C: Control group, Clx: Chlorhexidine group, P: Propolis group

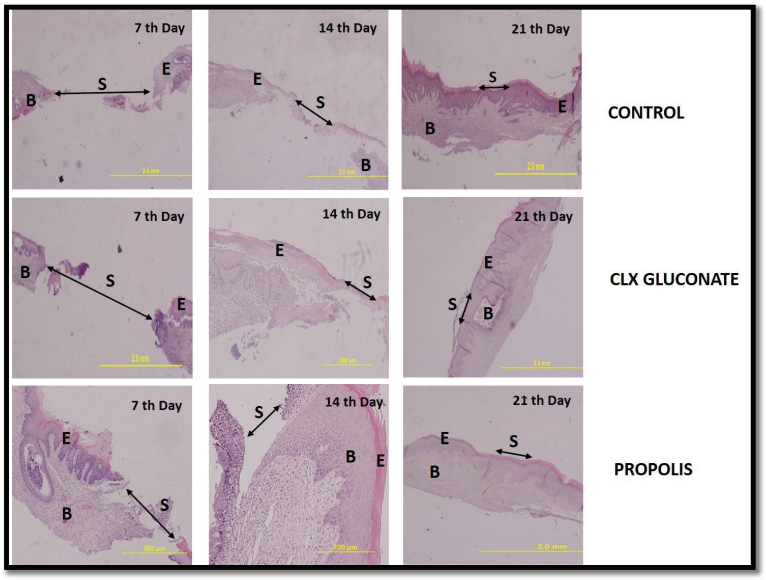

Figure 2. Histopathological sections of all groups (Hematoxylin and Eosin, S: Scarb, ( ) wound area, (E) epithelium, (B) connective tissue)

DISCUSSION

This work demonstrate that a single topical treatment with the plant bee resin propolis improves wound healing toward normal in a rat model of full-thickness cutaneous wound healing. The main endpoint of this study, epithelial closure, was significantly accelerated by propolis treatment of wounds in rats. Experiments were performed on rats, and propolis treatment was compared with saline treatment and conventional chlorhexidine gluconate treatment. The bacterial microflora in the oral cavity is very diverse, and these bacteria colonize the wounds.[23] Wounds on the palate are usually treated with antibacterial agents to prevent infections. In this study, we also used an antibacterial material, chlorhexidine gluconate, as a positive control. Propolis has also been previously reported to have antibacterial properties; therefore, this control allowed us to compare the efficacy of antibacterial treatment for wound healing. In the first two weeks of treatment, we observed the positive effects of antibacterial agents on oral wound healing in both propolis and chlorhexidine gluconate treatment, which promoted wound healing much more effectively than the control group. On the other hand, within the first two weeks, there was almost no difference between the group treated with propolis and the group treated with chlorhexidine gluconate, which shows the importance of the antibacterial properties for the initial phase of wound healing. Histological analysis showing granulation tissue with a constricted mucosal epithelial layer and complete repair and healing of the mucosal epithelium after propolis treatment also supports the critical effect of propolis on wound healing in palatal wounds.[24]

Propolis is considered to have antiseptic, antibacterial, antifungal, astringent, antispasmodic, anti-inflammatory, anesthetic, antioxidant, antifungal, anticancer, and immunomodulatory effects.[6,25] Some results confirm the therapeutic efficacy of propolis, namely, by quantitative and qualitative analyzes of the expression and degradation of type I collagen and III in the wound matrix, suggesting that propolis may have a favorable biochemical environment that supports re-epithelialization.[15]

The biological activities of propolis in wound healing and tissue regeneration might be related to its antimicrobial, anti-inflammatory and immunomodulatory properties.[26] Propolis shows immunostimulatory and immunomodulatory effects on macrophages in vitro, while in vivo it increases the ratio of CD4/CD8 T cells in mice. The results of this study showed that the application of propolis increased the rate of wound healing and re-epithelialization of diabetic wounds in rodents. It has also been suggested that propolis plays a different role in reducing neutrophil infiltration and normalizing macrophage influx into the wounded area.[27]

Wound healing and regeneration proceed through a finely tuned pattern of integrated phases, such as hemostasis, inflammation, cell proliferation, and tissue remodeling, involving a number of cellular and molecular processes.[16] This wound healing phenomenon includes migration and proliferation of epidermal cells and keratinocytes, adherence of fibroblasts, and contraction of the extracellular matrix (ECM). Propolis treatment stimulates a significant increase in ECM components in the initial phase of wound healing, followed by a decrease in ECM molecules. It is postulated that this biological effect of propolis is related to its ability to stimulate the expression of transforming growth factor-β (TGF-β), which is involved in the early stages of wound healing such as hemostasis and inflammation.[28,29]

Some works have studied the effect of propolis solutions in the treatment of animal wounds in clinical and experimental cases. The results showed that propolis is able to induce a good healing process, mainly by reducing the inflammatory response; therefore, the healing process was faster with propolis. The authors considered propolis suitable for wound treatment after the infection was eliminated.[1,30]

The healing properties of propolis may also be due to its

immunostimulant action. This property has been characterized in few clinical studies.[2,3] Propolis was administered, and cytokine secretion capacity was studied during and after treatment. Cytokine secretion capacity increased significantly and in a time-dependent manner during the treatment period. The authors concluded that propolis is able to induce immunoreactivity without side effects.[31]

The composition of propolis is complex and the samples from diferent areas are diferent from each other. Although drug substances that are prepared by using natural materials as starting materials are routinely used and are allowed to difer to a certain extent as batch-to-batch variations, it might be benefcial to use synthetic propolis preparations for future wound healing experiments as alternatives to these natural samples to achieve more chemically defned drug products.

CONCLUSION

The composition of propolis is complex and samples from different areas differ from each other. Although drugs prepared from natural materials are routinely used and may vary to some extent from batch to batch, it may be advantageous to use synthetic propolis preparations as an alternative to these natural samples for future wound healing trials to obtain chemically better defined drugs.

Ethical Approval

The study protocol and experimental design were approved by the Animal Ethics Committee of the Faculty of Medicine, Cumhuriyet University (approval number: B.30.2.CUM.0.01.00.00-50/100).

Peer-review

Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.A., H.Ö., Design: A.A., H.Ö., Data Collection or Processing: A.A., H.Ö., Analysis or Interpretation: A.A., H.Ö., Literature Search: A.A., H.Ö., Writing: A.A., H.Ö.

Conflict of Interest

The authors declared no conflict of interest.

Funding

The study was self-funded by the authors.

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DOI:10.34084/bshr.1269500 e-ISSN 2587-1641

Journal of Biotechnology and Strategic Health Research

Araştırma Makalesi /Research Article

http://dergipark.org.tr/tr/pub/bshr

Plasenta Yerleşim ve İnvazyon Anomalisi Olan Hastalarda Acil ve Elektif Sezaryenin Fetomaternal Sonuçlara Etkisi

The Effect of Emergency and Elective Cesarean Section on Fetomaternal Results in Patients with Placent Placement and Invasion Anomaly

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Geliş Tarihi / Received : 28-03-2023 **Kabul Tarihi / Accepted:** 12-06-2023 **Yayın Tarihi / Online Published:** 30-08-2023

Aksoy E.L., Çağlar A.T. The effect of emergency and elective cesarean section on fetomaternal results in patients with placent placement and invasion anomaly. J Biotechnol and Strategic Health Res. 2023;7(2):89-96

Özet

Amaç Plasenta previa; plasentanın alt uterin segmente yerleşip internal osu kısmen veya tamamen kapatması durumudur. Planlı sezaryene alınan plasenta previa ve plasenta akreata spektrumu (PAS) şüphesi olan hastalarda daha iyi fetomaternal sonuçlar elde edilmektedir. Çalışmamızda acil ve elektif sezaryene alınan hasta gruplarını fetomaternal sonuçlarını karşılaştırmayı amaçladık.

Gereç ve Yöntem Çalışmamıza Ocak 2011-Aralık 2015 tarihleri arasında hastanemizde plasenta previa ve PAS tanısıyla sezaryene alınan 236 hasta dâhil edildi. Hastaların demografik verileri, jinekolojik ve obstetrik öyküleri, laboratuvar parametreleri, kan ürünü transfüzyon miktarı, vakanın alınma şekli(acil/elektif), gelişen intraoperatif ve postoperatif komplikasyonlar, kullanılan ek cerrahi yöntemler, histerektomi varlığı, doğum haftası ve ağırlığı, yenidoğan APGAR skoru, yoğun bakım ihtiyacı, yatış süresi ve gelişen komplikasyon verilerine ulaşıldı. Hastalar acil ve elektif olmak üzere iki gruba ayrılarak fetomaternal verileri karşılaştırıldı.

Bulgular Hastalar vakaya alınma şekillerine göre karşılaştırıldığında intraoperatif komplikasyon, peripartum histerektomi, ek cerrahi yöntem kullanımı, invazyon anomalisi, postoperatif 6. saat hemoglobin değerleri arasında bir fark bulunmadı. Fakat acil alınan grupta postoperatif yatış süresi, transfüzyon ihtiyacı daha fazla iken, 2. saat hemoglobin (Hgb) düzeyi daha düşük bulundu. Acil alınan gruptaki yenidoğanlarda, doğum ağırlığı ve APGAR skoru daha düşük iken, yoğun bakım ihtiyacı, yatış süresi ve komplikasyon oranının daha yüksek olduğu tespit edildi.

Sonuç Hastalar multidisipliner yaklaşımın sunulabileceği, kan bankası ünitesi, erişkin yoğun bakım ve yeni doğan yoğun bakım ünitesi yeterli olan tersiyer merkezlere sevk edilmelidir. Olguların elektif olarak operasyona alınmasının fetomaternal morbidite ve mortalitenin azaltılmasında veya önlenmesinde önemli bir etkendir.

Anahtar Kelimeler Acil, plasenta akreata spektrumu, plasenta previa, sezeryan

Abstract

Aim *Placenta previa is the situation where the placenta settles in the lower uterine segment and partially or completely covers the internal os. Better fetomaternal results are obtained in patients with suspected placenta previa and plasenta accreta spectrum (PAS) undergoing planned cesarean section. In our study, we aimed to compare the fetomaternal outcomes of patient groups who underwent emergency and elective cesarean section.*

Material and Method *Our study included 236 patients who underwent cesarean section with the diagnosis of placenta previa and PAS in our hospital between January 2011 and December 2015. Demographic data of patients, gynecological and obstetric histories, laboratory parameters, amount of blood product transfusion, method of taking the case (emergency/elective), developing intraoperative and postoperative complications, additional surgical methods used, presence of hysterectomy, gestational week and weight, newborn APGAR score the data on the need for intensive care, length of hospital stay and complications were obtained. The patients were divided into two groups as emergency and elective, and fetomaternal data were compared.*

Results *When the patients were compared according to the way they were recruited, no difference was found between intraoperative complications, peripartum hysterectomy, use of additional surgical methods, invasion anomaly, and postoperative 6th hour hemoglobin values. However, while the postoperative hospital stay and the need for transfusion were higher in the emergency group, 2. hour hemoglobin (Hgb) level was found to be lower. While the birth weight and APGAR score were lower in the newborns in the emergency group, the need for intensive care, length of hospital stay and complication rates were found to be higher.*

Conclusion *Patients should be referred to tertiary centers where a multidisciplinary approach can be offered and blood bank units, adult intensive care units and neonatal intensive care units are sufficient.*

Keywords *Emergency, placenta acreata spectrum, placenta previa, cesarian*

GİRİŞ

Plasenta previa ve PAS özellikle son yıllarda sezaryen doğum sayısının artması ile sık görülmektedir. Plasenta previa insidansı her 1000 doğumda 3,5 ila 4,6 arasında değişmektedir.[1] Altta yatan etyolojik neden kesin olarak bilinmemekle beraber yapılan çalışmalarda bazı risk faktörleri tanımlanmıştır. Bunlar önceki previa öyküsü, geçirlmiş sezaryen, multiparite, ileri anne yaşı, düşük doğum öyküsü, intrauterin cerrahi müdahale öyküsü, sigara kullanımı, çoğul gebelikler, infertilite tedavisi ve erkek fetüstür.[2]

Plasenta previa ile komplike olmuş gebeler sıklıkla 2. trimester sonu ya da 3. trimesterda görülen ağrısız vajinal kanama şikayeti ile hastaneye başvururlar.[3-4] Bu nedenle 20. Gebelik haftasından sonra vajinal kanama şikayeti ile başvuran hastalara aşırı kanamalara neden olacağından USG ile plasenta previa tanısı dışlanmadan dijital muayene yapılmamalıdır. Plasenta previa aynı zamanda antepartum ve postpartum kanama, sezaryen ve sezaryen histerektomi, dissemine intravasküler koagülasyon (DİC), hipovolemik şok, preterm doğum, malprezantasyon, konjenital anomaliler, intrauterin gelişme geriliği (IUGR) gibi artmış fetomaternal morbitide ve mortalite ile ilişkilidir.[3]

Plasenta previa hastalarında görülen bir diğer komplikasyonsa yüksek mortalite ve morbitide riskine sahip PAS'dır. PAS ise plasenta akreata, plasenta inkreata ve plasenta perkreatayı kapsamaktadır. Artan sezaryen doğum oranları nedeniyle 750 doğumda 1 oranında görülmektedir.[5-7]

PAS için en önemli risk faktörü geçirilmiş sezaryen sonrası gelişen plasenta previadır. Diğer risk faktörleri arasında geçirilmiş uterin cerrahi, dilatasyon ve küretaj (D/C), sezaryen skar gebeliği, ileri anne yaşı ve endometrial defektler vardır.[6,8]

Bu çalışmada plasenta previa ve PAS tanısıyla acil ve elektif olarak sezaryana alınan hastaların fetomaternal sonuçlarını incelemeyi amaçladık.

GEREÇ ve YÖNTEM

Çalışmamızda Dr. Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi Eğitim Planlama ve Koordinasyon Başkanlığı Etik Kurulu onayı alındıktan sonra 01/01/2011 ve 31/12/2015 tarihleri arasında Dr. Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi perinataloji kliniğinde plasenta previa ve/veya plasenta akreata ön tanısı ile sezaryene alınan 24 hafta ve 500 gram üzeri 400 gebelik retrospektif olarak incelendi. 164 hasta dosya ve otomasyon sisteminden sağlıklı bilgiye ulaşılamaması nedeniyle çalışma dışı bırakılarak çalışmaya 236 hasta dahil edildi.

Çalışmamızda ISTH (International Society of Trombosis and Haemostasis) skorlamasında 5 ve üzeri skor alan hastalar DİC olarak kabul edildi.

Çalışmada yer alan yaş, bebek ağırlığı, gebelik süresi vb. sürekli değişkenlerin normal dağılıma uygunluğu Shapiro-Wilk testi ile incelenmiştir. Normal dağılım gösteren değişkenler ile bazı sürekli değişkenler ortalama±standart sapma (ort±ss) ve ortanca (minimum-maksimum); normal dağılım göstermeyen ve kesikli değişkenler ortanca (minimum-maksimum) ile ifade edilmiştir. Kategorik değişkenler sayı (%) şeklinde gösterilmiştir.

Acil ve Elektif gruplarının sürekli veya kesikli değişkenler bakımından karşılaştırılması grupların dengesiz olmasına bağlı olarak Mann-Whitney U testi ile incelenmiştir. Grupların kategorik değişkenler bakımından analizi Ki-kare (X2) testleri yardımıyla yapılmıştır.

Hemoglobin ve platelet ölçümlerinin zamana göre değişiminin gruplarda farklı olup olmadığı iki yönlü karma ANOVA ile incelenmiştir. Grup içi zamana göre farklılıklar değişkenin dağılımına bağlı olarak tekrarlı ölçümlerde ANOVA veya Friedman testi ile değerlendirilmiştir. Her bir zamanda gruplar arası karşılaştırmalar Mann-Whitney U testi ile yapılmıştır. İstatistiksel anlamlılık düzeyi $p<0,05$ kabul edilmiştir.

İstatistiksel analizler ve hesaplamalar için IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) programı ve grafik çizimi için MS Office Excel 2019 kullanılmıştır.

BULGULAR

Çalışmamız 01.01.2011-31.12.2015 tarihleri arasında Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi perinataloji kliniğinde plasenta previa tanısı ile sezaryene alınan 236 hasta üzerinde yapıldı. Hastalar sezaryene alınma şekillerine göre acil (n=71) ve elektif (n=165) olmak üzere iki gruba ayrıldı.

Hastaların demografik özellikleri incelendiğinde yaş ortalamasının 31,47 yıl olduğu hesaplanmıştır. En küçük yaş 18, en büyük yaş 42 olarak tespit edildi. Diğer demografik özellikler Tablo 1'de gösterilmiştir.

Tablo 1. Hastalara ait demografik veriler

	N	Min-Maks	Ortalama±Standart sapma
Yaş	236	18-42	31,47±5,19
Gravida	236	1-11	3,18±1,77
Parite	236	0-10	1,44±1,40
Abortus	236	0-5	0,44±0,83
D/C	236	0-4	0,28±0,60
C/S	236	0-4	0,66±0,89

Hastaların %9,7'sinin (n=23) sigara içtiği ve 4 hastada geçirilmiş uterin cerrahi (sezaryen haricinde) olduğu tespit edildi. İncelenen 236 hastanın 23'ünün sigara içtiği tespit edildi. Sigara kullanan hastaların 16'sında invazyon anomalisi yok iken, 7 hastada invazyon olduğu tespit edildi. Sigara kullanımı ve invazyon arasında istatistiksel olarak anlamlı fark bulunmadı (p=0,012).

Acil ve elektif gruplarında sırasıyla 5 (%7,1) ve 12 (%7,3) annede intraoperatif komplikasyon geliştiği; 15 (%21,1) ve 30 (%18,2) anneye peripartum histerektomi yapıldığı; 29 (%40,8) ve 64 (%38,8) annede bakri, hemostatik sütur vb. ek cerrahi yöntem kullanıldığı belirlenmiştir (Tablo 2). İntraoperatif komplikasyon varlığı, histerektomi durumu ve ek cerrahi yöntem kullanımı bakımından grupların benzer olduğu görülmüştür (p>0,05). İnvazyon anomalisi bakımından gruplar incelendiğinde acil grubunda 2 annede (%2,9) akreata, 1 annede (% 1,4) inkreata ve 5 annede (% 7,2) perkreata olduğu belirlenmiştir. Elektif grubunda ise ilgili anomalilerin gözlendiği hasta sayısı sırasıyla 7 (%4,3), 6 (%3,7) ve 8 (%4,9)'dir. İnvazyon anomalisi bakımından da grupların benzer olduğu tespit edilmiştir (p=0,649).

Tablo 2. Acil ve elektif grubun maternal intraoperatif komplikasyon, yönetim invazyon anomalisi bakımından karşılaştırması

	Acil Grup n (%)	Elektif Grup n (%)	Test İstatistiği	p
İntraoperatif komplikasyon varlığı		-	0,000	1,000
Yok	66 (92,9)	153 (92,7)	-	-
Var	5 (7,1)	12 (7,3)	-	-
Histerektomi		-	0,121	0,728
Yok	56 (78,9)	135 (81,8)	-	-
Var	15 (21,1)	30 (18,2)	-	-
Ek cerrahi yöntem		-	0,088	0,767
Yok	42 (59,2)	101 (61,2)	-	-
Var	29 (40,8)	64 (38,8)	-	-
Bakri balon	-	-	0,295	0,587
Yok	48 (67,6)	119 (72,1)	-	-
Var	23 (32,4)	46 (27,9)	-	-
Hemostatik sütur	-	-	1,410	0,235
Yok	65 (91,5)	140 (84,8)	-	-
Var	6 (8,5)	25 (15,2)	-	-
Hipogastrik arter ligasyonu	-	-	-	0,219
Yok	65 (91,5)	158 (95,8)	-	-
Var	6 (8,5)	7 (4,2)	-	-
Uterin arter ligasyonu	-	-	-	0,638
Yok	69 (97,2)	162 (98,2)	-	-
Var	2 (2,8)	3 (1,8)	-	-
İnvazyon anomalisi	-	-	1,646	0,649
Yok	63 (88,5)	144 (87,1)	-	-
Akreata	2 (2,9)	7 (4,3)	-	-
İnkreata	1 (1,4)	6 (3,7)	-	-
Perkreata	5 (7,2)	8 (4,9)	-	-

Acil grubuna elektif grubuna göre daha fazla eritrosit süspansiyonu (ES) verildiği belirlenmiştir (p=0,021). Grupların taze donmuş plazma (TDP) ve fibrinojen bakımından benzer olduğu tespit edilmiştir (p>0,05). Gruplarda annelerin gebelik süresi ortalaması sırasıyla 231,79±24,28 gün ve 259,10±13,07 gün olarak elde edilmiştir. Acil grubunda gebelik süresinin elektif grubuna göre daha kısa olduğu görülmüştür (p<0,001). Operasyon sonrası yatış süresi bakımından gruplar değerlendirildiğinde acil grubunun elektif grubuna göre hastanede daha uzun yattığı gözlenmiştir (p=0,015). Acil grubunda %16,9 (n=12) oranında DIC gelişimi olduğu ve bu oranın elektif grubundaki orandan daha yüksek olduğu belirlenmiştir (p=0,028) (Tablo 3).

Tablo 3. Acil ve elektif grubun transfüzyon miktarı, gebelik süresi, postoperatif yatış süresi ve DİC gelişimi açısından karşılaştırılması

	Acil Grup	**Elektif Grup**	**Test İstatistiği**	**p**
Eritrosit (ort±s)	2,58±3,44	1,68±2,91	2,314	**0,021**
Ortanca (min-maks)	2 (0-16)	0 (0-16)	-	-
TDP (ort±s)	1,59±2,81	0,98±2,01	1,631	0,103
Ortanca (min-maks)	0 (0-12)	0 (0-14)	-	-
Fibrinojen (ort±s)	0,29±0,88	0,16±0,53	0,695	0,487
Ortanca (min-maks)	0 (0-4)	0 (0-3)	-	-
Gebelik süresi (ort±s)	231,79±24,28	259,10±13,07	8,813	**<0,001**
Ortanca (min-maks)	235 (175- 287)	260 (191-286)	-	-
Postop yatış süresi (ort±s)	4,52±3,40	3,61±2,67	2,422	**0,015**
Ortanca (min-maks)	3 (2-18)	2 (2-14)	-	-
DIC gelişimi	-	-	4,805	**0,028**
Yok	62 (87,3)	158 (95,7)	-	-
Var	9 (12,7)	7 (4,3)	-	-

Hemoglobin, hematokrit ve plateletin zamana göre değişimlerinin gruplarda benzer olduğu belirlenmiştir. Acil grubunda operasyon öncesi, operasyonun 2. saati ve 6. sa-

atinde ölçülen hemoglobin düzeyinin ortalaması sırasıyla 11,59±1,22, 9,85±1,74 ve 9,70±1,77 olarak hesaplanmıştır (Tablo 4). Operasyonla beraber hemoglobin düzeyinde anlamlı bir düşüş olduğu (p<0,001); ancak 2 ve 6. saatler arasında anlamlı bir fark olmadığı (p>0,05) görülmüştür.

Elektif grubunda operasyon öncesi, operasyonun 2. saati ve 6. saatinde ölçülen hemoglobin düzeyinin ortalaması sırasıyla 11,93±1,16, 10,40±1,6 ve 10,03±1,59 olarak elde edilmiştir (Tablo 4). Operasyonla beraber hemoglobin düzeyinin anlamlı bir şekilde azaldığı görülmüştür (p≤0,001).

Tablo 4. Postoperatif maternal hemoglobin, hematokrit ve platelet değerlerinin karşılaştırılması

	Acil Grup Ort±S Ortanca (Min-Maks)	**Elektif Grup** Ort±S Ortanca (Min-Maks)	**Test İstatistiği**	**p**
Hemoglobin	-	-	--	
Operasyon öncesi	11,59±1,221,2	11,93±1,16a,b	1,954	0,051
2.saat	9,85±1,741	10,40±1,61a,c	2,251	**0,024**
6.saat	9,70±1,772	10,03±1,59b,c	1,273	0,203
Test İstatistiği; p	74,976; **<0,001**	188,831; **<0,001**	-	-
Platelet (x1000)	-	-	-	-
Operasyon öncesi	219,0 (77,0-397,0)1,2	200,0 (80,0-397,0)a,b	1,189	0,234
2.saat	183,0 (59,0-434,0)1	182,0 (62,0-390,0)a	0,142	0,887
6.saat	182,0 (61,0-334,0)2	177,0 (61,0-398,0)b	0,420	0,675
Test İstatistiği; p	36,371;**<0,001**	102,501;**<0,001**	-	-

Acil ve elektif grubundaki bebeklerin doğum ağırlığı ortancaları sırasıyla 2155 gr (min-maks: 680-4000) ve 3060 gr (min-maks: 710-4040) olarak hesaplanmıştır. Elektif grubunda doğan bebeklerin doğum ağırlığının daha fazla olduğu belirlenmiştir (p<0,001). Apgar 1 ve apgar 5 skorlarının elektif grubunda acil grubuna göre daha yüksek olduğu gözlenmiştir (p<0,001).

Acil ve elektif grubunda yenidoğan yoğun bakım (YDYB) ihtiyacı sırasıyla 51 (%70,8) ve 25 (%15,3) bebekte gözlenmiştir. Acil grubunda YDYB ihtiyacının daha fazla görüldüğü belirlenmiştir (p<0,001).

Acil grubunda 3 bebek ex olmuştur. Elektif grubunda ise 2 bebek ex olmuştur. Acil ve elektif gruplarındaki bebeklerin yenidoğan ünitesinde yatış süresi ortancası sırasıyla 8 gün (min-maks:0-124) ve 0 gün (min-maks: 0-121) olarak belirlenmiştir. Acil grubunda doğan bebeklerin daha uzun süre yattığı belirlenmiştir (p<0,001).

Acil grubunda elektif grubuna göre daha fazla yenidoğan komlikasyonu ve yatış endikasyonu görüldüğü tespit edilmiştir (p<0,001).

Gruplar yenidoğan komplikasyonu türleri bakımından incelendiğinde Gastrointestinal sistem (GİS ve anemi dışındaki komplikasyonların acil grubunda daha fazla gözlendiği belirlenmiştir (p<0,05) (Tablo 5).

Tablo 5. Acil ve elektif gruptaki yenidoğanların karşılaştırması

	Acil Grup Ort±S Ortanca (Min-Maks)	**Elektif Grup** Ort±S Ortanca (Min-Maks)	**Test İstatistiği**	**p**
Doğum ağırlığı	2140,76±797,85	2954,36±510,83	-	-
	2155 (680-4000)	3060 (710-4040)	7,473	<0,001
Apgar 1	5,86±1,65	6,74±1,01	-	-
	7 (1-8)	7 (0-9)	5,414	<0,001
Apgar 5	8,04±1,39	8,81±1,08	-	-
	8,5 (3-10)	9 (0-10)	6,814	<0,001
Yoğun bakım ihtiyacı	-	-	67,778	<0,001
Yok	21 (29,2)	138 (84,7)	-	-
Var	51 (70,8)	25 (15,3)	-	-
Yoğun bakım yatış süresi	14,02±22,38	1,60±10,01	-	-
	8 (0-124)	0 (0-121)	8,568	<0,001
Komplikasyon	-	-	64,311	<0,001
Yok	23 (34,3)	142 (87,7)	-	-
Var	44 (65,7)	20 (12,3)	-	-

TARTIŞMA

Obstetrik kanamalar, tıbbi gelişmelere rağmen dünya genelinde tek başına en önemli maternal ölüm nedenidir. Gelişmekte olan ülkelerdeki postpartum maternal ölümlerin yaklaşık yarısını obstetrik kanamalar oluşturur.[9]

Çalışmamızda, tersiyer bir merkez olan hastanemizde 01.01.2011-31.12.2015 tarihleri arasında plasenta previa ön tanısı ile doğumu gerçekleştirilen hastalarda anne ve yenidoğan verileri incelenerek sonuçlar değerlendirildi.

Tüm tıbbi gelişmelere rağmen obstetrik kanamalar maternal ölümlerin en önemli nedenidir. Ve yine plasenta yerleşim ve invazyon anomalileri antepartum kanamalar içinde önemli bir yer kaplamaktadır (%40). Başlıca risk faktörleri olan sezaryen doğum, geçirilmiş uterin cerrahi, ileri yaş gebelik, sigara içme, Yardımcı üreme teknikleri (YÜT) ve buna bağlı çoğul gebelik oranlarının artmasıyla birlikte hem anne hem de fetüs için mortalite ve morbiditesi yüksek bu durumlarla karşılaşma riski her geçen gün artmaktadır.

Çalışmalarda geçirilmiş sezaryenlerle plasenta previa arasında güçlü bir ilişki gösterilmiştir.[10] Bir çalışmada geçirilmiş 1 sezaryenle previa riskinin 2 kat arttığı, geçirilmiş 2 sezaryenle bu riskin 7 kat arttığı saptanmıştır.[11] Çalışmamızda da plasenta previası olan 236 hastanın 102'sinde (%43,3) 1-4 arasında değişen geçirilmiş sezaryen öyküsü olduğu saptandı.

Plasenta invazyon anomalileri (PİA) için en önemli risk faktörleri geçirilmiş sezaryen ve plasenta previadır.[12] Armstrong ve ark. 32 plasenta akreata olgusunun %78'inde geçirilmiş sezaryen öyküsü ve %88'inde ise plasenta previa olduğunu bildirmişlerdir.[13] Bizim çalışmamızda intraoperatif klinik bulgular ve patoloji ile doğrulanmış plasenta invazyon anomalisi olan 29 hastadan 28'inde geçirilmiş sezaryen öyküsü bulunmaktadır (%96,7).

Geçirilmiş sezaryen öyküsü 1, 2, 3, 4, 5 olan olgularda plasenta akreata sıklığı sırasıyla %15,6, % 23,5, % 29,4, % 33,3 ve % 50 olarak bildirilmiştir.[14] Bizim çalışmamızda PAS olan hastaların %24'ünde 1 sezaryen, %76'sında ise 2 ya da daha fazla sezaryen öyküsü vardı.

Yapılan çalışmalarda ileri maternal yaş ile plasentasyon anomalileri arasında ilişki bulunmuştur. Tuzovic ve ark. yaptıkları bir çalışmada, 30 yaşından büyük kadınların plasenta previa gelişimi için 2,5 kat yüksek riskli olduğunu bulunmuştur.[11] Bizim çalışmamızda literatür ile uyumlu olarak görmekteyiz.

Nullipar ve grandmultipar kadınların karşılaştırıldığı bir çalışmada plasenta previa riski nullipar kadınlarda 1000 gebelikte 2 iken, grand multipar kadınlarda 100 gebelikte 5 olarak bulunmuştur.[15] Çalışmamızda da parite sayısına göre gruplandırıldığında previa sıklığının arttığını görmekteyiz.

Konservatif yönetim veya sezaryen histerektomi ile ilgili kesin bir karar preoperatif alınmalıdır. Postpartum sezaryen histerektomi, özellikle acil şartlarda yapıldığında çok riskli ve yüksek komplikasyon oranlarına sahip bir cerrahi işlemdir.[16] Bu nedenle bu ameliyatların acil alınması yerine önceden planlanması maternal ve fetal iyilik hali açısından önem arz etmektedir.

Plasenta previa ve PİA konjenital anomali ve İUGR gibi fetüsü etkileyen bazı koplikasyonlar ile ilişkilendirilmiştir.[17] Fakat fetal mortalite ve morbiditenin ana nedeni hipoksi, anemi ya da gelişim kısıtlılığı yerine prematüritedir[18]. Çalışmamızda acil gruptaki bebeklerin ortalama doğum ağırlıkları 2140 gr, elektif gruptakilerin ise 2954 gr bulunmuştur (p=<0,001).

Plasenta previa ve PİA gerek prematürite gerekse İUGR ve fetal anomalilerle ilişkili olmasından dolayı yenidoğan yoğunbakım ihtiyacı normal popülasyona göre daha fazla olmaktadır.[18] Kassem ve ark. tarafından 122 plasenta previalı gebe üzerinde yapılan 3 yıllık bir retrospektif derlemede

34 hafta altında yenidoğan yoğun bakım ihtiyacının %100 (n=20/20), 34 ile 37 haftalar arasında %46 (n=18/39), 37 hafta üzerinde %7 (n=5/63) olduğunu bildirmiştir.[19] Bizim çalışmamızda bu oranlar 34 hafta altında %80 (n=33/41) , 34 ile 37 haftalar arasında %22 (n=23/103), 37 hafta üzerinde %17 (n=16/91) bulunmuştur. Acil gruptaki yenidoğanların %70,8'i (n=51/72), elektif gruptaki yenidoğanlarınsa %15,3'ü (n=25/165) yoğun bakım ihtiyacı duymuştur (p=<0,001). Yine her iki grup yenidoğan yoğun bakım yatış süreleri açısından karşılaştırıldığında acil grupta ortalama yatış süresi ortalama 14,02 gün iken elektif grupta 1,6 gündür ve bu istatistiksel olarak anlamlıdır (p=<0,001).

Çalışmamızda acil hasta grubunda maternal hemoglobin düşüşü, ES transfüzyon miktarı, DİC gelişimi, postoperatif maternal hastanede kalış süresi, yenidoğan APGAR skoru, yenidoğan yoğun bakım ihtiyacı ve süresi, yenidoğan komplikasyonları elektif gruba oranla daha fazla bulunmuştur. Türkiye'den Taşgöz ve ark. yapmış olduğu benzer bir çalışmada acil ve elektif sezaryen yapılan hastaların sonuçlarını karşılaştırmışlar ve acil alınan hastaların yenidoğan APGAR skorlarının düşük olduğu ve daha çok yoğun bakım ihtiyacı olduğunu bildirmişlerdir.[20]

Her ne kadar çalışmamızdaki acil ve elektif sezaryene alınan guruplar arasında intraoperatif komplikasyon, histerektomi ve kullanılan ek cerrahi yöntem açısından bir fark izlenmese de acil grupta postoperatif hemoglobin düşüşü ve buna bağlı ES transfüzyon miktarı, DİC gelişimi ve postoperatif hastanede yatış süresi daha fazla bulunmuştur. Yine benzer şekilde Asıcıoğlu ve ark. yapmış olduğu çalışmada intraoperatif tahmin edilen kan kaybının daha fazla olduğu, acil doğum vakalarında transfüzyon ihtiyacının fazla olduğu, çevre organ hasarı ve histerektomi oranlarının daha yüksek olduğunu bildirmişlerdir.[21]

Çalışmamızın limitasyonları; tek merkezli olması, retrospektif verilere dayanması ve tahmini kan kaybı değerlendirilmemiş olması sayılabilir.

SONUÇ

Sonuç olarak özellikle medikolegal sorunların arttığı günümüzde plasenta adezyon ve invazyon anomalisi düşünülen olgularda preoperatif hasta ve yakınlarının bilgilendirilmesi ve histerektomi dâhil tüm olası komplikasyonları içeren aydınlatılmış onamın alınması önemlidir.

Tüm bu fetomaternal komplikasyonları yönetmek için bu konuda tecrübeli bir ekip, erişkin ve yenidoğan yoğun bakımı ve kan bankası olan bir hastaneye ihtiyaç duyulur. Bu nedenle bu hastaların tersiyer merkezlere yönlendirilmesi uygun olacaktır.

Etik Onay

Bu çalışmada Dr. Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi Eğitim Planlama ve Koordinasyon Başkanlığı Etik Kurulu onayı alınmıştır (Karar No:6, Tarih:28/08/2015).

Yazar Katkıları

Konsept: E.L.A., A.T.Ç. Dizayn: E.L.A., A.T.Ç. Veri Toplama ve İşleme: E.L.A., A.T.Ç. Analiz ve Yorumlama: E.L.A., A.T.Ç. Literatür Tarama: E.L.A., A.T.Ç. Makale Yazımı: E.L.A., A.T.Ç.

Çıkar Çatışması

Yazarlar herhangi bir çıkar çatışması olmadığını beyan etmiştir.

Finansal Destek

Beyan edilecek mali destek yoktur.

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DOI:10.34084/bshr.1278592 e-ISSN 2587-1641

Journal of Biotechnology and Strategic Health Research

Araştırma Makalesi /Research Article

http://dergipark.org.tr/tr/pub/bshr

Maternal and Fetal Outcomes After Non-Obstetrical Surgery During Pregnancy

Gebelik Sırasında Geçirilen Non-Obstetri Cerrahi Sonrası Maternal ve Fetal Sonuçlar

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Geliş Tarihi / Received : 07-04-2023 **Kabul Tarihi / Accepted:** 12-06-2023 **Yayın Tarihi / Online Published:** 30-08-2023

Özcan A., Yüksel S., Gedik-Özköse Z., Özdemir İ. Maternal and fetal outcomes after non-obstetrical surgery during pregnancy. J Biotechnol and Strategic Health Res. 2023;7(2):97-105

Abstract

Aim In non-obstetric surgeries performed during pregnancy, the continuation of pregnancy and how it will affect the neonatal process are important for both the pregnant women and the surgeon. Studies on non-obstetric surgeries during the pregnancy are limited. The aim of this study is to evaluate maternal and fetal outcomes after non-obstetric surgery.

Material and Method Our study includes the retrospective evaluation of sixty pregnant patients who underwent non-obstetric surgery between January 2015 and August 2020 in our obstetrics clinic, which is a tertiary center. Patient information was obtained from electronic systems and archive files. Demographic characteristics of the patients, the gestational week of the surgery performed, follow-up, pregnancy, and neonatal outcomes were evaluated.

Results The mean age of the patients was 27.9±4.42, and the mean gestational week at which surgery was performed was 17.7±11.3. Among the surgical indications, the most common cause is appendicitis, with 45 patients (75%). Emergency surgery was performed in 88.3% of the pregnant women. The mean hospital stay was 3.3±3.2 days and the mean week to delivery was 21.1±8.6. The mean gestational week of the pregnant women at labor was 37.8±2.8. Laparotomy preference was found to be significantly higher than laparoscopy in patients who underwent emergency surgery (p=0.007). There was no difference in pregnancy outcomes and neonatal outcomes in the laparotomy and laparoscopy groups.

Conclusion Non-obstetric surgery during pregnancy may not lead to an increase in adverse pregnancy and neonatal outcomes. In addition, there was no significant difference between the laparotomy and laparoscopy groups in terms of pregnancy and neonatal outcomes. More extensive studies are needed on this subject.

Keywords Laparoscopy during pregnancy, non-obstetric surgery, surgery in pregnancy

Özet

Amaç *Gebelik sırasında yapılan non-obstetrik cerrahilerde gebeliğin devamı ve neonatal sürecin nasıl etkileyeceği hem gebe hem cerrah tarafından önem arz etmektedir. Non-obstetrik cerrahiler ile ilgili çalışmalar sınırlı sayıdadır. Bu çalışmamızın amacı non-obstetrik cerrahi sonrası maternal ve fetal sonuçların değerlendirilmesidir.*

Gereç ve Yöntem *Çalışmamız tersiyer bir merkez olan hastanemizin obstetri kliniğimizde Ocak 2015-Ağustos 2020 tarihleri arasındaki non-obstetrik cerrahi yapılan 60 gebe hastanın retrospektif değerlendirilmesini içermektedir. Hasta bilgilerine elektronik sistem ve arşiv dosyalarından ulaşıldı. Hastaların demografik özellikleri, cerrahi yapılan hafta, takipleri, gebelik ve neonatal sonuçları değerlendirildi.*

Bulgular *Hastaların ortalama yaşı 27,9±4,42, cerrahi yapılan gebelik haftası ortalama 17,7±11,3 idi. Cerrahi endikasyonlar arasında en sık neden 45 hasta ile (%75) apandisittir. Gebelerin %88,3'üne acil cerrahi yapıldı. Ortalama hastanede kalış süresi 3,3±3,2 gün, doğuma kadar geçen ortalama hafta 21,1±8,6 idi. Gebelerin ortalama doğum haftası 37,8±2,8 idi. Acil cerrahi yapılan hastalarda laparotomi tercihi laparoskopiye göre anlamlı olarak yüksek bulundu (p=0,007). Laparotomi ve laparoskopi grubunda gebelik sonuçları ve neonatal sonuçlar açısından fark saptanmadı.*

Sonuç *Gebelikte geçirilen non-obstetrik cerrahi olumsuz gebelik ve neonatal sonuçlarda artışa yol açtığına dair bir sonuca ulaşılamamıştır. Ayrıca cerrahi şeklini değerlendirdiğimizde; laparotomi ve laparoskopi yapılan gruplar arasında gebelik ve neonatal sonuçlar açısından anlamlı bir fark bulunmadı. Bu konuda daha geniş çaplı çalışmalara ihtiyaç vardır.*

Anahtar Kelimeler *Gebelikte laparoskopi, non-obstetrik cerrahi, gebelikte cerrahi*

INTRODUCTION

During a normal pregnancy, there are significant anatomical, physiological, and functional changes. This situation can lead to occasional different pathognomonic findings and require decisions regarding non-obstetric surgery during pregnancy, deviating from the known norms.

Suspected appendicitis during pregnancy is one of the most common indications for abdominal surgery during pregnancy.[1,2] Although the likelihood of a perforated appendix is higher in the later stages of pregnancy, acute appendicitis is more frequently observed in the second trimester (42%), as compared to the first (32%) and third trimesters (26%).[3]

In a study, it was observed that pregnant women with complicated appendicitis have a five-fold higher risk of surgical complications compared to pregnant women with simple appendicitis.[4] In the presence of supporting diagnostic findings for appendicitis, appendectomy should be performed in terms of maternal and fetal mortality and morbidity. While laparoscopic surgery is the most commonly preferred method in non-pregnant women, in pregnant women, laparoscopic surgery is more frequently chosen in the first and second trimesters, while an open surgical approach is preferred in the third trimester.[4] In cases of appendicitis during the third trimester, unless there is a life-threatening condition such as sepsis for both the mother and the fetus, there is no indication for a cesarean section.

One of the non-obstetric surgical indications in pregnancy is leiomyoma. The most significant indicators considered when making the decision for myomectomy during pregnancy are acute pelvic pain unresponsive to medical treatment for 72 hours, rapid growth of the myoma raising suspicion of a potential malignant condition, compression of pelvic organs caused by the myoma mass, and threats to the pregnancy such as fetal compression syndrome, oligohydramnios, intrauterine growth restriction (IUGR), bleeding, and abnormal placental implantation.5,6 However, myomectomy performed during pregnancy can lead to adverse pregnancy outcomes such as miscarriage (18-35%), preterm birth, infection, and uterine dehiscence due to uterine manipulations involved in the procedure.[5]

While the incidence of complications reported with conservative treatment varies within a wide range of 3-38%, it has been reported that untreated uterine myomas result in worse pregnancy outcomes compared to surgically treated myomas.[7] While laparotomic myomectomy was considered safe for complicated pregnancies involving leiomyomas until the end of the 19th century, recent studies have indicated that laparoscopic myomectomy should be considered as the first choice for abdominal and pelvic surgery during pregnancy, regardless of gestational age. The main reasons for preferring laparoscopy over laparotomy are the provision of better intraabdominal visualization, minimal invasive approach, and the possibility of early mobilization after surgery.[8]

Tubo-ovarian abscess (TOA) is a rare non-obstetric surgical cause during pregnancy, attributed to the prevention of ascending infection by the cervical mucus plug and the amniotic membrane.[9,10] When the decision for surgery is made for TOA, although laparoscopy can be challenging in the third trimester due to the enlarged size of the uterus, it can be performed either through laparotomy or laparoscopy depending on the surgeon's experience.

The incidence of acute cholecystitis during pregnancy is rare, ranging from 1 to 6 per 10.000 pregnancies. It is the second most common non-obstetric surgical cause for abdominal pain during pregnancy.[11] It is frequently observed due to a two-fold increase in the volume of the gallbladder and delayed complete emptying of the gallbladder during pregnancy.[12] Cholecystectomy can be safely performed in all trimesters.

Although intestinal obstruction is rare during pregnancy,

the mortality rates associated with obstruction are high. The main reasons for this are delayed diagnosis and a preference for conservative management over surgery.[13]

The aim of this study is to evaluate maternal and fetal outcomes following non-obstetric surgery.

MATERIAL and METHOD

Our retrospective cohort study was conducted at Istanbul Kanuni Sultan Suleyman Training and Research Hospital, Health Sciences University, between January 2015 and August 2020. Ethical approval was obtained from the ethics committee of Istanbul Kanuni Sultan Suleyman Training and Research Hospital, Health Sciences University, (Approval No: KAEK/2020.08.175) (03/09/2020). A total of 60 patients with complete medical records were included in the study. Patients' ages, body mass indexes, existing medical conditions, smoking status, gravidity, parity, gestational weeks at the time of surgery, length of hospital stay, type of surgery undergone, gestational weeks at delivery, pregnancy complications, use of tocolysis, pregnancy outcomes, neonatal outcomes, and the need for repeat surgery were recorded.

The mode of delivery, indication for birth, indication for cesarean section, birth weights of newborns, 1st and 5th minute Apgar scores, need for neonatal intensive care, length of hospital stay, and possible complications were recorded. Infants with estimated birth weight below the 3rd percentile were considered intrauterine growth restriction (IUGR). Low birth weight (SGA) was defined as birth weight <2500 g, and very low birth weight (VLBW) as <1500 g. Poor neonatal outcome was defined as 1) fetal or neonatal death, 2) admission to the neonatal intensive care unit (NICU), or 3) APGAR score at 5 minutes <7. Birth occurring before 37 weeks of gestation was classified as preterm birth, and between 34-37 weeks as late preterm birth. Patients diagnosed with preterm labor received betamethasone treatment, and those diagnosed with preterm labor below 32 weeks were given neuroprotective MgSO4 1g/hour for 24 hours.

The inclusion criteria for the study consisted of pregnant women between the ages of 18 and 45 who underwent non-obstetric surgery and were followed up in our hospital. Pregnant women under the age of 18, over the age of 45, pregnant women who underwent surgery for obstetric reasons, and patients who underwent non-obstetric surgery in our hospital but were not followed up were determined as exclusion criteria for the study.

SPSS 22.0 (IBM, IL Chicago) was used for statistical analysis. Categorical data were presented as n (%) and continuous variables as mean±standard deviation (SD), while non-normally distributed parametric data were defined as median (minimum-maximum). The normality of the data was assessed using the Kolmogorov-Smirnov test. The chi-square test was used for the comparison of categorical variables, and the student t-test was used for the comparison of normally distributed parametric variables. The Mann-Whitney U test was used for the comparison of non-normally distributed parametric variables. A p-value of <0.05 was considered statistically significant.

RESULTS

The mean age of our patients was 27.9±4.42, and the mean body mass index (BMI) was 26.1±4.2 kg/m2. A history of previous cesarean section was present in 25% of the pregnant women. The average gestational week at the time of surgery was 17.7±11.3. 88.3% of patients underwent emergency surgery. Of these, 23.3% underwent laparoscopy, while 71.7% underwent laparotomy. In 5% of the cases, conversion from laparoscopy to laparotomy was occurred during the surgery. Additionally, one pregnant woman who could not be diagnosed with appendicitis went into preterm labor at 29 weeks and 2 days of gestation and delivered vaginally. She underwent laparoscopy for perforated appendicitis on the second postpartum day. The demographic characteristics of the patients are summarized in Table 1.

Table 1. Demographic characteristics of the patients.	
Number of patients (n=60)	
Maternal age (years)	27.9±4.4
Smoking (Yes)	10 (16.7%)
BMI (kg/m2)	26.1±4,2
Gravidity	2.6±1.4
Parity	1.3±1.2
History of cesarean section	15 (25%)
Patients with multiple pregnancies	2 (3.3%)
History of abortion	10 (16.7%)
Comorbidity	13 (21.7%)
Gestational age at the time of surgery	17.7±11.3
Patients underwent emergency surgery	53 (88.3%)
Laparoscopy	14 (23.3%)
Laparotomy	43 (71.7%)
Conversion from laparoscopy to laparotomy	3 (5%)

The postoperative characteristics of the patients are shown in Table 2. Surgical complications developed in 13.3% of the patients, and the average length of hospital stay was 3.3±3.2 days. The mean weeks from surgery to the delivery was 21.1±8.6, and the average gestational week at birth was 37.8±2.8. Forty-five percent of the patients gave birth by cesarean section.

Table 2. Follow-up characteristics of patients.		
	Mean or %	Median
Decrease in hemoglobin(mg/dl)	0.4±0.6	0,1 (0-2.7)
Decrease in hematocrit	2.0±2.5	0.9 (0-8.8)
Patients who required blood transfusion	2 (3.3%)	
Surgical complications	8 (13.3%)	
Length of hospital stay (days)	3.3±3.2	2.5 (1-27)
Patients received tocolysis	28 (46.7%)	
Patients diagnosed with preterm labor	38 (63.3%)	
Weeks elapsed from surgery to delivery	21.1±8.6	21.7 (4-38.6)
Gestational age at birth	37.8±2.8	38 (28-42)
Those who had a cesarean delivery	27 (45%)	

The distribution of diagnoses for pregnant women undergoing non-obstetric surgery is shown in Figure 1. Among the patients, appendicitis was the most common non-obstetric surgical indication, accounting for 75% (45 patients). Other reasons included adnexal torsion in 5 patients (8.3%), adnexal torsion with ovarian cyst in 5 patients (8.3%), cholecystitis in 2 patients (3.3%), uterine myoma in 1 patient (1.7%), volvulus with appendicitis in 1 patient (1.7%), and ruptured ovarian cyst in 1 patient (1.7%).

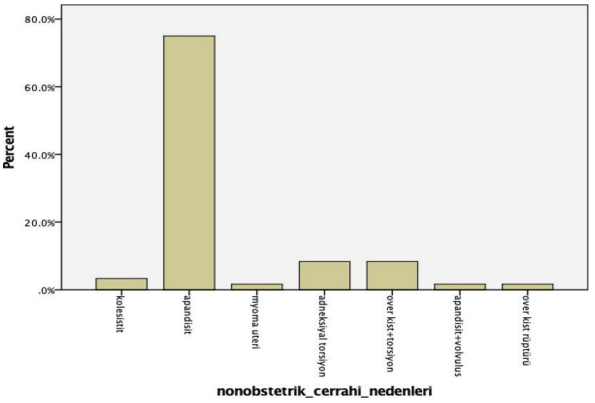

Figure 1. Distribution of diagnoses in pregnant women undergoing non-obstetric surgery.

The frequency of trimesters during which pregnant women underwent non-obstetric surgery is shown in Figure 2. It was observed that surgery was most commonly performed in the second trimester, accounting for 50% (30 patients).

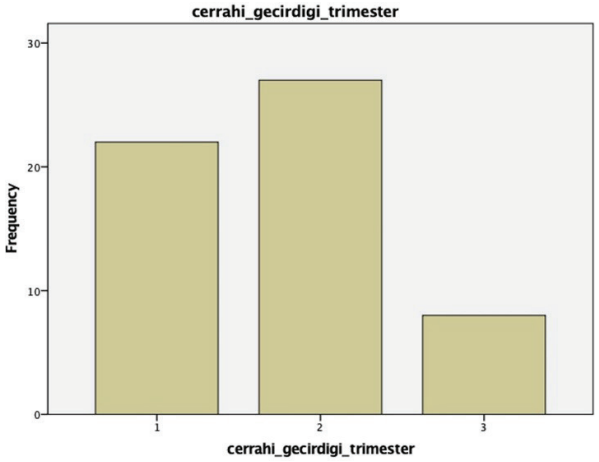

Figure 2. Trimesters of non-obstetric surgery in pregnant women undergoing surgery.

The patients' demographic characteristics were reclassified into two main categories: those who underwent laparoscopy and those who underwent laparotomy. The comparison of demographic characteristics of two groups is shown in Table 3. There was no significant difference observed between the two groups regarding these demographic characteristics. The median gestational age at the time of surgery was 16.7 weeks (6.3-33.3) in the laparoscopy group and 16.2 weeks (2-37.4) in the laparotomy group. Laparotomy rates were found more higher than laparoscopy rates in patients with emergency surgery (95.3% vs 64.3%, p=0.007).

Table 3. Comparison of demographic characteristics of patients undergoing laparoscopy and laparotomy.

Number of patients (n=60)	Laparoscopy (n=14)	Laparotomy (n=43)	p
Maternal age (years)	27 (20-33)	27 (21-39)	0.40
Smoking (Yes)	2 (14.3%)	8 (18.6%)	0.69
BMI (kg/m2)	26 (17-33)	26 (21-37)	0.32
Gravidity	3 (1-5)	2 (1-7)	0.77
Parity	1 (0-4)	1 (0-5)	0.48
Multiparity	9 (64.3%)	30 (70%)	0.61
History of cesarean section	5 (35.7%)	9 (21%)	0.11
Patients with multiple pregnancies	1 (7.1%)	1 (2.3%)	0.43
History of abortion	3 (21.4%)	6 (14%)	0.67
Comorbidity	3 (21.4%)	10 (23.3%)	0.46
Gestational age at the time of surgery	16.7 (6.3-33.3)	16.2 (2-37.4)	0.79
Patients underwent emergency surgery	9 (64.3%)	41 (95.3%)	0.007

BMI: Body mass index

The comparison of postoperative follow-up parameters between patients who underwent laparotomy and laparoscopy is shown in Table 4. There was no significant difference between the two groups regarding hemoglobin decrease and blood transfusion rates.

There was no difference between laparoscopy and laparotomy groups regarding median gestational week, the time interval from surgery to delivery. In the laparoscopy group, 8 patients (57.1%) received tocolysis treatment, 12 patients (85.7%) had no postoperative complications, 7 patients (50%) had preterm labor, 9 patients (64.3%) had no pregnancy complications, and 9 patients (64.3%) had a cesarean section. In the laparotomy group, 19 patients (44.2%) received tocolysis treatment, 37 patients (86%) had no postoperative complications, 28 patients (65.1%) had preterm labor, 27 patients (63%) had no pregnancy complications, and 16 patients (37.2%) had a cesarean section. There was no significant difference between the two groups in terms of these characteristics.

Table 4. Comparison of follow-up outcomes between patients undergoing laparotomy and laparoscopy.

	Laparoscopy (n=14)	Laparotomy (n=43)	p
Gestational age at birth	38 (28-41)	38 (29-42)	0.08
Weeks elapsed from surgery to delivery	20.5 (4-31.4)	22 (6.5-38.6)	0.56
Decrease in hemoglobin	0.2 (0-2.7)	0.1 (0-2.2)	0.30
Decrease in hematocrit	0.9 (0-7.7)	1.2 (0-8.8)	0.81
Length of hospital stay (days)	2.5 (1-22)	3 (1-10)	0.73
Patients who required blood transfusion	1 (7.1%)	1 (2.3%)	0.43
Patients received tocolysis	8 (57.1%)	19 (44.2%)	0.39
Those without perioperative complications	12 (85.7%)	37 (86%)	0.97
Those without pregnancy complications	9 (64.3%)	27 (63%)	0.67
Those who had a cesarean delivery	9 (64.3%)	16 (37.2%)	0.09

The comparative analysis of pregnancy complications in the laparotomy and laparoscopy groups is presented in Table 5. In the laparoscopy group, it was observed that the number of cases of preterm labor was 7 (50%), intrauterine growth restriction (IUGR) was present in 1 patient (7.1%), and sepsis was present in 1 patient (7.1%). In the laparotomy group, the number of cases of preterm labor was 28 (65.1%), placenta previa totalis was present in 1 patient (2.3%), IUGR was present in 2 cases (4.6%), pelvic dilatation was present in 1 patient (2.3%), gestational hypertension was present in 2 patients (4.6%), and preterm labor was accompanied by pelvic dilatation in 1 patient (2.3%).

Table 5. Pregnancy complications in the laparotomy and laparoscopy groups

	Laparoscopy (n=14)	Laparotomy (n=43)	p
Preterm labor	7 (50%)	28 (65.1%)	0.058
Placenta previa totalis	-	1 (2.3%)	-
IUGR	1 (7.1%)	2 (4.6%)	-
Pelviectasis	-	1 (2.3%)	-
Gestational hypertension	-	2 (4.6%)	-
Preterm labor + Pelviectasis	-	1 (2.3%)	-
Sepsis	1 (7.1%)	-	-

IUGR: Intrauterine growth restriction

The comparison of neonatal outcomes in the laparotomy and laparoscopy groups is shown in Table 6. In the laparoscopy group, the median birth weight was 2915 g (1025-4500), the median neonatal pH was 7.3 (7.0-7.3). There were 4 cases of small for gestational age (SGA) infants (28.6%), 5 newborns (35.7%) required neonatal intensive care unit (NICU) admission, and there were 14 live births (100%), with no cases of abortion or elective curettage. In the laparotomy group, the median birth weight was 3160 g (1380-4260), neonatal pH was 7.4 (range: 7.3-7.4), there were 4 cases of SGA infants (9.3%), 5 newborns (11.6%) required NICU admission, and there were 40 live births (93%). There was no significant difference in neonatal outcomes between the laparoscopy and laparotomy groups. No abortions were observed in the laparoscopy group, while 3 patients (7%) had abortion in the laparotomy group. In the group where laparoscopy was converted to laparotomy, 3 cases resulted in live births. Two pregnancies reached term, while one pregnancy underwent surgery at 20 weeks and delivered a live birth at 28 weeks after 8 weeks.

Table 6. Comparison of neonatal outcomes in the laparotomy and laparoscopy groups.

	Laparoscopy(n=14)	Laparotomy (n=43)	p
Birth weigth (g)	2915 (1025-4500)	3160 (1380-4260)	0.29
Neonatal ph	7.3 (7.0-7.3)	7.4 (7.3-7.4)	0.48
SGA	4 (28.6%)	4 (9.3%)	0.18
NICU	5 (35.7%)	5 (11.6%)	0.09
Live birth	14 (100%)	40 (93%)	0.47
Abortion	0 (0.0%)	3 (7%)	

NICU: Neonatal intensive care unit, SGA: Small for gestational age

DISCUSSION

The management of non-obstetric surgery in pregnant patients should be determined with a multidisciplinary approach involving obstetricians, general surgeons, anesthesiologists, and neonatologists. The main reason for this is the need for a careful assessment of the risk-benefit ratio regarding the maternal and fetal outcomes of non-obstetric surgery performed on pregnant patients. This is because when a surgical decision is made, the medical benefits of both maternal and fetal outcomes should outweigh the risks. Surgical, anesthetic, and perioperative management during pregnancy require special knowledge and experience due to their differences from non-pregnant patients.

In our study, the most common indication for non-obstetric surgery was appendicitis, accounting for 75% of cases, which is consistent with a study conducted by Prodromidou et al. in 2018.[14] The frequency of surgical indications in our study was also similar to Results of a study by Vujic et al.[15] A delayed diagnosis of perforated appendicitis can lead to sepsis, resulting in preterm birth, miscarriage, intrauterine fetal death, as well as maternal mortality and morbidity. In a study by Aggenbach et al. reported that patients who underwent surgery with suspected appendicitis but were found not to have appendicitis had a risk of preterm birth of 26% and a fetal loss risk of 3-7.3%.[16] We identified a pregnant patient who delivered prematurely at 29 weeks+2 days and underwent laparoscopic surgery for perforated appendicitis on the 2nd postpartum day.

The second most common non-obstetric surgical reason in pregnancy was adnexal torsion, accounting for 16.6% of cases. When adnexal torsion is diagnosed late, it can lead to adnexal necrosis and is considered an important gynecological emergency. Koo et al. compared two groups of women who underwent laparotomy and laparoscopy, and the mean gestational age and birthweight of the babies were found to be similar between the two groups. The rate of preterm birth was 8.6% in the laparotomy group, while it was 1.7% in the laparoscopy group.[17]

Two of our patients underwent laparoscopy due to cholelithiasis. One patient underwent laparoscopy in the 2nd trimester, and the other in the 3rd trimester. Similarly to our study, Date et al. reported that out of 19 patients who underwent laparoscopic cholecystectomy, only one reported complications. They reported that there was no increase in the risk of preterm labor or fetal death with an operative approach compared to conservative management. Conversely, in conservatively treated patients, the rate of fetal death due to gallstone pancreatitis was significantly higher.[18]

Of our patients, 38.6% underwent surgery in the first trimester, 47.4% in the second trimester, and 14% in the 3rd trimester. The American Society of Gastrointestinal Endoscopic Surgeons reported in 2011 that laparoscopy is feasible in every trimester.[19] If elective surgery is to be performed, it is particularly suitable to perform laparoscopy in the second trimester. Performing surgery in the 1st trimester increases the risk of abortion, while performing it in the 3rd trimester increases the likelihood of preterm labor.[20] Additionally, Fong et al. reported in their study that surgery should be avoided as much as possible in the 3rd trimester.[21]

In conclusion, our study found a low rate of postoperative complications after non-obstetric surgery during the pregnancy, indicating the safety of surgical treatment when necessary during pregnancy. Despite the high incidence

of preterm labor, the mean gestational age at delivery was found to be within the normal range following the surgery. Due to the relatively small number of total patients in our study, further research and data are needed to reach a consensus on the safety and management of non-obstetric surgery during pregnancy.

Acknowledgment

We thank Istanbul Kanuni Sultan Suleyman Training and Research Hospital, Health Sciences University, Department of Obstetrics and Gynecology, for his help in designing this study.

Ethical Approval

Istanbul Kanuni Sultan Suleyman Training and Research Hospital, Health Sciences University, Ethics Committee and following the Declaration of Helsinki (decision no: KAEK/2020.08.175, date: 03/09/2020).

Peer-review

Externally and internally peer-reviewed.

Author Contributions

Data curation, collection and reviewing: A.O., Conceptualization, methodology: A.O., S.Y., Z.O.G., I.O., Data analysis and interpretation: A.O., S.Y., Writing: A.O., S.Y., Reviewing and editing: A.O, S.Y., Z.O.G., I.O.

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding

This study received no financial support.

Informed Consent

Retrospective study.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Limitations of the Study

This study was conducted in a single center and with a small number of patients.

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DOI:10.34084/bshr.1284711 e-ISSN 2587-1641

Journal of Biotechnology and Strategic Health Research

Araştırma Makalesi /Research Article

http://dergipark.org.tr/tr/pub/bshr

Effects of A New Combination Folkloric Medicinal Plant Extract on Bone Formation in Orthopedically Expanded Suture in Rats

Yeni Bir Kombinasyon Folklorik Şifalı Bitki Ekstraktının Sıçanlarda Ortopedik Olarak Genişletilmiş Sütürde Kemik Oluşumu Üzerindeki Etkileri

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Geliş Tarihi / Received : 17-04-2023 **Kabul Tarihi / Accepted:** 08-06-2023 **Yayın Tarihi / Online Published:** 30-08-2023

Ezirganli S., Ozdemir H., Birlik M., Kazancioglu H.O., Aksakalli S., Esrefoglu M. Effects of a new combination folkloric medicinal plant extract on bone formation in orthopedically expanded suture in rats. J Biotechnol and Strategic Health Res. 2023;7(2):106-113

Abstract

Aim The aim of this study was to evaluate histological effects of a new combination folkloric medicinal plant extract on bone healing in premaxillary suture expansion in rats.

Material and Method Thirty male Sprague-Dawley rats were used in this study. Rats were evenly divided into three groups (one control and two experimental groups) of ten each. The animals were subjected to premaxillary suture expansion by helix springs. The only expansion group is defined as the control group (Group A). The experimental groups are defined as OstokinPlus-10 (Group B) and OstokinPlus-20 (Group C). In the experimental groups, 10 and 20 ml/kg OstokinPlus herbals were applied systemically after the expansion by use of an orogastric tube during the time of study. The springs were placed and activated to deliver a 30 cN force. After 5 days, the springs were removed and replaced with short lengths of rectangular retaining wire. Tooth separation was maintained for 15 days. After a consolidation period of 15 days, the animals were euthanatized and the maxillary bone containing the midpalatal suture cartilage was surgically removed. The specimens were prepared for histomorphometric assessment of the regenerated bone.

Results The midpalatal suture was successfully distracted following application of the activated helix spring. The distracted premaxillary suture was filled with new bone formation and unorganized fibrous tissues. Newly formed bone percentage and the bone area were found to have significant differences ($p< 0.05$). For investigated parameters, Group B and Group C revealed more positive results than Group A.

Conclusion OstokinPlus herbal had positive effects on bone healing and formation during premaxillary suture expansion.

Keywords Bone regeneration, histomorphometry, OstokinPlus herbal, rapid maxillary expansion

Özet

Amaç *Bu çalışmanın amacı, sıçanlarda premaksiller sütür ekspansiyonunda yeni bir kombinasyon folkrorik tıbbi bitki ekstratının kemik iyileşmesi üzerindeki histolojik etkilerinin değerlendirmektir.*

Gereç ve Yöntem *Bu çalışmada otuz erkek Spraque-Dawley sıçanı kullanılmıştır. Çalışma her biri eşit olmak üzere 10 sıçandan oluşan bir kontrol iki deney grubuna ayrılmıştır. Sıçanlar sarmal yaylar ile premaksiller sütür genişlemesine tabi tutulmuştur. Tek genişleme grubu kontrol grubu olarak (Group A) tanımlanmıştır. Deney grubu OstokinPlus-10 (Group B) ve OstokinPlus-20 (Group C) olarak tanımlanmıştır. Deney gruplarında, 10 ve 20 ml/kg OstokinPlus bitkileri, çalışma süresi boyunca orogastrik tüp kullanılarak genişletildikten sonra sistemik olarak uygulanmıştır. Yaylar yerleştirilmiş ve 30 SN kuvveti sağlayacak şekilde etkinleştirilmiştir. 5 gün sonra, yaylar çıkarılmış ve kısa uzunluklarda dikdörtgen tespit teli ile değiştirilmiştir. Diş ayrımı 15 gün sürdürülmüştür. 15 günlük bir konsolidasyon periyodundan sonra, hayvanlara ötenazi uygulanmış ve midpalatal sütur kıkırdağını içeren maksiller kemik cerrahi olarak çıkarılmıştır. Örnekler, rejenere kemiğin histomorfometrik değerlendirmesi için hazırlanmıştır.*

Bulgular *Aktive heliks yayı uygulamasının ardından midpalatal sütur başarılı bir şekilde ayrılmıştır. Ayrılan premaksiller sütur yeni kemik ve organize olmayan fibröz dokular ile dolmuştur. Yeni oluşan kemik yüzdesi ve kemik alanı arasında önemli farklılıklar bulunmuştur ($p< 0,05$). Araştırılan parametreler için Group B ve Group C, Group A daha iyi sonuçlar ortaya koymuştur.*

Sonuç *OstokinPlus ekstaratı premaksiller sütur genişlemesi esnasında kemik iyileşmesi ve formasyonunu olumlu yönde etkilemiştir.*

Anahtar Kelimeler *Kemik rejenerasyonu, histomorfometri, OstokinPlus bitkisi, hızlı maksiller genişleme,*

INTRODUCTION

Expansion of the median palatal suture with rapid maxillary expansion (RME) is a common procedure in orthodontic practice. This procedure is a well-accepted treatment for narrow maxilla in patients with posterior cross bite or dental crowding. In the RME, first the width of posterior dentition is increased, and then active bone regeneration occurs in the expanded suture area.[1-4]

RME was originally advocated for use in growing adolescents, with the sutures remaining patent, and this procedure has also been successfully used in skeletally mature adults.[5] Even after a retention period, the expanded maxilla has a strong tendency to rebound to its previous form, with up to a 90% relapse.[6] Although the actual causes of relapse are not yet fully understood, regulation of bone metabolism, retention period duration, rate and quality of bone regeneration in the midpalatal suture during and after expansion, soft-tissue adaptation, and age may all affect post-treatment relapse.[1,3,7-9]

The literature contains many studies about bone formation in the expanded suture or distracted callus that has been stimulated by herbals, using low level laser therapy (LLLT) or pharmacological, mechanical, electrical, or electromagnetic methods.[1-3,6,7,10-12] However, no study about the application of combination plant extracts on bone healing during premaxillary suture expansion was observed in the literature. Therefore, we aimed to investigate whether there is enhanced bone healing and regeneration during premaxillary suture expansion with the application of a new combination plant extract. In addition, if relapse after the expansion could be minimalized, it would be major interest for maxillary enlargement.

We used an Ostokin (Crystal Natural Pharmaceuticals, Yunnan, China) herbal product known in the China as OsteoKing. This product has been approved by China's State Food and Drug Administration (Guo yao zhun zi No. Z20025103), and it is a combination plant extract from the herbs astragalus membranaceus (9 gr/100 mL), panax ginseng (15 gr/100mL), carthamus tinctorius (7.5 gr/100 mL), citrus reticulata peel (6 gr /100 mL), pure water (62.2 gr/100 mL) and sorbic-benzoic acid (0.3 gr/100 mL). According to producers, Ostokin can be used for the following diseases: osteoarthiritis, osteonecrosis, osteoporosis, herniated disc and bone fractures. Till now it was reported that ostokin has notable effect in the treatment of bone illnesses such as femoral head necrosis or bone fractures.[13] Additionally, ostokin was found effective on prevention of osteoporosis in rabbits.[14] According to this literature support, Ostokin can be found effective on stability of maxillary expansion and stability. So, the purpose of the present experimental animal study was to evaluate the effect of this new combined folkloric medicinal plant extract when applied systemically for bone regeneration during premaxillary suture expansion in rats.

MATERIAL and METHOD

Sample and ethical statement

Thirty 50- to 60-day-old male Sprague-Dawley rats with a mean weight of 222.76±18.44 g were used in this study. The study was conducted in accordance with the accepted guidelines for the care and use of laboratory animals in research. All of the rats were housed in polycarbonate cages in an experimental animal room (22-24 o C, 55%-70% humidity, 1 atm pressure, with a 12-hour light/dark cycle). The rats were fed a standard laboratory diet, and drinking water was available ad libitum during the time of the study. This study's experimental procedures were approved by the Institutional Review Board and the Animal Use Committee of Bezmialem Vakif University (Animal Ethics Approval No. 2013/107). This study was conducted according to the principles of the Basel Declaration of 2010.

Experimental protocol and study design

The animals were randomly divided into three groups (a control group and two experimental groups) of 10 rats per group. The subjects were subjected to premaxillary suture expansion by helix springs. The expansion only group was

defined as the control group (Group A). The experimental groups were defined as Group B (10 ml/kg herbals) and Group C (20 ml/kg herbals). In the experimental groups, 10 and 20 ml/kg/d Ostokin (Yunnan Crystal Natural Pharmaceutical Co. Ltd 9/F JinTai Blds. No.48 Dong Feng Dong Lu, Kunming, Yunnan, China) herbals were systemically applied after the expansion, while 10 ml/ kg/d saline solution was systemically applied by means of an oro-gastric tube in the control group. It was applied systemically by the same person with a nasogastic tube, once a day at the same time of the day, for 15 days in both the experimental groups and the control group.

Placement of helix springs

The rats were anesthetized by intramuscular injection of 3 mg/kg xylazine hydrochloride (Rompuns, Bayer, Leverkusen, Germany) and 35 mg/kg ketamine hydrochloride (10% Ketasol®, Richter Pharma AG, Wels, Austria). After general anesthesia, a helix spring wire fabricated from a 0.012-inch piece of stainless-steel wire was used to perform the expansion of the midpalatal suture. The springs were placed on a grid and activated using pliers. The spring force, measured with a gauge, was 30 g. To obtain retention, a stainless-steel disc was used to prepare a groove at the level of the gingival papilla on the distal sides of the maxillary incisor teeth. Next, a 0.009-inch stainless-steel ligature wire was used to fix the spring to the maxillary incisors. The helix springs were placed and activated to deliver a force of 30 cN. During the expansion period of 5 days, a distance of minimum 1.5 mm was maintained between the maxillary incisors (Figure 1.). After the expansion period, the springs were removed and replaced with short lengths of rectangular retaining wire. Tooth separation was maintained for a consolidation period of 15 days.

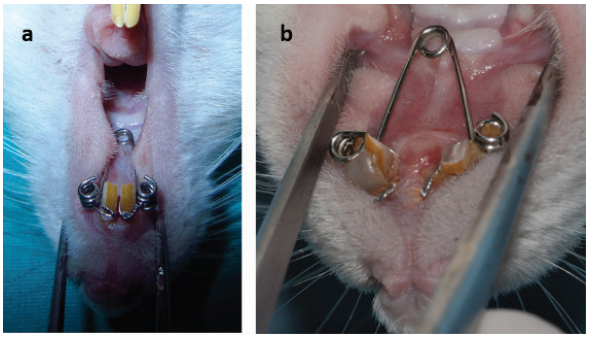

Figure 1. a) The helix spring was placed between the incisors. b) The spring is shown after an expansion period of 5 days.

Specimen preparation

After the consolidation period, the animals were sacrificed with an overdose of 200 mg/kg IV pentobarbital (Pentothal, Abbott, USA). The premaxillae of the animals were dissected out and fixed in 10% neutral formalin. After fixation, the retaining wires were removed. The premaxillae were rinsed with water and decalcified in 10% formic acid solution. After decalcification, the premaxillae were cut into blocks. One cut passed through the incisors at the alveolar crest and perpendicular to the sagittal plane; the second was cut 4 mm apical to the first. The plane passed through the center of the incisor at its gingival portion, and the maxillary incisor acted as the primary guide for orienting the sections. These specimens were dehydrated and embedded in paraffin. The paraffin blocks were sliced into sections 5 μm thick which were then stained with hematoxylin–eosin (HE) for histologic and histomorphometric analysis under light microscopy (Nikon, Tokyo, Japan).

Histologic and histomorphometric assessment

Histologic and histomorphometric analyses were performed by the same histologist, who was also blinded to the identity of the samples. Histomorphometric analysis was performed centered around the premaxillary suture and sections below the surface of the osseous palate facing the oral cavity, because bone regeneration of the surface area was sometimes irregular and unsuitable for quantita-

tive measurement. The presence of inflammatory infiltrate, connective tissue, material resorption, and bone regeneration was assessed. Computer-assisted histomorphometric measurements were performed using an automated image analysis system (ScanScope CS, Aperio®, Vista, California, USA). The images of the histologic sections in all groups were examined with a photomicroscope (Nikon Eclipse i5, Tokyo, Japan) coupled with a video camera on a light microscope (Nikon, DS-Fi1c, Tokyo, Japan), and downloaded to a computer. The number of osteoblasts and osteoclasts were measured with Image J software (US Institute of Health, Bethesta, MA, USA). Two straights were determined on the suture area, one beginning at the incisors and the other 2.5 mm from the beginning straight (Figure 1). Drawings were performed on the images and related areas were calculated in milimeter squares, so differences in the same sections could be compared. Afterwards, the regenerated new bone area (mm2) and the percent of the new bone formation were calculated using the NIS Elements version 4.0 image analysis system (Nikon Instruments Inc., Tokyo, Japan) in the expanded suture area with an original magnification of X40 on the fluorescent images (Figure 2). Eosin staining was used for fluorescent imaging and stained bone tissues can be seen in these images. The same imaging was used in a similar study.[15]

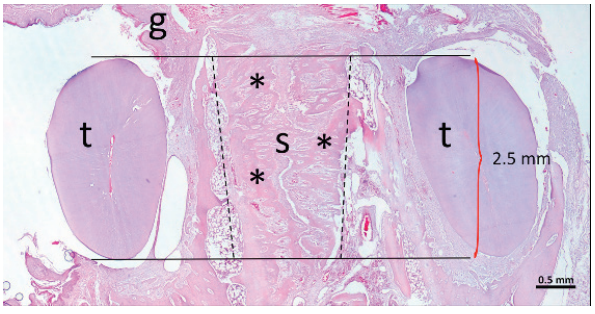

*Figure 2. Two straights were determined on the suture area. g: gingiva, s: suture area, t: tooth, *: new bone area.*

Statistical analysis

The statistical analysis was performed using a commercially available software program (SPSS 20; SPSS Inc., Chicago, IL, USA). To define the normality, the Shapiro–Wilk statistical test was used. For normally distributed data, one-way ANOVA followed post hoc (Tukey's) tests were performed to determine the presence of any significant difference between groups. The difference between groups was considered significant when a value of $p < 0.05$. For each group, the results were reported as median and mean ± standard deviation (n=10).

RESULTS

The expansion of the interpremaxillary suture was well tolerated. No adverse effects such as inflammation, dehiscence, or mucosal trauma were observed in any of the rats; however, three animals were excluded from the study as a result of spring appliance failure, and were replaced by three other rats. The average weight of each group was slightly decreased on Day 1 and had recovered by Day 2. No significant differences in mean body weight among the groups during the course of the experiment were observed. The midpalatal suture was successfully distracted following application of the activated helix spring. After an expansion period of 5 days, a digital caliper measured a distance of approximately minimum 1.5 mm between the maxillary incisors. It was reported that at least 1. 5 mm diastema is acceptable for maxillary expansion in rats.[16]

Figure 4. shows histological images of all the groups. The distracted premaxillary suture was filled with new bone formation and unorganized fibrous tissues. Percentages of newly formed bone and bone area revealed significant differences ($p<0.05$) (Table 1.) (Figure 3. and 4.).

Table 1. Results of the histomorphometric measurements.

Measurements	Control (Group A)	OstokinPlus-10 (Group B)	OstokinPlus-20 (Group C)	Results
Area (mm2) x ±Sd [median]	1.32±0.169* [1.40]	1.51±0.169 [1.57]	1.61±0.147 [1.68]	F= 8.06 **p=0.002**
Newly formed bone (%) x ±Sd [median]	42.68±1.632§ [42.92]	47.33±2.163† [46.96]	53.40±1.529‡ [53.14]	**F= 89.52 p<0.001**
x: Mean average, Sd: Standard deviation p<0.05: area (groups A vs all); percent (Group A vs all, Group B vs all)				

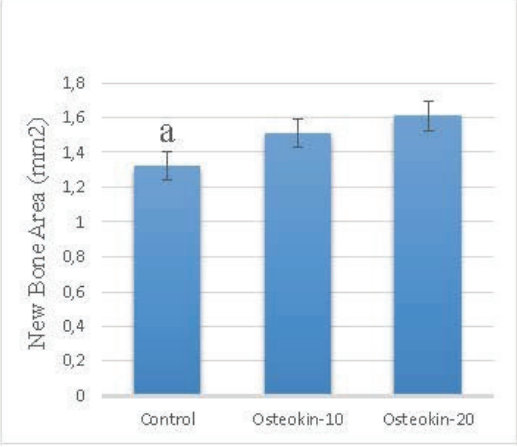

Figure 3. New bone area in all groups. p<0.05) formed bone

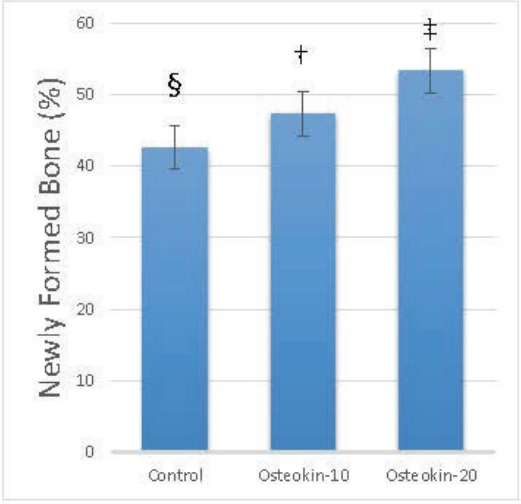

Figure 4. Newly formed bone in all groups (p<0.05)

For the investigated parameters, Group B and Group C revealed more positive results than Group A, with statistically significant differences (p<0.05) (Figure 5. and 6.). Group C also significantly differed from Group B with regard to percentage of newly formed bone (Figure 4.).

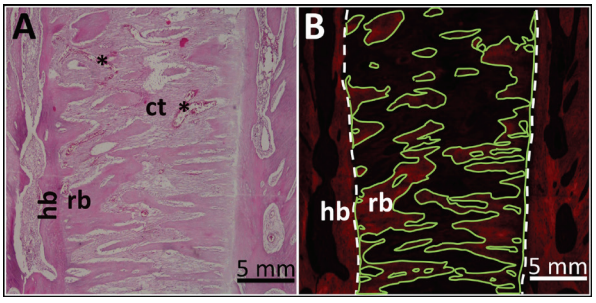

*Figure 5. The regenerated bones shown at original magnification (X40) in the expanded suture area (A: hematoxylin–eosin stain, B: regenerated bone areas in the fluorescent image, hb: host bone, rb: regenerated bone, ct: connective tissue, *: capillary).*

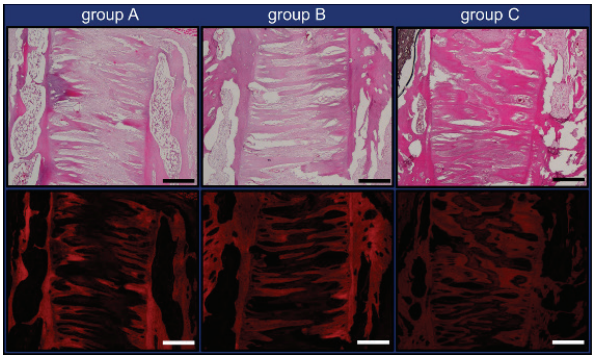

Figure 6. The histological images of all groups are shown as originally magnified (X40) with hematoxylin–eosin stain and fluorescent images (bars are 5 mm long).

DISCUSSION

One of the main causes of posterior cross bite is maxillary atresia. Expansion of the maxilla with RME is one of the most common treatments for maxillary atresia and has been used for more than 30 years.[1,17-19] The changes caused by this treatment are primarily located in the basal bone, increasing the upper jaw arch dimensions through the midpalatal suture, with posterior tooth movement through the alveolar processes.[17]

In this study, rats were used as the experimental animal model because rats have been used in so many similar studies and therefore the results of our study could be compared with those.[2,3,6,7,10-12,17,20-24] Different study protocols have used various parameters for analysis, such as number of osteoblasts[3,10,11] and osteoclasts[3,10], capillaries[3,10], proliferative and mineralizing hypertrophic chondrocytes in the suture cartilage[24], the mineralized area, the fibrosis area, the mineralized area/fibrosis area[7], bone perimeter, Feret's diameter, the newly formed bone percentage[6,11,12], and new bone area.[3,6,7,10-12,23,24] The common feature of most of these studies is the use of the amounts of new bone area as evaluation criteria. We assumed that other parameters, such as Feret's diameter, bone perimeter, and number of osteoblasts, and osteoclasts, were not particularly objective although we used number of osteoblasts and osteoclasts to check cellular activities as similar studies did. Determination of the exact number of osteoblasts and osteoclasts in the expanded area could not be realistic without immunohistochemical staining. The amount of the new bone area is already associated with the osteoblast number, so in this study we focused the new bone area and percentage of newly formed bone. In addition to histologic examinations, other researchers have used different analysis methods in their studies. Da Silva et al.[20] evaluated in vitro osteogenesis parameters and gene expression markers in their cell cultures after treating midpalatal suture expansions with LLLT. Rosa et al.[17] evaluated Raman spectroscopy, and Kobayashi et al.[25] researched alkaline phosphatase activity with histochemical staining.

The procedure for maxilla expansion includes an active phase associated with lateral forces and a passive phase using a retainer. The active phase lasts about 1-2 weeks, depending on the maxillary atresia[17] and expanded maxilla can relapse rapidly if a retainer is not used for a long time1, i.e., a minimum period of 3-5 months after the RME.[17] One of the main causes of relapse is insufficient new bone formation in the midpalatal suture. To avoid relapse, accelerated bone regeneration in the midpalatal suture would be beneficial.[1] The main benefit of accelerating bone formation in the palatal suture during and after expansion is to shorten the time required for bone remodeling in order to shorten retention time and to impede relapse of the skeletal base.[26] Various studies in the literature have investigated increasing bone regeneration in the midpalatal suture by using different mechanical stimulations or various pharmacological agents.[2,3,6,7,17] Saito and Shimizu1, da Silva et al.[20], and Rosa et al.[17] showed that applications of various LLLTs had a positive effect on bone healing in the midpalatal suture. Sawada and Shimizu[2] applied a single dose of Transforming Growth Factor-β1, and Uysal et al.[12] applied[16] a single dose of vitamin C for stimulation of the expanding suture. These studies found significantly stimulated bone regeneration in the midpalatal suture. Jiang et al.[23] showed that the local administration of a glycogen synthase kinase-3β inhibitor could stimulate bone formation in the midpalatal suture. Altan et al.[3] found that systemic use of propolis, a substance made by honeybees, may accelerate rats' new bone formation at the expanded suture. We investigated the effect of the Ostokin herbal product, a combination plant extract, on bone regeneration in the midpalatal suture in rats and found that this herbal agent stimulated bone regeneration during the expansion and consolidation periods. This product contains astragalus membranaceus, panax ginseng, carthamus tinctorius, and citrus reticulate peel.

Astragalus membranaceus is one of the most widely used medicinal herbs in Asian traditional medicine; it has an estrogenic effect that inhibits osteoclast development and

it improves MG-63 cell proliferation so this plant extract modified osteoclast numbers in the current study. This extract may have a synergic effect on improving bone mineral density.[27] In addition, Astragalus membranaceus has been used in traditional Chinese medicine to treat osteoporosis;[28], it has been found effective on rising osteoblastic activity. It improves intestinal calcium absorption, so it has an effect on bone metabolism.[27] In the current study, the number of osteoblasts was raised.

Ginseng has also been used for years in Asian countries. Panax ginseng (PG) is a tonic drug in traditional Chinese medicine. This agent could enhance bone marrow stromal cells and endothelial progenitor cell proliferation, and can increase the number of osteoblasts and bone formation[29] Avsar et al.[30] evaluated the protective effect of PG on bone metabolism in an experimental ovariectomy rat model of osteoporosis and showed that PG has a preventive effect against bone loss.

Carthamus tinctorius (safflower) seeds contain high level of minerals such as calcium, potassium, aluminum, iron, zinc, magnesium, and phosphorous. Traditionally, safflower has been used for purgative and alexipharmic effects in some Asian countries. In China, it has been used as a folk medicine to enhance bone formation.[31] Alam et al.[32] found that safflower seeds have possible roles in the improvement of osteoporosis induced in ovariectomized rats. Citrus reticulate peel comes from the mandarin[33] and has anti-carcinogenic effects.[34,35] No study on bone effects of citrus reticulate was observed in the literature.

Studies associated with the Ostokin or OsteoKing herbal products were also rare in the PubMed database. Hu et al.36 found that OsteoKing could effectively help repair steroid-induced femoral head necrosis in the early stages. In our study, the beneficial effect of bone formation was observed in premaxillary suture expansion.

CONCLUSIONS

The conclusion of the present study is that systemic application of this new combination plant extract can stimulate bone formation and increase bone regeneration in the midpalatal suture in a rat model. In the plant extract group, the number of osteoblasts and osteoclasts were supported this conclusion. This conclusion is only a beginning, and further experimental and clinical studies are needed to evaluate the effects of this herbal extract in humans.

This study showed that systemic application of the new combination plant could be enhanced osteoblastic activity. So, bone formation and improves healing increased in the interpremaxillary suture area during expansion. Eventually, this product could be applied for accelerating bone formation in the palatal suture. Relapse of expanded maxilla could be avoided and also retention period could be not a long time.

Ethics Approval

Ethical approval was obtained from the Institutional Review Board and the Animal Use Committee of Bezmialem Vakif University (Animal Ethics Approval No. 2013/107).

Peer-review

Externally and internally peer-reviewed.

Author Contributions

Concept: S.E., H.Ö., M.B., Design: S.E., H.Ö., H.O.K., Data Collection or Processing: M.E., H.Ö., Analysis or Interpretation: S.E., H.O.K., S.A., Literature Search: S.E., H.Ö., H.O.K., M.B., S.A., Writing: S.E., H.O., M.B., H.O.K., S.A., M.E.

Conflict of Interest

The authors declared no conflict of interest.

Funding

The study was self-funded by the authors

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DOI:10.34084/bshr.1308906 e-ISSN 2587-1641

Journal of Biotechnology and Strategic Health Research

Araştırma Makalesi /Research Article

http://dergipark.org.tr/tr/pub/bshr

Unpredictable Nightmare of Thyroid Surgery: Incidental Parathyroidectomy

Tiroid Cerrahisinin Önlenemez Kabusu: İnsidental Paratiroidektomi

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Geliş Tarihi / Received : 01-06-2023 **Kabul Tarihi / Accepted:** 30-06-2023 **Yayın Tarihi / Online Published:** 30-08-2023

Yazicioglu M.B., Ciftci A., Turgut H.T. Unpredictable nightmare of thyroid surgery: Incidental parathyroidectomy. J Biotechnol and Strategic Health Res. 2023;7(2):114-120

Abstract

Aim Incidental removal of the parathyroid gland is an unwanted minor complication of thyroidectomy and would occur even in experienced centers. The purpose of this study was to evaluate our clinic's outcomes, incidence, and risk factors for incidental parathyroidectomy.

Material and Method A total of 627 patients with an average age of 50.74±12.68 years were included in the study. Seventy-eight point nine percent of the patients had bilateral total thyroidectomy, 11.2% had a total lobectomy with isthmectomy, 4.8% had completed thyroidectomy, 4% had bilateral total thyroidectomy with bilateral central dissection and 1.1% had bilateral subtotal thyroidectomy. Incidental parathyroidectomy was observed in 6.4% (n=40) of all patients.

Results There was a significant correlation between incidental parathyroidectomy and bilateral total thyroidectomy and bilateral central neck dissection. There were no statistically significant differences between the incidental and nonincidental parathyroidectomy group with respect to age and gender. While the preoperative diagnosis of hyperthyroidism (20.6% vs 7.5%) was significantly higher in the non-incidental parathyroidectomy group than in the incidental parathyroidectomy group, and the diagnosis of malignancy was significantly higher in the incidental parathyroidectomy group (32.5% vs. 11.6%, p=0.001). Regarding parathyroid localization, our incidental parathyroidectomy rate was higher in intrathyroidal localized cases. Postoperative transient hypocalcemia (62.5%) was higher in the incidental parathyroidectomy group than in the non-incidental parathyroidectomy group (34.4%, p<0.001).

Conclusion Total thyroidectomy, thyroid pathology, and intrathyroidal parathyroid location are risk factors for incidental parathyroidectomy. Incidental parathyroidectomy during thyroid surgery can be a potential complication.

Keywords Hypocalcemia, incidental, parathyroidectomy

Özet

Amaç *Paratiroid bezinin tesadüfen çıkarılması, tiroidektominin istenmeyen küçük bir komplikasyonudur ve deneyimli merkezlerde bile meydana gelebilir. Bu çalışmanın amacı, kliniğimizin tesadüfi paratiroidektomi sonuçlarını, insidansını ve risk faktörlerini değerlendirmektir.*

Gereç ve Yöntem *Çalışmaya yaş ortalaması 50,74±12,68 olan toplam 627 hasta dahil edildi. Hastaların yüzde yetmiş sekiz nokta dokuzuna bilateral total tiroidektomi, %11,2'sine total lobektomi ile istmektomi, %4,8'ine tamamlayıcı tiroidektomi, %4'üne total tiroidektomi ile birlikte bilateral santral diseksiyonla ve %1,1'ine de bilateral subtotal tiroidektomi uygulandı. Tüm hastaların %6,4'ünde (n=40) rastlantısal paratiroidektomi görüldü.*

Bulgular *Tesadüfi paratiroidektomi ile bilateral total tiroidektomi ve bilateral santral boyun diseksiyonu arasında anlamlı bir korelasyon vardı. Yaş ve cinsiyet açısından tesadüfi ve tesadüfi olmayan paratiroidektomi grubu arasında istatistiksel olarak anlamlı bir fark yoktu. Preoperatif hipertiroidizm tanısı (%20,6'ya karşı %7,5) tesadüfi olmayan paratiroidektomi grubunda tesadüfi paratiroidektomi grubuna göre anlamlı olarak yüksek bulunurken, tesadüfi paratiroidektomi grubunda malignite tanısı anlamlı olarak daha yüksekti (%32,5'e karşı %11,6, p=0.001). Paratiroid lokalizasyonu açısından intratiroidal lokalize vakalarda tesadüfi paratiroidektomi oranımız daha yüksekti. Postoperatif geçici hipokalsemi (%62,5) tesadüfi paratiroidektomi grubunda tesadüfi olmayan paratiroidektomi grubuna göre daha yüksekti (%34,4, p<0,001).*

Sonuç *Total tiroidektomi, tiroid patolojisi ve intratiroidal yerleşimi paratiroid tesadüfi paratiroidektomi için risk faktörleridir. Tiroid cerrahisi sırasında rastlantısal paratiroidektomi potansiyel bir komplikasyon olabilir.*

Anahtar Kelimeler *Hipokalsemi, tesadüfi, paratiroidektomi*

INTRODUCTION

Currently, thyroidectomy is the most frequently performed endocrine surgical procedure.[1,2] Thyroid surgery is accepted as a safe surgical procedure because the overall complication rate is blow 5%, however, it requires both sufficient anatomical knowledge and a meticulous surgical technique.[1,2] Surgical experience could minimize the major complications of the procedure, such as postoperative bleeding, recurrent nerve injury, and hypocalcemia, but this may still occur.[1,3] Among these complications, hypocalcemia is most frequent, with a rate of 7-51% (1.6%-50% transient, 1.5%-4% permanent hypocalcemia).[4,5] Surgical trauma, the devascularization of the parathyroid gland during surgery, the extent of surgery, and incidental parathyroidectomy (IPT) increase the risk of postoperative hypocalcemia.[6] Postoperative hypocalcemia reduces quality of life sue to long-term use of calcium and increases the total cost of thyroidectomy by prolonging hospital stays.[7-9] IPT is defined as the presence of the parathyroid gland in the postoperative specimen and can be seen in 6-28% of thyroidectomies.[8-10] Several risk factors have been suggested to explain IPT in thyroid surgery, such as anatomical variation, preoperative diagnosis, type of surgery, presence of nodal metastases, reoperation, and central neck dissection.[6,11-15] Also, parathyroid glands are often surrounded by fat and connective tissue, making it difficult for surgeons to distinguish parathyroid tissue from lymph node or adipose tissue so that it may inadvertently be resected.[16] However, a common consensus on clinical and biochemical outcomes in IPT patients does not exist.[14,15,17] Theoretically, resection of a normal parathyroid gland should have no effect on serum calcium levels if three glands function normally. However, some studies have reported a correlation between temporary or permanent hypocalcemia and IPT, while some studies have reported no significant changes in postoperative calcium or parathormone (PTH) levels.[18-23] The purpose of this study was to assess clinical outcomes, incidence, and risk factors for incidental parathyroidectomy.

MATERIAL and METHOD

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. In our clinic, bilateral total thyroidectomy, near-total or total lobectomy with isthmectomy is currently the preferred treatment for thyroid diseases. Between January 2009 and November 2020, 786 patients were operated on in our clinic. Of the underwent thyroidectomy cases, 124 (19.8%) had surgery for hyperthyroidism, 422 (67.3%) for nonfunctional nodules, and 81 (12.9%) for malignancy. One hundred and fifty-nine cases in which parathyroid autoimplantation had been done during the operation were excluded from the study.

Six hundred and twenty-seven cases (106 males, 521 females) with a mean age of 50.74±12, 68 (range 18-86) were included in this study. Serum calcium levels were monitored before surgery, one day after surgery, the first week, and the sixth month of surgery. The patients were discharged home without complications on 1 postoperative day. But patients who developed hypocalcemia were discharged hospital the first day after the hypocalcemia was resolved and were followed for 6 months to see if the hypocalcemia was permanent or transitory. All patient reports were reviewed for both preoperative and final diagnosis of thyroid disease, presence of the parathyroid tissue in the resected specimen, the location of the gland (extracapsular or intrathyroidal), and the number of resected parathyroid glands Hypocalcemia was defined as the serum calcium concentration <8 mg/dl. In patients with postoperative Ca level below 8.00 mg/dl, a calcium effervescent tablet was began orally three times daily. Oral calcium was stopped following laboratory tests and improved clinical signs of hypocalcemia.

Operation

All thyroid surgeries were performed through extracap-

sular dissection by experienced thyroid surgeons. During thyroidectomy, we tried to find and preserve all the parathyroid glands with meticulous dissection and without disturbing the vascularization of the glands. At the end of the operation, the specimen was thoroughly checked for parathyroid tissue. Finally, 627 cases were divided into two groups: Group I IPT and Group II non-IPT.

Statistical analysis

Data were analyzed with IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). The normality assumptions were controlled by the Shapiro-Wilk test. Continuous data were summarized as the mean standard deviation for normally distributed data. Categorical variables were given with frequency (n) and percentage (%) and compared with the Pearson chi-square test and Fisher's Exact test. An independent t-test was used to compare the age between the groups. Post-hoc analysis was performed using the Bonferroni correction. Multivariate logistic regression analysis was used to determine the associated factors with the development of incidental parathyroidectomy. The results of the model were reported with the Odds ratio (OR) and the corresponding 95% confidence intervals (95% CIs). Two-sided p values <0.05 were considered statistically significant.

RESULTS

The average age of 627 patients participating in the study was 50.74±12.68 years and 83.1% were female. Of the patients, 67.3% had nonfunctional nodules, 19.8% had hyperthyroidism, and 12.9% had malignant tumors. The types of surgical procedures performed in these 627 patients were bilateral total thyroidectomy (BTT) in 78.9% of cases, total lobectomy with isthmectomy in 11.2 % of cases, completion thyroidectomy in 4.8% of cases, BTT and bilateral central dissection in 4% of cases, and bilateral subtotal thyroidectomy in 1.1% of cases. In 612 patients (97.6%), the parathyroid gland was located extracapsular and in 15 patients (2.4%) intrathyroidal location was seen. Histopathological examination of the resected thyroid specimens revealed nonfunctional nodules in 77.4% of cases, thyroid malignancy in 18.7% of cases, and thyroiditis in 4% of cases. Postoperatively, 227 patients (36.2%) had temporary hypocalcemia and 16 patients (2.6%) had permanent hypocalcemia.

Incidental parathyroidectomy (IPT) was present in 40 (6.4%) patients. There were no statistically significant differences in terms of age and sex in the IPT group (p=0.232 and p = 0.720, respectively). While the diagnosis of preoperative hyperthyroidism was statistically significantly higher in patients with non-IPT than in the IPT group (20.6% vs 7.5%), in the IPT group, the diagnosis of malignancy was statistically significantly higher (32.5% vs 11.6%, p=0.001). The diagnosis of preoperative hyperthyroidism (20.6% vs. 7.5%) was significantly higher in the non-IPT group and the diagnosis of malignancy (32.5% vs. 11.6%) was significantly higher in IPT (p=0.001). While the frequency of BTT was significantly higher in the non-IPT group than in the IPT group (80.6% vs 55%), BTT and bilateral central dissection were significantly higher in the IPT group (20% vs. 2.9%, p<0.001). The intrathyroidal parathyroid location ratio (37.5%) was significantly higher in the IPT group than in group two (p<0.001). Transient hypocalcemia (62.5%) was higher in group I than in group two (34.4%) (p<0.001) (Table 1.).

Table 1. Patient characteristics				
Variables	All patients	Non-IPT	IPT	
Number of patients (%)	627	587 (93.6)	40 (6.4)	
Age (years), mean±SD	50.74±12.68	50.9±12.65	48.43±13.11	0.232
Gender, n(%)				
Male	106 (16.9)	100 (17)	6 (15)	0.740
Female	521 (83.1)	487 (83)	34 (85)	
Preop diagnosis, n (%)				
Hyperthyroidism	124 (19.8)	121 (20.6)a	3 (7.5)b	**0.001**
Non-functional nodules	422 (67.3)	398 (67.8)a	24 (60)a	
Malignancy	81 (12.9)	68 (11.6)a	13 (32.5)b	
Operation, n(%)				
Bilateral total thyroidectomy	495 (78.9)	473 (80.6)a	22 (55)b	**<0.001**
Total lobectomy with isthmectomy	70 (11.2)	64 (10.9)a	6 (15)a	
Completion thyroidectomy	30 (4.8)	26 (4.4)a	4 (10)a	
Bilateral subtotal thyroidectomy	7 (1.1)	7 (1.2)a	0 (0)a	
Bilateral total thyroidectomy with bilateral santral diseksiyon	25 (4)	17 (2.9)a	8 (20)b	
Location, n(%)				
Intrathyroidal	15 (2.4)	0(0)	15(37.5)	**<0.001**
Extra-capsular	612(97.6)	587(100)	25(62.5)	
Final pathology, n(%)				
Thyroiditis	25 (4)	24(4.1)	1(2.5)	0.156
Non-functional nodules	485 (77.4)	458(78)	27(67.5)	
Malignancy	117 (18.7)	105(17.9)	12(30)	
Postop hipokalsemi, n(%)				
None.	384 (61.2)	372 (63.4)a	12 (30)b	**<0.001**
Transient	227 (36.2)	202 (34.4)a	25 (62.5)b	
Permanent	16 (2.6)	13 (2.2)a	3 (7.5)a	
Independent t-test, Pearson chi-square test, Fisher's Exact test. The same letters in a row denote the lack of statistically significant difference				

According to multivariate logistic regression analysis, the highest risk of IPT was found in patients undergoing bilateral total thyroidectomy and central lymph node dissection, which independently increases the occurrence of IPT (OR: 3.301; 95% CI: 1.007-10.819; p=0.049) (Table 2.).

Table 2. Multivariate logistic regression analysis for IPT		
Variables	OR (95% CI)	p
Age	0.993 (0.968-1.02)	0.618
Female gender	0.885(0.351-2.232)	0.796
Preop diagnosis hyperthyroidism	0.475 (0.139-1.629)	0.237
Preop diagnosis malignancy	1.745 (0.725-4.199)	0.214
Bilateral total thyroidectomy	0.555 (0.245-1.255)	0.157
Bilateral total thyroidectomy with bilateral santral diseksiyon	3.301 (1.007-10.819)	0.049

DISCUSSION

IPT is a relatively common complication of thyroidectomy, but can be reduced to 0.5- 4.0% with meticulous surgery.[6,21] Although there is uncertainty about its incidence and clinical significance, the reported rate varied between 2.9% to 31%.[1,6] Anatomically, the upper parathyroid gland is usually located in the upper pole of the thyroid gland; however, the lower parathyroid glands have some variations and can sometimes be localized intrathymic or differently.[12] Parathyroid tissue can be found in intrathyroidal (16.7-40%) or extracapsular (15.7-81.1%).[14,20-22] The different locations of the parathyroid glands may increase the risk of IPT. Although many authors recommend all parathyroid gland exploration during surgery to reduce the incidence of IPT, this may lead to unwanted Results.[20,21,23] In our study, incidental parathyroidectomy was observed in 40 (6.4%) cases and 37.5% of all were located intrathyroidal, which was statistically significantly higher than Group II ($p<0.001$). There has been a lot of controversy about the relationship of IPT to thyroid cancer or thyroiditis. Several previous studies showed a strong relationship; however, some studies found no connection between them.[4,18,21,23] Type of surgery may increase the risk of IPT. Khairy et al. reported that total thyroidectomy is a risk factor for IPT.[14] In our study, malignancies, total bilateral thyroidectomy, and bilateral central neck dissection were found to be risk factors for IPT. We believe that extensive dissection during bilateral total thyroidectomy and lymph node dissection are an important cause of this. Some literature suggests that gender is also a risk factor for IPT, especially in young patients.[12,15,21] In addition, Rix et al. showed that completing thyroidectomy is a risk factor for IPT.[24] However, age, gender, and surgical difficulty of completing thyroidectomy and re-exposure of the neck were not found to be risk factors for IPT in our study, as in Khairy's study. In many studies, the risk of IPT has been shown to increase because of scar tissue and bleeding from inflammation of the thyroid gland.[25] In our study, no statistically significant differences were found between thyroiditis and IPT. Although clinical hypocalcemia is less common, biochemical hypocalcemia rates can be up to 83% of cases, and transient hypocalcemia is the most common condition after thyroid surgery.[21] Specific factors such as parathyroid gland injury, devascularization, or one or more parathyroid gland excision have been claimed as the reason of hypocalcemia but remain multifactorial.[14, 26] However, there is controversy about the association of hypocalcemia with IPT in the literature.[4,20] In the study of Sippel et al. postoperative calcium levels were significantly lower in the IPT group.[15] In our study, transient hypocalcemia was seen in 25 cases (62.5%) and permanent hypocalcemia was seen in 3 cases (7.5%) of the IPT group and a significant difference was observed between the two groups ($p<0.001$).

In conclusion, IPT is a common condition in thyroid surgery pathological reports, even in experienced centers. In our study, bilateral total thyroidectomy and neck dissection, and intrathyroidal location of the parathyroid gland were found to be risk factors for IPT. Since only one parathyroid gland was removed during thyroid surgery, as in our study, permanent hypocalcemia is not often seen as a result of compensation of other intact glands. Even though sufficient anatomical knowledge and meticulous surgical techniques are the most important step of prevention of IPT, nothing can predict in which patient it will occur.

Acknowledgment

We thank University of Health Science, Kocaeli Derince Training and Research Hospital, Department of General Surgery, for his help in designing this study

Ethical Approval

University of Health Science, Derince Education and Research Hospital ethics Commitee and following the Declaration of Helsinki (decision no: No. 2021-1409).

Peer-review

Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.B.Y., A.C., Design: M.B.Y., A.C., H.T.T., Data collection or Processing: M.B.Y., A.C., H.T.T., Analysis or interpretation: M.B.Y., A.C., Literature Search: M.B.Y., A.C., Writing: M.B.Y.

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding

This study received no financial support.Conflict of interest.

Informed Consent

Retrospective study

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DOI:10.34084/bshr.1312716 e-ISSN 2587-1641

Journal of Biotechnology and Strategic Health Research

Araştırma Makalesi /Research Article

http://dergipark.org.tr/tr/pub/bshr

Thyroid Cancer Incidence and Clinicopathological Distribution in Bariatric Surgery Cases

Bariatrik Cerrahi Olgularında Tiroid Kanseri İnsidansı ve Klinikopatolojik Dağılımı

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Geliş Tarihi / Received : 10-06-2023 **Kabul Tarihi / Accepted:** 07-07-2023 **Yayın Tarihi / Online Published:** 30-08-2023

YAksoy E., Ergenc Z., Ergenc H., Karaca-Ocak O. Thyroid cancer incidence and clinicopathological distribution in bariatric surgery cases. J Biotechnol and Strategic Health Res. 2023;7(2):121-126

Abstract

Aim Obesity is strongly associated with increased risk of many cancer types. It is estimated that approximately 20% of all cancers are caused by overweight. It is considered that there is a direct relation between overweight and thyroid cancer. The aim of this study is to evaluate the incidence and clinicopathological distribution of thyroid cancer in bariatric surgery cases.

Material and Method The present study was conducted with a total of 2316 patients who underwent bariatric surgery because of morbid obesity in our metabolic and bariatric surgery clinic between April 2014 and November 2021.

Results It was found that the prevalence of thyroid cancer was 1.2% in morbidly obese cases. A total of 23 patients had papillary thyroid cancer (0.99%), 3 patients had follicular cancer (0.12%), 1 patient had medullary cancer (0.04%), and 1 patient had anaplastic cancer (0.04%).

Conclusion It was found in the present study that the most common cancer type was thyroid papillary cancer, and follicular, medullary, and anaplastic cancer were found to be less frequently. There appears to be a relation between Body Mass Index and the thyroid cancer risk.

Keywords Bariatric surgery, histopathological distribution, obesity, thyroid cancers,

Özet

Amaç *Obezite, birçok kanser türünün artan riski ile güçlü bir şekilde ilişkilidir. Tüm kanserlerin yaklaşık %20'sinin aşırı kilodan kaynaklandığı tahmin edilmektedir. Fazla kilo ile tiroid kanseri arasında doğrudan bir ilişki olduğu düşünülmektedir. Bu çalışmada amaç Bariatrik cerrahi olgularında tiroid kanseri insidansı ve klinikopatolojik dağılımını değerlendirmektir.*

Gereç ve Yöntem *Bu çalışma, Nisan 2014 ile Kasım 2021 tarihleri arasında metabolik ve obezite cerrahisi kliniğimizde morbid obezite nedeniyle obezite cerrahisi uygulanan toplam 2316 hasta ile gerçekleştirildi.*

Bulgular *Morbid obez olgularda tiroid kanseri prevalansının %1,2 olduğu saptandı. Toplam 23 hastada papiller tiroid kanseri (%0,99), 3 hastada foliküler kanser (%0,12), 1 hastada medüller kanser (%0,04) ve 1 hastada anaplastik kanser (%0,04) vardı.*

Sonuç *Bu çalışmada en sık görülen kanser tipinin tiroid papiller kanseri olduğu ve foliküler, medüller ve anaplastik kanserlerin daha az sıklıkta olduğu saptandı. Vücut Kitle İndeksi ile tiroid kanseri riski arasında bir ilişki var gibi görünmektedir.*

Anahtar Kelimeler *Bariatrik cerrahi, histopatolojik dağılım, obezite, tiroid kanserleri*

INTRODUCTION

The association between obesity and increased cancer incidence and cancer-related mortality has been established well in recent years. It is estimated that 14% of cancer deaths in men and 20% in women may be because of obesity.[1] Uncontrolled weight gain frequently causes metabolic disorders, altered steroid hormone production, and chronic subclinical inflammation. These pathophysiological effects have been associated with the development and progression of tumors.[2]

There has been a stable increase in the Thyroid Cancer (TC) incidence worldwide in the last three decades.[3] The incidence was later reported to be 0.02% with available data. The highest increase in incidence was reported in women, and stemmed from papillary thyroid cancer, which is the most common histological type.[4-5]

Previous studies showed that TCs are more aggressive in the obese population, and increase the rates of microscopic extra-thyroidal invasion and advanced stage. It has been recently shown that the prevalence of TC is 0.15% in men and 0.50% in women. TCs were also associated directly with increasing age, higher systolic blood pressure, lighter weight, and shorter stature. However, there are also several other studies which show the relation of TC with excessive BMI.[6-7] Although some studies mention a positive relation with obesity, especially in women, some other studies report that the relation between TC and obesity is a controversial one.[8-9] For this reason, the purpose of the present study was to determine the prevalence and histopathological distribution of TC that were detected in multidisciplinary evaluations in the management of obese patients before bariatric surgery. All of these patients were those who were found to have TC during pre-operative evaluation and scans when they applied to the obesity clinic.

MATERIAL and METHOD

The present study was conducted with a total of 2316 patients who underwent bariatric surgery because of morbid obesity in our metabolic and bariatric surgery clinic between April 2014 and November 2021. The evaluation results of each case were obtained from the files and electronic records. The anthropometric data, physical examination results, laboratory results, and ultrasonographic and pathological data of the cases were analyzed. The study had a cross-sectional descriptive design and was conducted by examining the data and files of the patients retrospectively after the approval of Medicana International Samsun Hospital Clinical Research Ethics Committee in line with ethical rules (decision no 7154, 01.11.2021).

The frequency and histopathological types of the cases with thyroid cancer were used as the data during the evaluations of the study group with a Body Mass Index (BMI) ≥ 40 kg / m2 with a multidisciplinary approach before bariatric surgeries. All cases were evaluated with Thyroid Ultrasonography before bariatric and metabolic surgeries. Biopsy and further examinations were performed from each nodule in the indication, and cancer prevalence was determined with these examinations. Thyroid fine needle aspiration biopsy decision was made based on the EU-TIRADS score. EU-TIRADS 3 nodules >20 mm (very low risk, malignancy risk 2-4%); EU-TIRADS 4 nodules >15 mm (low-intermediate risk, malignancy risk 6-17%); EU-TIRADS 5 TIAB was performed when nodules were >10 mm (moderate-high risk, risk of malignancy 26-87%).10 The cases between the ages of 18-65 were included in the study. Each patient was evaluated individually with the multidisciplinary study group in our hospital.

Statistics

The data were expressed as Mean ± Standard Deviation (SD), and the continuous variables were determined with baseline statistics (mean, standard deviation). Percentages were used for continuous variables, and $p<0.05$ was taken to be statistically significant. The data were analyzed with the SPSS Software (Statistical Package for the Social Sciences, version 22.0, Chicago).

RESULTS

Electronic and file records of 2316 patients were evaluated in the present study; and 1452 of the patients were female, and 864 were male. The mean age of the patients was 47.8 ± 8.4, and Body Mass Index (BMI) was 50.3±5.6 kg/m2. The sociodemographic and clinical characteristics of the study group are shown in Table 1.

Table 1. Clinical characteristics of patients

Parameter	Whole cohort
Age, year± SD	47.8 ± 8.4
Gender, female (%, n)	1452 (62.6%)
Weight, kg	110.3±14.5
BMI, kg/m2	50.3 ± 5.6
Nodule prevalence (with ultrasonography), n (%)	1482 (63.9%)
Fine needle aspiration biopsy, n (%)	1009 (68.0%)
Background thyroid tissue	
Normal	741 (31.9%)
Nodular goiter, n (%)	1482 (63.9%)
Lymphocytic thyroiditis, n (%)	416 (17.9%)
Hashimotos' thyroiditis, n (%)	324 (13.9%)
Lymph node surgery	
Central neck dissection, n (%)	9 (32.1%)
Lateral neck dissection, n (%)	3 (10.7%)
Tumor size, mm	21.4 ± 11.5
Extra thyroidal metastasis, n (%)	8 (28.5%)
Whole Cohort-n (%); SD: Standard Deviation.	

Bariatric surgeries were performed for the treatment of obesity in 65.6% (n=1521), and metabolic surgeries were performed for the treatment of Type 2 Diabetes in 34.3% (n=795) of the patients. The thyroid tissues were evaluated ultrasonographically in all cases. Thyroid parenchyma was found to be normal in 31.9%, thyroid nodule in 63.9%, and thyroiditis in 31.9%. Fine needle aspiration was performed for 43.5% of all cases; and 32.1% underwent central lymph node dissection, and 10.7% lateral lymph node dissection were performed in TC cases. Extra thyroidal metastases were 28.5%. The data are shown in Table 1.

The data on the prevalence and histopathological types of TC in morbidly obese patients are very rare. It was found that the prevalence of TC was 1.20% in morbidly obese cases (n=28). A total of 23 patients had papillary thyroid cancer (0.99%), 3 patients had follicular cancer (0.12%), 1 people had medullary cancer (0.04%), 1 patient had anaplastic cancer (0.04%). The frequency and histopathological distribution of the thyroid cancer in obese patients are shown in Table 2.

Table 1. Clinical characteristics of patients

Morbidities	Prevalence of morbidities n (%)
Papillary Cancer	23 (0.99%)
Classic variant	9 (39.1%)
Follicular variant	11 (47.8%)
Tall cell variant	2 (4.6%)
Hurtle cell variant	1 (4.3%)
Follicular cancer	3 (0.12%)
Medullary Cancer	1 (0.04%)
Anaplastic cancer	1 (0.04%)
Total	28 (1.20%)
Whole Cohort-n (%); SD: Standard Deviation.	

DISCUSSION

In recent years, the prevalence of thyroid cancer has increased dramatically largely because of the identification of subclinical disease. The latest epidemiological data and the recent developments in the recommendations to diagnose and treat thyroid cancer cases with low risk promise that the prevalence may begin to slow.[11-12] In previous studies, the prevalence of TC was reported to be 0.03-0.09%, and as high as 0.15-0.11% in many countries in Europe in recent years.[13] A significantly increased prevalence of TC was detected in obese cases in the present study.

Several previous studies showed that there is a prevalence of thyroid nodules of 2-6% with palpation, 19-35% with ultrasound, and 8-65% in autopsy data.[14] It was also shown that parenchymal hypoechogenicity, general prevalence of thyroid nodules, and the frequency of multiple nodules are higher in severely obese individuals.[15] It was found in the present study that there is an increased general frequency

of parenchymal hypoechogenicity, thyroiditis, and nodules; and the prevalence of nodules was 63.9% in severely obese cases. Fine needle aspiration biopsy was performed for 68.0% of these nodules. The prevalence of TC was 1.2% in morbidly obese cases, and extrathyroidal metastases were 28.5%. In previous studies, it was shown that the presence of lymph node metastasis is 30-50% in thyroid cancers at the time of diagnosis.[16-17]

Obesity is strongly associated with increased risk in many cancer types.[18] Increased prevalence of obesity is a serious health problem increasing the risk of various chronic diseases, including cancer.[19] It is estimated that approximately 20% of all cancer cases are caused by overweight. There are many prospective epidemiological studies which show that there is a direct relation between overweight and cancer.[20] TC was detected to be most common before bariatric surgery in previous studies.[21,22] Greater Body Mass Index was positively correlated with nodular thyroid disease in observational studies.

In the present study, it was found that the most common cancer was thyroid papillary cancer, and follicular, medullary, and anaplastic cancer were detected less frequently. Large case-control studies and meta-analyses showed that there are relations between Body Mass Indices and thyroid cancer risk in men and women.[23,24] There are also studies which show that obesity is associated with more aggressive features in thyroid cancers such as extrathyroidal spread and more advanced tumor stage.[25,26] More aggressive features of thyroid cancers were not detected in the present study.

Obesity and hyperinsulinemia are related closely with each other. Insulin increases hepatic insulin-like growth factor-1 (IGF-1) production. Serum IGF-1 levels are associated with increased cancer risk, including thyroid, prostate, colon, endometrium, and breast, with evidence that serum IGF-1 levels play critical roles in tumor progression and metastasis.[24] Obesity tends to have higher Thyroid Stimulating Hormone (TSH) levels, which may be an independent risk factor for thyroid cancer.[27-30] Again, as a disease strongly associated with obesity, Type 2 Diabetes Mellitus is also defined as a risk factor for increased TSH levels and thyroid cancer.[31-32]

The increased incidence of thyroid cancers stems from the increased diagnosis of differentiated thyroid cancers, particularly papillary thyroid cancers. The incidence rates of follicular, anaplastic, and medullary thyroid cancers have been stable for the last three decades.[33,34] In the present study, thyroid cancers were found to increase more because of increased differentiated thyroid cancers, similar to non-obese cases. The greatest increase was detected in papillary cancer type. Also, the distribution of papillary cancer variants in the present study was the most common follicular variant, and classical variant, tall cell variant, and hurtle cell variant were detected less frequently. Similar to our study, papillary cancer variants or differentiation patterns were reported to be the most common classical variants and follicular variants previous in studies.[33] Here, it was shown that the distribution rates of papillary cancer variants were similar in obese and non-obese cases.

CONCLUSION

The prevalence of obesity and thyroid cancer has increased in recent years in parallel on a global scale. When the present study and available evidence were considered, the increased incidence in differentiated thyroid cancer appears to be pathogenically linked to the spread of obesity. Some of the influencing factors that may explain this association were identified previously. Fighting and preventing obesity can reduce obesity-related cancer prevalence.

Ethical Approval

The ethics committee of this study was obtained from Medicana International Samsun Hospital Clinical Research Ethics Committee (7154 decision no, 01.11.2021).

Peer-review

Externally and internally peer-reviewed.

Author Contributions

Concept: E.A., Z.E., H.E., Ö.K.O., Design: E.A., Z.E., H.E., K.G., F.G., Data Collection or Processing: E.A., Ö.K.O., Analysis or Interpretation: E.A., Z.E., H.E., Ö.K.O., Literature Search: E.A., Z.E., H.E., Ö.K.O., Writing: E.A., Z.E., H.E., Ö.K.O.

Conflict of interest

The authors declare that they have no confict of interest.

Funding

This study received no financial support.

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DOI:10.34084/bshr.1313826 e-ISSN 2587-1641

Journal of Biotechnology and Strategic Health Research

Araştırma Makalesi /Research Article

http://dergipark.org.tr/tr/pub/bshr

Evaluation of RT-PCR Cycle Threshold Values of SARS-CoV-2 and Epidemiological Datas of COVID-19 Patients

SARS-CoV-2'nin RT-PCR Döngüsü Eşik Değerlerinin ve COVID-19 Hastalarının Epidemiyolojik Verilerinin Değerlendirilmesi

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Geliş Tarihi / Received : 03-07-2023 **Kabul Tarihi / Accepted:** 17-07-2023 **Yayın Tarihi / Online Published:** 30-08-2023

Tanriverdi-Cayci Y., Karacan G., Atilla A., Yasayancan O., Gur-Vural D., Bilgin K., Erdeniz H.E., Birinci A. Evaluation of RT-PCR cycle threshold values of SARS-CoV-2 and epidemiological datas of COVID-19 patients.
J Biotechnol and Strategic Health Res. 2023;7(2):127-133

Abstract

Aim COVID-19 infection is diagnosed by RT-PCR. In the RT-PCR test, results are interpreted according to the cycle threshold (Ct) values, provide indirect measurements of viral load. In this study we aimed to evaluate the relationship between Ct values and demographics datas and sypmtoms of patients.

Material and Method The nasopharyngeal swab of the patients suspectedof COVID-19 were collected and tested by RT-PCR for SARS-CoV-2. Demographics, medical history, timelines for exposure and symptoms of the patients diagnosed as COVID-19 by RT-PCR were obtained from the hospital information system.

Results Total of 619 patient result was enrolled in the study. Ct values were determined as 24.74 (20.95-27.64) for 18> years-old and 22.85 (20.14-26.22) ≥18 years-old, there was no statistically difference according to the age among Ct values. Hypertension was the most common comorbid disease (13.3%) among COVID-19 patients. A positive correlation was detected among the onset of the symptoms and Ct values, Ct values were lowest (corresponding to a higher viral RNA concentration) soon after symptom onset. Patients who had fever, headache, muscle-joint pain significantly had lower Ct values were than patients who did not have these sypmtoms.

Conclusion As a result it was detected that Ct values were lower soon after the occurence of the symptoms. It is important to early testing for SARS-CoV-2 among persons who have respiratory symptoms, and isolation of them when their viral load and transmission rate is higher.

Keywords COVID-19, cycle treshold value, epidemiology, SARS-CoV-2.

Özet

Amaç *COVID-19 enfeksiyonu, RT-PCR ile teşhis edilmektedir. Döngü eşiği (Ct) değerlerine göre yorumlanan RT-PCR testi sonuçları viral yükün indirekt ölçümlerini sağlar. Bu çalışmada hastaların demografik özellikleri ve semptomları ile Ct değerleri arasındaki ilişkiyi değerlendirmeyi amaçladık.*

Gereç ve Yöntem *COVID-19 şüphesi olan hastaların nazofaringeal sürüntüleri toplandı ve SARS-CoV-2 için RT-PCR ile test edildi. RT-PCR ile COVID-19 tanısı alan hastaların demografik bilgileri, tıbbi öyküleri, maruziyet zaman çizelgeleri ve semptomları hastane bilgi sisteminden elde edildi.*

Bulgular *Toplam 619 hasta sonucu çalışmaya dahil edildi. Ct değerleri 18> yaş için 24,74 (20,95-27,64) ve 22,85 (20,14-26,22) ≥18 yaş olarak belirlendi, Ct değerleri arasında yaşa göre istatistiksel olarak fark yoktu. Hipertansiyon, COVID-19 hastalarında en sık görülen yandaş hastalık (%13,3) oldu. Semptomların başlangıcı ile Ct değerleri arasında pozitif bir korelasyon saptandı, Ct değerleri semptom başlangıcından hemen sonra en düşüktü (daha yüksek bir viral RNA konsantrasyonuna karşılık gelir). Ateş, baş ağrısı, kas-eklem ağrısı olan hastalarda Ct değerleri, bu semptomları olmayan hastalara göre anlamlı olarak daha düşüktü.*

Sonuç *Sonuç olarak semptomların ortaya çıkmasından kısa bir süre sonra Ct değerlerinin daha düşük olduğu tespit edildi. Solunum yolu semptomları olan kişilerde SARS-CoV-2 için erken test yapılması, viral yük ve bulaşma hızlarının yüksek olduğu zamanlarda izole edilmesi önemlidir.*

Anahtar Kelimeler *COVID-19, döngü eşik değeri, epidemiyoloji, SARS-CoV-2.*

INTRODUCTION

Coronaviruses cause disease in humans and animals. Four (human coronaviruses 229E, NL63, OC43 and HKU1) coronaviruses typically infect only the upper respiratory tract and cause mild infections.[1]

World Health Organization (WHO) declared COVID-19 infection caused by SARS-CoV-2virus as a pandemic on March 2020. SARS-COV-2 is a beta coronavirus that is closely related to SARS-CoV.[2,3] There were more than 767 million confirmed COVID-19 cases in the whole world, and more than 6 million people had died by July, 2023.[4]

The diagnosis of COVID-19 in both symptomatic patients and asympyomatic suspected individuals is most frequently based on the detection of SARS-CoV-2RNA from respiratory tract specimens. The standard molecular method for COVID-19 diagnosis is via real-time reverse transcription polymerase chain reaction (RT-PCR).[5] Several studies have compared the performance of available RT-PCR tests using a split specimen approach and report 96% to 100% positive agreement (proxy for sensitivity) based on consensus test results.[6,7] Lower sensitivity of 75% to 90% has been reported for a rapid point-of-care (POC) molecular test when compared to laboratory-based RT-PCR assays.[8-11]

Real-time RT-PCR cycle threshold (Ct) values represent the number of amplification cycles required for the target gene to exceed a threshold level. Ct values are related to viral load and can provide an indirect method of quantifying the copy number of viral RNA in the sample.[6] The relationship between viral load and Ct is inversely proportional. In a clinical setting, the results of SARS-CoV-2RT-PCR tests are usually reported qualitatively as a binary positive or negative result using a specified cut-off, either based on Ct or integrated by an automatic algorithm interpreting different parameters of the potential amplification.[7]

Qualitative RT-PCR tests do not measure the viral load within a sample, but Ct values offer a semi-quantitative assessment of viral RNA load as lower Ct values correspond to higher viral RNA concentrations. Ct values can be effected from some factors including reaction conditions and amplification efficiency. But it is known that an increase of 3.3 units in Ct value corresponds to 10-fold less target RNA under optimum conditions.[8] Ct values can use as an indirect indicator of relative viral load in diagnostic samples of persons tested for Sars-Cov-2.[9]

In this study we aimed to determine the relationships between Ct values and onset of symptoms, demographic factors, and symptoms among laboratory-confirmed COVID-19 cases.

MATERIAL and METHOD

Individuals in this study were patients who admitted to Ondokuz Mayis University Hospital Respiratory Infection outpatient clinic between October 2020 and November 2020 and tested positive for SARS-CoV-2 on a nasopharyngeal (NP) swab. Some questions on demographics, medical history, timelines for assesment of exposure were asked to the patients. Symptom assessments were conducted by physicians at the time of specimen collection.

NP specimens were collected by physicians. For participants who tested positive more than once during the investigation period, Ct values from only the first positive test were included. All specimens were tested at the Ondokuz Mayıs University Hospital Microbiology COVID-19 Laboratory using the Bio-speedy® SARS CoV-2 Double Gene RT-qPCR (Bioeksen, Turkey). This assay amplifies and detects two targets (ORF1ab and N) of the virus with a limit of detection 200 genome per mL. Vnat tubes were used for extraction. The human housekeeping gene target RNAse P (RP) was measured in each sample for use in normalization. Bio-rad CFX96 was used for amplification

Results were considered positive if signal was detected (Ct<38) for RP, ORF1ab and N genes. Ct values for am-

plification of both viral targets ORF1ab and N genes were analyzed.

The presence of symptoms at the time of sampling of NP swab were asked to the patients and recorded. The asked symptoms were; fever, cough, headache, loss of smell and taste, runny nose, shortness of breath, muscle-joint pain, weakness, diarrhea, and any other symptoms (chest pain, vomiting, sore throat, back pain). The presence of comorbid conditions, story of house-hold contacts, story of travel to abroad or contact with individual who came from abroad and whether he/she can be a health-care worker were also questioned. The hospitalization status of the patients were controlled by the hospital information system. The study was a retrospective study, patient consent was not taken.

Ethical approvel was taken from Ondokuz Mayıs University Medical Faculty Clinical Ethic Committe (B.30.2.ODM.0.20.08).

The study was conducted in accordance with the Declaration of Helsinki and followed the ethical standards of the country of origin.

Statistical analysis

The compliance of the variables to normal distribution was examined by Kolmogorov-Smirnov/Shapiro-Wilk tests. The median and interquartile range were used for descriptive analysis. Variables and Ct values were compared using the Man-Whitney U test. The relationship between symptom onset time and Ct values was calculated using the Spearman test. Statistical tests for which $p<0.05$ were reported as statistically significant.

RESULTS

A total of 619 patients who tested positive for SARS-CoV-2 were included in this analysis. A majority of those with a positive for SARS-CoV-2 were male (52.4%). The median age was 41.56±17.38. Ct values ranged from 13.98 to 36.63 (median, 31.16). Ct values were determined as 24.74 (20.95-27.64) for 18> years-old and 22.85 (20.14-26.22) ≥18 years-old.

The most common symptom among the patients were weakness (65.8%) and followed by muscle-joint pain (59.9%) and cough (51.5%) (Table 1).

Table 1. Distribution of symptoms of COVID-19 patients.

	n (%)
Weakness	407 (65.8)
Muscle-joint pain	371 (59.9)
Cough	319 (51.5)
Fever	205 (33.1)
Runny nose	189 (30.5)
Headache	303 (48.9)
Loss of smell and taste	189 (23.9)
Diarrhae	100 (16.2)
Shortness of breath	92 (14.9)

The 12% of the positive patients were healthcare workers. And 46.5% of the patients were mentioned that they had a contact with SARS-CoV-2 positive person. The 16.3% of the patient needed hospitalization during the infection.

Total of 220 (35.5%) patients comorbid diseases at the time of sample collection. Hypertension was the most common comorbid disease (13.3%) (Table 2).

Table 2. Comorbid diseases/status of the patients.

Comorbid diseases	n (%)
Hypertension	82 (13.3)
Diabetes Mellitus	60 (9.7)
Asthma	20 (3.2)
Hyperthyrodism	9 (1.5)
Hashimoto's thyroiditis	6 (1.0)
Allergic rhinitis	6 (1.0)
Organ transplantation	5 (0.8)
Chronic renal deficiency	4 (0.6)
Pregnancy	1 (0.2)
Total	187 (30.2)

The relationship between Ct values and the age was evaluated in two groups as patients under 18 years of age and above, and no significant difference was detected.

A positive correlation was detected among the onset of the symptoms and Ct values, it was observed that the Ct value increased as the number of symptom days increased. (spearman correlation test, p<0.001).

Patients who had fever significantly had lower Ct values than patients who did not have (median Ct values of 22.39 and 23.11, respectively; p=0.007). Similarly, Ct values were significantly lower among those reporting headache compared to those with no headache (median Ct values of 22.54 and 23.21, respectively; p=0.003). Additionally, median Ct values were lower among patients had muscle-joint pain compared to patients who did not have. However, median Ct values of patients who mentioned that had loss of smell and taste higher among than who did not report that symptoms (median Ct values 24.17 and 22.70, respectively; p=0.031). No statistically differences seen in median Ct values among the symptoms of cough, runny nose, shortness of breath, weakness and diarrhae who had these symptoms or not. There was no signficant difference for Ct values of being healthcare-worker or not and hospitalization or not (Table 3).

Table 3. Statistically significant associations between cycle threshold value and symptoms.

	Ct values of patients meeting symptom/status	Ct values of patients not meeting symptom/status	p
Fever	22.39 (19.63-25.47)	23.11 (20.33-26.91)	0.007
Cough	22.87 (20.04-26.40)	22.96 (20.30-26.29)	0.493
Headache	22.54 (19.73-25.53)	23.21 (20.37-27.26)	0.003
Loss of smell and taste	24.17 (21.22-26.87)	22.70 (19.97-26.12)	0.031
Runny nose	22.05 (20.14-25.42)	23.18 (20.18-26.74)	0.059
Shortness of breath	22.82 (20.04-26.49)	22.89 (20.22-26.23)	0.894
Muscle-joint pain	22.51 (20.04-25.57)	24.11 (20.69-27.61)	0.001
Weakness	22.87 (20.25-26.10)	22.90 (19.91-27.15)	0.646
Diarrhae	23.14 (20.66-26.72)	22.85 (20.11-26.22)	0.623
Health-care worker	24.24 (20.78-27.36)	22.81 (20.04-26.19)	0.059
Hospitalization	23.07 (19.75-27.32)	22.82 (20.21-26.12)	0.326

DISCUSSION

In this analysis, we examined associations between SARS-CoV-2 RT-PCR Ct values and epidemiological charecteristics of patients with confirmed COVID-19.

The age and Ct value correlation investigated in some studies. Singanayagam et al.[10] reported that there was no significant difference in Ct values (p = 0.12) across the different age groups. And Buchan et al.[11] also reported that SARS-CoV-2 RT-PCR Ct values are similar among different age groups, suggesting equivalent test performance irrespective of patient age. However in the study of Sargent et al.[12], young children (<5 years-old) had significantly lower median (interquartile range) Ct values (6.5 [4.8-12.0]), indicating that young children have equivalent or more viral nucleic acid in their upper respiratory tract compared with older children (5-17 years–old) and adults. In our study, there was no significant difference in Ct values of children (<18 years-old) and adults.

The viral load and onset of the symptoms takes interest. Presence of virus in the pharynx was found very high during the first week of symptoms.[13] And Ct values were reported significantly correlated with the symptom onset.[9] We found a positive correlation between the onset of the symptoms and Ct values, as the onset of the symptoms increases, increase in the Ct values was seen. While Ct values are not direct quantitation of viral load, these results suggest that viral RNA levels in the pharynx are highest soon after symptom onset.

Fever was found common symptom among SARS-CoV-2 positive individuals.[14,15] In a study the most common symptom among SARS-CoV-2 positive healthcare-workers was fever (55.4%).[16] In USA a web-based self survey among the COVID-19 patients indicated that cough and muscle pain were the most common symptoms at the day of testing.[17] In a meta analysis by Struff et al.[18] the diagnostic accuracy of signs and symptoms to determine if a person presenting in primary care or to hospital outpatient settings was investigated. They found data on 84 signs and symptoms and reported that most of the symptoms had very low sensitivity and high specificity, only cough (25 studies) and fever (7 studies) had a pooled sensitivity of at least 50% but specificities were moderate to low. In a study conducted in UK, in the 71.5% of the SARS-CoV-2 positive patients, cough and fever were the most common symptoms.[19] However in our study, most common symptom was weakness, followed by muscle-joint pain and cough. The most prevelant comorbidity were hypertension and diabetes mellitus, same as our study.[15,20]

The number of studies that investigated the relationship between symptoms/epidemiological data and Ct value is limited. In some studies they reported that there was no significant relationship between Ct value (viral load) and demographics, symptom status and comorbidities.[21-24] However, in an analysis, the viral load in the respiratory samples of the patients was higher during the initial stage of the disease and higher loads in patients with severe disease was seen.[14] In a study, data suggest that lower Ct values may be associated with worse outcomes and that Ct values may be useful in predicting the clinical course and prognosis of patients with COVID-19.[7] Salvatore et al.[9] reported that Ct values were significantly lower in patients who had respiratory symptoms and Ct values among participants reporting different symptoms did not vary by age group. In a study by Soeroto et al.[25] the association between the severity of the COVID-19 disease and Ct values was investigated and they stated that there was no significant difference in RT-PCR Ct value among mild, moderate, severe and critical groups measured in the second week of illness.[25]

Kurzeder et al.[26] developed a simple scoring system based on data available shortly after hospital admission including the Ct value had a high predictive value for death and they mentioned that the score may also be useful to estimate the likelihood for required.[26] In our study, we found that Ct values changed among the symptoms, significant

differences was determined for some symptoms like fever, headache, anosmia/ageusia, muscle-joint pain. Ct values were significantly correlated with onset of the symptoms. Age was not found related with the Ct values.

Our study has some limitations. This study is a single centre study, and investigate the SARS-CoV-2 PCR results of patients who admitted to COVID-19 outpatient clinic. And viral load can be effected by various factors. We mainly focused on symptoms and demographics of the patients and their correlation of Ct values.

It is imported to access to SARS-CoV-2 tests immediately for individuals who have respiratory symptoms or have high-risk exposure. And identifying such individuals when Ct values are lowest and degree of infectiousness is high, and isolation of them to prevent transmission.

Ethical Approval

Ethical approvel was taken from Ondokuz Mayıs University Medical Faculty Clinical Ethic Committe (B.30.2.ODM.0.20.08).

Declaration of Helsinki

The study was conducted in accordance with the Declaration of Helsinki and followed the ethical standards of the country of origin (B.30.2.ODM.0.20.08).

Peer-review

Externally and internally peer-reviewed.

Authorship Contributions

Concept: Y.T.Ç., Design: Y.T.Ç., A.A., Data collection: Y.T.Ç., A.A, G.K., E.H.E., Analysis or interpretation: Y.T.Ç., O.Y., D.G.V., A.B. Liretarure search: Y.T.Ç., K.B. Writing: Y.T.Ç

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding

This this study received no financial support.

Informed consent

Retrospective study.

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DOI:10.34084/bshr.1324716 e-ISSN 2587-1641

Journal of Biotechnology and Strategic Health Research

Araştırma Makalesi /Research Article

http://dergipark.org.tr/tr/pub/bshr

Comparison of the Effect of Secondary Hyperparathyroidism Due to Vitamin D Deficiency on Bone with The Healthy Control Group

D Vitamini Eksikliğine Bağlı Sekonder Hiperparatiroidizmin Kemik Üzerindeki Etkisinin Sağlıklı Kontrol Grubu ile Karşılaştırılması

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Geliş Tarihi / Received : 09-07-2023 **Kabul Tarihi / Accepted:** 26-07-2023 **Yayın Tarihi / Online Published:** 30-08-2023

Demir H., Cihan C., Gönüllü E., Çapoğlu R., Yiğit M., Aka B.U., Harmantepe A.T. Comparison of the effect of secondary hyperparathyroidism due to vitamin D deficiency on bone with the healthy control group.
J Biotechnol and Strategic Health Res. 2023;7(2):134-140

Abstract

Aim In healthy individuals, to demonstrate that adequate vitamin D status protects against osteoporosis by improving bone mineral density and reducing the risk of fractures.

Material and Method Fifty patients with high parathyroid hormone secondary to low vitamin D level and 50 patients with normal parathyroid hormones were included in the study as the control group.

Results Of the 50 patients with secondary hyperparathyroidism due to vitamin D deficiency included in the study, 45 (90%) were female and 5 (10%) were male. In the control group with normal parathyroid hormone, 44 (88%) were female and 6% (12%) were male. The median age in the hyperparathyroid group was 70.5 (66-73) and in the parathyroid hormone normal group it was 71 (69-73). This median mean age was significant (p=0.004).
In the group with secondary hyperparathyroidism; The median PTH value was 99.5 (66-205.9) and 49.8 (27-61.5) in the control group, with a significant difference (p<0.001). While 25-Hydroxy Vitamin D level was 10.73 (4.64-34.1) in the group with normal parathyroid hormone level, it was 18.63 (6.21-65.1). This created a significant difference in both groups (p<0.001). According to the results of bone densitometry in the hyperparathyroidic and control groups. no significant difference was found between bone mineral density (BMD). 0.92 (0.66-1134), 0.93 (0.75 – 1293), (p=0.095).
However, for the femur, the results in T and Z scores were significant (p=0.027- p=0.027), whereas for the supine (spine), no significant difference was observed between the T and Z scores (p=0.358- p=0.265).

Conclusion Especially when the vitamin D level falls below 10 ng/mL, PTH begins to respond. Beyond these observations, a normal serum 25 (OH) D concentration is particularly important in preventing femur fractures, but its significance for vertebral fractures is unclear.

Keywords Osteoporosis, secondary hyperparathyroidism, vitamin D

Özet

Amaç *Sağlıklı bireylerde yeterli D vitamini durumunun, kemik mineral yoğunluğunu iyileştirerek ve kırık riskini azaltarak, osteoporoza karşı koruduğunu göstermektir.*

Gereç ve Yöntem *D vitamin seviyesi düşüklüğüne sekonder, paratiroid hormonu yüksek 50 hasta ile paratiroid hormonları normal olan, 50 hasta kontrol grubu olarak çalışmaya dahil edildi.*

Bulgular *Çalışmaya dahil edilen D vitamin eksikliğine bağlı sekonder hiperparatiroidizmli 50 hastanın,45'i (%90) kadın, 5'i (%10) erkekti. Paratiroid hormonu normal olan kontrol grubunda ise, 44'ü (%88) kadın, 6'sı (%12) erkekti Hiperparatiroidik grupta median yaş ortalaması 70,5 (66-73), paratiroid hormonu normal grupta ise 71 (69-73) idi. Bu median yaş ortalaması anlamlıydı (p=0,004).*
Sekonder hiperparatirodizmli grupta; PTH median değeri 99,5 (66-205,9), kontrol grubunda ise 49,8 (27-61,5) olup anlamlı fark gözlendi (p<0,001). 25-Hydroxy Vitamin D seviyesi 10,73 (4,64-34,1) iken, paratiroid hormon seviyesi normal olan grupta 18,63 (6,21-65,1) idi. Bu da her iki grupta anlamlı fark oluşturdu (p<0,001). Hiperparatiroidik ve kontrol grubunda çekilen kemik dansitometresi sonuçlarına göre. kemik mineral yoğunluğu (BMD) arasında anlamlı fark saptanmadı. 0,92 (0,66-1134), 0,93 (0,75-1293), (p=0,095).
Buna rağmen femur için, T ve Z scorlarındaki sonuç anlamlı iken (p=0,027- p=0,027), supin (omurga) için T ve Z scorları arasında anlamlı fark gözlenmedi (p=0,358- p=0,265).

Sonuç *Özellikle D vitamin seviyesi 10 ng/mLnin altına indiğinde PTH cevap vermeye başlamaktadır. Bu gözlemlerin ötesinde, serum 25 (OH) D konsantrasyonunun normal seviyede olması özellikle femur kırıklarından korumada önemli iken, vertebra kırıkları için önemi belirsizdir.*

Anahtar Kelimeler *Osteoporoz, sekonder hiperparatiroidizm, D vitamini*

INTRODUCTION

Little is known about the relationship between vitamin D deficiency and skeletal structure in patients with primary and secondary hyperparathyroidism (SHPT). Although there is evidence of changes in bone structure in the Asian population where 25-hydroxyvitamin D [25 (OH) D] deficiency is common, detailed studies are needed.

Osteomalacia occurs when combined with low dietary calcium and vitamin D levels. Maximum bone structure and strength; It is obtained by taking sufficient calcium in the diet, along with normal vitamin D levels. The biological activity of each of the bone major cell types (osteoblasts, osteoclasts and osteocytes) is compatible with adequate circulating 25-OH vitamin D levels.[1]

Available data suggest that vitamin D deficiency contributes to the etiology of at least two metabolic bone diseases, osteomalacia and osteoporosis. Numerous clinical data show that an adequate vitamin D status, represented by serum 25-hydroxyvitamin D concentration, protects against osteoporosis by improving bone mineral density and reducing the risk of fracture.[2]

As reported in meta-analyses on vitamin D, baseline 25-hydroxyvitamin D has no effect on bone density or fracture risk when >40 nmol/L.[3,4]

Parathyroid hormone (PTH) concentrations and vitamin D are routinely measured in the diagnosis and treatment of bone and kidney diseases. However, in healthy individuals whose vitamin D deficiency has not been evaluated, the median PTH values depending on vitamin D levels vary.[5]
In the department of breast-endorine surgery; In some patients who applied to the outpatient clinic with complaints of weakness, fatigue and bone pain, it has been drawing our attention for many years that the high level of parathyroid hormone is related to vitamin D deficiency. The effects on bone structure were investigated by comparing this patient group with the control group with normal parathyroid hormone. For this, help was received from the Physiotherapy and Rehabilitation department.

The aim of this study; It is the comparison of T and Z scores measured by bone densitometry in cases with SHPT due to vitamin D deficiency with a healthy control group with normal parathyroid hormone level and no disease.

MATERIAL and METHOD

After the approval of Sakarya University Ethics Committee, patients who developed secondary hyperparathyroidism due to vitamin D deficiency between January 2018 and July 2022 were retrospectively analyzed. Fifty patients with high parathyroid hormone secondary to low vitamin D levels and 50 healthy individuals with normal parathyroid hormones were included in the study as the control group. Vitamin D levels in the control group were not required to be in the normal range.

Study groups were randomly selected from among patients. At the same time, calcium (Ca) values of each patient in the study and control groups, T and Z scores and Bone Mineral Density (BMD) were compared in bone densitometry, femur and supine positions.

Vitamin D level; Values >40 ng/mL (>100 nmol/L) were considered normal. Values with a vitamin D level between 20 and 40 ng/mL (50-100 nmol/L) indicate the onset of vitamin D deficiency. Vitamin D deficiency was considered when the concentration was between 10–20 ng/mL (25–50 nmol/L) and values less than 10 ng/mL (<25 nmol/L).

In the study, the lower and upper limits of hospital laboratory normal values were considered as 8.8-10.6 mg/dL for Calcium (Ca), and 15-65 pg/mL for PTH. In bone densitometry; Those with a T femur score >-1.0 are considered normal. A T score between -1.0/-2.5 indicates osteopenia, and those below -2.5 indicate osteoporosis. The Z score, on the other hand, is compared to normal people of the same age, sex, weight and race as the individual. If it is above

-2.0, it means that it is in the expected range for age, and below -2.0 indicates that it is below the expected range for age. Bone Mineral Density (BMD); It determines the quantitative ratio of the mineral part such as calcium and phosphorus in the bone structure.

In the study; According to the laboratory results of the patients who applied to the outpatient clinic with complaints of weakness, fatigue and bone pain, individuals who were definitely known to have high parathyroid hormone levels due to vitamin D deficiency and who did not have any kidney, liver and bone disease were included. Those with a diagnosed disease were excluded from the study.

Statistical Analysis

Descriptive analyses were performed to provide information on the general characteristics of the study population. Kolmogorov-Smirnov test was used to evaluate whether the distributions of numerical variables were normal. Accordingly, the independent sample t-test or the Mann-Whitney U tests were used to compare the numeric variables between groups. The numeric variables were presented as mean ± standard deviation or median [minumum - maximum]. Categorical variables were compared by the Chi-Square test. Categorical variables were presented as a count and percentage. A p-value <0.05 was considered significant. Analyses were performed using SPSS statistical software (IBM SPSS Statistics, Version 23.0. Armonk, NY: IBM Corp.)

RESULTS

Of the 50 patients with secondary hyperparathyroidism due to vitamin D deficiency included in the study, 45 (90%) were female and 5 (10%) were male. In the control group with normal parathyroid hormone, 44 (88%) were female and 6% (12%) were male (Figure 1).

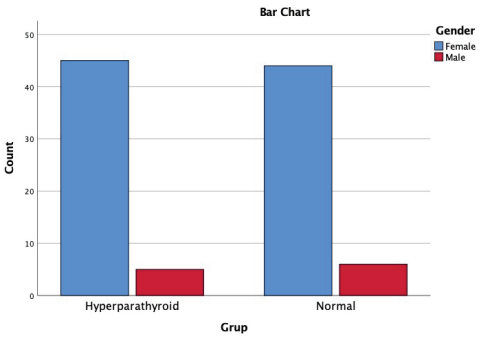

Figure 1. Demographic ratios of the hyperparathyroid group and the normal group

There was no significant difference between the two groups in terms of gender (p=0.749). The median mean age was 70.5 (66-73) in the hyperparathyroidic group and 71 (69-73) in the parathyroid hormone-normal group. This median mean age was significant (p= 0.004) (Table1).

Table 1. The relationship between sex and average age.

		Hyperparathyroid	Normal	p value
Gender	Male	5 (10%)	6 (12%)	0.749*
	Female	45 (90%)	44 (88%)	
Age		70.5 (66-73)	71 (69-73)	0.004**

* Chi-Square test, ** Mann Whitney-U test

In the group with secondary hyperparathyroidism; The median PTH value was 99.5 (66-205.9) and 49.8 (27-61.5) in the control group, with a significant difference (p<0.001). While 25-Hydroxy Vitamin D level was 10.73 (4.64-34.1) in the group with normal parathyroid hormone level, it was 18.63 (6.21-65.1). This created a significant difference in both groups (p<0.001).
Calcium level was 9.42∓0.42 in the secondary hyperparathyroidism group and 9.6∓0.41 in the normal group and was significant (p=0.007).

According to the results of bone densitometry in the hyperparathyroidic and control groups. no significant difference was found between bone mineral density (BMD). 0.92 (0.66-134), 0.93 (0.75-1293), (p=0.095).

However, for the femur, the results in T and Z scores were significant (p=0.027- p=0.027), while for the supine (spine), no significant difference was observed between the T and Z scores (p=0.358- p=0.265) (Table 2).

Table: 2 The relationship between PTH, Ca,25(OH)D and bone densitometry values of hyperparathyroid and normal groups.

	Hyperparathyroid	Normal	p value
PTH Value	99.5 (66.0 – 205.9)	49.8 (27.0 – 61.5)	<0.001*
25-Hydroxy Vitamin D	10.73 (4.64-34.1)	18.63 (6.21-65.1)	<0.001*
Calcium	9.42∓0.42	9.6∓0.41	0.007**
BMD	0.92 (0.66 – 1134)	0.93 (0.75 – 1293)	0.095*
T score femur	-0.94∓0.86	-0.52∓0.87	0.027**
T score supin	-2.0 (-3.3 – 1.40)	-1.65 (-4.1 – 3.2)	0.358*
Z score F	0.09∓ 0.89	0.52∓0.90	0.027**
Z score S	-0.1 (-1.4 – 3.40)	0.25 (-2.1 – 5.2)	0.265*
* Mann Whitney-U test, ** Independent samples t-test			

DISCUSSION

Maximum bone structure and strength depends on adequate vitamin D and a positive calcium balance. This is consistent with the 25 hydroxy vitamin D level. Osteoblasts; They have the ability to metabolize 25 hydroxy vitamin D [25-OH D] to 1.25 hydroxy vitamin D [1.25 (OH)2 D] to increase bone mineralization by osteocytes, as well as reduce bone resorption by osteoclasts. Numerous clinical data show that serum 25 (OH) vitamin D status protects against osteoporosis by improving bone mineral density and reducing the risk of fractures. Interestingly, adequate serum 1.25 (OH) 2D concentrations do not reduce the risk of fracture.[2]

In this study; In the group with low vitamin D, the significance of T and Z scores in the femur scan was not seen in the supine position. Therefore, we can say that the fracture risk for the "femur" increases relatively. However, it is difficult to explain the lack of difference for "supin".

There is no clear consensus when it comes to diagnosing vitamin D deficiency and determining exactly what level it is. Traditionally, vitamin D values below 5-7 ng/mL cause osteomalacia, values below 10–12 ng/mL lead to secondary hyperparathyroidism and osteoporosis, and levels above 18–20 ng/mL are considered normal.[6]

In our study, we observed that 25-OH vitamin D levels were below 7 ng/mL in most of the individuals with increased PTH levels, consistent with the literature.

The prevalence of vitamin D deficiency in the European elderly population was 36% of men and 47% of women. Surprisingly, most southern countries showed the lowest levels.[7]

In this study, vitamin D deficiency was observed in approximately 88-90% female and 10-12% male individuals, although the patient group was a very small series, mostly elderly. These percentages will likely vary in populations of all age groups and in large case series.

According to the balance between PTH and 25-hydroxyvitamin D obtained from different studies, the 25-hydroxyvitamin D concentration required for elderly people to have a normal PTH level should be 40 ng/mL.[8,9]

In clinical studies, vitamin D supplementation did not improve bone density, except in groups with 25-OH D <30 nmol/L. Vitamin D and calcium have different biological functions, so the need for supplementation, safety, and efficacy must be evaluated for each individually.

Meta-analyses of the effect of vitamin D supplements on bone density show no clinically relevant benefit.[10,11] However, two recent studies have shown that individuals with late winter 25-OH D levels <30 nmol/L have sustained bone loss of 1% per year when treated with placebo, and this loss is prevented by vitamin D.[12,13] However, when 25-hydroxyvitamin D >30 nmol/L, supplementation is ineffective.

A meta-analysis of studies supplementing with vitamin D alone found no effect on total fracture risk and hip fracture.[3,14]

Kanno et al.[15] reported that low vitamin D levels are more determinant in femur fractures than vertebral fractures. They emphasized that the secondary parathyroid hormone elevation was more common in those with vertebral fractures.

Although the statistical difference between T and Z scores in the "supin" and "femur" fractions was significant in our study, it is obvious that long-term vitamin D deficiency will lead to osteoporosis in some individuals. It would be pointless to generalize this situation to the entire population.

Vitamin D deficiency (25-hydroxyvitamin D <25 nmol/L) accelerates bone loss and may result in osteomalacia. Therefore, people with clinical risk factors for vitamin D deficiency (e.g. minimal sunlight exposure such as frail elderly and veiled, dark-skinned people living at high latitudes) should receive vitamin D replacement. Typically calciferol 400-1000 IU/day, but administration of supplements at weekly or monthly intervals may also be safe, effective and more convenient for patients.[16]

Vitamin D supplements appear to increase muscle strength (more so in individuals with baseline 25-hydroxyvitamin D levels <30 nmol/L), but not muscle strength or mass.[17]

In our study, serious improvements were detected with depot and intermittent daily treatments, especially in individuals with complaints of weakness and fatigue.

Sayed-Hassan et al.[18] reported that they could not find a significant relationship between 25-OH D and bone mineral density in the hip or lumbar spine.

In our study, no significant relationship was found in the secondary hyperparathyroidism patients and the control group.

CONCLUSION

The results of the findings were inconsistent when PTH and vitamin D were compared alone or in combination with calcium. Especially when the vitamin D level falls below 7 ng/mL, PTH begins to respond. Beyond these observations, a serum 25(OH)D concentration at a normal level is particularly important in protecting against femoral fractures, but its significance for vertebral fractures is unclear. Based on the available evidence regarding vitamin D supplementation, calcium intake, or a combination of both nutrients, it is difficult to make any concrete statements.

Acknowledgment

We thank Sakarya University Faculty of Medicine Department of Gastrointestinal Surgery, for their help in designing this study.

Ethical Approval

Sakarya University Faculty of Medicine Ethics Committee and following the Declaration of Helsinki (decision no: E-71522473-050.01.04-224500-59, date: 27.02.2023).

Peer-review

Externally and internally peer-reviewed.

Authorship Contributions

Concept: H.D., E.G., Design: H.D., C.C., R.Ç., Data Collection or Processing: B.U.A., A.T.H., Analysis or Interpretation: E.G., Literature Search: H.D., C.C., Writing: H.D, C.C.

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding

This study received no financial support.

Informed Consent

Retrospective study

Limitations of study

This study was conducted in a single center and with a small number of patients.

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DOI:10.34084/bshr.1006209 e-ISSN 2587-1641

Journal of Biotechnology and Strategic Health Research

Arastırma Makalesi /Research Article

http://dergipark.org.tr/tr/pub/bshr

Canlı Donörden Karaciğer Nakli Konusundaki Global Yayın Trendleri ve Türkiye Kaynaklı Yayınların Analizi

Global Trends of Publications on Live Donor Liver Transplant and Analysis of Publications From Turkey

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Geliş Tarihi / Received : 08-10-2021 **Kabul Tarihi / Accepted:** 11-11-2021 **Yayın Tarihi / Online Published:** 30-08-2023

Durgun C. Canlı Donörden Karaciğer Nakli Konusundaki Global Yayın Trendleri ve Türkiye Kaynaklı Yayınların Analizi, J Biotechnol and Strategic Health Res. 2023; 7(2):141-147

Öz

Amaç Son yıllarda karaciğer nakli konusunda bilimsel ilgi artmış olup, canlı donör karaciğer nakli de bu konunun bir alt grubudur. Canlı donör karaciğer nakli konusunda bilimsel üretkenliğin global değerlendirmesi ve Türkiye'den yapılmış yayınlar ile ilgili kıyaslamaların yapılması çalışmanın amacı idi.

Materyal ve Method Araştırmada bibliyometrik analiz yöntemi kullanıldı. Elsevier Scopus bibliyometrik veri tabanında, İngilizce dilinde anahtar kelimeler kullanılarak araştırma yapıldı. Başlık, özet ve anahtar kelimelerinde " living" ve donor " ve " transplant " ve " hepatic " veya " liver " anahtar kelimeleri içeren, 5 Ekim 2021 tarihine kadar sürede yapılmış yayınlara ulaşıldı.

Bulgulsar Çalışmamız konusunda yayınlanmış toplam 4714 yayına (%75,47'si araştırma makalesi) ulaşıldı. Yayın sayısının 2000'li yıllardan sonra hızlıca arttığı saptandı. Makalelerin çoğu İngilizce dilinde (%95,03) yazılmış olup, çoğunluğu (%28,78) Amerika Birleşik Devletleri kökenli kurumlardaki yazarlar tarafından üretilmişti. Japonya ve Güney Kore ilk üç sıradaki ülkeler iken; Türkiye ve Hindistan dördüncü sırayı birlikte paylaşmakta idi. Yayınların 4074'ü (%86,4) herhangi bir kurum tarafından desteklenmemişti. Yayınların 779'u (%16,5) hiç atıf almamıştı. En fazla atıf alan araştırmacılar İtalya'dan tek yayın ile Vincenzo Mazzaferro (1211 atıf) ve iki yayın ile Pakistan'dan Christopher Erich Broelsch (1140 atıf) idi. Türkiye'den 256 yayın vardı. En fazla yayın yapan kurumlar, Başkent Üniversitesi (n=83,%34,42) ve İnönü Üniversitesi (n=54,%21,09) idi. En fazla atıfı İtalya, Almanya ve Singapur'dan yapılan yayınların aldığı, ülkemizden olan atıf sayılarının göreceli düşük olduğu saptandı.

Sonuç Canlı donör karaciğer nakli konusundaki bilimsel faaliyetlerin desteklenmesi, Türkiye'den yapılan yayın sayılarının dördüncü sırada olmasına rağmen arttırılması gerekmektedir.

Anahtar kelimeler Canlı donör, karaciğer nakli, Türkiye, bibliyometrik analiz.

Abstract

Aim *Scientific interest in liver transplantation has increased in recent years, and living donor liver transplantation is a subgroup of this subject. The aim of this study was to make a global evaluation of scientific productivity on living donor liver transplantation and to make comparisons with publications from Turkey.*

Materials and Methods *The bibliometric analysis method was used in the study. The search was conducted in the Elsevier Scopus bibliometric database using English language keywords. The publications retrieved with the keywords "living" and donor and "transplant" and "hepatic" or "liver" in their title, abstract and keywords since October 5, 2021.*

Results *A total of 4714 publications (75,47% of research articles) published on our study were reached. It was determined that the number of publications increased rapidly after the 2000s. Most of the articles were written in English (95.03%) and the majority (28.78%) were produced by authors from institutions based in the United States. While Japan and South Korea are the top three countries; Turkey and India were sharing the 4th place together. 4074 (86.4%) of the publications were not funded by any institution. 779 (16.5%) of the publications were not cited at all. The most cited researchers were Vincenzo Mazzaferro (1211 citations) from Italy with a single publication and Christopher Erich Broelsch (1140 citations) from Pakistan with two publications. There were 256 publications from Turkey. The institutions that published the most were Başkent University (n=83, 34.42%) and İnönü University (n=54, 21.09%). The publications from Italy, Germany and Singapore received the most citations, and the number of citations from our country was relatively low.*

Conclusion *Scientific activities on living donor liver transplantation need to be supported and the number of publications from Turkey should be increased, although it is in the fourth place.*

Keywords *Living donor, liver transplant, Turkey, bibliometric analysis.*

GİRİŞ

Son yıllarda karaciğer nakli, dekompanse siroz, hepatoselüler karsinomun erken evresi ve akut karaciğer yetmezliği için kesin tedavinin son çaresi olmuştur.[1,2] Canlı donörden karaciğer nakli, karaciğer yetmezliğini gidermek için dünya çapında giderek artan sıklıkta yapılmaya başlayan bir tedavi yöntemidir. Ancak nakil yapılacak organ kısıtlılığı, kadavradan karaciğer naklinin önündeki en büyük engeldir.[2] Karaciğer nakli için mevcut vericilerin küresel sıkıntısı, alıcılar için olumlu tıbbi sonuçları olan canlı donör karaciğer nakli ile hafifletilebilir.[3]

İlk canlı donör karaciğer nakli (CDKN) vakasından bu yana, dünya çapında birçok merkez CDKN programını başlatmıştır.[2,3] Cerrahi yöntemler ve tıbbi tedavilerdeki iyileştirmelerin postoperatif morbiditeyi azaltmada olumlu bir etkisi olmasına rağmen, bu işlem sonrası biliyer komplikasyonların daha sık görülmesi ana dezavantaj olmaya devam etmektedir.[4] Bu hastaların nakil sonrası takipleri de oldukça önemlidir.[5]

İlk insan karaciğer nakli 1963 yılında yapılmış ancak sonuç alınamamıştır. Türkiye'de ilk kez kadavradan karaciğer nakli Haberal ve arkadaşları tarafından 1988 yılında gerçekleştirilmiştir.[6,7] Ancak Türkiye'den karaciğer nakli ile ilgili yayınların bilimsel çıktısı bilinmemektedir. Dünya Sağlık Örgütü'nün 2017 verilerine göre; 2019 yılı itibariyle dünyada 35.784, Türkiye'de 1.502 karaciğer nakli yapılmıştır.[8] Türkiye'de ilk kez canlı vericiden ilk segmental karaciğer nakli de yine Mehmet Haberal tarafından 1990 yılında gerçekleştirilmiştir.[6,7] Türkiye Cumhuriyeti verilerine göre 2020 yılında karaciğer nakli bekleyen 1715 hasta mevcuttur. Ülkemiz verilerine göre 46 farklı merkezde karaciğer nakli yapılabilmektedir.[9,10]

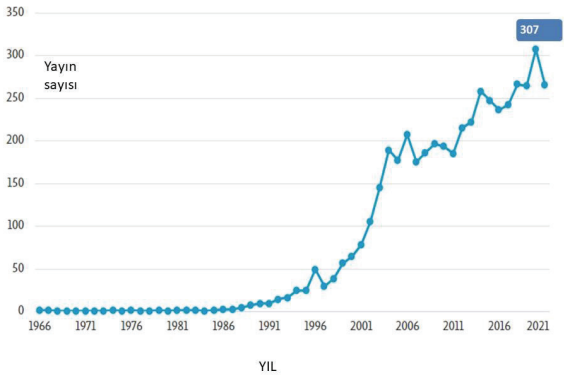
Son yıllarda giderek önem kazanan bir konu olan CDKN konusundaki bilimsel üretkenliğin global değerlendirmesi ve ülkemiz ile ilgili kıyaslamaların yapılması çalışmanın amacı idi.

GEREÇ ve YÖNTEM

Araştırmada önceki çalışmalarda kullanılan bibliyometrik analiz yöntemi kullanıldı.[11] Benzer çalışmada kullanılan yöntemle, Elsevier Scopus bibliyometrik veri tabanında, İngilizce dilinde anahtar kelimeler kullanılarak araştırma yapıldı.[11] Başlık, özet ve anahtar kelimelerinde " living" ve donor " ve " transplant " ve " hepatic " veya " liver " anahtar kelimeleri içeren, 5 Ekim 2021 tarihine kadar sürede yapılmış yayınlara ulaşıldı. Çalışmada bias yaratılmaması adına her gün artan bilimsel makalelerin sonucu değiştirmemesi amaçlı tek günde tarama yapıldı. Duplikasyon olan yayınlar tek seferlik incelemeye dahil edildi. Elde edilen veriler gerekli analizlerin yapılabilmesi için Excel elektronik tablosuna kaydedildi. Tanımlayıcı verilerin sunumunda yüzde ve frekans değerleri hesaplandı. Görselleştirmeler için Scopus veri tabanının verilerinden yararlanıldı.

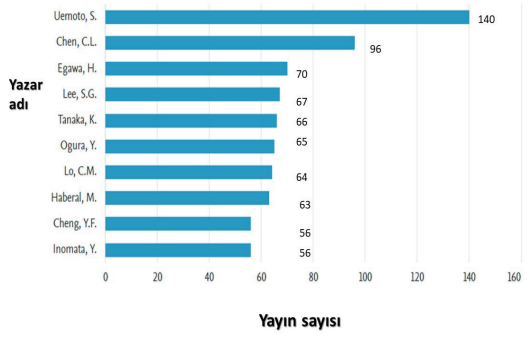
BULGULAR

Çalışmamız konusunda yayınlanmış toplam 4714 yayına (%75,47'si araştırma makalesi) ulaşıldı. İkinci sırada tercih edilen yayın türü derleme idi (n=596, %12,6). Bunların 1431'i (%29,9) açık erişimli yayınlar idi. İlk yayın 1966 yılında yayınlanmıştı. Yayın sayısının 2000'li yıllardan sonra hızlıca arttığı ve yıllık makale sayısının 2002 yılından beri 100'ün altına düşmediği saptandı. En fazla sayıda makale 2020 yılında yayınlanmıştı (Grafik 1).



Grafik 1. Yıllara göre yayınların dağılımı.

Canlı donörden karaciğer nakli konusunda en fazla yayın yapan yazar Japonya Kyoto Üniversitesi'nden Shinnji Uemoto idi (Grafik 2).



Grafik 2. Yazarlara göre yayın sayısı.

Makalelerin çoğu İngilizce dilinde (%95,03) yazılmış olup, çoğunluğu (%28,78) Amerika Birleşik Devletleri (ABD) kökenli kurumlardaki yazarlar tarafından üretilmişti. Japonya (%16,75) ve Güney Kore(%6,30) ilk üç sıradaki ülkeler iken; Türkiye (%5,43) ve Hindistan (%5,43) dördüncü sırayı birlikte paylaşmakta idi. Almanya, Çin, Tayvan, İngiltere, İtalya, İspanya, Kanada ve Mısır canlı donörden karaciğer nakli konusunda 100'den fazla yayın yapan ülkelerdi. Yayınların 4074'ü (%86,4) herhangi bir kurum tarafından desteklenmemişti. En fazla oranda fon sağlayan kurumlar; Ulusal Sağlık Enstitüleri (n=147), ABD Sağlık ve İnsan Hizmetleri Departmanı (n=143), Ulusal Diyabet ve Sindirim ve Böbrek Hastalıkları Enstitüsü (n=136), Japonya Bilimi Teşvik Derneği (n=130) idi. Çalışmamız konusunda en fazla yayının üretildiği kurum Japonya'dan Kyoto Üniversitesi idi (Tablo 1).

Tablo 1. Canlı donörden karaciğer nakli konusunda en fazla yayın üreten ilk 10 kurum (n=4714).

Kurum	Yayın sayısı	%
Kyoto Üniversitesi	249	5,28
Chang Gung Memorial Hastanesi	115	2,43
Kaliforniya Üniversitesi, San Francisco	113	2,39
Ulsan Üniversitesi Tıp Fakültesi	97	2,05
Asan Tıp Merkezi	93	1,97
Hong Kong Üniversitesi	91	1,93
Pittsburgh Üniversitesi Tıp Merkezi	76	1,61
Pensilvanya Üniversitesi	64	1,35
Başkent Üniversitesi	64	1,35
Queen Mary Hastanesi Hong Kong	64	1,35

Yayınların 779'u (%16,5) hiç atıf almamıştı. Bir tanesi 1000'in, 7 tanesi 500'ün, 29 tanesi 250'nin, 195 tanesi ise 100'ün üzerinde atıf almıştı. En fazla atıf alan araştırmacılar İtalya'dan tek yayın ile Vincenzo Mazzaferro (1211 atıf) ve iki yayın ile Pakistan'dan Christopher Erich Broelsch (1140) idi (Tablo 2).

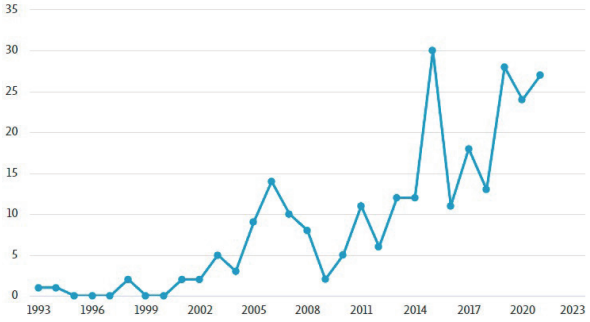
Türkiye'den Yayınlanan Canlı Donörden Karaciğer Nakli Konusundaki Yayınların Analizi

Türkiye'den 256 yayın olup, bu konudaki tüm yayınların ülkelere göre dağılımına göre dördüncü sırada idi. İlk yayın 1993 yılında yayınlanmıştı. En fazla 2015 yılında makale olup (30 makale), 2011 yılından beri 10 makale/yıl altındaki değerlere rastlanmadı (Grafik 3). Ülkemizden yapılan yayınların 34'ü (%13,28) açık erişimli olarak yayınlanmıştı. 255'i (%99,60) tıp alanında olan yayınların 216'sı (%84,37) araştırma makalesi idi. 251'inin (%98,04) finansal desteği yoktu. İki tanesine Başkent Üniversitesi ve birer tanesine Akdeniz Üniversitesi, Elmin Inkişafı Fondu (Azerbeycan) ve İnönü Üniversitesi tarafından finansal destek verilmişti. 250 tanesi (%97,65) İngilizce dilinde ve 5 tanesi Türkçe dilinde yayınlanmıştı. 1 yazıda ise yayın dili belirtilmemişti. En fazla yayın yapan kurumlar, Başkent Üniversitesi (n=83, %34,42) ve İnönü Üniversitesi (n=54, %21,09) idi (Tablo 3).

Tablo 2. En fazla atıf alan yayınların analizi.

Ülke, yıl	Birinci Yazar	Dergi Adı	Yayın adı	Atıf sayısı
İtalya,2009	Vincenzo Mazzaferro	The Lancet Oncology	Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis	1211
Almanya,2004	Gerhard Opelz	American Journal of Transplantation	Lymphomas after Solid Organ Transplantation: A Collaborative Transplant Study Report	794
Singapur, 1999	Tetsuya Kiuchi	Transplantation	Impact of graft size mismatching on graft prognosis in liver transplantation from living donors	764
İsviçre,2012	Pierre Alain Clavien	The Lancet Oncology	*Recommendations for liver transplantation for hepatocellular carcinoma: An international consensus conference report	644
Pakistan, 1991	Christopher Erich Broelsch	Annals of Surgery	*Liver transplantation in children from living related donors: Surgical techniques and results	613
İngiltere,2006	Roger M Williams	Hepatology	*Global challenges in liver disease	608
Pakistan, 1990	Christopher Erich Broelsch	Annals of Surgery	*Application of reduced-size liver transplants as split grafts, auxiliary orthotopic grafts, and living related segmental transplants	527
ABD, 2001	David E.R.S. Sutherland	Annals of Surgery	*Lessons learned from more than 1,000 pancreas transplants at a single institution	491
Fransa,2003	Renè A Adam	Liver Transplantation	Evolution of liver transplantation in Europe: Report of the European Liver Transplant Registry	471
İsviçre,2005	Felix Dahm	American Journal of Transplantation	Small-for-size syndrome after partial liver transplantation: Definition, mechanisms of disease and clinical implications	438

*Açık erişim.



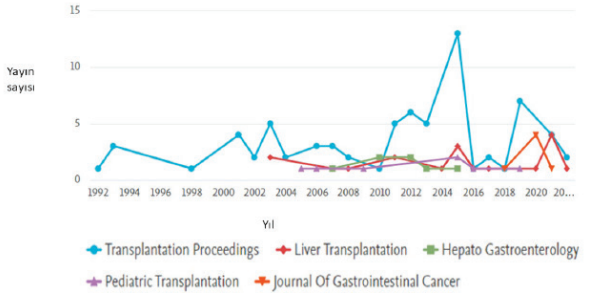
Grafik 3. Türkiye'den canlı donörden karaciğer nakli konusundaki yayınların yıllara göre yayınların dağılımı.

Ülkemizden en fazla canlı donörden karaciğer nakli konusunda yayını bulunan yazar 76 yayın (%29,68) ile Mehmet Haberal idi. Bu yazar dünya genel sıralamasında da 9.sırada yer almakta idi.

Mehmet Sükrü Sever 51 atıfla çalısmamız konusunda ülkemiz kaynaklı en fazla sayıda atıfı alan yazar idi. En fazla sayıda atıfı alan yayının dördü Transplantation Proceedings dergisinde yayınlanmıştı. Yayınlardan sadece Emre Arpalı tarafından 2020 yılında yayınlanan yazı açık erişim yazı idi. Yayınların genel analizi degerlendirildiğinde, bir yayın 50'nin, 16 yayın 25'in, 58 yayın 10'un, 109 yayın 5 ve üzerinde atıf almıştı. 205 tane yayın ise hiç atıf almamıştı. En fazla yayının yayınlandığı ilk 5 dergideki yayın sayıları ve yıllara göre yayın sayıları Grafik 3 ve Grafik 4 'te özetlendi.

Tablo 3. Türkiye'den canlı donörden karaciğer nakli konusunda en fazla yayın yapan 10 kurum (n=256).

Kurum	Yayın sayısı	%
Başkent Üniversitesi	83	34,42
İnönü Üniversitesi	54	21,09
Ege Üniversitesi Tıp Fakültesi	15	5,85
İstanbul Üniversitesi	15	5,85
Florence Nightingale Hastanesi	14	5,46
Ankara Üniversitesi	13	5,07
Demiroğlu Bilim Üniversitesi	13	5,07
Dokuz Eylül Üniversitesi	13	5,07
Koç Üniversitesi	9	3,51
Akdeniz Üniversitesi	7	2,73
Ege Üniversitesi	7	2,73



TARTIŞMA

Bir bilim alanındaki veya konusundaki yapılmış yayınların ve diğer bilimsel ürünlerin analizi ile, o alan gözler önüne konmuş olur. Çok farklı bibliyometrik analiz yöntemleri son yıllarda da tıp literatürüne de girmeye başlanmış olup, bu yöntem ile haritalandırma, grafikleştirme gibi yöntemlerle bu konuda yapılan analiz çalışmaları zenginleştirilebilir. İçerik analizi, bilimsel üretkenliğin yıllara, ülkelere, atıf sayılarına göre kıyaslaması gibi bir çok yöntem kullanılarak bu çalışmalar yapılabilir.[11-21] Bibliyometrik analizler için sıklıkla kullanılan veri tabanları, Pubmed, Scopus, Web of Science gibi kolay veri analizi sağlayan bibliyometrik veri tabanlarıdır. Ancak bunlar dışında tez veri tabanları ya da ülkelerin kendi veri tabanlarının araştırmacılar tarafından yapılan analizleri de bu yöntemde kullanılabilir.[11-21] Scopus veri tabanı, kapsamlı, iyi bir şekilde derlenmiş bir özet ve alıntı veritabanı olup, akademik literatürü birleştiren bir veri tabanıdır. Üyelik gerektiren bu veri tabanı metriklere ve analitik araçlara erişim sağlar. Bu veri tabanı sağladığı bibliyometrik analiz özelliği ile de farklı şekilde bir araştırma yöntemi olan yayın analizine olanak sağlar.[22,23] Bu çalışmada, Scopus veri tabanından yararlanılmıştır. Ayrıca Türkiye'den yapılan yayınların, global yayınlarla kıyaslaması yapılmış ve bu alanda çalışma yapacak araştırmacılara bakış açısı kazandırmak hedeflenmiştir.

Aynı veritabanında karaciğer nakli konusunda yapılmış yayınlara bakıldığında; karaciğer nakli ile ilgili toplam 45763 yayın bulunmakta olup ilk yayın 1940 yılında yapıldığı saptandı. Çalışmamız ise CDKN konusunda olup 4714 (tüm karaciğer nakli konulu yayınların %10,30'u) yayına rastlandı ve ilk yayın 1966 yılında yayınlanmıştı. CDKN konulu yayınların analizinde yayın sayısının gerek ülkemizde gerek de global olarak artma eğiliminde olarak saptanması, giderek artan organ verici sorununa paralel olarak yayınların daha da artacağı şeklinde yorumlanabilir. Yayın yapılan ülkelere bakıldığında çoğu çalışmada olduğu gibi, çalışmamız konusunda da en fazla makale ABD'den (%28,78) yayınlanmıştı.[11,17-19] Bu durum ABD'de bilimsel üretkenliğe verilen önemi, ülkenin maddi olanaklarına veya köklü kuruluşların varlığına bağlı olabilir. ABD organ nakil sayılarında da ilk sırada yer almakta olduğundan, bu durum bilimsel üretkenliğe yansımış olabilir.[24] Çalışmamız konusunda ABD'den sonra en fazla bilimsel üretkenlik ise; Japonya ve Güney Kore'de idi. Türkiye ve Hindistan dördüncü sırayı birlikte paylaşmakta idi. Kurumlara göre yayın sayısı değerlendirildiğinde ise en fazla yayın Japonya Kyoto Üniversite'sinden yayınlanmıştı. Bu durum yapılan nakil sayılarına bağlı olabilir. Veriler arasındaki bu heterojen bulgular ABD'de daha fazla merkezden yayın yapılıyor olmasına bağlı olabilir. Ülkemizde de en fazla yayın, gerek karaciğer nakli gerek de CDKN'nin en fazla yapıldığı iki öncül kurum olan Başkent Üniversitesi ve İnönü Üniversite'sinden yapılmıştı. En fazla yayın da Türkiye'de ilk kez canlı vericiden ilk segmental karaciğer nakli yapan Mehmet Haberal tarafından yapılmıştı.[6-10]

Yayın sayılarına bakıldığında global olarak en fazla yayın 2020 yılında, ülkemizde ise 2015 yılında yayınlanmıştı. Global yayınların 2021 yılı henüz tamamlanmadığından sayısı değişebileceğinden bu konuda yorum yapılamayabilir. Ancak pandeminin etkisine de bağlı olabilir. Ülkemizde ise 2015 yılından sonra göreceli azalma nedeni bilimsel olarak açıklanamamaktadır.

Yayın dillerine bakıldığında bu çalışma gerek ülkemizden gerek de global olarak yapılan yayınların %95'inden fazlasının İngilizce olarak yazıldığını göstermiştir. Bu durum hakim literatür dilinin İngilizce dilinin olmasına bağlı olabilir. İngilizce makaleler için daha fazla görünürlük ve daha fazla sayıda alıntı beklendiğinden, araştırmacıların çoğu çalışmalarını anadili İngilizce olmasa bile İngilizce olarak yayınlama eğilimindedir. Ayrıca İngilizce, bilim dünyasının ortak dili olarak kabul edilmektedir. Bununla birlikte, anadili İngilizce olmayanlar, belki de yerel veya bölgesel ilgi nedeniyle, daha düşük alıntı oranlarını açıklayan çalışmaları hala ana dillerinde yayınlamaktadır.[25] Ülkemizden yayınlanan alıntı sayıları en fazla olan makalelerin hepsi İngilizce dilinden ve uluslarası dergilerde yayınlanmıştı.

Çalışmamız konusundaki yayınların global olarak %86,4'inin ve ülkemizden yapılanların %98,04'inin herhangi bir fon sağlayıcısı bulunmamakta idi. Bu durum diğer bibliyometrik analizlerle karşılaştırıldığında oldukça düşük seviyede olarak saptandı. Çalışmamız oldukça önemli olan, CDKN konusunun bilimsel olarak da desteklenmesi gerekliliğini ortaya koymuş olabilir. Ayrıca bu konuda da yapılan makale sayısı da genel karaciğer nakli konulu yayınlara göre kısıtlı ıdı.

Atıf sayılarına bakıldığında en fazla atıfı İtalya, Almanya ve Singapur'dan yapılan yayınların aldığı, ülkemizden olan atıf sayılarının göreceli düşük olduğu saptandı.

Sonuç olarak, CDKN konusundaki bilimsel faaliyetlerin desteklenmesi, ülkemizden yapılan yayın sayılarının dördüncü sırada olmamıza rağmen arttırılması gerekmektedir.

Çalışmanın kısıtlılıkları

Çalışmamızda tek veri tabanından tarama yapılmıştır. Çalışmamızda ise içerik analizi yapılmamış sadece yayınların sayısal ve atıf özellikleri incelenmiştir. Artan bilimsel yayınlar nedeniyle çalışma verileri çalışma günümüze kadar olan bulguları yansıtmaktadır.

Etik Komite Onayı

Hayvan ve insan çalışması olmaması, makalelerle ilgili bir çalışma olduğu için etik kurul onayı alınmamıştır. Bu tarz çalışmalar için etik kurul izni şartı bulunmamaktadır.

Çıkar Çatışması

Tek yazar mevcuttur. Bu çalışmada yazarlar arasında çıkar çatışması bulunmamaktadır.

Destekleyen Kuruluş

Bu çalışma için herhangi bir kuruluştan destek alınmamıştır. Yazar bu çalışma için finansal destek almadığını beyan etmiştir.

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