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Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi

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On Behalf of Mugla Sitki Kocman University School Of Medicine

Prof. Dr. Süleyman Cüneyt KARAKUŞ (Dekan / *Dean*)

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Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesi Kötekli Mahallesi Marmaris Yolu Bulvarı No:50 48000/Menteşe/MUĞLA/TURKEY

Tel :+ 90 252 211 48 00

Faks / Fax :+90 252 211 13 45

e-posta / e-mail : muglatipdergisi@mu.edu.tr

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AMAÇ VE KAPSAM

Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi, Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesinin süreli yayın organıdır ve Nisan, Ağustos ve Aralık aylarında olmak üzere yılda 3 sayı yayınlanmaktadır. Derginin yayın dili Türkçe ve İngilizcedir.

Dergide, tıbbın her dalı ile ilgili prospektif, retrospektif ve deneysel araştırmalar, olgu sunumu ve derlemeler yayınlanır. Yayınlanan makalelerde konu ile ilgili en yüksek etik ve bilimsel standartlarda olması ve ticari kaygılarda olmaması şartı gözetilir. Yayın için gönderilen çalışmalar; orijinal, başka bir dergide değerlendirme sürecinde olmayan ve daha önce basılmamış olması koşullarıyla kabul edilir.

Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi; TR Dizin, Google Akademik, Crossref, Türkiye Atıf Dizini, Türk Medline, Academic Keys ve Research Bible Index tarafından indekslenmektedir.

Dergide yayınlanacak olan yazılar http://dergipark.gov.tr/muskutd web sayfası üzerinden gönderilmelidir. Yazım kuralları, teknik bilgiler ve diğer gerekli formlara bu sayfadan erişilebilir. Gönderilen yazılardaki tüm içerikler yazarların sorumluluğundadır.

Bu dergide yer alan yazı, makale, fotoğraf ve illüstrasyonların elektronik ortamlarda dahil olmak üzere kullanma ve çoğaltma hakları Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi'ne aittir. Yazılı ön izin olmaksızın materyallerin tamamının ya da bir bölümünün çoğaltılması yasaktır. Her hakkı saklıdır. Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi'nde yayınlanan içerikler yazar(lar)a aittir. Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesi, dergi editörleri, çalışanları ve yayıncı bu yazılar için mali, hukuki ve diğer yönlerden sorumluluk kabul etmemektedir.

AIMS AND SCOPE

Medical Journal of Mugla Sitki Kocman University is a periodical of Medical School of Mugla Sitki Kocman University and is published three times per year; in April, August, and December. The Medical Journal of Mugla Sitki Kocman University's publication languages are both Turkish and English.

The articles which could be prospective or retrospective on investigational studies, case reports and reviews of every aspect of medicine are published. The studies should have paramount ethical and scientific standards as well as no commercial concerns. Articles are accepted for publication on the condition that they are original, are not under consideration by another journal, or have not been previously published.

The Medical Journal of Mugla Sitki Kocman University is indexed by TR Dizin, Google Scholar, Crossref, Türkiye Atıf Dizini, Türk Medline, Academic Keys and Research Bible.

All manuscripts must be submitted electronically on the http://dergipark.gov.tr/muskutd. Instructions for authors, technical information, and other necessary forms can be accessed over this web page. Authors are responsible for all content of the manuscripts.

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Tel: + 90 252 211 48 00 **Faks / *Fax:*** +90 252 211 13 45
e-posta / *e-mail:* muglatipdergisi@mu.edu.tr
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YAZARLARA BİLGİ

http://dergipark.gov.tr/muskutd/page/4152

Genel Bilgiler

Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesinin süreli yayın organı olup özel sayılar hariç düzenli olarak yılda üç sayı olarak yayımlanır. Tıbbın her dalı ile ilgili prospektif, retrospektif ve deneysel araştırmalar, olgu sunumu ve derlemeler yayınlanmak için değerlendirilmektedir. Konu ile ilgili etik ve bilimsel standartlar olması ve ticari kaygıların olmaması şartı gözetilir. Yazarlar tarafından, başka bir dergide değerlendirme sürecinde olmayan ve daha önce basılmadığı beyan edilen yazılar incelemeye alınır. Editör onayı sonrasında en az yurt içi-yurt dışı iki hakem incelemesinden geçip gerek görüldüğü takdirde istenen değişiklikler yazarlar tarafından yapılıp hakemlerce kabul edildikten sonra yayımlanır.

Bilimsel Sorumluluk

Yazar olarak belirtilmiş tüm kişiler çalışmayı planlamalı veya gerçekleştirmeli, çalışmanın yazılmasında, gözden geçirilmesinde ve son halinin onaylanmasında rol almış olmalıdır. Kriterleri karşılayan bir metnin ortaya çıkması tüm yazarların sorumluluğudur.

Etik Sorumluluk

Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi, etik ve bilimsel standartlara uygun yazıları yayımlayarak bilimin doğru bir şekilde ilerlemesine katkı sağlamayı hedeflemektedir. Bu kapsamda, çalışmaların bilimsel etiğe uygunluğu önemlidir. Etik ilkeler COPE (Committee on Publication Ethics) tarafından hazırlanan yönerge (https://publicationethics.org/resources/resources-and-further-reading/international-standards-editors-and-authors) temel alınarak Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi tarafından benimsenmiş ve yazarlar, hakemler ve editörler tarafından da benimsenmesi önerilmektedir. Bu önerilerin bir kısmı aşağıda verilmiştir.

Yazarların Etik Sorumlulukları:

- Çalışmayla ilişkili veri kayıtlarını düzenli tutmak ve olası bir talep üzerine bu verilere erişim verebilmelidir.
- Gönderdiği makalenin başka bir yerde yayınlanmadığından veya kabul edilmediğinden emin olmalıdır.
- İnsan veya hayvan denek içeren tüm çalışmalar için ulusal ve uluslararası yasalara ve yönergelere uygun olmasını sağlamak, (örneğin, WMA Helsinki Bildirgesi, NIH Laboratuar Hayvanlarının Kullanımına İlişkin Politika, Hayvanların Kullanımına İlişkin AB Direktifi) gerekli onayların alındığını onaylamak, denek mahremiyete saygı göstermek. Çalışmasına dair ilgili etik kurul onaylarını ve araştırma detaylarını çalışmanın "Gereç ve Yöntem" kısmında belirtmek.
- Herhangi bir çıkar çatışması durumunda, makalesiyle ilgili etik bir ihlal tespit ettiğinde bunu editör ve yayıncı ile paylaşmak, hata beyanı, zeyilname, tazminat bildirimi yayınlamak veya gerekli görüldüğü durumlarda çalışmayı geri çekmelidir.

Hakemlerin Etik Sorumlulukları:

- Editörün karar verme sürecine katkıda bulunmak için makaleyi objektif olarak zamanında incelmeli ve sadece uzmanlık alanı ile ilgili çalışma değerlendirmeyi kabul etmelidir.
- Değerlendirmeyi nesnel bir şekilde sadece çalışmanın içeriği ile ilgili olarak yapmalıdır.
- Dini, siyasi ve ekonomik çıkarlar gözetmeden çalışmayı değerlendirmelidir.
- Yayınlanacak makalenin kalitesini yükseltmeye yardımcı olacak yönlendirmelerde bulunmalı ve çalışmayı titizlikle incelemelidir. Yorumlarını yapıcı ve nazik bir dille yazara iletmelidir.
- Editör ve yazar tarafından sağlanan bilgilerin gizliliğini korumalı, kör hakemliğe aykırı bir durum varsa editöre bildirmeli ve çalışmayı değerlendirmemelidir.
- Potansiyel çıkar çatışmalarının (mali, kurumsal, işbirlikçi ya da yazar ve yazar arasındaki diğer ilişkiler) farkında olmalı ve gerekirse bu yazı için yardımlarını geri çekmek konusunda editörü uyarmalıdır.

Editörlerin Sorumlulukları:

- Cinsiyet, dini veya politik inançlar, yazarların etnik veya coğrafi kökenleri üzerine ayrım yapılmaksızın görevlerini yerine getirirken dengeli, objektif ve adil bir şekilde hareket etmelidir.
- Dergiye gönderilen çalışmaları içeriğine göre değerlendirmeli, hiçbir yazara ayrıcalık göstermemelidir.
- Olası çıkar çatışmalarını önlemek adına gerekli önlemleri almalı ve varsa mevcut beyanları değerlendirmelidir.
- Etik ihlali niteliğinde bir şikayet olması durumunda, derginin politika ve prosedürlerine bağlı kalarak gerekli prosedürleri uygulamalıdır. Yazarlara, gelen şikâyete cevap vermek için bir fırsat vermeli, çalışma kime ait olursa olsun gerekli yaptırımları uygulamaktan kaçmamalıdır.
- Derginin amaç ve kapsamına uygun olmaması durumunda gelen çalışmayı reddetmelidir.

Tüm araştırma makalelerinde (retrospektif çalışmalarda dahil olmak üzere), çalışma için Etik Kurul Onayı alınmalı ve Etik Kurul Onayının alındığı yer, tarih (gün, ay ve yıl olarak) ve onay numarası Gereç ve Yöntem bölümünde belirtilmelidir. İnsan ile ilgili tüm çalışmalarda Helsinki Deklarasyonu'na (World Medical Association Declaration of Helsinki http://www.wma.net/en/30/publications/10policies/b3/index.html) göre çalışmanın yapıldığı mutlaka belirtilmelidir. Olgu sunumlarında, hastadan (ya da yasal vasisinden) tıbbi verilerinin yayınlanabileceğine ilişkin yazılı hasta onam belgesi alındı cümlesinin hasta onam tarihi ile birlikte belirtilmesi gereklidir. Hayvan deneyleri için laboratuvar hayvanlarının bakım ve kullanımı konusunda kurumsal veya ulusal yönergelerin takip edilmeli ve bildirmelidirler. Yazarların çalışmalarında kullandıkları cümlelerinden editör ve yayın kurulu sorumlu değildir. Bilimsel, hukuki ve etik sorumluluğu yazarlara aittir.

Sorumlu yazar, gönderilen çalışmanın başka bir yerde yayımlanmadığını ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığını belirtmelidirler. Çalışmanın bir kısmı kongrede sözlü veya poster bildiri olarak sunuldu ise başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir.

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Kabul edilen yazının tüm kullanım ve yayın hakkı derginin olur ve izinsiz olarak başka bir yerde yayınlanamaz.

Değerlendirme: Tüm makaleler çift-kör değerlendirme yöntemi kullanılarak en az iki yerli veya yabancı hakem tarafından değerlendirilir. Makalelerin değerlendirilmesi, bilimsel önemi, orijinalliği göz önüne alınarak yapılır. Yayına kabul edilen yazılar editörler kurulu tarafından içerik değiştirilmeden yazarlara haber verilerek yeniden düzenlenebilir.

İntihal taraması: Dergiye gönderilen makaleler format ve intihal açısından kontrol edilir. Formata uygun olmayan veya intihal benzerlik oranı yüksek (%20'den az olmalıdır) makaleler değerlendirilmeden sorumlu yazara geri gönderilir.

Çıkar çatışması: Çalışmaları ile ilgili taraf olabilecek tüm kişisel, ticari bağlantı veya çalışma için doğrudan veya dolaylı olarak maddi destek veren kurum var ise yazarlar; kullanılan ticari ürün, ilaç, firma ile ticari hiçbir ilişkisinin olmadığını veya varsa nasıl bir ilişkisinin olduğunu (konsültan, diğer anlaşmalar vs.), editöre sunum sayfasında bildirmek zorundadır. Herhangi bir çıkar çatışmasının olmadığı durumda metin içerisinde 'Yazarlar çıkar ilişkisi olmadığını beyan eder' şeklinde ifade edilmelidir.

Lisan

Derginin yayın dilleri Türkçe ve İngilizcedir. Türkçe metinlerde Türk Dil Kurumu'nca (www.tdk.gov.tr) yayınlanan Türkçe sözlük temel alınmalıdır. Gönderilmiş makalelerdeki tüm yazım ve imla hataları, anlam ve verileri değiştirmeksizin editör tarafından düzeltilebilir. Metnin kurallara uygun olarak düzenlenmesi yazarların sorumluluğundadır.

Telif Hakkı Bildirimi

Telif hakkı devrini bildirmek için kapak mektubunda 'Bu makalenin telif hakkı; çalışma, basım için kabul edilmesi koşuluyla Muğla Sıtkı Koçman Üniversitesi Tıp Dergisi'ne devredilir' şeklinde belirtilmelidir. Yazarlara ücret ödenmez.

Yazı Tipleri

Derleme: Derlemeler yeni veya tartışmalı alanlara ışık tutmalıdır. Türkçe ve İngilizce başlık ve tek paragraflık özetler ve anahtar kelimeler içermelidir. Dergi editörü derleme yazımı için davette bulunur.

Orijinal makaleler: Orijinal makaleler temel veya klinik çalışmalar veya klinik denemelerin sonuçlarını bildirir. Makale dili Türkçe veya İngilizce fark etmeksizin Türkçe özet, İngilizce özet, giriş, gereç ve yöntemler, bulgular/sonuçlar, tartışma, teşekkür (gerekliyse), kaynaklar ve şekiller ve tablolardan oluşmalıdır.

Olgu Sunumu: Tıbbın her alanındaki önemi olan olgu sunumlarını yayınlanır. Türkçe özet, İngilizce özet, giriş, olgu, tartışma, kaynaklardan oluşmalıdır.

Yazı Gönderimi

Tüm yazılar elektronik ortamda http://dergipark.gov.tr/muskutd adresi üzerinden gönderilmelidir.

Yazının Hazırlanması

Yazı hazırlığı iki satır aralıklı, satır numaraları verilmiş ve Times New Roman 12 punto karakter büyüklüğünde yapılmalıdır. Sayfalar başlık sayfasından başlamak üzere, sağ alt köşesinden numaralandırılmalıdır. Makale sistemine yüklenen word (*.doc, *.docx) dosyasının başlık sayfasında yazarlara ait isim ve kurum bilgileri yer almamalıdır.

Kapak Mektubu: Kapak mektubu gönderilen makalenin kategorisini, daha önce başka bir dergiye gönderilmemiş olduğunu, çıkar ilişkisi bildirimini, yayın hakkı devri bildirimini ve varsa çalışmayı maddi olarak destekleyen kişi ve kurumların adlarını mutlaka içermelidir.

Başlık sayfası: Bu sayfada çalışmanın tam Türkçe ve İngilizce ismi ve kısa başlığı olmalıdır. Katkıda bulunanların tüm yazarların isimleri, çalıştıkları kurumları ve ORCID numaraları listelenmelidir. Ücretsiz olarak bireysel ORCID numaraları http://orcid.org adresinden alınabilmektedir. Basım sürecinde dergi editörü ile iletişimde bulunacak olan yazışma yazarı belirtilmelidir. Çalışmanın bir kısmı kongrede sözlü veya poster bildiri olarak sunuldu ise başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir.

Özet ve Anahtar Kelimeler: Özet 250 kelimeyi geçmemelidir. Çalışmanın amacını, yöntemi, bulgu ve sonuçları özetlemelidir. En fazla 5 anahtar kelime verilmelidir. Kelimeler birbirlerinden virgül (,) ile ayrılmalıdır. İngilizce kelimeler Index Medicus'taki Medical Subjects Headings listesine uygun olmalıdır www.nlm.nih.gov/mesh/MBrowser.html. Türkçe anahtar kelimeler Türkiye Bilim Terimleri (TBT)'ne uygun olarak verilmelidir www.bilimterimleri.com

Giriş: Kısa ve açık olarak çalışmanın amaçlarını tartışmalı, çalışmanın neden yapıldığına dair temel bilgileri içermeli ve hangi hipotezlerin sınandığını bildirmelidir.

Gereç ve Yöntemler: Açık ve net olarak yöntem ve gereçleri açıklanmalıdır. İlk vurgulamada kullanılan araç ve cihazların model numaraları, firma ismi ve adresi (şehir, ülke) mutlaka belirtilmelidir. Tüm ölçümler metrik birim olarak verilmeli ve ilaçların jenerik adları kullanılmalıdır.

İstatistiksel Değerlendirme: Tüm çalışma makaleleri istatistiksel olarak değerlendirilmeli ve uygun plan, analiz ve bildirimde bulunmalıdır. p değeri yazı içinde belirtilmelidir. Kullanılan istatistik yöntem açıkça belirtilmelidir.

Sonuçlar: Sonuçlar metin, tablo ve şekiller kullanılarak sunulmalıdır. Tablo ve metinler tekrarlanmamalıdır. p değeri yazı içinde belirtilmelidir (p=0.014 gibi).

Tartışma: Çalışmanın farklılıklarına ve sonuçlarına vurgu yapılmalıdır. En önemli bulgu kısa ve net bir şekilde belirtilmeli, gözlemlerin geçerliliği tartışılmalı, aynı veya benzer konulardaki yayınların ışığında bulgular yorumlanmalı ve yapılan çalışmanın olası önemi belirtilmelidir. Çalışmanın esas bulgularının kısa ve özlü bir paragrafla vurgulanması önerilir.

Teşekkür: Yazarlar araştırmaya katkıda bulunan ancak yazar olarak yer almayan kişilere teşekkür etmelidir.

Tablo, Resim, Şekil ve Grafikler: Tüm tablo, resim, şekil, grafik ve diğer görseller ana metnin içinde geçiş sıralarına uygun şekilde, ardışık olarak numaralandırılmalıdır. Kullanılan görsellerde hasta ve doktor kimlikleri içeren bilgiler ve kurum adları görülmeyecek şekilde hazırlanmalıdır. Tablolar ana metin içinde kaynak listesinin sonrasında sunulmalıdır. Tablolar JPEG, TIFF veya diğer görsel formatlarda gönderilmemelidir. Mikroskopik şekillerde açıklayıcı

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bilgilere ek olarak, büyütme oranı ve kullanılan boyama tekniği de belirtilmelidir. Görseller sisteme minimum 300 DPI çözünürlükte yüklenmelidir. Şekil, resim, grafik ve fotoğrafların her biri ayrı *.jpg* veya *.gif* dosyası olarak sisteme eklenmelidir. Şekiller metin içinde kullanım sıralarına göre Arabik (1, 2, 3, v.b.) rakamla numaralandırılmalı ve metinde parantez içinde gösterilmelidir. Grafiklerde kullanılan çizgiler yayın hazırlığı aşamasında yeniden boyutlandırma sırasında meydana gelecek bozulmaları engellemek amacıyla yeterli kalınlıkta olmalıdır. Tablolarda kullanılan kısaltmalar tablo altlarında tanımlanmalıdır. Tablo ve şekil başlıklarında ve tablonun yazı içinde anılmasında Roma (I, II, II, v.b.) rakamları kullanılmamalıdır.

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Komite veya yazar grupları için örnek

The Standard Task Force, American Society of Colon and Rectal Surgeons: Practice parameters for the treatment of haemorrhoids. Dis Colon Rectum 1993;36:1118-20.

Kitaptan konu için örnek

Milson JW. Haemorrhoidal disease. In: Beck DE, Wexner S, eds. Fundamentals of Anorectal Surgery. 1 1992; 192-214. 1a ed. New York: McGraw-Hill

Kitap için örnek

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İÇİNDEKİLER / CONTENTS

Determination of Stenosis and Arrhythmia After Surgical Operation of Partial Anomalous Pulmonary Venous Drainage in Mid & Longterm (Comparison of Double/Single Patch and Warden Operation in Partial Anomalous Pulmonary Venous Drainage): A Comparative Study of Two Different Time Intervals

Parsiyel Pulmoner Venöz Dönüş Anomalisinin Cerrahi Onarımı Sonrası Orta ve Uzun Dönemde Aritmi ve Stenozun Değerlendirilmesi (Parsiyel Pulmoner Venöz Dönüş Anomalisinde Tek/Çift Yama ve Warden Operasyonlarının Karşılaştırılması): 2 Farklı Dönemin Karşılaştırmalı Çalışması

Hande İŞTAR, Buğra HARMANDAR

Muğla University Medical Faculty, Department of Cardiovascular Surgery, Muğla, Türkiye

Öz

Çalışmamızda, Hacettepe Üniversitesi Tıp Fakültesi Kalp-Damar Cerrahisi Bölümü'nde, parsiyel pulmoner venöz dönüş anomalisi (PAPVD) tanısıyla tek yama- çift yama ve Warden prosedürü ile opere edilen 20 hasta (grup A) ve Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesi'nde opere edilen 10 hasta ile Eskişehir Osmangazi Üniversitesi Tıp Fakültesi'nde opere edilen 62 hasta (grup B 72 hasta) retrospektif olarak incelendi. Farklı cerrahi tekniklerinin postoperative v. cava superior darlığı, pulmoner ven darlığı ve aritmi insidansı ile ilişkisi karşılaştırıldı. 2 farklı grup oluşturuldu: 2005-2011 yılları arasında, Hacettepe Üniversitesi Tıp Fakültesi'nde 20 hasta (A grubu) ve 2015-2022 yılları arasında Eskişehir Osmangazi Üniversitesi ile Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesi'nde opere edilen toplam 72 hasta (B grubu). A grubunda 12 kız, 8 erkek hasta ortalama yaş sırasıyla 5.7±3 yıl (0.42-11yıl), ortalama ağırlık 18.67±9.01 kg (5.5-41 kg) idi. B grubunda 39 kız, 33 erkek hasta ise ortalama yaş 6.68±3.70 yıl (1-17 yıl), ortalama ağırlık 23.58±14.75 kg (8-80 kg) idi. Klinik, elektrokardiyogram ve ekokardiyografi incelemeleri derlendi. Erken ya da geç mortalite yoktu. Ortalama izlem süresi sırasıyla 39.73 ay ve 49.82 aydı. İzlemde pulmoner ven,v. cava superior stenozu gelişmedi. A grubunda, Warden prosedürü ve çift yama tekniği ile opere edilmiş birer hastaya rezidüel atrial septal defekt nedeniyle reoperasyon yapıldı. B grubunda ise reoperasyon yoktu. A grubundan 6 hastada, B grubunda da 4 hastada postoperative erken dönemde aritmi gelişti. Takipte tüm hastalar sinus ritmine geri döndü. Pacemaker hiçbir hastada gerekmedi. PAPVD farklı cerrahi tekniklerle güvenli olarak opere edilebilir. Tüm yöntemlerde sinus nodu (SN) hasarından kaçınmak için, çevresinde dikkatli doku diseksiyonu yapılmalıdır.

Anahtar Kelimeler: Aritmi, Obstrüksiyon, Parsiyel Anormal Pulmoner Venöz Dönüş, Stenoz

Abstract

We retrospectively investigated 20 patients who underwent partial anomalous pulmonary venous drainage (PAPVD) surgery with single-double patch, and Warden operation after surgical treatment in Hacettepe Medical School, department of cardiovascular surgery (group A) and 62 patients who underwent surgery with double patch in Eskişehir Osmangazi Medical School and 10 patients in Muğla Sıtkı Koçman Medical School (group B including 72 patients) at different time intervals. We compared postoperative v. cava superior stenosis, pulmonary vein stenosis and arrhythmia in regards of different techniques. We constituted 2 groups: 20 patients of Hacettepe Medical School between 2005-2011 (group A) and 72 patients of Muğla Sıtkı Koçman and Eskişehir Osmangazi Medical School between 2015-2022 (group B). Group A included 12 females, 8 males, the mean age was 5.7±3 years, ranging between 0.42 and 11 years, the mean weight was 18.67±9.01 kg, ranging between 5.50 and 41 kg. Group B included 39 females, 33 males, the mean age was 6.68±3.70 years, ranging between 1 and 17 years, mean weight was 23.58±14.75 kg, ranging between 8 and 80 kg. Clinical findings, electrocardiographic, echocardiographic evaluations were obtained. We found neither early nor late mortality in both groups. The mean follow-up duration were 39.73 months and 49.82 months respectively. No pulmonary venous or v. cava superior stenosis occurred in both groups. Reoperation for residual atrial septal defects required in 1 patient who underwent Warden procedure,1 patient who underwent double patch technique in group A. It didn't require reoperation in group B. In group A, 6 patients presented rhythm disturbance in early postoperative period, as well as 4 patients in group B. In follow-up all patient recovered to sinus rhythm in both groups. Pacemaker wasn't required. PAPVD can be safely operated using different procedures. Meticulous dissection nearby sinus node (SN) should be emphasized to avoid injury of SN for all techniques.

Keywords: Arrhythmia, Obstruction, Partial Anomalous Pulmonary Venous Return, Stenosis

Introduction

Partial anomalous pulmonary venous drainage (PAPVD) is a congenital malformation that represents a physiologic left-to-right shunt with a risk for pulmonary vascular disease, Eisenmenger syndrome, and congestive heart failure (1). PAPVD may be present isolated or concomitant with atrial septal defect (ASD). The most frequent is sinus venosum ASD. Other types include right pulmonary vein (PV) draining into right atrium, connection of right PV to IVC (Scimitar Syndrome), and less frequent right PV draining to the azygos vein or coronary sinus (2,3). The left PV can connect to the left v. brachiocephalica through a vertical venous structure, and bilateral PAPVD is rare (3).

	ORCID No
Hande İŞTAR	0000-0002-7150-0171
Buğra HARMANDAR	0000-0002-7487-1779

Adres / Correspondence : Hande İŞTAR
Muğla University Medical Faculty, Department of Cardiovascular Surgery, Muğla, Türkiye
e-posta / e-mail : handeistar@yahoo.com

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The most common repair technique is using a patch to forward anomalous pulmonary venous return through the sinus venosus ASD with or without performing patch plasty on SVC. Other techniques are the Warden procedure and longitudinal or transverse transcaval incisions with or without superior vena cava (SVC) patch plasty, i.e. the Takahashi atrial flap (4-8).

In this retrospective study, we aimed to compare two different surgical techniques in PAPVD in regard to arrhythmia or obstruction of the PV's and the SVC. Additionally, we compared 2 different time interval and different centers in regards of surgical results and arrhythmia or obstruction of the PV's and the SVC.

Material and Method

Inclusion Criteria

All of 20 patients under 18 years of age who were diagnosed with PAPVD with or without sinus venosus type ASD's between June 2005-December 2011 in Hacettepe University Medical School, were included for group A in this retrospective study. Ethical approval was obtained from the institutional review board (LUT 12/22 05.06.2012), and written informed consent was obtained from legally authorized representatives priorly the study. Similarly, for group B, all of 62 patients under 18 years of age who were diagnosed with PAPVD with or without sinus venosus type ASD's between January 2015-December 2017 in Eskişehir Osmangazi University Medical School and 10 patients under 18 years of age who were diagnosed with PAPVD with or without sinus venosus type ASD's between January 2018-January 2022 in Muğla Sıtkı Koçman University Medical School were taken. Ethical approval for group B, was obtained from the institutional review board of Muğla Sıtkı Koçman University Medical School (19/01/2023: 2/XI) with a special permission of Eskişehir Osmangazi University Medical School. Our study was planned under the rules of declaration of Helsinki.

Controls of patients were made at the 1st, 3rd, and 6th month postoperative visits, and at the time of study. Electrocardiograms were recorded in 12 leads at 10 mm/mV amplitudes. For patients who had arrhythmia, we obtained Holter records for 24 hours. Echocardiographic evaluations were made by pediatric cardiologists.

Postoperative pulmonary venous and SVC stenosis were determined with transthoracic echocardiogram. Postoperative SN dysfunction was defined as follows: persistent sinus bradyarrhythmia (less than 50 per minute), nodal rhythm, or pause more than 3 seconds seen in Holter monitoring or electrocardiogram.

Demographic Features

The study included 2 groups:

Group A included 12 females 8 males, the mean age was 5.7±3 years, ranging between 0.42 and 11 years, the mean weight was 18.67±9.01 kg, ranging between 5.50 and 41 kg. Group B included 39 females, 33 males, the mean age was 6.68±3.70 years, ranging between 1 and 17 years, mean weight was 23.58±14.75 kg, ranging between 8 and 80 kg.

In group A 18 patients had associated ASD: 10 patients (50%) had high venosum ASD, 4 patients (20%) had secundum ASD, 3 (15%) had patent foramen ovale (PFO), 1 (5%) had low venosum ASD, and 2 patients had none (10%) (Table1). Four patients (20%) had left superior vena cava, 3 (15%) had pulmonary stenosis, 2 (10%) had v.azygos continuity, 2 (10%) had Scimitar Syndrome, and 2 (10%) had heterotaxia syndrome (Table 2). The mean value of the main pulmonary artery (MPA) pressure was 18.10 (15-24.25) mmHg for group A (Table 3).

Table 1. Type of ASD and additional PFO in the groups.

ASD types	Group A (n%)	Group B (n%)
High venosum	10 (50%)	35 (48.6%)
Secundum	4 (20%)	28 (38.9%)
PFO	3 (15%)	0 (0%)
Low venosum	1 (5%)	9 (12.5%)
None	2 (10%)	0 (0%)

Table 2. Associated cardiac anomalies in our patients. (n: number of patients).

	Group A (n%)	Group B (n%)
Persistent left SVC	4 (20%)	16 (22.2%)
Pulmonary stenosis	3 (15%)	10 (13,9%)
Azygos vein continuity	2 (10%)	4 (5.6%)
Scimitar Syndrome	2 (10%)	4 (5.6%)
Heterotaxia syndrome	2 (10%)	4 (5.6%)

In group B 72 patients had associated ASD: 35 patients (48.6%) had high venosum ASD, 28 patients (38.9%) had secundum ASD, and 9 (12.5%) had low venosum ASD (Table 1). Sixteen patients (22.2%) had left superior vena cava, 10 patients (13.9%) had pulmonary stenosis, 4 patients (5.6%) had v.azygos continuity, 4 patients (5.46%) had Scimitar Syndrome, and 4 patients (5.6%) had heterotaxia syndrome (Table 2). The median value of the main pulmonary artery (MPA) pressure was 25 (20.50-28) mmHg for group B (Table 3).

Operative Techniques

In group A, the surgical procedures varied according to the surgeons' preference.

All operations were initiated through a median sternotomy under hypothermic conditions (mean 26.9°C, range 22-29°C). The mean CPB time was 75.6 minutes (range 30-124), and the mean cross-clamp time was 49.1 minutes (range 20-93 minutes)

for all patients. For every patient, cold blood cardioplegia was given to obtain cardiac arrest.

In group A, for the subgroup in which the Warden procedure was preferred, after the sternotomy approach, the azygos vein was doubly ligated and transected to allow mobilization of the SVC. Cannulations of the ascending aorta, inferior vena cava and SVC above the highest anomalous PV were made. Then, the SVC was transected. The tip of the right atrial appendage was amputated and enlarged, similar to the diameter of the SVC. Excision of the trabeculae of the appendage was done. The caudal stump of the SVC was sutured with 5/0-6/0 propylene running sutures. After cutting and enlarging anteriorly, the cephalad SVC was sutured to the right atrial appendage with 5/0-6/0 propylene running sutures.

In group A for the subgroup in which single/double patch technique were preferred, standard cava-atrial cannulation was performed. It was preferred patch closure to divide the caval and pulmonary channels to redirect the SVC to the right atrium and the same aim for anomalous PV's to the left atrium. Right atriotomy was performed through the cava-atrial junction on the lateral side of the SVC. In the case of SVC obstruction, a second patch made of autologous pericardium treated with glutaraldehyde was sewn using a running polypropylene 5/0-6/0 suture.

Table 3. Demographic features of patients according to groups.

	Group A (n=20)	Group B (n=72)	p
Age (year)	5.7 (0.42-11)	6.68 (1-17)	0.992
Weight (kg)	18.67 (5.5-41)	23.58 (8-80)	0.310
Gender			
Female	12 (60)	39 (54.2)	0.834
Male	8 (40)	33 (45.8)	
MPA pressure (mmHg)	18.10 (15-24.25)	25 (20.50-28)	**<0.001**
Duration of CPB	76 (56.75-87)	65 (55.50-70)	**0.035**
Duration of clamping time	49.50 (36.75-59.75)	48.50 (41-57)	0.805
Lowest temperature in CPB (°C)	28 (26-28)	32 (31-32)	**<0.001**
Postoperative drainage (cc)	225 (192.50-300)	65 (50-365)	**<0.001**
Extubation time (hour)	7 (6-8.75)	5 (4.5-5)	**<0.001**
Duration of intensive care unit (ICU) (hour)	25 (24-32)	48 (48-48)	**<0.001**
Duration of hospitalization (day)	6.5 (5.25-7)	5 (5-6)	**0.002**
Arrhythmia in hospital stay	6 (30%)	4 (5.6%)	**0.006**
Reoperation	2 (10%)	0 (0%)	**0.045**
Residual ASD	2 (10%)	0 (0%)	**0.045**
Obstruction of systemic venous return	none	none	
Obstruction of pulmonary venous return	none	none	
Mortality	none	none	

In group B, only double patch technique was preferred and operations were done by single surgeon. All operations were initiated through a median sternotomy under moderate hypothermic condition (mean 31.5°C, range 30-33°C). The mean CPB time was 65.3 minutes (range 35-98), and the mean cross-clamp time was 50.5 minutes (range 30-81 minutes) for all patients. For every patient, cold blood cardioplegia was given to obtain cardiac arrest. While performing double patch technique, standard cava-atrial cannulation was performed. It was preferred patch closure to divide the caval and pulmonary channels to redirect the SVC to the right atrium and the same aim for anomalous PV's to the left atrium. Right atriotomy was performed through the cava-atrial junction on the lateral side of the SVC. A second patch made of autologous pericardium treated with glutaraldehyde was sewn using a running polypropylene 5/0-6/0 suture for all patients.

Statistical Analysis

The statistical analysis was executed using Statistical Packages for the Social Science (SPSS, IBM SPSS Statistics 11.5 (Chicago, Illinois, USA)). Quantitative variables were compared with Kolmogorov-Smirnov in order to control if they were appropriate to normal distribution. Independent samples were compared with Mann Whitney U test. Qualitative variables were analyzed with chi-square test. The descriptive statistics of the quantitative variables which were in normal distribution, were indicated as mean ± standard deviation. The descriptive statistics of the quantitative variables which were not in normal distribution, were indicated as median (25-75 percentiles). The descriptive statistics of the qualitative variables were indicated as frequency (%). $p<0.05$ value was considered significant.

Results

Group A and B were statistically homogenous in regards of age, weight and gender ($p>0.05$ Table 3). The mean follow-up duration were 39.73 months (3-82 months) in group A, and 49.82 (4.5-78 months) in group B, respectively. No mortality occurred in both groups. In group A the mean age of all patients at the time of operation was 5.70±3 years, and

6.68±3.70 years in group B. Other descriptive characteristics are shown in table 3.

Comparison was performed by 2 different series, moreover at different time interval. Group A included patient from 2005 to 2011 and group B from 2015 to 2022. Additionally, operations were performed by different surgeons in group A and by single surgeon in group B.

MPA pressure was significantly higher in group B (p=0.035). Duration of CPB was longer in group A (p=0.035). Lowest temperature was also significantly lower in group A (p<0.01). However, there was no significance in regards of the duration of ACT between groups.

Postoperative drainage (p<0.01), extubation time (p<0.001), duration of hospitalization (p=0.02) were significantly higher in group A related to group B. However, ICU stay was significantly longer in group B (p<0.01) due to the surgeon's preference.

There was no dysrhythmia in any patient prior to surgery in both groups. When we compare group A and B in regards of arrhythmia, the arrhythmia was observed significantly higher in group A (p=0.006).

In group A, 6 patients (30%) had arrhythmia (1 atrial fibrillation, 2 sinus bradyarrhythmia, 3 atrio-ventricular 1st degree (AV) block) following CPB, in ICU stay or in hospital stay and all of patients were discharged with sinus rhythm. We did not find any significant difference between the arrhythmia and non-arrhythmia groups according to the duration of CPB (p=0.603), the lowest degree during CPB (p=0.115), the duration of ACT (p=0.570), the duration of ICU stay (p=0.215), or the mean follow-up (p=0.137) among group A.

In group B, 4 patients (5%) had arrhythmia (sinus bradyarrhythmia) following CPB, in ICU stay or in hospital stay and all of the patients were discharged with sinus rhythm. We did not find any significant difference between the arrhythmia and non-arrhythmia groups according to the duration of CPB (p=0.502), the lowest degree during CPB (p=0.189), the duration of ACT (p=0.450), the duration of ICU stay (p=0.384), or the mean follow-up (p=0.196) among group B.

The duration of postoperative hospital stay was significantly higher in the arrhythmia group among group A (p=0.004). In group B, probably due to the sinus bradyarrhythmia, postoperative hospital stay was not significantly higher (p=0.332).

The arrhythmia subgroup of the group A had significantly lower mean age (p=0.032) and a mean weight (p=0.026) during the operation. Similarly, the arrhythmia subgroup of the group B had significantly lower mean age (p=0.003) and mean weight (p=0.015) were significantly lower during the operation.

Postoperative pulmonary venous obstruction, SVC or inferior vena cava (IVC) obstruction were not detected in both groups. Consequently, no significant difference was obtained in postoperative development of PV/SVC stenosis between two groups. Moreover reoperation (p=0.045) and residual ASD (p=0.045) were significantly higher in group A.

According to post-hoc power analysis results performed by arrhythmia in hospital stay statistics, the power of the study is calculated and 87.43% power was obtained with a value of 0.324 effect size.

Discussion

Even though the results in different time interval and those of different centers were compared, we concluded that in group A, duration of CPB, amount of drainage, duration of hospitalization, postoperative arrhythmia, reoperation, residual ASD were higher. Lowest degree during CPB was lower in group A. Previously, surgeons preferred lower temperature and this might extend the duration of CPB due to the weaning process and as a consequence, these reasons might cause more bleeding and longer hospitalization time. Residual ASD and reoperation in group A were observed in younger and lower-weight patients. The arrhythmia might occur due to the fact that the operations were performed by different surgeons with different techniques and in lower-weight patients which is the reason of difficult exploration.

In the literature, many studies have investigated arrhythmia in the pediatric population following PAPVD surgery (9). In childhood, the incidence of postoperative arrhythmia following congenital heart surgery is 48% (10). Arrhythmia has a close correlation with atrial incision length, myocardial damage, injury of the sinus node or sinus node artery due to cannulation of the SVC, sutures near the conduction system, and acute alterations in physiological parameters postoperatively (11-13). The duration of CPB and deep hypothermia have also important relationships with arrhythmia (14). Dramatic changes of the pressure in cardiac chambers caused by volume and pressure overload may be other reasons for postoperative early arrhythmia (10).

Injury to the SN or SN artery may lead to serious arrhythmias. Yet there is no consensus on the best technique to avoid this risk. The presence of long-term SN dysfunction following single or double-patch technique is contradictory; Alsoufi and Iyer reported no SN dysfunction with the single/double-patch technique (10,15-17). In contrast, Agarwal and Baron showed that the risk is diminished using the single patch technique (18-20). Nevertheless, Buz et al. presented a counterview of the continuity of the postoperative arrhythmia ratio, and they stated that the ratio was 7.3%. Buz et al. and Jaschinski et al. reported that extension of the incision through the cavoatrial union at the time of double-patch repair causes postoperative arrhythmias (44%) (21,22). For the Warden procedure, the ratio of arrhythmia is

10%, and the long-term incidence of arrhythmia is 2.5% (23). Nakahira et al. determined the incidence of arrhythmia following the Warden procedure to be 4% (24).

Some studies have concluded that redo surgery is a reason for postoperative arrhythmia (25). Postoperative AF developed in one of our patients who also underwent redo surgery.

Some studies have concluded that postoperative arrythmia after pediatric heart surgery has an association with different factors such as younger age, lower weight, electrolyte imbalance, prolonged CPB time, deep hypothermic circulatory arrest, surgery type, inotropic use, and cyanotic congenital heart disease (10,11,13,26,27).

Said didn't find any PV or SVC obstruction because of the contraction related with patch in spite of their material in his study (8). Hu and colleagues reported, the dimension of the patch in single-patch technique is the most important point for long-term systemic or pulmonary venous stenosis. A smaller patch increases the risk of PV obstruction; in contrast, a larger patch causes SVC obstruction (8). Alsoufi has been found to avoid cavoatrial stenosis, and anastomosis should be accomplished without tension by providing adequate mobilization of the brachiocephalic vein and SVC (15). In our study, SVC obstruction wasn't detected in both groups. Additionally, if superior enlargement of ASD enlargement is required in PAPVD surgery, it may lead to postoperative PV stenosis, as Hu has reported (8). In contrast, Hu and colleagues did not identify any PV stenosis, SVC stenosis or SN dysfunction (8).

Conclusion

We retrospectively investigated patients who underwent PAPVD surgery with single-patch, double-patch, and Warden procedures but at different time intervals and from different centers.

In the pediatric population, age and weight have a close relation. In some instances, failure of thrive is encountered in addition to congenital heart anomalies, and low weight is not uncommon in this population. At the time of surgery, lower weight may add difficulties for exposure during the operation and undesirable injuries to cardiac structures.

We believe that careful dissection and incision near the sinus node must be emphasized to prevent injury to the sinus node for all types of surgery and by means of the development in surgical era. Moreover, difficulties in exposure in low-weight pediatric patients lead tendency toward postoperative arrhythmia in our study.

We did not observe any postoperative PV/SVC stenosis between the single/double patch and Warden procedure among group A and between group A and group B.

The limitations of our study

Our study does not include a high volume of patients. The comparison was made between 2 different time interval and different centers: Surgical material options and opportunities obtained in time by congenital heart surgery teams might be better in time. In addition, while patients in group B were operated by single surgeon, those of group A were operated by different surgeons.

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Examination Family Physicians' Knowledge and Awareness of Specific Learning Disorder

Aile Hekimlerinin Özgül Öğrenme Bozukluğuna İlişkin Bilgi ve Farkındalık Düzeylerinin İncelenmesi

Esmehan ÖZER[1], Rahime Duygu TEMELTÜRK[2]

[1]Kirikkale University, Faculty of Education, Department of Special Education, Kirikkale
[2]University, Faculty of Medicine, Department of Child and Adolescent Psychiatry, Ankara

Öz

Özgül öğrenme bozukluğu (ÖÖB), bireye gerekli müdahaleler yapılmasına rağmen bireyin en az altı aydır devam eden öğrenme ve akademik becerilerini kullanmada yaşadığı güçlük olarak ifade edilmektedir. Aile hekimleri sorumluluğu altında olan hastaları tanı, tedavi, rehabilitasyon ve danışmanlık hizmetleri kapsamında bütüncül olarak ele alıp değerlendiren hekimlerdir. Dolayısıyla aile hekimlerinin kendilerine başvuran çocukların ÖÖB belirtilerini fark edip bu çocukları tanı-değerlendirme ve müdahale için yönlendirmelerinin önemli olduğu düşünülmektedir. Bu çalışmada, aile hekimlerinin ÖÖB'ye ilişkin bilgi ve farkındalık düzeylerinin incelenmesi amaçlanmaktadır. Araştırmanın amacı doğrultusunda Türkiye'nin çeşitli illerinde hizmet veren aile hekimlerine "Özgül Öğrenme Bozukluğu Bilgi ve Farkındalık Düzeyi İnceleme Anketi" araştırmacılar tarafından geliştirilerek uygulanmıştır. Veriler, elektronik ortamda 125 aile hekiminin gönüllü katılımıyla elde edilmiştir. Anket maddelerine ilişkin aile hekimlerinin verdikleri cevapların frekans ve yüzde değerleri hesaplanarak istatistiksel analizler gerçekleştirilmiştir. Araştırma bulgularına göre aile hekimlerinin ÖÖB'nin tanım, etiyoloji, yaygınlık, tanılama, değerlendirme ve müdahale süreçlerine ilişkin bilgi eksikliklerinin olduğu tespit edilmiştir. Ayrıca, aile hekimlerinin ÖÖB farkındalığının düşük olduğu, daha çok internet ve sosyal medya (Instagram/Twitter gibi) ile kitap/makaleler aracılığıyla bilgi edindikleri belirlenmiştir. ÖÖB erken tanısı ile birlikte gerekli müdahalelerin uygulanması oldukça önemlidir. Bu nedenle, aile hekimlerinin ÖÖB'li bireyleri erken çocukluk döneminde fark edip tanı-değerlendirme ve müdahale süreçlerine yönlendirebilmeleri için bilgi ve farkındalıklarının artırılmasının önemli olduğu düşülmektedir.

Anahtar Kelimeler: Aile Hekimi, Özgül Öğrenme Bozukluğu, Bilgi, Farkındalık

Abstract

Specific learning disorder (SLD) is defined as the difficulty an individual has been experiencing for at least six months in using their learning and academic skills despite appropriate interventions being provided. Family physicians are doctors who comprehensively evaluate individuals under their responsibility for diagnosis, treatment, rehabilitation, and counseling services. Therefore, it is important that family physicians notice the symptoms of SLD in children and direct them for diagnosis, evaluation, and intervention. The aim of this study was to examine the knowledge and awareness levels of family physicians about SLD. For the research, the Special Learning Disorder Knowledge and Awareness Level Questionnaire" was developed by the researchers and administered to family physicians serving in various cities in Turkey. The data were obtained with the voluntary participation of 125 family physicians in an electronic environment. Statistical analyses were conducted by calculating the frequency and percentage values of the responses given by the family physicians to the questionnaire items. According to the research findings, it was determined that family physicians have knowledge deficiencies regarding the definition, etiology, prevalence, diagnosis, evaluation, and intervention processes of SLD. Additionally, it was determined that the awareness of family physicians about SLD is low and they mostly acquire information through the internet and social media (such as Instagram/Twitter) and books/articles. It is vital to implement the necessary interventions along with the early diagnosis of SLD. Therefore, it is important to increase the knowledge and awareness of family physicians so that they can notice individuals with SLD in early childhood and direct them to the diagnosis-evaluation and intervention processes.

Keywords: Family Physician, Specific Learning Disorder, Knowledge, Awareness

Introduction

Specific Learning Disorder (SLD) is a diagnostic term employed to delineate a collective of specific learning disabilities that cannot be explained by physical, mental or neurological problems (1). SLD is defined as an individual's difficulty in learning and using academic skills, such as reading, writing, and mathematics, that persists for at least six months despite appropriate interventions in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (2). SLD is characterized by the presence of dyslexia, dysgraphia and dyscalculia together or separately. In addition to academic skills, SLD has a significant negative impact on daily activities and social areas. In addition to these difficulties experienced by individuals with SLD, 30 to 60% of these individuals have other comorbid psychiatric disorders (3,4). Attention deficit hyperactivity disorder (ADHD) is the most common comorbidity with SLD (5).

The incidence of SLD is witnessing a progressive escalation over time. According to DSM-5, the prevalence of SLD among school-age children varies between 5% and 15% (1). SLD is observed more frequently in boys compared to girls (6). However, SLD accounts for nearly half of the students with special needs in any diagnostic group in the United States of America (USA) (7), and this rate decreases to 3% in Turkey (8). The number of children with SLD in the USA is more than three times higher than that in Turkey. However, this

	ORCID No
Esmehan ÖZER	0000-0001-5919-8072
Rahime Duygu TEMELTÜRK	0000-0002-9303-5944

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Adres / Correspondence : Esmehan ÖZER
Kirikkale University, Faculty of Education, Department of Special Education, Kirikkale, Turkey
e-posta / e-mail : esmehanozer@kku.edu.tr

situation is not due to the low number of children with SLD in Turkey, but due to the fact that the diagnostic evaluation process and system is still developing (8). This development in the diagnostic-evaluation processes is expected to be further accelerated by updating and clarifying the diagnostic criteria of SLD, increasing the level of knowledge and awareness of specialists in the community (e.g. physicians, teachers), increasing the number of child and adolescent mental health and illness specialists and the number of consultations to these specialists, and the role of media/television/internet.

Child and adolescent mental practitioners working at secondary and tertiary hospitals take part in the diagnosis-evaluation processes of children with SLD in Turkey (9). For the last few years, this process has been carried out under the regulation on "Special Needs Assessment for Children (SNARC)". The medical board, recently defined as "Special Needs Report for Children", comprises specialists from various fields including child and adolescent psychiatry, pediatrics, ophthalmology, and neurology. Following the medical diagnosis, the child's educational diagnosis-evaluation process is initiated in guidance and research centers (GRCs). All these diagnostic evaluation processes should be carried out individually carefully for various reasons such as the causal disparities of SLD, the intense heterogeneity of subtypes (10).

Effective and efficient intervention programs are implemented for children with SLD to overcome their difficulties in academic skills such as reading, writing and mathematics (11). Word/reminder, repeated reading and story map strategies have been shown to be effective in developing fluent reading and reading comprehension skills of students with SLD (12). Additionally, self-management strategies are frequently used in the acquisition and development of reading comprehension skills of students with SLD (13). Self-organization strategy is generally utilized in the development of writing skills of students with SLD (14,15). Schema-based math problem solving strategy is efficient in solving math problems (16). With the intervention programs applied to children with SLD, the reading and writing skills of these students improve and their performance increases (17).

Family physicians are responsible for proving comprehensive and continuous personal preventive health services and first-step diagnosis, treatment, and rehabilitative health services to each person, without discrimination of age, gender, and disease, and who provide mobile health services when necessary (18). To put it differently, they evaluate individuals not only in the context of specific illnesses but also from a more holistic point of view. For example, they consider the risks associated with the symptoms presented by the individual (19). Given this circumstance, family physicians play important roles and responsibilities such as following and screenings related to child health (18).

To date, no study examining the knowledge and awareness levels of family physicians regarding SLD has been identified. However, for example, the level of knowledge and awareness of last year medical faculty students about autism spectrum disorder (ASD) (20), the level of knowledge of healthcare professionals about childhood ASD (21), and the awareness of healthcare professionals in family health centers about ASD (22) were examined. This study represents the initial examination in Turkey of the knowledge and awareness levels of SLD among family physicians. By employing this approach, it becomes possible to ascertain the knowledge and awareness levels of family physicians regarding SLD and to extend appropriate support to these practitioners when the need arises. Consequently, children exhibiting symptoms of SLD can be promptly referred to child and adolescent mental health outpatient clinics for early diagnosis and assessment processes, enabling timely interventions to prevent their difficulties from becoming long-lasting or permanent.

Material and Method

Design

The study was approved by the Kırıkkale University (11.01.2023, protocol number: 1/14). In this study, which aimed to examine the knowledge and awareness levels about SLD of family physicians working in various cities of Turkey, the survey method was used. Through this methodology, an endeavor was made to ascertain and define a situation that existed either in the past or continues to persist in its present state (23). In the study, data were collected using an electronic questionnaire.

Participants

The study participants consisted of 125 family physicians working in different cities of Turkey. The sample group for the study was determined using the snowball sampling method, whereby new participants are accessed through initial participants or groups of participants, thereby facilitating the expansion of the sample (24,25). Therefore, in this study, the participants were asked who else they could interview and be included in the research and proceeded. The study was naturally terminated when there were no new participants who could be asked and contacted. In this context, 125 participants were reached and the questionnaire sending process was completed. Demographic information about the participants was presented in Table 1, and information about their education and profession was presented in Table 2.

Table 1. Demographic characteristics of the participants

Characteristic (n=125)	**Result**
Age (year), mean ± Standard Deviation	38.95 ± 9.83
Gender, n (%)	
Female	81 (64.8)
Male	44 (35.2)
Having a child, n (%)	
No	41 (32.8)
Yes	84 (67.2)
An individual with SLD in familiar surroundings, n (%)	
Yes	19 (15.2)
No	84 (67.2)
I don't know	22 (17.6)
Working Institution, n (%)	
Family Health Center	94 (75.2)
Community Health Center	2 (1.6)
Integrated Hospital	29 (23.2)

Instruments

In this study, a Special Learning Disorder Knowledge and Awareness Level Examination Questionnaire" was prepared by the researchers based on a literature review to examine the knowledge and awareness levels of family physicians regarding SLD. The first section of the questionnaire consists of two sections; sociodemographic characteristics (age, gender, having a child, presence of an individual with SLD in familiar surroundings), professional characteristics (institution type, time (years) since graduation from medical faculty, the number of patients/children evaluated in a day and the age ranges of the children), and educational characteristics (the status of taking courses or training on SLD during education and professional service years). Furthermore, in this section of the questionnaire, physicians were specifically inquired about their awareness levels concerning SLD. The questions encompassed topics such as whether they had encountered any suspicion of SLD during medical examinations and the sources from which they obtained information about SLD. In the second part, in order to determine the level of knowledge of physicians, there are three items on the definition and etiology, two items on prevalence, ten items on characteristics, three items on diagnosis-assessment and intervention of SLD, and three questions to examine their awareness.

Table 2. Educational and professional characteristics of participants

Characteristic (n=125)	**Result n (%)**
The status of family physician specialty training	
Those without specialized training	40 (32)
Those with specialized training	67 (53.6)
Those with contracted family physician specialized training	18 (14.4)
Professional working duration (year)	
Total working duration after medical faculty graduation (year)	
<10	64 (51.2)
≥10	61 (48.8)
Working duration as a family physician (year)	
<5	57 (45.6)
≥5	68 (54.4)
Patient characteristics evaluated by family physicians	
The total number of patients per day	
<50	57 (45.6)
≥50	68 (54.4)
The total number of children patients per day	
0-10	43 (34.4)
11-20	42 (33.6)
>20	36 (28.8)
Suspicion of SLD in medical examinations	
Yes	57 (45.6)
No	68 (54.4)
Status of receiving training on SLD	
During medical faculty student	
Yes	48 (38.4)
No	77 (61.6)
During family physician	
Yes	14 (11.2)
No	111 (88.8)

The participants responded to the 18 questions asked to measure their level of knowledge with the options "yes, no and I do not know", while they responded to the three questions to examine the level of awareness as "strongly disagree, disagree, undecided, agree and strongly agree". While answering the question "Have you ever suspected the diagnosis of SLD during your examination before?" with the options "yes, no", they responded to the sources of information about SLD by choosing one or more of the following responses: "internet and social media (such as Instagram, Twitter), books and articles, courses/seminars/training, physician friends and through a relative/an acquaintance diagnosed with SLD". Thus, 23 questions were asked to each participant to examine their level of knowledge and awareness about SLD.

To test the content validity of the "Specific Learning Disorder Knowledge and Awareness Level Examination Questionnaire" draft form, the opinions and suggestions of three lecturers, one of whom is an expert in the fields of child and adolescent mental health, special education, and linguistics were obtained. It was evaluated whether each item of the draft questionnaire was a sufficient or an appropriate question to measure the defined behaviors (26). For example, a child and adolescent psychiatry specialist stated that the item "I try to get feedback on the child's special education process regarding SLD." which is the area of interest of child and adolescent mental health and diseases specialists, is not the responsibilities of family physicians and remains outside their borders. Therefore, this item was removed from the survey. The special education specialist stated that "The following factors play a role in the causes of SLD." would be a more suitable item instead of the item "Which factors play an important role among the causes of SLD?". As a result, the researchers reorganized the questionnaire items in the context of this and similar feedback from the experts.

In addition to content validity, face validity of the "Specific Learning Disorder Knowledge and Awareness Level Examination Questionnaire" was evaluated. In this context, the researchers sent the draft version of the questionnaire to two family physicians to examine whether the items were understandable. After this stage, the questionnaire consisting of two sections and 23 questions was finalized within the scope of the feedback from the physicians and made ready for the application. The Cronbach's Alpha reliability coefficient of the questionnaire items was calculated as .85. Since the coefficient is between 0 and 1.00 (27), the questionnaire is highly reliable.

Data Collection and Analysis

The questionnaire was sent electronically to family physicians over the internet via Google Forms. Data were collected between 16-22 January 2023. "Statistical Package for the Social Sciences (SPSS) 23" was used to analyze the data. Descriptive data were presented as number and percentage for categorical variables and mean and standard deviation for quantitative data. Thus, analyses were made with the number and percentages of the correct answers given by family physicians regarding the items in the questionnaire. The normal distribution of continuous quantitative variables was examined by Shapiro-Wilk test. In the comparison of independent groups, Mann–Whitney U-test was used when the number of groups was two and Kruskal Wallis-H test was used when the number of groups was more than two. Additionally, all the statistical tests were two-tailed with a threshold for significance of $\alpha = 0.05$.

Results

The findings obtained following the analysis of the data of this study, which aimed to examine the knowledge and awareness levels of family physicians regarding SLD, are presented under subtitles.

Participants' levels of Knowledge about Specific Learning Disorder

Table 3 shows the frequency and percentages of family physicians who responded to the questions.

The mean number of correct answers given by the participants to 18 items was calculated as 11.04±3.76. When the mean number of correct answers was compared by gender, female physicians scored 12 points while male physicians scored 11 points. The mean number of correct answers received by family physicians showed a statistically significant difference according to gender (p=0.020). However, there was no statistically significant difference in the mean number of correct answers according to whether or not having a child (p=0.226) and whether or not receiving family medicine residency training (p=0.378). Similarly, the mean number of correct answers was tested in terms of the number of patients evaluated per day (p=0.612), duration after medical faculty (p=0.680) and duration of professional working as a family physician (p=0.306) and no significant differences were found. In addition, when the mean number of correct answers was analyzed in terms of the total number of pediatric patients evaluated per day, no significant differences were found (p=0.903). On the other hand, the mean number of correct answers was compared by using Mann–Whitney U-test in terms of family physicians' received training on SLD during medical faculty years (p=0.001) and received training on SLD as a family physician (p=0.014), and significant differences were recorded.

Table 3. Findings related to participants' levels of knowledge about Specific Learning Disorder

Items Related to the Knowledge Level of SLD	n= 125		
	Yes	No	I Don't Know
	n (%)	n (%)	n (%)
Definition and Etiology			
SLD is a neurodevelopmental disorder.	87 (69.6)	15 (12.0)	23 (18.4)
The term dyslexia can be used instead of SLD. *	70 (56.0)	30 (24.0)	25 (20.0)
Both genetic and environmental factors play a role in the etiology of SLD.	119 (95.2)	3 (2.4)	3 (2.4)
Prevalence			
SLD is more common in boys than in girls.	48 (38.4)	11 (8.8)	66 (52.8)
The prevalence of SLD in school-age children is between 5 and15%.	57 (45.6)	12 (9.6)	56 (44.8)
Patient Characteristics			
Children diagnosed with SLD may have problems with speech-language skills in the preschool period.	105 (84.0)	1 (0.8)	19 (15.2)
SLD is usually diagnosed within the preschool period. *	35 (28.0)	71 (56.8)	19 (15.2)
SLD is a psychiatric disorder specific to childhood only. *	11 (8.8)	88 (70.4)	26 (20.8)
SLD is often comorbid with attention deficit hyperactivity disorder.	78 (62.4)	14 (11.2)	33 (26.4)
SLD can be treated with medication. *	17 (13.6)	76 (60.8)	32 (25.6)
Significant improvement in SLD symptoms can be achieved with early diagnosis and intervention program/special education.	117 (93.6)	0 (0.0)	8 (6.4)
There are subtypes of SLD.	95 (76.0)	1 (0.8)	29 (23.2)
Individuals with SLD may have special abilities and skills.	99 (79.2)	4 (3.2)	22 (17.6)
Individuals with SLD usually have below-average intelligence. *	10 (8.0)	89 (71.2)	26 (20.8)
Individuals with SLD often have difficulties in academic skills.	84 (67.2)	14 (11.2)	27 (21.6)
Items Related to Diagnosis, Assessment and Intervention Processes			
Neurologists make the diagnosis of SLD. *	20 (16.0)	75 (60.0)	30 (24.0)
EEG (electroencephalogram) and/or neuroimaging should be performed to confirm the diagnosis of SLD. *	28 (22.4)	46 (36.8)	51 (40.8)
Some children with SLD spontaneously overcome their reading difficulties over time without any intervention. *	53 (42.4)	41 (32.8)	31 (24.8)

*Items having "No" as the correct answer

Awareness Levels of Participants about Specific Learning Disorder

Table 4 shows the frequency and percentages of family physicians who answered the questions. Of 125 participants, 62% (n=78) of them disagreed, 24% (n=30) of them strongly disagreed with the item "I think the knowledge I have about SLD is sufficient". For the item "Awareness of SLD is low among family physicians.", 50% (n=63) of family physicians agreed, 18% (n=33) strongly agreed, and 25% (n=31) were undecided. The item "I think I will benefit from trainings on SLD." agreed by 38% (n=47) of family physicians and 56% (n=70) strongly agreed.

When family physicians' suspicions of SLD during the examination was analyzed, 55% (n=68) did not experience such a suspicion. In addition, the sources of information on SLD reported by the physicians are shown in Figure 1 as percentages (%). Among family physicians, 63 (50%) stated that they obtained information about SLD from the internet and social media (such as Instagram/Twitter), 55 (44%) from books/articles, 48 (26%) from courses-seminars-trainings, 48 (26%) from physician friends and 10 (8%) through a relative/acquaintance with SLD.

Table 4. Findings related to participants' awareness of Specific Learning Disorder

Items Related to SLD Awareness Level (n=125)	Strongly Disagree	Disagree	Undecided	Agree	Strongly Agree
	n (%)	n (%)	n (%)	n (%)	n (%)
I think that my knowledge about SLD is sufficient.	30 (24)	78 (62.4)	10 (8)	6 (4.8)	1(0.8)
Awareness of SLD is low among family physicians.	1 (0.8)	7 (5.6)	31 (24.8)	63 (50.4)	23 (18.4)
I think I will benefit from training on SLD.	2 (1.6)	1 (0.8)	5 (4)	47 (37.6)	70 (56)

Discussion

The aim of this study was to determine the level of knowledge and awareness of family physicians in Turkey regarding SLD. In the context of the results obtained, family physicians have a lack of knowledge or confusion, especially in some items related to SLD. In this context, more than half of the family physicians responded correctly to the incorrect statement "The concept of dyslexia can also be used instead of SLD", while some of them answered "I don't know". However, SLD is an umbrella disorder and is characterized by the presence of reading (dyslexia), written expression (dysgraphia), and math (dyscalculia) disorders together or separately (2). In this context, it can be

said that family physicians need various information such as what kind of a disorder SLD is, what its subtypes are, and what kind of heterogeneity it may exhibit.

There are several family physicians who answered "I don't know" and "incorrect" to the item "SLD is more common in boys than in girls" in the questionnaire. However, SLD is a disorder seen more frequently in boys than in girls (6). In addition, family physicians gave many "incorrect" and "I don't know" answers to the item "The prevalence of SLD in school-age children is between 5 and15%". However, according to DSM-5, the prevalence of SLD among school-age children varies between 5% and 15% (1). Since the diagnosis-assessment processes and systems for children with SLD are still developing in Turkey, this rate is as low as 3% (8). Therefore, family physicians may have lack of knowledge on the items related to the definition, etiology, and prevalence of SLD.

Regarding the diagnosis, assessment and intervention processes of SLD, some of the family physicians gave the correct answer to the incorrect statement "EEG and/or neuroimaging should be performed to confirm the diagnosis of SLD". In addition, most participants have inaccurate and incomplete information on the item "Some children with SLD overcome their reading difficulties spontaneously over time without any intervention". However, there are appropriate intervention programs to increase the performance levels of children with SLD by improving their academic skills such as reading (12,13), writing (14,15) and mathematics (16). In addition, a study carried out in Turkey a few years ago reported that intervention programs for children with SLD, especially for their reading and writing skills, were effective (17).

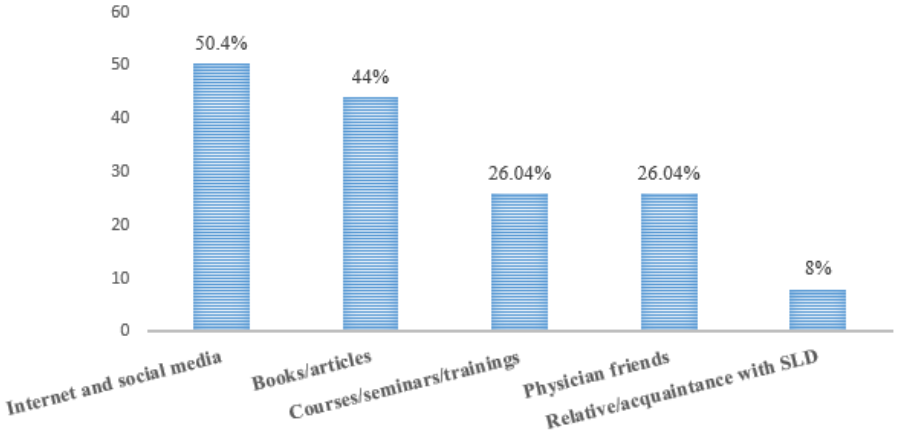

Figure 1. Sources of information on Specific Learning Disorder stated by family physicians

When the knowledge levels of family physicians regarding SLD were examined according to gender, having children, and having family physician residency training, the knowledge levels were statistically significantly different only according to gender. This result is consistent with the result (28) that female family physicians and pediatricians provide more guidance than males in cases of developmental delay in children. Similarly, the mean number of correct answers showed statistically significant differences in the cases in which family physicians received training on SLD in medical faculty and received training on SLD during their working as family physicians. In this context, family physicians can be included in training programs on SLD with a multidisciplinary approach in pre-graduation medical education curricula and in-service training programs when they start working.

When the answers given by the family physicians to the items related to the awareness of SLD are examined, the awareness level is not sufficient, and the sources of information are mostly the internet and social media (such as Instagram/Twitter) and books/articles. Therefore, participants' levels of awareness of SLD is low and their level of knowledge is insufficient. Within this context, the knowledge and awareness of physicians can be enhanced through educational and professional training programs tailored for family physicians. It is important for family physicians to recognize children with SLD at an early stage and direct them to the child and adolescent psychiatry outpatient clinics for the assessment and intervention processes with accurate information obtained from reliable sources. Thus, physicians will be able to carry out primary care diagnosis, treatment, rehabilitation, and counseling services as a whole (18,19).

In this study, the knowledge and awareness levels of family physicians about SLD were determined with a single measurement tool. In future, studies reaching more participants with more than one and standardized assessment tools can be planned. Mixed method studies with qualitative data can be carried out. On the other hand, family physicians can be included in an in-service training

programme on SLD and their knowledge and awareness levels can be re-evaluated.

Conclusion

According to the results of this study, most of the family physicians stated that there were no individuals with SLD in their familiar surroundings, that they did not suspect SLD during the medical examinations, and that they did not receive any training on SLD during their medical faculty years as well as working as family physicians. The knowledge and awareness levels of family physicians regarding Specific Learning Disorder (SLD) exhibit certain limitations. It is crucial to increase the knowledge and awareness of family physicians to recognize individuals with SLD in early childhood and guide them to diagnosis-assessment and intervention processes. In conclusion, both courses on SLD should be included in the medical faculty curriculum and informative in-service training on SLD should be organized for family physicians serving in the field. In addition, legal regulations can be made to enable family physicians, special educators, and child and adolescent mental health specialists to work together.

Conflict of interest statement

The authors have no conflicts of interest regarding this study.

Ethics Committee Approval: The study was approved by the Kırıkkale University (11.01.2023, protocol number: 1/14).

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A Retrospective Analysis of Intra-Uterine Fetal Demise Cases in Our Clinic

Kliniğimizde Gerçekleşen İntra-Uterin Fetal Ölüm Vakalarının Retrospektif Olarak Değerlendirilmesi

Özge ŞEHİRLİ KINCI[1], Firangiz MİRZAZADA[2], Mehmet Onur ARSLANER[2], İsmail GÖKBEL[3]

[1]Liv Hospital, Obstetrics and Gynecology Department, Ankara, Türkiye
[2]Muğla University Education and Research Hospital, Obstetrics and Gynecology Department, Muğla, Türkiye
[3]Menteşe State Hospital, Obstetrics and Gynecology Department, Muğla, Türkiye

Öz

Tersiyer bir merkez olan kliniğimizde, 2015-2022 yılları arasında doğumu gerçekleşen intra-uterin fetal ölüm vakalarının sıklığını, demografik özelliklerini, risk faktörlerini ve sonuçlarını retrospektif olarak değerlendirmek. Ocak 2015-Aralık 2021 tarihleri arasında Muğla Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniğinde intra-uterin fetal ölüm nedeni ile doğumu gerçekleşen, 22-41 hafta arasındaki, 92 gebe değerlendirildi. Gebelerin başvuru anındaki yaş, gravida, parite, vücut kitle indeksi (VKİ) verileri, gebelik haftaları, doğum sonrası ise doğum ağırlıkları, doğum şekilleri, bebek cinsiyeti ve patolojik inceleme sonuçları kayıt edildi. Belirtilen tarihler arasında 92 intra-uterin fetal ölüm gerçekleşmiştir. Doğum sayısına oranı 1.03% olarak saptanmıştır. 88 (%95.65) tanesi tekil gebelik, 4 (%4.34) tanesi çoğul gebelik idi. Yaş ortalamaları 29.47±5.71 idi. 1'er (%1.08) gebe 18 yaşın altında ve 40 yaşın üzerine idi. VKİ ortalamaları 25.54±3.90 kg/m^2 iken, 2 (%2.16) gebenin VKİ'si morbid obez (≥40 kg/m^2) seviyesinde izlenmiştir. Gestasyonel yaşları 31.07±4.87 hafta idi. İntra-uterin fetal ölüm nedenleri değerlendirildiğinde, 12 (%13.18) gebede plasenta dekolmanı saptanmıştır. Plasenta dekolmanı saptanan gebelerin 6 (%50)'sinde gebeliğin hipertansif bozuklukları mevcuttu. 5 (%5.49) gebede diabetes mellitus, 2 (%2.19) gebede plasenta previa saptanmıştır. 7 (%7.60) gebenin yatışında uteroplasental yetmezlik bulgusu olan anhidroamniyoz saptandı. 20 (%21.97) gebede fetal anomali izlenmiştir. 1 (%1.09) gebede dissemine intravasküler koagülasyon gelişmiştir. 3 (3.26%) gebede ise COVID-19 saptanmış olup hospitalize edilmiştir. İntra-uterin fetal ölüm vakalarının ön görülebilirliği düşüktür. Fakat bu duruma rağmen, her merkez kendi sonuçlarını değerlendirerek ve risk faktörlerini belirleyerek pro-aktif yaklaşım ile intra-uterin fetal ölüm vakalarını kısmi olarak azaltabilir.

Anahtar Kelimeler: Intra-Uterin Fetal Ölüm, Ölü Doğum, Risk Faktörü

Abstract

The present study aims to retrospectively analyze the frequency, demographic characteristics, affecting risk factors and outcomes of intra-uterine fetal death (IUFD) cases delivered between 2015 and 2022 in our clinic, a tertiary center. Between January 2015 and December 2021, 92 pregnant women between 22-41 weeks of gestational age who gave birth due to IUFD in Muğla University Education and Research Hospital clinic were included in the study. Age at presentation, gravida, parity and body mass index (BMI) data, gestational weeks, and if after birth, birth weight, mode of delivery, infant sex and pathologic examination results were recorded. There were 92 cases of IUFD between the specified dates. The ratio of cases to the number of births was 1.03%. Of the cases, 88 (95.65%) were singleton pregnancies and 4 (4.34%) were multiple pregnancies. The mean age was 29.47±5.71 years. Among the cases, 1 (1.08%) pregnant woman was under 18 years of age and 1 pregnant woman was over 40 years of age. The mean BMI was 25.54±3.90 kg/m2 and 2 (2.16%) pregnant women were morbidly obese (≥40 kg/m2). The mean gestational age was 31.07±4.87 weeks. When the causes of IUFD were evaluated, placental abruptio1n was observed in 12 (13.18%) pregnant women. Hypertensive disorders of pregnancy were present in 6 (50%) of the pregnant women with placental abruption. While 5 (5.49%) pregnant women had diabetes mellitus, 2 (2.19%) had placenta previa. A total of 7 (7.60%) pregnant women had anhydroamniosis, a sign of uteroplacental insufficiency, during hospitalization, while 20 (21.97%) pregnant women had fetal anomaly. One (1.09%) pregnant woman developed disseminated intravascular coagulation. In addition, 3 (3.26%) pregnant women had COVID-19 and were hospitalized. The predictability of IUFD cases is low. But despite this, each center can partially reduce the incidence of IUFD with a pro-active approach by evaluating its own outcomes and identifying risk factors.

Keywords: Intra-Uterin Fetal Death, Stillbirth, Risk Factor

Introduction

Fetal death is defined by the World Health Organization (WHO) as the death of a fetus prior to the complete removal or abortion of a product of conception from the mother, regardless of the duration of pregnancy (1). However, the main problem with the definition is the difference of opinion on the limit of fetal viability. The WHO considers a fetal weight of 500 g, a gestational age of 22 weeks and a crown-heel length of 25 cm to be the limit (2). In European countries, there are approaches ranging from the 16th to the 26th week of gestation to define it (1). It is difficult to give clear information about the frequency of cases due to differences in definitions, registration systems of countries etc. In addition to studies reporting a prevalence between 0.5% and 1%, there are also studies reporting a prevalence of around 3% (3-5). In our country, WHO criteria are applied and the frequency of cases is 0.9% (6). What is not in dispute, however, is the high incidence of cases in countries in South Asia and Sub-Saharan Africa (3).

	ORCID No
Özge ŞEHİRLİ KINCI	0000-0001-6439-0798
Firangiz MİRZAZADA	0000-0003-0677-3584
Mehmet Onur ARSLANER	0000-0002-1573-8556
İsmail GÖKBEL	0000-0002-6034-8987

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Kabul Tarihi / Accepted : 24.11.2023

Adres / Correspondence : Özge ŞEHİRLİ KINCI
Liv Hospital, Obstetrics and Gynecology Department, Ankara, Türkiye
e-posta / e-mail : drozgesehirlikinci@gmail.com

When analyzing the etiologic factors, it is useful to divide them into maternal, fetal and placental factors. Comorbid diseases before and during pregnancy [spectrum of hypertensive diseases, diabetes mellitus (DM)], age, uterine and cervical pathologies, smoking, infections and obesity are the leading maternal factors. Genetics, congenital anomalies and utero-placental anomalies and intra-uterine growth retardation (IUGR) are among the fetal and placental factors (7). However, in some fetal deaths, no cause can be found despite obstetric follow-up and pathology examinations after intra-uterine fetal death (IUFD). This condition is called "Sudden intrauterine unexplained death (SUID)" (8). SUID poses a medicolegal problem for obstetricians and a psychological problem for pregnant women, especially in developed countries.

In the current study, the frequency, demographic characteristics, risk factors and outcomes of IUFD cases delivered in our clinic between 2015-2022 are evaluated retrospectively.

Material and Method

Between January 2015 and December 2021, a total of 92 pregnant women who delivered due to IUFD in gynecology and obstetrics clinic were included in this study. IUFD was evaluated in proportion to the total number of deliveries between the specified dates. The ethical approval was granted from the Muğla Sıtkı Koçman Hospital ethical committee (Number: 70, Date: 06.09.2022). Since the study was planned retrospectively, no consent form was taken from the participants. All reported research involving "human beings" were conducted in accordance with the principles outlined in the Helsinki Declaration Fortaleza, October 2013. Pregnant women with a gestational age between 22-41 weeks without fetal heartbeat were included in the study. Age at presentation, gravida, parity, body mass index (BMI), gestational age, birth weight, mode of delivery and sex of the baby were recorded. Gestational weeks were determined by correlating the last menstrual date and first trimester ultrasonography data. Women were excluded if any of the following criteria was met: IUFD cases referred from other centers, pregnant women with a gestational age of less than 22 weeks, and pregnant women with unavailable data.

Statistical Analysis

The statistical analyses were performed with SPSS 22.0 for Windows program. The Independent Sample T-test was applied for normally distributed data. The results obtained were expressed as mean±SD. The Mann-Whitney U test was applied for non-normally distributed data. The results were expressed as median (min, max) and frequencies and percentages.

Results

A total of 92 pregnant women who met the inclusion criteria were included in the study. Of these pregnant women, 88 (95.65%) were Turkish citizens, while 4 (4.34%) were foreign nationals. In addition, 88 (95.65%) were singleton pregnancies and 4 (4.34%) were multiple pregnancies. The mean age was 29.47±5.71 years. While 1 (1.08%) pregnant woman was under 18 years of age, 45 (48.91%) pregnant women were between 18-29 years of age, 45 (48.91%) pregnant women were between 30-39 years of age and 1 (1.08%) pregnant woman was 40 years of age or older. The mean BMI was 25.54±3.90 kg/m^2 and 42 (45.65%) pregnant women were between 18.5 and 24.9 kg/m^2, which is the ideal BMI. Two (2.16%) pregnant women were morbidly obese (≥40 kg/m2). The mean parity of pregnant women was 2.03±1.16. The number of nulliparous patients was 50 (54.34%). A total of 52 (56.52%) fetuses were female. The mean gestational age of the pregnant women was 31.07±4.87 weeks with gestational ages ranging between 22 and 41 weeks. While 19 (20.87%) pregnant women were in the 22-27^{th} gestational week, 58 (63.73%) pregnant women were in the 28-36^{th} gestational week and 15 (16.30%) pregnant women were in the 37^{th} or more gestational week. The mean birth weight was 1654.01±947.07 g. While 38 (41.75%) fetuses were between 0-1000 g, 22 (24.17%) fetuses were between 1000-2000 g, 24 (26.37%) fetuses were between 2000-3000 g, 7 (7.69%) fetuses were between 3000-4000 g and 1 (1.08%) fetus was over 4000 g. The demographic characteristics of the pregnant women are shown in Table-1. A total of 52 (56.52%) pregnant women delivered by cesarean section (C/S), while 40 (43.47%) pregnant women delivered vaginally after induction. Dinoposton and Misoprostol were used as induction methods. The most common indications for C/S were previous C/S in 26 (50%) cases and failed induction in 15 (28.84%) cases.

Table 1. Demographic characteristics of pregnant women

	Overall (n=92)
Maternal's Age (year)	
Mean (SD)	29.47±5.71
Median (Range)	30.00 (17.00, 40.00)
Median (Q1, Q3)	30.00 (25.00, 34.00)
Parity (n)	
Mean (SD)	2.03±1.16
Median (Range)	2.00 (0.00, 5.00)
Median (Q1, Q3)	2.00 (1.00, 3.00)
Gestational week (n)	
Mean (SD)	31.07±4.87
Median (Range)	31.00 (22.00, 41.00)
Median (Q1, Q3)	31.00 (28.00, 35.00)
Birth weight (g)	
Mean (SD)	1654.01±947.07
Median (Range)	1500.00 (430.00, 4200.00)
Median (Q1, Q3)	1500.00 (800.00, 2210.00)

A total of 13 (14.13%) pregnant women had the spectrum of hypertensive disorders of pregnancy, including 12 (13.18%) with preeclampsia (PE) and 1 (1.09%) with eclampsia. Besides, 12 (13.18%) pregnant women had placental abruption. Hypertensive disorders of pregnancy were present in 6 (50%) of the pregnant women with placental abruption. While 5 (5.49%) pregnant women had DM, 2 (2.19%) had placenta previa. A total of 7 (7.60%) pregnant women were hospitalized with anhydroamniosis, a sign of uteroplacental insufficiency, while 20 (21.97%) pregnant women had fetal anomaly. Disseminated intravascular coagulation (DIC) developed in 1 (1.09%) pregnant woman. The pregnant woman who had DIC recovered with medical treatment in the anesthesia intensive care unit after delivery. COVID-19 was seen in 3 (3.26%) pregnant women, resulting in their hospitalization. Risk factors for IUFD are presented in Table 2.

Table 2. IUFD risk factors

Risk Factor	Proportion n (%)
Unknown cause	29 (31.52%)
Fetal Anomaly	20 (21.97%)
Preeclampsia / eclampsia	13 (14.13%)
Placental abruption	12 (13.18%)
Anhydroamnios	7 (7.60%)
Diabetes Mellitus	5 (5.43%)
Uteroplacental Insufficiency	3 (3.26%)
COVID-19	3 (3.26%)
Placenta Previa	2 (2.17%)
Disseminated Intravascular Coagulation	1 (1.08%)

Discussion

In the present study, a total of 92 cases of IUFD in our clinic between January 2015 and December 2021 were retrospectively evaluated.

In the study by DeGraaf et al. the prevalence of IUFD was found to be 0.7% (9). In the study by Sharma et al. it was found to be 3.6%. A history of IUFD was present in 9.2% of these pregnant women (10). Congenital malformations were present in 8.8% of the infants. Hydrocephalus and anencephaly were the most common congenital anomalies. In the study by Ohana et al. the prevalence of IUFD was found to be 7.4% (11). The biggest risk factor has been shown as "previous adverse perinatal outcome". The prevalence of IUFD in the hospital was found to be 1.03%. In a review study of IUFD cases, Wojcieszek et al. blamed infections in 5%-22%, congenital anomalies in 6%-22%, and unexplained causes in up to 76% of the cases (12). In the present study, fetal anomaly was the most common cause with 20 (21.73%) cases. We think that the most important reason why the prevalence of IUFD in the literature is quite different is related to the health registration system. We think that another important reason is the differences in perinatal follow-up frequencies.

The most common fetal anomalies were hydrocephalus and anencephaly with 10 (50%) cases. Unexplained causes were at a rate of 31.52%. This rate is consistent with the literature. The inconsistent result with the literature is that IUFD due to infection was not observed. The reason for this situation is that only toxoplasma, rubella and CMV IgM screening is performed at the beginning of pregnancy in our clinic. The fact that fetuses and stillbirths are not examined for infectious diseases is a shortcoming of our clinic. The increased risk of fetal loss in pregnant women infected with COVID-19 has been attributed to the predisposition of COVID-19 infection to thromboembolic events (13). Data collection for the current study started in 2015 and COVID-19 infection emerged in 2019. Therefore, it is not accurate to give rates regarding IUFD.

There is a correlation between the gestational week at which IUFD occurs and the causes of IUFD (14). Especially in pregnant women with a history of IUFD, preventability can be achieved with a proactive approach in subsequent pregnancies. Patient data on history of IUFD was not available and this is a limitation of the present study. While events associated with infection and congenital anomalies occur at earlier gestational weeks, causes such as hypertensive disorders of pregnancy and post-term are seen at later gestational weeks. When the timing of delivery was evaluated in the study by Monacho et al., 65% IUFD occurred in early preterm (PT) (<34 weeks), 20% in late PT (34 weeks to 37 weeks) and 15% in term (>37 weeks) period (3). In the study by De Graaf et al. the timing of delivery was found to be 30.68±0.66 weeks (9). In the study by Sharma et al. 47.2% of IUFD cases occurred in preterm and 52.8% in term period (10). In the study by Ohana et al, this was found to be 32.0+5.62 weeks. A total of 28.7% of cases were at term period (11). In the present study, the mean gestational age was 31.07±4.87 weeks. While 19 (20.87%) pregnant women were in the 22-27th gestational week, 58 (63.73%) pregnant women were in the 28-36th gestational week and 15 (16.30%) pregnant women were in the 37th and above gestational week. The results of the study are similar to those obtained in the study by Monacho et al. and are consistent with the current literature. It is considered that the most appropriate method for partial prevention of IUFDs between 28-36 weeks and at term is fetal movement monitoring. Randomized controlled studies should be conducted on the subject.

The birth weight of an IUFD fetus is correlated with the gestational week at the time of fetal loss. This may change only in pregnant women with fetal growth restriction (15). In the study by De Graaf et al. the mean weight of infants with IUFD was found to be 1738.47±112.31 g (9). In the study by Sharma

et al., 26% of stillborn fetuses had a birth weight between 2001-2500 g (10). Fetuses weighed between 1501-2000 g and 2501-3000 g in descending order. In the present study, the mean birth weight was 1654.01±947.07 g and 41.75% of the fetuses were in the 0-1000 g range. These results are consistent with the current literature. The relationship between fetal gender and fetal loss has been a subject of curiosity in the literature. In the study by Monacho et al., the ratio of male:female fetuses was found to be 1:1.7 (3). In the study by De Graaf et al., 52.3% of fetuses were female (9). In the present study, however, fetuses were female at a ratio of %56.52. These results are consistent with those in the literature.

From the moment the diagnosis of IUFD is made, the mode and timing of delivery becomes important. The risk of DIC is correlated with the time the products of conception spend as intra-uterine (16). The mode of delivery is important in terms of morbidity and the pattern of subsequent deliveries. In the study by Sharma et al., 70.8% of fetuses with IUFD were born with vaginal delivery (10). In the study by Ohana et al. 9.4% of deliveries occurred by C/S (11). In the present study, the rate of C/S delivery was 56.52%. The most common indication for C/S was previous C/S in 26 (50%) and failed induction in 15 (28.84%). This rate is much higher than other studies. When evaluating the C/S rate, it is necessary to take into consideration the frequency of pregnant women who have had previous C/S deliveries due to the increased C/S rate in our country (17,18).

Factors such as PE, hypertensive disorders of pregnancy such as eclampsia, spectrum of DM, oligohydramnios are partially preventable factors for IUFD (19). In the study by Monacho et al. PE was 39%, abruptio placentae was 4%, oligohydramnios 5%, and pregestational DM/GDM A1/GDM A2 were 2%/3%/2% (3). In the study by De Graaf et al, however, 10.9% pregnant women had pre-gestational DM, 11.6% had GDM, 3.1% had PE, and 4.7% pregnancy hypertension (9). In the study by Sharma et al., 14.4% had gestational hypertension, 8% had PE, and 8.4% had eclampsia (10). In the present study, however, 14.13% pregnant women had PE/eclampsia, 5.43% had DM, 13.04% had placental abruption, and 4.34% anhydramnios. Although there are no preventive methods in pathologies other than DM, it is important to follow up in the light of the recommendations of the guideline. This was proven by the study by Kafadar et al. (20). In cases where IUFD occurs, fetal autopsy is considered the "gold standard" method to determine the cause of IUFD (21). Encouraging parents to perform fetal autopsy and examination of the placenta will lead to more accurate results and save the obstetrician from medico-legal problems. Fetal autopsy is not accepted by parents due to some cultural or religious beliefs. In such cases, partial autopsy, imaging methods and genetic examinations are recommended (12).

The risk of IUFD is 50% higher among pregnant women aged 15-19 years (22). There is also an increased risk from the age of 35, although it is higher over the age of 40 (23). In the study by Monacho et al. the mean maternal age was 26 years (18–36 years) (3). In the study by De Graaf et al., however, this was found to be 27.98±0.51 (9). In the study by Ohana et al., the maternal age was found to be 29.28+6.73 and it was between the age range of 19-29 at a rate of 50.9% (11). In the present study, the mean age of women with IUFD was 29.47±5.71. Only 1 (%1.08) pregnant woman was under the age of 18 and 1 was over the age of 40. In the study by Monacho et al., the mean BMI was found to be 27.98±0.67 kg/m^2 (3). The increased BMI category was associated with an increased risk of IUFD. The riskiest group was identified as morbidly obese (≥40 kg/m^2). While the BMI mean of the pregnant women included in this study was 25.54±3.90 kg/m^2, it was seen that 2 (%2.16) pregnant women were morbid obese. It is considered that prenatal outcomes may improve with weight control, especially in the pre-gestational stage, in pregnant women with a history of IUFD and in pregnant women with DM, GDM or obese women.

In the studies carried out other risk factors for IUFD are stated to include smoking, primiparity, multiple pregnancies, post-term pregnancy, etc. (12, 24). In this study, 54.34% of pregnancies were primiparous and 4.34% were multiple pregnancies. Being primiparous is not a changeable condition. However, it is very important that these pregnant women are informed about the situation during follow-up and delivery processes. The definition and approach to post-term pregnancy remains controversial (25). In our clinic, elective induction is performed in pregnant women who reach 41 weeks of gestation. Patient data on smoking was not available and this is a limitation of the present study.

Evaluating the results of our clinic, which is the only tertiary central hospital in our province, for a long period of 7 years is a strong aspect of our study.

Conclusion

In conclusion, due to their low predictability, IUFD cases are medico-legal for obstetricians and physiologically and psychologically harmful for pregnant women. Each clinic can partially reduce this situation with a pro-active approach by evaluating its own outcomes and identifying risk factors. However, especially high-risk pregnant women should be informed that this situation cannot be prevented to a large extent.

One of the limitations of our study is that perinatal infections could not be evaluated. Another limitation is the retrospective design of the study.

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Regarding the limitations of our study, this was a retrospective review with a small sample size in a single center in a restricted region.

Conflict of interest statement

Authors declare that there is no conflict of interest between the authors of the article.

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The Effect of Histopathological Subtype on 5 Year and 10 Year Overall Survival in Primary Malign Tumors of the Chest Wall

Göğüs Duvarının Primer Malign Tümörlerinde Histopatolojik Alt Tipin 5 Yıllık ve 10 Yıllık Genel Sağkalıma Etkisi

Burak ODABAŞI[1], Mehmet YILDIRIM[1], İsmail DAL[1], Melek Didem AYDEMİR[1], Kemal DEMİRCAN[1], Deniz Ezgi MAHMUTOĞLU[1], Seçkin DENİZ[1], Semih BULUKLU[1], Aybiyçe Elif SİLPAĞAR[1], Murat YAŞAROĞLU[2], Bülent AYDEMİR[1], Tamer OKAY[1]

1 University of Health Sciences Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Türkiye
10 Başkent Üniversity İstanbul Hospital, Thoracic Surgery Department, İstanbul, Türkiye

Öz

Göğüs duvarının primer tümörleri, torasik neoplazmların %5'ini oluşturan nadir tümörlerdir. Mevcut çalışma, göğüs duvarının primer malign tümörlerinde histopatolojik alt tipin 5 yıllık ve 10 yıllık genel sağkalıma ve bölgesel nüks durumlarına etkisini değerlendirmeye yönelik tasarlanmıştır. Aralık 2007'den Aralık 2019'a kadar, 20 hastanın verileri geriye dönük olarak incelendi. Histopatolojik alt tipler arasında; genel sağkalım oranları, ortanca sağkalım, bölgesel tümör nüksü saptanma oranları ve ortanca hastalıksız sağkalım geriye dönük olarak kıyaslandı. Kondrosarkom (n=7), desmoid tümör (n=6), indiferansiye pleomorfik sarkom [(İPS), (n=4)], Ewing sarkomu (n=1), malign periferik sinir kılıf tümörü (n=1) ve liposarkom (n=1) tespit edilen alt tiplerdi. İPS histopatolojik alt tipinde daha düşük ortanca sağkalım tespit edildi (p = 0.004). Kondrosarkom grubunda 5 ve 10 yıllık genel sağkalım oranları sırasıyla, %71 ve %37; desmoid tümörlerde sırasıyla, %83 ve %42 saptandı. İPS'de ise 5 yıllık sağkalım gösteren hasta olmadı. Yan duvar yerleşimli kitlelerde, ön ve arka duvar yerleşimli kitlelere kıyasla daha kısa ortanca sağkalım tespit edildi (p = 0.001). Takip süresince 10 hasta (%50) hayatını kaybetti. İPS alt tipinde ortanca hastalıksız sağkalımın, diğer alt tiplere kıyasla daha kısa olduğu görüldü (p = 0.002). Bölgesel nüks oranları, kondrosarkom, desmoid tümör ve İPS için sırasıyla, %57; %17 ve %75 olarak saptandı. Göğüs duvarının primer malign tümörlerinden İPS'de, 5 yıllık ve 10 yıllık genel sağkalım oranlarının ve ortanca sağkalımın; kondrosarkom ve desmoid tümör gruplarına kıyasla anlamlı ölçüde daha kısa olduğu saptandı.

Anahtar Kelimeler: Bölgesel Nüks, Genel Sağkalım, Göğüs Duvarı Primer Malign Tümörü, İndiferansiye Pleomorfik Sarkom

Abstract

Primary tumors of the chest wall are rare tumors comprising 5% of thoracic neoplasms. The current study was designed to evaluate the effect of histopathological subtype on the 5-year and 10-year overall survival and regional recurrence in primary malignant tumors of the chest wall. From December 2007 to December 2019, the data of 20 patients were analyzed. Overall survival rates, median overall survival, regional tumor recurrence and median disease-free survival rates were compared retrospectively between histopathological subtypes. Chondrosarcoma (n=7), desmoid tumor (n=6), undifferentiated pleomorphic sarcoma [(UPS), (n=4)], Ewing's sarcoma (n=1), malignant peripheral nerve sheath tumor (n=1), and liposarcoma (n=1) were the subtypes identified. A lower median overall survival was detected in the UPS histopathological subtype (p = 0.004). The 5 and 10-year overall survival rates in the chondrosarcoma group were 71% and 37%, respectively; desmoid tumors were found in 83% and 42%, respectively. There was no patient with 5-year survival in UPS. A shorter median overall survival was found in lateral wall masses compared to anterior and posterior wall masses (p = 0.001). During the follow-up, 10 patients (50%) died. It was observed that the median disease-free survival in the UPS subtype was shorter compared to the other subtypes (p = 0.002). The regional recurrence rate was 57%, 17% and 75% in chondrosarcoma, desmoid tumor and UPS, respectively. In UPS, a primary malignant tumor of the chest wall, 5-year and 10-year overall survival rates and median overall survival; it was found to be significantly shorter than the chondrosarcoma and desmoid tumor groups.

Keywords: Chest Wall Primary Malignant Tumor, Overall Survival, Regional Recurrence, Undifferentiated Pleomorphic Sarcoma

	ORCID No
Burak ODABAŞI	0000-0002-9469-380X
Mehmet YILDIRIM	0000-0003-4147-4053
İsmail DAL	0000-0002-5118-0780
Melek Didem AYDEMİR	0000-0003-1028-0600
Kemal DEMİRCAN	0000-0002-0028-3798
Deniz Ezgi MAHMUTOĞLU	0000-0001-9630-8760
Seçkin DENİZ	0000-0001-5637-0973
Semih BULUKLU	0000-0002-1153-7036
Aybiyçe Elif SİLPAĞAR	0000-0002-9274-7982
Murat YAŞAROĞLU	0000-0001-9791-9387
Bülent AYDEMİR	0000-0001-7073-5131
Tamer OKAY	0000-0002-3058-3708

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Adres / Correspondence : Burak ODABAŞI
Acıbadem Mh. Çeçen Sk. 46G/190 Üsküdar/İSTANBUL

e-posta / e-mail : burakodabasi@gmail.com

Introduction

Chest wall tumors originate from the soft tissue, bone or cartilage tissues that make up the rib cage. Primary tumors of the chest wall are rare tumors. They correspond to 5% of thoracic neoplasms. Approximately 50-60% of primary chest wall tumors are malignant (1).

Some histopathological subtypes of primary malignant tumors of the chest wall are resistant to chemotherapy and radiotherapy. This increases the importance of surgical resection. In the surgical treatment of primary malignant chest wall tumors, full thickness (en-bloc) chest wall resection increases the success in surgical management. In order to reduce regional recurrence rates and contribute to survival, primary malignant tumors of the chest wall require wide resection to create a tumor-free surgical margin. In addition, in these patients, the defect created in the chest wall is closed with a patch if necessary. Although radiotherapy in

solitary plasmacytoma and chemotherapy in osteosarcoma and Ewing's sarcoma are applied in the first place, surgical resection and reconstruction are the priority in most of the chest wall malignant tumors (2).

55% of primary malignant tumors of the chest wall originate from cartilage or bone tissue, and 45% from soft tissue (3). Tumors originating from soft tissue are generally painless growing masses; bone-derived tumors usually apply to the clinic with complaints of pain due to periosteal damage. Pain is an indicator of poor prognosis. The most common primary malignant tumors of the chest wall; malignant fibrous histiocytoma (currently IPS), chondrosarcoma and fibrosarcoma (4).

Primary Malign Tumors of the Chest Wall

Chondrosarcoma: It constitutes 30% of malignant primary bone tumors. It is the most common malignant primary bone tumor of the chest wall in adults. Since it originates from the cartilage tissue, it is frequently observed in the anterior chest wall or sternum (1). It manifests as a painful, hard, fixed and slowly growing mass on the anterior chest wall (5). It usually occurs in the third and fourth decades of life. Radiographically, they appear as a lobulated mass with extensive calcification on CT imaging. In this group of tumors where chemotherapy is ineffective, surgical resection forms the basis of treatment (1,7,8). In low-grade tumors, resection can be performed with a 2 cm surgical margin; high-grade tumors should be resected with a 4 cm surgical margin. Radiation therapy can be applied in cases with no chance of resection and in patients with tumor-positive surgical margins, but it is largely ineffective. The presence or absence of tumoral tissue at the surgical margin is a significant predictor of regional recurrence. While recurrence is observed at a rate of 4% among patients with tumor-negative surgical margins, this rate increases to 73% among patients with positive surgical margins (7). Factors that increase survival; absence of metastasis, no regional recurrence, being under 50 years old and tumor grade (8,9,10). 5-year overall survival (OS) is between 64-80% (7,8,11). Distant metastases usually occur to the lung.

Osteosarcoma: Although it is the most common malignant primary bone tumor, it is the second most common malignant primary bone tumor of the chest wall after chondrosarcoma. It constitutes 10% to 15% of malignant tumors of the chest wall. It is more common in young adult males. It manifests itself as a rapidly growing painful mass. It has a poor prognosis. It is typical to occur with costa, clavicle or scapula involvement (1,2,6). Unlike chondrosarcomas, it responds positively to chemotherapy. Surgical treatment is applied after neoadjuvant chemotherapy (1,12). It tends to metastasize distantly and metastasizes mostly to the lung, lymph nodes and liver. The presence of metastases despite effective treatment reduces the 5-year survival to 15% (2). Tumor burden, tumor response to chemotherapy, and presence of metastases are the factors that have the greatest impact on OS (6).

Ewing's sarcoma: It is a small, round cell, malignant tumor with widespread (t11;22) and (q24;q12) translocations, belonging to the malignant primitive neuroectodermal tumors (PNETs) family. Approximately 15% of Ewing's sarcoma originates from the chest wall. This tumor, which constitutes 5% to 10% of malignant tumors of the chest wall, is frequently seen in the second decade of life. It is an aggressive tumor with regional recurrence and tendency to metastasize (2). Patients apply to the physician with complaints of pain and swelling. In the radiography, areas of bone destruction are observed in places. The appearance of "onion skin" due to periosteal elevation and subperiosteal new bone tissue formation is characteristic (1,13). Diagnosis is made by incisional biopsy. After neoadjuvant chemotherapy, wide regional excision followed by adjuvant chemotherapy forms the basis of treatment. Whether the tumoral area determined by detailed evaluations before treatment can be completely resected and the positive or negative response to chemotherapy are predictive of regional recurrence. The 5-year survival rate is over 60% in cases treated with chemotherapy and surgery (1,14). Although definitive radiation therapy is among the preferred methods, radiation therapy is mostly applied after surgical resection. Post-surgical radiation therapy is a method generally used in cases where the tumor cannot be completely resected or there is a negative response to adjuvant chemotherapy (15). At the time of diagnosis, 20-30% metastases can be detected. The most common metastases are to the lung, bone and bone marrow. Metastasectomy can be applied in lung metastases (13).

Solitary plasmacytoma/myeloma: Costal solitary plasmacytoma is rare. It is the name given to the chest wall involvement of multiple myeloma. Pain without a detectable mass is the most common symptom. On radiological evaluation, lesions indicating bone destruction accompanied by cortical thinning and opacities around the rib are often found. Pathological fractures are common. The main treatment for solitary plasmacytoma is extensive radiotherapy. In radiotherapy-resistant cases, surgical resection can be performed to provide pain control. The most important prognostic factor in survival is the development of multiple myeloma. 5-year survival is between 40% and 60% (2).

Desmoid tumor: It is also called aggressive fibromatosis or desmoid fibromatosis. It is a tumor originating from fibroblasts or myofibroblasts. It is also thought to result from the proliferation of mesenchymal stem cell precursors (16). Although

most desmoid tumors are seen in the abdominal wall, the chest wall and shoulder girdle are also common areas outside the abdominal region. Its incidence increases in the second and third decades of life. Desmoid tumors can also be seen in patients diagnosed with familial adenomatous polyposis. Although it is not a malignant tumor histologically, it is considered a low-grade fibrosarcoma and is treated like a malignant tumor due to its tendency to grow into surrounding tissues, cause compression symptoms, and high recurrence rate (2,13). If technically possible, extensive surgical resection is the primary treatment method. Recurrence rates are higher in cases with microscopic tumor-positive surgical margins. It has been reported that the 5-year recurrence rate increased from 37% to 89% in cases with positive surgical margins (17). In cases of multiple relapses, tumors that cannot be completely resected, and cases with positive tumor margins, radiation therapy is applied, but its effectiveness is not clearly known (18). In cases where systemic treatment is indicated, the use of tamoxifen has been shown to be effective against desmoid tumors (19). There are also studies showing that the use of imatinib, a selective tyrosine kinase inhibitor, increases progression-free survival (20).

Undifferentiated pleomorphic sarcoma (UPS): This tumor, defined as malignant fibrous histiocytoma in previous classifications, is generally observed between the ages of 50 and 70 (1). The reason why it was called malignant fibrous histiocytoma in the past was because it was thought that this tumor might be of fibrohistiocytic origin. Thanks to electron microscopy, immunohistochemical techniques and advanced molecular studies, it has been revealed that there is no evidence in favor of fibrohistiocytic differentiation. In addition, after other poorly differentiated sarcomas were added to this group, the World Health Organization reclassified the tumor group defined as malignant fibrous histiocytoma as UPS in 2012 (21). Diagnosis is usually made by incisional biopsy. The main treatment is extensive surgical resection. Although radiation therapy and chemotherapy are not considered very effective, surgery and adjuvant chemotherapy can also be applied after neoadjuvant chemotherapy (1). Regional recurrence and distant metastasis are observed at high rates. Even in cases where extensive surgical resection was performed, regional recurrence rates are over 30% (22). In 30% to 50% of cases, metastatic lesions are present at the time of diagnosis. 5-year survival is 38% (2,23).

Rhabdomyosarcoma: It is the second most common malignant chest wall tumor in children. It is rare in adults. Following neoadjuvant chemotherapy and radiation therapy, extensive surgical resection is required. Adjuvant chemotherapy and radiation therapy are also sometimes administered. 5-year survival is between 60% and 75% (24).

Malignant Peripheral Nerve Sheath Tumor: These are tumors associated with neurofibromatosis (2). Neurofibrosarcoma develops in approximately one-third of cases with neurofibromatosis (8). It typically presents as a painful, gradually growing mass. Malignant peripheral nerve sheath tumor, also called malignant schwannoma or neurofibrosarcoma, often arises from neurofibromas of intercostal nerves, brachial plexus or spinal nerve roots. These lesions tend to cause both regional recurrence and metastasis. In treatment, adjuvant chemotherapy is applied after surgical resection. In cases with positive tumor surgical margins, postoperative radiation therapy may be applied (1,8). 5-year survival is 55% (2,8).

Liposarcoma: It is most common in men between the ages of 40-60. The history may include trauma. In treatment, extensive regional surgical resection of the tumor is essential. Chemotherapy and radiation therapy have limited place. Regional recurrence rates are high. Tumor grade, surgical margin status and histological profile are associated with survival. 5-year survival is 60% (23).

Primary malignant tumors of the chest wall are very rare and there are few studies on this subject in the literature. Few studies have reported predominantly reconstruction materials, resection size, and recurrence rates. Studies investigating the relationship between histopathological subtype and survival in primary malignant tumors of the chest wall are also limited in the written literature. The aim of this study is to evaluate the effect of histopathological subtype on survival in primary malignant tumors of the chest wall.

In the current study, the determination of histopathological subtypes of patients who underwent chest wall resection due to a primary malignant tumor of the chest wall in our clinic; statistical comparison of 5-year and 10-year OS and disease-free survival (DFS) data among histopathological subtypes; in addition, it is aimed to determine the rates of regional tumor recurrence in patients.

Material and Method

This study was conducted on patients who were operated on at the Department of Thoracic Surgery, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, from December 2007 to December 2019, over a 13-year period. The study was designed in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines and the principles of the Declaration of Helsinki were adhered to.

Study Design and Patient Characteristics

Patients between the ages of 18-90 who were operated on in our clinic were included in the study. Benign tumors, regional invasion of the adjacent organ malignancies to the chest wall, and metastases of other primary malignancies were excluded. From December 2007 to December 2019, chest wall tumors were detected in 98 patients in our clinic. 60 patients were excluded from the study because of benign tumor pathology, 14 patients due to regional invasion of adjacent organ tumors (breast and lung) to the chest wall, and 4 patients due to metastasis of the primary tumor (colon carcinoma, parathyroid carcinoma) to the chest wall and/or lung. Twenty patients who met the inclusion criteria were included in the study.

Histopathological subtypes were determined by examining the medical records and pathology reports of the cases. Six subtypes were detected histopathologically in the patients included in the study. Chondrosarcoma in 7 patients, desmoid tumor in 6 patients, UPS in 4 patients, Ewing's sarcoma in 1 patient, malignant peripheral nerve sheath tumor in 1 patient and liposarcoma in 1 patient was detected.

Among the patients included in the study, there was 1 patient diagnosed with Ewing's sarcoma. She wasn't included in the survival analysis because she was in clinical remission at the 47th month of his clinical follow-up and 12 months according to the last follow-up date.

1 patient with liposarcoma and 1 patient with malignant peripheral nerve sheath tumor weren't included in the survival assessments because they could not provide statistically significant data. Both patients were alive as of the last follow-up date. Three histopathological subtypes (chondrosarcoma, desmoid tumor, and UPS) with a moderate sample size were included in the survival assessment and statistical analysis.

OS; it was defined as the time from the date of pathological diagnosis to the death of the patient from any cause or the last follow-up date of the patient. DFS; it was defined as the time from the date of pathological diagnosis to the detection of findings consistent with recurrence/metastasis in clinical evaluation and radiological imaging or death from any cause, or until the last follow-up date of the patient. The 5-year and 10-year OS data between the subtypes were statistically compared.

Surgical Technique and Follow-Up

The main principle in the surgery of malignant tumors of the chest wall is that the tumor can be resected at the pathological (R0) level. The main goal in chest wall resection is full-thickness R0 resection as wide as possible. In this study, the R classification, evolved by The Union for International Cancer Control (UICC) to "R+1 mm", was used. The minimal distance between tumor and resection margin of >1 mm, specimens were considered microscopically negative. This condition was defined as R0. The minimal distance between tumor and resection margin of ≤1 mm, specimens were judged as microscopically positive. This condition was defined as R1. Macroscopic residual tumor was categorized as R2 (25). In chest wall resections, total surgical resection of the relevant tumor tissue with negative surgical margins is the most effective treatment. In the current study of us, the tumoral tissues were excised with the surrounding ribs and/or surrounding soft tissues. Wide resection was applied to prevent regional recurrences in patients. A minimum surgical margin of 2 cm has been attempted for low-grade tumors, and a surgical margin of 4-6 cm for high-grade sarcomas. Resection of the entire involved rib and partial resection of one rib above and below the rib with the tumor were performed. If necessary, reconstruction was performed for the defect formed after resection, to protect the underlying organs, to improve respiratory function, and for cosmetic reasons. The cases included in the study were operated by five different surgeons.

Follow-up evaluation after surgery consisted of regular physical examination and imaging. In addition to physical examination findings, thoracic computed tomography (CT) and positron emission tomography (PET) findings were used in the follow-up of the patients and in the evaluation of the recurrence status. Follow-up physical and radiological examinations of the patients, starting from the date of diagnosis of the tumor, at 6-month intervals during the first 5 years; after completing 5 years, it was applied in the form of annual control examinations. Control thorax CT examination was routinely performed at the 3rd month following the surgical intervention. Thoracic CT examination if deemed necessary or suspected of recurrence; PET and magnetic resonance imaging (MRI) was preferred. Central Population Management System records and Death Notification System records were used to determine survival status.

World Health Organization guidelines were used in histopathological classification (21).

End Point of the Research

Evaluation of the effect of histopathological subtype on 5-year and 10-year OS in primary malignant tumors of the chest wall is the primary endpoint of this study.

Determination of regional recurrence rates in patients; evaluation of the effect of tumoral grade, location, metastatic disease, and surgical margin on regional recurrence and OS were the secondary endpoints of this study.

Statistical Analysis

SPSS version 21 package program was used to analyze the data. Frequency and percentage values were used for qualitative variables, median values

were used for quantitative variables. Normality test was performed and it was evaluated whether the data were normally distributed. Kaplan Meier method was used in the examinations in terms of survival and recurrence times, and the Log Rank test was used for comparisons. Continuous data are given as median (25% percentiles, 75% percentiles). Mann Whitney U test was performed for ordinal or continuous values which were distributed not normally. Finding a p-value less than 0.05 in the study was considered statistically significant.

Results

The median age of the patients was 60[Interquartile range (IQR) %25-%75, 40:69]; median overall survival (mOS) 74 months (IQR %25-%75, 27:108.5); median disease-free survival (mDFS) was 52 months (IQR %25-%75, 17.5:104.5).

Specific to histopathological subtypes, the clinical data of the patients are summarized in Table 1.

When all histopathological subtypes were evaluated together, the regional recurrence rate was 45%. Considering the subtypes, regional recurrence rates were 57% in the chondrosarcoma group; 17% in the desmoid tumor group; it was found to be 75% in the UPS group.

Descriptive statistics of the patients, disease and treatment characteristics are shown in Table 2.

Table 1. Clinical and histopathological features of the patients included in the study. The chart was arranged primarily by histopathological subtype.

Age	Sex	Chest Wall Position	Histopathological Subtype	Grade	R	Repair and/or Reconstruction	Neoadjuvant Treatment	Adjuvant Treatment
45[1]	Male	Posterior	Chondrosarcoma	Medium	R0	Primary Repair		Chemotherapy
71	Female	Anterior	Chondrosarcoma	Low	R0	Polypropylene Mesh		
71	Female	Anterior	Chondrosarcoma	Low	R0	Polypropylene Mesh		Radiotherapy
79[1]	Female	Anterior	Chondrosarcoma	Medium	R1	Polypropylene Mesh		Radiotherapy
72	Male	Anterior	Chondrosarcoma	Medium	R0	Polypropylene Mesh		
58[1]	Female	Posterior	Chondrosarcoma	Medium	R1	Polypropylene Mesh	Chemotherapy	
48[1]	Female	Posterior	Chondrosarcoma	Medium	R0	Primary Repair		
54[1]	Male	Anterior	UPS	High	R0	Polypropylene Mesh + Skin Islanded Pediculated Muscle Flap + Free Skin Graft	Chemotherapy	Chemotherapy + Radiotherapy
71[1]	Male	Posterior	UPS	High	R2	Primary Repair	Radiotherapy	
60	Female	Lateral	UPS	High	R0	Titanium Plate + Polypropylene Mesh		Chemotherapy + Radiotherapy
72[1]	Male	Lateral	UPS	High	R1	Primary Repair		Chemotherapy + Radiotherapy
42[1]	Female	Anterior	Desmoid Tumor	Low	R0	Primary Repair		Radiotherapy
82	Female	Anterior	Desmoid Tumor	Low	R0	Polypropylene Mesh		
70	Male	Posterior	Desmoid Tumor	Low	R0	Primary Repair		Radiotherapy
74	Male	Lateral	Desmoid Tumor	Low	R0	Polypropylene Mesh		
66	Male	Posterior	Desmoid Tumor	Low	R0	Primary Repair		Radiotherapy
44	Female	Posterior	Desmoid Tumor	Low	R0	Titanium Plate + Polypropylene Mesh		Radiotherapy
21	Female	Anterior	Ewing ‘s sarcoma	Medium	R0	Dual Mesh	Chemotherapy	Chemotherapy + Radiotherapy
82[1]	Male	Anterior	Malignant Peripheral Nerve Sheath Tumor	High	R0	Titanium Mesh + Muscle Transposition		
49	Male	Anterior	Liposarcoma	Low	R0	Primary Repair		

R: Resection, UPS: Undifferentiated pleomorphic sarcoma[1].These patients underwent repeated surgeries due to recurrences.

Table 2. Descriptive statistics of patients, disease and treatment characteristics

	N		N
Gender		**Grade**	
Male	10	**Low**	9
Female	10	**Medium**	6
Mortality		**High**	5
Alive	10	**Preoperative diagnosis**	
Ex	10	**Undiagnosed**	11
Relapse		**Diagnosed**	9
None	11	**Frozen section examination during surgery**	
Yes	9	**None**	7
Type		**Yes**	13
CS	7	**Neoadjuvant KT**	
DT	6	**None**	17
ES	1	**Yes**	3
UPS	4	**Neoadjuvant RT**	
OSTS	2	**None**	19
Complaints		**Yes**	1
Pain	5	**Adjuvant KT**	
Palpable mass	8	**None**	15
Growth in mass	7	**Yes**	5
Location		**Adjuvant RT**	
Anterior wall	10	**None**	10
Lateral wall	3	**Yes**	10
Posterior wall	7	**Complication**	
Metastasis		**None**	15
None	18	**Yes**	5
Yes	2	**Origin of tumor**	
		Bone-cartilage	8
		Soft tissue	12

CS: Chondrosarcoma; **DT**: Desmoid tumor; **UPS**: Undifferentiated pleomorphic sarcoma; **OSTS**: Other soft tissue sarcomas

Comparison mDFS of subgroups are presented in Table 3.

When the relationship between histopathological subtype and survival was examined, a statistically significantly lower survival time was found in the UPS subtype. In addition, a significant statistical relationship was found between the location of the tumor and the survival time. Comparison mOS of subgroups are shown in Table 4.

In the chondrosarcoma subtype, the 5-year and 10-year OS rate was respectively, 71% and 37%. The 5-year and 10-year OS rate in desmoid tumors was respectively, 83% and 42%. There were no patients in the UPS group with an OS of 5 years [(p=0.004), (Figure 1A)].

There was no patient with 5-year survival in chest wall tumors located in the lateral wall. The 5-year OS rate for tumors located in the posterior wall was 57%. For tumors located in the anterior wall, the 5-year and 10-year OS rate was respectively, 90% and 53% [(p=0.001), (Figure 1B)].

In patients with negative surgical margins, the 5-year and 10-year OS rate was respectively, 75% and 52%. The 5-year OS rate was found to be 25% in patients with positive surgical margins. No patients showed an OS of 10 years [(p=0.025), (Figure 1C)].

While there was no patient with a 5-year OS in patients with distant metastases; in cases without metastasis, the 5-year OS rate was 72%, and the 10-year OS rate was 43% [(p=0.008), (Figure 1D)].

When the relationship between pathological cell type and DFS was examined, the 5-year and the 10-year DFS rate was 43% in the chondrosarcoma subtype. The 5-year and 10-year DFS rate in desmoid tumors was calculated as 80%. No patients showed 5-year DFS in UPSs [(p=0.002), (Figure 1E)].

In patients with negative surgical margins, the 5-year and 10-year DFS rate was 64%. There was no patient with 5-year DFS in patients with positive surgical margins [(p=0.001), (Figure 1F)].

When the relationship between DFS and tumor grade was examined, the 5-year and 10-year DFS rates were found to be 88% in low-grade tumors. In moderate tumors, the 5-year and 10-year DFS was 33%. No patients showed 5-year DFS in high-grade tumors [(p=0.003), (Figure 1G)].

Discussion

Chondrosarcoma

In our study, the 5-year and the 10-year DFS rate in the chondrosarcoma was 43%. The available data are similar to the previous study (27). Compared to some studies in the literature (8,39), we can attribute the lower survival rate in our study to the fact that the R1 resection rate of the patients was 29%.

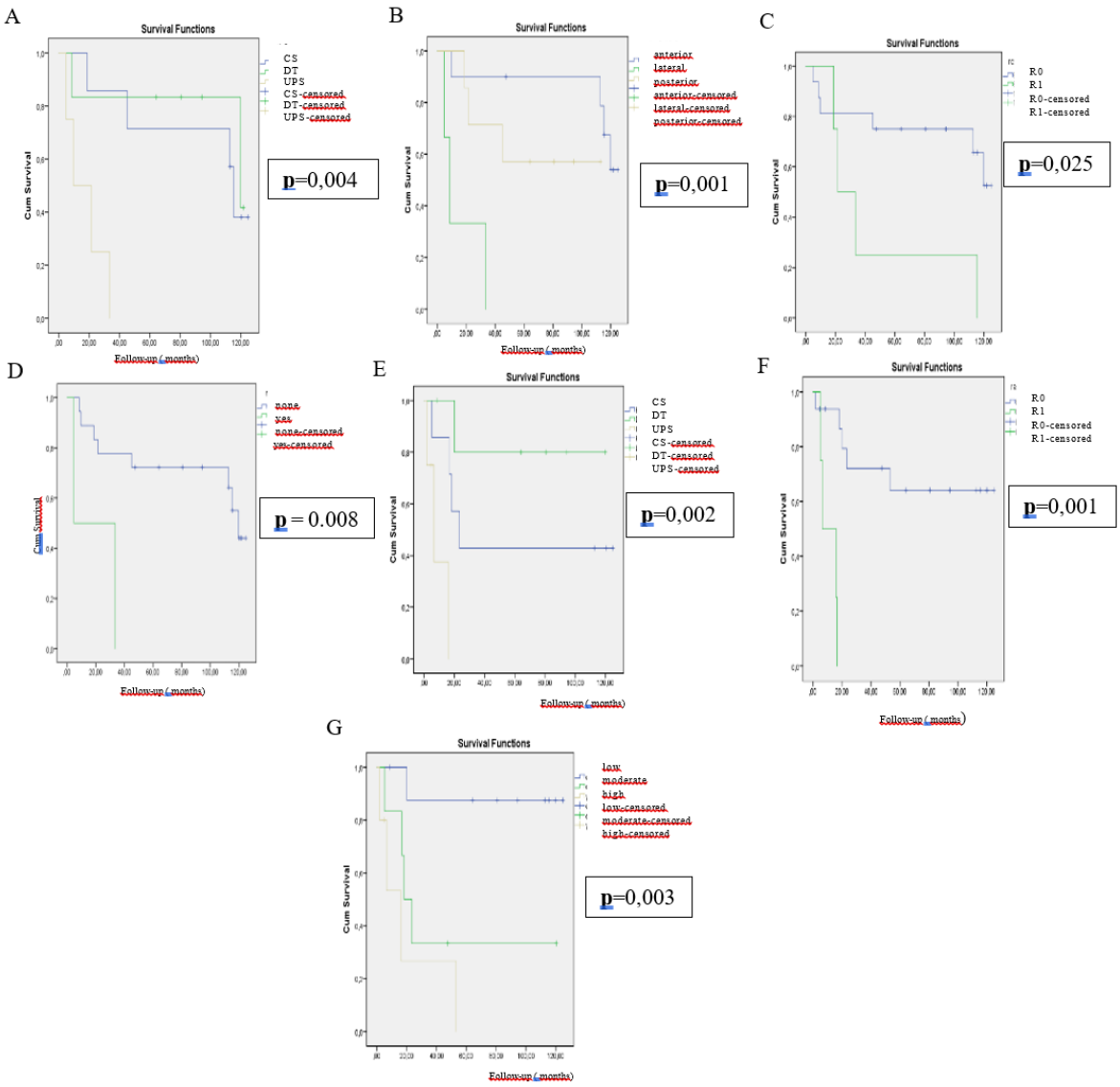

Figure 1. A) Estimated OS curves by histopathological subtype. B) Estimated OS curves by tumor location C) Estimated OS curves by resection status. D) Estimated OS curves by metastasis. E) Estimated DFS curves by histopathological subtype. F) Estimated DFS curves by resection status. G) Estimated DFS curves by tumor grade.

In our study, 5-year and 10-year OS rate in the chondrosarcoma subtype was 71% and 37%. Previous studies in the literature (7,8,9,29-34); 5-year OS, 73.6%-80%; the 10-year OS is in the range of 64-80%. We obtained low survival values according to the literature in both survival parameters. In the current study, 58% of patients with a diagnosis of chondrosarcoma were over 70 years of age. In the study of Shewale et al., it was stated that age progression is an independent negative predictor of OS (29). In previous studies (8,9,29,32,34), the median age varied between 45 and 60; in our study, the median age was found to be 63.4 years in the chondrosarcoma subtype. Considering the data obtained in previous studies (8,28,29,34), the high average age of the patients in our study can be shown as the reason for the low OS rates.

In addition, 71% of chondrosarcoma patients had the first surgical intervention performed in another center (redo case), which may be among the reasons for the low survival rates.

Desmoid tumor

The reason why the DFS, which was calculated as 80% in the desmoid tumor, was slightly higher than in previous studies (17,34), may be the fact that R0 resection was achieved in all desmoid tumors in our study.

In our study, regional recurrence was observed in 17% of the desmoid tumor subtype. The first surgical intervention of all patients in this group was performed by us. In the current study, the 5-year and the 10-year OS rate for desmoid tumors was calculated as 83% and 42%.

Table 3. Comparison mDFS of subgroups

	mDFS (month)	(95% CI)	p
Gender			
Male(n=10)	52	(33.2-99.5)	0.732
Female(n=10)	50.5	(40.2-111.6)	
Histopathological subtype			
CS(n=7)	23	(22.3-102.5)	
DT(n=6)	74	(64.8-134.7)	**0.002**
UPS(n=4)	11.5	(1-16.7)	
Origin of tumor			
Bone-cartilage(n=8)	28.5	(32.3-108.1)	0.940
Soft tissue(n=12)	60	(40.3-102.9)	
Complaint			
Pain(n=5)	81	(66.9-134.9)	
Palpable mass(n=8)	60	(20.6-104)	0.329
Growth in mass(n=7)	51	(18.1-67)	
Location			
Anterior wall(n=10)	77.5	(48.4-114.8)	
Lateral wall(n=3)	68	(16.2-84.5)	0.566
Posterior wall(n=7)	23	(20.7-78.5)	
Metastasis			
None(n=18)	52	(49.2-100.5)	0.159
Yes(n=2)	42	(16.9-58.7)	
Grade			
Low(n=9)	102	(87.6-135.6)	
Medium(n=6)	20.5	(10.9-90.3)	**0.003**
High(n=5)	16	(0-43)	
Resection			
R0(n=16)	68	(63-114.4)	**0.001**
R1/R2(n=4)	16	(5.1-17)	
Surgical Border			
> 4 cm(n=3)	121	(113.4-124.6)	
2-4 cm(n=10)	42.5	(49.8-118)	0.064
< 2 cm(n=3)	17	(6.9-54.2)	

mDFS: Median Disease-Free Survival; **CI**: Confidence interval; **KS**: Chondrosarcoma; **DT**: Desmoid tumor; **UPS**: Undifferentiated pleomorphic sarcoma

UPS

No patient achieved a 5-year DFS in the UPS subtype. Compared to previous studies (27,34,39); among the reasons for the low survival rate in this group, both the histopathological subtype diversity in other studies and the high R1 resection rate of 50% in patients with UPS included in our study can be counted.

The diagnosis of UPS can be made after diagnosing malignant tumors with similar morphological findings, such as malignant melanoma, sarcomatoid carcinomas, anaplastic lymphoma, or other types of sarcoma (35).

Some authors include UPS in the group of heterogeneous and unclassified tumors in pleomorphic morphology (36).

In a study by Bagheri et al., it was revealed that the mortality rate was significantly higher in soft tissue sarcoma subgroups such as UPS, and the presence of distant metastases was one of the main factors affecting survival (37). King et al. stated that the prognosis in chest wall chondrosarcomas was significantly better than in patients with UPS. The 5-year OS rate was found to be 38% in the UPS group (32). In our study, there was no patient with a 5-year OS in the patient group with UPS histopathology. As one of our cases, a 60-year-old female patient who was diagnosed with UPS and underwent chest wall resection and reconstruction is shown in Figure 2.

Sawai et al. reported the mOS as 23.2 months in patients who underwent surgical treatment for chest wall UPS (38). In our study, mOS of 15.5 months was found in UPS.

Location and Surgical Margin

The location of the tumor tissue on the chest wall can be important in terms of providing resection in a way that ensures negativity of the surgical margin. In our study, the OS probability of 5 years was zero in tumors located in the lateral wall.

The relationship between resection and surgical margin status and OS was evaluated. High-grade tumors accounted for 25% of the patients included in our study. R0 resection in 80% of the patients in our study; R1-R2 resection was performed in 20% of them. Compared to previous studies (8,29), the high rate of R1 resection in our study may explain the low 5 and 10-year OS rates.

Regional Recurrence and Distant Metastasis

Rahman et al., in their study, stated that histopathological subtype and surgical margin

positivity increased regional recurrence rates (26). When Shah et al. examined the 115 patients who underwent surgical resection for primary malignant tumor of the chest wall, the regional recurrence rate was 50%; distant metastasis rate was 38% (40). In our study, when all histopathological subtypes were evaluated together, the regional recurrence rate was 45%; distant metastasis rate was 10%. Considering the subtypes, regional recurrence rates were 57% for chondrosarcoma, desmoid tumor and UPS, respectively; it was determined as 17% and 75%. In both patients with distant metastases, the histopathological subtype of UPS was present and the organ with metastasis was the lung.

Limitations

There were also some limitations in our study. Especially the small number of patients included in our study; our results make it difficult to generalize our observations. In addition, the study was carried out retrospectively; although the surgeries are performed by 5 different surgeons, they reflect the experiences of a single center; the absence of a standard resection and reconstruction protocol; the histopathological subtype diversity of the tumors included in the study; evaluation of subtypes with poor prognosis and subtypes with slower invasion and metastasis negatively affects our generalization of OS and regional recurrence results.

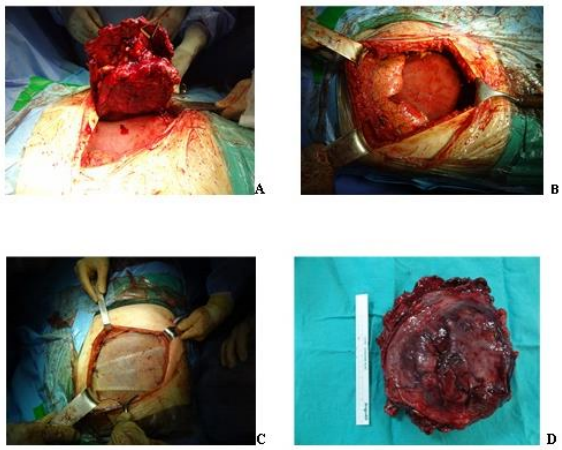

Figure 2. Chest wall resection and reconstruction performed on a 60-year-old female patient with a diagnosis of UPS. A) Fragment of resected chest wall (Patient's head is at 9 o'clock). B) Defect after chest wall resection. C) Reconstruction with polypropylene mesh and titanium plates. D) Chest wall specimen removed with tumoral tissue. (From the archive of Dr. Mehmet YILDIRIM)

Table 4. Comparison mOS of subgroups

	mOS (month)	(95% CI)	P
Gender			
Male(n=10)	48	(41.65-103.72)	0.776
Female(n=10)	104	(71.03-125.15)	
Relapse			
None(n=11)	81	(73.87-126.48)	0.295
Yes(n=9)	45	(36.26-98.53)	
Histopathological subtype			
CS(n=7)	107	(64.5-124.7)	
DT(n=6)	74	(68.5-135.4)	**0.004**
UPS(n=4)	15.5	(4.6-29.8)	
Complaint			
Pain(n=5)	81	(76.81-127.62)	
Palpable mass(n=8)	60.5	(30.93-105.82)	0.998
Growth in mass(n=7)	67	(56.65-125.09)	
Location			
Anterior Wall(n=10)	108.5	(89.1-131)	
Lateral Wall(n=3)	9	(0-33.2)	**0.001**
Posterior Wall(n=7)	51	(45.1-108.1)	
Metastasis			
None(n=18)	90.5	(72.21-114.64)	**0.008**
Yes(n=2)	19	(0-47.23)	
Grade			
Low(n=9)	102	(85-131.8)	
Medium(n=6)	72.5	(56-122.2)	0.130
High(n=5)	21	(0.5-75.8)	
Resection			
R0(n=16)	81	(73.1-118.8)	**0.025**
R1/R2(n=4)	33	(2.2-92.1)	
Surgical Border			
> 4 cm(n=3)	113	(105.4-124.6)	
2-4 cm(n=10)	66	(61.5-120.7)	0.324
< 2cm(n=3)	33	(26.1-98.8)	

mOS: Median Overall Survival; **CI**: Confidence interval; **CS**: Chondrosarcoma; **DT**: Desmoid tumor; **UPS**: Undifferentiated pleomorphic sarcoma

Conclusion

The UPS, which is among the primary malignant tumors of the chest wall, the OS rates of 5 and 10 years, and the mOS; it was concluded that it was significantly lower than chondrosarcoma and desmoid tumor, which are the other histopathological subtypes in our study. It was determined that the DFS and regional recurrence rates of patients who underwent surgery for UPS were significantly shorter compared to the chondrosarcoma and desmoid tumor groups.

We believe that the results obtained will contribute to future studies and meta-analysis. We think that it is important to plan patient-specific treatment involving multiple medical disciplines and to remove the tumoral tissue with the surrounding tissue in a way that will ensure surgical margin negativity.

Conflict of interest statement

There is no conflict of interest in our study.

Ethics Committee Approval: Approval was obtained from the Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (Approval Number: HNEAH-KAEK 2019/106).

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Implantation of Totally Implantable Access Ports via The Internal Jugular Vein in Oncological Patients - A Single General Surgeon Experience

Onkolojik Hastalarda İnternal Jügüler Ven Yoluyla Venöz Port Implantasyonu- Tek Bir Genel Cerrahın Deneyimi

Muharrem ONER

Al-Zahra Hospital Dubai, Department of Surgery, Dubai, United Arab Emirates

Öz

Santral venöz erişim tekrarlayan kemoterapi, hemodiyaliz, kan transfüzyonları, total parenteral beslenme ve kan örnekleri alımı gereken onkoloji hastaları için kritik öneme sahiptir. Bu çalışma, genel anestezi altında ve ultrasonografi ve floroskopi rehberliğinde bir genel cerrahın Totally Implantable Access Port (TIAP) implantasyon deneyimini sunmayı ve erken ve geç komplikasyonları değerlendirmeyi amaçlamaktadır. Bir retrospektif çalışma, Ocak 2020 ile Aralık 2022 tarihleri arasında TIAP implantasyonu yapılan hastalar üzerinde yürütüldü. Solid tümörler için intravenöz kemoterapi uygulanan hastalar dahil edildi. İşlemlerin tamamı tek bir genel cerrah tarafından gerçekleştirdi. Bütün hastalara genel anestezi uygulandı ve bir perkütan Seldinger tekniği kullanıldı. Erken ve geç komplikasyonlar izlendi ve ilgili veriler toplandı. Çalışma, yaş ortancası 46 yıl, çoğunluğu kadın (%65.1) olan 186 hasta içeriyordu. Genel başarı oranı %99.5 idi. Erken ve geç komplikasyonlar sırasıyla vakaların %1.6'sında ve %5.9'unda meydana geldi. En yaygın geç komplikasyonlar port yerinde enfeksiyon (%1.6) ve semptomatik tromboz (%1.6) idi. Bir hastada oluşan port migrasyonu aynı gün düzeltildi. Pnömotoraks vakası gözlenmedi. Kemoterapisi sonlanan 92 hastada port çıkarıldı. TIAP implantasyonunun ultrasonografi ve floroskopi rehberliğinde ve genel anestezi altında bir genel cerrah tarafından gerçekleştirilmesi durumunda yüksek başarı oranı ve düşük komplikasyon oranı söz konusudur. Bu bulgular, özel bir hastane ortamında ve genel anestezi altında TIAP implantasyonunun güvenli ve etkili olduğunu vurgulamaktadır. Çalışma, genel cerrahların onkoloji hastaları için etkili ve güvenli bir şekilde TIAP implantasyonunu gerçekleştirmelerini destekleyen bir kanıt olarak değerlendirilebilir. Böylelikle farklı klinik ortamlarda daha yaygın olarak kullanılmasını sağlayabilir.

Anahtar Kelimeler: Genel Anestezi, Genel Cerrah, Hastane Onkoloji Servisi, Vasküler Erişim Cihazı

Abstract

Central venous access is pivotal for patients undergoing repetitive chemotherapy, hemodialysis, blood transfusions, total parenteral nutrition, and blood tests. This study aims to present the single-center experience of a general surgeon in Totally Implantable Access Port (TIAP) implantation under general anesthesia using ultrasonography and fluoroscopy guidance and assess early and late complications. A retrospective study was conducted on patients who underwent TIAP implantation between January 2020 and December 2022. Patients eligible for intravenous chemotherapy with solid tumors were included. A single general surgeon performed the procedures. General anesthesia was administered in all patients, and a percutaneous Seldinger technique was utilized. Early and late complications were monitored, and relevant data were collected. The study comprised 186 patients with a median age of 46, predominantly female (65.1%). The overall success rate was 99.5%. Early and late complications occurred in 1.6% and 5.9% of cases. The most common late complications were pocket infection (1.6%) and symptomatic thrombosis (1.6%). Port migration occurred in one patient but was promptly corrected. No pneumothorax cases were observed. Port removal was performed in 92 patients upon chemotherapy completion. Implantation of TIAPs under general anesthesia, guided by ultrasound and fluoroscopy, resulted in a high success rate and low complication rate when performed by a skilled general surgeon. These findings underscore the safety and efficacy of TIAP implantation under general anesthesia in a private hospital setting. The study contributes to the growing body of evidence supporting general surgeons in providing effective and safe TIAP implantation for oncology patients, potentially expanding its availability in diverse clinical settings.

Keywords: General Anesthesia, General Surgeon, Hospital Oncology Service, Vascular Access Devices

Introduction

Central venous access is a critical concern for oncology patients who require repeated administration of chemotherapy, hemodialysis, blood transfusions, total parenteral nutrition, and blood tests (1,2). Prolonged chemotherapy cycles in cancer patients can make accessing peripheral veins increasingly challenging, potentially disrupting treatment. While Hickmann and Broviac tunneled externalized central venous catheters are commonly used in chemotherapy patients due to their ease of implantation (3-5), they are not without drawbacks, including a higher risk of infections from skin microflora (6,7), thrombotic complications leading to catheter malfunction (8), and restrictions on patient activities (9). Besides the type and technique used during the catheter insertion, the central venous access insertion site might influence the early or late occurrence of complications (1). Additionally, the choice of catheter type, insertion technique, and access site can impact the success and maintenance of catheters in chemotherapy patients (10,11).

Totally implantable access ports (TIAPs) provide a safe alternative for venous access with lower infection and malfunction rates than external systems. Access points, such as the subclavian,

	ORCID No
Muharrem ONER	0000-0002-6835-584X

Adres / Correspondence : Muharrem ONER
Al-Zahra Hospital Dubai, Department of Surgery, Dubai, United Arab Emirates
e-posta / e-mail : muharremoner@hotmail.com

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jugular, and upper extremities, can be used for venous access (12). Different techniques, including direct percutaneous puncture using the Seldinger technique or venous cutdown with open insertion, can be employed for catheter insertion, each with unique advantages and disadvantages. However, procedural complications may increase with blind approaches for venous access localization, necessitating ultrasound, and fluoroscopy-guided percutaneous techniques to minimize risks (13,14). Several guidelines, including National Institute for Health and Care Excellence (NICE) recommendations, endorse using ultrasound when inserting central venous catheters (11,15).

The insertion of TIAPs can be performed by interventional radiologists, general or vascular surgeons, or anesthesiologists (16,17). Depending on patients' characteristics, catheter insertion under general anesthesia by surgeons was common practice (2,18). Nevertheless, limited circumstances for general anesthesia availability in interventional radiology might influence the trends in central venous catheter insertions for each hospital (17). So, the choice of who performs the procedure may depend on various factors, including the availability of interventional radiology and the patient's specific characteristics. In our tertiary hospital for oncology patients, general surgeons have been inserting TIAPs under general anesthesia for over a decade.

In this study, we aim to present the experience of a single general surgeon in TIAP implantation using ultrasonography and fluoroscopy guidance and assess early and late complications.

Material and Method

Study

A retrospective study was conducted on patients who underwent TIAP placement between January 2020 and December 2022. The local institutional review board approved the study (11.07.2023; 2023,14/301). All procedures adhered to ethical standards outlined by the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in 2008. Given the study's retrospective nature and the data's unanimity, written informed consent could not be obtained from the patients.

Patients

The study included all consecutive patients with solid tumors eligible for intravenous chemotherapy who underwent TIAP placement at Al Zahra Private Hospital Dubai, United Arab Emirates, between January 2020 and December 2022. Exclusion criteria encompassed an American Society of Anesthesiologists (ASA) grade of 5, active infections, coagulopathy (defined as a platelet count less than 50,000/µl and/or international normalized ratio >1.5), life expectancy less than six months, and incomplete follow-up (1,2).

All procedures were performed by a single general surgeon with 23 years of experience in the field but no previous experience in port insertion. The initial ten operations were conducted under the supervision of an experienced surgeon.

Surgical technique

General anesthesia was administered for all operations following a preoperative anesthesia assessment. Prophylactic treatment included a single dose of 1.2-gram amoxicillin-clavulanic acid, with ciprofloxacin 400 mg provided for patients with penicillin allergies. All procedures utilized the percutaneous Seldinger technique (19), with a single-lumen implantable port/titanium PowerPort® (Becton, Dickinson and Company, New Jersey, USA) inserted for all patients (Figure-1).

Figure 1. Single-lumen implantable port / titanium PowerPort® (Becton, Dickinson and Company, New Jersey, USA)

The preferred venous access site was the right internal jugular vein, with the left internal jugular vein used for patients with right-sided breast cancer or in cases of unsuccessful attempts at the right jugular vein. Before induction, the internal jugular vein was visualized using 2D ultrasound, with a 500 ml saline bolus administered to increase vessel diameter when necessary. Patients were supine in the Trendelenburg position, and a headring was employed to stabilize the neck. After a timeout, patients were draped in a sterile manner. Once prepared, ultrasound-guided access to the right/left internal jugular vein was identified. The needle was introduced, and the guidewire was advanced to the superior vena cava and right mid-atrium. Subsequently, dilators and the catheter were introduced 13-15 cm from the skin area, with fluoroscopy used to confirm the placement of dilators and the catheter. Following these steps, a

transverse incision was made in the subclavian area, creating a pocket for the port. The catheter was tunneled subcutaneously to the pocket in the right/left subclavian area, where the port was connected to the catheter and secured in place (Video). The position of the port and catheter was confirmed by fluoroscopy for the final time (Figure 2a). Adequate inflow and outflow were verified with heparinized saline. The port was secured to the deep fascia using a 3-0 polyglactin suture. Subcutaneous skin closure was performed with a 3/0 polyglactin suture, followed by subcuticular closure with a 2/0 polyglactin suture. A waterproof dressing was applied to the wound.

A chest X-ray was obtained before discharge to reconfirm the tip's position and rule out pneumothorax (Figures 2b and 2c). All procedures were performed as day-case surgeries, and patients were discharged the same day after review by the surgical team.

Figure 2. a) Final image of port and catheter of flouroscopy during the procedure, b) Chest X-ray after right-side port-a-cath placement, and c) Chest X-ray after left-side port-a-cath placement.

Follow-up

Early and late complications were documented, with any complications occurring within the first seven to ten days after implantation considered early complications (20). All patients were followed up in the outpatient clinics of the department for six months postoperatively. Additionally, all patients were subjected to sonography at least every six months during their oncology clinic follow-up to check for venous thrombosis. Removal of TIAPs due to local infectious findings was classified as port infection (20). In cases with clinical signs suggestive of wound infection, broad-spectrum antibiotics were initiated as the first-line treatment. Symptomatic patients with port thrombosis underwent immediate ultrasound examination.

Variables and data collection

The medical records of patients were retrieved from the hospital information system. Demographic data (age, sex), clinical characteristics (diagnosis, access site, success rate), and follow-up data (port removal, follow-up duration) were collected and recorded.

Statistical analysis

The Shapiro-Wilk test was used to assess the normal distribution of numerical variables. The median with minimum and maximum values was employed for continuous variables without normal distribution for descriptive statistics. Categorical variables were presented as numbers and percentages.

Results

The study included 186 patients with a median age of 46 years, with the majority being female (65.1%). Breast cancer (48.4%) and gastrointestinal malignancies (26.9%) were the most prevalent oncological diagnoses in the study group. The right jugular vein was the most commonly selected access route (93.0%). The overall success rate was 99.5% (n=185). The access was unsuccessful in one patient with sizeable cervical lymph nodes around the right internal jugular vein. Nevertheless, the left-sided intervention was performed without any complications. Detailed demographic and clinical characteristics are provided in Table 1.

Table 1. Demographic and clinical characteristics of the patients.

Gender	Value (N=186)
Age (year) †	46 (17-76)
Sex ‡	
Female	121 (65.1)
Male	65 (34.9)
Diagnosis ‡	
Breast cancer	90 (48.4)
Gastrointestinal	50 (26.9)
Stomach	14 (28.0)
Colorectal	33 (66.0)
Esophagus	3 (6.0)
Hepatopancreatobiliary	10 (5.4)
Pancreas	5 (50.0)
Liver	5 (50.0)
Female reproductive	14 (7.5)
Ovarian	7 (50.0)
Cervix	4 (28.6)
Uterus	3 (21.4)
Male reproductive	11 (5.9)
Testis	2 (18.2)
Prostate	9 (81.8)
Osteosarcoma	4 (2.2)
Renal	7 (3.8)
Access side ‡	
Right jugular vein	173 (93.0)
Left jugular vein	13 (17.0)

†: median (min-max), ‡: n (%)

The median follow-up duration was 396 days, ranging from 180 to 583 days. Early and late complications occurred in 1.6% and 5.9% of cases, respectively (Table 2).

Port migration occurred in the fifth patient of the study group, which was promptly corrected under local anesthesia. No cases of pneumothorax were observed.

The most frequent late complications were pocket infection (1.6%) and symptomatic thrombosis (1.6%), occurring in three patients.

All patients received at least one cycle of chemotherapy. Port removal was performed in 92 patients upon completion of chemotherapy during the follow-up period. However, in six patients, TIAP devices were removed before completing chemotherapy due to port leak (n=1), port infection (n=2), and catheter-associated venous thrombosis (n=3).

Table 2. Distribution of the early and late complications in patients with TIAP.

	Value (N=186)
Follow up (days) †	396 (180-583)
Early complications ‡	3 (1.6)
Port migration	1 (0.5)
Hematoma	1 (0.5)
Arterial puncture	1 (0.5)
Late complications ‡	11 (5.9)
Port infection	2 (1.1)
Pocket infection	3 (1.6)
Port leak	1 (0.5)
Symptomatic thrombosis	3 (1.6)
Asymptomatic thrombosis	2 (1.0)

†: median (min-max), ‡: n (%)

Discussion

In this study, we have demonstrated that a general surgeon's implantation of TIAPs under general anesthesia yields a remarkably high success rate of 99.5% and relatively lower rates of both early and late complications. These findings provide valuable insights into the safety and efficacy of TIAP implantation, mainly when conducted by a general surgeon in a private hospital setting.

Several professional societies, such as the Japanese Society of Interventional Radiology and the Shanghai Expert Consensus, have developed clinical questions and guidelines for central venous port placement (11,21). These guidelines emphasize blood vessel selection, port implantation site, antimicrobial prophylaxis, image guidance, disinfection, and post-administration procedures for drugs via the CV port. Adhering to these guidelines and recommendations can contribute to more favorable outcomes and should be considered in practice.

Our results align with previous research indicating the advantages of port-a-cath implantation using the Seldinger technique, including high success rates, extended indwelling times, cost-effectiveness, and a reduced incidence of complications (22-24). However, it is worth noting that a recent Cochrane review found no significant difference in overall complication rates between the Seldinger and venous cutdown techniques (10). Our study employed the Seldinger technique with the inferior jugular vein for all patients. While most clinical trials have utilized the subclavian vein for venous access, some have opted for the internal jugular vein (10,21). Prospective studies are necessary to determine the superiority of one technique or venous insertion site over another definitively.

Although many studies in the literature have demonstrated the safety of chemotherapy ports, the majority of these procedures have been performed by interventional radiologists (26,2). Recent studies have indicated a shift in the healthcare landscape even for the non-tunneled vascular catheters. The numbers of non-tunneled central venous catheter insertions decreased for surgeons, radiologists, and anesthesia providers. In contrast, line insertions performed by emergency physicians, advanced practice nurses, and physician assistants increased (17). A recent study by Karolin et al. (27) reported results of TIAP procedures performed exclusively by a general surgeon in a single-center setting, albeit using a standardized open approach. Several other single-center studies have reported positive outcomes with large case volumes, employing various techniques performed by general surgeons (28,29). Notably, Jeon et al. (20) demonstrated that TIAP implantation can be safely and effectively performed by surgical residents, suggesting that TIAP placement should be considered a fundamental surgical technique for resident training across various specialties. These findings might have implications for resident training and maintenance of competence for surgeons in future.

In our study, all TIAP implantation procedures were performed by a single general surgeon under general anesthesia, using the Seldinger technique via the internal jugular vein with guidance from ultrasonography and fluoroscopy. We, alongside other researchers, believe that ultrasound guidance offers significant advantages in visualizing vessel anatomy and diameter (30,31). While some physicians may rely on anatomical landmarks to assess the internal jugular vein, it has been shown that ultrasound-guided prepuncture of the vein facilitates cannulation (1,6). In our study, the remarkable 99.5% success rate in accessing the vein can be attributed to ultrasound guidance, reinforcing the importance of visualizing vessels before puncture and recommending the routine use of ultrasound guidance.

Thrombosis leading to catheter blockage and catheter-related infections are complications that may necessitate port removal. Several risk factors,

including catheter type, insertion site, catheter usage duration, cancer type, chemotherapy treatment frequency, and port usage for nutrition and blood draws, contribute to thromboembolic events following TIAP implantation (31). In our study, we observed symptomatic thrombosis in only three patients during the follow-up period, and our rate of symptomatic port thrombosis was lower than previously reported rates (22). The reasons for such variations in reported rates remain unclear (31). However, the localization of the catheter tip placed in the upper portion of the superior vena cava may be associated with an increased risk of port thrombosis (2,29). So, careful placement of the tip of the catheter during the procedure by fluoroscopy and adjustment of its length might be vital in reducing thrombotic complications (29). Monthly flushing of ports with a heparinized saline solution mixture may also help prevent such complications, although results in the literature are conflicting (31,32).

Numerous studies have shown that TIAPs are associated with fewer infections than external devices. Avoiding exposure to the external environment and cutaneous contamination significantly reduces the risk of catheter infections (6,33). Our infectious complication rates were consistent with previously reported outcomes (34,35). Variations in infection rates may be linked to patients' characteristics (2).

The major limitation of our study is its retrospective design. We did not perform a learning curve analysis at the initiation of the study. Nonetheless, the study benefits from substantial sample size and meticulous data collection through a prospectively maintained database. Furthermore, the study was conducted by a surgeon in a private hospital with a comprehensive oncology center, where patients received close and thorough follow-up care. This aspect may be crucial in accurately assessing both complications and procedure success rates.

Conclusion

In conclusion, our findings suggest that TIAP insertion under general anesthesia, guided by ultrasound and fluoroscopy, is a safe procedure associated with a low complication rate. Notably, this procedure can be successfully performed by trained general surgeons. The results of our study contribute to the growing body of evidence supporting the role of general surgeons in providing effective and safe TIAP implantation for oncology patients, potentially expanding the availability of this valuable intervention in various clinical settings.

Conflict of interest statement

There is no conflict of interest, or nothing to disclose.

Ethics Committee Approval: Ethics committee approval was obtained from Al Zahra Hospital Dubai (11.07.2023; 2023,14/301) for the study.

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Determination of Inhibitory Effects of Newly Synthesized Potential HIF Inhibitors on Non-Small Cell Lung Cancer Under Hypoxic Conditions

Yeni Sentezlenen Potansiyel HIF İnhibitörlerinin Hipoksik Koşullarda Küçük Hücre Dışı Akciğer Kanseri Üzerindeki İnhibitör Etkilerinin Belirlenmesi

Demet TAŞDEMİR KAHRAMAN[1,2], Pınar YUMRUTAŞ[2], Esra BOZGEYİK[3], İbrahim BOZGEYİK[4], Ayşegül İYİDOĞAN[5], Emine Elçin EMRE[5], Serdar ÖZTUZCU[2,6], Ahmet Ferudun IŞIK[2,7]

[1]Department of Medical Biochemistry, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey
[2]Respiratory Diseases and Respiratory Surgery Research and Practice Center, Gaziantep University, Gaziantep, Turkey
[3]Department of Medical Services and Techniques, Vocational School of Health Services, Adiyaman University, Adiyaman, Turkey
[4]Department of Medical Biology, Faculty of Medicine, Adiyaman University, Adiyaman, Turkey
[5]Department of Organic Chemistry, Faculty of Arts and Sciences, Gaziantep University, Adiyaman, Turkey
[6]Department of Medical Biology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey
[7]Department of Thoracic Surgery, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey

Öz

Küresel tahminlere göre her yıl akciğer kanseri nedeniyle 2,3 milyon yeni vaka ve 1,8 milyon ölüm yaşanmaktadır. Tanı ve tedavideki son gelişmelere rağmen devam eden zorluklar, akciğer kanseriyle etkili bir şekilde mücadele etmek için yeni tedavi yöntemlerine ve yenilikçi yaklaşımlara olan acil ihtiyacı vurgulamaktadır. Dolayısıyla, bu çalışmada HIF-1α'nın potansiyel inhibitörleri olan 7a ve 7b bileşiklerinin antikanser özelliklerinin araştırılması amaçlanmıştır. Çalışmada HTB-54 ve BEAS-2B hücre hatları kullanılmıştır. Yeni sentezlenen HIF inhibitörleri 7a ve 7b'nin normoksik ve hipoksik koşullar altında hücre canlılığı üzerindeki etkisini belirlemek için MTT hücre canlılığı deneyleri yapılmıştır. HIF1A'nın kantitatif ekspresyon seviyeleri, Real-Time PCR yöntemi ile belirlenmiştir. HTB-54 hücrelerinde 7a bileşiğinin yarı maksimum inhibitör konsantrasyonu (IC_{50}) normoksik koşullar altında 10,37 µM iken hipoksik koşullar altında 10.63 µM olarak bulunmuştur. HTB-54 hücrelerindeki diğer bir HIF inhibitörü 7b'nin IC_{50} değeri normoksik koşullar altında 8,80 µM, hipoksik koşullar altında ise 9.54 µM olarak bulunmuştur. Hipoksik koşullarda, 7a ve 7b bileşikleri ile maruz bırakılan hücrelerde HIF1A ekspresyon düzeyinin kontrol grubuna göre daha düşük olduğu gösterilmiştir. Normoksi koşullarda ise HIF1A ekspresyon düzeyi 7a bileşiği ile maruz bırakılan hücrelerde kontrol grubuna göre 6,5 kat ($p<0.0001$), 7b'ye maruz kaldığında ise yaklaşık 9 kat ($p<0.0001$) arttığı bulunmuştur. Sonuç olarak hem 7a hem de 7b bileşikleri akciğer kanserine yönelik gelecekteki terapötik girişimler için büyük umut vaat etmektedir.

Anahtar Kelimeler: Akciğer Kanseri, HIF inhibitörleri, Hipoksi

Abstract

According to global estimates, there are 2.3 million new cases and 1.8 million fatalities due to lung cancer each year. Despite recent progress in diagnosis and treatment, persistent challenges highlight the urgent need for novel therapeutics and innovative approaches to combat lung cancer effectively. Accordingly, in the present study, we aimed to investigate the anticancer properties of potential inhibitors of HIF-1α, compound 7a and 7b. In the study, HTB-54 and BEAS-2B cell lines were used. MTT cell viability experiments were performed to determine the effect of newly synthesized HIF inhibitors 7a and 7b on cell viability under normoxic and hypoxic conditions. Quantitative expression levels of HIF1A were determined by real-time PCR approach. While the half maximum inhibitory concentration (IC_{50}) of compound 7a in HTB-54 cells was 10.37 µM under normoxic conditions, it was found to be 10.63 µM under hypoxic conditions. The IC_{50} value of another HIF inhibitor 7b in HTB-54 cells was found to be 8.80 µM under normoxic conditions and 9.54 µM under hypoxic conditions. The expression level of HIF1A was found to be lower in cells exposed to compounds 7a and 7b under hypoxia compared to the control group. Conversely, in normoxia, HIF1A expression level in cells exposed to compound 7a increased 6.5-fold ($p<0.0001$) compared to the control group, while it was found to increase approximately 9-fold ($p<0.0001$) when exposed to 7b. Consequently, both compound 7a and 7b holds great promise for future therapeutic interventions to lung cancer.

Keywords: Lung Cancer, HIF Inhibitors, Hypoxia

Introduction

The worldwide incidence of lung cancer is estimated to be approximately 1.86 million new cases, and the associated death rate is around 1.6 million annually (1-2). The majority of cases of lung cancer (85%) are non-small cell lung cancer (NSCLC). More than 50% of patients are diagnosed at an advanced stage and have a poor prognosis (2-4).

Current treatment strategies in NSCLC include surgical resection, chemotherapy, radiotherapy, targeted therapy, or combinations of these treatments (5). Many cancer cases are diagnosed at a late stage, which unfortunately reduces the chance for surgical treatment. As a result, chemotherapy and radiotherapy are the primary treatment options for managing non-small cell lung cancer (NSCLC). Currently, cisplatin and carboplatin are commonly used as the first-line chemotherapy agents for treating various solid tumors, including lung cancer. Nevertheless, the development of resistance to cisplatin over time remains a significant challenge,

	ORCID No
Demet TAŞDEMİR KAHRAMAN	0000-0002-7038-3831
Pınar YUMRUTAŞ	0000-0002-9378-9383
Esra BOZGEYİK	0000-0002-8726-3182
İbrahim BOZGEYİK	0000-0003-1483-2580
Ayşegül İYİDOĞAN	0000-0002-8088-6010
Emine Elçin EMRE	0000-0001-6840-9660
Serdar ÖZTUZCU	0000-0001-6871-6521
Ahmet Ferudun IŞIK	0000-0002-8687-3819

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Adres / Correspondence : Demet TAŞDEMİR KAHRAMAN
Department of Medical Biochemistry, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey
e-posta / e-mail : demettasdemir@gmail.com

impacting the prognosis and survival of patients with the disease (3,5,6). Hence, the development of novel drugs that target specific oncogenic mechanisms is crucial for effectively treating patients with NSCLC. Instead of focusing exclusively on the malignant cells themselves, the tumor microenvironment (TME) contributes significantly to the emergence of drug resistance and the dysfunction of immune system cells in the course of cancer treatment. (7). Studies have shown that TMD in solid tumors supports the progression and metastasis of cancer through various mechanisms including drug resistance. Studies have also highlighted the critical role of the tumor microenvironment (TME) in driving the progression of non-small cell lung cancer (NSCLC) (2). The rapid and uncontrolled growth of tumors leads to the expansion of tumor tissue. However, within the tumor, certain regions experience chronically reduced oxygen levels due to inadequate blood vessel development. This persistent and uninterrupted hypoxic state is a common characteristic of the microenvironment in almost all solid tumors (2,7,8). The increased level of HIF protein in hypoxic TME activates the transcription of a number of genes, resulting in an acidic tumor environment. Decreased extracellular pH inhibits cellular and humoral immune functions, leading to drug resistance by multiple mechanisms, including reduced apoptotic potential, genetic alterations, and high activity of the multidrug transporter P-glycoprotein (P-gp) (7-9).

New selective HIF inhibitors were synthesized for lung cancer in our project, which was previously funded by TÜBITAK (114Z960). These 34 compounds are new chiral molecules designed by combining benzoxadiazole and sulfonamide on the same molecule. All compounds were examined on the A549 alveolar epithelial lung cancer cell line for their in vitro cytotoxic activities, apoptotic effects, and effects on the HIF gene. As a result, several compounds have been designed which inhibit the HIF gene and induce apoptosis in cancer cells. The compounds 7a and 7b, whose HIF potential was determined in the previous study, are enantiomers of one another and were selected for this study.

For the study, a hypoxic environment was artificially induced using cobalt chloride ($CoCl_2$) and increased HIF-1α gene levels were validated using the RT-PCR method. The potential cytotoxic effects of compounds 7a and 7b on NSCLC cell HTB-54 under hypoxia/normoxia conditions were determined by cell viability assays.

Material and Method

Cells culture conditions

Commercially, ATCC provided HTB-54 non-small cell lung epidermoid carcinoma and BEAS-2B bronchial epithelial cells. The medium was Roswell Park Memorial Institute 1640 (RPMI-1640; Hyclone, USA), which contained 1% penicillin-streptomycin-amphotericin B solution (Sigma Aldrich, USA), 10% fetal bovine serum (FBS; Gibco, Carlsbad, CA, USA), and 2 Mm L-glutamine (Sigma Aldrich, USA). Cells were kept at 37°C in an incubator with 95% humidified CO_2 (5%) (10).

$CoCl_2$-induced chemical hypoxia mimetic model

HTB-54 and BEAS-2B cell lines were seeded in 12-well culture dishes at $2x10^5$ cells/ml and incubated overnight. For hypoxic conditions, cells were exposed to SF, 50,100, 200 and 400 µM doses of $CoCl_2$ prepared in serum-free RPMI-1640 medium for 3, 6, 12 and 24 hours as previously described (11-12). Cells were not exposed to $CoCl_2$ under normoxic conditions. At each time interval, cells were collected using Trypsin-EDTA solution for RNA isolations.

Cell viability assay

MTT (3-(4,5-dimethyltriazol-2-yl)-2,5-diphenyltetrazolium bromide) cell viability test was performed to evaluate cell viability. Briefly, human HTB-54 and BEAS-2B cells were seeded into 96-well plates at approximately $6x10^5$ cells/ml. Under hypoxic and normoxic conditions, cells were exposed to compound 7a and 7b at varying concentrations (6.25, 12.5, 25, 50 and 100 µM) for 24 hours. Following incubation, cells were rinsed with PBS and treated with 1mg/ml MTT for 60 minutes. Then, MTT solution was discarded and formed formazan crystals were solubilized using 100 µl DMSO. Plates were read at 550 nm with the help of Multiskan GO spectrophotometer (Thermo Scientific). The obtained optical density (OD) values were used to calculate half maximum inhibitory concentration (IC_{50}) of hypoxia inhibitors 7a and 7b.

RNA isolations, cDNA synthesis and qPCR

For the RNA isolations, Qiagen RNeasy mini kit (Qiagen, Germany) was used. Briefly, cells were lysed using buffer RLT supplemented with β-mercaptoethanol. Lysate was further mixed with ethanol and transferred to spin columns. Columns were then rinsed with wash buffers and RNA eluted using ddH2O. RNA quality and quantity was determined using NanoDrop ND1000 spectrophotometer. Complementary DNA (cDNA) synthesis was achieved using RT^2 HT First Strand (Qiagen, Germany) according to the recommendations of the manufacturer. RNA concentrations were adjusted to 100 ng/□L for cDNA synthesis. For the qPCR analysis, QuantiTect SYBR green PCR kit was used. Gene-specific primer pairs for HIF-1α (Forward: 5'-GATCACCCTCTTCGTCGCTT -3', Reverse: 5'-CCTCCATGGTGAATCGGTCC- 3') and GAPDH (Forward: 5'- GATCATCAGCAATGCCTCCT -3', Reverse: 5'- TGTGGTCATGAGTCCTTCCA - 3') were designed using Primer Blast. For the following

PCR reaction was prepared; 10 µL SYBR Green Master Mix, 1 µL forward primer, 1 µL reverse Primer, 5 µL RNase-free water and 3 µL cDNA. Reactions were held in Rotor-Gene Q instrument using following cycling conditions; 15 minutes at 95°C, 40 cycles of 15 sec at 95°C, 30 sec at 60°C, 30 sec at 72°C. After the reaction, Ct (cycling threshold) values were taken at an appropriate threshold. The $2^{-\Delta Ct}$ formula was used to determine gene expressions ($\Delta Ct= (Ct_{HIF1A} – Ct_{GAPDH})$.

Statistical analysis

At least three times each of the experiments were repeated. All data were statistically analyzed with GraphPad Prism version 8.0 (GraphPad, San Diego, CA, USA). Shapiro-Wilk test and Kolmogorov-Smirnov test were used for normalization of the data. For multiple group comparisons, ANOVA or Kruskal-Wallis test was used according to normality of distribution, And t-test was used for pairwise group comparisons. The mean ± SD (standard deviation) and median (25%, 75%) values of the results were calculated. Differences between groups were considered statistically significant when the p value was <0.05.

Results

$CoCl_2$ was used to establish the mimetic hypoxia model. Cells were exposed to different concentrations of $CoCl_2$ for different time periods and HIF1A expression level was determined. Significant increase in expression level of HIF1A gene was detected in both cells after exposure with 400 µM $CoCl_2$ for 3 h and hypoxia conditions were determined (p<0.0001) (Figure 1).

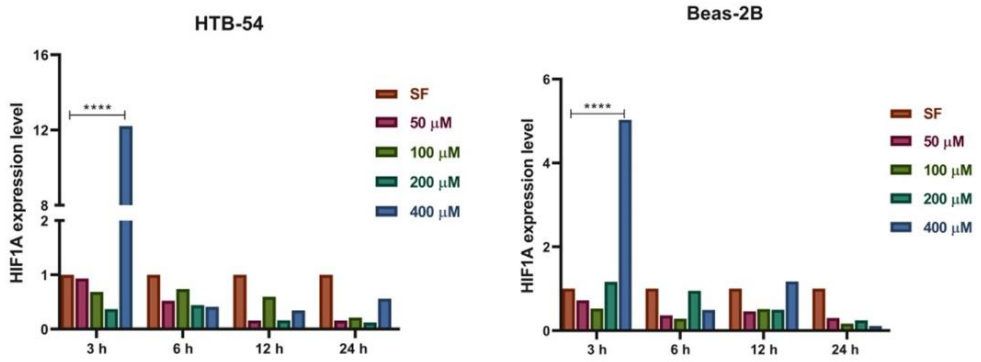

Figure 1. The expression level of HIF1α was demonstrated in HTB-54 and Beas-2B cells by exposure to $CoCl_2$ at different periods and different concentrations. **** p<0.001. One Way ANOVA test was used to analyze the HIF1A expression level in each time period.

MTT experiments were performed to determine the effect of newly synthesized HIF inhibitors 7a and 7b on cell viability under normoxic and hypoxic conditions. In HTB-54 cells, the IC_{50} value of compound 7a was found to be 10.37 µM (95% CI: 5.73-17.96; p=0.0047) under normoxic conditions, while it was 10.63 µM (95% CI: 5.24-18.93; p=0.0052) under hypoxic conditions (Figure 2A). In addition, the IC_{50} value of compound 7a in BEAS-2B cells was 24.89 µM (95% CI: 15.80-34.01; p=0.0011) under normoxic conditions, while it was 33.32 µM (95% CI: 17.12-61.29; p=0.0037) under hypoxic conditions. (Figure 2B). The IC_{50} value of another HIF inhibitor 7b in HTB-54 cells was 8.80 µM (95% CI: 5.78-13.12; p=0.0053) under normoxic conditions and 9.54 µM (95% CI: 5.73-15.05; p=0.0067) under hypoxic conditions. found (Figure 3A). In BEAS-2B cells, it was found to be 22.01 µM (95% CI: 15.21-29.35; p=0.0013) under normoxic conditions and 31.27 µM (95% CI: 17.89-50.69; p=0.0044) under hypoxia (Figure 3B).

qPCR experiments were performed to determine the effect of the effective dose of HIF inhibitors 7a and 7b on the expression level of the HIF1A gene in HTB-54 lung cancer cells under normoxic and hypoxic conditions. The expression level of HIF1A was found to be lower in cells exposed to compounds 7a and 7b in hypoxia compared to the control group. Conversely, in the normoxia condition, the expression level of HIF1A in cells exposed to compound 7a increased 6.5-fold compared to the control group (p<0.0001), while it was found to increase approximately 9-fold when exposed to 7b (p<0.0001) (Figure 4).

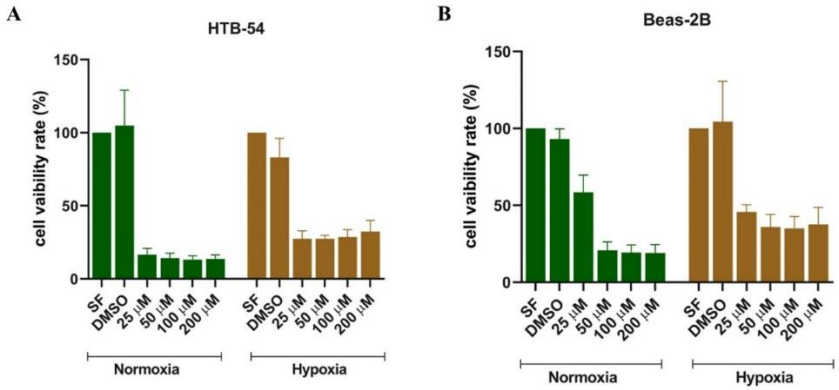

Figure 2. The effect of compound 7a on cell viability was demonstrated under normoxic and hypoxic conditions in HTB-54 (A) and Beas-2B (B) cells. Kruskal-Wallis test was used for the statistical evaluations.

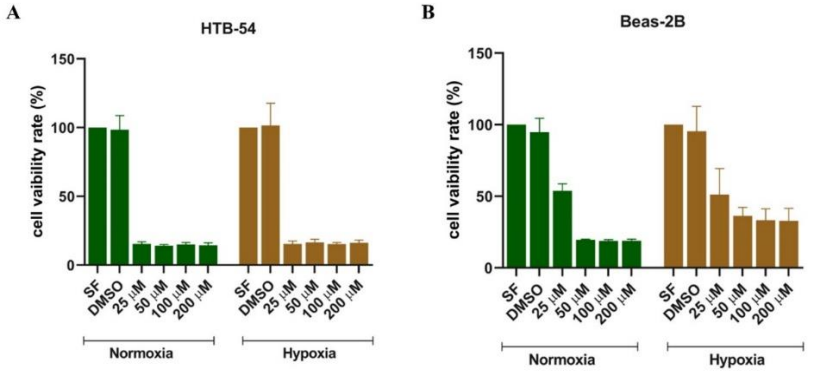

Figure 3. The effect of compound 7b on cell viability was demonstrated under normoxic and hypoxic conditions in HTB-54 (A) and Beas-2B (B) cells. Kruskal-Wallis test was used for the statistical evaluations.

Discussion

In recent years, with the clearer understanding of the HIF-1 pathway in the pharmaceutical industry, researchers have turned to genetic manipulations to increase or decrease the cellular HIF-1 gene level. The HIF gene has become an attractive target, especially since it can lead to non-invasive treatments for diseases such as ischemia and cancer (13). Hypoxic TME plays an active role in the proliferation of cancer cells by reprogramming the cellular energy metabolism through regulating the transition to anaerobic metabolism within tumor cells (7). Increased HIF expression is a sign of a poor prognosis in many cancers (14). Therefore, it is thought that the progression of cancer can be suppressed by inhibiting the HIF1 gene under hypoxic conditions. Therefore, it is of great interest to develop novel chemical inhibitors of HIF1 expression (15). Cobalt or nickel are frequently used to provide a hypoxic environment in vitro hypoxic cellular study. Since cobalt (II) and Nickel (II) ions in cells remove iron from the active sites of 2OG hydroxylases, it is thought to increase HIF-1 activity and provide in vitro hypoxic TME (16).

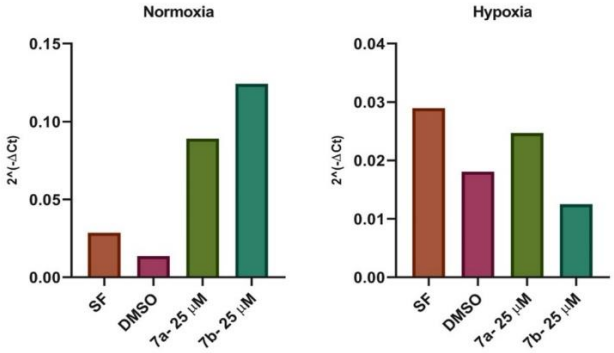

Figure 4. The changes in HIF1α expression level after exposure of HTB-54 cells with 25 µM 7a and 25 µM 7b under normoxia and hypoxia conditions are shown. t-test was used to analyze the HIF1A expression level.

Clinical and preclinical research on HIF inhibition is still in progress, and drug development studies focusing on the HIF signaling pathway have shown that these medicines have very high anticancer potential. Recently, arylsulfonamide has been identified as a new group of pharmacophores with high HIF-1α inhibitory activity in a cell-based study (17). Another study discovered that benzoxadiazole-containing drugs rapidly and specifically linked to HIF-2a (18). The sulfonamide structure, which was found to be an inhibitor of HIF-la, and the benzoxadiazole core, which is an inhibitor of HIF-2a, were combined to create new HIF inhibitors as 7a and 7b compounds.

In our study, compounds 7a and 7b, which are novel potential HIF inhibitory molecules (19), showed cytotoxic effects on the lung cancer cell HTB-54 at low doses (7a: 10.37 and 7b: 10.63 μM). The fact that they do not affect healthy cells at the determined IC_{50} doses makes them promising candidate anticancer agents for lung cancer chemotherapy. In hypoxic conditions, the decrease in oxygen level together with the increase of HIF gene expression much above normal accelerates the development of tumor cells from the vessels (20). Therefore, targeted small molecule synthesis increases in chemotherapy. Our medical study, it is tried to suppress the increased HIF gene expression in cancer with newly synthesized 7a and 7b compounds. The most crucial aspect of this, however, is that there won't be a mechanism by which these inhibitors may control or affect healthy cells because healthy cells, unlike cancer, won't have an excessive increase in the HIF gene. As a result, we believe that cancer cells will have less of an impact on healthy cells. Notably, both compounds were found to increase HIF gene expression under normoxia conditions and suppressed the increased cellular HIF level under hypoxia conditions compared to control. This suggests that both compounds have the potential to regulate hypoxic TME by suppressing increased HIF expression in lung cancer therapy.

Conclusion

Consequently, herein we showed that two candidate HIF1A inhibitors, 7a and 7b, have strong inhibitory activity against HIF1A under hypoxic conditions. Both compounds were shown to be selectively activated under hypoxic conditions but not under normoxia in lung cancer cells. To better understand the mechanistical details, further comprehensive studies are needed. Particularly, gain of function and loss of function studies of HIF1A will be more valuable. Moreover, further studies utilizing tumor xenograft models and/or genetically or chemically modified mouse models of lung cancer are necessary to gain a comprehensive understanding of the anticancer potential of HIF1A inhibitors 7a and 7b.

Conflict of interest statement

There is no conflict of interest to declare.

Ethics Committee Approval: This study did not involve the use of any human or animal tissues.

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A Simple and Effective Technique for Torn Hernial Sac Occurred During Large Inguinal Hernia Repair or Orchiopexy: Incision

Dev İnguinal Herni Onarımı veya Orşiopeksi Sırasında Yırtılan Fıtık Kesesi İçin Basit ve Etkili Bir Teknik: İnsizyon

Süleyman Cüneyt KARAKUŞ, Alev SÜZEN, Nazile ERTÜRK

Department of Pediatric Surgery, Mugla Sıtkı Kocman University, Faculty of Medicine, Mugla, Turkey

Öz

Dev inguinal herni onarımı veya orşiopeksi sırasında yırtılan fıtık kesesinin onarımı, uzman ellerde bile büyük zorluk oluşturur. Burada, fıtık kesesinin yırtılması ile karşılaşılan vakalarda yüksek ligasyon yapmayı kolaylaştıran bir tekniği sunmayı amaçladık. İnsizyon tekniğimizin adımları şöyledir: Kesenin lateralindeki yırtılmış kenarlar forseps yardımıyla tutularak, yırtık olmayan kısım gerdirilir. 15 no bistüri kullanılarak keseye insizyon yapılırken altındaki testiküler damarlar ve vas deferens'in yaralanmamasına dikkat edilir. Daha sonra ince doku forsepsi ve bistüri kullanılarak insizyonun proksimalindeki kese kenarları iç ringe doğru itilir ve kaldırılır. Proksimal kesenin tüm duvarları tek bir forseps içinde tutulur ve iç halka seviyesine kadar kremasterik liflerden ve kalan yapışıklıklardan nazikçe disseke edilir. Hastaların yaş ortalaması 13.9±18.1ay (aralık, 3 Hafta-7 yıl) idi. On yedi (%63) hasta inguinal herni ve 10 hasta (%37) inmemiş testis tanısı ile operasyona alınmıştı. Hastaların 7 (%25.9) tanesinde büyük kasık fıtığı kesesi mevcuttu. İntraoperatif ve postoperatif komplikasyon görülmedi. Bu yöntem, herniotomi sırasında fıtık kesesi yırtılan hastalarda kesenin daha fazla yırtılma riskini azaltan ve ameliyat süresini kısaltan güvenli ve etkili bir teknik olup vas deferens ve damarlara zarar vermemek için cerrahi büyüteç veya mikroskop kullanılarak da uygulanabilir.

Anahtar Kelimeler: Hidrosel, İnguinal Herni, İnmemiş Testis, Orşiopeksi, Prosessus Vaginalis

Abstract

Tearing of hernial sac during giant inguinal hernia repair or orchiopexy presents a challenge to the pediatric surgeons, even in expert hands. We here describe a technique that is easy for performing high ligation in cases complicated with torn hernial sac. The steps of our incision technique is: Non-separated part was tightened with the help of forceps localized at the lateral aspects of teared sac. The incision to the sac was fashioned by scalpel No 15, while taking care to avoid injury to the underlying testicular vessels and vas deferens. Then, wound edges of the proximal hernia sac were moved forward by using fine tissue forceps and scalpel. The walls of proximal sac were totally grasped in one forceps and dissected gently from the remaining adhesions and cremasteric fibers up to the level of the internal ring. The mean age of the patients was 13.9±18.1 months (range 3 weeks-7 years). The diagnosis of the patients was inguinal hernia in 17 (63%) and undescended testis in 10 (37%). Seven (25,9%) of the patients had a large inguinal hernia sac. There were no intraoperative and postoperative complications. This is a safe and effective technique in patients complicated with torn hernial sac during herniotomy. It reduces the risk of further tearing of hernial sac. Short duration is another advantage. This technique can also be performed with using surgical loupe or microscope to care not to damage the vas and vessels.

Keywords: Hydrocele, Inguinal Hernia, Undescended Testis, Orchiopexy, Processus Vaginalis

Introduction

Indirect inguinal hernia repair and orchiopexy are probably the most frequently performed surgical procedures in childhood throughout the world (1). Repairs of large inguinal hernia repair can be complicated with tearing of hernial sac; a factor associated with inguinal hernia recurrence. Furthermore, herniotomy is considered to be an effective part of a successful orchiopexy and helps prevent inguinal hernia in patients with undescended testis. Undescended testis with thin processus vaginalis present a challenge to the pediatric surgeons, even in expert hands. The presence of testicular vessels and vas deferens in close proximity to the peritoneum leads to tearing of hernial sac during the dissection. We here describe a technique that is easy and effective for performing high ligation in cases complicated with torn processus vaginalis or hernial sac.

	ORCID No
Süleyman Cüneyt KARAKUŞ	0000-0002-3906-2538
Alev SÜZEN	0000-0001-8040-300X
Nazile ERTÜRK	0000-0001-7660-5688

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Adres / Correspondence : Alev SÜZEN
Department of Pediatric Surgery, Mugla Sıtkı Kocman University, Faculty of Medicine, Mugla, Turkey
e-posta / e-mail : alevsuzen@hotmail.com

Material and Method

The herniotomy was performed under general anesthesia with a caudal block for postoperative pain relief. A 1-2 cm long incision in the skin of the inguinal crease just lateral to the pubic tubercle is made followed by identification and incision of Scarpa's fascia. Dissection is then extended medially along inguinal ligament at the level of external oblique to identify the external ring. The ring is incised and the hernia sac, localized usually anteromedially to the cord is identified. The "white line," indicative of the margin of the sac, is grasped with clamps and the sac dissected bluntly from the adhesions, testicular vessels and vas deferens using fine tissue forceps.

The processus vaginalis associated with cryptorchidism can be particularly thin and fragile or a large hernial sac can be difficult to dissect. It is possible to inadvertently tear the hernia sac at the level of connection between the sac and cord

structures. If there is a tear at this stage, the non-separated part is grasped with forceps localized at the lateral aspect of torn sac. The incision to the sac is made with No. 15 blade scalpel, while taking care to avoid injury to the underlying testicular vessels and vas deferens (Figure 1). Then, wound edges of the proximal hernia sac are moved forward by using fine tissue forceps and scalpel (Figure 2). The wall of proximal sac is fully grasped in one forceps and gently dissected from the remaining adhesions and cremasteric fibers up to the level of the internal ring (Figure 3). Once the sac is confirmed to be empty, it is twisted on itself and a transfixion suture placed through it, followed by excision of redundant sac tissue. The incised aponeurosis of the external abdominal oblique muscle, Scarpa's fascia and skin are closed with absorbable sutures, respectively. Nonsteroidal analgesics are prescribed when required. All were discharged on the same operative day, except for patients less than 2 months of age, who were discharged on postoperative day 1 because of a risk of postoperative apnea. All patients were followed up by inguinoscrotal examination at 1 month, 3 months and 1 year postoperatively. This study had local ethical committee approval of the Mugla Sıtkı Kocman University Faculty of Medicine (2020/34) and was conducted in accordance with the Helsinki Declaration of 2013.

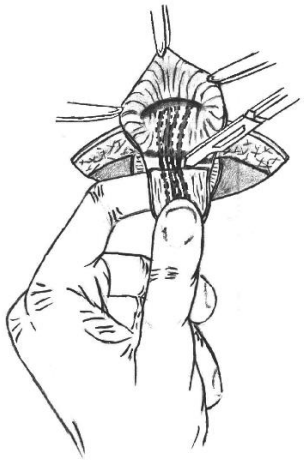

Figure 1. The incision to the sac is made with No. 15 blade scalpel, while taking care to avoid injury to the underlying vessels and vas.

Results

This study is a retrospective review of 27 male patients where herniotomy were complicated with the tearing of hernia sac. All torn sacs were accomplished by the incision technique performed by the first author between August 2016 and July 2019. None of the cases included in the study had incarcerated hernia or nonpalpable testis. The mean age of the patients was 13.9±18.1 months (range 3 weeks-7 years). The diagnosis was inguinal hernia in 17 (63%) patients and undescended testis in 10 (37%). Seven (25,9%) of the patients had a large inguinal hernia sac. There was no intraoperative complication noted. We did not need to extend the wound in any of our cases. No postoperative complications including testicular atrophy, recurrent hernia and postoperative hydroceles occurred in the present study.

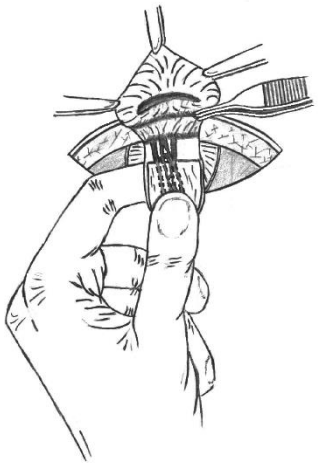

Figure 2. Wound edges of the proximal hernia sac are moved forward by using fine tissue forceps.

Figure 3. The wall of proximal sac is fully grasped in one forceps.

Discussion

Indirect inguinal hernia is common in the pediatric age group. It is often congenital and arises from a patent processus vaginalis, a peritoneal channel that has failed to close and is also found in up to 90% of undescended testes (1-3). Although some surgeons suggested the nonligation of the processus vaginalis in the context of a indirect hernia and orchidopexy, their findings were based on limited evidence to be interpreted with suspicion

(4,5). On the other hand, failure to ligate the sac high enough at the internal ring has been reported as a factor leading to recurrences in open hernia repair (1). Traditionally, surgeons dissect the patent processus vaginalis from the testicular vessels and vas deferens, and ligate it at the level of internal ring with or without resection of the distal sac. High ligation was considered as essential to avoid recurrence of indirect inguinal hernia and is also the standard part of inguinal orchiopexy for patent processus vaginalis (1,6-8). Sonmez et al. demonstrated the importance of dissection and high ligation of processus vaginalis to prevent hernia formation and provide a tension-free orchidopexy procedure (2).

Children with large hernia present a challenge to the pediatric surgeon (9-11). The extensive hernia sac dissection from testicular vessels and vas deferens in such patients may lead to injury of these structures (12). Furthermore, the flimsy and thin hernial sac in premature children or in association with undescended testis is also technically difficult to dissect and prone to tearing. Traditionally, surgeons tunnel between the hernia sac and the cord structures using blunt dissection in order to accomplish the repair of torn sac. Then, they grasp and transect the proximal part of dissected hernia sac. After this procedure is repeated several times, the walls of hernia sac totally grasped in one forceps. Some authors named this procedure as Zig technique (13). We experienced that tearing continued up to the internal ring in some cases where we used this technique. We then had to perform extensive dissection extending over to the retroperitoneum or close the internal ring tight enough to allow the passage of cord structures only. Therefore, we have developed the described incision technique. Although we were concerned about the injury of testicular vessels and vas deferens in our first few cases, we did not encounter such complications and also any additional tearing up to the internal ring. Even so, we recommend gradual incision instead of deep incision to the wall of patent processus vaginalis until the surgeon becomes experienced. This technique can also be performed with using surgical loupe or microscope to avoid damage to the vas and vessels.

Shorter operation duration is another advantage of this incision technique. Although we did not keep time, we observed that our technique was performed in a shorter time than classical zig technique.

Conclusion

Incision of torn patent processus vaginalis is a simple, safe and effective technique that does not require any additional dissection or maneuver. From present experience, the applicability of the technique has been tested in patients with indirect inguinal hernia and undescended testis, but we believe that it may also be used in hydrocele repair. Further research involving prospective studies with larger patient samples will allow us to evaluate the operative time and results of our technique.

Conflict of interest statement

None.

Ethics Committee Approval: This study had local ethical committee approval of the Mugla Sıtkı Kocman University Faculty of Medicine (2020/34) and was conducted in accordance with the Helsinki Declaration of 2013.

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Demographic, Clinical and Treatment Characteristics of Patients with Hepatocellular Cancer: 10 Years of Experience of a Single Center

Hepatoselüler Kanser Tanılı Olguların Demografik, Klinik ve Tedavi Özellikleri: Tek Merkezin 10 Yıl Deneyimi

Ezgi AVANAZ[1], Dinç DİNÇER[2], Ali AVANAZ[3], Gülsüm Özlem ELPEK[4], Esra ÇOBANKENT AYTEKİN[5], Erdem AYIK[6]

[1]Akdeniz University, Department of Nephrology, Antalya, Turkiye
[2]Akdeniz University, Department of Gastroenterology, Antalya, Turkiye
[3]Akdeniz University, Department of General Surgery, Antalya, Turkiye
[4]Akdeniz University, Department of Pathology, Antalya, Turkiye
[5]Konya State Hospital, Pathology Clinic, Konya, Turkiye
[6]Ağrı Education and Research Hospital, Pathology Clinic, Ağrı, Turkiye

Öz

Karaciğerin primer kanserleri, kansere bağlı ölümlerde 3. sırada yer almaktadır. Hepatoselüler karsinom (HSK), primer hepatik malignitelerin yaklaşık %80'ini oluşturur. Barcelona Clinic Liver Cancer (BCLC) sınıflaması HSK'yı 5 evreye böler ve tedavileri tahsis eder. Bu çalışmanın amacı merkezimizdeki HSK hastalarının aldıkları ilk tedavilerin incelenerek kılavuzlardaki yaklaşım ile karşılaştırmaktır. Çalışmamızda, 2006-2016 yılları arasında HSK tanısı almış hastaların verileri geriye dönük irdelendi. Hastaların yaş, cinsiyet, etiyoloji, Child-Pugh skoru, BCLC evresi, model for end-stage liver disease skoru, alfa fetoprotein düzeyi, tümör özellikleri, aldıkları ilk tedavi türü ve sağ kalım süresine bakıldı ve istatistiksel analizi yapıldı. Hastaların ortalama yaşı 61±10,5; 228'i erkek, 33'ü kadındı. Çalışmada yer alan hastaların 130'unun BCLC evresi değerlendirilebildi. Bu hastaların 77'sinin BCLC evre C olduğu saptandı. BCLC sınıflamasına göre hastaların ilk tedavilerini değerlendirdiğimizde, 22 hastaya sorafenib, 16 hastaya rezeksiyon, 15 hastaya TAKE, 14 hastaya Yitrium-90, 14 hastaya sorafenib dışı sistemik kemoterapi, 11 hastaya transplantasyon, 8 hastaya palyatif tedavi ve 4 hastaya ablasyon uygulandığı bulundu. Sağkalım süresinin 11.9 (8,1-15,9) ay ve bir yıllık sağ kalımın %32, üç yıllık sağ kalımın %19, beş yıllık sağ kalımın %16 olduğu saptandı. Merkezimizde HCC hastalarının yönetiminde BCLC kılavuzunun yanı sıra güncel literatür ve NCCN kılavuzundan da faydalanıldığı saptandı. Tedavi almayan hasta sayısının fazla olması da Evre D hastalara yeterli klinik ilgiyi göstermemiz gerektiğinin göstergesi olabileceğini düşündürdü.

Anahtar Kelimeler: Hepatoselüler Karsinom, Sağkalım, Tedavi Protokolleri

Abstract

Primary cancers of the liver are in the 3rd place in cancer-related deaths. Hepatocellular carcinoma (HCC) accounts for approximately 80% of primary hepatic malignancies. The Barcelona Clinic Liver Cancer (BCLC) classification divides HCC into 5 stages and allocates treatments. The aim of this study is to examine the initial treatments of HCC patients in our center and compare them with the approaches in the guidelines. The data of patients diagnosed with HCC between 2006 and 2016 were recruited retrospectively. Age, gender, etiology, Child-Pugh score, BCLC stage, model for end-stage liver disease score, alpha-fetoprotein level, tumor characteristics, type of first treatment and survival time were evaluated. There were 228 men and 33 women. The mean age was 61±10.5. Of the 130 patients 77 were found on BCLC stage C. The first treatment according to BCLC stage were sorafenib in 22, resection in 16, TACE in 15, Ytrium-90 in 14, systemic chemotherapy other than sorafenib in 14, transplantation in 11, palliative treatment in 8, and ablation in 4 patients. The median survival time was 11.9 (8.1-15.9) months. One-year survival was 32%, three-year survival was 19%, and five-year survival was 16%. The management of HCC patients was performed according to more than just BCLC guidelines in our center. The high number of patients who did not receive treatment may indicate that we need to show sufficient clinical attention to Stage D patients.

Keywords: Hepatocellular Carcinoma, Survival, Treatment Protocols

Introduction

Primary liver cancers ranked in sixth place among all cancer types worldwide in 2020 and also ranked in third place on cancer-related deaths (1). According to the American Cancer Society, primary liver cancer ranked fifth in cancer-related deaths in males, and the estimated number of new primary liver cancer cases was reported to be 41210 in all sexes (2). Hepatocellular carcinoma (HCC) exists in approximately 80% of hepatic malignancies (1). Chronic hepatitis B virus (HBV) and HCV infections, aflatoxin-contaminated foods, heavy alcohol consumption, smoking, type 2 diabetes mellitus, and being overweight are the main risk factors for HCC (3).

Many scoring methods have been discussed for treatment selection in patients, regardless of the tumor node metastasis staging system. One of these is The Barcelona Clinic Liver Cancer (BCLC) classification system. BCLC classification allocates treatments by dividing the disease into five stages based on tumor size, number, vascular invasion,

	ORCID No
Ezgi AVANAZ	0009-0002-7974-4514
Dinç DİNÇER	0000-0001-6769-9344
Ali AVANAZ	0000-0002-4559-4258
Gülsüm Özlem ELPEK	0000-0002-1237-5454
Esra ÇOBANKENT AYTEKİN	0000-0002-0500-7987
Erdem AYIK	0000-0002-1850-9812

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Adres / Correspondence : Ali AVANAZ
Akdeniz University, Department of General Surgery, Antalya, Turkiye
e-posta / e-mail : aliavanaz@hotmail.com

metastasis status, Child-Pugh Score (CPS), and patient performance score (4-6). The European Association for Study of Liver (EASL) reported the HCC management guidelines in 2000 and accommodated the usage of BCLC classification since 2012 (7-9). Today, ablation methods, liver resection, liver transplantation (LT), transarterial chemoembolization (TACE), transarterial radioembolization (TARE), sorafenib, monoclonal antibodies, and palliative treatments can be applied in the treatment of HCC (6).

We aimed to compare the treatment approaches conducted in our center, which has high-level treatment facilities such as organ transplantation and interventional radiology, with guidelines by examining the applied first treatment modality in HCC patients with this study.

Material and Method

We examined the data of 273 patients over 18 years old diagnosed with HCC in our center or referred to our hospital for treatment between 2006 and 2016. We excluded twelve patients from the study because of missing survival data. We collected the data of the remaining 261 patients retrospectively. We evaluated the data of patients' age, gender, etiology of HCC, CPS, BCLC stage, the model for end-stage liver disease (MELD) score, alpha-fetoprotein (AFP) level, metastasis, tumor specifications (location and dimension), portal vein thrombosis (PVT), first treatment modality, and survival time. We obtained ethics approval to conduct this study from the Akdeniz University Faculty of Medicine Ethics Committee (decision date: 01.03.2017 / decision number: 140).

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows version 20.0 (IBM, Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine the distribution of the data. Parametric data were presented as mean and standard deviation (SD), and non-parametric data were presented with median and interquartile range (IQR). Categorical variables were shown as numbers and percentages. Survival analysis was performed by the Kaplan-Meier method, and statistical differences were confirmed by log-rank test. The p-value was considered as 0.05 to determine the differences in the analyses.

Results

The mean age of all patients was 61±10.5 years. The majority of patients are men (87%, n=228) and cirrhotic patients (85%, n=221). The most common etiologic factor was HBV infection with 131 (50%) patients (Table 1).

Table 1. Demographic and clinical characteristics of the patients.

Age, year ±SD	61 ±10.5
Gender, n (%)	
Female	33 (13)
Male	228 (87)
Ethiology, n (%)	
HBV	131 (50)
HCV	38 (15)
HBV + HCV	3 (1)
HBV + HDV	9 (3)
Alcohol	32 (12)
Others	76 (36)
BCLC, n (%)	
Stage 0	1 (1)
Stage A	8 (6)
Stage B	7 (5)
Stage C	77 (59)
Stage D	37 (29)
Child-Pugh score, n (%)	
Class A	139 (63)
Class B	66 (30)
Class C	16 (7)
MELD score, n (%)	
<10	114 (51)
10-20	99 (45)
>20	8 (4)
Patient with metastasis, n (%)	
Yes	64 (25)
Abdominal lymph node	17 (24)
Periton	12 (17)
Bone	13 (18)
Lung	10 (14)
Lung + Bone	3 (4)
Adrenal gland	3 (4)
Kidney	3 (4)
Other organs	10 (14)
No	197 (75)
Portal Vein Trombosis, n (%)	
Yes	64 (29)
No	154 (71)
AFP level, n (%)	
<20 ng/ml	97 (40)
20-200 ng/ml	63 (27)
>200 (ng/ml)	79 (33)

We evaluated 130 of 261 patients by BCLC stage and found that 77 (59%) were on Stage C. According to CPS, the number of patients with class A, B, and C were 139 (63%), 66 (30%), and 16 (7%), respectively. The MELD score was below 10 in 114 (51%), between 10 and 20 in 99 (45%), and above 20 in 8 (4%) patients. The AFP level was below 20 ng/ml in 97 (40%), above 200 ng/ml in 79 (33%), and between 20 to 200 ng/ml in 63 (27%) patients (Table 1).

The tumor was most frequently located in the right lobe (n=137, 55%), the tumor diameter was 5 cm or more in 52% (n=129) of the 246 patients whose tumor diameter could be determined, and 55% (n=137) of the 248 patients whose tumor number was determined had multiple tumors (Table 2). We found that 153 (57%) patients were diagnosed with HCC by biopsy, and 25 (10%) patients were diagnosed in an external center.

Table 2. Tumor features.

Variable	n (%)
Tumor location	
Right lobe	137 (55)
Left lobe	21 (8)
Bilobar	91 (37)
Tumor diameter	
<2 cm	15 (6)
2-5 cm	102 (42)
>5 cm	129 (52)
Tumor count	
Single	111 (45)
Multiple	137 (55)

We found that PVT was diagnosed in 64 (29%) of 218 evaluated patients. Metastasis was found in 64 (25%) patients (Table 1). The most common metastasis locations were abdominal lymph node (n=17), peritoneum (n=12), bone (n=13), and lung (n=10) (Table 1).

We found the distribution of the first choice treatment modalities according to BCLC stage as sorafenib to 22, resection to 16, TACE to 15, yttrium-90 (y-90) to 14, non-sorafenib systemic chemotherapy to 14, LT to 11, palliative care to 8 and radiofrequency ablation (RF) to 4 patients. We found no treatment was administered to the remaining 26 patients (Table 3). Upon thorough analysis of the treatment methods per the guideline, we found that in Stage 0, a single patient underwent resection, whereas in Stage A, three out of eight patients underwent LT or RF. In Stage B, only one out of seven patients received TACE. Furthermore, in Stage C, sixteen out of seventy-seven patients received sorafenib; in Stage D, six out of thirty-seven received palliative treatment. Table 4 displays the treatment modalities that were administered to all patients.

Table 3. The administered first treatment modality counts according to BCLC stages.

BCLC	LT	Resection	RF	TACE	Y-90	Sorafenib	Palliative	No treatment	Chemotherapy
0	-	1	-	-	-	-	-	-	-
A	1	2	2	2	1	-	-	-	-
B	1	2	-	1	2	1	-	-	-
C	4	8	2	10	11	16	2	12	12
D	5	3	-	2	-	5	6	14	2
Total	11	16	4	15	14	22	8	26	14

The median survival time was 11.9 (IQR=8.1-15.9) months. The 1-, 3-, and 5-year survival rates were 32%, 19%, and 16%, respectively. The survivals according to treatment modalities are shown in Figure 1.

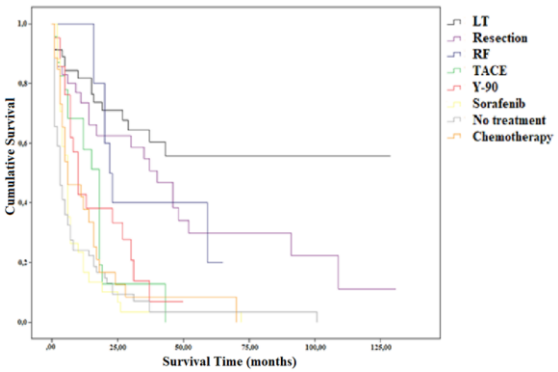

Figure 1. Survival of the patients according to the treatment modalities.

Discussion

The most recent BCLC classification recommends ablation treatment as the first option in very early stage tumors. If the patient is a potential candidate for LT, resection and transplantation are recommended as first options according to liver functions. In early stage tumor, the first line treatment options resection, ablation and transplantation choice depend on liver functions. In intermediate stage tumor TACE, transplantation and systemic treatment can be administered according to tumor size, AFP level, portal flow, and tumor specifications. In advanced stage and terminal stage, only systemic treatment and palliative treatment is recommended, respectively (6).

Table 4. The administered treatment modality counts of all cohort.

Treatment modality	n (%)
Liver transplantation	46 (%22)
Liver resection	35 (%17)
Radiofrequency ablation	13 (%6)
Transarterial chemoembolisation	23 (%11)
Y-90	21 (%10)
Sorafenib	34 (%16)
Palliative	10 (%5)
No treatment data	53 (%20)
Systemic chemoterapy (non-sorafenib)	26 (%13)

According to previous and current guidelines, sorafenib treatment is recommended in BCLC grade C patients (6,8). We observed that sorafenib was preferred as first-line treatment in one patient at an out-center clinic instead of TACE because the tumor size was 8 cm and multiple. It was a conflicting treatment choice with the previous guideline. The current guideline recommends systemic treatment in Stage B patients if the tumor is diffuse, infiltrative, extensive, or bilobar (6). We found that the oncologists administered sorafenib treatment to 5 patients who were considered on Stage D. According to the National Comprehensive Cancer Network (NCCN), CPS is preferred over BCLC in treating

HCC (10). We found that these five patients in CPS class A or B who are not suitable for local treatment were considered as appropriate candidates for sorafenib by the oncologists.

The previous guideline recommended liver resection in Stage 0 patients (8). In our study, two patients on Stage A underwent liver resection. One had a 3 cm single tumor, and the other underwent resection at an out-center clinic. According to the current guideline, liver resection can applied to patients on Stage 0 if the performance score is 0 and potential candidates for LT, and on Stage A if the performance score is 0 and liver functions are well-preserved (6). We found two patients who underwent liver resection on Stage B. One underwent liver resection while waiting for LT, and the other was referred directly to a general surgeon from an out-center clinic for liver resection to an undiagnosed liver mass. We found that three of the eight patients underwent resection and then were administered sorafenib, who were on Stage C. It was reported that patients who underwent sorafenib treatment following liver resection had better survival than only sorafenib (11). This approach is different from the guidelines but compatible with the literature. There were three patients on Stage D who underwent liver resection. We found that all of them were diagnosed with HCC after resection and then referred to the oncologists by general surgeons.

Liver transplantation was performed in 10 patients who were not on Stage A, even though it was not recommended in the previous guidelines. In the current guideline, LT is a treatment option in selected patients with Stages A and B (6). One patient with a 6 cm tumor at Stage B underwent LT in compliance with University of California San Francisco criteria. According to the BCLC staging system, portal vein infiltration or performance score of ≥1 is classified as Stage C (6-8). Two patients with a performance score of 1 underwent LT despite being on Stage C. We considered that performance scores could have been interpreted differently according to a given anamnesis by a patient to a clinician. The remaining seven patients in Stages C and D underwent LT from a living donor.

According to the guidelines, TACE is recommended for Stage B (6,8,9). In Stage A, TACE was preferred over RF for one patient due to tumor proximity to the diaphragm, and the other patient received initial treatment at an out-center clinic. Ten patients in Stage C received TACE instead of sorafenib. One of these patients received treatment in an out-center clinic. Since the number of tumors in four patients was only one, TACE might have been preferred over sorafenib. The remaining five patients received this off-label treatment, according to EASL. Since sorafenib treatment is not contraindicated after TACE treatment, NCCN applies this treatment in cases deemed clinically appropriate (10). Chen et al. (12) reported that patients who received TACE + sorafenib combination had a better disease control rate, survival, and disease progression time than those who received only sorafenib. It is stated that lesions larger than 5 cm that cannot be resected should be evaluated for arterial therapy (TACE/TARE) or sorafenib, according to NCCN. In addition, arterial treatments are relatively contraindicated in patients with bilirubin >3 mg/dl, portal vein thrombosis, and CPS class C if selective segmental injection is not performed (10). Transarterial chemoembolization was performed on two patients in Stage D. We believe that this situation, which does not comply with the EASL guideline, is an unnecessary preventive treatment approach, as the survival of these patients in the follow-up is not even one month.

Fourteen patients in our study received systemic chemotherapy. It was observed that 12 patients in Stage C and two patients in Stage D were given systemic chemotherapy other than sorafenib. Non-sorafenib systemic chemotherapy is not recommended in EASL (8). On the other hand, NCCN mentions that it can be applied within the scope of clinical trials (10). Ten of the twelve patients on Stage C were administered sorafenib after the non-sorafenib chemotherapy protocol. We observed that this type of treatment modality, which is not considered in the guidelines, was applied because sorafenib was reimbursed only for patients resistant to non-sorafenib chemotherapy. Only two patients received non-sorafenib chemotherapy at an out-center clinic on Stage D.

The previous guideline recommends RF for Stage A patients (8). There were two patients on Stage A and two patients on Stage C who received RF. One of the patients on Stage C underwent RF at an out-center clinic. The other patient was considered Stage C by general surgery because of suspicious invasion on dynamic computed tomography; however, the patient was reconsidered by gastroenterology, and RF was applied as a treatment. Also, this patient was considered a candidate for LT and underwent TACE as a bridge therapy on the waitlist. With this information, we assumed that the radiology report had been reconsidered in the multidisciplinary council.

There were 14 patients who received y-90 treatment. Of these patients, 11 were found on Stage C. This treatment modality was not covered in the previous EASL and American Association for the Study of Liver Disease guidelines (8,13). However, recent guidelines recommend y-90 for HCC treatment (6,9). The other patients in Stages A and B underwent y-90 treatment as bridge therapy while waiting for LT. We found that this treatment type was compatible with the guidelines.

Two patients received palliative treatment in BCLC Stage C according to their wishes, and six patients in Stage D received palliative treatment. It was determined that 26 patients in Stages C and D

did not receive treatment. Based on research findings among patients diagnosed with cirrhosis, it has been observed that only 17% of them followed through with their regular follow-up appointments, and a worrying 38% had an inconsistent attendance record (14). Another study demonstrated that just 20% of cases with HCC received consistent clinical follow-up (15). We thought that those who did not receive treatment in our study did not come up to follow-up after the diagnosis or refused treatment.

Alacacioglu et al. (16) reported that the median survival time of the HCC patients was 4 (1-50) months. In our study, the survival time was 11.9 months, 1-year survival was 32%, 3-year survival was 19%, and 5-year survival was 16%. It was reported that the overall survival time of 394 patients with HCC was 14.2 months in an 8-year follow-up period (17). Also, 5-year survival ranged from 23 to 44% in patients with hepatocellular carcinoma (18-20). In other studies, 5-year survival between 2002 and 2008 was reported as 15% in the United States and 12% in Europe between 2000 and 2007 (21). Our survival rates were lower because patients were diagnosed at a more advanced stage of BCLC.

Conclusion

The management of HCC patients was performed according to more than just BCLC guidelines in our center. Even in out-of-extended criteria patients, liver transplantation was performed, and NCCN guidelines or literature knowledge were followed for HCC treatment. Non-sorafenib chemotherapy was administered because of the Social Security reimbursement protocol in our center. However, the high number of patients who did not receive treatment may indicate that we need to show sufficient clinical attention to Stage D patients.

Conflict of interest statement

The authors have no conflict of interest to declare.

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Medical Journal of Mugla Sitki Kocman University 2023;10(3):191-197 *Cartı Dorterler and Demirbaş*
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Caries Risk Determination of 5-8 Year Old Children and Their Mothers in Muğla Province

Muğla İlinde 5-8 Yaş Grubu Çocukların ve Annelerinin Çürük Riski Değerlendirilmesi

Özgül CARTI DORTERLER[1], Ayşegül DEMİRBAŞ[2]

[1]Muğla Sıtkı Koçman Üniversitesi Dişhekimliği Fakültesi Çocuk Diş Hekimliği Anabilim Dalı, Muğla, Türkiye
[2]Muğla Sıtkı Koçman Üniversitesi Dişhekimliği Fakültesi Restoratif Diş Tedavisi Anabilim, Muğla, Türkiye

Öz

Bu çalışmada Muğla ilinde yaşayan, Muğla Sıtkı Koçman Üniversitesi Diş Hekimliği Fakültesi'ne müracaat etmiş 5-8 yaş arası 204 çocuk ve annesinin dental muayeneleri sonrasında elde edilen dental verilerin, yaşadıkları yer, annenin eğitim düzeyi ve çalışma durumu dikkate alınarak değerlendirilmesi amaçlandı. Çalışma grubu, çalışmanın amacı ve içeriği açıklandıktan sonra gönüllü katılım isteyen anne ve çocuklardan oluşturuldu. Süt dentisyonun çürük profilini belirlemek için dmft, daimi dentisyonunkinde DMFT kullanıldı. Annenin ve çocuğun ait olduğu ailenin yaşam şartlarının, annenin eğitim düzeyinin ve çalışma durumunun belirlenebilmesi için hazırlanan soruları yanıtlamaları istendi. Ağız içi muayene sonrası oluşturulan indeks ve yanıtlarından oluşan sonuçları IBM SPSS v23.0 (IBM Corp. 2015, Armonk, NY, US) kullanılarak istatistiksel olarak değerlendirildi. Değişkenlerin normalliği Kolmogorov-Smirnov testi ile incelendi. Demografik değişkene göre indeks değerleri arasındaki farklar bağımsız gruplar için Mann-Whitney U-testi ve Kruskal-Wallis testi ile değerlendirildi. İkili karşılaştırmada Dunn testi kullanıldı. Ayrıca Spearman korelasyon analizi de uygulandı. Annelerin eğitim düzeyinin, çocukların dmft ve DMFT indeks değerleri üzerinde anlamlı bir etkiye sahip olduğu görüldü($p<0.05$). Annelerin eğitim düzeyi yükseldikçe çocukların çürük profilinde azalma görüldü. Annelerin DMFT indeks değeri ile çocukların dmft indeks değeri arasında istatistiksel olarak anlamlı pozitif korelasyon olduğu tespit edildi ($p<0.05$, $r=0.017$). Ayrıca çalışan annelerin çocuklarının dmft indeks değerlerinin çalışmayan annelerin çocuklarınkinden anlamlı derecede düşük olduğu istatistiksel olarak belirlendi($p<0.05$). Çalışmada annenin çürükten etkilenme düzeyinin, eğitim düzeyinin ve çalışma durumunun çocukların diş çürüğünden etkilenme düzeyi üzerinde etkili olduğu görülmüştür. Ebeveynlerde özellikle annelerde ağız ve diş sağlığına yönelik bilgi ve tutum geliştirme girişimleri, gelecek neslin ağız sağlığının iyileştirilmesinde önemli bir etkiye sahip olacaktır.

Anahtar Kelimeler: Çürük Riski, Dmft/DMFT, 5-8 Yaş Çocuklar Ve Anneleri

Abstract

It was aimed to evaluate dental data obtained after dental examinations of 204 children aged 5-8 years and their mothers who lived in Muğla and applied to Muğla Sıtkı Koçman University Faculty of Dentistry, taking into account their place of residence, mother's education level and working status. To determine caries profile of primary dentition, dmft was used, and for permanent dentition, DMFT was used. They were asked to answer prepared questions. Results, consisting of formed index after intraoral examination and answers to questions, were statistically evaluated using IBM SPSS v23.0 (IBM Corp. 2015, Armonk, NY, US). Normality of variables is examined by Kolmogorov-Smirnov test. Due to variables do not follow a normal distribution, differences between index values per demographic variable were tested with Mann-Whitney U-test and Kruskal-Wallis test for independent groups. To make pairwise (multiple) comparison, we used Dunn's test. Spearman correlation analysis was also applied. According to results obtained, it was observed that mother's education level had a significant effect on children's dmft and DMFT index values ($p<0.05$). As education level of mothers increased, caries profile of children decreased. A statistically significant positive correlation was found between mother's DMFT index value and child's dmft index value($p<0.05$, $r=0.017$). Additionally, it was statistically determined that dmft index values of children with employed mothers significantly lower than those of children whose mothers unemployed($p<0.05$). The study showed that mother's level of being affected by decay, education level, and employment status were effective on the level of children being affected by tooth decay.

Keywords: Caries Risk, Dmft/DMFT, Children Aged 5-8 Years And Their Mothers

Introduction

Dental caries is one of the most common bio-film mediated, sugar-based, multifactorial chronic childhood diseases affecting both growth and quality of life, and resulting in phasic demineralization of the hard tissue of the tooth (1). Dental caries continues to be a significant public health problem, with negative effects on the nutrition, growth and general health status of children (2). The discomfort associated with dental caries in children, pain, sleep problems, absenteeism from school, learning disorders, and communication and psychosocial problems all affect the quality of life of the child (3). Consumption of sugar in the diet, saliva flow and composition, oral hygiene and fluoride exposure have an impact on dental caries (4). Current evidence indicates that non-biological markers associated with the social structure, economy, environment and healthcare system play an important role in the etiology of dental caries (5). Many social, behavioral and demographic factors, such family income, oral hygiene, parental knowledge of oral hygiene and the level of education of the mother all influence the

	ORCID No
Özgül CARTI DORTERLER	0000-0002-8123-7629
Ayşegül DEMİRBAŞ	0000-0003-1563-5378

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Adres / Correspondence : Özgül CARTI DORTERLER
Muğla Sıtkı Koçman Üniversitesi Dişhekimliği Fakültesi Çocuk Diş Hekimliği Anabilim Dalı, Muğla, Türkiye
e-posta / e-mail : ozgulcarti@mu.edu.tr

production of dental caries (6). Behaviors of parents, especially the mothers, are deemed to have a considerable impact on the oral health of the children (7). Maternal oral hygiene is thought to be directly linked with the development of dental caries in children; accordingly, improving the oral health of parents is considered to be an effective approach to decrease the risk of dental caries in children (8).

The DMFT (Decay, Missing, and Filled Tooth) index has become a vital tool for the monitoring of trends in the distribution of dental decay, and is applied by WHO (World Health Organization) in oral health evaluations that reflect the intensity or frequency of tooth decay (9). The DMFT index is one of the most frequently and easy-to-use index values aiding the epidemiological research of dental caries (10). The DMFT index of permanent teeth and the dmft index of the primary teeth are important indicators of the oral health of children in society (11).

Demography involves the place of residence as well (12). However, international pediatric dental health studies comparing urban and rural areas have yielded controversial results. In some studies, the dental health of children living in rural areas was found to be better than their counterparts residing in urban areas, although some studies report similar levels and others found out that country-dwellers enjoy better oral health (13-15).

Similar to the Mediterranean diet, the general structure of the nutritional habits in Muğla consists of vegetables, fruits, wild herbs, cereal products, seafood, olives and olive oil (16,17). There is evidence to support the relationship between eating habits and dental caries (18). In the literature, the greater the adherence to the Mediterranean diet, the lower the amount of caries. It has been reported that the less adherence to the Mediterranean diet, the greater the amount of caries (17). In this study, it was aimed to determine the degree of caries exposure of children and their mothers living in Muğla province and therefore fed similarly to the Mediterranean diet, and to compare them with the average of Türkiye and the Aegean region. There is no study investigating the oral health of children and mothers in Muğla. The present study evaluates the dmft/DMFT index values of a group of randomly selected children aged 5–8 years residing in the city of Muğla to determine the associations between the index and the place of residence, the level of education of the mother, the maternal DMFT index value and the maternal employment status.

Material and Method

The study began upon obtaining approval from the Health Sciences Ethics Board of Muğla Sıtkı Koçman University. (2020-5/200004) The study population included subjects randomly selected from among the patients who applied to the Department of Pediatric Dentistry of the Faculty of Dentistry of Muğla Sıtkı Koçman University, and who matched the inclusion criteria of the study. Written informed consent prepared in accordance with the Declaration of Helsinki was obtained from the families of the children who met the inclusion criteria.

While determining the sample size, the statistical tests used in the study were taken into consideration, and the total sample size was determined as n=202, with a Type I error $\alpha=0.05$, a power of the test $1-\beta=0.95$ and a medium effect size d=0.5, using the G*Power program. The desired sample size determined for the study was achieved, and the analysis results are presented for n=204 subjects.

Inclusion criteria

-Participants who agreed to participate in the study with their mothers

-Residing in the city of Muğla

-Aged 5–8 years

-Children rated positive or definitely positive according to the Frankl behavior rating scale.

Exclusion Criteria

-Declined participation in the study

-Not residing in the city of Muğla

-Not aged between 5 and 8 years

-Children rated negative or definitely negative according to the Frankl behavior rating scale

Oral examination

The clinical oral examination and diagnosis of dental caries in the children and their mothers were carried out by the single calibrated dentist using the criteria defined by the World Health Organization (19). The dmft and DMFT index values were used for the determination of the degree of affection of primary dentition from dental caries, and the degree of affection of permanent dentition from dental caries, respectively. The DMFT index was used for the determination of the mothers' affection from dental caries.

Each child was examined on dental chair under light illumination using an oral mirror and a sond for communal periodontal indexing (WHO sond). Prior to the examination, all surfaces of the teeth were dried, and cavitations and lesions in the initial phase in which the cavitation had not yet formed in the pits, fissura or smooth surfaces were classified as decay (d/D). Any tooth with one or more restoration was accepted as having a filling (f/F). Teeth extracted due to caries were accepted as missing (m/M), while primary teeth that had exfoliated spontaneously due to the underlying tooth eruption and teeth that have not yet erupted were ignored. The DMFT index values, education level, employment status and location of residence of the mothers of the children (rural/urban areas) were recorded.

Statistical Analysis

All analyzes were performed with IBM SPSS v23.0 (IBM Corp. 2015, Armonk, NY, US). For descriptive purposes, minimum, maximum, mean, standard deviation, median and interquartile range are provided in the tables. The normality of the variables is examined by Kolmogorov-Smirnov test. Due to variables do not follow a normal distribution, the differences between the index values per demographic variable were tested with the Mann-Whitney U-test and Kruskal-Wallis test for independent groups. To make pairwise (multiple) comparison, we used Dunn's test. The Spearman correlations are obtained, and p-values are presented in the related table. A $p<0.05$ value was taken into account to determine whether there was a statistically significant difference in all tests.

Results

A total of 204 patients, including 110 girls and 94 boys, were included in the study. The mothers of the patients are between the ages of 28-42. The distribution of patients according to demographic data is given in Table 1. Minimum, maximum and mean dmft and DMFT index values of the children and the DMFT index values of their mothers are given in Table 2. The analysis of the dmft index value of the primary teeth and DMFT index of the permanent teeth of children according to their demographic characteristics is given in Table 3. According to the results obtained, there is no statistically significant difference between the genders in terms of dmft index value ($p>0.05$). However, it was determined that the dmft index value of boys was relatively higher than that of girls. There is no statistically significant difference in terms of place of residence ($p>0.05$). The dmft index values of the children of employed mothers were statistically significantly lower than those of the children of unemployed mothers ($p<0.05$). There was no statistically significant relationship between the DMFT index value of the permanent teeth of the children and the gender, place of residence and employment status of the mothers ($p>0.05$) (Table 3).

It was determined that the education level of the mothers had a statistically significant effect on the dmft index of the children's primary teeth and the DMFT index value of the permanent teeth of the children . As the education level increased, the dmft index value and the DMFT index value of the children decreased shown in Table 4 ($p<0.05$).

In Table 5, correlation coefficients are provided. The positive correlation between the child's dmft index and the mother's DMFT index values is statistically significant (p=0.015<0.05) with a coefficient of r=0.170 and this value can be interpreted as a weak level of correlation. On the other hand, there is no significant correlation between the child's DMFT index values and the mother's DMFT index values.

Table 1. Frequencies of demographic variables

	n	%
Gender		
Boy	94	%46.07
Girl	110	%53.93
Location of residence		
Rural	99	%48.52
Urban	105	%51.48
The employment status of the mother		
Employed	106	%51.96
Unemployed	98	%48.04
Education level of the mothers		
Primary	23	%11.27
Middle	30	%14.07
High	59	%28.92
University	92	%45.09
Age		
5 years old	47	%23.03
6 years old	49	%24.01
7 years old	53	%25.98
8 years old	55	%26.96

Table 2. The caries status of children and their mothers

	Min-Max	Mean± Std. Dev.
Child's dmft index value	0-16	4.63±3.01
Child's DMFT index value	0-3	1.56±0.72
Mother's DMFT index value	0-16	5.63±3.71

Discussion

In the present study, the dmft/DMFT index values of a randomly selected group of children aged 5–8 years living in the city of Muğla, as well as the DMFT index values of their mothers, were assessed, along with the association with the education level, employment status and location of residence of the mothers.

The significance of oral health in evaluations of the general health of an individual is well known (20). The most frequently used epidemiologic scale for the determination of oral health is the DMFT index for permanent teeth, and the dmft index for primary teeth (11). Accordingly, dmft and DMFT values pertaining to different age groups and regions are required to be investigated at times to check the trends of change in those indexes and to evaluate the measures taken in the country. Besides, periodic studies are needed to evaluate oral health status, and to provide statistical and supportive documents with the aim of preparing and applying required protective practices and treatment programs (11).

When the oral and dental health profile in Türkiye is examined, it has been reported that the dmft index value of 5-year-old individuals is 3.64, while the dmft value is 2.78 in the Aegean Region (21). The average dmft index value in this study was

4.63. Although individuals living in the province of Muğla are fed similarly to the Mediterranean diet, which is less affected by caries, the degree of exposure to caries is above the average of both Türkiye and the Aegean region. Nutrition alone is not a determinant in the degree of exposure to caries. In addition to following the Mediterranean diet and promoting healthy eating habits, it requires the implementation of more strategies to stop the appearance of dental caries. Elements necessary to improve children's oral health include adequate fluoride content, proper toothbrushing flossing, use of chemical agents such as chlorhexidine, and administration of probiotics that compete with cariogenic bacteria by inhibiting the fermentation of sugar (22).

Table 3. Evaluation of children's dmft and DMFT index value according to demographic characteristics

	n	%	dmft Mean± Std. Dev.	Median (IQR)	Normality test (p-val)	Mann-Whitney U-Statistic*	p
Gender							
Girl	110	53.93%	4.36±2.74	4.00 (5.00)	<0.001	5.308	0.884
Boy	94	46.07%	4.95±3.29	4.00 (5.00)	0.001		
Location of Residence							
Urban	105	51.50%	4.28±2.83	4.00 (4.00)	<0.001	4.550	0.122
Rural	99	48.50%	5.01±3.16	5.00 (5.00)	0.004		
The employment status of the mother							
Employed	106	51.96%	4.01±2.84	3.00 (4.00)	<0.001	6.440	0.003
Unemployed	98	48.04%	5.29±3.06	5.00 (4.00)	0.023		
	n	**%**	**DMFT Mean± Std. Dev.**	**DMFT Median (IQR)**	**Normality test (p-val)**	**Mann-Whitney U-Statistic***	**p**
Gender							
Girl	59	54.62%	1.75±0.71	2.00 (1.00)	<0.001	17.00	0.267
Boy	49	45.38%	1.37±0.74	1.00 (0.75)	<0.001		
Location of Residence							
Urban	55	50.90%	1.25±0.46	1.00 (0.75)	<0.001	18.00	0.161
Rural	53	49.10%	1.87±0.83	2.00 (1.75)	<0.001		
The employment status of the mother							
Employed	59	54.62%	1.60±0.84	1.00 (1.25)	<0.001	30.00	0.999
Unemployed	49	45.38%	1.50±0.54	1.50 (1.00)	<0.001		

*: Scaled test statistic

Table 4. The effect education level of mother's on children's dmft and DMFT index value

	n	%	dmft Median (IQR)	Normality test (p-val)	Statistic	p	Group comparisons	Dunn's Statistic	p
Education level of the mothers									
Primary	23	11.3%	5.00 (5.00)	0.096	15.117	0.002	University< Primary	30.76	0.025
Middle	30	14.7%	5.50 (3.50)	0.194			University< Middle	42.84	0.001
High	59	28.9%	1.00 (0.00)	0.091			University< High	21.63	0.027
University	92	45.1%	1.50 (7.75)	0.000			-	-	-
	n	**%**	**DMFT Median (IQR)**	**Normality test (p-val)**	**Statistic**	**p**	**Group comparisons**	**Dunn's Statistic**	**p**
Education level of the mothers									
Primary	15	13.8%	-	<0.001	8.409	0.038	-	-	-
Middle	15	13.8%	1.00 (0.75)	0.002			Middle< High	-7.583	0.019
High	31	28.7%	3.00 (0.00)	<0.001			University< High	7.583	0.008
University	47	43.5%	1.00 (0.75)	<0.001			-	-	

The 2018 oral and dental health profile report for Türkiye lists a university graduate rate of 9.3% for the female guardians of the 5-year-old participants (21), while university graduates accounted for 45.09% of the participating mothers in the present study conducted in Muğla. Turkish Statistical Institute (TUIK) data for 2020, on the other hand, reports an employment rate of 26.3% for women (23), while 51.96% of the participating mothers in the present study were in gainful employment. Based on these data, it can be said that women in Muğla are above average of Türkiye in terms of both education level and employment status.

Table 5. Correlation between mothers DMFT index value and their children's dmft and DMFT index value.

	Mother DMFT index value	
	r	**p**
Child dmft index value	0.170	0.015
Child DMFT index value	-0.349	0.186

The adoption of good oral hygiene habits in childhood is generally possible if education is started in childhood in the home with the parents, and especially the mother, as the primary role model in the development of child behaviors (24). Previous studies have focused on the effects of the oral health, habits, attitude and knowledge of mothers on the oral health of children, and their association and correlation with each other, since mothers are traditionally accepted as the main caregiver. Mothers thus play an important role in the adoption of oral health practices, and the attitudes and behavior of their children related to oral health (24). Studies conducted to date have shown that the mother continues to play a very important role in the lifestyles of children related to oral health, despite the changing roles and responsibility areas within families (25,26). The level of education of a mother is known to raise awareness in subjects related to health. The children of mothers with a high level of education have been shown to have better dental health in previous studies (27,28). Szatko et al. reported that the attitudes and general knowledge of mothers related to oral health were influential on the oral health behaviors and statuses of their children (29). Similarly, Hallet et al. identified a strong association between the dmft index values of children and the education level of their mothers (30). Similar to the findings of earlier studies, the dmft and DMFT index values of the children of mothers with a higher level of education in the present study were found to be lower than those with a low level of education. This was attributed to the increased awareness of oral hygiene, dental health and preventive dentistry associated with an increased level of education.

A positive and significant correlation was found between the DMFT index values of the mothers and the dmft index values of the children in the present study, although no statistically significant correlation could be identified between the DMFT index values of the mothers and DMFT index values of the children. The results of the present study are similar to those of the study by Oter et al., who reported a positive correlation between the dmft index values of children with the DMFT index values of mothers (31). We consider this to be associated with the presence of the primary teeth in the oral medium for a long time in the age group evaluated in the present study, and that the permanent teeth continued to erupt.

The employment status of the mother is an indicator of the socioeconomic status of the individual. High rates of dental caries continue to be prevalent in socioeconomically disadvantaged children, in spite of the development of oral health in children (32,33). The present study found that the dmft index values of the children of employed mothers were statistically significantly lower than those of the children of unemployed mothers. This finding concurred with the results of the study by Marcia et al., in which a higher dmft index value was determined in the children of unemployed mothers (34). Ghandehari Matlagh et al. also reported a higher dmft index value among the children of mothers who were housewives than those of the children of employed mothers (35). It can be attributed to the fact that employed mothers have a higher level of education than those who are unemployed, they are more efficient in terms of the utilization of social oral and dental health education, and are more likely to seek better dental conditions for both themselves and their children. Furthermore, employed mothers may enjoy a greater economic purchasing power, and so have easier access to hygiene products for the benefit of both themselves and their children. The fact that the employment status of the mothers was questioned but not their ages or occupation can be considered a limitation of the study. The age and occupational status of mothers are significant factors affecting the oral hygiene of their children, the provision of nutrition, and access to oral care products and dental health services.

Location of residence affects greatly the nutritional habits of children and their access to dental hygiene products, affecting also the presence of oral healthcare facilities and the level of access to such facilities, all of which have an accumulative effect on the oral health of children. The prevalence of dental caries varies based on sociodemographic and geographic qualities (13). Studies investigating the dental health of children in rural and urban areas have produced inconsistent results. Assessing Türkiye's oral and dental health profile, the study by Gökalp et al. reported a high prevalence of dental caries in 5-year-old and 12-year-old children in rural areas, while the prevalence was similar for 15-year-olds in rural and urban areas (36). A study by

Masereijan et al. reported a higher frequency of dental caries in urban areas than in rural areas (14). Similarly, the study by Levin et al. involving a Scottish sample reported better oral health among children living in rural areas (37). In this study, although statistically insignificant, the dmft and DMFT index values of children living in rural areas were found to be higher than children living in urban areas. The findings of the present study concur with those of the study by Vargas et al. carried out in Maryland, who reported that children in rural areas experienced more caries than their counterparts in the urban setting (38). Furthermore, Matilla et al. and Paunio et al. reported in their studies that the children living in rural areas had a higher level of dental caries, which is similar to the results of the present study (39,40).

Efforts to encourage good oral health behaviors in children may affect the general welfare of future generations, considering the important role of oral health in general health. The level of affection of the mother from dental caries, their education level and employment status, and their location of residence have all been found to affect the degree of affection in the children from dental caries. Accordingly, dentistry awareness-raising programs that focus especially on oral and dental health in mothers is required, as it is believed that this will lead to the raising of a generation with healthier teeth in the future, contributing to the provision of protective, simple and low cost treatment methods rather than difficult, long-lasting, challenging and expensive dental treatment processes. The results of the present study reveal more areas for research, and the need for more extensive studies in the city of Muğla to ascertain the level of oral health of children, and the factors that are influential in this regard. In the present study, no data were collected on the oral hygiene practices, diet, individual socioeconomic conditions, access to dental services, or attitudes towards oral health of the surveyed children. More extensive multi-regional studies are recommended for the evaluation of dental data alongside the demographic, attitudinal and behavioral survey data of children.

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Prediction of Colchicine Response in Children with Periodic Fever Aphthous Stomatitis Pharyngitis and Cervical Adenitis Syndrome

Periyodik Ateş Aftöz Stomatit Farenjit Servikal Adenit Sendromlu Çocuklarda Kolşisin Yanıtının Belirleyicileri

Hakan KISAOĞLU, Özge BABA, Mukaddes KALYONCU

Karadeniz Technical University, Faculty of Medicine, Department of Pediatrics, Division of Pediatric Rheumatology, Trabzon, Turkiye

Öz

Kolşisin profilaksisi, periyodik ateşli aftöz stomatit, farenjit ve servikal adenit (PFAPA) sendromlu hastaların yönetiminde tedavi seçeneklerinden biridir, ancak tedavi yanıtı değişkenlik göstermektedir. Burada kolşisin profilaksisinin etkinliğini ve profilaksiye olumlu yanıtla ilişkili faktörleri araştırmayı amaçladık. Çalışmaya 5 yaşından önce kolşisin tedavisi başlanan PFAPA tanılı hastalar dahil edildi. Profilaktik tedaviye cevap ateşlenme aralıklarındaki değişime göre değerlendirildi ve ateş aralığında> %50 artış olması olumlu yanıt olarak kabul edildi. Olumlu yanıt veren hastalarda ise >3 ay ateşsiz dönem olması tam yanıt olarak kabul edildi. Çalışmaya katılan 41 hasta arasında, 20 (%48.8) hastada olumlu bir yanıt gözlendi ve olumlu yanıt verenler arasında 8 (%19.5) hasta ise tam yanıt verdi. Olumlu yanıt vermeyen diğer hastalardan 9'u (%22) kolşisin profilaksisine yanıtsız olarak değerlendirildi. Kolşisin yanıtının, MEFV mutasyonları ve önceki kortikosteroid kullanımı dahil olmak üzere klinik ve laboratuvar özelliklerle ilişkisi olmamasına rağmen, daha kısa ateş aralıklarının, kolşisine olumlu yanıt verme olasılığını önemli ölçüde artırdığı bulundu. Bu bilgi, PFAPA'lı hastaların tedavisinde terapötik kararlara yardımcı olabilir.

Anahtar Kelimeler: Ateş Aralığı, Kolşisin, PFAPA, Tedavi Yanıtı

Abstract

Colchicine prophylaxis is one of the treatment options in management of patients with periodic fever aphthous stomatitis pharyngitis and cervical adenitis (PFAPA) syndrome, but variability exists in response to the treatment. Here we aimed to investigate the efficacy of colchicine prophylaxis and factors associated with a favorable response. Patients diagnosed with PFAPA in whom colchicine was employed before 5 years old age were included. Response to the prophylaxis was assessed by the change of fever intervals and an increase of fever interval >50% after treatment was accepted as favorable response. Complete response was defined as a fever free interval of > 3 months in patients displayed favorable response. Among 41 patients, a favorable response, was observed in 20 (48.8%) patients, and among favorable responders, 8 (19.5%) patients displayed complete response. Of the remaining patients without a favorable response, 9 (22%) demonstrated no response to colchicine prophylaxis. Despite colchicine response was not associated with clinical and laboratory features including MEFV mutations and previous corticosteroid usage, shorter fever intervals were found to be significantly increased the odds of a favorable response to colchicine, which might aid in therapeutic decisions in management of patients with PFAPA.

Keywords: Fever Intervals, Colchicine, PFAPA, Treatment Response

Introduction

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) is considered to be the most common periodic fever syndrome (1). The disease was first described by Marshall et al. (2) and characterized by an abrupt onset of fever, aphthous stomatitis, pharyngitis, and cervical lymphadenopathy with spontaneous resolution of fever in 4 to 5 days. Fever episodes occur periodically between 2-8 weeks at early stages and interval of fever episodes might increase with age (3). Also, fever episodes resolve in a significant proportion of patients by age (4,5). Corticosteroid treatment was effective in the cessation of fever but associated with an increased frequency of fever episodes in half of the patients (6). Tonsillectomy might result in the resolution of fever episodes, and colchicine treatment could be used to decrease the frequency of fever episodes (7,8). However, to date, no consensus has been achieved in the management of patients with PFAPA.

In patients with PFAPA, prophylactic colchicine treatment was found to be effective by several studies with varying degrees (8–11). However, most of these studies were conducted in patients with a high frequency of fever episodes and had small sample sizes. Furthermore, no study has investigated the predictors of colchicine response in children with PFAPA. In this study, we aimed to investigate the efficacy of colchicine prophylaxis and factors associated with a favorable response to colchicine treatment in a well-defined cohort of PFAPA patients.

	ORCID No
Hakan KISAOĞLU	0000-0002-1095-3222
Özge BABA	0000-0002-2442-1550
Mukaddes KALYONCU	0000-0001-5378-939X

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Adres / Correspondence : Hakan KISAOĞLU
Karadeniz Technical University, Faculty of Medicine, Department of Pediatrics, Trabzon, Turkiye
e-posta / e-mail : kisaoglu@outlook.com.tr

Material and Method

Medical charts of the children, diagnosed with PFAPA in a reference center between May 2016 and June 2021 were reviewed. Diagnosis of PFAPA was made as an expert opinion in the presence of regularly occurring fever episodes, onset before 5 years of age, associated with either tonsillopharyngitis or cervical lymphadenitis and/or aphthous stomatitis with the absence of clinical

features associated with monogenic autoinflammatory diseases. Patients who did not fulfilled the Eurofever/PRINTO criteria for the diagnosis of PFAPA (12), in whom colchicine was employed after 5 years of age and patients with a previous history of either tonsillectomy or adenoidectomy were excluded. In addition, to minimize bias in the determination of the treatment response, only patients with an observed fever episode at the time of colchicine initiation were included. Because familial Mediterranean fever is endemic in our region, genetic analysis for common MEFV gene mutations was performed in all patients and patients carrying homozygote or compound heterozygote MEFV mutations were also excluded.

Demographic, clinical and laboratory features were extracted from the medical charts of the patients. Response to colchicine was evaluated at the 6th month of treatment and the longest fever free interval between the 3rd and 6th months of treatment was used to evaluate the changes in the interval after colchicine prophylaxis. If a patient was attack free for at least two months at the 6th month of treatment, the first fever episode after the 6th month was also included for the determination of the colchicine response.

Colchicine treatment was started at a dose of 0.5 mg/day and dose adjustments were made in the first three months of treatment by increments of 0.25 mg according to the colchicine response. At the 3rd month of treatment, patients were either under the maximum tolerable dose or the minimum efficient dose of colchicine treatment. None of the patients received a colchicine dose more than 1 mg/day.

As an outcome measure, two distinct descriptions were used. Response to colchicine was evaluated by the increase of fever intervals. Favorable response was defined as an increase of fever intervals > 50% after colchicine initiation (10). Additionally, a definition of a complete response was described as an at least one fever free interval ≥ 3 months (13). Changes of the fever interval within 25% of the interval before treatment or < 7 days were accepted as variation, and changes of the fever intervals within the described variation were considered as nonresponders.

Descriptive statistics were presented as frequency with percentage, mean with standard deviation, or median with interquartile range (IQR). The normal distribution of the data was assessed by the Kolmogorov-Smirnov test. Analysis of the continuous variables before and after the initiation of colchicine was performed using the paired sample T-test or Wilcoxon signed rank test. Comparison of the categorical variables was analyzed using Fisher's exact test. Comparison of continuous variables between groups was performed by the students' T test when data were normally distributed or Mann-Whitney-U test when the data were not normally distributed. The Spearman test was used for the correlation analysis. Receiver operating characteristic (ROC) curve analysis was performed to identify the optimum cut-off value of continuous variables associated with colchicine response. Multivariable logistic regression analysis was performed to identify the odds of favorable colchicine response. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 23 (IBM), with a statistical significance set at $p < 0.05$. This study was approved by the local ethical committee.

Results

Medical charts of the 99 children, diagnosed with PFAPA between May 2016 and June 2021, were reviewed. 19 patients, who did not use colchicine, were excluded. Furthermore, 11 patients without an observed fever episode before colchicine initiation and 8 patients, in whom the interval between attacks in the patient history was not consistent with the observed attack interval at the time of the fever episode, were excluded from the study. Among the remaining patients, 4 patients with a homozygote/compound heterozygote MEFV mutation, 6 patients, in whom colchicine was initiated after 5 years of age and, 3 patients, who had a history of tonsillectomy and/or adenoidectomy before initiation of colchicine, were also excluded. Of the remaining patients, 3 were lost on follow-up before the 6th month of colchicine treatment, and 4 patients did not have sufficient data for the determination of the fever episodes after colchicine prophylaxis. A total of 41 patients were included in the data analysis.

Among patients, 31 (75.6%) were male and mean age at the onset of fever episodes was 17.9 months. A family history suggestive of PFAPA was present in 13 (31.7%) of the patients and consanguinity was observed in 4 (9.8%). Tonsillopharyngitis (90.2%) was the most common finding associated with fever episodes, followed by cervical lymphadenopathy (61%) and stomatitis (36.6%). The mean interval between fever episodes was 24.5±5.6 days and the mean duration of fever was 4.5±1.2 days. Mean age at colchicine initiation was 31.3±3.1 months and median time from the onset of fever episodes to colchicine treatment was 12 (IQR: 5 - 18.5) months. Either diagnostic or on-demand corticosteroid therapy was employed in 27 (65.9%) of the patients.

The mean colchicine dose was 0.58±0.17 mg per day and 13 (31.7%) patients experienced treatment side effects associated with a dose increase, in which all of them were gastrointestinal, such as diarrhea and abdominal pain. MEFV mutation analysis was performed in all patients, and a heterozygote mutation was detected in 13 (31.7%) patients. The most common MEFV mutation was the E148Q variant, observed in five patients followed by M694V and M680I in three and two patients

respectively. V726A, A744S and P369S mutations were the other MEFV mutations each detected in one patient.

Favorable response, was observed in 20 (48.8%) patients, and among favorable responders, 8 (19.5%) patients displayed complete response. Of the remaining patients without a favorable response, 9 (22%) demonstrated no response to colchicine prophylaxis. Demographic, clinical and laboratory features, and response to the colchicine treatment are shown in Table 1.

Table 1. Demographical, clinical and laboratory features and characteristics of colchicine treatment in patients with PFAPA syndrome

	n: 41
Demographical features	
Gender (male)	31 (75.6%)
Age at first attack (months)	17.9±10.4
Family history of PFAPA	13 (31.7%)
Consanguinity	4 (9.8%)
Clinical features	
Fever	41 (100%)
Tonsillopharyngitis	37 (90.2%)
Cervical lymphadenopathy	25 (61.0%)
Stomatitis	15 (36.6%)
Abdominal pain	10 (24.4%)
Arthralgia	4 (9.8%)
Headache	2 (4.9%)
Fever interval (days)	24.5±5.6
Duration of fever (days)	4.5±1.2
Treatment features	
Age at colchicine initiation (months)	31.3±3.1
Previous corticosteroid treatment	27 (65.9%)
Duration from onset of fever to colchicine initiation (months)#	12.0 (5.0-18.5)
Colchicine dose (mg/day)	0.58±0.17
Colchicine side effect	13 (31.7%)
Laboratory features	
MEFV mutations	13 (31.7%)
C-reactive protein$^{\Delta}$ (mg/L)	99.9±56.3
ESR$^{\Delta}$ (mm/hr)	37.4±15.8
Serum amyloid A$^{\Delta}$ (mg/L)#	143 (39-209)
Response to the colchicine treatment	
Complete response	8 (19.5%)
Favorable response	20 (48.8%)
No response	9 (22.0%)

Data are presented as mean ± standard deviation, #median (interquartile range) or number (%). PFAPA: periodic fever aphthous stomatitis pharyngitis cervical adenitis, n: number, ESR: erythrocyte sedimentation rate. Δ Values in the attack period

Colchicine treatment resulted in a significant increase in the interval between fever episodes (24.5±5.6 days vs. 54.6±26.6 days, p<0.001) and a decrease in the duration of fever (4.5±1.2 days vs. 2.8±1.2 days, p<0.001) in patients with PFAPA. Besides, patients without a favorable response to colchicine also demonstrated a significant increase in the interval between fever episodes (27.5±4.4 days vs. 37.4±7.3 days, p<0.001) and a decrease in the duration of fever (4.3±1.3 days vs. 3.2 ±1.4 days, p=0.001). Despite patients with no response displayed a significantly increased duration between fever episodes, it remained in the described range of variation. Moreover, in patients with no response to colchicine, treatment showed no significant effect on the duration of fever episodes (4.0±1.7 days vs. 3.4±1.7 days, p=0.18). Changes in the interval and the duration of the fever episodes before and after colchicine prophylaxis are shown in Table 2.

When the features of the disease were compared according to the colchicine response, age at onset, gender, family history of PFAPA, clinical manifestations, duration of fever, age at colchicine initiation, acute phase reactants at the time of fever episode and presence of MEFV mutations were not significantly different according to the presence of a favourable response. Besides, the presence of exon-10 mutations was not different between patients with and without favorable response [M680I (2), V726A (1) and A744S (1) in favorable group; M694V (3) in patients without a favorable response]. In addition, a MEFV variation was observed only in 2 patients with complete response (M694V, E148Q). However, patients with a favorable response had a significantly shorter interval between fever episodes before colchicine treatment than patients without a favourable response (21.4±5.2 days vs. 27.5±4.4 days, p: 0.001). A similar association was observed between patients displaying a complete response compared to patients without complete response (20.9±5.5 days vs. 25.4±5.4 days, p=0.001), and between patients with complete response and no response (20.9±5.5 days vs. 28.3±3.3 days, p=0.01). Additionally, none of the features, except fever intervals, were found to be different according to the presence of complete response or between patients with a complete response and those with no response. Comparisons of the features according to the presence of a favorable colchicine response are shown in Table 3.

Correlation analysis revealed a significant moderate negative correlation between the interval of fever episodes before colchicine and the percentage of increase in fever intervals after colchicine (r: -0.612, p<0.001) (Fig. 1). ROC analysis revealed that the interval of fever episodes, longer than 23 days, identified patients without a favorable response to colchicine treatment with a sensitivity of 90% and specificity of 75% (AUC: 0.794, p=0.001) in patients with PFAPA. A univariate logistic regression analysis was performed to examine the odds of a favorable response to colchicine treatment. Among variables tested, only interval between fever episodes <24 days was significantly associated with an increased odd of favorable response to colchicine prophylaxis (OR: 9.6, CI: 2.3 – 39.9, p=0.002). The results of the regression analysis are shown in Table 4.

Table 2. Assessment of the change of the intervals and duration of fever episodes before and after colchicine prophylaxis in children with PFAPA

	Before colchicine	After colchicine	*p* value
All patients with PFAPA (n:41)			
Interval between fever episodes (days)	24.5±5.6	54.6±26.6	<0.001
Duration of fever episodes (days)	4.5±1.2	2.8±1.2	<0.001
Patients with a favorable response (n:20)			
Interval between fever episodes (days)	21.4±5.2	47.1±10.8	<0.001
Duration of fever episodes (days)	4.6±1.1	2.8±0.9	<0.001
Patients without a favorable response (n:21)			
Interval between fever episodes (days)	27.5±4.4	37.4±7.3	<0.001
Duration of fever episodes (days)	4.3±1.3	3.2±1.4	0.001
Patients with no response (n:9)			
Interval between fever episodes (days)	28.3±3.3	32.8±3.5	0.007
Duration of fever episodes (days)	4.0±1.7	3.4±1.7	0.18

Data are presented as mean ± standard deviation. PFAPA: periodic fever aphthous stomatitis pharyngitis cervical adenitis, n: number.

Table 3. Comparison of the disease features according to the presence of a favorable colchicine response in children with PFAPA

	Patients with a favorable response n:20	Patients without a favorable response n:21	*p* value
Gender (male)	15 (75.0%)	16 (76.2%)	>0.99
Age at first fever episode (months) [#]	16.5 (12-30)	12 (10-22)	0.19
Consanguinity	3 (15.0%)	1 (4.8%)	0.34
Family history of PFAPA	6 (30.0%)	7 (33.3%)	>0.99
Tonsillopharyngitis	18 (90.0%)	19 (90.5%)	>0.99
Stomatitis	7 (35.0%)	8 (38.1%)	>0.99
Cervical lymphadenopathy	13 (65.0%)	12 (57.1%)	0.75
Abdominal pain	5 (25.0%)	5 (23.8%)	>0.99
Duration of fever (days)	4.8±1.0	4.3±1.3	0.17
Interval between fever episodes (days)	21.4±5.2	27.5±4.4	**0.001**
Previous corticosteroid treatment	14 (70%)	13 (61.9%)	0.74
Age at colchicine initiation (months) [#]	36 (24-42)	25 (18-39)	0.21
Duration from onset to colchicine prophylaxis (months) [#]	12 (4.3-21.3)	11 (6-18.5)	0.63
MEFV gene mutation	6 (30%)	7 (33.3%)	>0.99
C-reactive protein$^{\Delta}$ (mg/L) [#]	91 (51-145)	97 (64-126)	0.81
ESR$^{\Delta}$ (mm/hr) [#]	38 (24-46)	30 (25-50)	0.89
Serum amyloid A$^{\Delta}$ (mg/L) [#]	173 (31-241)	140 (45-199)	0.64

Data are presented as mean ± standard deviation, #median (interquartile range) or number (%). PFAPA: periodic fever aphthous stomatitis pharyngitis cervical adenitis, n: number, ESR: erythrocyte sedimentation rate. Δ Values at the fever episode.

Discussion

The results of this study suggest that a shorter interval between fever episodes before colchicine prophylaxis is a predictor of favorable response to prophylaxis in children with PFAPA. Literature knowledge on the efficacy of colchicine prophylaxis in patients with PFAPA supports our findings that colchicine was effective in patients with frequent attacks (8,9,14). However, to the best of our knowledge, no study has reported an association between the frequency of fever episodes and colchicine response. In 2008, Tasher et al. (9) reported for the first time that colchicine treatment might be effective in the prophylaxis of patients with frequent fever episodes. In that study, colchicine treatment resulted in the prolongation of fever episodes in eight of the nine patients and, the mean interval between fever episodes before treatment was 1.7 weeks. Also, in a study from Spain, colchicine was reported to be effective in 13 patients with PFAPA with frequent episodes and a decrease in both duration and number of the episodes were observed (14). In contrast, a study with 20 PFAPA patients shown that colchicine response, described as at least 50% reduction in number of fever episodes, was observed in nine of the patients, and no significant difference was observed in terms of the intervals between fever episodes (10). In an open label prospective study, in which eight of the 18 patients were on colchicine prophylaxis for three months, colchicine treatment was resulted with a decrease in number of the fever episodes. Besides, in patients with colchicine prophylaxis median interval between fever episodes before and after treatment was 17 and 40 days respectively (8). In addition to these knowledges, finding of the no significant difference in fever durations before and after colchicine treatment in non-responders in this study suggests that the effect of colchicine on decreasing the duration of fever episodes is more pronounced in colchicine responders.

Table 4. Logistic regression analysis of features associated with a favorable response to colchicine in children with PFAPA

Features	OR	*Univariate analysis* 95% CI		*p* value
		Lower	Upper	
Onset <12 months age	1.3	0.4	4.6	0.64
Colchicine initiation <24 months age	1.3	0.4	4.7	0.62
Fever duration <4 days	3	0.8	10.7	0.09
Fever interval <24 days	9.6	2.3	39.9	**0.002**
Family history of PFAPA	0.9	0.2	3.2	0.82
MEFV mutation	0.9	0.2	3.2	0.82

OR: odds ratio, CI: confidence interval, PFAPA: periodic fever aphthous stomatitis pharyngitis cervical adenitis.

A consensus management approach is not yet developed for children with PFAPA and research on this topic is limited, mostly due to the benign and self-resolving nature of the disease. Additionally, outcomes measures for the prophylactic approach are not uniformly described. In two prospective trials, the efficacy of prophylaxis was assessed by the decrease of the fever episodes and one described favorable response as twice less fever episode, similar to our description (8,10). More recently, investigators of CARRA suggested outcome measures as complete and partial response (13). In this study, both outcome measures were investigated and unlike the low attainment rate of complete response, favorable response was evident in nearly half of the patients. Since the course of the disease is benign and choice of treatment is often fashioned by the preferences of parents with respect to the quality of life, a favorable response could be as acceptable as complete response.

In a recent study, colchicine was effective in decreasing both physician and parent reported disease activity in 27 patients with PFAPA (15). Our results also suggest that colchicine is effective in the prevention of fever episodes and that resulted in a favorable response in half of the patients. A study from Turkey, which included 356 patients with PFAPA with a mean interval between fever episodes of 18.8 days, reported that 85% of the patients showed an increase in the duration between fever episodes and colchicine response was reported to be more frequently encountered in patients with MEFV mutations (11). In contrast, a study conducted from an endemic region for familial Mediterranean fever (FMF) reported a 19% rate of concomitant FMF diagnosis in patients with PFAPA and did not find a significant difference in colchicine response between patients with and without FMF (16). Although we did not find any association between MEFV mutations and colchicine response, this finding might be due to the limited sample size of our study. We also excluded patients with a homozygote/compound heterozygote MEFV mutation to decrease the bias in determination of the colchicine response in case of concomitant FMF and PFAPA. MEFV mutations were thought to have a modifier effect on the clinical findings of PFAPA with a shorter duration of fever and a lower dose of steroid requirement for the abortion of fever in patients with heterozygote MEFV mutations (17). In contrast, Batu et al. (18) compared the clinical characteristics of patients in two cohorts, one from Turkey and the other from the United States and reported that patients from Turkey were younger and had a shorter duration of fever. In addition, MEFV mutations were not found to be significantly influenced by the disease phenotype in that study (18). Similarly, we did not find any association between colchicine response and MEFV mutations in patients with PFAPA, also our results were not indicative of a modifier effect of MEFV mutations in the disease phenotype.

The use of colchicine for the prophylaxis of fever episodes of PFAPA is mostly based on the experience of patients with FMF (9). In addition to FMF, colchicine has been suggested for treating a varying spectrum of inflammatory disorders, including idiopathic recurrent pericarditis, coronary artery disease, recurrent aphthous stomatitis and Behcet's disease (19,20). The anti-inflammatory and anti-fibrotic effects of colchicine were mainly due to the blockage of assembly and polymerization of microtubules. Microtubules are involved in various cellular processes including intracellular trafficking, cytokine secretion and cell migration. Besides, colchicine concentrates intensively in leukocytes and inhibits neutrophil chemotaxis, adhesion, and recruitment to the site of inflammation (21).

Because of the curative role of tonsillectomy in patients with PFAPA, a triggering role of tonsils in the pathogenesis of the fever episodes has also been suggested (22). Besides, a different subset of lymphocyte population restricted to the tonsils was shown in the tonsils of the patients with PFAPA compared to the tonsils of the patients with obstructive sleep apnea (23). Furthermore, tonsillar microbiota was found to be different in patients with PFAPA and alteration of tonsillar microbiota was implied in the development of fever episodes (24). In a small sample sized study, probiotic supplementation was shown to decrease the frequency of fever episodes in patients with PFAPA (25). Based on this knowledge, variability of the response to colchicine and the association with the interval between fever episodes might be related to a

possible effect of colchicine in sensing the alterations of oral/tonsillar microbiota.

The retrospective nature and patient reported fever episodes were the most notable limitations of this study. In addition, the association of fever intervals with colchicine response might need external validation. Furthermore, selection of the longest interval of the fever episodes to assess the colchicine response might produce bias given the variability of the fever intervals. Another limitation was MEFV testing which might limit the assessment of MEFV mutations in the determination of colchicine response. Although common MEFV mutations were studied in all patients, heterogeneity exists in the number of mutations tested and the number of mutations analyzed differs among patients.

Conclusion

Colchicine prophylaxis resulted in a favorable response in half of the patients. Besides, colchicine shortens the duration of fever, but this effect is less pronounced in nonresponders. Our results suggest that colchicine is more effective in patients with frequent fever episodes and interval of fever episodes shorter than 24 days significantly increase the odds of a favorable colchicine response. This knowledge might help both clinicians and caregivers in selecting the most suitable treatment option.

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Ethics Committee Approval: Study complies with the Declaration of Helsinki and was performed according to ethics committee approval of Karadeniz Technical University Ethical Comittee (30/06/2021-2021/150).

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Pilonidal Sinus at The Appendectomy Incision

Apendektomi İnsizyonunda Gelişen Pilonidal Sinüs

Mesud FAKİRULLAHOĞLU[1], Tolga KALAYCI[2], Mustafa YENİ[1], Murat KARTAL[3]

[1]Erzurum Regional Education and Research Hospital, General Surgery Clinic, Erzurum, Turkey.
[2]Ağrı İbrahim Çeçen University Faculty of Medicine, Department of General Surgery, Ağrı, Turkey.
[3]Ataturk University Faculty of Medicine, Department of General Surgery, Erzurum, Turkey.

Öz

Pilonidal sinüs, cildin epidermis tabakasına nüfuz eden kıllar nedeniyle iltihaplanma ile ilerleyen bir hastalıktır. Bu olgu sunumunda apendektomi kesisinde oluşan insizyonel pilonidal sinüs olgusunun tanı ve tedavi süreci sunulmuştur. 47 yaşında erkek hasta apendektomi kesisinde yaklaşık üç gündür pürülan akıntı ve kızarıklık şikâyeti ile başvurdu. Hastaya yaklaşık sekiz yıl önce sağ paramedian kesi ile apendektomi yapılmış olup ameliyat sonrasındaki dönemde kesi izinde tekrarlayan apseler gelişmişti. Apse kesesi de dahil olmak üzere deri ve deri altı dokuları cerrahi olarak eksize edildi. Hastadan alınan eksizyon materyalinde tüm dermisi kaplayan kıllarla yoğun inflamatuar reaksiyon ve epidermisin erozyon ve ülserasyonu mevcuttu.

Anahtar Kelimeler: Apendektomiler, Cerrahi Yara, Pilonidal Sinüs

Abstract

Pilonidal sinus is a disease that progresses with inflammation due to hairs that penetrate the epidermis layer of the skin. This case report presented the diagnosis and treatment process of the incisional pilonidal sinus case, which occurred at an appendectomy incision. A 47-year-old male patient was admitted with purulent discharge and erythema for about three days in the appendectomy incision. The patient underwent appendectomy with a right paramedian incision approximately eight years ago, and recurrent abscesses developed in the incision scar in the postoperative period. The skin and subcutaneous tissues, including the abscess sac, were surgically excised. In the excision material taken from the patient, there was an intense inflammatory reaction with hair covering the entire dermis and erosion and ulceration of the epidermis.

Keywords: Appendectomies, Surgical Wound, Pilonidal Sinus

Introduction

Pilonidal sinus (PS) is a disease that progresses with inflammation due to hairs and hairs penetrating the epidermis layer of the skin (1). Although PS is generally located in the sacrococcygeal region, it can also be atypical in other regions of the axillary area, inter-mammary area, navel, clitoris, penile skin, scalp, and post-auricular (2,3). In this case report, the diagnosis and treatment process of a case of the pilonidal sinus in an appendectomy incision, an area that has never been described before, is presented.

Case

A 47-year-old male patient was admitted to the general surgery outpatient clinic with purulent discharge and redness for about three days in the surgical incision in October 2021. About eight years ago, he was taken to emergency surgery with the diagnosis of acute appendicitis, and an appendectomy was performed with a right paramedian incision. He did not have any complaints two years after the appendectomy—an abscess developed in the incision scar in the third year after the operation. The abscess was drained, and the abscess area returned to normal with daily cleaning. On his history check, he had recurrent abscess three-four times yearly in the incision (Figure 1).

	ORCID No
Mesud FAKİRULLAHOĞLU	0000-0002-5871-5688
Tolga KALAYCI	0000-0002-6977-1757
Mustafa YENİ	0000-0003-2384-2094
Murat KARTAL	0000-0003-1396-5365

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Kabul Tarihi / Accepted : 22.11.2022

Adres / Correspondence : Tolga KALAYCI
Ağrı İbrahim Çeçen University Faculty of Medicine Department of General Surgery, Ağrı, Turkey
e-posta / e-mail : dr.tolgakalayci@gmail.com

Figure 1. Preoperative view of the wound.

On physical examination, his vital findings were as follows: blood pressure: 138/68 mmHg, pulse rate: 78 beats per minute, oxygen saturation on room air: 97%, and body temperature: 36.7° Celsius. On physical examination, there was an inflamed, edematous PS in the incision scar. Other system

examinations, including the abdomen, were unremarkable. He only had mild leukocytosis ($11.8x10^9$/L) on laboratory evaluation. Then, ultrasonography (USG) was performed to rule out foreign body reactions due to suture material. USG only showed a fistula tract of approximately 17 mm in depth. No significant intra-abdominal extension/fascial extension was observed in USG. Elective surgery was planned. The fascia was reached by passing the skin and subcutaneous layers over the old incision scar. The fascia was in a completely natural appearance. The skin and subcutaneous tissue were excised, including the abscess pouch. The wound was closed primarily. Since there was no problem in the follow-up of the patient who was taken to the service, the patient was discharged on the third postoperative day. In the excision material taken from the patient, there was an intense inflammatory reaction, with hair covering the entire dermis and erosion and ulceration of the epidermis (Figure 2). In the 6-month follow-up, no pathological finding was detected in the incision scar (Figure 3).

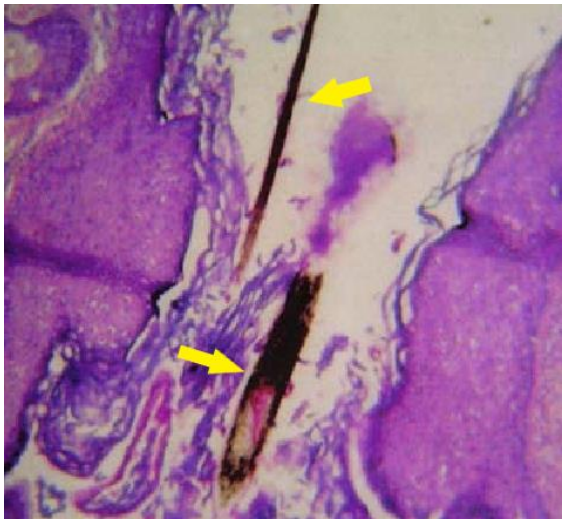

Figure 2. Pathological view of the specimen (yellow arrows indicate hair in the follicle).

Discussion

The pilonidal sinus (PS) consists of an abscess and hair content that creates a cavity surrounded by inflammatory processes. While the most common site for PS, at rates up to 97.8%, is the sacrococcygeal region, the umbilical region is the most common location outside the sacrococcygeal area. A literature review searched the common extra sacrococcygeal PS cases, including 302 patients, and the prevalence of umbilical PS was 90.1% (3). Apart from the umbilical region, PS can also be seen in atypical areas such as the axilla, suprapubic area, inguinal region, neck, face, clitoris, penis, nose, and the endoanal canal (2,3). However, until now, no case of PS has been defined in the incision site. For this reason, we presented the diagnosis and treatment process of a PS case that occurred in a new location.

Male gender, excessive hairy body structure, hair type, poor body hygiene, prolonged sitting, local microtraumas, deep intergluteal sulcus, and obesity predispose factors for PS (4). PS is more common in men, and occupations requiring prolonged sitting suggest that factors such as hair density and regional microtrauma are also influential in addition to hormonal factors (5). In the case we have presented, although the male gender is seen as a predisposing factor, the main predisposing factor is previous surgery. In addition, our case occurred in the abdominal wall that was not significantly exposed to pressure.

Figure 3. Wound image of the patient at six months.

PS symptoms depend on the stage of the disease at presentation, acute or chronic. In the acute form, inflammation and abscess formation are seen in the sinuses. In the chronic form of PS, serous/seropurulent/purulent discharge is seen in the sinus and a fistula orifice away from the sinus (6). Recurrent abscesses that may be in remission for many years may also occur in chronic form. USG, computed tomography (CT), magnetic resonance imaging, and colonoscopy are helpful in diagnosis in cases of sacrococcygeal PS if there is a deep-located abscess, anal fistula suspected, and Crohn's disease is suspected (7). In patients with extra sacrococcygeal localization, additional imaging tools/tests are required according to the localization of the lesion. In the present case, suture reaction was primarily considered since he had a history of surgery. Since only a fistula tract smaller than 20 mm was seen on USG and there was no significant relationship between the fistula tract and anterior abdominal fascia, additional imaging techniques such as CT or fistulogram/sinogram were not considered by the patient.

The primary treatment in PS cases is the excision of the lesion and primary closure. Surgical resection with clean margins is inevitable, especially in chronic infections with recurrent abscesses. In this case, primary resection and closure were performed due to recurrent infection.

Conclusion

The pilonidal sinus consists of an abscess and hair content that creates a cavity surrounded by inflammatory processes. Most pilonidal sinus cases are present in the sacrococcygeal area and umbilical area. There are also cases of pilonidal sinus outside the sacrococcygeal and umbilical regions. Until now, no case of PS has been defined in the incision site. Whether in the typical location or the atypical location, the treatment decision depends on recurrent infection/abscess. In our case of incisional pilonidal sinus, our treatment recommendation is resection of the lesion with a solid margin and primary closure.

Written consent: Written consent of the patient was obtained on 18.10.2021.

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How to Manage an Arterio-Venous Extracorporeal Membrane Oxygenator Establishment in Case of Persistent Left Vena Cava Superior?

Persistan Sol Superior Vena Cava Varlığında Arteriyo- Venöz Ekstrakorporeal Membran Oksijenatör Kurulumu Nasıl Yönetilmelidir?

Hande ISTAR

Mugla Sitki Kocman University Faculty of Medicine, Department of Cardiovascular Surgery, Mugla, Turkey

Öz

Ekstrakorporeal Membran Oksijenatörü (ECMO), yenidoğan ve infantlarda vasküler yapıların ince oluşu nedeniyle sıklıkla v.jugularis interna ve ana karotid arter yoluyla hastaya bağlanmaktadır. Olgu sunumumuzda sağ v.cava superior'u ince kalibrasyonda olan konjestif kalp yetmezliği ve Ellis Van-Creveld Sendromu tanılı hastada, daha geniş çaplı persistan sol superior vena cava (PSSVC) yoluyla ECMO uygulaması sunulmaktadır.

Anahtar Kelimeler: ECMO, Ellis Van-Creveld Sendromu, Persistan Sol Süperior Vena Cava

Abstract

Extracorporeal membrane oxygenator (ECMO) can be established via v.jugularis interna and carotid artery in neonates and infants because of inadequate calibration of the other peripheral vessels. We aimed to introduce the ECMO establishment via persistent left v. cava superior in an infant patient whose right v.cava superior was inadequate in size.

Keywords: ECMO, Ellis Van-Creveld Syndrome, Persistent Left Vena Cava Superior

Introduction

Extracorporeal membrane oxygenator (ECMO) can be established via v. jugularis interna, carotid artery in neonates and infants because of inadequate calibration of the other peripheral vessels. We aimed to introduce the ECMO establishment via persistent left v. cava superior (VCS) in an infant suffering congestive heart failure (CHF) and Ellis Van-Creveld Syndrome, in case of inadequate size of right VCS.

Case

A four-month-old, 3.2 kg in weight female patient was admitted to our hospital because of CHF. She was hospitalized in the pediatric intensive care unit and intubated. Inotropic medical treatments were given. Echocardiogram evaluated CHF with an ejection fraction 40%, single atrium, complete atrioventricular septal defect and bilateral VCS. Atrioventricular valves had a severe incompetence. Pulmonary artery pressure was measured as 65 mmHg. Right and left VCS were 1.2 mm and 3.2 mm in diameter respectively. She had Ellis Van-Creveld Syndrome; polydactyly in hands, abnormal toes of feet were detected (Figure 1C, 1D). Left VCS was draining to the coronary sinus. Despite inotropic agents, cardiac decompensation occurred in 5 days. Before the decision of surgery, we decided to establish arterio-venous (AV) ECMO for life support. Informed consent was obtained from the patient's relatives in 2016.

Femoral veins were less than 1 mm in Doppler ultrasound investigation.

Under general anesthesia, with a cut-down method on the left side of the neck, left main carotid artery (LMCA), PLVCS were explored and cannulated with 8 F and 10 F cannulas (Medtronic) for the arterial and venous cannulations respectively. ECMO establishment was completed. To have a better venous return, the cannula was advanced forward to the coronary sinus (Figure 1A, 1B) following the measurement of the coronary sinus which showed an adequate diameter with echocardiogram. Coronary sinus damage was eliminated by screening with echocardiogram again, the venous return was adequate. Under ECMO support, we could diminish doses of inotropic agents in 10 days; however, thrombocytopenia occurred due to the destroying effect of ECMO circulation. Because of complications of massive transfusion, bleeding and bacterial sepsis, we lost our patient.

Discussion

ECMO is being widely used in case of congenital heart disease (CHD) and severe respiratory failure (1). PLVCS is frequently associated with CHD (2). PLVCS is found to be problematic in case of cardiac surgery while the cannulation process of cardiopulmonary bypass or insertion of pacemaker leads. Frequently, PLVCS is smaller in diameter

	ORCID No
Hande ISTAR	0000-0002-7150-0171

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Adres / Correspondence : Hande ISTAR
Mugla Sitki Kocman University Faculty of Medicine, Department of Cardiovascular Surgery, Mugla, Turkey
e-posta / e-mail : handeistar@yahoo.com

rather than right VCS in CHD associations. In literature, right VCS agenesia in a sporadic manner (2).

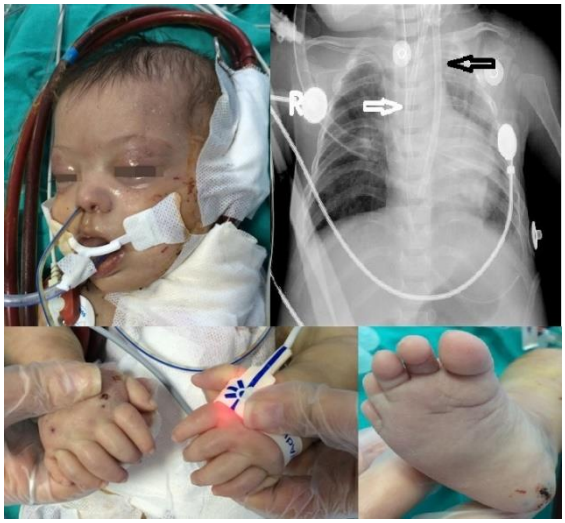

Figure 1. A: ECMO establishment via left main carotid artery and PLVCS. B: X-Ray view of arterial and venous cannulas following the ECMO establishment. C: Polydactyly of Ellis Van-Creveld Syndrome in hands. D: Structural abnormalities in feet about Ellis Van-Creveld Syndrome.

Even though our patient was 4-month-old, she was 3.2 kg in weight. Moreover, she had a hypoplastic right VCS. Before ECMO cannulation, bilateral VCS existence, their diameters should be evaluated by Doppler ultrasound.

We believe that in case of low weight infant who requires ECMO support if PLVCS is larger than the right side, it is safe to perform the venous cannulation. However, the position of the venous cannula should be checked by echocardiogram and X-Ray particularly for possible rupture of coronary sinus and position of cannulas.

Written consent: Written consents of the patients were obtained on 10.10.2021.

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Yazışmadan Sorumlu Yazar / *Corresponding Author* **İmza / *Signature***

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