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YAZARLARA BİLGİ/YAZIM KURALLARI

Selçuk Tıp Dergisi (Selcuk Med J), Necmettin Erbakan Üniversitesi'nin bilimsel, bağımsız, hakemli, açık erişimli yayın organıdır. Tıp doktorları, araştırmacılar ve bilim adamlarından oluşan geniş bir kitleye hitap eden disiplinli bir dergidir. Temel amaç Tıp/Sağlık alanında, tanı ve tedavideki güncel gelişmelerin, cerrahi yenilikler ve bilim dünyasına katkıda bulunacak çalışmaların ulusal ve uluslararası literatürde paylaşımının sağlanmasıdır.

Selçuk Tıp Dergisi, tıp bilimine ve akademik çalışmalara katkısı olan, klinik ve deneysel çalışmaları, editöryal yazıları, klinik olgu bildirimlerini, teknik ve eğitici derlemeleri, orijinal görüntü raporlarını ve editöre mektupları yayınlar. Anket/mülakat çalışmaları; Editörün ilk değerlendirmesi sonucunda çok değerli bir katkı sunuyorsa değerlendirmeye alınabilir.

Dergi gönderim kurallarına ve dergi kapsamına uygun görülen, editöryal çalışmalar hariç tüm yazılar alanında uzman hakemlere bilimsel değerlendirme için gönderilir. En az iki hakem kararı aranır. Yayımlanan tüm makaleler çift taraflı kör akran değerlendirmesi sürecine tabidir. Uygunluğunu tartışılan çalışmalarda yardımcı editörler hakemlerin yorumlarını dikkate alarak kendi değerlendirmelerini eklerler. Gönderilen tüm yazılar için nihai karar Baş Editör'e aittir. Bütün makaleler için süreçlerin editör ve yayın kurulu tarafından en geç üç ay içerisinde sonuçlandırılması hedeflenir. Fakat elde olmayan gecikmelerden dolayı bu süre uzayabilir.

Yayın kurulu kararları ile belirlenen bazı konular hakkındaki yazılar, yayın kurulu üyelerinin tamamının incelemesine sunulur. İncelemeler sonucu oy çokluğuna ulaşan çalışmaların dergideki süreçleri devam edecektir. Yayın kurulu kararları dergi web sitesinde yayınlanmaktadır.

Yayına kabul edilen yazıların her türlü yayın hakkı yazarlara ve Selçuk Tıp Dergisine aittir. Selçuk Tıp Dergisi, ilave olarak websitesinde bulunan telif hakları bildirim belgesinin de yazarlar tarafından onaylanarak imzalanmasını ve ıslak imzalı formun sisteme eklenmesini talep etmektedir. Dergi her yıl mart, haziran, eylül ve aralık aylarında olmak üzere dört sayı olarak yayımlanmaktadır. Derginin yayın dili İngilizcedir.

Gönderilen yazıların daha önce herhangi bir yerde/dergide yayınlanmamış olması ve yayın için başka bir dergiye gönderilmemiş olması gerekmektedir [Bilimsel kongrelerde sunulan sözlü bildiri ve posterler (özet ya da tam metin olabilir) bildirilmek kaydı ile hariçtir]. Dergide yayımlanan yazıların her türlü sorumluluğu (etik, bilimsel, yasal vb.) yazarlara aittir. Dergide yayımlanan yazılarda ifade edilen ifadeler veya görüşler yazarların görüşleri olup, editörlerin, yayın kurulu ve yayıncının görüşlerini yansıtmaz; editörler, yayın kurulu ve yayıncı, bu tür materyaller için herhangi bir sorumluluk veya yükümlülük kabul etmemektedir. Yazım kurallarına uygun olarak hazırlanmamış olan yazıların incelenmeye alınıp alınmaması Editör ve Editöryal Kurulun insiyatifindedir.

Tüm çalışmalarda etik kurul onayı ve bu onamın belgelendirilmesi gerekmektedir. Tüm çalışmalarda yazarların çalışmaya katkı düzeyi ve onayı bildirilmelidir. Çalışmada veri toplanması, deney aşaması, yazım ve dil düzenlemesi dahil olmak üzere herhangi bir aşamasında finansal çıkar çatışması olmadığı bildirilmelidir. Çalışmada varsa ticari sponsorluk bildirilmelidir. Selçuk Tıp Dergisi'nde intihal programı (iThendicate) kullanılmaktadır. Akademik atıf sınırını aşan benzerlik taşıyan makaleler ve yayın kurallarına uygun olarak hazırlanmamış makaleler değerlendirmeye alınmayacaktır. Dergi intihal tarama raporunu yazardan talep edeceği gibi kendisi de tarama yapabilir.

Derginin yayın politikası ve süreçleri Uluslararası Medikal Dergisi Editörleri Komitesi (International Committee of Medical Journal Editors-I**CMJE),** Dünya Tıbbi Editörler Derneği (World Association of Medical Editors-**WAME),** Bilim Editörleri Konseyi (Council of Science Editors-**CSE),** Avrupa Birliği Derneği Bilim Editörleri (European Association of Science Editors-**EASE)** ve Yayın Etiği Komitesi (Committee on Publication Ethics-**COPE)** ve Ulusal Bilgi Standartları Örgütü (National Information Standards Organization-**NISO)** yönergelerini takip eder. Dergimiz 'Şeffaflık ve Akademik Yayıncılık En İyi Uygulamalar İlkelerine' (Principles of Transparency and Best Practice in Scholarly Publishing) **(doaj.org/bestpractice)** uygundur. Yayın Kurulu, dergimize gönderilen çalışmalar hakkındaki intihal, atıf manipülasyonu ve veri sahteciliği iddia ve şüpheleri karşısında **COPE** kurallarına uygun olarak hareket edecektir.

Derginin Yayın Kurulu, itiraz ve şikâyet vakalarını, COPE rehberleri kapsamında işleme almaktadır. Yazarlar, itiraz ve şikayetleri için doğrudan baş editör veya editör/yayın kurulu ile temasa geçebilirler. İhtiyaç duyulduğunda Yayın Kurulu'nun kendi içinde çözemediği konular için tarafsız bir temsilci atanacaktır. İtiraz ve şikayetler için karar verme süreçlerinde nihai kararı Baş Editör verecektir. Yayıncı ve editör gerektiğinde düzeltmeler, açıklamalar, geri çekilmeler ve özürler yayınlamaya her zaman hazırdır.

Selçuk Tıp Dergisi ile ilgili tüm yazışmalar, makale gönderme, makalenin takibi, danışman raporları, düzeltmelerin yapılıp yüklenmesi, kabul yazısı gönderimi ve diğer tüm makale ile ilgili formların yüklenmesi **https://www. selcukmedj.org s**ayfasından yapılacaktır. Bu site üzerinden yüklenecek makaleler için kurallar aşağıda belirtilmiştir.

Selçuk Tıp Dergisi, ücretsiz, açık erişim politikası benimsemektedir. Bu bağlamda dergide yayınlanan tüm yazılar https://www. selcukmedj.org adresinden erişime açık olup yazarlardan hiçbir ek ücret talep edilmeyecektir.

Yazarlık

Selçuk Tıp Dergisi'ne gönderilen çalışmalarda yazar olarak listelenen herkesin ICMJE (www.icmje.org) tarafından önerilen yazarlık koşullarını karşılaması gerekmektedir. ICMJE, yazarların aşağıdaki 4 koşulu karşılamasını önermektedir:

- Çalışmanın konseptine/tasarımına; ya da çalışma için verilerin toplanmasına, analiz edilmesine ve yorumlanmasına önemli katkı sağlamış olmak;
- Yazı taslağını hazırlamış ya da önemli fikirsel içeriğin eleştirel incelemelerini yapmış olmak;
- Yazının yayından önceki son halini gözden geçirmiş ve onaylamış olmak;
- Çalışmanın herhangi bir bölümünün geçerliliği ve doğruluğuna ilişkin soruların uygun şekilde soruşturulduğunun ve çözümlendiğinin garantisini vermek amacıyla çalışmanın her yönünden sorumlu olmayı kabul etmek.

Yazar olarak belirtilen her kişi yazarlığın dört koşulunu karşılamalıdır ve bu dört koşulu karşılayan her kişi yazar olarak tanımlanmalıdır. Yazar olarak atanan tüm kişiler yazarlık için hak kazanmalı ve hak kazanan herkes listelenmelidir. Dört kriterin hepsini karşılamayan kişilere makalenin başlık sayfasında teşekkür edilmelidir. Finansman alımı, veri toplanması ya da araştırma grubunun genel gözetimi, kendi başlarına, yazarlığı haklı çıkarmaz. Bir ya da daha fazla yazar, çalışma başlangıcından yayınlanmış makaleye kadar, bütün olarak çalışmanın bütünlüğünün sorumluluğunu üstlenmelidir.Çok merkezli çalışmalarda yazarlık bir gruba atfedilir. Yazar olarak adlandırılan grubun tüm üyeleri, yukarıdaki yazarlık kriterlerini tam olarak karşılamalıdır. Bu kriterleri karşılamayan grup üyeleri, onayları ile birlikte listelenmelidir. Mali ve maddi destek de kabul edilmelidir.

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Yazar Değişikliği Talepleri
Yazar listesindeki yazar isimlerinin eklenmesi, silinmesi veya yeniden düzenlenmesi ancak makale kabul edilmeden önce ve ancak dergi Editörü tarafından onaylandığı takdirde yapılabilir.
Böyle bir değişikliği talebi olursa Editör, sorumlu yazardan (a) yazar listesindeki değişikliğin nedeni ve (b) tüm yazarlardan eklemeyi kabul ettiklerine dair yazılı onay (e-posta), talep eder. Editör, yalnızca istisnai durumlarda, makale kabul edildikten sonra yazarların eklenmesini, silinmesini veya yeniden düzenlenmesini dikkate alacaktır.

Makale Yazımı
Orijinal araştırma makalesi kaleme alanlar, konuyu özgün bir şekilde ve nesnel bir tartışma ile ele almalıdır. Makale, başkalarının çalışmayı tekrarlamasına izin vermek için yeterli ayrıntı ve referansları içermelidir. Hileli veya bilerek yanlış beyanlar etik dışı davranış teşkil eder ve kabul edilemez.

Özgünlük
Yazar makalenin orijinal olduğu, daha önce başka bir yerde yayınlanmadığı ve başka bir yerde, başka bir dilde yayınlanmak üzere değerlendirmede olmadığı konusunda teminat sağlamalıdır. Makale yazımının yapay zekâ sistemleri kullanılarak yapıldığı çalışmalar kabul edilmemektedir. Yapay zekâ sistemleri, sadece yazıların dil düzenlemeleri için kullanılabilir.

Orijinal Kaynak Kullanımı ve Atıf Yapma
Yazarlar, tamamen özgün eserler yazdıklarından ve başkalarının eserlerini veya sözlerini kullanmışlarsa, bunun uygun şekilde alıntılandığından emin olmalıdır. Üçüncü taraflarla konuşma, yazışma veya tartışmalarda olduğu gibi özel olarak elde edilen bilgiler, kaynağın açık ve yazılı izni olmadan kullanılmamalıdır.

Veri Erişimi ve Muhafazası
Yazarlardan, editör incelemesi için makalelerini destekleyen araştırma verilerini sağlamaları ve/veya derginin açık veri gereksinimlerine uymaları istenebilir. Yazarlar, mümkünse, bu tür verilere kamu erişimi sağlamaya ve bu tür verileri yayınlandıktan sonra makul bir süre boyunca saklamaya hazır olmalıdır. Dergimiz, araştırma verilerinin TUBITAK'ın Aperta Portalı'na yüklenmesini tavsiye etmektedir.

Çoklu ve Eşzamanlı Yayın
Bir yazar aynı araştırmayı içeren makalesini birden fazla dergisinde yayımlamamalıdır. Aynı makalenin aynı anda birden fazla dergiye gönderilmesi etik dışı davranıştır. Bir yazar, özet şeklinde yayınlanmış olması dışında, daha önce yayınlanmış bir makaleyi başka bir dergide değerlendirilmek üzere sunmamalıdır.

Anket ve Mülakata Dayanan Çalışmaların Yayını ve Etik Kurul Onamları
Etik kurul izni gerektiren, tüm bilim dallarında yapılan araştırmalar için (etik kurul onayı alınmış olmalı, bu onay makalede belirtilmeli ve belgelendirilmelidir. Etik kurul izni gerektiren araştırmalarda, izinle ilgili bilgilere (kurul adı, tarih ve sayı no) yöntem bölümünde, ayrıca makalenin ilk/son sayfalarından birinde; olgu sunumlarında, bilgilendirilmiş gönüllü olur/onam formunun imzalatıldığına dair bilgiye makalede yer verilmelidir. Anket çalışmaları ve mülakata dayanan çalışmaların etik kurul onam belgeleri alınmış olmalı ve makale yüklenirken dergi sistemine eklenmelidir.

Çıkar Çatışması
Kişinin yaptığı işte çelişkiye düşmesine yol açacak, objektifliğini önemli oranda bozabilecek veya herhangi bir kişi ya da kuruluş lehine adil olmayan avantaj sağlayabilecek herhangi finansal ya da diğer tür çıkarlardır. Araştırmanın yürütülmesi ve makalenin hazırlanması sürecinde alınan tüm mali destek kaynakları ve sponsorların çalışmadaki rolü açıklanmalıdır. Finansman kaynağı yoksa bu da belirtilmelidir. Açıklanması gereken olası çıkar çatışması örnekleri arasında danışmanlıklar, maaş alımı, hibeler yer alır. Potansiyel çıkar çatışmaları mümkün olan en erken aşamada açıklanmalıdır.

Hata Bildirimi
Bir yazar yayınlanmış çalışmasında önemli bir hata veya yanlışlık fark ettiğinde, derhal dergiye bildirimde bulunmalıdır. Editör tarafından gerekli görüldüğü takdirde makaleyi geri çekmek veya düzeltmek için iş birliği yapmak da yazarın yükümlülüğüdür. Editör veya yayıncı, yayınlanan bir çalışmanın hata içerdiğini üçüncü bir şahıstan öğrenirse, yazarın konu hakkında editöre bilgi vermek de dahil olmak üzere editörle iş birliği yapması yazarın yükümlülüğüdür.

Görüntü Bütünlüğü
Bir görüntüde belirli bir özelliği geliştirmek, karartmak, taşımak, kaldırmak veya eklemek kabul edilemez. Yazarlar, dergi tarafından uygulanan grafik görseller için belirlenen politikaya uymalıdır.

Düzeltme ve Yayından Geri Çekme Talepleri
Selçuk Tıp Dergisi tarafından yayımlanan makaleler nihai versiyondur. Bu nedenle yayımlandıktan sonra düzeltme talepleri, Yayın Kurulu tarafından **COPE** yönergelerine göre değerlendirilir. Yayından geri çekme talepleri, makale kabulünden önce yapılmalıdır ve Editör Kurulu onayına tabidir. Makale kabulü sonrasında henüz yayınlanmadan önce bir geri çekme talebi olursa, gerekçesi ile birlikte baş editöre mail yolu ile ulaştırılmalıdır. Gerekçeler editör kurulu toplantısında değerlendirilerek nihai karar verilecek ve yazara mail yolu ile bildirilecektir. **Yayın aşamasına alınmış bir makalenin geri çekme talep başvuruları dikkate alınmayacaktır.** Yayımlanmadan önce çalışmasını geri çekme talebinde bulunmak isteyen yazar (lar), Geri çekme formunu doldurarak her bir yazarın ıslak imzası ile imzalanmış ve taratılmış halini editor@selcukmedj.org.tr adresi üzerinden e-posta aracılığıyla Baş Editör ve Editör kuruluna iletmekle yükümlüdür. Geri çekme formuna web sitemizin indirmeler sayfasından ulaşabilirsiniz(https://www.selcukmedj.org/tr-tr/indirmeler/). Editör Kurulu geri çekme bildirimini inceleyerek en geç 15 gün içerisinde dönüş sağlar.
Yazar isimleri, bağlantıları, makale başlıkları, özetler, anahtar kelimeler, herhangi bir bilgi yanlışı ve dijital nesne anımlayıcılardaki [digital object identifier (DOI)] yazım hataları, bir "erratum" ile düzeltilebilir.

Makale Değerlendirme Süreci
Dergiye gönderilen makalelerin hızlı bir şekilde değerlendirilmesi ve yayınlanması hedeflenmiştir. Tüm makaleler çift kör hakem değerlendirme sürecine tabidir. Makaleler, içerik, özgünlük, alandaki önem, istatistiksel analizin uygunluğu ve sonuçların çıkarılması için alanında uzman hakemler tarafından gözden geçirilecektir. En az iki hakem kararı aranacaktır. Hakemler arasında tutarsızlıklar olması durumunda, makale üçüncü ya da dördüncü bir hakeme gönderilebilecektir. Hakem kararları yardımcı editörler tarafından değerlendirilerek değerlendirme sonuçları baş editöre gönderilecektir. Gönderilen makalelerin kabulüne ilişkin nihai karar, baş editöre aittir.

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Hakemler tarafından bildirilen ve yazarlar için faydalı oldukları değerlendirilen yorum ve değerlendirmeler yazarlara gönderilir. Hakemler tarafından yapılan talimat, itiraz ve talepler kesinlikle yerine getirilmelidir. Hakem(ler)e cevap dosyası ayrıca bir Word belgesi halinde oluşturulmalıdır. Yazının gözden geçirilmiş şekliyle yazarlar, bu dosyada, hakemlerin taleplerine uygun olarak atılan her adımı açık ve net bir şekilde belirtmelidir. Yazar açıklama notları, hakemlerin değerlendirme sırasına göre numaralandırılmış olarak listelenmelidir. Ayrıca makale içerisinde de gerekli değişiklikleri yapmalı ve bunları makale içerisinde belirterek (boyayarak), revize edilmiş makale ve hakem önerilerine verilmiş yanıtları içeren formlar https://www. selcukmedj.org adresinden titizlikle yüklenmelidir.

Yazıların Gönderilmesi

Yazarlar Yayın Hakları Bildirim Formunu sisteme yüklemelidir. Tüm yazışmalar sorumlu yazara gönderilecektir. İlgili sorumlu yazarın, tüm diğer yazışmalar için bir e-posta adresi bildirilmelidir. Yazarlar makalelerininin alındığından kendisine verilen numara ile haberdar edilirler. Bildirilen makale numarası yapılan tüm yazışmalarda kullanılmalıdır. Yazarlara beyan edilir ki; editör ofisinin ilk değerlendirmesi sonucu okuyucunun menfaatine dönük olarak makalelerin içeriği dolayısıyla makalesi geri iade edilebilir. Bu hızlı reddetme süreci, yazarın başka bir yerde makalesini yayınlanmasına olanak sağlar.
Selçuk Tıp Dergisi'ne makale gönderilmesi, tüm yazarların, derginin yayın politikalarını ve yayın etiğini okuduğu ve kabul ettiği anlamına gelir. Makale gönderimi ve ilgili diğer tüm işlemler https://www. selcukmedj.org adresinden online olarak yapılacaktır.

Yazıların Hazırlanması

Yazarların, materyallerini göndermeden önce aşağıdaki kuralları okumaları ve makalelerini bu kurallara uygun halde sisteme yüklemeleri gerekmektedir:

Genel yazı biçimi: Tüm makaleler, her tarafta 2,5 cm genişliğinde kenar boşlukları bulunan standart A4 boyutunda bir word dosyası kullanılarak yazılmalı, kaynaklar, resim şekil ya da tablolar metinde geçiş sırasına göre numaralandırılmalıdır. Metin, sol hizalı ve heceli satır sonları olmayan 12 puntolu bir fontta çift boşluk kullanılarak ve Times New Roman karakterinde yazılmalıdır. Kelimeler arasında ve cümle noktası sonrasında tek boşluk bırakmaya özen gösterilmelidir. Paragraf için sol girintiyi sekme tuşu ile bir kez tıklayarak ayarlanmalıdır. Ölçüm birimleri için Uluslararası Birimler Sistemi (SI) kullanılmalıdır. Makalenin tüm sayfaları sayfa sonunda numaralandırılmalıdır. Tüm yazılar yazım kurallarına uymalı, noktalama işaretlerine uygun olmalıdır.

Tüm makalelerde; Kapak sayfası, Ön yazı (cover letter), makale dosyası, Etik kurul onay Belgesi (kurumdan alınan), intihal analiz raporu, Şekiller ve Resimler, Telif Hakları Devir Formu, ve gerekli ise hasta onam formu ayrı dosyalar olarak yüklenmelidir.
Kaynaklar makale dosyasında, makale biter bitmez değil ayrı bir sayfada başlamalıdır. Tablolar, tablo açıklamaları, resim/şekiller ve resim/şekil açıklamaları ayrıca makale ana dosyasına kaynakların ardından ayrı bir sayfada eklenmelidir. Tablo/Resim/şekil açıklamaları; Tablo/Resim/şekillerin hemen altlarında olmalıdır.

Makale bölümleri hakkında

1-Kapak Sayfası: Makalenin İngilizce tam başlığı ve 50'den fazla karakter içermeyen kısa bir başlık, tüm yazarların açık şekilde adları ve soyadları, ORCID numaraları, kurumları, sorumlu yazar ismi iş veya cep telefonu, e-posta ve yazışma adresi belirtilmelidir.Makale daha önce tebliğ olarak sunulmuş ise tebliğ yeri ve tarihi belirtilmelidir. Yazarlar ve kurumları hakkındaki bilgiler başlık sayfası haricinde ana metinde (materyal metot bölümü dahil), tablolarda, şekillerde ve video dokümanlarında yer almamalıdır. Herhangi bir hibe ya da diğer destek kaynaklarının detayları, makalenin hazırlanmasına katkıda bulunan ancak yazarlık kriterlerini karşılamayan bireylere teşekkür bölümü de kapak sayfasına eklenmelidir.

2-Ana makale dosyası; Ana makale dosyası, yazar isimleri ve kurumları gibi bilgiler içermemelidir. Ana makale dosyası:
1. Başlık, 2. Özet ve Anahtar Kelimeler, 3. Makale ana metni, 4. Kaynaklar, 5. Tablolar ve açıklamaları, 6. Resim ve Şekil açıklamaları ile birlikte resim ve şekiller, 7. Alt yazılar şeklinde dizilmelidir.
Başlık: Makale Word dosyasında en baş kısımda makalenin yazım dilinde tek uzun başlığı yer almalıdır.
Özet: Editöre Mektup haricinde tüm yazılar özet içermelidir. Orijinal araştırma makalelerinin özetleri Amaç, Gereçler ve Yöntem, Bulgular ve Sonuç alt başlıklarını içermelidir. Özetler; kaynak, şekil veya tablo numarası içermemelidir. Sözcük sayısı ve özellikler için Tablo 1'deki veriler dikkate alınmalıdır.
Anahtar sözcükler:Özelerin sonunda en az üç ile en fazla beş anahtar sözcük bildirilmelidir. Anahtar sözcükler kısaltmalar olmaksızın tam olarak listelenmeli birbirinden virgül ya da noktalı virgül kullanılarak ayrılmalıdır. Anahtar kelimeler, "Tıbbi Konu Başlıklarına **(MESH)"** uygun olmalıdır (Bakınız: www.nlm.nih.gov/mesh/MBrowser.html).
Kısaltmalar:Özetlerde ve başlıklarda kısaltmalar kullanılmamalıdır. Makalede kullanılacak kısaltmalar, mümkünse ulusal veya uluslararası kabul görmüş olmalı, ilk kullanıldığında metin içinde tanımlanmalı ve parantez içinde yazılmalıdır. Daha sonra metin boyunca o kısaltma kullanılmalıdır. Yaygın olarak kabul edilen kısaltmalar ve kullanım için lütfen "Bilimsel Stil ve Biçim"e bakınız. (https://www.scientificstyleandformat.org/Home.html). Ana metinde Bir ticari markalı ilaç, ürün, donanım veya yazılım programı ana metinde yer aldığında, ürün bilgisi, ürünün adını, ürünün imalatçısını ve şirket ile şirket merkezinin bulunduğu ülkeyi aşağıdaki biçimde parantez içinde verilmelidir: "Discovery St PET / CT tarayıcı (General Electric, Milwaukee, WI, ABD).
Makale ana metni:
Giriş: Konuyu ve çalışmanın amacını açıklayacak spesifik bilgilere yer verilir.
Gereçler ve Yöntem: Çalışmanın gerçekleştirildiği yer, zaman ve çalışmanın planlanması ile kullanılan elemanlar ve yöntemler bildirilmelidir. Verilerin derlenmesi, hasta ve bireylerin özellikleri, deneysel çalışmanın özellikleri ve istatistiksel metotlar detaylı olarak açıklanmalıdır. Çalışmaya alınanlar ve çalışmayı yürütmek için kullanılan tüm yöntemler ayrıntılı olarak açıklanmalıdır. Kullanılan yeni veya modifiye yöntemler ayrıntılı olarak açıklanmalı kaynak belirtilmelidir. İlaçların ve kimyasal ajanların dozları, konsantrasyonları, verilme yolları ve süresi belirtilmelidir. Elde edilen verileri özetlemek ve önerilen hipotezi test etmek için kullanılan tüm istatistiksel yöntemlerin kısa bir raporu, istatistiksel olarak anlamlı farklılık için belirlenen p değeri ölçütleri de dahil olmak üzere bir alt başlık altında sunulmalıdır. Yapılan istatistiksel değerlendirme ayrıntılı olarak açıklanmalıdır. Olabildiğince standart istatistiksel yöntemler kullanılmalıdır. Nadiren kullanılmış veya yeni istatistiksel yöntemler kullanılmışsa konuya ilişkin ilgili referanslar belirtilmelidir. Gerekirse, olağandışı, karmaşık veya yeni istatistiksel yöntemlerle ilgili daha ayrıntılı açıklamalar, çevrimiçi ek veri olarak okuyucular için ayrı dosyalarda verilmelidir.
Bulgular: Elde edilen veriler istatistiksel sonuçları ile beraber ayrıntılı olarak verilmelidir. Bulgular şekiller ve tablolar ile desteklenmelidir. Rakam ve tablolarda verilen bilgilerin gerekli olmadıkça metinde tekrarlanmamasına özen gösterilmelidir.
Tartışma: Çalışmanın sonuçları literatür verileri ile karşılaştırılarak değerlendirilmeli, yerel ve/veya uluslararası kaynaklarla desteklenmelidir. Yazıyla alakasız veya gereksiz genel bilgiler eklenmemeli, yazının amacına uygun yeterli uzunlukta olmalıdır.
Kaynaklar: Kaynaklar ayrı bir sayfaya yazılmalıdır. Kaynaklar APA 7 sistemine uygun olarak belirtilmelidir. Buna göre, kaynak numaraları cümle sonuna nokta konmadan () içinde verilmeli, nokta daha sonra konulmalıdır. Kaynak yazar isimleri cümle içinde kullanılıyorsa ismin geçtiği ilk yerden sonra () içinde kaynak verilmelidir. Birden fazla kaynak numarası veriliyorsa arasına ",", ikiden daha fazla ardışık kaynak numarası veriliyor ise rakamları arasına "-" konmalıdır [ör. (1,2), (1-4) gibi. Yazar sayısı 3 ve daha azsa tüm yazarların ismi olmalı, 3'dan daha fazla ise ilk3 yazar yazılıp diğerleri için et al. kullanılmalıdır. Kaynaklar metindeki kullanılış sırasına göre numaralandırılıp listelenmelidir. Atıf doğruluğu, yazarın sorumluluğundadır. Kaynaklar orijinal yazım, aksan, noktalama vb. ile tam olarak uyumlu olmalıdır. Metin içindeki tüm kaynaklar belirtilmelidir. Kaynak listesinde mükerrer yazım yapılmamalıdır. Farklı yayın türleri için kaynak stilleri aşağıdaki örneklerde sunulmuştur:

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Araştırma Makalesi:

- Mirza E, Oltulu R, Oltulu P, et al. Dry eye disease and ocular surface characteristics in patients with keratoconus. Saudi J Ophthalmol. 2022;36(1):117-21. doi: 10.4103/sjopt.sjopt_37_21.
- Vikse BE, Aasarød K, Bostad L, et al. Clinical prognostic factors in biopsy-proven benign nephrosclerosis. Nephrol Dial Transplant. 2003;18(3):517-23. doi: 10.1093/ndt/18.3.517.

Tek Yazarlı Kitaplar:

- Danovitch GM. Handbook of Kidney Transplantation. Boston: Little, Brown and Company (Inc.), 1996: 323-8.

Kitap Bölümü:

- Soysal Z, Albek E, Eke M. Fetüs hakları. Soysal Z, Çakalır C, ed. Adli Tıp, Cilt III,İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi Yayınları, İstanbul, 1999:1635-50.
- Davison AM, Cameron JS, Grünfeld JP, et al. Mesengiocapillary glomerulonephritis In: Williams G, ed. Oxford Textbook of Clinical Nephrology.New York:Oxford University Press, 1998: 591- 613.

Baskıdan önce çevrim içi olarak yayımlanan dergi makalesi:

- Doğan GM, Sığırcı A, Akyay A, Uğuralp S, Güvenç MN. A Rare Malignancy in an Adolescent: Desmoplastic Small Round Cell Tumor. Turkiye Klinikleri J Case Rep. 10.5336/caserep.2020-77722. Published online: 31 December 2020.
- Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging.DiagnIntervRadiol. 2016 Feb 24.doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Toplantı Raporları:

- Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Bilimsel veya Teknik Rapor:

- Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Tez:

- Kaplan SI. Post-hospital home health care: elderly access and utilization (dissertation). St Louis (MO): Washington Univ; 1995.

Web sayfası ve Sosyal Medya araçları: Yazar. Başlık. Erişim linki: URL. Erişim tarihi ve yılı

3-Tablolar ve açıklamaları: Tablolar, ana makale metnine dahil edilmelidir, kaynak listesinden sonra sunulmalı ve ayrı bir sayfada olmalıdır. Ana metinde yer alan sıraya göre numaralandırılmalıdır. Her bir tablonun üzerine açıklayıcı bir başlık konulmalıdır. Tabloda kullanılan kısaltmalar, tablonun altında dipnotlarla tanımlanmalıdır (ana metin içerisinde tanımlanmış olsa bile). Tablolar kolay okunması için açık bir şekilde düzenlenmelidir. Tablolarda sunulan veriler, ana metinde sunulan verilerin tekrarı olmamalı, ancak ana metni desteklemelidir.

4-**Şekil ve Resimler:** Şekil, grafik ve resimler makale gönderim sistemi aracılığıyla ayrı dosyalar (TIFF veya JPEG formatında) halinde yüklenmeli ilaveten ana makale dosyasında ayrı bir sayfada tablolardan sonra ana metin içinde de gösterilmelidir. Sisteme ayrı olarak yüklenmeyen sadece makale içerisinde geçen resimler kabul edilmeyecektir. Şekil ve resimler mutlaka isimlendirilmeli ve numaralandırılmalı, metin içinde sıralamaya dikkat edilerek belirtilmelidir. Ana metine eklenecek resim, şekil ve grafik altına açıklamaları da eklenmelidir. Resimler minimum 300 dots per inch (dpi) çözünürlüğünde ve net olmalıdır. Şekil ve resim altlarında kısaltmalar kullanılmış ise, kısaltmaların açılımı alfabetik sıraya göre alt yazının altında belirtilmelidir. Mikroskobik resimlerde büyütme oranı ve tekniği açıklanmalıdır. Yayın kurulu, yazının özünü değiştirmeden gerekli gördüğü değişiklikleri yapabilir. Şekil alt birimleri olduğunda, alt birimler tek bir görüntü oluşturmak için birleştirilebilir. Şekiller, alt birimleri göstermek için işaretlenmeli ve her birinin açıklamaları (a, b, c, vb.) yazılmalıdır. Şekilleri desteklemek için kalın ve ince oklar, ok uçları, yıldızlar, yıldız işaretleri ve benzer işaretler kullanılabilir. Makale içeriği gibi şekiller de kör olmalıdır. Bir birey ya da kurumu tanımlayabilecek resimlerdeki olası bilgiler anonimleştirilmelidir. Hasta fotoğrafı paylaşımlarında kimliğin birebir tanınmamasına özen göstermeli, hastalığı belirlemeye yetecek yeterlilikte görüntü paylaşılmalıdır. Hastanın kimliğini açık eden resim paylaşımları için, hastanın resminin paylaşımına izin verdiği onam formu şarttır.

Tablo 1. Makale türlerine göre sınırlamalar

Makale türü	Sözcük sınırı	Özet sınırı	Kaynak sınırı	Tablo sınırı	Şekil sınırı
Araştırma makalesi	3500	300	50	6	6
Derleme	5000	300	80	6	10
Olgu sunumu	1500	200	15	3	5
Editöre mektup	1000	Özet yok	8	Tablo içermez	Şekil içermez
Editöryal	1000	Özet yok	20	3	3
Orijinal görüntü raporu	200	Özet yok	5	1	3

Makale Türleri

Selçuk Tıp Dergisi'nde aşağıda kısaca açıklanan makale türleri yayınlamaktadır:

Araştırma Makaleleri: Orijinal araştırmalara dayanan yeni sonuçlar sağlayan en önemli makale türüdür. Orijinal makalelerin ana metni Giriş, Yöntemler, Bulgular, Tartışma, Sonuç ve Kaynaklar alt başlıklarıyla yapılandırılmalıdır. Sözcük sayısı ve özellikler için lütfen Tablo 1'e bakınız. İstatistiksel analiz genellikle sonuçları desteklemek için gereklidir. İstatistiksel analizler uluslararası istatistik raporlama standartlarına uygun olarak yapılmalıdır (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983:7;1489–93). İstatistiksel analizler hakkında bilgi Materyaller ve Yöntemler bölümünde ayrı bir alt başlık ile sağlanmalı ve süreç boyunca kullanılan istatistiksel yazılım belirtilmelidir. Birimler Uluslararası Birimler Sistemine (SI) uygun olarak hazırlanmalıdır.
Makalenin kısıtlılıkları, sakıncalar ve eksik yönler, sonuç paragrafından önce Tartışma bölümünde belirtilmelidir.

Derleme Makaleleri: Yeterli sayıda bilimsel makaleyi tarayıp, konuyu bugünkü bilgi ve teknoloji düzeyinde özetleyen, değerlendirme yapan ve bulguları karşılaştırarak yorumlayan yazılar olmalıdır. Temel ve uygulamalı bilim alanlarında tüm gelişmeleri ile birlikte son bilimsel çalışmalardaki teknik ve uygulamalar değerlendirilir. Belirli bir alan hakkında kapsamlı bilgi sahibi olan ve bilimsel geçmişi yüksek atıf potansiyeli olan yazarlar tarafından hazırlanan derlemeler dergimiz tarafından kabul edilecektir. Bu yazarlardan makale kabul şekli davet yöntemiyle de olabilir. Ana metin Giriş, Klinik ve Araştırma Sonuçları ve Sonuç bölümlerini içermelidir. Sözcük sayısı ve özellikler için lütfen Tablo 1'e bakınız.

Olgu Sunumları: Tanı ve tedavide zorluk teşkil eden, yeni tedaviler sunan veya literatürde yer almayan bilgileri ortaya koyan nadir olgu veya durumlar hakkında eğitici olgu sunumları dergimizde yayınlanmak için kabul edilir. Olgu sunumu, Giriş, Olgu Sunumu ve Tartışma ve Sonuç alt başlıklarını içermelidir.

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İlginç ve sıra dışı resimler değerlendirme sürecinde bir avantajdır. Hasta tanımlayıcı resimlerde hasta kimliği açık ediliyorsa resmin paylaşımına izin veren hasta onamı mutlaka olmalıdır. Sözcük sayısı ve özellikler için lütfen Tablo 1'e bakınız.

Editöre Mektuplar: Bu yazı türü, daha önce yayınlanmış bir makalenin önemli kısımlarını, gözden kaçan yönlerini veya eksik kısımlarını tartışır. Derginin dikkatini çekebilecek konular başta olmak üzere, okuyucuların dikkatini çekebilecek konular hakkında makaleler, özellikle eğitici konularda Editöre Mektup şeklinde sunulabilir. Okuyucular, yayınlanmış yazılar hakkındaki yorumlarını Editöre Mektup olarak da sunabilirler. Özet, Anahtar Sözcükler ve Tablolar, Şekiller, Görüntüler ve diğer medya eklenmemelidir. Metin alt başlıkları içermemelidir. Sözcük sayısı ve özellikler için lütfen Tablo 1'e bakınız.

Editöryal: Tıbbın herhangi bir alanında bir görüşün açıklandığı ya da başkalarının görüşlerinin yayınlandığı, kısa makalelerdir. Normal bir dergi makalesine göre daha yaratıcı yazabilme olanağı sağlar. Dergide yakın zamanda yayınlanmış bir makale tartışılabilir, Tarihi materyal, Halk sağlığına dair konular, Sağlık politikaları, Tıp Eğitimi ve Tıpta teknolojik gelişmeler hakkındaki yazılar bu bölümde değerlendirilebilir. Tam bir derleme olamayacak bir konuda kısa derleme bu başlık altında değerlendirilebilir. Dergi editörü; okuyuculara kişisel mesaj iletmek, aynı sayıdaki bir makale ile ilgili yorum yapmak, okuyucunun dikkatini yeni gelişmelere çekmek isterse bu bölüme yazabilir. Bilimsel makalelerin tipik yazım bölümlerini içermez. Temel mesaj bir cümlede özetlenebilmelidir. Bu cümleyi editoryali yazmaya başlamadan belirlemek yazımı kolaylaştırır. Bu mesaj konusunda okuyucuyu ikna etmek için mantıklı bir tartışma yürütmelidir. Şekiller, Görüntüler ve diğer medya eklenebilir. Sözcük sayısı ve özellikler için lütfen Tablo 1'e bakınız.

Orijinal Görüntü Raporu: Tıbbın her alanına ait ilgi çekici, tanımlayıcı veya eğitici görüntüler (ilustrasyon ya da Fotoğraf) birkaç satırlık açıklayıcı metin ve referanslarla birlikte bu bölümde değerlendirmeye sunulabilir. Makale uzunluğu 200 kelimeyi geçmemelidir. Özet, tartışma veya sonuca gerek yoktur ancak kısa bir başlık eklenmelidir. Sözcük sayısı ve özellikler için lütfen Tablo 1'e bakınız.

Hakem Raporu Sonrasında Değerlendirme

Yazarlar hakem raporunda belirtilen düzeltme istenen konuları maddelendirerek bir cevap olarak kendilerine ayrılan cevap bölümüne yazmalıdırlar ve hakem (ler)e cevap başlıklı ek bir dosya şeklinde https://www. selcukmedj.org adresinden yüklenmelidir. Ayrıca makale içerisinde de gerekli değişiklikleri yapmalı ve bunları makale içerisinde belirterek (boyayarak) online olarak tekrar gönderilmelidir.

Son Kontrol

1. Yayın hakkı devir ve yazarlarla ilgili bildirilmesi gereken konular formu gereğince doldurulup imzalanmış,
2. Ana makale metni ve özetlerde gerekli kelime sayıları aşılmamış
3. Yeterli sayıda anahtar kelime eklenmiş,
4. Başlık uzun ve kısa başlık şeklinde yazılmış,
5. Kaynaklar kurallara uygun olarak yazılmış,
6. Tablo, resim ve şekillerde bütün kısaltmalar açıklanmış olmalıdır.

Online Yükleme Basamakları, https://www. selcukmedj.org sayfasında;

1. Makale türü *
2. Uzun Başlık *
3. Kısa başlık *
4. Özet*
5. Anahtar kelimeler *
6. Yüklenmesi gerekli bölümler (Kapak sayfası, Ön yazı (cover letter), makale dosyası, Etik kurul onay Belgesi (kurumdan alınan), intihal analiz raporu, Şekiller ve Resimler, Telif Hakları Bildirim Formu ve gerekli ise hasta onam formu şeklinde tamamlanmalıdır.

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- Vikse BE, Aasarød K, Bostad L, et al. Clinical prognostic factors in biopsy-proven benign nephrosclerosis. Nephrol Dial Transplant. 2003;18(3):517-23. doi: 10.1093/ndt/18.3.517.

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Single Author Books:
- Danovitch GM. Handbook of Kidney Transplantation. Boston: Little, Brown and Company (Inc.), 1996: 323-8.

Book Chapter:
- Soysal Z, Albek E, Eke M. Fetüs hakları. Soysal Z, Çakalır C, ed. Adli Tıp, Cilt III,İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi Yayınları, İstanbul, 1999:1635-50.
- Davison AM, Cameron JS, Grünfeld JP, et al. Oxford Textbook of Clinical Nephrology. In: Williams G, ed. Mesengiocapillary glomerulonephritis. New York: Oxford University Press, 1998: 591- 613.

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- Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging.DiagnIntervRadiol. 2016 Feb 24.doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Meeting Reports:
- Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report:
- Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

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Review	5000	300	80	6	10
Case Presentations	1500	200	15	3	5
Letters to the Editor	1000	(-)	8	(-)	(-)
Editorial	1000	(-)	20	3	3
Original Image Report	200	(-)	5	1	3

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OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

The Efficacy of Tonsillar Ablation with Coblator in Treating Pediatric Halitosis Due to Chronic Caseous Tonsillitis

Çocuklarda Coblator Parsiyel Tonsillektominin Kazeoz Tonsillite Bağlı Halitozis Tedavisinde Etkinliği

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ÖZET

Amaç: Ağız kokusu bireyi ve sosyal çevreyi etkileyen bir sorundur. Halitozisin en sık kaynağı oral kavitedir. Palatin tonsillerin kriptlerinde biriken kazeom halitozise neden olabilir. Palatin tonsil kazeomu tedavisinde total tonsillektomi veya koblator gibi aletlerle tonsil ablasyon cerrahileri yapılmaktadır. Bu retrospekrif çalışmanın amacı çocuk hastalarda kronik kazeoz tonsillite bağlı halitozis tedavisinde coblator ile parsiyel tonsillektominin etkinliğini değerlendirmektir.

Hastalar ve Yöntem: Haziran 2016- Haziran 2019 tarihleri arasında kronik kazeoz tonsillit nedeniyle coblator ile parsiyel tonsillektomi uygulanan 116 çocuk çalışmaya alındı. Adenoid hipertrofisi olan ve eş zamanlı adenoidektomi ameliyatı yapılan hastalar çalışmaya dahil edilmedi. Operasyon öncesi ve sonrası koku olup olmadığı Finkelstein testi ile değerlendirildi. Koku şiddeti ise Vizüel Analog Skala ile değerlendirildi. Postoperatif koku düzelme oranı ebeveynler için oluşturulan ölçek ile değerlendirildi.

Bulgular: Hastaların tamamında kazeom varlığı ameliyat öncesi teyit edildi. Çalışmaya dahil edilen hastaların yaş ortalaması 6,77 idi. Çalışmaya alınan olguların 65'i erkek; 51'i kızdı. Hastaların takip süresi 10 ile 43 ay arası (ort 25,9) değişmekteydi. Coblator tonsil ablasyonu öncesi Vizüel Analog Skala ile ölçülen kötü koku düzeyi 6,97 iken, cerrahi sonrası 1,75 bulundu. Sonuçlar istatistiki olarak çok anlamlı bulundu ($p < 0,001$). Finkelstein testinde tonsillerin palpe edilip hasta ebeveynine koklatılarak koku olup olmadığı soruldu. İşlem öncesi tüm hastalarda Finkelstein testinde koku mevcuttu. Postoperatif hastaların %71'inde (n= 82) Finkelstein testinde koku saptanmadı. Annelere postop kokunun düzelme düzeyi soruldu. Ebeveynler tarafından Hastaların % 82'sinde (n= 95) kokunun tam ve tama yakın düzeldiği bildirildi. Hiç düzelme olmayan hastalar ise % 6 idi (n=7).

Sonuç: Coblator ile parsiyel tonsillektomi çocuk hastalarda tonsil kazeomuna bağlı halitozis tedavisinde etkinliği yüksek ve güvenli bir yöntemdir.

Anahtar Kelimeler: Pediatrik halitozis, coblator, kazeom, tonsillit

ABSTRACT

Aim: Halitosis is a condition that impacts both the individual and their social interactions. The most common source of halitosis is the oral cavity. Caseum accumulated in the crypts of the tonsils can cause halitosis. In treating tonsil caseum, total tonsillectomy or tonsil ablation surgeries are performed with instruments such as coblator. This retrospective study evaluates the effectiveness of tonsil ablation with coblator in treating halitosis caused by caseous tonsillitis in children.

Patients and Methods: A total of 116 children who underwent tonsil coblation for caseous tonsillitis between June 2016 and June 2019 were included in the study. Patients who underwent simultaneous adenoidectomy were not included in the study. The presence of odor before and after the operation was evaluated using the Finkelstein test. The pre-operative and post-operative halitosis levels were evaluated with a Visual Analog Scale. The recovery levels were determined by the postoperative halitosis recovery scale.

Results: The presence of caseum was confirmed perioperatively in all patients. The mean age of the patients was 6.77 years, with 65 males and 51 females included in the study. The follow-up periods of the patients varied between 10 and 43 months (mean: 25.9). The level of halitosis on the visual analog scale before tonsil coblation was 6.97, and it was found to be 1.75 in the postoperative evaluation. The results were statistically significant ($p< 0.001$). The mothers were asked about recovery in postoperative halitosis levels. Mothers reported that 82% of patients (n = 95) had complete or nearly complete improvement in halitosis. 6% of patients (n = 7) showed no improvement.

Conclusion: Palatine tonsil coblation is an effective and safe method for the treatment of halitosis because of tonsil caseum.

Keywords: Pediatric halitosis, coblator, caseum, tonsillitis

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INTRODUCTION

Halitosis refers to bad breath, which can affect not only the individual but also their family and social environment. The terms "breath odor" or "malodor" are also used synonymously with halitosis. Halitosis is a general term used to describe unpleasant breath, regardless of its source, whether intra or extra-oral. The air exhaled through the nose is also included in halitosis. The term 'oral malodor' specifically refers to the smell that originates from the oral cavity (1). Halitosis is common in society with a prevalence varying between 30-40% in children (2). Causes originating from the oral cavity constitute 85-90% of halitosis. Frequently, tooth, tongue, and tonsil pathologies in the oral cavity are the sources of halitosis. However, the cause of halitosis is also extra-oral sinonasal diseases, respiratory and gastrointestinal system diseases, liver-kidney disorders, and metabolic syndromes at a rate of 10-15% (3,4).

A common cause of chronic halitosis is palatine tonsils. Crypts show tubular extension from the surface of palatine tonsils toward their deep parenchyma. Epithelium debris, keratin debris, and foreign particles accumulate in these crypts and form yellowish caseum with a bad odor resembling cheeseballs. Caseum may be seen in both genders, in one or both tonsils. Caseum may be seen not only in large-sized tonsils but also in small-size tonsils. Besides halitosis because of caseum, symptoms such as discomfort in the throat, stinging, and feeling a foreign object in the throat may also occur (4). Volatyl Sulfur Components (VSCs) are formed as a result of metabolizing substances that constitute the caseum by proteolytic anaerobe bacteria. These gases are the source of the characteristic sulfur smell in bad breath. H2S, CH3SH, and CH3SCH3 make up 90% of VSC gases, which cause oropharyngeal halitosis (5).

All studies in the literature on surgical treatments of chronic caseous tonsillitis (CCT) induced halitosis other than total tonsillectomy have been conducted in adult patients (4,6-10). In this study, the effectiveness of tonsil ablation with a coblator treatment method in the treatment of CCT-induced halitosis in children was investigated.

PATIENTS AND METHODS

Trial design and participants

A total of 116 children who underwent tonsil coblation for caseous tonsillitis between June 2016 and June 2019 were included in the study. Local ethics committee approval was obtained for the study (protocol number of ethics committee approval: 2020/003).

All patients had halitosis complaints with recurrent tonsillitis. It was seen that caseum was discharged from crypts with tonsil palpation before perioperative ablation in all patients. Patients without halitosis who underwent coblator tonsil ablation because of snoring or only chronic tonsillitis, patients with dental diseases, patients who did not live with their mothers, those with type 1 diabetes, patients with gastroesophageal reflux disease, patients with postnasal drainage detected during examination and patients who were on chronic medication were not included in the study. In addition, patients with adenoid hypertrophy and those who underwent simultaneous adenoidectomy were not included in the study.

Forms and scales used in the study

Written informed consent forms stating the benefits and risks of the treatment of the disease were received from all parents. Detailed anamnesis and oral and endoscopic nasal examinations were performed in the evaluation of all patients. Finkelstein's palpation test was used to determine whether the source of the odor was the tonsil. In this test, tonsils are palpated.

The patient's mother was asked whether there was any smell or not by smelling it. The same test was used in the post-treatment evaluation. Palpation was performed with a latex-free plastic bag glove. In this way, the latex smell was prevented from being felt. It was asked by the mothers of the patients to score the halitosis disorder with VAS before and after the treatment. They were asked to score between 0 and 10 by using VAS to indicate how the child perceived the severity, frequency, and duration of halitosis, how uncomfortable they were with halitosis, "0" showing no odor, and "10" severe odor. The mothers of the patients were also asked to score the rate of recovery after the treatment. The mothers were asked to indicate the rate of odor improvement after treatment in the prepared form (1= complete improvement, 2= nearly complete improvement, 3= moderate improvement, 4= improvement in a small amount, and 5= no improvement).

Interventions

All patients who were included in the study underwent tonsil ablation with coblator under general anesthesia with Arthrocare ENT Coblator® II device and Evac 70 coblator probe. Coblator probe has 2 pedals in the foot compartment. The power mode was set as 8 with the ablation pedal. The power mode was set as 6 in the cobalt pedal used for bleeding control. Local anesthesia or dexamethasone injection was not applied to patients before the procedure. Tonsil volume was reduced by approximately 90% by preserving the anterior and posterior tonsil plicas by using the ablation probe. All cryptic surfaces of the tonsils have been removed.

The cauterization feature of the same probe was used for bleeding control. No plica suturation was performed in any patient. Patients were hospitalized for 6 hours in the postoperative period and were given intravenous acetaminophen for postoperative pain control. All patients were discharged on the same day by prescribing oral paracetamol and amoxicillin-clavulanate. Patients who had a penicillin allergy were prescribed oral clarithromycin. Patients were called for follow-ups 1 week after the surgery and were evaluated in terms of pain and diet.

Statistical Analysis

The data, such as name, gender, age, follow-up time, Halitosis improvement levels, and VAS scores of patients were recorded in SPSS for Windows 11.5 Statistical Analysis Program (Statistical Package for the Social Sciences SPSS Inc., Chicago, Illinois, USA). The mean values of the continuous variables (i.e. age, halitosis duration, follow-up times, VAS scores), standard

Table 1. Post-operative recovery rates according to the statements of the mothers of children with halitosis.

Recovery rate	n
Complete	41 (35.3%)
Near-complete	54 (46.6%)
Moderate	8 (6.9%)
Mild	6 (5.2%)
No recovery	7 (6%)

deviation, minimum-maximum values, and normal dispersions were analyzed in statistical analyses. The difference between preoperative and postoperative VAS scores was analyzed with a Paired Samples t-test, and comparative analyses were also performed. Post-treatment recovery rates were calculated using the Chi-Square Test. $P \leq 0.05$ was considered as statistically significant.

RESULTS

A total of 65 of the 116 patients included in the study were male (56%), and 51 were female (44%). The age range of the patients was 2–14, and the mean age was 6.77±2.316. Patients were followed up for an average period of 25.1±9.95 months (10 months - 43 months).

In the Finkelstein test, the tonsils were palpated and the mothers were asked to smell whether there was any odor. Before the procedure, odor was present in the Finkelstein test in all patients. No odor was detected in the Finkelstein test in 71% of postoperative patients (n=82).

Halitosis VAS scores that were reported by mothers before and after the treatment were 6.97±1.93 and 1.75±2.14, respectively. According to a paired sample t-test done to compare odor VAS values, VAS halitosis scores decreased after treatment at statistically significant levels (p=0.0001). Mothers were asked how much the surgery decreased halitosis. Complete improvement was achieved in 41 patients (35.3%), near-complete improvement was achieved in 54 (46.6%), and moderate improvement was achieved in 8 (6.9%) patients. Mild improvement was reported in 6 patients (5.2%), and the number of patients with no improvement was 7 (6%) (Table 1).

None of the patients had velopharyngeal insufficiency, and no patients were hospitalized again because of malnutrition. Postoperative hospitalization was needed in 2 patients because of bleeding. Bleeding control was achieved by conservative methods in these patients. Tonsil ablation was well tolerated in all patients. No serious side effects were seen in any patient.

DISCUSSION

The crypts in the structure of palatine tonsils are tubular structures extending to the deep tissue of tonsils from their surface. Epithelial debris, keratin debris, and foreign particles accumulating in crypts constitute the caseum, which are also known as tonsil stones (4). Anaerobic proteolytic bacteria decompose this caseum and cause VSC to appear, which causes the halitosis smell. Approximately 77% of patients with CCT have halitosis (6). It was shown with objective measurement methods in previous studies that patients with halitosis due to palatine tonsil caseums had high levels of VSCs (7,11).

Antibiotics, such as Metronidazole or Amoxicillin-Clavulanate can provide temporary relief in the medical treatment of CCT. Mouthwash solutions, mouth sprays, tonsil massages, or removing the caseum gently are among other methods employed in this respect (12). Mouthwash, alcoholic mouthwashes, or sprays are not easy to use in children. Also, occasional tonsil massage or caseum removal will not be easy, especially in children.

The most effective treatment of CCT is total tonsillectomy. The recovery in total tonsillectomy might be prolonged up to 2 weeks. Difficulty in feeding because of the pain during this period is a common condition; and bleeding might also occur, which is one of the most undesirable complications of total tonsillectomy because of secondary infection in the tonsil bed (4).

Many studies are conducted on radiofrequency or laser cryptolysis, which are more conservative methods compared with tonsillectomy in the treatment of CCT-related halitosis in adults (4,6-9). It was reported that tonsil ablation with radiofrequency could reduce halitosis in more than 70% of patients in a single session (4). It was reported in another study that it was 90% effective when two sessions were performed (8). In studies conducted with laser cryptolysis, 52.8% improvement was reported in a single session (9). In another study, improvement was reported in all patients as a result of 4-session laser cryptolysis (7). Although satisfactory results can be achieved with laser cryptolysis, there is the risk of laser-related eye damage and burns (4).

Coblation is a technique using bipolar radiofrequency energy for soft tissue dissolving. The serum is separated into physiological ions in coblation with an electric current, and a plasma medium consisting of active ions ablating the tissue occurs. Coblation causes molecular dissolution at low temperatures (60°C). In this way, coblation causes minimal necrosis in the neighboring tissue and reduces the target tissue in terms of volume (13). In tonsils ablation with coblator, nutrition is better because the pain is less than in total tonsillectomy. Returning to a normal diet is faster, and wound healing is also faster compared to total tonsillectomy. Also, the amount of intraoperative and postoperative bleeding is less. In coblation tonsil ablation, the surgical duration is shorter than in traditional tonsillectomy; and the hospitalization duration of patients is also shorter (13,14). It is a significant disadvantage that the coblation hand probe is costly as it has a disposable use feature (14).

In a study evaluating the effectiveness of tonsil ablation with coblator in the treatment of halitosis due to chronic caseous tonsillitis in adult patients, organoleptic measurements showed that 75% of the patients did not have halitosis after surgery (10).

In our study, complete and near-complete recovery rates were achieved in 82% of patients as a result of the single-session coblator tonsil ablation, which is a more conservative method in the treatment of CCT-related halitosis compared to

total tonsillectomy. The preoperative VAS halitosis score was 6.97±1.93 and dropped to 1.75±2.14 after the procedure, which was found to be statistically significant. Since mothers spend a lot of time with their children and are often responsible for their care, they can better grasp the illnesses of their children than fathers (15). For this reason, the halitosis levels and recovery rates of children were evaluated only with the expressions of mothers in our study. No significant complications were seen because of the coblation in the patients who were included in our study. Postoperative bleeding was seen in only 2 patients, who were treated with conservative methods.

There are some limitations in the study. This study is first conducted regarding the coblator tonsil ablation in children because of tonsil caseum. However, subjective VAS scale and subjective recovery rate scales that were filled according to the declaration of mothers for their children with halitosis were used in the study. The effectiveness of coblator tonsil ablation in the treatment of tonsil-related halitosis in children must be validated with future studies in which VSCs are measured objectively.

CONCLUSION

Cryptolysis with local anesthesia and with radiofrequency and laser, which is reported to be effective in adults, might be difficult to tolerate in children. There is also the risk of laser-related eye damage and burns. More than one session may be necessary in both methods. Cryptolysis may be carried out with laser or radiofrequency in children under general anesthesia. However, since more tonsil ablation can be done in a single session with coblator, coblation may be a more suitable method in CCT treatment in children.

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Testicular Sparing Surgery in Small Testicular Lesions: Functional and Oncological Outcomes

Küçük Testiküler Lezyonlarda Testis Koruyucu Cerrahi: Fonksiyonel ve Onkolojik Sonuçlar

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ÖZET

Amaç: Testiküler germ hücreli tümörler, dünya çapında artış eğilimi gösteren, 20-34 yaş arası erkek popülasyonunda en sık görülen solid tümörlerdir. Testis kitlelerinde altın standart birinci basamak tedavi radikal orşiektomidir. Ancak radikal orşiektomi özellikle genç hastalarda beden imajı bozukluklarına, cinsel işlev bozukluklarına ve infertiliteye neden olabilir. Avrupa Üroloji Derneği kılavuzlarında tümör belirteçleri negatif olan küçük testiküler kitlelerde aşırı tedaviyi önlemek ve testis fonksiyonlarını korumak için testis koruyucu cerrahinin (TKC) uygulanabileceği belirtilmektedir. Çalışmamızda kliniğimizdeki testis koruyucu cerrahi deneyimlerimizi değerlendirmeyi, onkolojik ve fonksiyonel sonuçları özetlemeyi amaçladık.
Gereçler ve Yöntemler: Kliniğimizde 2008-2023 yılları arasında testis tümörü nedeniyle TKC uygulanan hastalar çalışmaya dahil edildi. Çalışmaya tek testiste tümörü, iki taraflı testis tümörü olan hastalar ile karşı testisi normal olan ve tümörü 2 cm'den az veya testis hacminin %30'undan az olan hastalar dahil edildi. Hastaların demografik verileri, tümör özellikleri ve takip verileri toplandı ve istatistiksel olarak analiz edildi.
Bulgular: TKC uygulanan toplam 26 hasta değerlendirildi. Dokuz hastada Germ Hücreli Tümör (GHT), 17 hastada ise benign testiküler kitle tespit edildi. Ortalama hasta yaşı 25±6.1 (18-69) yıldı. Ortalama tümör boyutu 12.9±4.4 (7-24) mm idi. GHT'li hastalar ortalama 21.8±7.8 (10-36) ay takip edildi. Bir hastada takipte lokal nüks görüldü ve radikal orşiektomi uygulandı. Takip süresince diğer hastalarda nüks veya metastaz görülmedi. Benign lezyonlar 21.5±9.3 (10-38) ay süreyle takip edildi. Lokal nüks gözlenmedi. Ameliyat sonrası testosteron düzeylerinde anlamlı bir azalma olmadı (p=0.3).
Sonuç: Bu çalışmada TKC ile benign testiküler tümörler için mükemmel klinik sonuçlar elde edildi. Ayrıca germ hücreli tümörü olan hastalarda TKC güvenli ve etkin bir tedavi seçeneği olarak önerilebilir. Ancak TKC'nin potansiyel riskleri ve yararları konusunda daha geniş hasta verilerini içeren daha fazla seriye ihtiyaç vardır.

Anahtar Kelimeler: Bilateral testis tümörü, germ hücreli tümör, soliter testis, testis koruyucu cerrahi

ABSTRACT

Objective: To evaluate our testis-sparing surgery (TSS) experiences in our clinic and outline its oncological and functional outcomes.
Materials and Methods: Patients who underwent TSS due to testicular mass in our clinic between 2008 and 2023 were included in the study. Patients with a mass in solitary testis, bilateral testicular mass as well as patients with a normal contralateral testis and a mass of less than 2 cm or less than 30% of the testicular volume were included in the study. Patient demographics, tumor characteristics, and follow-up data were collected and analyzed statistically.
Results: A total of 26 patients who underwent TSS were evaluated. Germ Cell Tumor (GCT) was detected in 9 patients, and benign testicular mass was detected in 17 patients. The mean patient age was 25±6.1 (18-69) years. The mean tumor size was 12.9±4.4 (range 7-24) mm in all patients. Patients with GCTs were followed up for a mean of 21.8±7.8 (10-36) months. Local recurrence was observed in one patient during follow-up, and radical orchiectomy was performed. No recurrence or metastasis was observed in other patients during the follow-up period. Benign lesions were followed up for 21.5±9.3 (10-38) months. Recurrence was not observed. There was no significant decrease in testosterone levels after surgery (p=0.3).
Conclusions: Excellent outcomes for benign tumors using TSS were obtained in the present study. TSS could be suggested as a safe and effective treatment option in patients with germ cell tumors, as in the present study. However, more data regarding the potential risks and benefits of TSS with a larger patient series is needed.

Keywords: Bilateral testicular tumor, germ cell tumor, solitary testis, testis sparing surgery

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INTRODUCTION

Annually, three to ten novel cases in 100,000 men are diagnosed with germ cell testicular cancer (GCT), representing 1% of all male neoplasms and 5% of all urologic tumors (1). It is the most widely seen solid tumor in the male population between 20-34 years of age, with a globally rising tendency (2). Testicular cancer is usually determined as a unilateral testicular scrotal mass by the patient or incidentally during an ultrasound (US) imaging. Small asymptomatic testicular masses have increased due to increased rates of self-examination and the use of ultrasound (3). 60-70% of palpable and non-palpable small testicular masses are benign lesions (4-6). However, the pathological nature of small testicular masses cannot be clearly distinguished by pre-operative imaging and physical examinations.

The gold standard first-line treatment in testicular masses is radical orchiectomy (RO) (7). The treatment algorithm is arranged together with the evaluation of testicular histopathology, tumor markers, and imaging examination. Radical orchiectomy may lead to disorders concerning body image, sexual dysfunction, and infertility, especially in younger patients (8).

According to European Association of Urology (EAU) guidelines, testicular sparing surgery (TSS) in testicular cancer should be performed in patients with single testis to preserve fertility and hormonal function (7). In small masses with negative tumor markers, TSS is recommended in selected cases to prevent over-treatment and protect testicular functions. Currently, there is no evidence supporting any size cut-off for a testicular lesion to be safely followed up (9). EAU recommends histopathological evaluation due to the risk of malignancy (7). Most clinicians agree that TSS should be considered first in bilateral testicular tumor or solitary testicular tumor. The latest American Urological Association (AUA) guidelines indicate that it will be an alternative in highly selected patients with regular contralateral testis, testicular mass <2 cm, tumor markers negative, and equivocal ultrasound/physical exam findings (10).

In recent years, small series of TSS results with normal contralateral testis have been published (4, 11-14). Generally, oncological and functional short-term results have been reported as promising.

In our study, we recommended TSS for all patients with bilateral testicular masses or solitary testes as well as for patients with small testicular masses with normal contralateral testis. This study aims to evaluate our testis-sparing surgery experiences in our clinic and to outline outcomes regarding the course of cancer and the function of the testes post surgically.

MATERIALS AND METHODS

The study included patients who had undergone TSS due to testicular mass in our clinic between 2008 and 2023. Patients with a mass in solitary testis, bilateral testicular mass, and normal contralateral testis and a mass of less than 2 cm or less than 30% of the testicular volume were included in the study.

We did not include patients classified as high risk according to EAU guidelines (testicular volume<12 ml, history of cryptorchidism, and age<40) in our study. Therefore, testicular biopsy from normal parenchyma was not performed in any patient for the diagnosis of GCNIS. In addition, patients with multiple (concurrent or recurrent) testicular lesions were not included in the study.

TSS patients' data were analyzed retrospectively. Patient demographics, tumor characteristics, and follow-up data were collected. TSS was performed under general anesthesia with the inguinal incision. First, the spermatic cord was suspended with a rubber tourniquet to prevent vascular invasion; then the testis was mobilized and removed from the scrotum. Tunica vaginalis was opened, and the mass was palpated and excised together with the surrounding parenchyma. If the mass could not be evaluated clearly by palpation, intraoperative ultrasound was used. After the lesion site was marked, the lesion was sharply excised with the surrounding parenchyma tissue and tunica albuginea. Frozen section examination (FSE) biopsy was conducted on the tumor base in patients with high tumor markers and suspicion of malignancy over 1 cm tumors. A biopsy was not performed on the remaining testicular parenchyma. After hemostasis was achieved, the tunica albuginea was closed. The tourniquet was released, and the testicle was placed in the scrotum. Dartos muscle and skin were covered in two layers.

All patients were dismissed on the first postoperative day. After TSS, all patients underwent standardized protocol follow-ups according to pathology results and stages. Physical examination was performed at all follow-up visits of the ipsilateral testis, and ultrasound was performed periodically. In testicular cancers, if there is no problem in the follow-

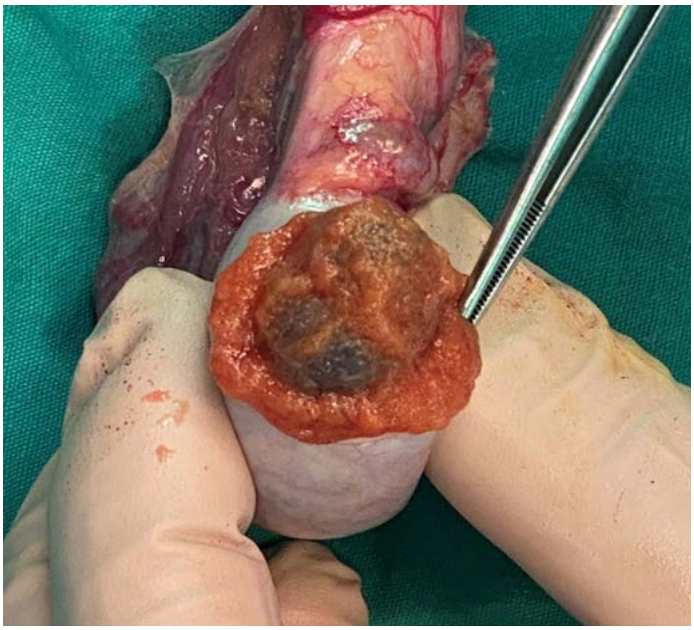

Figure 1. Intraoperative Germ Cell Tumor

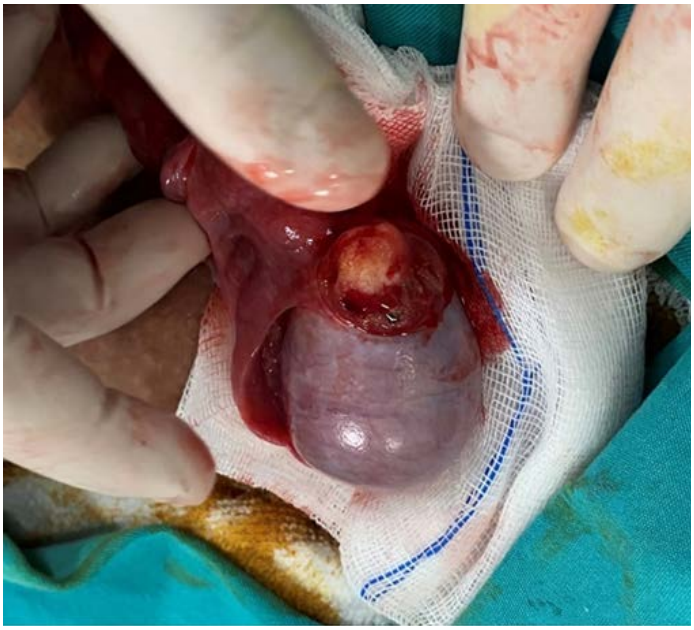

Figure 2. Intraoperative Leydig Cell Tumor

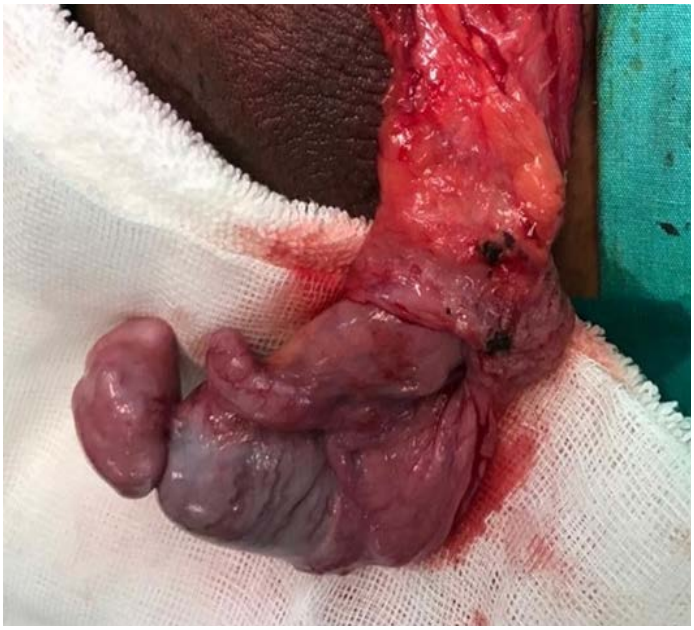

Figure 3. Intraoperative Paratesticular Pseudotumor

up (residual or recurrent mass), the first year is followed by ultrasound 4 times, the second year 3-4 times, and up to 5 years twice a year. In benign lesions, a 3rd-month control ultrasound was performed, only repeat ultrasound if new clinical concern and followed up once a year.

Statistical Analysis:

SPSS, v.23.0 statistical software (SPSS, Inc., Chicago, IL, USA) package program was utilized for statistical analysis. Descriptive analysis was used to define quantitative variables. The mean and minimum-maximum values were provided. Shapiro Wilk test was applied to evaluate whether the data conformed to normal distribution. Wilcoxon test was applied to compare data in the dependent group.

Ethics and Consent to Participate:

All procedures performed in this study were conducted by 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. Ethics Committee approval was obtained before starting the study, in line with the Declaration of Helsinki (No: 2024/4774).

RESULTS

A total of 26 patients who underwent TSS were evaluated. GCT was detected in 9 patients, and benign testicular mass was detected in 17 patients. The mean patient age was 25±6.1 (18-69) years. Nine (34.6%) patients had left testicular tumors, and 17 (65.4%) patients had right testicular tumors. The mean tumor size was 12.9±4.4 (range 7-24) mm all of the patients. The mean tumor size was 12.2±4.6 (7-24) mm in benign masses. In those with GCT, the mean tumor size was 14.3±3.7 (10-20) mm. In 19 cases, the mass was palpable. Six cases had non-palpable mass. In these cases, perioperative ultrasound was performed. Testicular pain was present in 6 patients. Only 3 of the patients had limited tumor marker elevation. FSE was obtained from 12 patients from the tumor bed, and the results were negative. In 10 of the 12 patients in whom we performed FSE, the final pathology was similar.

After the final pathological examination, GCT was detected in 9 patients (34.6%). In addition, 5 benign Leydig cell tumors, 4 fibrosis, 2 adrenal rest tumors, 2 paratesticular pseudotumor, 2 paratesticular adenomatoid tumors, 1 epidermoid cyst, and 1 angiomyolipoma were detected. There were 2 seminomas, 5 non-seminomatous germ cell tumors (NSGCT) and, 2 Intratesticular germ cell neoplasia (ITGCN) in GCT patients. Surgical margins were not positive in any of our patients.

Indication and demographic data of patients who underwent testicular sparing surgery are given in Table 1. Twenty-two (84.6%) patients had a small mass with normal contralateral testis, 2 (7.7%) had bilateral testicular mass, and 2 (7.7%) had a mass in solitary testis. Two patients with solitary testis had previously undergone radical orchiectomy for GCT.

Patients with GCTs were followed up for a mean of 21.8±7.8 (10-36) months. Local recurrence was determined in one patient during follow-up, and radical orchiectomy was performed. None of the remaining patients had recurrence or metastasis during the follow-up period. Benign lesions were followed up for 21.5±9.3 (10-38) months without any recurrence.

For patients undergoing partial orchiectomy, testosterone levels were examined before and 3 months after the operation. Whereas average testosterone level was determined as benign pathology patients 360±91 (184-540) ng/dl before surgical intervention, it was determined as 358±90 (190-533)

Table 1. Patient's Data

TSS İndications	Age (Years)	Size (mm)	Side (L/R)	Tumor Markers	Malign/ Benign	Histopathology (M/B)	Preoperative Testosteron Levels (ng/dl)	Postoperative Testosteron Levels (ng/dl)	Follow-Up (months)	Local Recurrence	Management	Status
Small Mass	22	10	R	Normal	M	Seminoma	378	375	26	no	Surveillance	Disease Free
Small Mass	38	10	R	Normal	B	Leydig Cell Tumor	254	256	32	no	Surveillance	Disease Free
Small Mass	40	20	L	Normal	B	Leydig Cell Tumor	320	317	36	no	Surveillance	Disease Free
Small Mass	30	7	R	Normal	B	Leydig Cell Tumor	385	386	19	no	Surveillance	Disease Free
Small Mass	21	17	R	Normal	B	Adrenal Rest Tumor	489	490	28	no	Surveillance	Disease Free
Small Mass	22	11	L	Normal	M	NSGCT	365	357	24	no	Surveillance	Disease Free
Small Mass	39	20	R	Normal	M	ITGCN	387	390	36	no	Surveillance	Disease Free
Small Mass	28	10	R	Normal	B	Leydig Cell Tumor	380	375	38	no	Surveillance	Disease Free
Bilateral Mass	35	15	L	Normal	M	Seminoma	190	188	22	no	CHT	Disease Free
Small Mass	18	10	R	Normal	B	Fibrosis	445	432	36	no	Surveillance	Disease Free
Small Mass	18	7	L	Normal	B	Adrenal Rest Tumor	385	390	12	no	Surveillance	Disease Free
Small Mass	35	12	L	Normal	B	Leydig Cell Tumor	290	293	24	no	Surveillance	Disease Free
Small Mass	23	14	R	Normal	B	Adenomatoid tumor	395	410	12	no	Surveillance	Disease Free
Solitary Testicular Mass	21	15	R	Elevated	M	NSGCT	188	190	10	no	CHT	Disease Free
Small Mass	38	9	L	Normal	B	Fibrosis	411	407	10	no	Surveillance	Disease Free
Small Mass	34	14	L	Normal	B	Angiomyolipoma	184	190	16	no	Surveillance	Disease Free
Small Mass	35	24	R	Normal	B	Paratesticular Pseudotumour	540	533	18	no	Surveillance	Disease Free
Small Mass	69	12	R	Normal	B	Paratesticular Pseudotumour	240	232	18	no	Surveillance	Disease Free
Small Mass	54	10	R	Normal	B	Epidermoid Cycst	285	280	20	no	Surveillance	Disease Free
Small Mass	25	10	R	Normal	M	Teratoma	360	364	15	no	Surveillance	Disease Free
Small Mass	24	15	L	Normal	B	Adenomatoid tumor	345	321	21	no	Surveillance	Disease Free
Small Mass	30	10	R	Normal	B	Fibrosis	385	387	16	no	Surveillance	Disease Free
Small Mass	19	7	L	Normal	B	Fibrosis	403	400	10	no	Surveillance	Disease Free
Small Mass	37	18	R	Normal	M	ITGCN	328	347	18	no	Surveillance	Disease Free
Solitary Testicular Mass	22	16	R	Elevated	M	NSGCT	190	182	24	yes	CHT	Disease Free
Bilateral Mass	27	20	R	Elevated	M	NSGCT	228	200	8	no	CHT	Disease Free

(CHT: Chemotherapy, ITGCN: Intratubuler Germ Cell Neoplasia, NSGCT: Non-Seminomatous Germ Cell Tumor, TSS: Testis Sparing Surgery)

ng/dl postoperatively. There was no significant decrease in testosterone values (p=0.3). In patients with GCT, pre-operative testosterone was 298±91 (188-387) ng/dl, and post-operative testosterone was 299±93 (182-390) ng/dl (p=0.78).

DISCUSSION

Testicular sparing surgery will certainly play an important role in testicular masses in the following years. Testis-sparing surgery is recommended in special cases according to existing guidelines (7, 10). In our current series, apart from being testicular masses, small masses, synchronous masses, and small masses in the solitary testicle have TSS oncological acceptable results in testicular cancer.

In recent years, especially with the increase in US use, there has been an increase in the frequency of testicular small masses determined. The general opinion about small testicular masses is that most of them are benign (4, 5, 9, 15). 80% of non-palpable masses were considered as benign (9, 16). In palpable lesions whereas Shilo et al. reported in their recent study (6) 69% (11/16) of testicular masses under 25 mm as benign (both palpable and non-palpable), Gentile et al. (5) reported 86.7% of the masses (13/15) as of benign pathology. Ates et al. recently reported in their study that 93.3% of all cases smaller than 25 mm as of benign pathology (14/15) (17). Considering the mass dimensions, Keske M et al. reported in a multicenter study with 212 participants that whereas 54.3% of the masses below 1 cm were benign, between 2.1 cm and 3.0 cm, 14,4% were considered benign (18). Scandura et al. They stated that 69% (81/56) of small testicular masses under 10 mm were benign (9). In our study, patients with GCT had larger tumors than patients with benign lesions. Most of the testicular masses smaller than 10 mm in our study were not malignant.

Definitive differentiation of small testicular masses in terms of malignity cannot be made clinically. The imaging features of benign solid testicular lesions vary largely and mostly mimic malignant lesions (i.e., intra-testicular lesions; there is no definitive feature that distinguishes malignant and benign lesions by ultrasound.) (19). Therefore, in many benign masses, futile radical orchiectomy is performed. One of the frequently used methods for benign-malign differentiation is perioperative FSE (20). However, FSE can be difficult and the pathologist's personal experience is the major determinant for a meaningful FSE of testicular masses (21). In their study, Bianjiang Liu et al. conducted TSS with 11 patients with testicular mass of benign characteristics defined with intraoperative FSE (22). They stated that they had similar results with the final pathology. Nason et al. It is one of the largest partial orchiectomy studies in the literature, and they did not recommend FSE because of its high false negative rate (14).

In recent years, studies have been published in the opposite direction, advocating the necessity of performing FSE. Connolly et al. reported a 94.2% positive predictive value and 92.6%

Table 2. Publications About Testis Sparing Surgery

Author:	Year	N	TSS Indications	Tumor Size (mm)	Bening Testicular Mass (N)	Malign Testicular Mass (N)	Complementary Orchiectomy	Local Recurrence	Treatment of Local Recurrence	Adjuvan Radiotherapy for Testis	RPNLD	Adjuvant CHT	Preoperative Testosteron Levels (ng/dl)	Postoperative Testosteron Levels (ng/dl)	Disease Free	Follow-Up (months)
Gaosi (15)	2016	28	small lesion	9.3	22	6 Seminoma	6	NA	NA	NA	NA	NA	NA	NA	NA	NA
Gentile (5)	2013	15	small lesion	9.5	14	1 Seminoma	2	NA	NA	NA	NA	NA	NA	NA	NA	19
Ferrelti (29)	2014	25	bilateral lesion/solitary testis	11.4	5	11 Seminoma, 9 NSGCT	No	3	RO	5	NA	1	361	346	AS	42.2
Shio (6)	2009	16	small lesion/ bilateral lesion	8-25	11	3 Seminoma, 2 NSGCT	5	No	No	NA	NA	1	NA	NA	AS	48
Lawrentsch (27)	2011	27	solitary testis	12	10	9 Seminoma, 5 NSGCT	No	2	RO	1	1	1	NA	NA	AS	67
Heidenreich (13)	2001	73	bilateral lesion/ solitary testis	15	0	42 Seminoma, 31 NSGCT	No	4	RO	42	NA	3	400-450	300-350	AS / 1 dead	91
Bojanic (11)	2014	26	bilateral lesion/ solitary testis	<20	0	16 Seminoma, 7 NSGCT	No	7	RO	NA	1	10	NA	NA	NA	54
Bojanic (12)	2017	28	small lesion	11.4	18	6 Seminoma, 4 NSGCT	1	1	RO	NA	NA	NA	NA	NA	AS	40.9
Keske (18)	2019	13	bilateral lesion/ solitary testis/ small lesion	14.6	9	1 Seminoma, 3 NSGCT	No	1	RO	1	NA	1	3	2	AS	47.2
Nason (14)	2019	77	bilateral lesion/ solitary testis/ small lesion	15	41	28 Seminoma, 15 NSGCT	6	10	RO	1	2	1	209	273	AS / 3 dead	43.5
Our Study	2024	26	bilateral lesion/ solitary testis/ small lesion	12.9	17	2 Seminoma, 5 NSGCT 2ITGCN	1	1	RO	0	NA	4	329	302	AS	21.6

AS: Active Surveillance, CHT: Chemotherapy, ITGCN: Intratesticular germ cell neoplasia, NSGCT: Non-Seminomatous Germ Cell Tumor, RO: Radical Orchiectomy, RPLND: Retroperitoneal Lymph Node Dissection, TSS: Testis Sparing Surgery

negative predictive value for malignancy in 80 patients (23). Matei D.V. et al. reported from 144 patients that the sensitivity and specificity of FSA were 93% and 98%, respectively, for malignant tumors and 90% and 99%, respectively, for benign tumors (24). In our study, the FSE result obtained from 12 patients was compatible with the final pathology in 10 of them. In our opinion, FSE should be removed if it will affect the surgical method. Especially in cases with high tumor markers and large testicular masses, the frozen biopsies we performed from the tumor base were negative for the tumor.

The standard treatment for suspected malignancy in testicular masses is radical orchiectomy. The reason why TSS is not considered in the first place is the high recurrence rate with accompanying Intratesticular germ cell neoplasia (ITGCN). The multifocality rate in tumors smaller than 4 cm increases up to 26% (21). Secondly, the presence of ITGCN is almost invariably present in the precursor lesion of the GCT, which is evident in 80% of the normal-appearing testicular tissues surrounding the germ cell tumor mass (13). However, data presented recently suggest the prevalence of ITGCN could be decreased if a tumor lesion is smaller than 1 cm (21). Heinrich et al. In their study, they proposed 16 Gy radiotherapy to the testis in the presence of intratesticular neoplasia in bilateral testicular tumors, solitary testicles, tumor bed and resection area biopsy, and normal parenchyma biopsy results (13). Bojacis et al. In the study, local recurrence after TSS indicated that ITGCN had a worse prognosis, but they mentioned that radiotherapy might be delayed to the testis in patients who want to become a father (12).

Bojanic et al. reported a 29% local recurrence rate (7/26) subsequent to TSS in bilateral or solitary testis tumors. All patients with local recurrence had ITGCN and had poor prognosis criteria. Moreover, they underwent further TSS or RO with only 1 developing metastasis (retroperitoneal nodes). The rate of survival was 100% (12). A 5.5% local recurrence rate was determined by Heidenreich et al. in a series of partial orchiectomy in patients with bilateral tumors or a solitary testis and all were salvaged successfully with RO (13). Bojanic et al. In another study, 10 of 28 patients with normal contralateral testis and TSS had GCT, and only 1 patient reported local recurrence at 39 months (11). In the present study, GCT was detected in 8 patients. The mean follow-up period of GCT patients was 21.8±7.8 (10-36) months without metastasis.

Table 2 presents a list of selected published TSS series. One of the publications with a high number of malignant patients in the current literature is Bojacis et al. In their study, 37.5% of

patients had GCT, and stromal tumors and various lesions were found in 64.3% of patients (12). Neither contralateral tumors nor distant metastases were observed in any of the patients in their cohort. Overall survival was achieved in all patients. (11). In line with the findings of the present study, benign testicular tumors were observed in 18 patients. In the present study, 8 of 25 cases (32%) were GCT, other 17 patients (68%) had stromal tumors and various lesions. Nason et al. have reported a large series of TSS in the Canadian population. They performed TSS on 77 patients, of which 25 had benign lesions (32.5%), 28 (36.4%) had malignant lesions, seminomas, 15 (19.5%) had non-seminomas, and 9 (11.7%) had sex-cord stromal tumor with a median follow-up was 43.5 months (range 1–258) (14). The overall local recurrence rate reported was 12.9% (n = 10) who underwent salvage RO. 6 of the patients who underwent RO were followed up. Only three received systemic chemotherapy. All patients became disease-free. In their study, three of the follow-up patients died, two due to testicular cancer. Both of them initially presented with widespread metastatic disease. However, our series has many strengths, especially because we provide information about the long-term oncological outcomes of testicular cancer with small testicular mass. The present study reports the entire experience of TSS, whereas other series have focused on bilateral lesions, solitary testis, and small lesions independently or confirmed stromal tumors (Table 2).

Nason and Bojanic studies had similar oncologic results between radical orchiectomy and TSS (12,14). In our study, the oncological results of TSS in GCT can be accepted. Hence, TSS could be established as a feasible method without compromising survival rates and with potential benefits. In the present study, no distant metastases were observed in the patients in the long-term follow-up period. Local recurrence was observed in one patient during local follow-up, and radical orchiectomy was performed. Nevertheless, the present study has determined a recurrence-free period of at least 38 months with all of the potential benefits of the preserved testis.

Preserving testicular function is an important issue. Out of the long-term testicular cancer survivors, up to 17% report changes in body image (5,25) that are independently associated with sexual dysfunction. Hence, TSS is most likely to improve body image and sexuality in testicular cancer (26). Moreover, in a large-scale Norwegian study comparing the general population with patients who underwent TSS, the 10-year paternity rate among TSSs is reduced by 30% (8).
Testicular tissue preservation could improve these rates. In the study of Nason et al., no statistical difference was found in the comparison of pre and post-operative testosterone (14). Bojanic et al. reported normal testosterone levels in all TSS patients along with a successful conception in a proportion (11). The testosterone levels of the participants in the present study were also followed up. No statistically significant change was observed in the postoperative period compared to the preoperative period.

However, almost one-third of TCSs report fear of cancer recurrence (FoR), and elevated levels of emotional distress were associated with elevated FoR rates with statistical significance (27). As the high local recurrence rate after TSS is widely accepted, FoR can be expected in these patients. Although frequent follow-up visits, in line with the protocol established, provide safety from an oncologic perspective, these lead to increased follow-up visit-associated anxiety.

Although Leydig cell tumors (LCT) are very rare, these constitute the most widely spread form of testicular stromal tumors, representing 1–3% of all adult testicular tumors (1). The EAU guidelines recommend abstention from immediate radical orchiectomy for the sake of organ-sparing procedures in small intraparenchymal lesions and the obtainment of a pathological diagnosis, especially in patients with symptoms of gynecomastia or hormonal disorders in which a non-germ cell tumor should be considered (7).In the literature, local and metastatic relapse was not observed in LCT patients who underwent TSS (28). However, Florian Laclergerie et al. reported in their study comparing radical orchiectomy with 35 patients and TSS with 21 patients that two out of 56 patients had local recurrence and no distant metastasis(27). Benign lesions have no recurrence risk (5, 6). Hence, TSS is a safe modality in these types of tumors. Organ-sparing surgery is a reasonable and reliable alternate modality for testicular tumors with benign tendencies (29,30). In our study, we did not detect local recurrence at 21.5±9.3 (10-38) months in non-germ cell testicular masses.

Our study is retrospective and has some limitations. Small testicular masses do not have a standard treatment in the literature. Many factors, such as patient age, size of the testicular mass, environmental factors, patient's desire, and especially the preference of the urologist, affect testicular sparing surgery. In addition, our series includes all forms of testicular lesions. When evaluated together with other series, TSS has many advantages, such as long-term survival advantage, protection of testicular functions, and psychological and cosmetic factors. However, TSS as an alternative surgical approach is to be performed by experienced urologists in centers with large series of cases.

CONCLUSIONS

Excellent outcomes for benign tumors using TSS were obtained in the present study. TSS could be suggested as a safe and effective treatment modality in patients with germ cell tumors as in the present study. However, more data with larger patient series is needed regarding the potential risks and benefits of TSS.

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ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Effect of Different Doses of Lutein and Zeaxanthin on Macular Pigment Optical Density

Maküler Pigment Optik Yoğunluğuna Farklı Doz Lutein Ve Zeaksantinin Etkisi

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ÖZET

Amaç: Sağlıklı bireylerde, iki farklı lutein ve zeaksantin dozunun maküler pigment optik yoğunluk (MPOY) üzerindeki etkilerini heterokromatik fliker fotometre (MPS II) yöntemi ile değerlendirmek.

Gereçler ve Yöntemler: 20 sağlıklı bireyin 20 sağ gözü çalışma kapsamına alındı. Olgular eşit sayıda olmak üzere randomize iki gruba ayrıldı. Grup 1'deki olgular 5 mg lutein ve 1 mg zeaksantin takviyesi alırken Grup 2'deki olgular 10 mg lutein ve 2 mg zeaksantin takviyesi aldı. Grup 1 ve Grup 2 olgularda takviye öncesi ve takviye sonrası 1.ay MPOY değerleri karşılaştırıldı.

Bulgular: Olguların yaş ortalaması grup 1'de 34.0±6.9 iken grup 2'de 33.4±6.8 idi. Grup 1'deki olguların sağ gözlerinin destek tedavisi öncesi ve destek tedavisi sonrası 1.ay MPOY değerleri sırasıyla ortalama 0.41±0.09 ve 0.41±0.10 olarak ölçüldü. Sol gözlerinin destek tedavisi öncesi ve destek tedavisi sonrası 1.ay MPOY değerleri ise sırasıyla ortalama 0.44±0.14 ve 0.42±0.12 olarak ölçüldü. Grup 2'deki olguların sağ gözlerinin destek tedavisi öncesi ve destek tedavisi sonrası 1.ay MPOY değerleri sırasıyla ortalama 0.39±0.10 ve 0.37±0.11 olarak ölçüldü. Sol gözlerinin destek tedavisi öncesi ve destek tedavisi sonrası 1.ay MPOY değerleri ise sırasıyla ortalama 0.41±0.12 ve 0.39±0.11 olarak ölçüldü. Değerler istatistiksel olarak anlamlı bulunmadı (p>0.05).

Sonuç: Sağlıklı bireylerde, 5 mg lutein ve 1 mg zeaksantin takviyesinin (Grup 1) ve 10 mg lutein ve 2 mg zeaksantin takviyesinin (Grup 2) MPOY üzerine 1.ayda istatistiksel olarak anlamlı etkisi bulunmamıştır.

Anahtar Kelimeler: Hetereokromatik fliker fotometre, lütein, maküler pigment optik yoğunluk, zeaksantin

ABSTRACT

Aim: To evaluate the effects of two different doses of lutein and zeaxanthin on macular pigment optical density (MPOD) in healthy subjects using heterochromatic flicker photometer (MPS II) method.

Materials and Methods: 20 right eyes of 20 healthy subjects were included in the study. The subjects were randomly divided into two groups with equal numbers. Group 1 received 5 mg lutein and 1 mg zeaxanthin supplements, while Group 2 received 10 mg lutein and 2 mg zeaxanthin supplements. MPOD values before and 1 month after supplementation were compared in Group 1 and Group 2 subjects.

Results: The mean age was 34.0±6.9 years in group 1 and 33.4±6.8 years in group 2. The mean MPOD values of the right eyes of the subjects in group 1 before and 1 month after supplement treatment were 0.41±0.09 and 0.41±0.10, respectively. The mean MPOD values of the left eyes of the subjects in group 1 before and 1 month after supplement treatment were 0.44±0.14 and 0.42±0.12, respectively. The mean MPOD values of the right eyes of the subjects in group 2 before and 1 month after supplement treatment were 0.39±0.10 and 0.37±0.11, respectively. The mean MPOD values of the left eyes of the subjects in group 2 before and 1 month after supplement treatment were 0.41±0.12 and 0.39±0.11, respectively. The values were not statistically significant (p>0.05).

Conclusion: In healthy subjects, 5 mg lutein and 1 mg zeaxanthin supplementation (Group 1) and 10 mg lutein and 2 mg zeaxanthin supplementation (Group 2) had no statistically significant effect on MPOD at 1 month.

Keywords: Hetereochromatic flicker photometer, lutein, macular pigment optical density, zeaxanthin

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INTRODUCTION

Lutein and zeaxanthin (L/Z) are two fat-soluble antioxidants belonging to the carotenoids class (1, 2). Together with their isomer meso-zeaxanthin, they are the primary components of macular pigment (MP). Among the more than 1000 carotenoids found in nature, only L/Z and their metabolites are found in the human macula (3). Humans can not synthesize L/Z and must obtain them through dietary sources (4). These carotenoids are more concentrated in the macular region of the retina and are responsible for maintaining central vision (1). MP helps to protect the macula from the phototoxicity of blue light with its 460 nm absorption spectrum (5). Additionally, it acts as a free radical scavenger, protecting the macula from photochemical damage and serving an antioxidant function (5). Studies indicate that low MP levels are a risk factor for age-related macular degeneration (AMD), the leading cause of blindness in developed countries (6). Macular pigment optical density (MPOD) is a measure of L/Z concentrations in the macula (7). A relationship has been demonstrated between MPOD and visual function, contrast sensitivity, and photostress recovery (8). Dietary L/Z intake has been shown to support visual function by increasing MPOD and reduce the risk of developing AMD (9, 10). Ma et al. concluded that L/Z supplements could increase MPOD in patients with AMD and healthy subjects and reported a dose-response relationship (11). One of the first comprehensive studies on carotenoids, Eye Disease Case-Control Study, which compared nutrition with the risk of developing AMD, demonstrated that individuals with higher serum L/Z levels had a significantly lower risk of developing eye diseases (12). Furthermore, those consuming a diet containing 5.8 mg L/Z daily had a lower risk of AMD compared to those consuming a diet containing 1.2 mg L/Z daily (12).

Following the recognition of L/Z's effects on eye health, supplementation through dietary means or commercially available preparations has been considered. There is no consensus on the appropriate daily dose for L/Z supplementation. Toxicology studies have shown that L/Z does not pose health risks even at high doses (4, 40 and 400 mg/kg body weight) (13). The ocular effects of dietary L/Z intake at doses <5 mg/day are not fully evident (4). Studies have shown that total L/Z intake of <5 mg/day does not result in a statistically significant change in MPOD (4).

Further research is necessary to determine the minimum L/Z dose and duration required to elicit clinically significant effects on MPOD and visual function. The aim of this study is to determine whether there is a minimum concentration of L/Z intake that causes a statistically significant and/or clinically important change in MPOD over a 1-month period, and to evaluate the dose-response relationship between L/Z intake and MPOD.

MATERIALS AND METHODS

The entire study protocol was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee (date/number: 05.06.2023/18362). Patients who visited the ophthalmology clinic of Konya City Hospital between January 2021 and December 2021, underwent MPOD measurements following routine ophthalmologic examination, and were prescribed L/Z supplementation were analyzed. Patients with visual acuity of 10/10 on the Snellen chart and refractive error with a spherical equivalent value below ±2.0 D were included in the study. Patients with any eye disease or media opacity, intraocular surgery history, pregnancy, smoking history or systemic disease were excluded. After applying these criteria, 20 eyes of 20 healthy individuals were included in the study. The subjects were randomly divided into two groups with equal numbers. Group 1 consisted of patients who received 5 mg lutein and 1 mg zeaxanthin supplementation, while Group 2 consisted of patients who received 10 mg lutein and 2 mg zeaxanthin supplementation. MPOD values before and 1 month after supplementation were compared in both groups.

Examination protocol

MPOD measurements were taken using a device employing the heterochromatic flicker photometry (HFP) technique (MPSII®, Elektron Technology, Switzerland). The device measures the amount of blue light absorbed by the MP in the patient's retina layer. A small stimulus alternating between green (530 nm) and blue (465 nm) is seen on a white background. If the brightness of blue and green light is not equal or the frequency of alternation is too high, the stimulus appears to flicker. Initially, the blue brightness is set to a relatively high value and the frequency is reduced until flicker is detected. Blue light is absorbed by the MP while green light is not. Patients are handed a device with a button and instructed to look at the target in the center. The device starts to display the alternating lights and the patients are instructedto press the button when a flicker is noticed. The MPOD value is automatically calculated by the MPSII device's software based on the graph generated from the patient's button presses during each flicker event. Normal MPOD values are between 0.00 and 1.00, with higher MPOD values indicating higher MP levels.

Statistical analysis

Statistical analysis was performed using SPSS 22 (SPSS Inc., Chicago, Illinois, USA). The Kolmogorov Smirnov test was used to determine whether the data conformed the normal distribution. Parametric tests were preferred due to normal distribution. The Independent Samples Test was used to compare the parameters between the groups. The Mixed ANOVA test was used to compare the parameters before and after supplementation and to compare values between right and left eyes. P values <0.05 were considered statistically significant.

RESULTS

Group 1 and Group 2 each comprised 5 males (50%) and 5 females (50%). The mean age of the patients was 34.0±6.9 years (min:29, max:40 years) in Group 1 and 33.4±6.8 years (min:30, max:39 years) in Group 2. In Group 1, mean MPOD values for right eyes of the patients before and 1 month after supplemenatation were 0.41±0.09 and 0.41±0.10, respectively

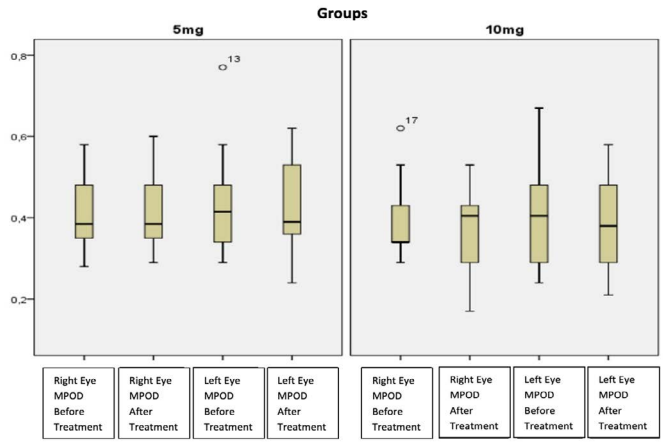

Figure 1. Box-plots of the groups before and after supplement treatment

(Figure 1). For left eyes, the values were 0.44±0.14 and 0.42±0.12, respectively. In Group 2, mean MPOD values for right eyes of the subjects before and 1 month after supplementation were 0.39±0.10 and 0.37±0.11, respectively. The mean MPOD values for left eyes before and 1 month after supplement treatment were 0.41±0.12 and 0.39±0.11, respectively.

The changes in MPOD values for right eyes of the subjects in Group 1 before and 1 month after the supplementation were not statistically significant (p=0.768) (Table 1). The changes in MPOD values for right eyes of the subjects in Group 2 before and 1 month after the supplementation were not statistically significant (p=0.559). The changes in MPOD values for left eyes of the subjects in Group 1 before and 1 month after the supplementation were not statistically significant (p=0.494). The changes in MPOD values for left eyes of the subjects in Group 2 before and 1 month after the supplementation were not statistically significant (p=0.349).

The mean spherical equivalent values for patients in Group 1 and Group 2 were -0.67±0.22D and -0.62±0.19D, respectively (p=0.802). There was no significant correlation between spherical equivalent value and MPOD (p=0.873, r=0.32 for male, p=0.914, r=0.37 for female). When right and left eyes of the patients in Group 1 were compared, mean MPOD values were 0.41±0.09 and 0.44±0.14 (p=0.303), respectively. When the right and left eyes of the patients in Group 2 were compared, the mean MPOD values were 0.41±0.10 and 0.42±0.12 (p=0.716), respectively.

DISCUSSION

AMD is a multifactorial disease and oxidative stress caused by short wavelength blue light is considered to be an important factor in the disease (1). Numerous studies have investigated the relationship between MP and AMD, as MP protects against blue light hazards (1). Some studies have found significantly lower MPOD levels in AMD patients compared to normal eyes (6). Supplementation with macular xanthophyll carotenoids and antioxidants has been associated with delaying progressive macular diseases such as AMD (1). The large-scale clinical study investigating the effects of lutein and zeaxanthin supplements on preventing AMD (Age-Related Eye Disease Study 2 Research Group 2013) recommended antioxidant supplements containing L/Z (14). These AMD-preventive effects of carotenoids are due to their biochemical (anti-oxidant) and photochemical (blue light filtration) properties (5).

Studies have demonstrated that dietary L/Z intake is associated with the amount of MPOD (15, 16). However, the precise dosage required to increase MPOD remains unclear. Randomized, placebo-controlled studies investigating the effects of dietary L/Z intake of <5 mg/day on MPOD, have not shown statistically significant increases in MPOD (17, 18). In these studies, dietary L/Z intake was between 0.5 and 4.5 mg/day and participants were followed up for 3 to 6 months (17, 18). Whereas, studies using L/Z supplements between 5-20 mg/day for 3-12 months have shown statistically significant increases in MPOD (19, 20). Similarly, a statistically significant increase in MPOD value was also observed in studies in which L/Z supplementation was higher than 20 mg/day (21, 22).

MPOD is expected to increase by 0.003 optical density units (95% CI: 0.001 to 0.006) for every 1 mg increase in total daily L/Z intake (4). The increase in MPOD value was significantly higher in studies with ≥5 mg/day L/Z supplementation compared to those using <5 mg/day L/Z supplementation (4). There is a lack of literature evaluating MPOD effects using total daily L/Z doses between 5 and 10 mg. Comparing studies where L/Z was provided through dietary sources with those using L/Z-containing supplements, it is evident that patients can achieve higher L/Z doses with supplements (4). The total daily L/Z dose in dietary intervention studies typically remains <5 mg,

Table 1. Macular Pigment Optical Density Changes Before and After Supplement Treatment

	Group 1			Group 2		
	Before Treatment	**After Treatment**	**p***	**Before Treatment**	**After Treatment**	**p***
MPOD right	0.41±0.09	0.41±0.10	0.768	0.39±0.10	0.37±0.11	0.559
MPOD left	0.44±0.14	0.42±0.12	0.494	0.41±0.12	0.39±0.11	0.349
		Group 1			**Group 2**	
SE		-0.67±0.22D			-0.62±0.19D	0.802#

MPOD, Macular Pigment Optical Density; SE, Spherical Equvalan; *Mixed ANOVA #Independent samples test

while studies using supplements often reach levels ≥12 mg (4). When comparing studies using supplements containing only L/Z with those using preparations that include L/Z along with vitamin C, vitamin E, zinc, copper, and ω-3 fatty acids, no significant difference was observed in their effects on MPOD (20, 23).

Cardinault et al. (24) investigated MPOD changes in two groups aged 20-35 years and 60-75 years by giving 9 mg lutein and 0.45 mg zeaxanthin daily for 5 weeks and found no significant change in both groups. Similarly, our study showed no significant changes in MPOD levels in the right eye at either doses (p=0.168 for Group 1, p=0.559 for Group 2). This may be due to the relatively low additional L/Z dose and short supplementation period. A review of 46 studies suggested that L/Z intake for ≥3 months and at doses above 5 mg/day could increase MPOD concentrations by 0.04 to 0.11 optical density units in healthy adults (4). It has been observed that L/Z intake increases the MPOD value in healthy adults, especially at doses >10 mg/day. In our study, an increase in MPOD may not have been observed because low doses of L/Z were given. There seems to be a dose-response relationship in which higher doses of L/Z have a greater effect on MPOD. Since most studies of low doses of L/Z have evaluated dietary supplementation, it is difficult to determine the dose of L/Z, the effect of the dose of L/Z given and other effects of the dietary source.

CONCLUSION

Our study found no statistically significant change in the amount of MPOD after 1 month in patients taking 5 mg lutein 1 mg zeaxanthin supplementation and 10 mg lutein 2 mg zeaxanthin supplementation. With the expected increase in AMD incidence due to global population aging, the optimal L/Z dosage and its relationship with MPOD remain unclear. Our study contributes to preventing unnecessary L/Z supplementation and ensuring adequate dosing. Future research is needed to determine the L/Z dose and duration that causes clinically significant increases in MPOD.

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OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Predictive Value of Crp-Albumin and Neutrophil-Lymphocyte Ratio in Preterm Premature Rupture of Membranes

Preterm Prematür Membran Rüptüründe Crp-Albümin Oranı ve Nötrofil-Lenfosit Oranının Prediktif Değeri

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ÖZET

Amaç: Bu çalışmada, Crp-Albumin oranı (CAR), Nötrofil-Lenfosit oranı (NLR), Trombosit-Lenfosit oranı (PLR) ile Prematüre Preterm Membran Rüptürü (PPROM) arasındaki ilişkiyi değerlendirmeyi amaçladık.

Gereçler ve Yöntemler: Bu prospektif çalışmanın örneklemini Ocak 2021-Temmuz 2021 tarihleri arasında Necmettin Erbakan Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Kliniğine poliklinik veya acil servisten su gelmesi şikayeti ile başvuran ve 24-37. gebelik haftalarında PPROM tanısı ile doğum yapan 143 gebe oluşturmaktadır. Kontrol grubunu ise spontan preterm doğumu başlayan ve PPROM tanısı olmayan 108 gebe oluşturmaktadır. Demografik veriler, tam kan sayımı sonuçları kaydedildi ve karşılaştırıldı.

Bulgular: Hastaların temel demografik özelliklerini incelediğimizde gruplar arasında yaş, gravida, parite, gestasyonel yaş açısından istatistiksel olarak anlamlı fark saptanmamıştır (sırasıyla p=0.881, p=0.888, p=0.912, p=0.916). PPROM grubunda CAR ve NLR kontrol grubuyla kıyaslandığında istatiksel olarak anlamlı derecede yüksek bulunmuştur (Her iki oran için de p<0.001). CAR'ın PPROM'u teşhis etme yeteneği, ROC eğrisi analizi kullanılarak değerlendirildiğinde AUC 0,734'dür (p<0,001). PPROM ve kontrol grubunda CAR için cut off değer %64,81 duyarlılık ve %73,97 özgüllükle 0.1433 olarak bulundu. NLR'nin PPROM'u teşhis etme yeteneği, ROC eğrisi analizi kullanılarak değerlendirildiğinde AUC 0,650'dir (p<0,001). Gruplar arasında NLR için cutt off değer %49,59 duyarlılık ve %87,67 özgüllükle 5,3937 olarak tespit edildi. PLR ise gruplar arasında karşılaştırıldığında anlamlı bir fark tespit edilmemiştir (p= 0.121).

Sonuç: CAR ve NLR, maternal ve neonatal iyilik halinin sağlanmasına yardımcı olabilecek, PPROM'un erken teşhisi için kullanılabilecek uygun maliyetli, kullanımı kolay ve pratik bir belirteç olabilir.

Anahtar Kelimeler: Albümin, CRP/albümin oranı, prematüre preterm membran rüptürü, nötrofil/lenfosit oranı, trombosit/lenfosit oranı

ABSTRACT

Objective: This study aimed to evaluate the relationship between C-reactive protein to albumin ratio (CAR), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and preterm premature rupture of membranes (PPROM).

Materials and Methods: This prospective study included 143 pregnant women diagnosed with PPROM between 24 and 37 weeks of gestation who presented with leakage of fluid to the Obstetrics and Gynecology Clinic of Necmettin Erbakan University Meram Faculty of Medicine between January 2021 and July 2021. The control group consisted of 108 pregnant women with spontaneous preterm birth without PPROM. Demographic data and complete blood count results were recorded and compared.

Results: There were no statistically significant differences between the groups regarding age, gravidity, parity, and gestational age (p=0.881, p=0.888, p=0.912, p=0.916, respectively). CAR and NLR were significantly higher in the PPROM group compared to the control group (p<0.001 for both ratios). The ability of CAR to diagnose PPROM, evaluated using ROC curve analysis, yielded an AUC of 0.734 (p<0.001). The cut-off value for CAR was 0.1433 with 64.81% sensitivity and 73.97% specificity. The ability of NLR to diagnose PPROM, evaluated using ROC curve analysis, yielded an AUC of 0.650 (p<0.001). The cut-off value for NLR was 5.3937 with 49.59% sensitivity and 87.67% specificity. There was no significant difference in PLR between the groups (p=0.121).

Conclusion: CAR and NLR may be cost-effective, easy-to-use, and practical markers for the early diagnosis of PPROM, which could contribute to improved maternal and neonatal well-being.

Keywords: Albumin, CRP/Albumin Ratio, Preterm Premature Rupture of Membranes, Neutrophil/Lymphocyte Ratio, Platelet/Lymphocyte Ratio

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INTRODUCTION

Premature rupture of membranes (PROM) is defined as the rupture of fetal membranes before the onset of uterine contractions, regardless of gestational age. Preterm premature rupture of membranes (PPROM) refers to rupture before 37 weeks of gestation. PPROM complicates approximately 5-10% of all pregnancies (1) and is responsible for 40% of spontaneous preterm births (2).

PPROM is the most common cause of premature birth requiring neonatal intensive care and neonatal complications. Common complications in preterm births due to PPROM include respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and sepsis. In neglected cases, maternal complications such as endometritis, sepsis, disseminated intravascular coagulopathy, adult respiratory distress syndrome, and renal failure can develop as a result of chorioamnionitis (3). The fetus is at greater risk than the mother for morbidity and mortality associated with PPROM (4).

Although the pathophysiological mechanism is speculative, infection and inflammatory processes play a significant role in the etiology of PPROM (5). The immune response to bacterial colonization of the endocervix and/or fetal membranes can lead to localized weakening of the fetal membranes and trigger numerous inflammatory cascades that can result in PPROM (6). The role of inflammation in PPROM has been evaluated in numerous studies, and a significant relationship has been reported between various inflammatory markers and PPROM (7-9). C-reactive protein (CRP), due to its short half-life, can be used as a marker in the early stages of inflammation. Several studies have shown that CRP is elevated in pregnant women with PPROM who have chorioamnionitis or intra-amniotic inflammation and can predict the time to delivery (latent period) (10,11).

In chronic inflammatory processes, megakaryocytic lineages progressively increase, and lymphocyte counts tend to decrease due to severe apoptosis. Consequently, markers such as the platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR), obtained from complete blood counts, can be affected in severe chronic inflammatory diseases (12,13). Albumin, a negative acute-phase reactant synthesized by the liver, decreases in concentration during inflammation. Previous studies have shown that albumin levels are associated with inflammation severity, disease prognosis, and mortality (14,15).

Despite extensive research, an ideal marker that can predict the latent period and enable early detection of infection or chorioamnionitis in PPROM has not yet been translated into clinical practice. This study aimed to investigate the relationship between PPROM and C-reactive protein to albumin ratio (CAR), NLR, and PLR, which are increasingly researched and thought to be elevated due to inflammation, a key factor in the etiology of PPROM.

MATERIALS AND METHODS

This prospective observational study included 143 pregnant women diagnosed with PPROM who presented with leakage of fluid to the Obstetrics and Gynecology Clinic of Necmettin Erbakan University Meram Faculty of Medicine between January 2021 and July 2021. The control group consisted of 108 pregnant women with spontaneous preterm birth without PPROM.

The study was initiated following approval from the Necmettin Erbakan University Meram Faculty of Medicine Clinical Research and Ethics Committee (Number: 2021/2996). All participating pregnant women were informed about the study, and their consent was obtained through written and verbal informed consent forms. The study was conducted in accordance with the latest principles of the Declaration of Helsinki.

Cases with PPROM diagnosed between 24 and 37 weeks of gestation and eligible for recording complete blood samples and other clinical perinatal findings were included in the study. The exclusion criteria included maternal systemic disease, hematological disease, malignancy, autoimmune disease, infection or acute febrile illness, any inflammatory disease of pregnancy such as gestational diabetes mellitus and preeclampsia, severe anemia (Hgb < 10 g/dL), fetal chromosomal disease, intrauterine growth restriction and stillbirth, any invasive procedure (amniocentesis, etc.), smoking or alcohol use, and use of steroid-containing or other medications that could affect blood parameters.

Age, gestational week, gravidity, and parity were recorded. Complete blood counts and biochemistry results from maternal antecubital vein blood samples taken upon admission were recorded. All biochemical parameters were analyzed from a single serum sample. Complete blood counts were tested using an Automated Blood Cell Analyzer (Pentra 120 Retic Hematology Analyzer, ABX, Montpellier, France). Biochemical parameters were determined by an Automated Biochemical Analyzer 7600-120 (Hitachi High Technologies, Japan).

Leukocyte, lymphocyte, neutrophil, monocyte, platelet, CRP, and albumin values were obtained from peripheral blood samples. NLR was calculated by dividing the neutrophil count by the lymphocyte count; PLR by dividing the platelet count by the lymphocyte count; and CAR by dividing the CRP level by the albumin level.

Healthy pregnant women in the control group with preterm labor and confirmed absence of premature rupture of membranes were selected to match the PPROM group in terms of age, gestational week, and body mass index (BMI). Since CRP levels are known to be affected by conditions involving endothelial damage and infectious inflammatory events, healthy pregnant women without any morbidity that could cause endothelial damage were included in the control group.

The PPROM group consisted of 143 pregnant women diagnosed with premature rupture of membranes who presented to our clinic with vaginal fluid drainage or perineal wetness, showed active leakage or pooling of fluid upon sterile speculum examination, and had a positive nitrazine test or Amnisure™ kit test based on PAMG-1 detection. All cases with confirmed PROM admitted to our clinic received antibiotic

prophylaxis. Antenatal corticosteroids (betamethasone, 12 mg intramuscularly, 2 doses 24 hours apart) were administered to all cases with gestational age less than 34 weeks.

Statistical Analysis

All collected data were analyzed using the Statistical Package for the Social Sciences, version 23 (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was used to assess the normal distribution of continuous variables. Normally distributed continuous variables were expressed as mean ± standard deviation, non-normally distributed continuous variables as median (25th percentile - 75th percentile), and categorical variables as number (%). Student's t-test was used to compare normally distributed continuous variables, while the Mann-Whitney U test was used for non-normally distributed continuous variables. The chi-square test was used to compare categorical variables. Statistical significance was set at $p < 0.05$.

RESULTS

There were no statistically significant differences between the groups in terms of age, gravidity, parity, and gestational age. The mean age was similar in both groups: 28.3 ± 5.4 years in the PPROM group and 28.6 ± 5.4 years in the control group (p=0.881). The mean gestational age was also similar: 33.8 ± 3.1 weeks in the PPROM group and 34.8 ± 1.1 weeks in the control group (p=0.916). Gravidity and parity were 2.0 (1.0, 4.0) and 1 (0, 2) for the PPROM group, and 2.0 (1.0, 3.5) and 1 (0, 1) for the control group, respectively (p=0.888 and p=0.912). (Table 1)

Regarding hematological parameters, the median leukocyte count was 11.550 (10.375-13.965)/mm^3 in the PPROM group and 10.300 (8.790-11.500)/mm^3 in the control group. Neutrophil counts were 8.665 (7.800-10.757)/mm^3 and 7.550 (6.565-8.900)/mm^3 in the PPROM and control groups, respectively. Statistically significant differences were observed between the groups for both neutrophil and leukocyte counts (p<0.001). Lymphocyte counts were 1.795 (1.375-2.420)/mm^3 and 1.750 (1.460-2.330)/mm^3, and monocyte counts were 650 (500-860)/mm^3 and 580 (485-755)/mm^3 in the PPROM and control groups, respectively. There were no significant differences between the groups for lymphocyte and monocyte counts (p=0.510 and p=0.154, respectively). While CRP values differed significantly between the groups [PPROM group: 7.9 (3.6, 12.6) mg/dL, control group: 3.3 (2.0, 5.4) mg/dL] (p<0.001), albumin values [PPROM group: 37.5 (33.4, 40.5) g/L, control group: 38.8 (36.4, 40.4) g/L] (p=0.069) did not show a statistically significant difference.

The NLR was 4.6 (3.5, 7.2) in the PPROM group and 4.1 (3.7, 5.2) in the control group, showing a statistically significant elevation in the PPROM group (p<0.001). The CAR was 0.18850 (0.09003, 0.34868) in the PPROM group and 0.08097 (0.05601, 0.14917) in the control group, also significantly higher in the PPROM group (p<0.001). The PLR was 133.2 (105.4, 163.9) in the PPROM group and 117.7 (100.2, 143.0) in the control group, with no significant difference between the groups (p=0.121). (Table 2)

The ability of CAR to diagnose PPROM was evaluated

Table 1. Comparison of Demographic Characteristics of the Groups

	PPROM grup (n=143)	Control Group (n=108)	p-value
Age (years)	28.3 ± 5.4	28.6 ± 5.4	0.881[a]
Gestational Age (weeks)	33.8 ± 3.1	34.8 ± 1.1	0.916[a]
Gravida (number)	2.0 (1.0, 4.0)	2.0 (1.0, 3.5)	0.888[b]
Parity (number)	1 (0, 2)	1 (0,1)	0.912[b]

Data are presented as mean ± standard deviation, median (25th Percentile – 75th Percentile), or number (%). p-values were determined using Student's t-test or Mann-Whitney U test PPROM: Preterm Premature Rupture of Membranes; n: number

Table 2. Comparison of Laboratory Parameters of the Groups

	PPROM Group (n=143)	Control Group (n=108)	p-value
Leukocytes (/mm^3)	11550 (10375-13965)	10300 (8790-11500)	**<0.001[b]**
Neutrophils (/mm^3)	8665 (7800-10757)	7550 (6565-8900)	**<0.001[b]**
Lymphocytes (/mm^3)	1795 (1375-2420)	1750 (1460-2330)	0.510[b]
Monocytes (/mm^3)	650 (500-860)	580 (485-755)	0.154[b]
Platelets (/mm^3)	245158 ± 63864	228931 ± 68622	0.655[a]
Albumin (g/L)	37.5 (33.4-40.5)	38.8 (36.4-40.4)	0.069[b]
CRP (mg/dL)	7.9 (3.6-12.6)	3.3 (2.0-5.4)	**<0.001[b]**
Neutrophil/Lymphocyte Ratio	4.6 (3.5-7.2)	4.1 (3.7-5.2)	**<0.001[b]**
Platelet/Lymphocyte Ratio	133.2 (105.4-163.9)	117.7 (100.2-143.0)	0.121[b]
CRP/Albumin Ratio	0.18850 (0.09003-0.34868)	0.08097(0.05601-0.14917)	**<0.001[b]**

Data are presented as mean ± standard deviation, median (25th Percentile – 75th Percentile), or number (%). P-values were determined using Student's t-test a, Mann-Whitney U test b . Significant p-values are shown in bold. WBC: White Blood Cell; CRP: C-Reactive Protein

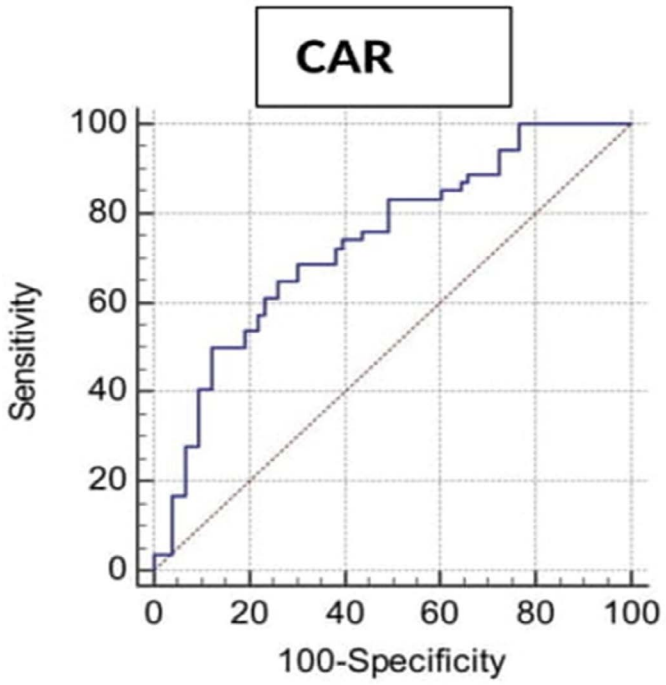

Figure 1. Receiver operating characteristics (ROC) curve analysis of C-reactive protein to albumin ratio (CAR) between the PPROM and Control groups (Optimal ROC cutoff value: 0.1433 with 64.81% sensitivity and 73.97% specificity, AUC: 0.734, p<0.001)

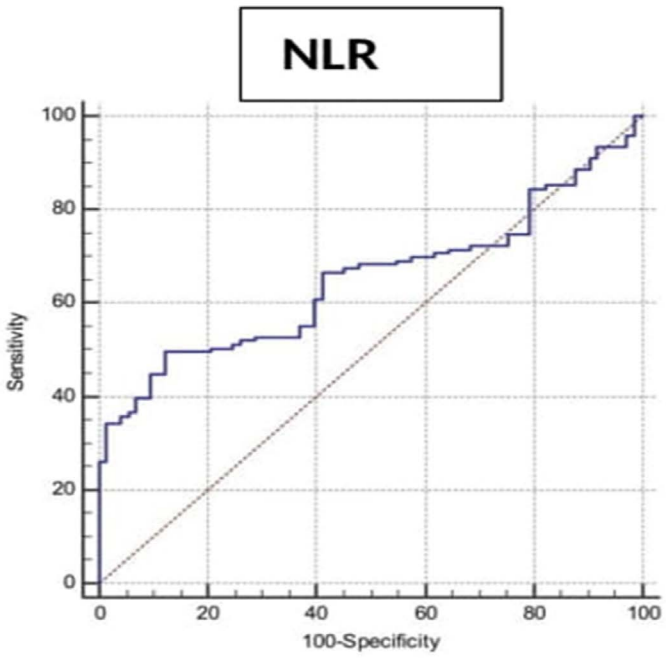

Figure 2. Receiver operating characteristics (ROC) curve analysis of neutrophil-lymphocyte ratio (NLR) between the PPROM and Control groups (Optimal ROC cutoff value: 5.3937 with 49.59% sensitivity and 87.67% specificity, AUC: 0.650, p<0.001)

using ROC curve analysis, yielding an AUC of 0.734 (p<0.001). The cut-off value for CAR was determined to be 0.1433 with 64.81% sensitivity and 73.97% specificity (Figure 1). The ability of NLR to diagnose PPROM was also evaluated using ROC curve analysis, yielding an AUC of 0.650 (p<0.001). The cut-off value for NLR was 5.3937 with 49.59% sensitivity and 87.67% specificity (Figure 2).

DISCUSSION

The main findings of our study are: Both NLR and CAR were significantly higher in the PPROM group compared to the control group. However, there was no significant difference in PLR between the groups. Furthermore, an NLR value >5.3937 and a CAR value >0.1433 were associated with an increased risk of PPROM.

PPROM remains a significant problem in obstetrics due to challenges and uncertainties in its etiology and associated serious maternal and fetal risks. PPROM occurs in approximately 1-3% of all pregnancies and in about one-third of preterm births (16). Although its exact pathophysiology is still debated, PPROM leads to common and severe pregnancy complications such as RDS, intraventricular hemorrhage, necrotizing enterocolitis, sepsis, and sudden intrauterine death due to umbilical cord compression. Recent studies have shown that the primary etiological mechanism of PPROM is inflammation (17,18).

Cytokines involved in inflammatory reactions have been reported to be associated with PPROM. Satar et al. reported increased interleukin (IL)-8 levels in maternal serum and umbilical cord in PPROM. Similarly, IL-6 was found to be elevated only in the umbilical cord, especially in PPROM with microbial invasion and histological chorioamnionitis (19). CRP is another frequently used marker indicating the early stages of inflammation. Another study by Popowski et al. (20) showed that CRP is elevated in PPROM patients with clinical and histopathological chorioamnionitis.

NLR has recently been used as a marker of subclinical inflammation and has been found useful in detecting inflammation along with other inflammatory markers in various diseases such as different types of cancer, psoriasis, rheumatoid arthritis, and keratoconus (21-24). In a study by Köseoğlu et al. (25), NLR was found to be higher in the PPROM group compared to the control group, concluding that NLR is a useful marker for predicting PPROM. Consistent with the literature, our study found higher NLR levels in the PPROM group.

PLR is a widely used marker proven to predict thrombotic events, inflammatory diseases, and malignancies. In pregnant women, PLR has been investigated in conditions like gestational diabetes and acute pancreatitis (26,27). Toprak E. et al. (28) also showed that PLR was statistically significantly higher in the PPROM group compared to the control group, suggesting that PLR could be an independent marker in detecting PPROM. Although our study found higher PLR in the PPROM group, the difference was not statistically significant.

CAR has been found to correlate with inflammation severity and mortality in various inflammatory diseases and malignancies such as osteosarcoma, ovarian cancer, and colon cancer (29,30). CAR has been proposed as a better indicator of the inflammatory response in septic patients compared to CRP or albumin alone (31). Our study found that this ratio was statistically significantly higher in patients with PPROM compared to the control group. Furthermore, to our knowledge, our study is the first in the literature to demonstrate the relationship between CAR and PPROM.

The first limitation of this study is its single-center design and the relatively small sample size. Secondly, it does not provide insight into predicting the latent period. Serological parameters examined in this study are nonspecific, and undiagnosed diseases (subclinical hypothyroidism, etc.) or pathologies without clinical manifestations could be misdiagnosed in both the PPROM and control groups.

In conclusion, CAR and NLR were significantly higher in the PPROM group compared to controls. CAR and NLR may be cost-effective, easy-to-use, and practical markers for the early diagnosis of PPROM, potentially contributing to improved maternal and neonatal outcomes. Further research is needed to determine the applicability of CAR and NLR as early diagnostic markers for PPROM.

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Unusual Presentations of Pediatric Brucellosis: A Case Series from a Single Center

Pediatrik Brusellozun Sıra Dışı Sunumları: Tek Bir Merkezden Bir Vaka Serisi

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ÖZET
Amaç: Bu çalışma, nadir ve ciddi komplikasyonlarla ilişkili on pediatrik bruselloz vakasını bildirmeyi amaçlamaktadır.
Hastalar ve Yöntemler: Belgelenen klinik semptomlar, laboratuvar test sonuçları, tanı ve tedavi yöntemleri, 2018 ile 2021 yılları arasında brusellozun nadir komplikasyonlarıyla başvuran on pediatrik hasta için hastane dosyalarının retrospektif olarak incelenmesi ile elde edildi.
Bulgular: Çalışmaya dahil edilen hastalardan birinde diskit, üç hastada epididimo-orşit, iki hastada tek gözde ezotropya, bir hastada immün trombositopeni, iki hastada hemofagositik lenfohistiyositoz tanısı vardı ve bir hastaya da juvenil idiyopatik artrit tanısı yanlış olarak konmuştu. Tüm vakalarda ortak bulgu, tüm hastalarda ondulan olarak karakterize edilen ateşti. Tüm çocuklarda pozitif etiyolojik veya serolojik kanıt bruselloz enfeksiyonunu doğruladı ve Brucella için standart tüp aglütinasyon testi 1:160 veya daha yüksek titrede pozitifti ve iki hastada kan kültürleri de pozitifti. Tüm hastalar yaşa göre ayarlanmış dozlarda rifampisin (10-20 mg/kg/gün, oral) ile trimetoprim/sülfametoksazol (trimetoprim 10 mg/kg/gün ve sülfametoksazol 50 mg/kg/gün) veya doksisiklin (4,4 mg/kg/gün, oral) kombinasyonu ile tedavi edildi. Yedi hastaya gentamisin (5-7,5 mg/kg/gün, intravenöz) ile ek tedavi uygulandı ve iki hastada tedaviye seftriakson (100 mg/kg/gün) eklendi. Hemofagositik lenfohistiyositoz geliştiren iki hastadan biri yoğun bakım ünitesinde tedavi edildi ve her iki hastaya da bruselloz tedavisinin yanı sıra hemofagositik lenfohistiyositoz için önerilen ek tedavi (intravenöz immünglobulin 1 gr/kg/gün, 2 gün; deksametazon 10mg/m2/gün) uygulandı. Sonunda dokuz hasta sağlıklı bir şekilde taburcu edildi, bir hasta ise komplikasyonlar sonucu öldü.
Sonuç: Brucella enfeksiyonunun yaygın olduğu bölgelerde, alışılmadık komplikasyonlara sahip pediatrik hastalardaki klinik belirtilerin bruselloz ile ilişkili olabileceğini ve diğer hastalıklardan ayırt etmek için dikkatli bir ayırıcı tanı gerektirdiğini düşünmek önemlidir.

Anahtar Kelimeler: Bruselloz, çocuklar, diskitis, epididimo-orşit, hemofagositik lenfohistiyositoz, immün trombositopeni, juvenil idiyopatik artrit, nörobruselloz

ABSTRACT
Purpose: This study aims to report ten cases of pediatric brucellosis associated with rare and severe complications.
Patients and Methods: Documented clinical symptoms, laboratory test results, diagnosis, and treatment methods were retrospectively reviewed for 10 pediatric patients who presented with rare complications of brucellosis between 2018 and 2021.
Results: One of the patients included in the study had discitis, three had epididymo-orchitis, two had esotropia in one eye, one patient had immune thrombocytopenia, two patients had hemophagocytic lymphohistiocytosis, and one patient was misdiagnosed with juvenile idiopathic arthritis. A common finding in all cases was fever, which was characterized as undulant in all patients. All children positive etiological or serological evidence confirmed the brucellosis infection and the standard tube agglutination test for Brucella was positive at a titer of 1:160 or higher, and blood cultures were also positive in two patients. All patients were treated with age-adjusted doses of rifampicin (10-20 mg/kg/day, orally), in combination with either trimethoprim/sulfamethoxazole (trimethoprim 10 mg/kg/day and sulfamethoxazole 50 mg/kg/day) or doxycycline (4.4 mg/kg/day, orally). Seven patients received additional treatment with gentamicin (5-7.5 mg/kg/day, intravenously) and ceftriaxone (100 mg/kg/day) was added to the treatment in two patients. One of the two patients who developed hemophagocytic lymphohistiocytosis was treated in the intensive care unit, and both patients received additional treatment recommended for hemophagocytic lymphohistiocytosis [intravenous immunoglobulin 1 gr/kg/day, for 2 days; dexamethasone 10 mg/m2 /day] alongside brucellosis treatment. Eventually, nine patients were discharged in good health, while one patient died as a result of complications.
Conclusion: In regions where Brucella infection is prevalent, it is important to consider that clinical manifestations in pediatric patients with unusual complications may be associated with brucellosis, warranting a careful differential diagnosis to distinguish it from other diseases.

Keywords: Brucellosis, children, discitis, epididymo-orchitis, hemophagocytic lymphohistiocytosis, immune thrombocytopenia, juvenile idiopathic arthritis, neurobrucellosis

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INTRODUCTION

Brucellosis is the most prevalent zoonotic infection. In endemic areas, the reported prevalence of brucellosis in children ranges from 10% to 30%. Brucella melitensis is the species most commonly associated with human infections. In children, the infection is typically transmitted through the consumption of unpasteurized milk and dairy products, direct contact with infected animals, and less frequently, through aerosol inhalation. Clinical manifestations can vary widely, ranging from mild illness to severe disease complicated by life-threatening conditions (1). Clinically, brucellosis is manifested by nonspecific symptoms, including fever, profuse sweating, malaise, loss of appetite, testicular enlargement, epididymitis, joint pain, skin rash, and enlarged liver, spleen, and lymph nodes. Despite the diverse symptoms, fever and arthralgia are the primary clinical signs (2). Involvement of vital organs complicates the course of the disease and is a significant cause of morbidity and mortality, especially in endemic regions (3).

Brucellosis is a significant public health concern in developing countries. Due to the nonspecific nature of clinical symptoms, misdiagnosis is common, leading to life-threatening complications. This study aims to increase awareness of brucellosis among clinicians by describing pediatric patients with severe complications of brucellosis.

PATIENTS AND METHODS

A total of 183 patients diagnosed with brucellosis at the pediatric infectious diseases clinic of a tertiary training and research hospital between 2018 and 2021 were included in the study. The medical files of these patients were reviewed retrospectively. 173 patients were excluded for not meeting the inclusion criteria. Ultimately, the study focused on 10 patients with confirmed pediatric brucellosis who presented with rare complications. The clinical symptoms, laboratory test results, diagnosis, and treatment of these patients were reviewed. Informed consent was obtained from the parents of the patients for their participation in the study.

The inclusion criteria for the study were children aged between 1 month and 18 years (216 months), with a positive Brucella standard tube agglutination (STA) test with a titer of 1/160 or higher, and unusual brucellar complications. The exclusion criteria were age outside of the prespecified range, a STA test titer below 1/160, and parental refusal to provide consent for involvement of their children in the study.

Ethics Statement

Approval was obtained from the local ethics committee for the study (No: 2024/125).

CASE PRESENTATION

Case # 1

A 199-month-old male patient presented with complaints of back pain, limping while walking, high-grade (38.5º C) fever, loss of appetite, and malaise for one month. During the physical examination, the patient was able to walk with support but exhibited limping, and there was limited active or passive spinal movement. Severe pain was noted upon percussion and palpation in the lumbar region. No palpable mass was found. The neurological examination was unremarkable. The patient had a history of living in a rural area, consuming unpasteurized milk and dairy products, along with high-grade fever, loss of appetite, and malaise. Magnetic resonance imaging (MRI) of the lumbar spine and Brucella STA test were performed for the differential diagnosis of the patient, whose laboratory findings are shown in Table 2. The lumbar MRI revealed narrowing of the L4-L5 disc space and heterogeneous contrast enhancement in the endplates, but no mass was observed (Figure 1). The Brucella STA test result was positive at a titer of 1/1280. The patient was diagnosed with brucellosis-associated discitis with the current findings. The patient was started on treatment with doxycycline (4.4 mg/kg/day, orally) and rifampicin (10-20 mg/kg/day, orally) in combination with gentamicin (5-7.5 mg/kg/day, intravenously). Gentamicin was discontinued on the 14th day of treatment, and the patient received treatment for a total of 16 weeks. The patient improved without any sequelae, and no complications developed during follow-up.

Cases # 2,3, and 4

Three patients (aged 55, 110, and 190 months, respectively) presented with swelling, redness, and pain in the scrotum. On

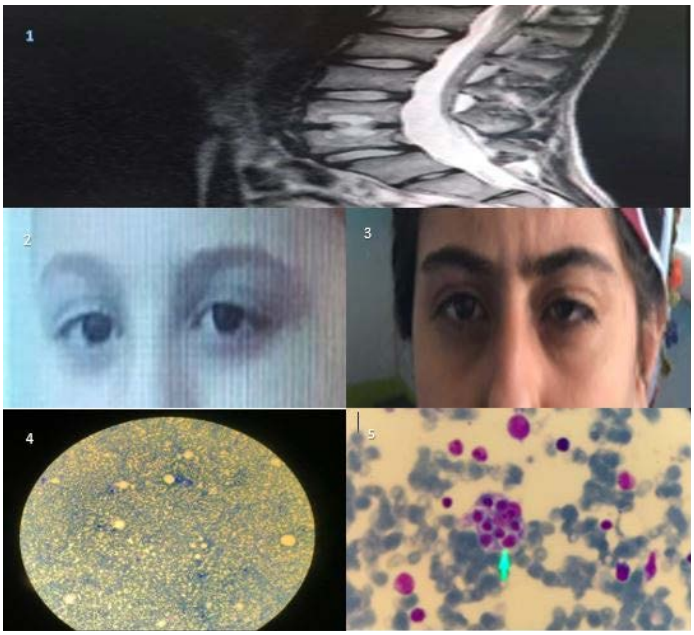

Figure 1A. Magnetic resonance imaging of the vertebra in a patient diagnosed with discitis **2A.** Image of the eyes of a patient diagnosed with neurobrucellosis. **3A** Image of the eyes of a patient diagnosed with neurobrucellosis. **4A.** Bone marrow aspiration smear image of a patient diagnosed with IT. **5A.** Bone marrow aspiration smear image of a patient diagnosed with HLH

Table 1. Epidemiological data, diagnosis and treatment of the patients

Case #	1	2	3	4	5	6	7	8	9	10
Diagnosis	Brucellosis	Brucellosis	Brucellosis	Brucellosis	Brucellosis	Brucellosis	Brucellosis	Brucellosis	Brucellosis	Brucellosis
Complication	Discitis	Epididymo-orchitis	Epididymo-orchitis	Epididymo-orchitis	Neuro-brucellosis	Neuro-brucellosis	Immune-mediated Thrombo-cytopenia	HLH	HLH	JIA
Age (months)	199	55	110	190	135	196	59	46	11	86
Sex	Male	Male	Male	Male	Female	Female	Female	Female	Male	Female
Presenting Symptoms	Fever, Loss of appetite, Malaise, Back pain, Limping	Fever, Loss of appetite, Malaise, Arthralgia, Scrotal swelling, Scrotal redness, Testicular pain	Fever, Loss of appetite, Malaise, Arthritis Testicular swelling, Testicular pain	Fever, Loss of appetite, Malaise, Arthralgia, Testicular swelling, Testicular pain	Fever, Headaches, Nausea, Malaise Diplopia, Ptosis	Fever Headaches, Nausea, Malaise Diplopia, Ptosis	Fever Weight Loss, Malaise, Knee Pain, Jaundiced Skin	Fever, Rash, Malaise Loss of appetite, Arthralgia	Fever, Malaise, Abdominal swelling	Fever, Malaise, Rash, Arthritis
Medications and Treatment Duration for Brucellosis	Doxycycline (16 weeks) Rifampicin (16 weeks) Gentamicin (2 weeks)	TMP-SMX (6 weeks) Rifampicin (6 weeks) Gentamicin (5 days)	Doxycycline (6 weeks) Rifampicin (6 weeks) Gentamicin (5 days)	Doxycycline (6 weeks) Rifampicin (6 weeks) Gentamicin (5 days)	Doxycycline (6 months) Rifampicin (6 months) Ceftriaxone (1 month)	Doxycycline (6 months) Rifampicin (6 months) Ceftriaxone (1month)	TMP-SMX (6 weeks) Rifampicin (6 weeks) Gentamicin (5 days)	TMP-SMX (6 weeks) Rifampicin (6 weeks) Gentamicin (5days)	TMP-SMX (17 days) Rifampicin (17 days) Gentamicin (5 days)	TMP-SMX (6 weeks) Rifampicin (6 weeks)

HLH, Hemophagocytic lymphohistiocytosis; JIA: juvenile idiopathic arthritis; TMP-SMX: Trimethoprim/Sulfamethoxazole

physical examination, the scrotum appeared red, painful to touch, and swollen, and body temperature was elevated. One patient had hepatomegaly, another had hepatosplenomegaly, while the third had no organomegaly. Scrotal color Doppler and ultrasound (US) examinations of the patients, whose laboratory findings are presented in Table 2, revealed heterogeneous structures of the testicles, expansion of the epididymis and spermatic cord, and increased echogenicity and vascularity. It was learned that all three had elevated fever, loss of appetite, malaise, symptoms of arthralgia and/or arthritis, along with a history of consuming unpasteurized milk and dairy products. For differential diagnosis, PPD skin test (for tuberculosis) and Brucella STA test were performed for the patients (Table 2). The patients were diagnosed with bilateral epididymo-orchitis associated with brucellosis. The patients were started on treatment for 6 weeks with age-appropriate doses of rifampicin (10-20 mg/kg/day, orally), in combination with either trimethoprim (TMP) /sulfamethoxazole (SMX) (TMP 10 mg/kg per day and SMX 50 mg/kg per day) or doxycycline (4.4 mg/kg/day, orally). Additionally, gentamicin (5-7.5 mg/kg/day, intravenously) was administered for 5 days (Table 1). Follow-up scrotal Doppler and US examinations were performed on the 15th and 42nd days of treatment, revealing resolution of all symptoms.

Cases # 5 and 6

Two female patients (aged 135 and 196 months, respectively) presented with complaints of headache, high-grade fever, nausea, malaise, diplopia, and ptosis. On physical examination, both patients had fever (38.7° C and 38.4 ° C), and the right and left upper (respectively) eyelids were ptotic, downward and inward deviation of the eyes, with limited outward gaze in both patients, while other eye movements were normal (Figures 2 and 3). Fundoscopic examination showed papilledema and abducens nerve palsy. Other systemic and neurological examination results were normal. Their laboratory results are shown in Table 2. Both patients had a history of living in areas where brucella is prevalent and consuming unpasteurized milk and dairy products. Brucella SAT test results were positive with a titer of 1/5120 for both patients. To exclude other potential causes of abducens nerve palsy, radiological imaging studies and lumbar puncture were performed. There were no remarkable findings in the orbital MRI and MR angiography of the patient (Case# 5), whose LP test results are given in table 2; however, cranial MRI showed several nonspecific hyperintense foci in the white matter of bilateral frontoparietal lobes on FLAIR imaging. The other patient's (Case# 6) orbital MRI, cranial MRI, and MR angiography were normal. In addition LP-specific laboratory results are presented in Table 2. With these findings, both patients were diagnosed with neurobrucellosis. The patients were started on treatment with ceftriaxone (100 mg/kg/day, intravenously), doxycycline (4.4 mg/kg/day, orally), and rifampicin (10-20 mg/kg/day, orally). On the 15th day of treatment, it was observed that eye movements were normal, except for mild limitation of outward gaze. Ceftriaxone was discontinued after four weeks. After two months, eye movements returned to normal in all directions. Treatment with the other medications (doxycycline and rifampicin) continued for six months, and by the sixth month, the Brucella agglutination tests were negative. No recurrence was observed during the one-year follow-up.

Table 2. Laboratory Investigations

Case #	1	2	3	4	5	6	7	8	9	10
Hemoglobin (g/dL)	13.2	10.5	12	12.8	11.7	13.06	7.05	8.1	5.5	8.3
Platelets (mm^3/uL)	322,000	9,800	103,000	554,000	275,000	355,000	62,720	109,000	59,000	705,000
WBC (mm^3/uL)	9131	3700	11500	22500	7167	8617	3500	4080	7700	25450
Neutrophils (10^3/uL)	5436	2730	7900	18400	3018	4126	890	3250	5320	18700
Lymphocytes(10^3/uL)	2460	954	2900	3680	3706	3769	2430	755	1990	4560
Urea(mg/dL)	51	29	19	34	23	15	21	51	39	11
Creatinine (mg/dL)	0.71	0.6	0.34	0.84	0.62	0.65	0.56	1.2	0.91	0.34
AST (U/L)	54	65	93	156	25	32	594	110	99	38
ALT (U/L)	49	94	80	221	22	35	251	174	86	45
LDH (U/L)	184	351	162	278	205	187	1414	421	895	301
Triglyceride (mg/dL)	98	-	-	-	-	-	-	511	304	-
Fibrinogen (mg/dL)	-	-	-	-	-	-	-	148	186	-
CRP (mg/dL)	18.2	42	32	66	17	29	11.5	78	57	71
ESR (mm/h)	51	40	21	53	7	32	28	63	48	98
Ferritin (ng/dL)	-	-	-	-	-	-	-	1295	>1500	-
Blood culture	Brucella spp.	No growth	No growth	No growth	No growth	No growth	No growth	Brucella spp.	No growth	No growth
Brucella STA Test	1/1280	1/640	1/640	1/1280	1/5120	1/5120	1/2560	1/5120	1/1280	1/320
CSF Protein (mg/dL)	-	-	-	-	145	37	-	-	-	-
CSF Glucose (mg/dL)	-	-	-	-	28 (blood glucose: 74)	39 (blood glucose: 86)	-	-	-	-
CSF Cellularity (/mm^3)	-	-	-	-	12 (lymphocytes)	8 (lymphocytes) 5-6 (erythrocytes)	-	-	-	-
CSF Culture	-	-	-	-	No growth	No growth	-	-	-	-
CSF Brucella Tube Agglutination Test	-	-	-	-	1/80	1/160	-	-	-	-
Toxoplasma Ig M	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Epstein-Barr Virus PCR	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Herpes Simplex Virus PCR	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Cytomegalovirus PCR	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Rubella IgM	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Parvovirus B19 PCR	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
HIV Ag/Ab	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Mumps Ig M	-	Negative	Negative	Negative	-	-	-	-	-	-
PPD	-	4 mm	0 mm	5 mm	-	-		-	-	-
ANA	-	-	-	-	-	-		-	-	Negative
RF (IU/mL)	-	-	-	-	-	-	-	-	-	Negative

ANA, anti-nuclear antibody; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CSF, cerebrospinal fluid; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; PCR, polymerase chain reaction; PPD, purified protein derivative; RF, rheumatoid factor; STA, standard tube agglutination; WBC, white blood cell

Case # 7

A 59-month-old girl presented with symptoms of persistent high-grade fever (38.6º C), malaise, knee pain, weight loss, and jaundice for one month. Physical examination revealed jaundiced skin and sclera, as well as hepatosplenomegaly. Other systemic examinations were unremarkable. The patient had a history of consuming unpasteurized dairy products. STA with Coombs' antiserum showed a positive titer of 1/2560. Abdominal US findings of the patient, whose laboratory results are presented in Table 2, confirmed hepatosplenomegaly. Treatment was initiated with trimethoprim/sulfamethoxazole (TMP 10 mg/kg per day and SMX 50 mg/kg per day), rifampicin (10-20 mg/kg/day, orally), and gentamicin (5-7.5 mg/kg/day, intravenously) for five days. At the 15th-day follow-up, the patient's fever was under control, and all blood values were normal. However, on the 38th day of treatment, the patient returned with complaints of bruising and rash on various parts of her body. Aside from generalized ecchymoses and petechiae, no abnormal physical examination findings were noted. Laboratory tests revealed thrombocytopenia. Prothrombin time and activated partial thromboplastin time were normal. STA test was positive at a titer of 1/640. The bone marrow aspiration showed increased number of megakaryocytes and no hemophagocytosis was observed (Figure 4). Based on the aforementioned findings, the patient was diagnosed with immune-mediated thrombocytopenia (IT) induced by brucellosis and was treated with intravenous immunoglobulin (1 g/kg/day for 2 days). Following treatment, the platelet count rose to 240,000/mm^3. At the one-year follow-up, she received treatment once more for IT relapse, but no relapse related to brucellosis was observed.

Case # 8

A 46-month-old girl presented with high-grade fever (39º C), joint pain, malaise, and loss of appetite persisting for 2-3 weeks. On physical examination, the patient had a petechial rash that did not fade when pressed, and hepatomegaly. There was also swelling, increased temperature, and limited movement in the left knee. From the patient's history, it was learned that her mother had been diagnosed with brucellosis one month prior and that the patient also consumed unpasteurized dairy products. The patient's STA test was positive at a titer of 1/5120. Brucella spp. growth was observed on her blood culture. Given the patient's poor general condition, she was hospitalized and started on intravenous supportive therapy along with TMP (10 mg/kg per day and SMX 50 mg/kg per day), rifampicin (10-20 mg/kg/day, orally), and gentamicin (5-7.5 mg/kg/day, intravenously) for five days. However, fever persisted despite treatment, and the patient was re-evaluated on the sixth day of treatment. See Table 2 for the patient's laboratory results. Her clinical and laboratory findings led to the suspicion of Brucellosis-induced hemophagocytic lymphohistiocytosis (HLH), and a bone marrow aspiration was performed to confirm HLH (Figure 5). The results of bone marrow aspirate examination were consistent with HLH. While continuing the treatment for brucellosis, additional HLH-targeted therapies (intravenous immunoglobulin 1g/kg/day dose and 2 days, dexamethasone 10mg/m2/day for 2 weeks, then dexamethasone dose was tapered and stopped) were initiated, and fever control was achieved within 48 hours. After 14 days of in-hospital treatment, the patient was discharged for outpatient follow-up. At the third-week follow-up, her general condition was good, arthritis had completely resolved, and she had not had a fever for 15 days. Thereafter, the patient's treatment was continued on an outpatient basis for a total of 42 days.

Case # 9

An 11-month-old boy presented with complaints of persistent high-grade fever, malaise, yellowing of the skin, and abdominal swelling for two weeks. Physical examination revealed jaundiced skin and hepatosplenomegaly. Abdominal US imaging confirmed hepatosplenomegaly. The patient was fed unpasteurized dairy products by his mother. STA test was positive at a titer of 1/1280. Treatment was initiated with TMP (10 mg/kg per day and SMX 50 mg/kg per day), rifampicin (10-20 mg/kg/day, orally), and gentamicin (5-7.5 mg/kg/day, intravenously) for five days. Despite treatment with antibiotics, fever persisted and the patient developed pronounced hypotension, and required intensive care due to respiratory distress. His ferritin and triglyceride levels were elevated, and fibrinogen level was low (Table 2). Given the suspicion of Brucella-induced HLH, a bone marrow aspiration was performed; however, no evidence of hemophagocytosis was found. The patient, already receiving brucella treatment, was diagnosed with HLH due to the fulfillment of the other five (fever, bicytopenia, splenomegaly, hyperferritinemia, hypertriglyceridemia) criteria. Treatment for HLH (intravenous immunoglobulin at a dose of 1g/kg/day/IV, 2 day and dexamethasone 10 mg/m2/day/IV) was initiated but the patient didn't respond to the pharmacological treatment and passed away on the 17th day of treatment.

Case # 10

An 86-month-old girl presented with fatigue, widespread rash on her body, fever. She also presented with swelling, pain, redness and increased heat in her right knee. From her history, it was learned that her complaints had started approximately five weeks ago, that she lived in a rural area, and that her family was involved in animal husbandry. On physical examination, the right knee was swollen, red, and had limited mobility. Additionally, hepatosplenomegaly was present. The patient also had macular, erythematous rashes throughout her body that blanched with pressure, along with fever.

The patient was diagnosed with juvenile idiopathic arthritis (JIA) and had been on methylpredisolone 1 mg/kg/day treatment for eight days. Prior to methylpredisolone therapy, a bone marrow aspiration was performed, which did not reveal any findings suggestive of malignancy. Rheumatic tests were requested; however, treatment with corticosteroids had already begun before the results were available (Table 2). After the initiation of methylpredisolone therapy, her symptoms didn't resolve, and her STA test was positive at a titer of 1/320. The patient's methylpredisolone treatment for JIA was discontinued and TMP/ SMX (TMP 10 mg/kg per day and

SMX 50 mg/kg per day), rifampicin (10-20 mg/kg/day, orally) treatment was started. By the fourth day of treatment, fever control was achieved, and by the 17th day, all other clinical findings resolved. The patient received treatment for a total of 42 days. At the one-year follow-up, she was symptom-free and no relapse was observed.

DISCUSSION

Brucellosis is a zoonotic disease caused by Brucella, a gram-negative coccobacillus. Brucella can be transmitted directly through contact with infected animals or indirectly through the consumption of unpasteurized dairy products. In humans, brucellosis can affect any organ or system. The most common complication is osteoarticular involvement, which includes arthritis, spondylitis, and sacroiliitis, along with a multitude of nonspecific clinical symptoms such as fever and chills, muscle and joint pain, headaches, and sweating (4).

The treatment of brucellosis involves the use of rifampicin in combination with doxycycline or TMP-SMX, taking into account the patient's age. Depending on the severity of the disease and the presence of complications, gentamicin or streptomycin may also be added to the treatment regimen. The duration of treatment varies based on the presence of complications and the affected organs, ranging from six weeks to six months (4,5).

The most prevalent osteoarticular manifestation in children is monoarticular arthritis (usually in the knees and hips), while in adults, the sacroiliac joints (up to 80%) and spinal joints (up to 54%) are most commonly involved. In our patient (Case #10), JIA was initially considered due to the presence of fever and skin rash along with knee arthritis. After excluding malignancy, corticosteroid treatment was initiated. Although it was possible for the patient to receive a diagnosis of JIA based on the existing findings, it is essential to first consider brucellosis in an endemic region, as the likelihood of cure without sequelae is much higher with appropriate treatment. Studies on spinal brucellosis indicate that the predominant radiological finding is spondylitis or spondylodiscitis, followed by pre- or paravertebral abscesses. The most frequently affected area is at the L5-S1 level (6-9).

Spinal brucellosis typically manifests as back pain radiating to the legs, fever, sweating, and weight loss. Neurological symptoms may occur, and the severity of the symptoms depends on the extent of disk involvement, inflammation of the vertebral body, and the pressure effects on the spinal canal (10). Diagnosis is challenging due to symptom overlap with other chronic disorders, including tuberculosis and pyogenic osteomyelitis. The diagnosis of spinal TB primarily relies on the clinical manifestations of the disease, the history of exposure to the infectious source, spinal imaging findings, and laboratory investigations. MRI is the preferred imaging modality for diagnosing spinal brucellosis due to its high diagnostic sensitivity. Spinal MRI can reveal spondylitis, spondylodiscitis, or spinal canal stenosis along with epidural abscesses (11). Brucellar spondylitis requires a longer duration of antibiotic treatment compared to uncomplicated brucellosis and may necessitate surgical intervention. Delayed initiation of treatment can lead to long-term disability (4). A literature review revealed a lack of studies regarding brucellar discitis in children. In our patient (Case #1), lumbar MRI showed narrowing at the L4-L5 disc space and heterogeneous contrast enhancement in the endplates on T1- and T2-weighted images, which were suggestive of discitis. The STA test results also supported the diagnosis of brucellosis, and the patient was treated with oral doxycycline and rifampicin for four months. Additionally, gentamicin was administered during the first two weeks of treatment. The patient was followed at the pediatric infectious diseases clinic for six months. With early diagnosis and treatment, the patient recovered without sequelae.

Brucellar epididymo-orchitis, which occurs very rarely in children and adolescents, can present as the first sign of systemic disease or develop later on. The most common symptoms of the disease include pain and swelling in the testes, with less frequent occurrences of scrotal redness and increased temperature, as seen in our patient. Brucella species can cause granulomatous orchitis, which can mimic neoplasia in both clinical and ultrasound examinations. If the testis is focally involved, differential diagnoses should include testicular tumor, abscess, intratesticular hematoma. Early and accurate diagnosis of brucellar epididymo-orchitis is crucial to prevent severe complications and unnecessary orchiectomy due to misdiagnosis. In patients presenting with scrotal pain and swelling, brucellar epididymo-orchitis should always be considered among the differential diagnoses, especially when risk factors such as living in an endemic area and consumption of unpasteurized milk and dairy products are present. As with other forms of brucellosis, epididymo-orchitis should be treated for at least six weeks using a combination of rifampicin with TMP-SMX or doxycycline. Aminoglycosides may also be added for 5-7 days (4,12-14).

Neurobrucellosis occurs very rarely in the pediatric age group, accounting for approximately 0.8% of brucellosis cases. The involvement of the nervous system in brucellosis can lead to meningitis, encephalitis, meningoencephalitis, cerebellar dysfunction, radiculitis, myelitis, epidural abscess, meningovascular disease, cranial nerve involvement, seizures, brain abscess, and demyelination (16). Isolated cranial nerve involvement in neurobrucellosis is extremely rare, with only a few reports of isolated abducens nerve paralysis. The pathogenesis of abducens nerve paralysis involves the spread of meningeal infection and possible vasculitic process (17). Neurobrucellosis can develop at any stage of the disease. Due to the slow-growing nature of Brucella bacteria, cerebrospinal fluid (CSF) and blood cultures may yield negative results. Therefore, serological methods are typically used to optimize diagnosis. Definitive diagnosis is made upon detection of Brucella antibodies in CSF (18). Neurobrucellosis is a serious and rare complication of brucellosis, and although it is rare, it should be suspected in almost all neurological symptoms, particularly when they occur in individuals residing in endemic regions. The clinical and radiological manifestations of the disease are highly diverse and tend to mimic many other

diseases. Therefore, suspicion of brucellosis and investigation of the history of consuming unpasteurized dairy products are essential for early diagnosis with brucella-specific serological tests.

Active brucellosis may present with hematological findings including anemia, leukopenia, thrombocytopenia, and rarely, pancytopenia. Mild anemia and leukopenia are the most common hematological findings, while severe thrombocytopenia has been reported less frequently. The prevalence of thrombocytopenia ranges from 5% to 40%. (19,20). In our patient (Case #7), the initial decrease in platelet count occurred as a secondary effect of brucellosis and returned to normal shortly after the initiation of treatment. However, thrombocytopenia later re-emerged due to unidentified triggers. The Coombs' Controls test with antiserum and STA were performed due to the newly developed thrombocytopenia, and no increase in titer was observed. The Brucella IgM test was negative, while the Brucella IgG test was positive. The patient was diagnosed with IT as a result of bone marrow aspirate examination. The platelet counts returned to normal with appropriate treatment of IT. This case report highlights that thrombocytopenia in brucellosis may not always be part of the disease and can emerge in the form of IT, which requires entirely different treatment and management.

HLH is classified into primary and secondary types. Secondary HLH (sHLH) is associated with systemic viral, bacterial, fungal, or parasitic infections, malignancies, and autoimmune diseases (21,22).

Hyperactivation of the immune system in response to infections and the subsequent development of HLH are common triggers in patients with genetic predisposition as well as in sporadic cases without an underlying genetic cause. While the most common infectious triggers are viral infections, particularly Epstein-Barr virus, HLH can rarely develop due to infections like brucellosis (23). Although there are few reports on brucellosis-induced hemophagocytosis, it has been observed that HLH can be controlled with treatment targeting the triggering pathogen (24). Among our patients diagnosed with HLH based on clinical and laboratory findings (Cases # 8 and 9), one responded to treatment rapidly, while the other patient (Case 9) was unresponsive to HLH-targeted treatment added to the Brucella treatment, with no improvement in clinical symptoms. This suggests that there may be a genetic disorder in the patient that predisposes them to HLH. In patients with persistent high-grade fever in whom an infectious agent is identified, but treatment targeting the pathogen fails to achieve the expected improvement, HLH should be considered, and appropriate investigations should be conducted.

CONCLUSION

In children, brucellosis typically presents with characteristic clinical findings and is often accompanied by systemic symptoms. However, in regions where Brucella infection is prevalent, it is important to consider that clinical manifestations in pediatric patients with unusual complications may be associated with brucellosis, warranting a careful differential diagnosis to distinguish it from other diseases.

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OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Evaluation of the Readability of Package Inserts for Hormone Replacement Therapy, Combined Oral Contraceptives, and Progestin-Only Pills: A Cross-Sectional Analytical Study

Hormon Replasman Tedavisi, Kombine Oral Kontraseptifler ve Yalnızca Progestin İçeren Hapların Prospektüslerinin Okunabilirliğinin Değerlendirilmesi: Analitik Araştırma: Kesitsel Çalışma

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ÖZET

Amaç: Yazılı bir metnin anlaşılması, okunabilirliği ile doğrudan ilişkilidir. Okunabilirliği objektif bir şekilde ölçmek için belirli formüller vardır. İlaç prospektüslerinin okunabilirliği de halk sağlığı açısından önemlidir. Özellikle reçetesiz satılan ve doğrudan temin edilebilen ilaçlarda bu prospektüslerin anlaşılabilirliği ve okunabilirliği daha da önem arz etmektedir. Bu çalışmada hormon replasman tedavisi (HRT), kombine oral kontraseptiflerin (COCP) ve sadece progestin içeren hapların (POP) prospektüslerinin okunabilirlik düzeyinin belirlenmesi amaçlanmıştır.

Materyal ve Metod: Türkiye İlaç ve Tıbbi Cihaz Kurumu' nun resmi web sitesinden eczanelerde satılan ve kadınların kullanabildiği tüm reçetesiz ve reçeteli hormon preparatlarının listesini oluşturdu. Türkiye' de reçeteli veye reçetesiz olarak satılan hormon preparatları içeriklerine göre HRT, COCP ve POP olarak üçe yarıldı. İlaç prospektüs metinleri okunabilirlik hesaplama motoruna aktarıldı ve metinlerindeki hece, kelime ve cümle sayıları hesaplandı. Türkçe metinler için geçerli olan Ateşman, Bezirci-Yılmaz ve Çetinkaya-Uzun okunabilirlik formülleri, bu metinleri değerlendirmek için kullanıldı. Araştırma, %5 çift yönlü anlamlılık sınırı ve %95 güven düzeyi ile gerçekleştirilmiştir.

Bulgular: Üç ilaç grubu için Ateşman okunabilirlik endeksinin ortalama değerleri 70,5 ile 71,3 arasında oldukça benzerdir (p=0.690). Çetinkaya-Uzun okunabilirlik endeksinin ortalama değerleri, 49,9 ile 50,7 arasında oldukça benzerdir (p = 0,627). Bezirci-Yılmaz, üç ilaç grubu için okunabilirlik endeksinin iki kategoriye ayrıldığını göstermektedir: 7-8 sınıf ve 9-10 sınıf. Her bir ilaç grubuna ait prospektüslerin çoğunluğunun 7-8 sınıf kategorisine girdiğini, prospektüslerin okunmasının ve anlaşılmasının oldukça kolay olduğunu göstermektedir. Üç farklı ilaç grubu için Bezirci-Yılmaz okunabilirlik endeksi arasında anlamlı bir fark yoktur (p=0.534).

Sonuç: Türkiye'deki ortalama eğitim seviyesi göz önüne alındığında bu preparatraların prospektüslerinin okunabilirlik seviyesi yüksektir. İlaç prospektüslerinin ortalama eğitim seviyesine göre yazılması okunabilirliğini ve dolayısıyla anlaşılabilirliğini artıracaktır.

Anahtar Kelimeler: Hormon replasman tedavisi, kombine oral kontraseptifler, okunabilirlik, prospektüs, sadece progestin içeren haplar

ABSTRACT

Aim: The comprehension of a written text is directly related to its readability. There are specific formulas to objectively measure readability. The readability of package leaflets is also important for public health. This study aimed to determine the readability level of the package inserts of hormone replacement therapy (HRT), combined oral contraceptives (COCP), and progestin-only pills (POP).

Material and Methods: The official website of the Turkish Medicines and Medical Devices Agency created a list of all over-the-counter and prescription hormone preparations that are sold in pharmacies and can be used by women. Hormone preparations sold with or without a prescription in Turkey are divided into three groups according to their content: HRT, COCP, and POP. Ateşman, Bezirci-Yılmaz, and Çetinkaya-Uzun readability formulas, which are valid for Turkish texts, were used to evaluate these texts. The research was conducted with a two-sided 5% significance level and a 95% confidence level.

Results: The mean values of the Ateşman readability index for the three drug groups were quite similar, between 70.5 and 71.3 (p = 0.690). The mean values of the Çetinkaya-Uzun readability index were quite similar, between 49.9 and 50.7 (p = 0.627). Bezirci-Yılmaz shows that the readability index for the three drug groups is divided into two categories: 7-8 grade and 9-10 grade. The majority of the package inserts for each drug group fall into the 7-8 grade category, indicating that the package inserts are quite easy to read and understand. There is no significant difference between the Bezirci-Yılmaz readability index for three different drug groups (p = 0.534).

Conclusion: Considering the average level of education in Turkey, the readability level of the package inserts for these preparations is high. Adjusting the language and structure of package inserts to align with the average education level will increase the readability and, therefore, the comprehensibility. Future studies could incorporate factors such as visual presentation and user feedback to enhance the comprehensibility of package inserts.

Keywords: Hormone replacement therapy, combined oral contraceptives, readability, package insert, progestin-only pills

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INTRODUCTION

Hormone replacement therapy (HRT) is generally recommended for climacteric, peri-, and postmenopausal symptoms (1). Combined oral contraceptives (COCs) are used as a means of preventing pregnancy but can also be used in many cases of menstrual irregularities (2). Additionally, progestin-only pills (POP) are used especially in women who may have difficulty with COCs and in breastfeeding women for birth control purposes (3).

Package inserts are documents that provide information about the use, dosage, side effects, safety, and risks of a drug. It aims to help patients and healthcare professionals make informed decisions about the safe and appropriate use of medicines. It is important that patients understand the information in the package insert so that they can use the medicine safely and effectively. However, it is important to consider the readability of the package inserts for these medications so that patients can understand the package insert information and make informed decisions about their own health. However, studies have shown that package inserts are often difficult to read and understand for the general public, especially those with low literacy levels or limited health knowledge (4, 5).

Readability measures the ease with which a text can be grasped and understood, and then relates this rating to the level of difficulty in understanding the text. Readability level is one of the main criteria used to evaluate whether the package inserts are understood by patients (6). It is therefore important to evaluate the readability of drug package inserts and examine whether there are any differences between different drug groups.

The primary aim of the current research was to measure the readability level of the package inserts of hormone-containing drugs that are widely used by women in Turkey and can be used without a doctor's supervision. In addition, the study aimed to determine the specific age groups for which the text content of the prospectuses in question is most appropriate and the level of education at which readability is possible.

MATERIALS AND METHODS

The study was approved by the relevant ethics committee of Necmettin Erbakan University (No: 2024/5089). These data were obtained from the official website of the Turkish Medicines and Medical Devices Agency (7). The package inserts published on this website have been approved by the relevant institution during the registration and marketing of drugs. Therefore, this study can be considered a reliable and valid source of data to evaluate the readability of drug package inserts. The list of all prescription or over-the-counter hormone preparations actively sold in pharmacies and available to women was obtained by the authors from the official website of the Turkish Medicines and Medical Devices Agency (7). Existing drugs were divided into three groups according to their content: HRT, COCP and POP.

Drug package insert texts were copied and transferred to the readability calculation engine at "https://www.webfx.com/tools/readable". The number of syllables, words and sentences in the drug package insert texts were calculated. Readability values were calculated using formulas developed by Ateşman, Bezirci-Yılmaz and Çetinkaya-Uzun.

Ateşman readability formula: The readability score of the text is calculated according to the number of syllables in the words and the number of words in the sentences. Texts with a high number of syllables and a low number of sentences are more difficult to read. As the score increases, the readability of the text also increases. Readability score: 198.825–40.175 x word length (total syllables/total words)–2.610 x sentence length (total words/total sentences). Readability scores of texts vary between 0 and 100. 100 points represent the easiest-to-read texts (Table 1) (8).

Bezirci-Yılmaz readability formula: It is a formula used to measure the readability of texts written in Turkish. It gives a score calculated based on the sentence length and word length of the text. Readability score =√OKS x ((H3 x 0.84) + (H4x1.5) + (H5x3.5) + (H6x26.25) (Table 1) (9).

Çetinkaya-Uzun readability formula: It is a method developed in 2010. It gives a score calculated based on the average word length and average sentence length of the text. The higher the score, the easier the text is to read. Readability Score = 118.823 – 25.987 x average word length, calculated by 0.971 x average sentence length (Table 1) (10).

Statistical analysis

SPSS® 26 software was used for data analysis. Frequency and percentage values were used to represent categorical data, while mean and standard deviation were used to represent numerical data. Kolmogorov Smirnov and Shapiro Wilk tests and histograms were used for normality distribution. One way ANOVA was used to compare numerical data, and Chi-square and Fisher Exact tests were used to compare categorical data. Pearson correlation test was used to correlate the readability indexes. The statistical analyses used in the research were carried out with a 5% two-sided significance limit and a 95% confidence level.

RESULTS

Readability scores are numerical measures of how easy or difficult it is to read and understand a text. The table compares the readability scores of Ateşman, Bezirci-Yılmaz, and Çetinkaya-Uzun, which are commonly used in Turkish. Table 1 shows the comparison of three different readability scores and their corresponding education levels. Ateşman readability score varies between 10 and 90, with higher scores indicating easier texts. The score is based on the average number of syllables per word and the average number of words per sentence. The table also shows the level of education corresponding to each score range, from primary school to postgraduate level and above.

Bezirci-Yılmaz readability score varies between 1 and 16, with lower scores indicating easier texts. The score is based on the number of sentences, words, and syllables in a text. The table also shows the grade level corresponding to each score range, from 4th grade and below to academic-level education.

Table 1. Comparison of Ateşman, Bezirci-Yılmaz, and Çetinkaya-Uzun readability scores and related education levels

Ateşman			Bezirci–Yılmaz		Çetinkaya-Uzun	
Score	**Education level**	**Grade**	**Education level**	**Score**	**Readability Level**	**Education Level**
90–10	Primary school 4th grade and below	1-8	Primary education	> 51	Independent Reading	5th, 6th and 7th grade
80–89	5th - 6th grade					
70–79	7th - 8th grade					
60–69	9th - 10th grade		Secondary and high school	35-50	Instructional Reading	8th and 9th grade
50–59	11th - 12th grade	9-12		0-34	Frustration Level	10th, 11th and 12th grade
40–49	13th - 15th grade	12-16	Licence education			
30–39	Undergraduate level		Academic level			
≤29	Postgraduate level and above	> 16	education			

Table 2. Descriptive statistics of the characteristics of the package inserts of hormone replacement therapy, combined oral contraceptive pill, and progesterone-only drugs.

Parameters	Type	Mean	SD	Median	Minimum	Maximum
Page count	HRT	14.0	6.0	13	5	29
	COCP	17.7	5.6	18	8	31
	POP	11.3	5.1	10.00	6	25
Word count	HRT	3771.3	2264.7	3361	1196	9978
	COCP	5104.6	1471.8	5469	2073	7266
	POP	2724.7	1354.9	2192.50	946	6418
Character count	HRT	30279.7	18033.1	27349	9463	79286
	COCP	40776.7	11684.8	43109	17206	59271
	POP	22162.6	11197.7	18015.50	7697	53755
Difficult word count	HRT	141.7	103.2	140	42	440
	COCP	141.5	52.2	150	59	237
	POP	89.6	42.5	96.50	24	183
Short word count	HRT	694.3	449.2	682	202	1963
	COCP	906.0	276.9	949	356	1463
	POP	463.2	222.6	363.00	152	924
Percentage of short words	HRT	18.2	1.5	18	16	22
	COCP	17.5	0.8	18	16	19
	POP	17.1	1.4	17.00	14	20
Characters without spaces	HRT	26251.6	15587.0	23716	8199	68635
	COCP	35513.3	10318.2	37525	14826	51631
	POP	19272.8	9717.8	15687.5	6706	46804
Sentence count	HRT	728.2	402.7	632	254	1772
	COCP	932.1	284.5	976	347	1446
	POP	549.9	260.0	470.5	246	1254
Paragraph count	HRT	524.0	277.8	497	176	1253
	COCP	675.7	200.2	725	262	924
	POP	390.7	173.9	336.0	168	850
Average word count	HRT	2.8	0.05	2.85	2.68	3.01
	COCP	2.8	0.08	2.85	2.68	2.97
	POP	2.8	0.19	2.87	1.97	2.97
Average sentence count	HRT	5.1	0.66	5.00	3.70	6.20
	COCP	5.5	0.66	5.50	4.10	7.50
	POP	4.9	0.54	5.00	3.80	6.10

HRT: Hormone replacement therapy, COCP: Combined oral contraceptive pill, POP: progesterone-only pill.

Table 3. Comparison of the readability indices according to the groups of drugs.

Readability index		HRT (n=13)	COCP (n=27)	POP (n=24)	Total (n=64)	p value
Ateşman		71.3 ± 3.02	71.0 ± 3.03	70.5 ± 2.51	70.9 ± 2.81	0.690*
Çetinkaya-Uzun		49.9 ± 2.95	50.7 ± 2.47	50.0 ± 5.08	50.3 ± 3.70	0.627*
Bezirci – Yılmaz	7-8 grade	9 (69.2%)	14 (51.9%)	15 (62.5%)	38 (59.4%)	0.534**
	9-10 grade	4 (30.8%)	13 (48.1%)	9 (37.5%)	26 (40.6%)	

* One way ANOVA, ** Chi-Square test. HRT: Hormone replacement therapy, COCP: Combined oral contraceptive pill, POP: progesterone-only pill.

Table 4. Correlation of readability indices of package inserts of drugs.

		Ateşman readability index	Çetinkaya-Uzun readability index	Bezirci–Yılmaz readability index
Ateşman readability index	r	1		
	p			
Çetinkaya-Uzun readability index	r	0.375	1	
	p	0.002		
Bezirci–Yılmaz readability index	r	-0.763	-0.211	1
	p	0.0001	0.094	

p: p values; r: Pearson correlation coefficient.

Çetinkaya-Uzun readability score varies between 0 and 51, with higher scores indicating easier texts. The score is based on the percentage of difficult words and short words in a text. The table shows the education level corresponding to each score range from 5th grade to 12th grade.

Table 2 shows descriptive data on HRT, COCP, and POP package inserts. The table compares each medication type's mean, standard deviation, median, minimum, and maximum text features (pages, words, characters, etc.). COCP package inserts are the longest and most thorough of the three medication categories, with the highest mean values for pages, words, characters, phrases, and paragraphs. POP package inserts are the smallest and most brief of the three drug categories, with the lowest average pages, words, characters, sentences, and paragraphs. HRT package inserts utilize more complicated vocabulary and shorter words than the other two classes of drugs, with the highest mean values for difficult terms and proportion of short words. Compared to the other two drugs, COCP package inserts employ the fewest difficult terms and short words. POP package inserts had the greatest mean average word count, showing they utilize more words than the other two drugs. HRT box inserts feature the fewest sentences compared to the other two categories of drugs. COCP package inserts had the largest mean number of sentences, indicating longer sentences than the other two drugs.

Table 3 compares drug group readability indices. Ateşman finds that the three drug groups had similar readability index values of 70.5 to 71.3. A One-way ANOVA test demonstrates that the three drug groups' Ateşman reading index mean values are not significantly different ($p = 0.690$). The typical Çetinkaya-Uzun readability index values are comparable, ranging from 49.9 to 50.7. A One-way ANOVA test indicates no significant change in the mean Çetinkaya-Uzun reading index values across the three medication groups ($p = 0.627$). Bezirci-Yılmaz identifies two readability index categories for three medication groups: 7-8 and 9-10. The data demonstrates that most medication group leaflets are class 7-8, indicating that they are easy to read and understand. The Chi-Square test indicates no significant difference in Bezirci-Yılmaz readability index categories across the three medication groups ($p = 0.534$). The table illustrates that the three medication classes have similar readability and complexity indices.

Table 4 shows the correlation of the readability indices of drug package inserts. The Ateşman readability index has a positive and moderate correlation with the Çetinkaya-Uzun readability index ($r = 0.375$, $p = 0.002$) and a negative and strong correlation with the Bezirci-Yılmaz readability index ($r = -0.763$, $p < 0.0001$). shows. It shows that the Çetinkaya-Uzun readability index has a negative and weak correlation with the Bezirci-Yılmaz readability index ($r = -0.211$, $p = 0.094$).

DISCUSSION

Readability is a concept that measures how easy it is to understand and comprehend a text based on how it is written. This metric correlates with how difficult the text is to read based on how it is written. M any recent studies in the literature have evaluated the readability of scientific articles (11). Nowadays, developed formulae can be used to assess the intelligibility and consistency of a written document. These tools can be used to accurately and objectively assess the intelligibility and consistency of documents (8). The extent to which a patient's behavior (such as taking medication, following a diet, changing habits, or attending clinics) matches the recommendations of medical or healthcare professionals is known as compliance (12). Understanding the drug package insert is one of the most

important factors affecting compliance with treatment (13). To achieve optimal therapeutic results, drug information must be of high quality and be understandable and readable. Studies in the literature on the readability of drug package inserts, which facilitate access to health information, are limited. To our knowledge, there is no study examining the readability levels of the package inserts of HRT, COCP, and POP, which are frequently used in gynecology practice, using a Turkish formula. Our study shows that the majority of the package inserts for each drug group fall into the 7-8 class category, which shows that the package inserts are quite easy to read and understand.

Health literacy is "the capacity of individuals to obtain, process, and understand basic health information and services necessary to make appropriate health decisions."(14). Health literacy is crucial to action on treatment choices, medication use, patient support, and health information (15). Patients are expected to have access to appropriate drug information in an era dominated by information and communication technology. Package inserts, in addition to the verbal and/or pictorial information given to patients when taking medications, are crucial to ensuring they use medications safely and effectively and comply with instructions.

Various mathematical techniques can be used to determine the readability and suitability of a text according to its educational level. Flesch developed the first readability formula in the first half of the 1900s (16). Readability formulas, informed consent, behavior therapy manuals, and psychological tests are increasingly used to evaluate the field's written resources (17). Although readability tests do not give a definitive idea of the understandability of the text, they do give an idea of the level of understandability of the text (18).

HRT, COCP and POPs can be purchased without a prescription in our country and many countries. People who want to learn about the use and possible side effects of these drugs can read the package inserts. As the use of these agents becomes increasingly common, relevant information and an understanding of the potential side effects associated with their use are needed to improve patient safety and public health. However, some patients may discontinue or discontinue use of these medications in the dosage and manner recommended by their doctor. Therefore, drug package inserts should be easy to read and understand.

In our study, we found that COCP package inserts were the longest and most detailed documents of the three drug types and had the highest average number of pages, words, characters, sentences, and paragraphs. We have observed that POP package inserts are the shortest and most concise documents. We found that HRT leaflets used a shorter and more complex vocabulary than the other two types of medicines. Compared to the other two types of medications, COCP package inserts had the lowest mean values for the number of difficult words and the percentage of short words. This shows that they use longer vocabularies and more complex vocabularies. We observed that longer words were used in POP package inserts than in the other two types of drugs. We found that HRT package inserts used shorter sentences, on average, compared to the other two types of medicines. We found that COCP package inserts used longer sentences, on average, compared to the other two types of medications. When we compared the drug groups according to their readability indices, we found that most of the package inserts for each drug group fell into the 7–8 class category; there was no significant difference in readability indices between the three drug groups, and they had the same readability and complexity levels. This shows that no matter how different the age of use and package inserts of these agents are, they do not make a difference in terms of readability. Although the package insert of HRT, which is used especially in older age groups, seems to be more complex, the use of shorter sentences does not make its readability different from other agents. While the average years of education of the population aged 25 and over in our country was 7.3 years in 2011, it increased by 26% to 9.2 years in 2022. In 2022, the years of education for women was 8.5 years and for men was 10.0 years (19). The fact that most of the package inserts for each drug group are in the 7th to 8th grade category and that the years of education for women in our country is 8.5 years explains why these texts have similar readability levels.

In a study evaluating the readability of antidepressant drug package inserts, it was determined that the average Ateşman readability score was 71.4 and that 7th or 8th grade education was required for readability. Bezirci-Yılmaz's readability level was found to be 7-8. Çetinkaya-Uzun's readability score is 45.4, and an 8–9 grade level was determined. There was no statistically significant difference between different antidepressant agents in terms of readability (5). In another study, they investigated the level of patient information in the package inserts of antidepressant drugs. In the study, the content, design, and readability of drug package inserts and their role in improving patients' knowledge and skills regarding drug use were examined. Although the readability scores of drug package inserts are not very low, other factors affecting readability are emphasized, and it is concluded that package inserts are inadequate for answering patients' questions or making decisions regarding drug use (20).

In Ay et al.'s study on the readability of eye drop drug package inserts, it was observed that drug leaflets could be read with an average undergraduate degree (21). Informed consent forms for intravenous and intramuscular injection were of medium difficulty (grades 9–12) according to the Ateşman readability formula and grades 7-8 according to the Bezirci-Yılmaz readability formula. It was determined that it was at grade level. These texts were found to be difficult to read (22). A study conducted in Qatar investigated how readable and understandable the package inserts of antidiabetic drugs were. These findings showed that the materials were readable at at least a fourteenth grade level and that most patients were unable to understand them. They concluded that because only English versions were evaluated and US-based comprehensibility scores were used for some formulas, they may not be applicable to the diverse population in Qatar (23).

In the study of Dağdelen et al., the readability of the

consent forms used in gynecology and obstetrics clinics was investigated. Using the Bezirci-Yılmaz and Ateşman readability formula, it was found that longer training periods were necessary for the readability of the consent forms in obstetrics and gynecology (24).

There are several limitations to this research. Since the number of drugs included in the study was limited, it may not be correct to generalize the research results for all drugs. The font and point size used in the analyzed texts were not taken into account. Points about visual organization and the absence of patient feedback are other limitations of the study. Additionally, how well patients were able to understand these package inserts has not been examined.

CONCLUSION

In recent years, the number of studies on the readability of consent forms, health-related websites, and drug package inserts has increased. There is no research comparing the Turkish readability formulas of HRT, COCP, and POP package inserts, which are prescribed by doctors in gynecology and obstetrics practice or can be purchased without a prescription from pharmacies. Considering that the average education level of women in Turkey is 8.5 years according to 2022 data, it seems that the prospectuses are suitable in terms of readability as they fall into the 7-8 grade category. However, this study only reviewed the readability of drug package inserts. No layout, text style, appearance, or attention-grabbing elements have been used. These factors should also be taken into account. New research should examine readers' characteristics such as age, mental status, and visual acuity, as well as their educational level. Improving the readability and accessibility of package inserts is essential for enhancing patient compliance and safety, particularly in populations with lower health literacy.

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OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Re-do Hypospadias Repair: Comparative Analysis of Surgical Techniques and the Role of Hyperbaric Oxygen Therapy

Yeniden Hipospadias Onarımı: Cerrahi Tekniklerin Karşılaştırmalı Analizi ve Hiperbarik Oksijen Tedavisinin Rolü

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ÖZET

Amaç: Hipospadias onarımında amaç, fonksiyonel ve kozmetik olarak normal bir penis elde etmektir. Başarısız vakalar için yapılan yeniden onarım, rekonstrüktif ürolojide en zorlu işlemlerden biridir.Komplikasyon ve başarısızlık riskleri primer vakalara göre daha yüksektir. Hiperbarik oksijen terapisi (HBOT), uygun endikasyonlarla seçilmiş hastalara uygulanarak doku iyileşmesine katkıda bulunabilir. Bu çalışmada yeniden hipospadias onarımı yapılan hastaların cerrahi tipi ve HBOT uygulanıp uygulanmamasına göre karşılaştırmalı sonuçlarını sunmayı amaçladık.

Hastalar ve Yöntem: Bu retrospektif klinik çalışma, Ocak 2021 ile 2024 tarihleri arasında başarısız hipospadias cerrahisi sonrası tarafımıza başvurup yeniden onarım geçiren 0-17 yaş arası hastaları içermektedir. Preoperatif, peroperatif ve postoperatif veriler, operasyon türüne ve HBOT alımına göre analiz edilmiş ve karşılaştırılmıştır.

Bulgular: Yeniden operasyon geçiren 34 hastanın içinde, 4'ü TIPU onarımı, 20'si tek aşamalı G-TIPU ve 10'u iki aşamalı onarım geçirmiştir. TIPU ve G-TIPU grubundaki hastaların ortalama yaşları 6,5±3,8 yıl, aşamalı onarım grubundaki hastaların ortalama yaşları ise 9,7±5,6 yıl idi (p=0,070). Kordi düzeltmesi en sık TIPU ve G-TIPU grubunda Baskin plikasyonu ile yapılmıştır (n=9), iki aşamalı grupta ise Essed-Schroder plikasyonu (n=3) ve ventral korporatomi (n=3) teknikleri daha sık kullanmıştır (p=0.004). Postoperatif HOSE skorları önemli ölçüde artış göstermiştir (preop HOSE: 8.5±2.9, postop HOSE: 13.6±1.6, p=<0.001). Gruplar arasında başarı oranlarında anlamlı bir farklılık bulunmamış olup, genel başarı oranı %76.5'tir. Greftli onarım yapılan hastaların 11'i (%36.7) postoperatif dönemde HBOT almıştır. HBOT grubunda başarı oranları daha yüksek olmakla birlikte aradaki fark istatistiksel olarak anlamlı değildir (n=9 (%81.8) vs. n=13 (%68.4), p=0.137).

Sonuç: Yeniden onarım yapılan vakalarda, greftli onarımın tek aşamalı veya iki aşamalı yaklaşımla kullanılması, klinik ve cerrahi değerlendirmelere dayanmalıdır. İstatistiksel olarak anlamlı olmasa da, seçilmiş vakalarda greft kullanımının başarıyı potansiyel olarak artırabileceği ve HBOT eklenmesiyle komplikasyonları azaltabileceği düşünülmektedir.

Anahtar Kelimeler: Hipospadias, yeniden onarım, bukkal greft, prepüsyel greft, hiperbarik oksijen tedavisi (HBOT), çocuk ürolojisi

ABSTRACT

Aim: Re-do hypospadias surgery is among the most challenging in reconstructive urology, with higher risks of complications and failure compared to primary cases. Hyperbaric oxygen therapy (HBOT) can be applied on a patient-specific basis with appropriate indications to contribute to postoperative tissue healing. We aimed to present our surgical outcomes and comperative results based on receiving and non receiving HBOT patients who underwent re-do hypospadias repair

Patients and Methods: This retrospective clinical study included the patients aged 0-17 who had undergone unsuccessful hypospadias surgery and were subsequently re-operated between January 2021 and 2024. Preoperative, peroperative and postoperative data were analysed and compared according to operation type and HBOT receiving.

Results: Among the 34 patients who underwent reoperation, 4 underwent TIPU repair, 20 underwent single-stage G-TIPU, and 10 underwent two staged repair. The mean ages of patients were 6.5±3.8 years in the TIPU and G-TIPU group, and 9.7±5,6 years in the staged repair group (p=0.070). Chordee repair was most commonly performed using Baskin plication in the TIPU and G-TIPU groups (n=9), while in the staged group, Essed-Schroder plication (n=3) and ventral corporatomy (n=3) techniques were more frequent (p=0.004). Postoperative HOSE scores showed a significant increase (preop HOSE: 8.5±2.9, postop HOSE: 13.6±1.6, p=<0.001). There was no significant difference in success rates between groups, with an overall success rate of 76.5%. Eleven (36.7%) of the patients who underwent graft repair received HBOT in the postoperative period. While success rates were higher in the HBOT group, the difference was not statistically significant (n=9 (81.8%) vs. n=13 (68.4%), p=0.137).

Conclusions: For re-do cases, the decision on using graft-based repair in a single-stage or two-stage approach should be based on clinical and surgical evaluation. Although not statistically significant, the use of grafts in selected cases is believed to potentially enhance success and reduce complications with the addition of HBOT.

Keywords: Hypospadias re-do hypospadias surgery, buccal graft, preputial graft, hyperbaric oxygen therapy (HBOT), pediatric urology

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INTRODUCTION

Hypospadias is the most common congenital malformation of the penis, occurring in approximately one out of every 250 male children (1,2). Characterized by a ventrally located meatus, various degrees of penile curvature, and malformations of the prepuce. The most commonly used classification system is the Duckett classification, which categorizes cases based on meatal localization into anterior (glandular, coronal, distal penile), penile (midshaft, proximal penile), and posterior hypospadias (penoscrotal, midscrotal, perineal). About 70% of cases are classified as glandular or distal as mild forms, while the remainder are categorized as severe and complex (3).

In hypospadias surgery, there are three strategic objectives; achieving normal micturition, sexual intercourse, and closest to normal external appearance for psychological satisfaction (4). Various techniques have been described for repair. The choice of surgical repair depends on the severity of the condition, the surgeon's experience, and the expectations of the patient and parents. The outcomes of primary hypospadias surgeries include significantly higher complications compared to many other surgeries performed on children (5). Reoperations following unsuccessful initial attempts pose even greater challenges for surgeons. Different terms have been used to describe this group of patients and procedures, such as complex hypospadias surgery, secondary hypospadias surgery, re-do hypospadias surgery, failed hypospadias surgery or cripple hypospadias. Issues such as fibrotic tissue, relative hypovascularity, residual or recurrent chordee, fistula, diverticulum, urethral stricture and loss or inadequate penile skin often require simultaneous operation.

In clinical practice, techniques commonly used for primary repair are also applied to re-do cases (6). The decision on the type of surgical repair is based on the severity of the disease, the quality of tissue available for repair, and the surgeon's experience and preference. Although there is limited data and anecdotal use to enhance surgical healing, hyperbaric oxygen therapy (HBOT) can be applied on a patient-specific basis with appropriate indications to contribute to postoperative tissue healing (7).

For re-do hypospadias repair, the 2024 European Association of Urology pediatric urology guidelines do not propose a standardized surgical technique (8). Contributing to the literature with our results of re-do hypospadias repair, aiming to provide an approach tailored to the patient and the use of HBOT, remains our goal in this challenging field of pediatric urology where clear consensus has not yet to be established.

PATIENTS AND METHODS

The study included the patients aged 0-17 who had undergone unsuccessful hypospadias surgery and were subsequently re-operated between January 2021 and 2024. Retrospective file reviews were conducted after ethical approval and written and verbal consent obtained from parents.

Decision for surgery was made jointly by two pediatric urology specialists and the family. Patients with disorders of sexual development, additional anomaly except undescended testes, and those who declined re-repair and underwent only meatoplasty or fistulectomy were excluded from the study. Patient demographics including age, presenting complaint, meatal localization, number of previous surgeries, HOSE score (Hypospadias Objective Scoring Evaluation) (9), presence of prepuce, and chordee status were recorded preoperatively. Surgical details such as repair type, presence of chordee, repair technique, type of urethral graft if used, type of covering flap tissue if used, and administration of HBOT in the postoperative period were documented. Patients were evaluated at postoperative 1 and 6 months for complications (fistula, meatal/urethral stricture, tissue dehiscence, diverticulum, residual chordee), postoperative HOSE score, and surgical success which was defined as no need for further surgery due to complications.

Surgical procedure

All surgeries were performed jointly by two experienced pediatric urology specialists (AS and BT). When deciding on the approach to be applied, factors such as the family's expectations, meatal localization, presence and quality of ventral skin, presence of prepuce, quality and width of urethral plate, and degree of chordee were evaluated.

The surgical approach involved the following methods:

TIPU Technique:

- Standard procedure started with degloving, followed by artificial erection testing (AET) to assess chordee.
- For chordee <30°, dorsal midline Baskin plication (10) was performed.
- After preparing glans wings, the urethral plate was incised vertically at the midline.
- Urethroplasty was done using 7/0 PDS sutures over an age-appropriate urethral catheter.
- Spongioplasty was performed, followed by ventral or dorsal dartos tissue as a covering flap if suitable.
- The surgery was continued with glanuloplasty, frenuloplasty, and skin reconstruction
- The catheter was replaced with a smaller one after removing the existing catheter.
- The catheter was removed after 5-7 days

G-TIPU Technique:

- Degloving was followed by chordee evaluation using AET
- For mild chordee midline dorsal Baskin plication was performed; for severe cases, Essed-Schröder plication was performed after neurovascular bundle release (11)
- After preparing glans wings, the urethral plate was incised
- A preputial or buccal graft was harvested
- The inlay graft was placed with multiple base fixation sutures
- Similar to TIPU, urethroplasty, spongioplasty, flap covering, glanuloplasty, frenuloplasty, and catheter insertion were performed respectively
- The catheter was removed after 10 days.

Staged Repair:

First Stage:

- After degloving and chordee evaluation, ventral fibrotic tissue was excised, and corporotomy incisions were made for severe chordee (>30°)
- A preputial or buccal graft was prepared and sutured to form a new urethral plate using 7/0 PDS sutures, followed by tie-over dressings

Second Stage:

- At least 6 months later, if the graft appeared healthy, the second stage involved degloving, excising unhealthy graft edges, and performing urethroplasty and flap covering.
- In cases where sufficient dartos tissue was not available, the tunica vaginalis flap was used
- Penile and scrotal reconstruction concluded the procedure, with the catheter removed after 10 days

In all type of surgeries, a feeding tube of appropriate size for the patient's age was used as the urethral catheter

Hyperbaric Oxygen Therapy Protocol

All patients were started on HBOT within 24 hours postoperatively. HBOT was administered once a day in a multiplace chamber. Patients inhaled pure oxygen at a pressure of 2.4 ATA (absolute atmospheric pressure) in 3 periods of 25 minutes. Some patients inhaled oxygen with a full face mask and child/infant patients recieved oxygen with a hood (Figure-1)

Statistical Analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS). Quantitative data are presented as mean ± standard deviation. Categorical data are reported as frequency (n) and percentages (%). Differences between groups in categorical parameters were assessed using chi-square tests or Fisher's exact tests. Continuous variables were analyzed using t-tests for comparisons between groups. The normality of data distribution was evaluated with the Shapiro-Wilk test. For data that did not meet the normality assumption, non-parametric tests, such as the Mann-Whitney U test, were used. A mixed ANOVA was used to analyze the correlated data between groups across preoperative and postoperative assessments. Statistical significance was defined as $p < 0.05$.

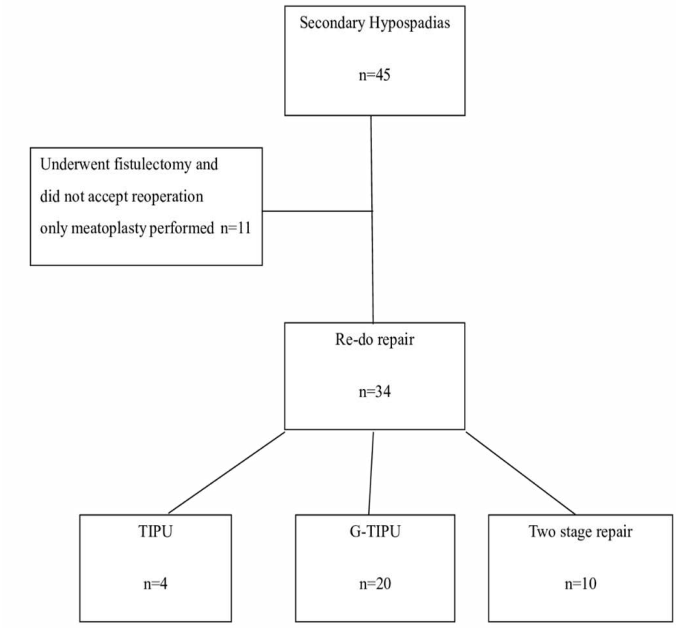

Figure 1. Flowchart of the study

RESULTS

The data of a total of 45 patients with an average follow-up duration of 13.5±6.3 months were evaluated. Eleven patients who did not accept reoperation and underwent only meatoplasty or fistulectomy were excluded from the study. Among the 34 patients who underwent reoperation, 4 underwent TIPU repair, 20 underwent single-stage G-TIPU, and 10 underwent two staged repair. It was notable that families who did not accept reoperation had significantly higher numbers of previous failed surgeries compared to those who underwent reoperation (Non-acceptors: 2.9±1.9 vs. Acceptors: 1.7±0.7, p=0.010). The study flowchart is shown in Figure-2.

The mean ages of patients were 6.5±3.8 years in the TIPU and G-TIPU group, and 9.7±5.6 years in the staged repair group (p=0.070). Sixty-five percent of patients primarily presented due to urinary complaints, while penile curvature and cosmetic issues were less frequently seen presenting symptoms. Regarding meatus localization, patients in the TIPU and G-TIPU group were predominantly distally located, whereas those undergoing staged repair had penile and proximal localizations (p=0.001).

The number of previous surgeries was higher in the staged repair group, although the difference was not statistically significant (TIPU and G-TIPU: 1.5±0.8, Staged: 1.9±0.5, p=0.280). Chordee repair was most commonly performed using Baskin

Figure 2. Two hypospadias patients with their father in a multiplace hyperbaric chamber

Table 1. Preoperative, perioperative, and postoperative data according to the type of surgery

	TIPU and G-TIPU n=24	Two-staged n=10	p
Age (year)*	6.5±3.8	9.7±5.6	0.070
Symptoms, n(%)			
Urinary problems	16(66.7%)	6(60%)	
Penile chordee	5(20.8%)	3(30%)	
Cosmetic problems	3(12.5%)	1(10%)	
Meatal location , n(%)			0.001
Distal	15 (62.5%)	0	
Penile	9 (37.5%)	5 (50%)	
Proximal	0	5 (50%)	
Number of previous operations *	1.5±0.8	1.9±0.5	0.280
Chordee repair n(%)			0.004
Baskin	9(37.5%)	0	
Essed- Schröder	1(4.2%)	3(30%)	
Corporatomy	0	3(30%)	
Graft, n(%)			0.124
Preputial	7(29.2%)	1(10%)	
Buccal	13(54.2%)	9(90%)	
Flap, n(%)			0.001
Ventral	16(66.6%)	0	
Dorsal	2(8.3%)	5(50%)	
Tunica vaginalis	0	2(20%)	
HBOT, n(%)	8(33%)	3(30%)	0.680
HOSE score*			
Preoperative	9.9±2.5	5.8±2	<0.001
Postoperative	13.8±1.5	12.9±1.3	0.064
Success , n(%)	20(83.3%)	6(60%)	0.144
Complications, n(%)	6 (25%)	4 (40%)	0.644

* mean ± standard deviation

Table 2. Comparison of data between patients receiving HBOT and not receiving HBOT in graft procedures

	HBOT receiving n=11	HBOT non receiving n=19	p
Age (year)*	6±4.5	8.3±3.6	0.141
Meatal location , n(%)			0.331
Distal	3(27%)	8(42%)	
Penile	5(46%)	9(47%)	
Proximal	3(27%)	2(11%)	
Number of previous operations *	1.7±0.7	1.8±0.7	0.475
Chordee repair n(%)			0.103
Baskin	3(27%)	5(26%)	
Essed- Schröder	1(10%)	3(15%)	
Corporatomy	0	3(15%)	
Graft, n(%)			0.924
Preputial	3(27%)	5(26%)	
Buccal	8(73%)	14(74%)	
Flap, n(%)			0.108
Ventral	4(36%)	10(52%)	
Dorsal	4(36%)	3(15%)	
Tunica vaginalis	1(10%)	1(5%)	
HOSE score*			
Preoperative	9.1±3	7.8±2.9	0.253
Postoperative	13.6±1.4	13.6±1.8	0.913
Success , n(%)	9(81.8%)	13(68.4%)	0.137
Complications, n(%)	2(18%)	7(36%)	0.142

* mean ± standard deviation

plication in the TIPU and G-TIPU groups (n=9), while in the staged group, Essed-Schroder plication (n=3) and ventral corporatomy (n=3) techniques were more frequent (p=0.004). Eight patients received preputial grafts, while 22 received buccal mucosa grafts. Sixteen patients had flaps placed on the tubularization line, and there was a statistically significant difference between groups regarding flap use and preferred flap location (p=0.001).

Preoperative HOSE scores differed significantly between the groups ($p < 0.001$). Postoperative HOSE scores demonstrated a significant increase in both groups ($p < 0.001$), with the magnitude of the increase significantly differing between the groups ($p<0.001$). There was no significant difference in success rates between groups, with an overall success rate of 76.5% (p=0.144). Complications did not significantly differ between groups (p=0.644). No complications were observed after the first stage in patients who underwent staged surgery. Table-1 summarizes preoperative, perioperative, and postoperative data according to the type of surgery performed.

Eleven (36.7%) of the patients who underwent graft repair received HBOT in the postoperative period. There were no statistically significant differences between the HBOT and non-HBOT groups in terms of age, meatal location, number of previous operations, chordee repair type, graft and flap type (p=0.141, p=0.331, p=0.475, p=0.103, p=0.924, p=0.108 respectively). While success rates were higher and complication rate lower in the HBOT group, the differences were not statistically significant (n=9 (81.8%) vs. n=13 (68.4%), p=0.137 and n=2(18%) vs. n=7(36%) p=0.142 respectively). The comparative data on HBOT and non-HBOT are presented in Table-2.

DISCUSSION

In re-do hypospadias repair, the goal remains achieving a functional and cosmetically normal penis (12). This type of surgery is among the most challenging in reconstructive urology, with higher risks of complications and failure compared to primary cases. The reported complication rates following reoperations vary widely, ranging from 14% to 50% (13). Several factors contribute to these higher risks, including the lack of detailed surgical history, abnormal residual tissue for repair, and the need for more complex interventions. Typically, modifications of techniques used in primary repairs rather than entirely new surgical approaches are employed in reoperations. The choice of method depends on factors such as the quality and structure of available tissues, surgeon experience, expectations of the family and child, and psychological considerations.

The TIPU technique, which does not necessitate the use of grafts during urethroplasty, is advantageous in cases where the urethral plate is sufficient, scar-free, well-vascularized, and without significant chordee in redo cases (6). Eliçevik et al. reported the largest series in the literature with a study of 100 patients undergoing re-do TIPU. They reported a complication rate of 26%, with only 3 cases requiring residual chordee repair with Nesbit plication in their series. They also reported that if previous unsuccessfull surgery was performed in a flap-based fashion, the complication rate is lower in re-do TIPU repair. Third redo tubularized incised plate urethroplasty was performed for neourethral stenosis and dehiscence in 3%. Although the diameter of the neourethra was adequate after a deep third midline incision, the outcome was a failure in those patients (14). Similar to the authors' findings, in our series, TIPU was preferred in 4 of our patients, who had only one previous failed operation story including 3 patients underwent Mathieu repair and 1 patient underwent TIPU repair, due to good urethral plate quality and absence of residual chordee, and all patients who underwent re-do TIPU achieved satisfactory slit-like meatus.

According to the algorithm proposed by Snodgrass et al. for redo cases, tubularization with an inlay graft (G-TIPU) is recommended for cases where there is a narrow urethral plate but no significant scarring on it and the degree of chordee is not severe (<30°). For cases with scarred urethral plates which have no viable tissue or with severe chordee, staged substitution repair is preferred (6). Preputial grafts are often used if available; otherwise, buccal grafts may be considered. Rarely, retroauricular grafts have also been reported (15). Schwentner et al. reported using inguinal skin grafts (16); however, the use of bladder mucosa and skin has been largely abandoned nowadays (17). Snodgrass and Bush collected data on hypospadias repairs (TIPU, G-TIPU, and two-staged). In contrast to the 12% complication rate in primary TIPU repair, complications in reoperative urethroplasty occurred in 32% of TIPU cases, 35% in G-TIPU, and 40% in two-stage repairs (18). In our series, consistent with the literature, success rates were found to be 80% in the G-TIPU group and 60% in the two-stage repair group. In cases where there is insufficient penile skin, procedures such as the Cecil procedure (19) (burrying the penis in the scrotum temporarily) or skin graft harvesting may be necessary. None of the cases in our series required such interventions.

Evaluation of surgical outcomes in hypospadias was historically based on the surgeon's assessment, but nowadays, validated scoring systems are available. However, there is no universally accepted objective assessment system (20). An ideal scoring system should be reproducible, free of inter-observer variability, and include significant functional and aesthetic criteria, as well as relevant surgical complications. We use the HOSE system, which includes evaluating meatal position and shape, urinary stream, straightness of erection, and presence and complexity of urethral fistula, to assess outcomes. The authors recommending this scoring system suggest that achieving 14 or more points out of 16 is acceptable (9). In our study, patients undergoing TIPU achieved 100% with 14 or more points, those with G-TIPU achieved 80%, and those with two-stage repairs achieved 60% according to the HOSE classification. The difference between these groups was not found to be statistically significant. However, it should be noted that the recommendation of 14 points or more may be more applicable to primary cases.

As previously mentioned, the likelihood of complications

increases with repeated surgeries in hypospadias repair, leading to decreased success rates. According to a study, urethroplasty complications are twice as likely in patients undergoing a secondary repair compared to those undergoing primary repair, and this risk exceeds 40% in patients undergoing three or more procedures (18). Each unsuccessful surgery can cause significant psychological distress for both patients and parents. Additionally, certain complications such as glans dehiscence may be perceived differently by families and surgeons. In patients who undergone multiple unsuccessful surgeries, functional outcomes may be prioritized over cosmetic results (21). It is also theorized that meatal retrusion to the sulcus after glans dehiscence might have some beneficial effects. The glans is the most rigid part of the urethra, so glans dehiscence might improve urinary function, especially in cases where a long neourethra is created, such as in proximal hypospadias repairs (22). The clinical relevance of glans dehiscence should be considered in relation to the severity of hypospadias. Successful glans reconstruction may be more critical in distal repairs, where surgery typically has a lower complication rate and achieving good cosmetic outcomes is the primary goal (23). In our own series, as the number of surgeries increases, families' cosmetic expectations tend to decrease while functional expectations become more prominent. It has been noted that families who do not accept further repairs for their children have significantly higher numbers of previous unsuccessful operations compared to those who consent to further repairs ($p=0.010$). For these families, children underwent only meatoplasty due to glans dehiscence causing micturition problems. Although quality of life scores were not measured, families expressed satisfaction in the post-operative period. Families should be evaluated from this perspective as well, and psychological support should be provided when necessary.

Hyperbaric oxygen therapy is currently utilized as a salvage therapy for compromised grafts and ischemic non-healing wounds (24). Its beneficial effects are attributed to several mechanisms, including hyperoxygenation, stimulation of fibroblast proliferation, deposition of collagen, angiogenesis, and vasculogenesis. HBOT alters local ischemic conditions, thereby facilitating various wound healing processes. Additionally, it enhances endothelial progenitor cell mobilization and stimulates hypoxia-inducible factor, which aids in the formation of new blood vessels (angiogenesis) and can reverse tissue ischemia, a common cause of graft failure (24,25). A systematic review and meta-analysis by Anand et al., involving 4 studies and 176 patients, reported that HBOT reduces graft failure and complications while being safe to use (26). Neheman et al. applied HBOT in cases of cripple hypospadias and found it to be safe in pediatric patients, potentially reducing the high surgical failure rates due to graft contraction (7). Although in the literature HBOT is primarily recommended for staged repairs to stabilize grafts, in our study, we also used it in appropriate cases of single-stage inlay grafts (G-TIPU). While success rates in HBOT receiving patients were higher compared to unreceived patients in our study, this difference did not reach statistical significance, possibly due to the small number of cases. Consistent with the literature, in our series, HBOT protocol completion was unsuccessful in only one patient due to child non-compliance and in another due to ear pain.

The cost of HBOT is always a matter of debate. Failure of hypospadias surgeries causes problems for both the patient and the healthcare system (27). According to our observations, the involvement of patients in repeated surgical procedures also affects the mental state of the patient and their family. The burden of repeated surgical procedures on the health insurance system should be evaluated. In terms of cost-effectiveness, we think that HBO therapy provides an advantage in terms of saving patients from recurrent surgical procedures for a long time in selected patients.

We believe that our study can contribute to the literature on re-do hypospadias repair and the use of HBOT, which is newly introduced in this patient group lacking standardized treatment algorithms. However, our study has some limitations. Firstly, its retrospective nature, small sample size, and heterogeneous patient group make it challenging to draw robust comparisons. Secondly, the selection of the surgical technique was not based on objective and quantitative measurement criteria, and there was a lack of measurement of perioperative parameters that could affect surgical outcomes, such as urethral plaque width, glans diameter, and tube length. Lastly, in a condition significantly affecting the psychology of both patients and families, postoperative quality of life and psychological status were not measured. Considering these limitations, interpretation and generalization of the results should be done cautiously.

CONCLUSION

Our findings support that TIPU in re-do hypospadias surgeries may be suitable for cases only with distal meatal location, no significant chordee and a healthy urethral plate adequate width. For more complex cases, the decision on using graft-based repair in a single-stage or two-stage approach should be based on the surgeon's evaluation. Although not statistically significant, the use of grafts in selected cases is believed to potentially enhance success and reduce complications with the addition of HBOT. High-volume randomized controlled trials in this regard would provide guiding evidence.

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OPEN

OLGU SUNUMU / CASE REPORT

Acute Coronary Syndrome In Patient With Susac Syndrome: A Case Report

Susac Sendromu Olan Hastada Akut Koroner Sendrom: Olgu Sunumu

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ÖZET

Susac sendromu beyin, iç kulak ve retinadaki mikrovasküler hasara sekonder geliştiği düşünülmekte olup nadir görülen bir hastalıktır. Patogenezinde anti endotelyal hücre antikorlarının rol oynadığı göz önüne alındığında tedavi büyük ölçüde immünsüpresif ilaçlar ile sağlanmaktadır. Sendromun tedavisine erken başlanması ve agresif tedavi, uzun vadeli sonuçlar üzerinde olumlu etkiye sahiptir. Susac sendromunun tromboza yatkınlık oluşturduğuna dair net bir kanıt bulunmamakla birlikte, olgumuzda göğüs ağrısı şikayeti ile başvuran, bilinen Susac sendromu tanısı olan ve akut koroner sendrom ön tanısı ile koroner anjiyografi yapılan bir hastada revaskülarizasyon gerektirecek ciddi koroner arter hastalığının saptanması bu düşünceyi desteklemektedir. Hastada uygun revaskülarizasyon sağlandıktan sonra şikayetleri gerilemiş ve takiplerinde tekrar revaskülarizasyon gereksinimi olmamıştır. Bu olgu sunumunda Susac sendromlu hastada revaskülarizasyon sürecinde yaşanan zorluklar, alınan kararlar ve diğer alternatif yaklaşımlar gözden geçirilecektir. Olgumuz Susac sendromu ile akut koroner sendromun birlikteliği açısından literatürde ilk olma özelliği taşımaktadır. Susac sendromunu ve kardiyak etkilerini aydınlatmak için daha fazla vaka raporuna ihtiyaç vardır. .

Anahtar Kelimeler: Akut Koroner Sendrom,Susac Sendromu,Koroner Arter Hastalığı

ABSTRACT

Susac syndrome is a rare disease thought to develop secondary to microvascular damage in the brain, inner ear, and retina. Considering that anti-endothelial cell antibodies are involved in its pathogenesis, treatment is largely provided with immunosuppressant drugs. Early initiation of treatment and aggressive therapy have a positive effect on long-term outcomes. Although there is no clear evidence that Susac syndrome creates a predisposition to thrombosis, in our case, the detection of significant coronary artery disease that would require revascularization in a patient diagnosed with Susac syndrome who presented with acute coronary syndrome clinic supports this idea. In this case report, the difficulties in the revascularization process, the decisions made, and other alternative approaches in the patient with Susac syndrome will be reviewed. Our case is the first in the literature to describe the coexistence of Susac syndrome and acute coronary syndrome. More case reports are needed to further elucidate Susac syndrome and its cardiac effects.

Keywords: Acute Coronary Syndrome,Susac Syndrome,Coronary Artery Disease

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INTRODUCTION

Susac syndrome is characterized by encephalopathy, hearing loss, and retinal artery disease. It was first described by John Susac in 1979 (1). Approximately 300 cases have been reported worldwide, and it is generally diagnosed in individuals aged 20 to 40. It is more common in women than in men (2). Patients typically present with severe headaches, behavioral changes, apathy, hearing loss, tinnitus, and partial vision loss. The diagnosis of Susac syndrome can be missed or delayed due to its rarity and because similar symptoms are also seen in more commonly diagnosed conditions, such as acute disseminated encephalomyelitis and multiple sclerosis. In this case report, we present the acute coronary syndrome and its management in a patient with Susac syndrome.

CASE REPORT

A 50-year-old male patient with a known diagnosis of hypertension and Susac syndrome (diagnosed 5 years ago after the development of bilateral hearing loss and vision impairment, and currently on 50 mg Azathioprine twice daily) presented to an external center with complaints of chest pain and nausea of a compressive nature in November 2021. The patient's electrocardiogram (ECG) was unremarkable, with no ST-segment changes(Figure 1). Echocardiography did not reveal any left ventricular wall motion defects or major valve pathology. The patient was taken to the coronary angiography laboratory with

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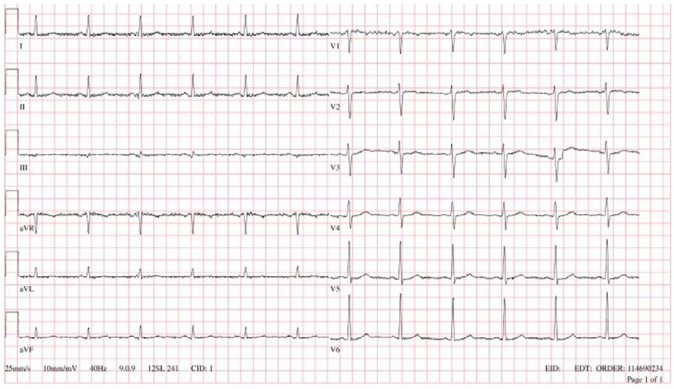

Figure 1. The patient's admission ECG with no ST-T changes.

a diagnosis of acute coronary syndrome, as his troponin level was elevated and his chest pain persisted.

During coronary angiography, advanced ectasia of the left main coronary artery (LMCA) and proximal left anterior descending artery (LAD) was observed. There was 80% stenosis in the LAD after the ectasia, and 85% stenosis was noted in the proximal D1 branch arising from the distal end of the ectasia. The circumflex artery (CX) obtuse marginalis (OM1) branch showed 90% ostial stenosis, and after the separation of OM1, 99% stenosis was observed in the CX. Additionally, there was 70% stenosis in the mid-region of the right coronary artery (RCA). The responsible lesion was considered to be in the CX. A 3.5x16 mm bare-metal stent (BMS) was implanted, and the heart team recommended intervention for the other vessels.

The patient was referred to the Cardiovascular Surgery clinic of our hospital, where coronary artery bypass grafting (CABG) was recommended following consultation with the heart team, and the operation was performed in December 2021. However, during the CABG procedure, the patient's pericardium was found to be highly adherent. The RCA and diagonal (D1) vessels could not be located due to pericardial adhesions, and the operation was terminated with the bypassing of the left internal mammary artery (LIMA) to the LAD.

The patient returned one month later, in January 2022, with chest pain and exertional angina similar to his initial myocardial infarction. After evaluation, a control coronary angiography was planned. In the recent coronary angiography, the LIMA-LAD graft was patent (Figure 2A). Ectasia of the distal and proximal LMCA and LAD was noted, with 95% stenosis at the D1 ostium (Figure 2B). The proximal and mid-region stent in the CX was patent, and the mid-region stenosis of the RCA was assessed as 40%.

Considering that the patient's symptoms were primarily related to the D1 branch, percutaneous coronary intervention

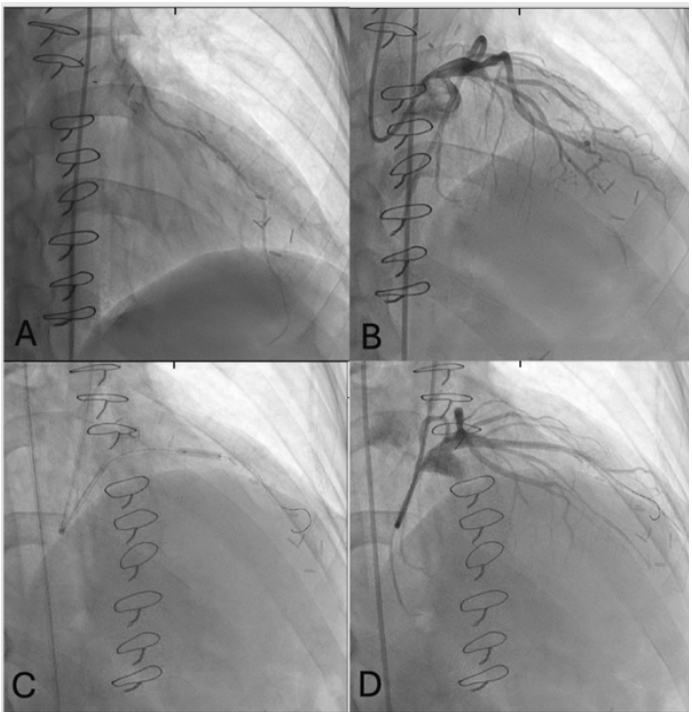

Figure 2. Coronary angiography images
A) LIMA-LAD graft is patent with no significant stenosis. **B)** 95% stenosis at the ostium of diagonal artery. **C)** Implantation of a 3x29 mm DES at the osteal segment of D1. **D)** Post-DES implantation and POT application, the D1 image.

was decided upon for the D1 branch. A 3x29 mm drug-eluting stent (DES) was implanted in the D1 branch extending to the LAD (Figure 2C), followed by POT (proximal optimization technique) with a 4x8 mm non-compliant balloon. No complications occurred, and the procedure was completed successfully (Figure 2D). The patient was discharged with appropriate cardiac medical treatment, including the initiation of dual antiplatelet therapy. In his one-month follow-up, it was observed that his anginal complaints had regressed, and he was clinically stable.

DISCUSSION

Susac Syndrome is recognized as a condition that occurs due to damage to microvascular structures in the brain, inner ear, and retina, as indicated by its clinical triad. In 2011, Susac et al. conducted studies suggesting that anti-endothelial cell antibodies (AECA) may be a cause in the pathogenesis of the disease (3). Indeed, a recent cohort study by Jarius et al. found AECA to be positive in almost 30% of Susac syndrome patients (4). For these reasons, it is accepted that immune mechanisms

contribute to the disease's pathogenesis, leading to the initiation of treatments with immunosuppressive agents (5).

The treatment approaches for this disease are primarily based on clinical experience and expert opinions. It has been observed that patients often have a long-term stable course when aggressive treatments are initiated early. Since the disease progresses in episodes, the goal is to reduce these relapses as much as possible. During these relapse periods, the predisposition to thrombosis remains unclear, and antiplatelet and anticoagulant agents have been initiated in some patients with limited benefit. However, widespread expert opinion recommends the use of antithrombotic agents in the presence of procoagulant risk factors (6).

The cardiac effects of this disease are not yet well understood. It is thought that the severe coronary lesions and coronary ectasia observed in our case may be due to immune-mediated vascular complications of Susac syndrome. Additionally, coronary ectasia can occur in rheumatologic patients who use long-term intensive immunosuppressants. The presence of severe epicardial adipose tissue encountered during coronary artery bypass grafting, along with the inability to perform coronary grafts due to pericardial adhesions, is a complication that should be considered during the course of the disease.

Our case serves as a guide for potential cardiac events that may arise during the course of the disease. It highlights the need for more frequent evaluations for cardiac involvement in the follow-up of patients with Susac syndrome.

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OLGU SUNUMU / CASE REPORT

Malignant Phyllodes Tumor of the Breast with Liposarcomatous Differentiation, A Rare Case

Memenin Liposarkomatöz Diferansiasyon Gösteren Malign Filloides Tümörü, Nadir Bir Olgu

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ÖZET
Filloides tümörler nadir görülen fibroepitelyal neoplazmlardır ve tüm meme tümörlerinin %1'inden azını oluştururlar. Bu tümörlerde nadiren heterolog sarkomatöz farklılaşma izlenmekte olup çalışmamızda heterolog liposarkom komponenti içeren filloides tümör vakası sunulmaktadır. 86 yaşında kadın, sol memede hızla büyüyen kitle nedeniyle genel cerrahi polikliniğine başvurdu. Mammografik incelemede BI-RADS 4 nodüler lezyon tespit edilmiş olup filloides tümör açısından şüpheli değerlendirildi. Laboratuvarımıza sol modifiye radikal mastektomi materyali gönderildi. Makroskopik incelemede meme dokusu kesitlerinde 9,5x9x8 cm ölçülerinde fokal infiltratif sınır izlenen nodüler kitle tespit edildi. Histolojik kesitlerde hipersellüler, pleomorfik stromaya sahip yer yer filloides tümörün tipik yapraksı mimarisinin saptandığı tümöral lezyon dikkati çekti. Tümörde bir veya daha fazla vakuole sahip berrak sitoplazmalı, hiperkromatik nükleusa sahip lipoblast karakterinde hücreleri içeren iyi diferansiye liposarkom komponenti gözlendi. Tüm bulgular ışığında olgu, heterolog liposarkom komponenti içeren malign filloides tümör olarak raporlandı. Heterolog sarkomatöz farklılaşma gösteren filloides tümörler oldukça nadir olup memede sarkomatöz neoplazi görüldüğünde ayırıcı tanıda filloides tümör dikkate alınmalıdır. Sarkomatöz farklılaşma gösteren filloides tümörünü, primer meme sarkomlarından ayırt edebilmek için, çok sayıda örnek alınarak tümörün benign epitelyal bileşeninin gösterilmesi oldukça önemlidir.

Anahtar Kelimeler: Filloides tümör, meme, liposarkom

ABSTRACT
Phyllodes tumors are rare fibroepithelial neoplasms and comprise less than 1% of all breast tumors. Heterologous sarcomatous differentiation is rarely observed in phyllodes tumors and in this study, a case of phyllodes tumor containing heterologous liposarcoma component is presented. A rapidly expanding mass in the left breast of an 86-year-old woman led to her admission to the general surgery outpatient clinic. A BI-RADS 4 nodular lesion was detected in the mammographic examination and was evaluated as suspicious for phyllodes tumor. Left modified radical mastectomy material was sent to our laboratory. Macroscopic examination revealed a nodular mass measuring 9.5x9x8 cm with focal infiltrative borders in breast tissue sections. In histological sections, the tumoral lesion was noted to have hypercellular, pleomorphic stroma and in some places the typical leaf-like architecture of phyllodes tumor. A well-differentiated liposarcoma component was observed in the tumor, containing lipoblast-like cells with single and multiple vacuoles, clear cytoplasm, and hyperchromatic nuclei. In the light of all the findings, the case was reported as malignant phyllodes tumor containing heterologous liposarcoma component. Phyllodes tumors showing heterologous sarcomatous differentiation are quite rare and when sarcomatous neoplasia is seen in the breast, phyllodes tumor ought to be taken into account while making a differential diagnosis. In order to distinguish phyllodes tumor with sarcomatous differentiation from primary breast sarcomas, it is very important to show the benign epithelial component of the tumor by taking multiple samples.

Keywords: Phyllodes tumor, breast, liposarcoma

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INTRODUCTION

Phyllodes tumors are uncommon breast tumors that comprise both stromal and epithelial components (1). Less than 1% of breast tumors are phyllodes tumors and only 10% to 15% of phyllodes tumors are malignant (2). The World Health Organization (WHO) has classified phyllodes tumors into three categories: benign, borderline, and malignant, based on their stromal cellularity, stromal nuclear pleomorphism, stromal overgrowth, mitotic activity, and tumor margins. Tumors with all of these features are classified as malignant phyllodes tumors, while tumors with some of these features are classified as borderline phyllodes tumors (3). Regardless of these criteria, the presence of malignant heterologous elements is considered as a malignant phyllodes tumor

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(4). The sarcomatous component may exhibit features of angiosarcoma, leiomyosarcoma, liposarcoma, osteosarcoma, chondrosarcoma and rhabdomyosarcoma (5). Phyllodes tumors containing sarcomatous elements are quite rare and we describe a case of phyllodes tumor with a well-differentiated liposarcoma component in this study.

CASE REPORT

A rapidly expanding mass in the left breast of an 86-year-old woman led to her admission to the general surgery outpatient clinic. The patient had a breast mass for 1 year. She applied to the hospital because the increasing size of a mass in the last 2 months. On physical examination, the nipple and breast skin appeared normal and no retraction was detected. On palpation, a mobile, firm mass measuring approximately 7x5 cm was detected at the 2 o'clock position and 4-5 cm away from the areola. It was learned that the patient, who had a known history of hypertension, had previously undergone cholecystectomy. No history of cancer was found. Mammographic examination revealed a BI-RADS 4 nodular lesion in the left breast. The lesion has doubled in size compared to the previous imaging and phyllodes tumor could not be excluded. Left modified radical mastectomy material was sent to our laboratory. On macroscopic examination 9.5x9x8 cm off-white colored tumoral lesion with nodular and cystic areas that extended to the upper and lower outside quadrants was observed in the breast tissue sections. The tumor was well-circumscribed in large areas and focal infiltrative borders were observed. In histological sections, a tumoral lesion with heterogeneous morphology, prominent stromal cellularity and pleomorphism, and in some places the typical leaf-like architecture of phyllodes tumor was noted. 32 mitotic figures were observed in stromal cells in 10 high power fields (HFP). Stromal overgrowth (at least one microscopic area consisting of stroma without an accompanying epithelial component) and necrosis were seen. A small number of benign ductal structures were detected trapped between the stromal cells. A well-differentiated liposarcoma component was observed in the area adjacent to the pleomorphic spindle stromal cells, containing lipoblast-like cells with single and multiple vacuoles, clear cytoplasm, and hyperchromatic nuclei (Figure 1). Fourteen reactive lymph nodes were detected within the axillary fatty tissue. Considering all the data, the case was defined as phyllodes tumor with heterologous well differentiated liposarcomatous component. No recurrence was detected in the 6th month follow-up of the patient.

DISCUSSION

Breast sarcomas are extremely rare tumors, accounting for less than 1% of all breast malignancies (6). These tumors may occur primarily or secondarily. The incidence of liposarcoma among breast sarcomas varies between 2% and 10% in the literature. Some of them develop de novo; some of them occur as phyllodes tumor differentiation (7).

Filloides tumors are rare biphasic tumors of the breast first described as Cystosarcoma filloides by Muller in 1838 (8). These tumors are closely related to fibroadenomas in the spectrum of fibroepithelial lesions. MED12 mutations identified in the stroma of both tumors reinforce this conclusion (9). Filloides tumors are most common in women, around the age of 50, but are rarely observed in men (10,11). Clinically, they manifest as a rapidly expanding mass that is average 4 cm in size. These tumors exhibit different biological behaviors, from benign to malignant. Phyllodes tumor metastasized to the lungs was

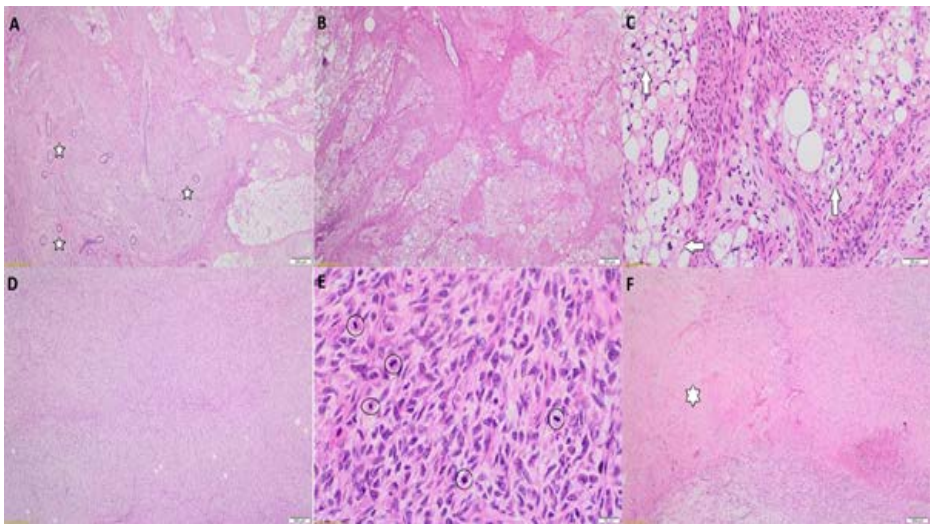

Figure 1. A. Spindle stromal cells and benign epithelial component in phyllodes tumor (Hematoxylin&Eosin, x40 magnification), **B.** Heterologous lipomatous differentiation (Hematoxylin&Eosin, x40 magnification), **C.** Lipoblasts with single and multiple vacuoles (Hematoxylin&Eosin, x200 magnification), **D**. Stromal overgrowth (Hematoxylin&Eosin, x40 magnification), **E.** Increased mitotic activity in stromal cells (Hematoxylin&Eosin, x400 magnification), **F.** Necrosis in the stroma (Hematoxylin&Eosin, x40 magnification).

reported as the first malignant behaving case (12). Histologically, they are fibroepithelial neoplasms with a leaf-like stroma lined by double-layered epithelium (myoepithelial cells and luminal cells), usually with an intracanalicular growth pattern (13). Phyllodes tumors were categorized by the WHO as benign, borderline and malignant based on tumor margins, mitotic activity, stromal cellularity, stromal nuclear pleomorphism, and stromal overgrowth (13). Tumors with all of these features are defined as malignant phylloides tumors. The presence of any of the heterologous elements even in the absence of these histological parameters guarantees malignancy. However, in the WHO 2019 breast tumor classification, it was concluded that well-differentiated liposarcoma differentiation does not have metastatic potential and it was stated that it does not diagnose malignancy alone in the absence of other criteria (13). Malignant stromal transformation in phyllodes tumors usually occurs as fibrosarcomatous differentiation and heterologous sarcomatous elements can rarely be seen. Sarcomatous stromal elements include liposarcoma, leiomyosarcoma, osteosarcoma, angiosarcoma, chondrosarcoma, and rhabdomyosarcoma. Liposarcomatous differentiation can consist of well-differentiated, myxoid, round cell, and pleomorphic liposarcomatous elements (14).

Malignant heterologous elements in Phyllodes tumors are uncommon, and limited information is available to assess the prognosis and adjuvant treatment of these tumors. However, surgical resection is the gold standard for all histological grades and adjuvant treatment can be preferred on a patient basis (15).

CONCLUSION

Malignant phyllodes tumors are rare tumors and may contain of malignant heterologous component. Due to the heterogeneous morphology of these tumors, it is very important to demonstrate the benign epithelial component of the tumor with multiple samplings, especially to distinguish it from primary sarcomas.

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