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Dergimiz yayın hayatına 5. yılının 3. sayısı ile devam etmektedir.
Bu sayımızda 5 araştırma makalesi, 1 olgu sunumu ve 1 derleme yazısı ile karşınızdayız.
Dergimiz tıbbın hemen hemen her alanından yayın kabul etmeye devam etmekte olup özellikle İngilizce yazılan makalelere öncelik verilmektedir.
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Bu süreçte yayın kalitesinde şu ana kadar koyduğu hedefleri daha da yükselterek 3 ayda bir yayınlanmaya, belli konulara odaklanmış özel sayılar çıkarmaya, belli kongrelerin bildiri özetlerini yayınlamaya devam edecektir.

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Dil Editörü, Ön Kontrol Danışmanı

Hakan Cinemre

Selçuk Yaylacı

Cemil Bilir

İbrahim Vedat Bayoğlu

İlhan Hacıbekiroğlu

Hamad Dheir

İletişim Kurulacak Kişi

Cemil Bilir, Editör

Sakarya Üniversitesi Tıp Fakültesi,

Email: cemilbilir@sakarya.edu.tr

Telefon: (+90)0535-253-5124

Selçuk Yaylacı, Editör Yardımcısı

Sakarya Üniversitesi Tıp Fakültesi,

Email: yaylacis@hotmail.com

Telefon: (+90)0506-287-9796

Editorial Office – Journal of Human Rhythm

Responsible Editor: Ramazan Akdemir – Tıp Fakültesi Morfoloji Binası, Kat: 4, Korucuk, Adapazarı, Sakarya, 54290, Turkey. E-mail: manuscriptjhr@gmail.com ISSN: 2149-455X

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Genel Bilgiler

Journal of Human Rhythm uluslararası bir dergidir. Gözlemsel çalışmalar, deneysel araştırmalar, klinik araştırmalar, vaka raporları, Tıptaki simgeler, uzman konsültasyonları, editöre mektup ve incelemeler de dahil olmak üzere tıbbın tüm alanlarından orijinal, hakemli dergileri üç ayda bir yayımlanır.

Journal of Human Rhythm'e gönderilen makaleler başka bir yere sunulmamalıdır. Tüm yazıların yayınlanmadan önce ayrıntılı bir dil ve biçim kontrolü yapılmıştır. Eğer yazılar yazarlara bilgi için uygun değilse ve aynı zamanda dil düzenlemeye ihtiyaç duyarsa, ilgili yazara geri gönderilir. İnsan vücudu üzerindeki fizyoloji inceleyen, mevsimsel ve diğer ritmik değişikliklerin organ sistemlerine etkilerini içeren yazılar öncelikle kabul edilmektedir.

Dergiye gönderilen tüm yazılar, 6 haftada karara varılır.

Yeni ve düzeltilmiş yazılar ve yazı işleri bürosuna yazışmalar için adres:

Makale Ofisi - İnsan Ritim Dergisi

Editör Şef: Ramazan AKDEMİR - Tıp Fakültesi Morfoloji Binası, Kat: 4, Korucuk, Adapazarı, Sakarya, 54290, Türkiye.

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Etik İnsanları ilgilendiren tüm çalışmalar, çalışmanın yapıldığı yerdeki etik kurullarının onayına ve tüm kişilerin bilgilendirilmiş onamlarına ihtiyaç duyar.

Dergi Makale Bölümleri

Editörden: Editör 1.500 kelimeyle ve 20 referansla sınırlıdır ve yayınlanan verilere dayanarak yazarın kararını verir.

Orijinal Araştırma Yazısı: Orijinal veya klinik bilimsel bulguları bildiren makale 4.000 kelimeyi, altı şekil veya tabloyu geçmemeli ve 40'dan fazla referans içermemelidir. Türkçe ve İngilizce özet 250 kelimeyi geçmemelidir. Tüm özetler amaç, materyal ve method ve sonuç olarak yapılandırılmalıdır.

Uzman Danışmanlığı: Bu, bir öğretim amacı ile yazılmış ve hastanın klinik karar verme ve tedavisi ile ilgili açık görüşler sunan vaka raporudur. Orijinal bilimsel makalelerin gerekliliklerine uymalıdır.

Görüş: Yazarın herhangi bir konu, prosedür veya tedavide speküle edileceği şekilde editörler kadar yer verilen görüşlerdir.

Vaka Raporları: Klinik uygulamayla ilgili belirli noktaları gösteren ve tartışan vaka raporları yayınlanacaktır. Makaleler resim gibi herhangi bir kanıt içermez veya benzeri raporlar yayınlanmaz. Olgu sunumlarında en fazla üç yazar, 1,500 kelime, 10 referans ve 2 rakam ve / veya tablo bulunmalıdır. Bir özet (150 kelimeye kadar) sağlanmalıdır.

Makale İncelemeler: Makaleleri, alanında uzman kişiler tarafından tartışılan genel tıbbi bir sorunla ilgilidir. Konu, geniş bir okuyucu kitlesine ilgi duymalı ve önemli tıbbi sonuçları içermelidir. Yazarlar konuyu tarihsel bir perspektiften ele almalı, ancak incelemenin kapsadığı alanda son gelişmelere öncelik vermelidir.

Tıpta Görüntüleme: Bu kategori, elektrokardiyogramlar, ekokardiyogramlar, x ışınları, taramalar veya patoloji örnekleri gibi açıklayıcı tıbbi görüntüler içindir. Resim, en fazla 250 kelime olmalıdır.

Editöre Mektup: Journal of Human Rhythm, son altı ay içerisindeki mektupları kabul eder. Mektuplar çift aralıkla yazılmalı ve 600 kelimeyi ve altı referans uzunluğunu geçmemelidir. Bütün yazarlar mektubu imzalamalıdır.

Kitap Eleştirileri: Journal of Human Rhythm tıp alanındaki seçili kitapları inceler. Kitap rewievları yazar tarafından Journal of Human Rhythm Editorial Office'e gönderilmelidir.

Makale hazırlama: Tüm yazılar, http://www.icmje.org/ adresinde (Ekim 2004'de güncellenir) bulunan Uluslararası Tıp Dergisi Editörleri Kurulu tarafından "Biyomedikal Dergilere Sunulan Yazıların Tekdüzen Gereksinimleri" nde açıklanan şekilde hazırlanmalı ve sunulmalıdır. Buna ek olarak, yazarlar sistematik incelemeler ve meta-analiz raporlarını hazırlarken PRISMA Beyanına (http:// www.prisma-statement.org) danışmalıdırlar ve CONSORT Bildirgesi (http://www.consort-statement.org) randomize kontrollü çalışmaların raporlarının hazırlanmasında kullanılmaktadır.

Metin, referanslar, fi gürler, görüntüler ve tablolar dahil olmak üzere tüm yazılar İngilizce / Türkçe olarak 1 kopyasını e-posta adresine gönderilmelidir. İngilizce yazılar için Türkçe özet ve Türkçe yazılar için İngilizce özet gerekmektedir.

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Makale, iki taraflı, her iki tarafa en az 2.5 cm kenar boşluğu ile klavye ile yazılmış olmalıdır. Makaleler, (1) başlık sayfası, (2) özet (veya vaka raporları için özet), (3) metin, (4) uygun alıntılar alındığında, (5) tartışılan konular, (6) referanslar, (7)) başlıkları ve şekiller olan tablolar ve rakamlar.

Yazarlık ve Telif Hakkı: Yazarlar, yazar olarak listelenen tüm kişilerin yazılarını hazırlamaya katkıda bulunduklarını ve listelenen yazarlardan başka hiçbir kişi veya kişinin hazırlanmasında önemli katkıda bulunmadığını şart koşan, tüm yazarlar tarafından imzalanmış ayrı bir kapsam mektubu sunmalıdır. Yazarlar, yayına kabul edilen makalelerin telif hakkı Canadian Society for Clinical İnvestigation'a aktarılmalıdır. Yayınlanan makalelerin giriş mektubu önceden basılmış materyal veya konuyu açıklayan örnekleri tanımlamaya izin veren kelimeleri içermelidir. Giriş yazısı, basım masrafl arının kabul edildiğini kabul etmeli, üç (3) yorumcu önermeli ve telif hakkının CIM'e imzalandığına dair anlayışa sahip olduğunu kabul etmelidir. Klinik Araştırmalar Etik kurula uygun olmayan insanlar üzerinde yapılacak olan klinik çalışma yayına kabul edilmeyecektir. Hayvanlar üzerinde yapılacak olan çalışmalar hayvan etik kurulundan geçmeden yayınlanamaz.

Özerklik ve gizlilik: Hastaların onamı alınmadan özeli ifşa edilmemelidir. Hastanın adı ve dosya numarası gibi kimlik bilgileri yazılmamalı, fotoğraf ve soy ağacı gibi bilgiler tıbbi gereklilik olsa dahi hasta veya velisinin onamı olmadıkça basılmamalıdır. Aydınlatılmış onamda hasta ile ilgili bilgilerin basılmasının onayı yer almalıdır.

Başlık Sayfası (Sayfa 1, ancak numara verme): Başlık sayfası 50 karakterden daha kısa bir kısa başlık, yazarların tam ve soyadları, ünvanları, çalıştıkları hastaneler ve akademik ünvanları içermelidir. Yazışmalar için adres değişikliği olmuşsa son adreste yazarın tam adı, adresi, telefon, faks numarası ve e-posta adresi yeniden yazışma adresine gönderilmelidir.

Sonraki Başlıklar: Sonraki başlıklar 2-6 kelime arasında ilk sayfada olmalıdır. ÖZET (Sayfa 2) Orijinal bilimsel makalelerin yazarları, aşağıdaki başlıklar altında en fazla 250 kelimeden oluşan bir özet sunmalıdır: Amaç (çalışma gerekçesini açıklayın), Yöntemler ve Sonuçlar (yöntemlerin kısa açıklaması ve önemli sonuçların sunulması), Tartışma (konu ile ilgili bilgileri destekleyen iddialar).

Abstract (Page 2): Olgu sunumları, ana noktaları 150 kelimeyle özetleyen bir özet oluşturmaktadır. Özette referans kullanmayın ve kısaltmalar fazla sayıda kullanmayın. **Anahtar Kelimeler**: En fazla 6 anahtar kelime olmalıdır.

Metin: Metin yeni bir sayfada başlamalı ve bölümler halinde düzenlenmelidir: Giriş, Yöntemler, Sonuçlar, Tartışma. Kalın, küçük harf ve italik başlıklar kullanarak uygun başlıkları ve alt başlıkları yapılmalıdır. Metinde ilk kez belirtildiği üzere şekil ve tabloları sayısal sırayla gösteriniz (Şekil 1, Şekil 2, Tablo 1). İlaçlar için jenerik ismi kullanılmalıdır. Hastalara baş harfl eri ile değil numaralandırma (örneğin hasta 4) ile adlandırılmalıdır. Kısaltmalar SI üniteleri ile tanımlanmalıdır. Kan basıncı mm Hg olarak verilmelidir. Makale sonuna referanstan önce ilaç, ödenek, ekipman desteklerinin ayrıntıları yazılmalıdır.

Çıkar Çatışması: Yazarlar arasında fi kir ayrılığı varsa belirtilmeli yoksa "çıkar çatışması yoktur" yazısı eklenmelidir.

Referanslar: Metin içindeki referanslar Kaynaklar metinde göründükleri gibi sıralı olarak numaralandırılmalıdır. Metindeki referans numaraları üst yazı olarak (parantez içermez) verilmelidir. Referans listesindeki referanslar Index Medicus'un Ulusal Tıp Kütüphanesi stiline göre süreli yayınların başlıklarını kısaltın. Her referansta her yazarın belirtilmesi gerekir. Yazarın baş harfl erinden sonra periyodları kullanmayın.

Dergi Makaleleri – Örnek: Soyadı RS, Soyadı FW, Soyadı GR, Soyadı AJ. Makale başlığı. Kısaltılmış gazete başlığı 2008; 52: 228-34. Et.al'ı kullanın. referans dörtten fazla ada sahipse.

Kitapta Bölüm – Örnek: Soyad SY. Bölüm başlığı. In: Soyadı MM, ed. Kitap başlığı. Yayınevi, Şehir, 2008: 228-34. Özet / tamamlayıcı - Örnek Soyadı R, Soyadı F. Makale başlığı (soyut). Kısaltılmış gazete başlığı 1996; 52 yardımcı 3:48.

Şekiller: Şekil açıklamaları, ayrı sayfalarda çift aralıklarla yazılmalıdır. Rakamlarda görünen kısaltmalar her şeklin sonunda yazılmalıdır. Daha önce basılan herhangi bir materyal için yayıncılardan yazılı izin alınmalıdır.

Figürler: Figürler netlik için gerekli sayıyla sınırlandırılmalıdır. Resimler, tablolarda veya metinde verilen verileri taklit etmemelidir. Renkli olarak sunulan resimler renkli olarak basılacaktır.

Tablolar: Tablolar açıklayıcı olmalıdır ve veriler metni tekrar etmeyecek şekilde eklemelidir. Tablolar, tablonun numarası ve başlığı tablonun üstünde ve açıklayıcı notlarla birlikte ayrı sayfalara çift aralıklarla yazılmalıdır. Tablonun numaraları Arabic olmalı ve metinde sırayla numaralandırılmalıdır. Tabloda kullanılan kısaltmalar dipnot edilmelidir ve alfabetik olarak açıklanmalıdır.

Bütçe: Renkli yazdırma maliyetinin bir kısmı yazardan tahsil edilecektir. Yazarın maliyetleri, renk rakamlarının maliyeti ve yeniden yazdırma maliyetini içerir (asgari miktar elli tekrar baskıdır). Tekrarlayan basımlar için yazarlara fatura gönderilecektir. Sayfa ücreti yok.

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Makale sunumunun bir parçası olarak, eşlik eden bir mektupta şunları belirtmelidir:

1. Çalışmanın tasarımı ve yürütülmesi tüm yazarlar tarafından gerçekleştirilmeli,
2. Makale tüm yazarlar tarafından yazılmış, okunmuş ve onaylanmış olmalı,
3. Bu materyal daha önce veya kısmen yayınlanmamış olması ve başka yerlerde yayınlanması düşünülmediği,
4. Sayfa ücretlerinin kabul edildiğini kabul edildiği,
5. Üç (3) yorumcu önerilmesi,
6. Telif hakkının CIM'e imzalandığına dair bir anlayış olduğunun beyan edilmesi.
7. Çalışma ve olası çıkar çatışmaları için maddi destek açıklanması gerekmektedir.

Scope: Journal of Human Rhythm is an international journal. It publishes three months original, peer-reviewed articles from all areas of medicine Health Sciences including observational studies, experimental investigations, clinical trials, case reports, Images in Medicine, expert consults, letter to the editors and reviews. Papers submitted to Journal of Human Rhythm should not be submitted elsewhere. All manuscripts underwent a detailed language and format check before. If manuscript does not suitable for information for authors and also needs the language editing, sent back to the corresponding author. The manuscripts dealing with the biological rhythms in human body, effects of seasonal and other rhythmic changes on organs systems are preferentially accepted.

All manuscripts submitted to the journal reach the final decision within 6 weeks.

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Ethics: All Studies involving human subjects need their written local ethical committee approval where the study is performed and informed consent from the all subjects.

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RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

The relationship between myocardial viability and plasma NT-proBNP levels

Miyokard canlılığı ve plazma NT-proBNP düzeyleri arasındaki ilişki

Kudret Keskin MD[1], Deniz Güzelsoy MD[2]

[1]Health Sciences University, Şişli Hamidiye Etfal Education and Research Hospital, Department of Cardiology

[2]Istanbul University-Cerrahpaşa, Institute of Cardiology

Corresponding author: Kudret Keskin, MD

Şişli Hamidiye Etfal Education and Research Hospital, Department of Cardiology, Cardiologist

Sisli 34377 Istanbul/TURKEY

Phone: 0090(505)401-5847

e-mail: keskinkudret@yahoo.com

ORCID

Kudret Keskin https://orcid.org/0000-0002-9049-1530

Deniz Güzelsoy https://orcid.org/0000-0003-0372-16XX

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ABSTRACT

Aim: There is no biochemical marker that indicates myocardial viability in the late phase after myocardial infarction. The aim of our study was to identify whether plasma NT-proBNP levels indicate the presence of viable myocardium after myocardial infarction.

Material and Methods: Patients with myocardial infarction and left ventricular ejection fraction of less than 45% were included in the study. Exercise or pharmacological myocardial perfusion scintigraphy was performed to investigate viability in the infarction region. The left ventricle was divided into 19 segments where the necrotic area and viable myocardium within it was measured. Blood samples for NT-proBNP measurement were obtained from all patients on the same day scintigraphy performed.

Results: A total of 60 patients were included in the study (10 females, 50 males, mean age 62 ± 9 years). 48 (80%) patients underwent exercise scintigraphy. The mean exercise time was 7.1 ± 2.3 minutes. The infarct area was located in anterior segments in 16 patients, inferior in 25, and in both locations in 19 patients. The mean left ventricular ejection fraction was 36 ± 8%. There was a negative correlation between left ventricular ejection fraction and serum NT-proBNP levels ($r = -0.03$ $p < 0.01$). On the other hand, there was no correlation between plasma NT-proBNP levels and the presence or extent of viable myocardium within the necrotic area ($P = 0.8$).

Conclusion: There was no correlation between plasma NT-proBNP levels and the presence of viable myocardium in the infarct zone in patients with myocardial infarction.

Keywords: myocardial infarction, viable myocardium, NT-proBNP, myocardial perfusion scintigraphy

ÖZET

Amaç: Miyokard enfarktüsü sonrasında enfarkt bölgesindeki rezidü miyokard canlılığını gösteren herhangi bir biyokimyasal parametre bulunmamaktadır. Çalışmamızda miyokard enfarktüsü sonrası dönemde serum NT-proBNP seviyeleri ile miyokard canlılığı arasındaki ilişkiyi araştırdık.

Metod: Çalışmaya miyokard enfarktüsü geçiren ve sol ventrikül ejeksiyon fraksiyonu %45'in altında olan hastalar alındı. Egzersiz ya da farmakolojik miyokard perfüzyon sintigrafisi yapılarak enfarktüs bölgesinde iskemi ve canlılık araştırıldı. Sol ventrikül toplam 19 segmente bölünerek ilgili nekrotik ve canlı bölgelerin alanı hesaplandı. Serum NT-proBNP ölçümü için tüm hastalardan işlem sabahı serum örnekleri alındı.

Bulgular: Çalışmaya toplam 60 hasta alındı (10 kadın, 50 erkek, ortalama yaş 62±9 yıl). Hastaların 48'i (%80) egzersiz yaptı. Ortalama egzersiz süresi 7,1±2,3 dakika idi. Enfarkt alanı 16 hastada anterior, 25 hastada inferior ve 19 hastada ise her iki bölgedeydi. Hastaların ortalama sol ventrikül ejeksiyon fraksiyonu 36±8 olarak hesaplandı. Sol ventrikül ejeksiyon fraksiyonu ile serum NT-proBNP arasında negatif korelasyon tespit edildi ($r=-0.03$ $p<0.01$). Öte yandan serum NT-proBNP seviyeleri ile enfarkt bölgesindeki canlı ya da iskemik alan arasında bir korelasyon tespit edilmedi ($P=0,8$ ve $0,7$).

Sonuç: Miyokard enfarktüsü geçirmiş kişilerde enfarkt bölgesindeki canlı doku alanı ile serum NT-proBNP seviyeleri arasında ilişki saptanmadı.

Anahtar kelimeler: miyokard enfarktüsü, miyokard canlılığı, NT-proBNP, miyokard perfüzyon sintigrafisi

Introduction:

In patients with myocardial infarction (MI), left ventricular function is one of the most important factors for prognosis.[1] Various studies has shown that impaired left ventricular function may improve after revascularization.[2] However, it is not always easy to decide whether those with severe LV dysfunction will benefit from coronary revascularization. Therefore, myocardial viability should meticulously be demonstrated before revascularization in such patients. In order to assess myocardial viability in the necrotic area, several imaging modalities like dobutamine stress echocardiography, myocardial perfusion scintigraphy, positron emission tomography, and cardiac magnetic resonance imaging have been used for several years.[3,4] On the other hand, apart from imaging studies, there has been no biochemical marker capable of demonstrating the viable tissue in the late phase after myocardial infarction.

Natriuretic peptides (NP) are neurohormones that are secreted by the ventricular myocardium as a response to pressure and volume overload[5]. BNP is the biologically active form which is

then cleaved into the inactive form called NT-proBNP.[6] There are several areas where natriuretic peptides are used. One of them is heart failure.[7] It is used to diagnose, follow-up and guide heart failure therapy[8]. As new researches are being conducted new indications arise. Today, besides heart failure, NP's are investigated in clinical situations like diastolic dysfunction, valve diseases, pulmonary hypertension and acute coronary syndromes.[9]

The purpose of the study was to investigate whether serum NT-proBNP levels indicate the presence of viable myocardium after MI. We planned to detect post infarction myocardial viability by myocardial perfusion scintigraphy and investigate if there is a relationship between viability and the serum NT-proBNP levels.

Methods:

This prospective study group was composed of patients who had applied to our outpatient clinic with a history of myocardial infarction. All patients had some angina complaints and myocardial perfusion scintigraphy imaging was planned to search ischemia by their own physicians. Patients with left ventricular ejection fraction over 45% (assessed by echocardiography), morbid obesity (body mass index > 35 kg/m^2), chronic renal failure (estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2), nonischemic left ventricular dysfunction, chronic obstructive lung disease, severe valvular heart disease, previous stroke, chronic inflammatory disease, and liver dysfunction were excluded from the study. Local ethics committee approved the study and written informed consent was obtained from all patients.

Echocardiography was performed in left lateral decubitis position and standard left parasternal long axis, short axis, apical four chamber and five chamber views were obtained in all patients (Acuson Sequoia, Siemens Medical Solution, Mountain view, CA, USA). eGFR was estimated using the formula of Modification of Diet in Renal Disease (MDRD) as previously defined.[10] Serum samples for measuring NT-proBNP, BUN, creatinine, fasting blood glucose, lipid profiles and complete blood count were taken after 12 hours fasting in the morning of myocardial scintigraphy day. Routine biochemical parameters were studied with commercially available kits. Plasma NT-proBNP samples were collected to a heparin containing Vacuette tubes. After waiting for 5 minutes in the room temperature, all blood samples were centrifuged at 3500 rpm for 10 minutes. We particularly paid attention to prevent hemolysis and samples were stored in -80 C until analysis. After all samples were

collected, plasma NT-proBNP levels were measured using chemoluminescence method with a Immulite 1000-Siemens device (Siemens medical solutions diagnostics, Deerfield, USA). The results were reported as pg/ml.

Tc-99m-Sestamibi Imaging Protocol

Patients discontinued their medications that can effect exercise testing 48 hours before according to the current guidelines. Patients performed exercise testing after a 3-hour fasting and they were not allowed to drink tea/coffee or smoke. All patients underwent a standard exercise test using the Bruce protocol. Blood pressure, heart rate and 12-lead ECG were recorded at rest, during each stage of exercise and at peak exercise and for at least 5 minutes after recovery. The electrocardiogram and ST segment deviation were continuously displayed and measured automatically by a computer assisted system. 10 mCi Tc-99 m-sestamibi was given intravenously to all patients in the maximum exercise. Exercise images were taken 45 minutes after the end of exercise. In patients who were unable to exercise, the test was performed using dipyridamole in which 0.56 mg/kg dipyridamole was administered intravenously and rest perfusion images were acquired in the same manner from both the exercise and dipyridamole patients. For imaging; low energized, large surface, two gamma cameras were placed with 90 degree angle to each other and parallel perforated collimator was used (Apex SPX Cardial Elscint Israel).

Assessment of images

Short axis, horizontal long axis and vertical long axis images were created through computer programs from tomographic images that was acquired by single photon emission computed tomography. Basal, mid and apical segments were evaluated in the horizontal planes, septum apical and lateral walls were evaluated in the long axis vertical planes, anterior, apical and inferior walls were evaluated in the long axis horizontal planes. Perfusion was considered normal when all myocardial sections hold homogenous material in the stress images. If any perfusion defect occurred after stress in any myocardial segment and disappeared after rest images, it was considered as transient perfusion defect, ischemia. If the perfusion defect persisted in the rest images after stress images, it was considered as MI or scar. If the amount of material which is held in the constant defect segments was higher than 40% of normal segments in semiquantitive evaluation of if the defect was lower than 60% , ,t was considered

as viable tissue in the myocardial infarction site. If the perfusion defect which was clear in stress images becomes nearly normal in rest but persisted, then it was considered as ischemia in the myocardial infarction site.

Statistics

The continuous variables were expressed as mean and standard deviation. Categorical variables were reported as number and percentages. The Kolmogorov-Smirnov test was used to assess the distribution of the continuous variables. Categorical data was compared by using the chi-square test. The relation between two quantitive variables was compared with Pearson correlation analysis. A p value of <0.05 was considered to be statistically significant.

The statistical analysis was performed using SPSS version 16 (SPSSInc., Chicago, IL, USA)

Results:

The study included 60 patients (10 women, 50 men, mean age 62±9.7 years). Baseline clinical characteristics of the study patients are presented in Table 1. 47 (78%) patients had hypertension, 27 (45%) had diabetes mellitus. Mean LV ejection fraction was 36±8%. 48 (80%) patients underwent exercise scintigraphy. The mean exercise time was 7.1 ± 2.3 minutes. Plasma NT-proBNP levels ranged from 150 to 13584 pg/ml (mean: 1622±2751 pg/ml). The localization of infarction was in anterior segments in 16(26%) patients, inferior in 25 (41%) and both locations in 19 (31%) patients respectively.

Myocardial perfusion scintigraphy results are presented in Table 2. The term anterior and inferior MI represents the patients who had necrotic tissue in both areas. Viable tissue within the infarcted region was detected in 38(63%), ischemia within the necrotic area in 12 (20%), ischemia in 5(8%) and total infarction was seen in 5(8%) patients.

Table 3 shows the correlation analysis between NT-proBNP and several other parameters. There was a statistically significant negative correlation between plasma NT-proBNP levels and LV ejection fraction and exercise duration (r=-0.39, P<0.002 and r=-0.40, p=0.005 respectively) (Figure 1-2). However, there was no significant correlation between the presence or the degree of myocardial viability and plasma NT-proBNP levels (all p>0.05).

Discussion:

In our study, we did not find any relationship between plasma NT-proBNP levels and the extent of viable myocardial tissue in the infarct zone in patients with previous myocardial infarction.

In fact, the role of natriuretic peptides goes beyond the diagnosis and treatment of heart failure. Recent studies have demonstrated that B-type natriuretic peptide (BNP) is secreted from hypoxic myocardium, even in the absence of left ventricular dysfunction and thus it might be a marker of myocardial ischemia[11]. Moreover, NP's have been shown to predict adverse cardiovascular outcomes in patients with acute myocardial infarction[12]. Therefore, it has been concluded that ischemic heart disease affects cardiac endocrine function independent of left ventricular function. A strong correlation is demonstrated between NT-proBNP and extent of reversible ischemia even in patients with normal LV functions[13]. This interaction between coronary artery disease and BNP/NTproBNP has been attributed to increased BNP gene expression and release by cardiomyocytes in response to ischemia[11]. So it is suggested that ischemia itself, rather than changes in left ventricular wall stress secondary to ischemia, promotes the release of BNP, but the responsible mechanisms still remain to be elucidated.

There are numerous studies conducted in patients with either acute or chronic ischemia showing a positive correlation between natriuretic peptides and the severity or extent of coronary artery disease.[14] Each study had a different methodology. For instance Sarullo et al found a relationship between serum BNP levels and residual ischemia after reperfusion therapy is ST elevation MI[15]. In this study, patients with protected LVEF (>40%) were investigated in the first month after MI and serum NT-proBNP levels and SPECT findings were compared. However, in our study the average time after MI was not homogenous and LVEF was lower. Zaid et al found a positive correlation between serum BNP levels and extent of ischemia by using the exercise SPECT[16]. Likewise, this study was conducted in patients with normal LV function. However, in our study, we included patients with moderate to severe LV dysfunction with different time periods from the infarction. Probably at this level of LV dysfunction with some degree of remodeling, the total performance of LV seems to be the main factor affecting the NT-proBNP levels. Trying to detect a varying degree of viable area in a big infarcted territory and LV dysfunction is out of proportion to the degree of NT-proBNP levels.

Limitations of the study

Small sample size and being a single center study were the main limitations of this study. If we had conducted the study in a much larger population, we might have found a correlation between plasma NT-proBNP levels and amount of viable myocardium within the infarct territory. In addition, Tc-99 m-sestamibi was the agent used for viability study. However, Thallium-201 would be more suitable for viability assessment. Finally, this study did not include the data regarding the occlusion in the infarct related artery and also we did not report viability in terms of percentages.

Conclusion:

There is no relationship between myocardial viability in the infarcted area and plasma NT-proBNP levels.

Acknowledgements: None

Conflict of interest: None

Table 1: Baseline clinical characteristics of the study patients

Patients (n=60)	**(Mean ± SD) or (%)**
Age (years)	62±9.7
Gender (female)	10 (16%)
Hypertension	47 (78%)
Diabetes mellitus	27 (45%)
Hyperlipidemia	45 (75%)
LVEF (%)	36±8
BUN (mg/dl)	19±5
Creatinine (mg/dl)	0.9±0.2
NT-proBNP (pg/ml)	1622±2751 (100-13854)
Anterior infarction	16 (26%)
Inferior infarction	25 (41%)
Anterior + inferior infarction	19 (31%)

Abbreviations: BUN: blood urea nitrogen; LVEF: left ventricular ejection fraction

Table 2: Myocardial perfusion scintigraphy findings

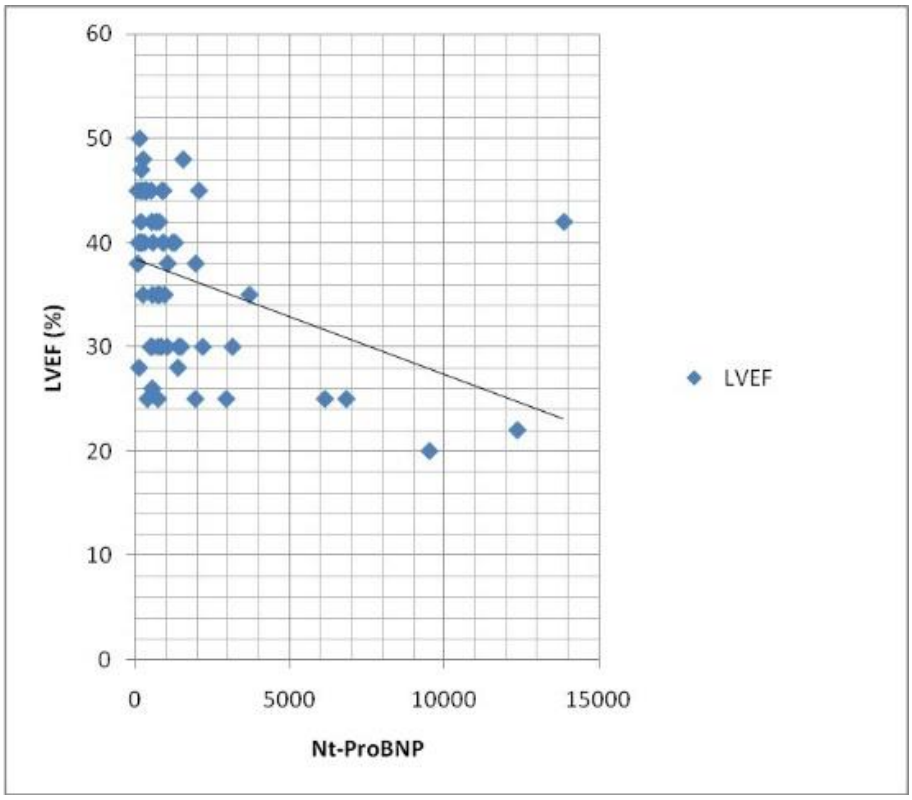
	Number of patients (%)
Viable tissue in the infarction area	38 (63%)
Ischemia in the infarction area	12 (20%)
Pure necrosis	5 (8%)
Ischemia	5 (8%)

Table 3: Correlation between NT-proBNP and several other parameters

	R	P
Age	0,166	0,208
BUN	*0,267*	*0,041*
Creatinine	-0,102	0,441
LVEF	*-0,392*	*0,002*
Ischemia within the infarction area	0,040	0,764
Viable tissue within the infarction area	0,025	0,853
Pure necrosis	-0,013	0,923
Exercise duration (minutes)	-0,404	*0,005*

Abbreviations: BUN: blood urea nitrogen; LVEF: left ventricular ejection fraction

Figure 1: Correlation between NT-proBNP and left ventricular ejection fraction



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RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

Klinik Takiplerinde Enfeksiyöz ve Non-Enfeksiyöz Sebepli Ateş Tespit Edilen Hastalarda Komorbid Hastalıkların Karşılaştırılması

The Comparison of Comorbid Diseases in Patients with Infectious and Non-Infectious Causes of Fever in Clinical Follow-up

Cengiz Karacaer

Department Of Internal Medicine, Sakarya University Training and Research Hospital, Sakarya, Turkey

Corrresponding Author: Cengiz Karacaer.

Sakarya Training and Research Hospital Internal Medicine Clinic, Adnan Menderes St. (Sağlık St.) No: 195 Adapazarı Sakarya, Turkey

Tel: +905057400168

Email: karacaerc@yahoo.com

ORCID

Cengiz Karacaer https://orcid.org/0000-0001-6951-899X

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ÖZET

Amaç: Kliniğimize herhangi bir nedenle yatırılan enfeksiyon ya da enfeksiyon dışı ateşi olan hastalarda komorbid hastalıkların dağılımını incelemeyi amaçladık.

Materyal ve Metod: Çalışmamızda Sakarya Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi (SÜEAH) İç Hastalıkları Kliniğine son 5 yıl içerisinde herhangi bir nedenle yatıp takiplerinde ateş tespit edilip kan kültürleri alınan hastaların retrospektif olarak dosyaları taranarak klinik ve laboratuvar verileri kayıt altına alındı. Hastaların demografik verileri, antibiyoterapiler, komorbid hastalıkları ve kullandıkları ilaçları retrospektif dosya verilerinden kaydedildi. Çalışma verileri MS excel dosyasına alındıktan sonra SPSS 15 versiyon ile istatistik verileri hesaplandı. $p< 0.05$ altında olanlar anlamlı kabul edildi.

Çalışma, Sakarya Üniversitesi Tıp Fakültesi Etik Kurulu tarafından onaylandı (71522473/050.01.04/47).

Bulgular: Çalışmaya 501 hasta alındı. 325 hasta non-enfeksiyöz (grup I) ve 176 hasta enfeksiyöz grupta (Grup II) idi. Grup I/Grup II karşılaştırıldığında 113/82 diyabetes mellitus, 79/39 hematoloji dışı malignite(HDM), 67/16 anemi, 61/44 kronik böbrek yetmezliği(KBY), 52/38 hipertiroidi, 26/19 serebrovasküler hastalık(SVH), 22/4 gastrointestinal sistem kanaması,16/6 hematolojik malignite(HM)tespit edildi.

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Tartışma: En fazla non enfeksiyöz sebep Diyabetes Mellitus, Hematoloji dışı maligniteler(HDM) ve anemi idi. Enfeksiyöz hastalarda ise en fazla komorbidler diyabetes mellitus, KBY ve HDM idi. Diyabetes Mellituslu hastalarda ateş hem enfeksiyöz hem de non enfeksiyöz tablolarda sık görülen bir komorbiditedir. Diyabetes Mellitus ve KBY enfeksiyonun en sık görüldüğü bulgudur. Bu hastalarda enfeksiyon kontrol önlemleri konusunda daha dikkatli olunmalıdır.

Anahtar kelimeler: Ateş, Komorbidite, Enfeksiyon

ABSTRACT

Aim: We aimed to investigate the distribution of comorbid disease in patients with infectious or non-infectious fever in our patients hospitalized due to fever with unknown cause.

Methods: The study was performed retrospectively and the clinical and laboratory data of the patients who were admitted to the internal medicine clinic of Sakarya University Training and Research Hospital (SUTRH) due to fever in the last 5 years were recorded. Patients who had fever and blood culture were included in the study. Antibiotherapies and comorbid diseases were taken from retrospective data. The drugs they used were recorded. After the data were transferred to MS excel file, statistical data were calculated with SPSS 15 version. P <0.05 was considered significant.

The study was approved by Sakarya University Faculty of Medicine Ethics Committee (71522473/050.01.04/47).

Results: The study included 501 patients. 325 patients were non-infectious (group I) and 176 were in the infectious group (Group II). When Grup I/Grup II compared, it was found that;113/82'ü diabetes mellitus, 79/39 non-haematological malignancies(NHM), 67/16 anemia, 61/44 cronic renal failure(CRF), 52/38 hyperthyroidism, 26/19 cerebrovasculer diseases(CVD), 22/4 gastrointestinal systems hemoragy,16/6 haematological malignancies (HM).

Discussion: The most non-infectious causes were diabetes, non-hematological malignancies and anemia. In infectious patients, the most common comorbidities were diabetes mellitus, cronic renal failure(CRF) and non-hematologic malignancy(NHM). Fever in patients with diabetes mellitus is a frequent comorbidity in both infectious and non-infectious cases. Diabetes mellitus and CRF infection are the most common findings. In these patients, we should be more careful about infection control measures.

Key words: Fever, Comorbidity, Infection

Giriş:

Ateş, vücutta bireyin vücut sıcaklığının ortalama aralığının üzerine çıkmasıdır ve çoğu kez enfeksiyonun karakteristik bir özelliğidir, fakat aynı zamanda otoimmün ve otoenflamatuar hastalıklar gibi bir dizi bulaşıcı olmayan hastalıkların belirtisidir.[1] Hastanın durumunda kritik bir değişiklik olması durumunda hekimi uyaran genellikle ateştir. Basit ve yaygın olarak uygulanan bir ölçüm metodu olsa da , son zamanlarda termoregülasyonda karmaşık fizyolojik bir sürecin işlediği anlaşılmıştır. Proinflamatuar sitokinler PG-E2 oluşumunu uyarır ve ateşin

başlamasına katkıda bulunur.[2] Bu pirojenik sitokinler tüm ateş vakalarını açıklayamadığı için diğer nörolojik ve metabolik yolakların da etkilenmesi muhtemeldir.[3]
Semptomların lokalizasyonu, süresi, eşlik eden durumlar, seyahat, hayvan teması, immünsüpresyon durumu, ilaç ve intoksikasyon durumu, antibiyotikler sorgulanmalıdır.

Bu çalışmada amacımız, herhangi bir nedenle iç hastalıkları kliniğimize yatan hastalarımızda enfeksiyon ya da non-enfeksiyöz ateşi olan hastalarda komorbidlerin dağılımını incelemeyi amaçladık.

Metod:

Çalışma Sakarya Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi (SÜEAH) iç hastalıkları kliniğine son 5 yıl içerisinde yatarak takip edilen ve ateşi olan hastalar retrospektif olarak dosya taranarak klinik ve laboratuvar verileri kayıt altına alındı. Çalışmaya ateşi olup kan kültürü alınan hastalar alındı. Hastaların aldıkları antibiyoterapiler, komorbid hastalıkları retrospektif dosya verilerinden çıkarıldı. Kullandıkları ilaçlar kaydedildi. Çalışma verileri MS excel dosyasına alındıktan sonra SPSS 15 versiyon ile istatistik verileri hesaplandı. $p< 0.05$ altında olanlar anlamlı kabul edildi.

Çalışma, Sakarya Üniversitesi Tıp Fakültesi Etik Kurulu tarafından onaylandı (71522473/050.01.04/47).

Bulgular: Çalışmaya 501 hasta alındı. 325 hasta non-enfeksiyöz (grup I) 176 hasta enfeksiyöz grupta (Grup II) idi. Grup I/Grup II karşılaştırıldığında 113/82 diyabetes mellitus, 79/39 hematoloji dışı malignite(HDM), 67/16 anemi, 61/44 kronik böbrek yetmezliği(KBY) , 52/38 hipertiroidi, 26/19 serebrovasküler hastalık(SVH), 22/4 gastrointestinal sistem kanaması,16/6 hematolojik malignite(HM), 12/2 pankreatit, 11/2 subklinikhipotiroidi, 10/2 ilaç intoksikayonu, 5/2 romatoid artrit(RA), 3/4 diyabetik ketoasidoz(DKA), 3/0 myokard infarktüsü(MI), 3/0 sistemik lupus eritematozus(SLE), 2/0 gut, 2/0 vaskülit, 2/0 epilepsi, 2 pulmoner tromboemboli(PTE), 2 inflamatuar barsak hastalığı(IBH), 1/0 erişkin still hastalığı(ESH), 1/0 ailesel akdeniz ateşi(FMF), 1/0 Behçet, 1/0 sarkoidoz, 1/0 dermatoyozit, 1/0 adrenal yetmezlik, 0/1 hemolitik üremik sendrom(HUS), 1/0 immün trombositopenik purpura(ITP) olarak bulundu.

Tablo 1:Enfeksiyöz ya da non-enfeksiyöz ateşli hastalarda tanılar

	Grup 1	**Grup 2**	
TANILAR	**(n=325)**	**(n=176)**	**p**
Diabetes Mellitus	113	82	**0,01**
Kronik Böbrek Hastalığı	61	44	0,10
Hipertiroidi	52	38	0,14
Anemi	67	16	**0,001**
Hematoloji dışı malignite	79	39	0,65
Gis kanama	22	4	**0,03**
Serebro Vazküler Hastalık(SVH)	26	19	0,32
Hematolojik Malignite	16	6	0,50
Pankreatit	12	2	0,15
Subklinik Hipotiroidi	11	2	0,15
İlaç intoksikasyonu	10	2	0,23
Pulmoner Tromboemboli(PTE)	2	0	0,54
Gut	2	0	0,54
Myokard Enfarktüsü(MI)	3	0	0,55

Tablo 2:Enfeksiyöz ya da non-enfeksiyöz ateşli hastalarda tanılar

TANILAR	**Grup 1 (n=325)**	**Grup 2 (n=176)**	**p**
Vaskülit	2	0	0,54
Behçet Hastalığı	1	0	1
Dermatomiyozit	1	0	1
Hemolitik Üremik Sendrom(HÜS)	0	1	0,35
İmmün Trombositopenik Purpura(ITP)	1	0	1
İnflamatuar Barsak Hastalıkları(IBH)	2	0	0,54
Erişkin Still Hastalığı(ESH)	1	0	1
Epilepsi	2	0	0,54
Familial Mediterranian Fever(FMF)	1	0	1
Sistemik Lupus Eritematozus(SLE)	3	0	0,55
Romatoid Artrit(RA)	5	2	1
Sarkoidoz	1	0	1
Diyabetik Ketoasidoz(DKA)	3	4	0,24
Adrenal yetmezlik	1	0	1

Tartışma:

Ateş genellikle enfeksiyon gibi bir uyarana sistemik enflamatuar cevap olarak oluşur. Ateşin varlığı dehidratasyon, artmış metabolik hız ve oksijen tüketimi gibi potansiyel metabolik sonuçlarla ilişkilidir. Ateş varlığının uzaması halinde beslenme ihtiyacı artabilir ve beslenme yetersizliği gelişebilir.[4] Ateşe neden olan hastalıklar coğrafi bölgeye, hastanın yaşına, sağlık hizmetlerine ulaşma kolaylığına, ülkenin sosyoekonomik durumuna göre değişmektedir.[5] Ateş etiyolojisinin bulunması hikaye, fizik muayene, laboratuvar ve radyolojik değerlendirmelerden elde edilen sonuçların değerlendirilmesini içerir. Ateşte altta yatan hastalığı teşhis edebilmek için basamak tanısal testler uygulanmalıdır.[6] İlk başlangıçta; hemogram, periferik yayma, rutin biyokimyasal tetkikler, idrar analizi, kan kültürü, akciğer grafisi, idrar kültürü, abdominopelvik ultsanografi, bölgenin epidemiyolojik özelliklerine göre enfeksiyon serolojisi, birinci basamakta; ESH(Eritrosit sedimantasyon hızı), CRP(C-reaktif protein), RF(Romatoid faktör), ASO(anti-streptolisin O), CMV(sitomegalovirüs) IgM, EBV(epstain bar virüs) IgM, HBsAg(hepatit B yüzey antijeni, CK(kreatin kinaz), ANA(antinükleer antikor), ds-DNA, TSH(tiroid stümulan hormon), PPD(purifiye protein derivesi), Brusella aglutinasyonu, Salmonela aglutinasyonu, gayta ve balgam kültürü, balgam ve gayta mikroskobisi, balgamda AARB(asit alkole dirençli basil), ikinci basamakta; Serum protein elektroforezi, ACE(angiotensin döünüştücü enzim), ANCA(anti nükleer sitoplazmik antikor), IgG, IgA, IgM, ENA(ekstrakte edilebilir nükleer antijen) paneli, C3, C4, kriyoglobulin , T3, T4, Mikoplazma-Toksoplazma- Treponoma-Yersinia hücre kültürleri, lenf nodu biyopsisi ve kültürü, karaciğer biyopsisi, kemik iliği biyopsisi, temporal arter biyopsisi, tiroid biyopsisi, 24 saatlik idrarda VMA(vanilmandelik asit, tiroglobulin , antimikrozomal antikor, PSA(prostat spesifik antijen), HIV(insan immünyetmezlik virüsü), HCV(hepatit C virüs), plazma kortizolü, ekokardiyografi, abdomino-pelvik BT(bilgisayarlı tomografi), toraks BT, rektosigmoidoskopi, baryum enema, sinus grafisi, diş muayenesi, fundus muayenesi, lökosit sintigrafisi, üçüncü basamakta; Tüm biyopsiler, laparoskopi, laparatomi, endoskopik inceleme gibi tüm invaziv işlemler uygulanabilmektedir. [7-9]

Tüm çabalara rağmen bir grup hastada ateş nedeni ortaya konulamamaktadır. Yaşlılarda ateş etyolojisinde gençlerden farklı olarak infeksiyon ve malignite sıklığının arttığı bilinmektedir. Malignite kaynaklı ateş nedenleri arasında hem Hodgkin hem de non-Hodgkin lenfomalar en sık nedenlerden biri olarak bildirilmiştir. [10]

Çalışmamızda en fazla non enfeksiyöz sebep diyabetes mellitus, hematoloji dışı maligniteler(HDM) ve anemi idi. Enfeksiyöz hastalarda ise en fazla komorbidler diyabetes mellitus, KBH(Kronik Böbrek Hastalıkları) ve HDM idi. Diyabetes mellituslu hastalarda ateş hem enfeksiyöz hem de non enfeksiyöz tablolarda sık görülen bir komorbiditedir. Diyabetes mellitus ve KBY enfeksiyonun en sık görüldüğü komorbidlerdir. Bu hastalarda enfeksiyon kontrol önlemleri konusunda daha dikkatli olunmalıdır.

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RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

Temporal Artery Biopsy: Review of 36 Patients

Temporal Arter Biopsisi:36 Hastalık Seri

Özgür Altınbaş[1], Yüksel Dereli[2], Ömer Tanyeli[2]

[1] Duzce University, Medical Faculty, Department of Cardiovascular Surgery,Duzce

[2] Necmettin Erbakan University, Meram Medical Faculty, Deparment of Cardiovascular Surgery, Konya

Corresponding author: Özgür Altınbaş
Duzce University, Medical Faculty, Department of Cardiovascular Surgery, Duzce
Tel: 0505 657 05 77
Mail: ozgur_altinbas@yahoo.com

ORCID
Özgür Altınbaş https://orcid.org/0000 0002 6819 2454
Yüksel Dereli https://orcid.org/0000-0002-3794-1045
Ömer Tanyeli https://orcid.org/0000-0001-6275-7744

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ABSTRACT

Aim: Temporal arteritis is a systemic vasculitis that affects large and medium sized vessels. Vasculitis signs have to be shown for accurate diagnosis; hence temporal artery biopsy is still the gold standard for diagnosis. In this study, we evaluated the patients in whom temporal artery biopsies were performed.

Material Methods: In between September 2004 and June 2014, we peformed temporal artery biopsy in 36 patients, who had temporal arteritis complaints. Patients were retrospectively evaluated for their clinical properties, performed procedures and their results.

Results: Thirty-six patients were enrolled into study, who were referred to our clinic for temporal artery biopsy. Of these, 11 (30.5%) were male, 25 were female (69.5%) and mean age was 61.1 (range between 56-81) years. Mean erythrocyte sedimentation rate was 56.3 mm/hr (range between 51-130). In our study, 7 (19.4%) patients had concordant findings which were representative of temporal arteritis. As a complication, only one patient had ecchymosis on the right orbital region that lasted in one week.

Conclusion: Different results are published in the literature for positivity rates of temporal artery biopsies. A number of different factors such as atypical symptoms, skip lesions, suboptimal sampling and ongoing steroid treatment affect the results. Temporal artery biopsy is an easily-performed and reliable diagnostic method if only made after accurate clinical evaluation and if adequate sampling was made in early period.

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Key Words: Temporal artery biopsy, Temporal arteritis, Vasculitis

ÖZET

Amaç: Temporal arterit, büyük ve orta boy damarları etkileyen sistemik bir vaskülittir. Doğru tanı için vaskülit belirtileri gösterilmelidir. Bu nedenle temporal arter biyopsisi tanı için hala altın standarttır. Bu çalışmada temporal arter biyopsisi yapılan hastaları değerlendirdik.

Gereç ve Yöntemler: Eylül 2004-Haziran 2014 tarihleri arasında temporal arterit yakınması olan 36 hastanın temporal arter biyopsi işlemi yapıldı. Hastalar klinik özellikleri, uygulanan prosedürleri ve sonuçları için retrospektif olarak değerlendirildi.

Bulgular: Temporal arter biyopsisi için kliniğimize başvuran 35 hasta çalışmaya alındı. Bunlardan 11'i (% 30.5) erkek, 25'i kadın (% 69,5) ve yaş ortalaması 61.1 (56-81 arasında) idi. Ortalama eritrosit sedimentasyon hızı 56.3 mm / saat idi (51-130 arası). Bizim çalışmamızda, 7 (% 19.4) hastada temporal arterit ile uyumlu bulgular vardı. Komplikasyon olarak, sadece bir hastada sağ orbital bölgede bir hafta süren ekimoz vardı.

Sonuç: Literalde temporal arter biyopsilerinin pozitiflik oranları ile ilgili farklı sonuçlar yayınlanmıştır. Atipik semptomlar, atlanan lezyonlar, suboptimal örnekleme ve devam eden steroid tedavisi gibi bir takım farklı faktörler sonuçları etkilemektedir. Temporal arter biyopsisi, sadece doğru klinik değerlendirmeden sonra yapılırsa ve erken dönemde yeterli örnekleme yapıldığında kolay ve güvenilir bir tanı yöntemidir.

Anahtar Kelimeler: Temporal arter biyopsisi, Temporal arterit, Vaskülit

INTRODUCTION

Temporal artery biopsy (TAB) is still the gold standart diagnostic method for temporal arteritis (TA). Histopathological examination of TAB samples shows granulomatous inflammation, often with multinucleated giant cells in the arterial wall, and interruption of the internal elastic laminea [1] .TAB is a simple and well tolerated technique, however, its sensitivity has been questioned. This is primarily due to the nature of the TA which is characterized by skip lesions, and pathological changes may be missed in a TAB taken in a free segment of arteritis. Therefore, there is a need for a 2 cm or greater length of sample and multipl histological sections for diagnostic TAB[2]. Here, patients who underwent temporal artery biopsy were evaluated in our clinic.

MATERIAL and METHODS

The medical records of patients who underwent TAB in our clinic, between September 2004 and June 2014 were reviewed retrospectively, with the written and signed permission of department of cardiovascular surgery council members. A total of 36 consecutive patients

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included in this study. Patients with a diagnosis of polymyalgia rheumatica, previous temporal artery biopsy, and recently started corticosteroid therapy, were excluded. Demographic features and results of patients were presented in Table 1. Procedure was performed under local anesthesia for all patients. Monitoring included arterial blood pressure and electrocardiogram. The surgical technique consisted of determination of the superficial temporal artery trace, skin incision, identifying the superficial temporal artery and biopsy specimen excision (Fig 1a, 1b, 1c, 1d). Desicion of unilateral or bilateral TAB was based on clinical findings and a total of 48 TAB were performed for 36 patients. Biopsy samples were taken at least 2 cm in length. Postoperative complications (hemorrhage, wound infection, ocular complaints…etc) were reviewed. Datas were collected retrospectively from patient records.

RESULTS

Between September 2004 to June 2014, 36 consecutive patients, who referred to our department with a clinical suggestion of active temporal arteritis were enrolled in this study. Patient characteristics and clinical features are shown in Table-1. Twenty five patients (69.5%) were female and eleven (30.5%) were male. Mean age was 61.1 (range 56 to 81) years. In these patients, the most common presenting symptom was unilateral headache in 28 (77.8%) patients. Mean erytrocyte sedimentation rate (ESR) was 56.3 (range 51 to 130) mm/hr. All patients were discharged at the same operation day. The mean length of the biopsy specimen was 2.3 (range 2.1 to 3.6) cm. Procedure was performed bilaterally in 12 (33.3%) pateints. In our study, a total of 7 (19.4%) patients had positive biopsies and they all were over 65 years old with ESR higher than 80 mm/hr. There were no mortality and significant postoperative complications in this study. Only 1 (2.8%) patients had transient ecchymosis on the right periorbital region and healed in a few days spontaneously.

DISCUSSION

TA or GCA is a primary systemic vasculitis that affects 18/100 000 of the people over the age of 50. The incidence rises steadily after age 50 years and is highest between 70-80 years of age. TA is two to four times more common in women compared to men[3]. It appears to have a distinct racial and geographical distribution and higher incidence of this condition is seen in population from Northern European countries. TA affects large and medium sized arteries

with a predilection for the external carotid artery branches[4]. The most common presenting symptoms of TA include headache, jaw claudication, polymyalgia rheumatica and visual problems[5]. The most feared complication of the disease is blindness and loss of vision is usualyy irreversible despite treatment. On the other hand, TA is an inflammatory disease with good response to steroid therapy. But prolonged steroid therapy can lead to some adverse effects such as osteoporosis, pathological fractures, and gastrointestinal bleeding[6]. Therefore, early and accurate diagnosis is very important.

The American College of Rheumatology (ACR) defined clinical classification criteria for TA diagnosis and for the diagnosis of TA, at least any three of criteria, listed in Table 2, must be presented which yield 93.5% sensitivity and 91.2 % specificity.

Positive TAB provides the most definite evidence of TA, but the positive yield of this test is low. In the literature, very different rates are available and ranges from 5% to 34%. In our study, the positive biopsy rate was 19.4% with a total of 7 patients, and these results were similar to the literature. A number of factors that has been advanced to explain false negative TAB results, such as clinical and/or laboratory evaluation, length of the sample taken, unilateral or bilateral procedure, steroid used in the treatment, and histological examination[7]. Thus, selection of the appropriate patient before the TAB is very important.

Careful physical examination, including palpation of the temporal arteries, accompanied by an accurate medical history and laboratory findings are all imperative fort he diagnosis of TA[8]. For example, headache, jaw pain, and visual disturbances are the most common symptoms but these findings can be seen in many diseases; e.g. hypertansion, migraine and trigeminal neuralgia. The diagnosis of TA should be considered in a patient over the age of 50 years who presents with new onset unilateral headache and accompanied visual disturbances or jaw claudication. ESR is usually elevated, but is not spesific. ESR levels exceeding 100 mm/hr have been shown to be associated also for serious infections, connective tissue disorders or metastatic tumors. Thus ESR is a useful confirmative test in patients with a suggestive history but it is not always elevated at diagnosis[9]. Before the procedure, steroid use in treatment can yield false results. However, positive biopsy results may be found following steroid treatment for TA. Achkar et al. reported that steroids have little effect on the histological diagnosis within two-week of time frame[10]. Some authors adviced that biopsy should be done bilaterally to improve the diagnostic sensitivity. In a study, a positive biopsy sample was found in 5% of

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those who had a normal TAB from the opposite side[11]. In this study, a total of 7 (19.4%) patients had positive biopsies and all were over 65 years old and mean ESR higher than 80 mm/hr. Bilateral TAB was performed in 12 patients and a total of 48 TAB were performed for 36 patients.

Negative biopsy results do not always exclude the diagnosis due to the skipping characteristics of the disease. TA is typically defined as having skip lesions and can be found in any temporal artery segment as short as 330 μm in length. Because of the segmental characteristics of the inflammatory involvement in TA, pathological findings may be missed in a TAB taken in free-segment of artery. Therefore, it is necessary to maximize the biopsy sample. According to some investigators samples should be taken at least 2 cm or longer, but TAB length yielding optimal diagnostic sensitivity remains unknown[1]. In our study, the mean length of the biopsy specimen was 2.3 (range 2.1 to 3.6) cm.

TAB is a simple procedure and often performed under local anesthesia. However, this operation is not without complications and may cause some discomforts. Possible complications include postoperative hematoma, scalp or skin necrosis, wound infection, facial nerve injury, eyebrow dropping and rarely stroke[12]. In addition, samples may be venous or nerve origin unintentionally[13]. Thus, different diagnostic methods have been investiagated for TA.

Color doppler ultrasonography (CDU) is a noninvasive, cheap and simple diagnostic method and results can be obtained quickly. It can be performed bilaterally and can be performed along the artery which may reduce the chance of false-negative results associated with skip lesions. In 1995, Schmidt et al was the first to report the use of CDU in the diagnosis of TA as an alternative to TAB. Hypoechoic halo sign is highly spesific CDU finding for TA. It is a dark area around the vessel lumen probably due to arterial wall edema[14]. However, the diagnostic value of CDU has been debated. Salvarani et al reported low sensitivity (40%) and specificity (79%) for CDU[15]. Schmidt et al reported that hypoechoic halo sign disappeared after 10 to 16 days (total range, 7-56 days) of corticosteroid therapy[14]. In addition, evaluation is person-dependent and requires experience. Today, CDU is used primarily as an adjunct to TAB in the diagnostic process, rather than an alternative[16].

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Recently, high-resolution magnetic resonance imaging (MRI) of the superficial cranial arteries was introduced, with promising results. Here, images can be easily acquired with a standardized protocol of short duration and making the data asquisition independent of the observer. There is no significant difference between CDU and MRI sensitivity and specificity rates. Compared with CDU, however, high-resolution MRI is more expensive and less widely available[17,18].

CONCLUSION

TA can be diagnosed using ACR scoring system, but histological examination of TAB specimens is still the gold standart for the diagnosis of TA. Although headache, jaw claudication and visual disturbances are the most common symptoms, these findings can be seen in many diseases, such as hypertansion, migraine and trigeminal neuralgia. Thus, most clinicians prefer to have pathological confirmation before starting treatment. Positive biopsy has a specificity of 100%, but negative biopsy does not always exclude the diagnosis due to the segmental nature of disease. If the histological result is negative, clinicians should follow the algorithm described in the ACR scoring system.

Clinical, laboratory and histological data should be analyzed carefully for correct diagnosis and help guide the clinician's choice of appropriate therapy. CDU is a cheap, non-invasive, reproducible and easy to perform method that should precede TAB for TA patients.

Conflicts of interest: There is no conflicts of interest

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Feature		
Gender (%)	**Female**	69.5 (n=25)
	Male	30.5 (n=11)
Mean age (years)		61.1 (range 56 to 81)
Headache (%)		77.8 (n=28)
Mean ESR (mm/h)		56.3 (range 51 to 130)
Mean biopsy length (cm)		2.3 (range 2.1 to 3.6)
Bilateral TAB (%)		33.3 (n=12)
Positive TAB (%)		19.4 (n=7)
Complication rate (%)		2.8 (n=1)

Table 1: Patient Characteristics

Criteria	
1. Age at disease onset ≥ 50 years	Development of symptoms or findings beginning at age 50 years or older
2. New headache	New onset of or new type of localized pain in the head
3. Temporal artery abnormality	Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries
4. Elevated ESR	ESR ≥ 50 mm/h by the Westergren method
5. Abnormal artery biopsy	Biopsy specimen with artery showing vasculitis characterised by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells
Not: For purposes of classification, a patient shall be said to have TA if at least three of these five criteria are present.	

Table-2: American College of Rheumatology Criteria For Temporal Arteritis

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Fig 1a: Determination of the superficial temporal artery trace

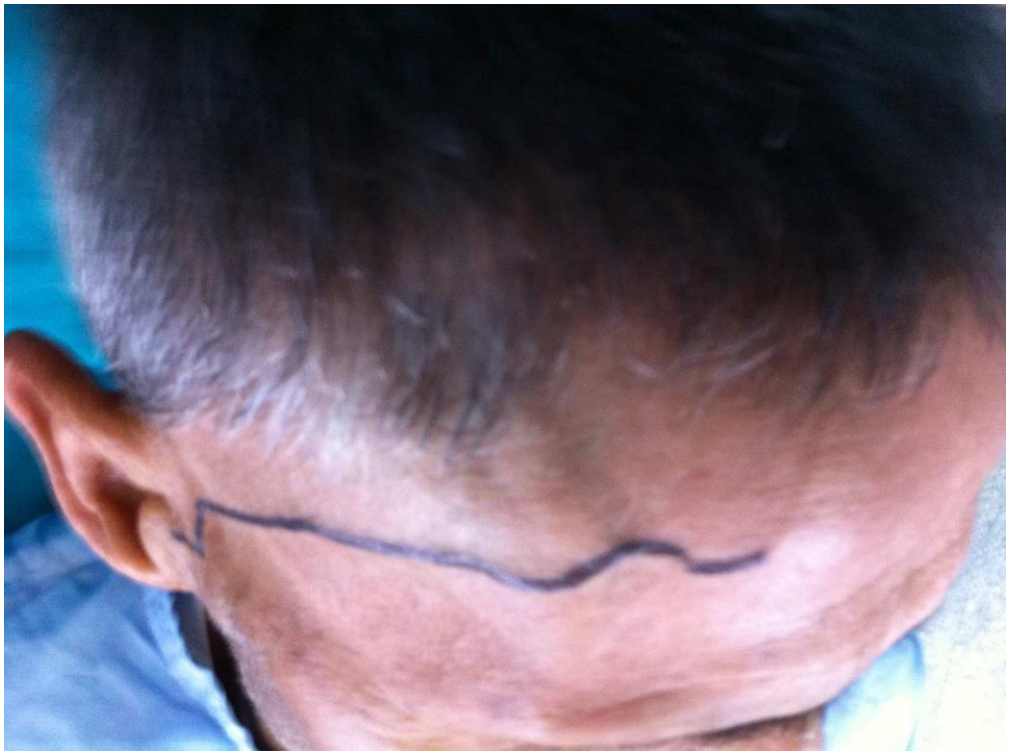


Fig 2a: Skin Incision

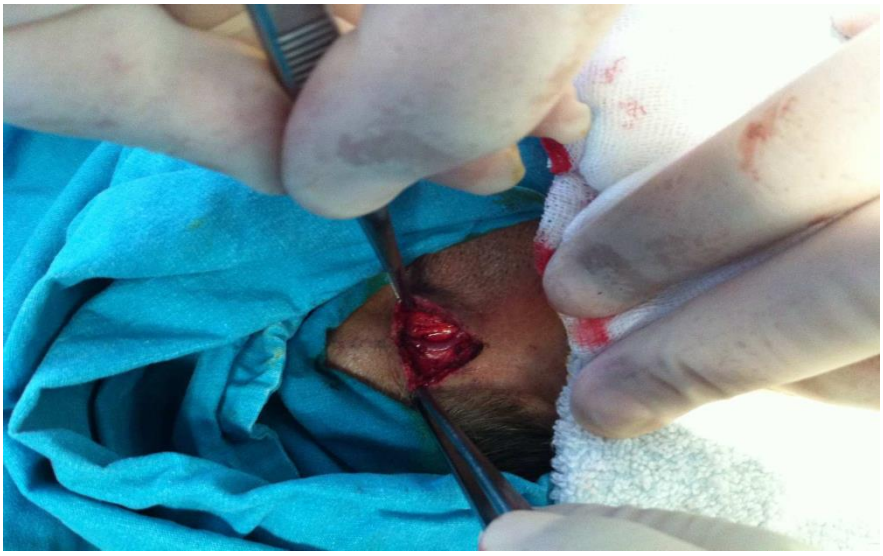


Fig 3a: Identifying the temporal artery

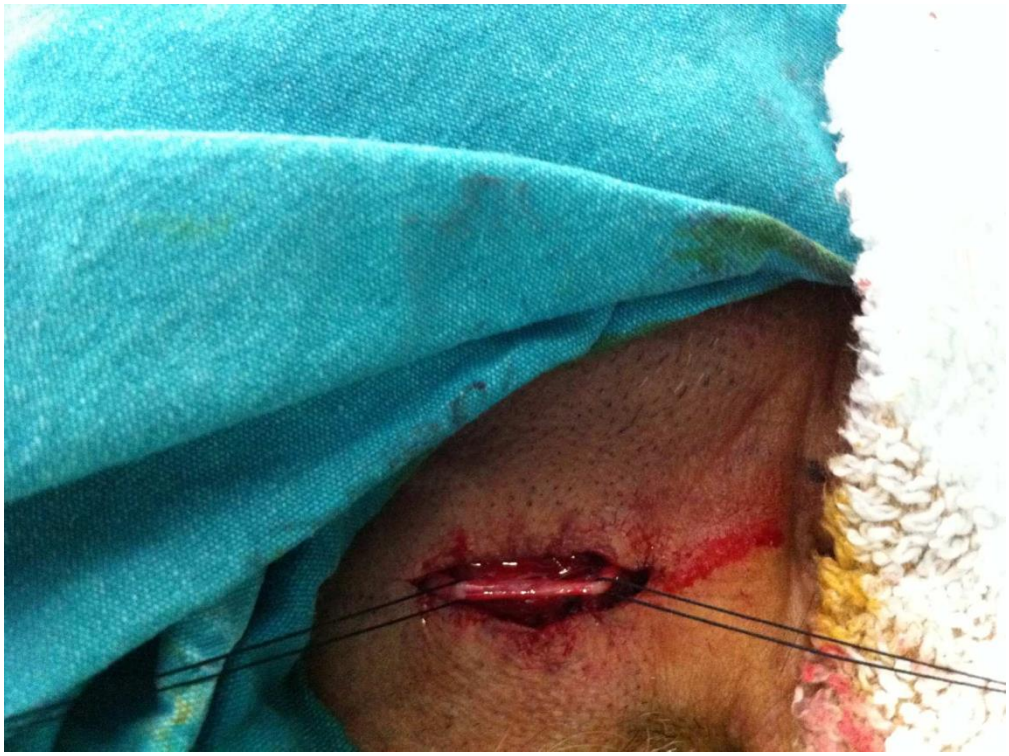
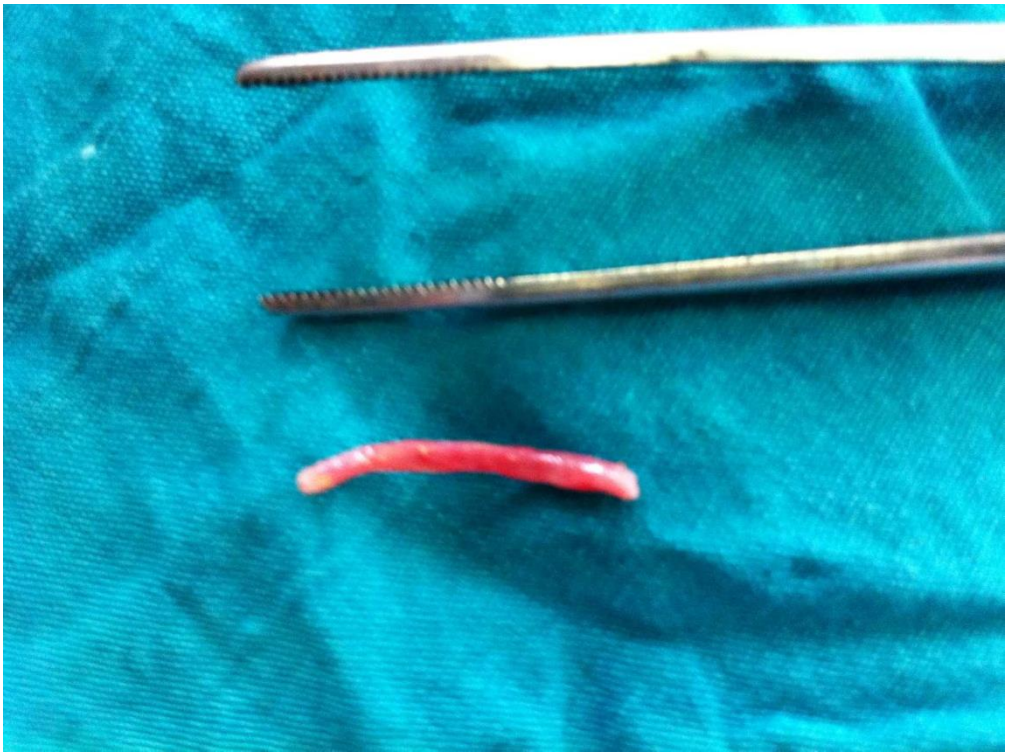


Fig 4a: Biopsy Specimen



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RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

Investigation Of The Relationship Between P Wave Dispersion And Atrial Septal Aneurysm In Pregnancy

Gebelikte P Dalga Dispersiyonu ve Atrial Septal Anevrizma Arasındaki İlişkinin İncelenmesi

Veciha Özlem Bozkaya[1], Yaprak Engin Üstün[2]

[1]Zekai Tahir Burak Women's Health Education and Research Hospital, Department of Cardiology, Ankara, Turkey
[2] Zekai Tahir Burak Women's Health Education and Research Hospital, Department of Obstetric and Gynecology Ankara, Turkey

Corresponding Author: Veciha Özlem Bozkaya
Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey
E-mail address: vobozkaya@gmail.com
Tel:Fax: +903123065917

ORCID
Veciha Özlem Bozkaya https://orcid.org/0000-0002-2876-9239
Yaprak Engin Üstün https://orcid.org/0000-0002-1011-3848

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ABSTRACT

Background: Aim of this study is to determine the impact of atrial septal aneurysm on atrial electrophysiology in pregnancy by the investigation of P-wave duration and P-wave dispersion on electrocardiography.

Method: This study includes 98 pregnant women, divided in two groups according to presence of atrial septal aneurysm (ASA) (n=48 ASA positive group, n=50 ASA negative group). P-wave dispersion was calculated by using the 12-lead electrocardiogram with a speed of 50 mm/sec for each participant. Cardiac functions and morphology of the aneurysm were measured using conventional echocardiography. ASA was defined if the excursion of the septum primum into the left/right atriums exceeded 10 mm or the total excursion distance was more than 15 mm.

Results: Demographic and clinical findings were similar between ASA positive group and ASA negative group, there was no significant difference. Compared to the ASA negative group, pregnant women with ASA showed significantly longer maximum P wave dispersion (PWD) (54.10±12.42 ms vs. 37,42±14,27 ms , p = 0.0001). Similarly, the maximum duration of the P wave (Pmax) in the

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ASA positive group was significantly longer than the ASA negative group (118,35±11,41 ms vs. 110,54±9,452 ms , p=0,0004). P wave dispersion and Pmax were not correlated with age, gravida, parity, gestational week, body mass index or M mode Echocardiographic parameters.

Discussion: In this study, it was shown that P-wave dispersion is prolonged in pregnant women with atrial septal aneurysm. PWD may be a pre-determinative for atrial structural anomalies or atrial arrhythmias in pregnancy and this non invasive method should be used to predict cardiac risk at the beginning of pregnancy.

Key Words: Pregnancy, atrial septal aneurysm, P wave dispersion

ÖZET

Amaç: Bu çalışmanın amacı elektrokardiyografide P-dalga süresi ve P-dalga dispersiyonunu inceleyerek; atriyal septal anevrizmanın gebelikte atriyal elektrofizyoloji üzerindeki etkisini, saptamaktır.

Yöntem: Çalışma;Atrial septal anevrizma (ASA) varlığına göre 2 gruba ayrılan 98 gebe içermektedir.(n=48 ASA pozitif grup, n=50 ASA negatif grup). P-dalgası dispersiyonu, her katılımcı için 50 mm/sn hızında 12 elektrotlu elektrokardiyogram kullanılarak hesaplandı. Kardiyak fonksiyonlar ve anevrizmanın morfolojisi, geleneksel ekokardiyografi kullanılarak ölçüldü. ASA, septum primumun sol/sağ atriyumların içine 10 mm'nin üzerinde yer değiştirmesi veya toplam yer değiştirme hareketinin 15 mm'den fazla olması olarak tanımlandı.

Bulgular: Demografik ve klinik bulgular ASA pozitif grup ile ASA negatif grup arasında benzerdi, anlamlı fark yoktu. ASA negatif gruba kıyasla, ASA'lı gebelerde anlamlı olarak daha uzun P dalga dispersiyonu görüldü. (54.10±12.42 ms vs. 37,42±14,27 ms , p = 0.0001). Benzer şekilde, ASA pozitif grubundaki P dalgasının (Pmax) maksimum süresi ASA negatif grubundan anlamlı olarak daha uzundu.(118,35±11,41 ms vs. 110,54±9,452 ms , p=0,0004). P wave dispersion and

Pmax; yaş, gravida, parite, gebelik haftası, vücut kitle indeksi veya M modu Ekokardiyografik parametrelerle korele değildi.

Sonuç: Bu çalışmada, atriyal septal anevrizması olan gebelerde P dalgası dispersiyonunun uzadığı gösterilmiştir.PDD, gebelikte atriyal yapısal anomaliler veya atriyal aritmiler için bir ön belirleyici olabilir ve bu non-invaziv yöntem, gebeliğin başlangıcında kardiyak riskini tahmin etmek için kullanılmalıdır.

Anahtar Kelimeler: Gebelik, atrial septal anevrizma, P dalga dispersiyonu

INTRODUCTION: An atrial septal aneurysm (ASA) is a localized or generalized deformity of the interatrial septum (IAS). Generally it occurs at the level of fossa ovalis but rarely it may involve entire atrial septum which bulges into the right or left atrium or both.[1] Prevalence of ASA varies in literature but Transtorasic Echocardiography (TTE) studies estimated the rates between 0.08% and 1.2%.[2] In a large autopsy series, the prevalence of ASA was reported as 1%.[3] ASA is often associated with other atrial septal abnormalities, particularly with atrial

septal defect type ostium secundum or patent foramen ovale.[4] Association between ASA and atrial tachyarrhythmias has been suggested in previous studies.[5] Despite of its clinical importance, there were no clear guidelines about management and follow up of ASA among pregnant women. Although ASA is mainly congenital, clinical symptoms of ASA such as dyspnoea, palpitation, angina or thromboembolic accidents appear during the second or third decades of patients' lives.[6] However, pregnancy is associated with a marked plasma volume expansion and cardiac output increase, which significantly loads the cardiovascular system. The physiologic adaptations of pregnant females to these hemodynamic loading include increasing both heart rate and stroke volume and fall in vascular resistance and blood pressure.[7] Because of dyspnoea, palpitation and limitation in effort capacity are common complaints of pregnant women, diagnosis of ASA is disingenuous with pregnancy as its clinical picture is similar to a wide range of normal pregnancy complaints. Otherwise, routine cardiac screening is not recommended for all pregnant women, so it is difficult to reveal presence of ASA among pregnant women according to suspect of clinical symptoms.

Electrocardiography (ECG) is an important tool to evaluate cardiovascular complications during pregnancy. P-wave dispersion (PWD), which is the difference between the smallest and the largest P-wave lengths,. is an accurate and sensitive marker to evaluate atrial electrophysiology on ECG and a non-invasive indicator of atrial arrhythmogenicity.[8] An increase in PWD is assumed to be associated with heterogeneity in atrial conduction and therefore increases the occurrence and recurrence risk of atrial arrhythmia.[9] Since it is easy to apply, cheap and accessible, It may be a good tool to evaluate the risk of atrial arrhythmia in patients with atrial septal aneurysm among pregnant women. As a contribution to the development of new strategies about management and follow up of ASA during pregnancy, in this study it was aimed to show the impact of ASA on atrial electrophysiology in pregnancy with the evaluation of P wave dispersion on ECG and thus to anticipate clinical risks of ASA during pregnancy.

MATERIAL AND METHOD: This was a single center study conducted over a period of six months from March 2017 to September 2017 by the department of Cardiology at a tertiary deliver center, Ankara, Turkey. First trimester pregnant women of aged 17 to 42 years, referred to Cardiology Department were included in the study. Written and verbal consents were obtained from all patients. The study protocol was approved by local institutional ethics

committee (Ethics Committee number:46). All patients' medical history, demographic features (age, gravida, parity, gestational week, Body Mass Index (BMI)) and heart rate were recorded at the first admission. Patients with a history of chronic systemic disease, cardiovascular disease and/or a family history of early onset cardiovascular disease, anemia, multiple pregnancies were excluded from the study. Cases with high-risk pregnancy were additionally excluded from the study. ECG and TTE were performed for all included pregnant.

After the evaluation according to the exclusion criteria, 48 pregnant with ASA remained for further analysis . Fifty- age- matched individuals who had normal echocardiographic findings were randomly selected from the same echocardiography database as the control group. A total of 98 pregnant women who met inclusion criteria were enrolled to the study. They were divided into 2 groups according to presence of ASA. (n=48 ASA positive group , n=50 ASA negative group).

Following 10 minutes of rest, each participant underwent a surface- resting 12-lead ECG in the supine position, conducted at a speed of 50 mm/sec with an amplitude of 1 mV/cm (Montara Instrument EU 250 Electrocardiograph, Milwaukee, WI, USA). The ECG recordings were scanned with a high-resolution scanner (Scanjet 8200 flatbed scanner, Hewlett Packard, Houston, Texas, USA). All ECG recordings were transferred to a computer and ECG recordings was undertaken using digital calipers by EP Callipers, version 2.12 (EP Studios Inc. 2015-2019). The starting point of the first positive wave moving in an upward direction or the first negative wave moving in a downward direction that could be observed from the isoelectric line was considered the origin of the P-wave. The turning point of the wave toward the isoelectric line was considered the end of the P-wave. P wave dispersion (PWD) was calculated with the measured values of the longest (Pmax) and shortest (Pmin) P-waves in any lead of the 12-lead ECG (PWD = Pmax – Pmin).[11] Moreover, to minimize the measurement errors, analyses of ECG parameters (Pmin, Pmax and PWD) were performed in duplicate on two separate days.

Echocardiographic examination of the patients in both groups was performed in the left lateral decubit position using a TTE (Vivid S5 System, GE Health-care, USA). All measurements were performed by the same cardiologist. Parasternal long-axis, short-axis, and apical 4-chamber and 2-chamber images were obtained and evaluated using M-mode, 2-D, continuous wave Doppler, pulse wave Doppler, and tissue Doppler methods according to American

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Echocardiography Society criteria. The existence of aneurysmatic excursion of the interatrial septum and the presence of other associated cardiac lesions were evaluated. As reported by Agmon et al,[9] ASA was defined if the excursion of the septum primum into the left/right atriums exceeded 10 mm or the total excursion distance was more than 15 mm. Left ventricular ejection fraction was provided using Teichholtz in M-mode echocardiography. The pulsed Doppler sampling volume was placed between the tips of the mitral valve leaflets to obtain maximum filling velocities. Early diastolic flow (E), atrial contraction signal (A) and E deceleration time (DT) were measured. Isovolumetric relaxation time (IVRT) was determined as the interval between the end of the aortic outflow and the start of the mitral inflow signal.

Statistical analysis was carried out with JMP®, Version 12.0. (SAS Institute Inc., Cary, NC, 1989-2019). All the values are expressed as mean ±standard deviation. Shapiro-Wilk W test was performed to test normality of of data. Differences between independent groups were assessed by t-tests for normally distributed data and Wilcoxon Rank Sum test was used for non-normal distributions. Using Pearson correlation analysis, the relationship between P wave variables and clinical and echocardiographic variables were assessed. P-values less than 0.05 were considered significant for all statistical tests.

RESULTS: The demographic features of study population are shown in Table 1. There were no statistically significant differences between the ASA positive group and controls with respect to age, gravida, parity, gestational week, weight, height, heart rate, BMI. However; LVEDD, RAEDD, RVEDD were higher in ASA positive group compared to ASA negative group but they were in normal range for both group (p=0,029, p=0,0008, p= 0,0018) (Table 2) All participants were in sinus rhythm. Compared to the ASA negative group, pregnant with ASA showed significantly longer maximum P wave duration (PWD) (54,10 ±12.42ms vs. 37,42 ±14,27 ms, p = 0,0001). Similarly, the maximum duration of the P wave (Pmax) in the ASA positive group was significantly longer compared with ASA negative group (118,35±11,41ms vs 110,54±9,452 ms , p=0,0004).

In correlation analysis; it was seen that P wave dispersion and Pmax were not correlated with age, gravida , parity, gestational week, BMI or M mode echocardiographic parameters.

Table 1: Comparison of P wave variables for ASA positive group versus ASA negative group

Parameter	ASA NEGATIVE (n=50)	ASA POSITIVE (n=48)	P value
	Mean ± Std Dev	Mean ± Std Dev	
Age, years	26,47 ± 6,40	26,83 ± 5,75	NS
G, n	2,04 ± 1,12	2,34 ± 1,38	NS
P, n	0,76 ± 0,90	0,98 ± 1,00	NS
Gestational Age, weeks	7,66 ± 1,51	7,02 ± 1,44	NS
BMI, kg/m2	23,93 ± 4,62	24,66 ± 3,16	NS
LVEF, %	67,55 ± 2,01	67,72 ± 2,06	NS
E, m/s	0,98 ± 0,12	1,01 ± 0,14	NS
A, m/s	0,75 ± 0,10	0,78 ± 0,11	NS
IVRZ, ms	78,40 ± 13,45	75,19 ± 17,35	NS
LVEDD, cm	4,21 ± 0,35	4,38 ± 0,26	<0,05
RAEDD, cm	2,86 ± 0,30	3,06 ± 0,38	<0,001
RVEDD, cm	2,03 ± 0,24	2,18 ± 0,19	<0,01
LAEDD, cm	2,78 ± 0,38	2,90 ± 0,36	NS
HR, bpm	77,50 ± 7,33	76,94 ± 12,97	NS

NS Not significant (p>0.05); G Gravida, P parity , , BMI Body mass index, LVEF left ventricul ejection fraction, LAEDD Left atrium end diastolic diamater , LVEDD Left ventricular end-diastolic diamater, LVEF Left ventricular ejection fraction, RVEDDD Right ventricular end-diastolic diamater, ,HR Heart rate, RAEDDD Right atrial end diastolic diamater, IVRT: Isovolumetric relaxation time. E Early diastolic flow, A Atrial contraction signal.

Table 2: Clinical and echocardiographic features of atrial septal aneurysm patients and controls

Parameter	ASA NEGATIVE (n=50)	ASA POSITIVE (n=48)	P value
	Mean ± Std Dev	Mean ± Std Dev	
Pmax, ms	110,54 ± 9,45	118,35 ± 11,41	<0,001
Pmin, ms	73,12 ± 10,99	64,25 ± 7,01	<0,0001
PWD, ms	37,42 ± 14,27	54,1 ± 12,42	<0,0001

Pmax: Maximum P wave duration, Pmin: Minimum P wave duration, PWD: P wave dispersion.

DISCUSSION: Physiological changes in pregnancy such as increase in maternal intravascular and extravascular fluid volumes, atrial and ventricular size, adrenergic responsiveness and elevation in hormonal levels (Estrogen and progesterone levels) affects the mechanism of arrhythmogenesis.[10] These changes alter the electrophysiologic properties of the myocardium, thus promote arrhythmogenesis.[11] Common complaints of pregnant women such as dyspnoea, palpitation and limitation in effort capacity are also result of these physiological changes. Signs and symptoms of pregnancy can mimic heart diseases so that it may be difficult to suspect a cardiovascular disease in pregnancy and it poses a particular problem especially in pregnant women, in whom the diagnosis is often delayed or missed. Therefore, observation of the clinical predictors for maternal CVD risk at the beginning of pregnancy gains importance. The California Pregnancy-Associated Maternal Morbidity and Mortality Committee Cardiovascular Disease in Pregnancy and Postpartum Task Force suggest an algorithm that includes an overview of clinical assessment and management strategies based on risk factors, presentation signs and symptoms, vital sign abnormalities, and physical examination findings.[12] To diagnose CVD, cardiac screening to pregnant women with high clinical risk factors was advised in this Task Force. Routine cardiac screening during pregnancy is not recommended in the guidelines, however early diagnosis of cardiovascular disease is important for decreasing maternal morbidity and mortality. In this study, we aimed to analyse the effect of ASA on ECG by using PWD , thus we investigated

whether PWD as a non invasive and cheap method could be a pre-determinative for atrial structural anomalies or atrial arrhythmia in pregnancy. P-wave dispersion is a non-invasive technique providing a risk estimation for atrial arrhythmia. Although there are many studies on the relationship between ASA and cardiac arrhythmia in adult patients, to the best of our knowledge, the present study is the first in pregnant women with ASA.

ASA increases the risk of maternal morbidities as atrial arrhythmias, systemic embolism and myocardial dysfunction up to heart failure.[6] The prevalence of supraventricular arrhythmia has been reported to be 40%, atrial fibrillation (18%), atrial flutter (4%), atrioventricular nodal re-entrant tachycardia (8%), and miscellaneous (18%) in adult patients with atrial ASA.[13] There are some studies in the literature about the proarrhythmia mechanism of ASA. Russo at all, showed that the echocardiographic atrial electromechanic delay (AEMD) indices (intra-left and inter-AEMD) was significantly increased in healthy ASA subjects.[14] The heterogeneity of atrial geometry caused by ASA may lead to changes in electrophysiological dynamics of the atrial myocardium. Morelli, claimed that re-entry mechanism could be dependent on an electro anatomical barrier and/or different electrophysiological properties between ASA and the remaining atrial septum.[15] Despite of the clinical importance of ASA, in the literature there were no clear guidelines about management of such condition during pregnancy. Diagnosis of ASA may be missed in pregnancy as its clinical picture is similar to a wide range of normal pregnancy complaints. Therefore, it is important to determine predictive parameters in terms of cardiac disorder at the begining of pregnancy. Some parameters obtained from surface electrocardiography (ECG) recordings are used for determining patients at risk for the development of atrial arrhythmias. Among these parameters, PWD is the most frequently used parameter in clinical cardiology. PWD is an electrocardiographic marker associated with a nonhomogeneous and discontinuous distribution of the sinus impulse.[8] In addition, PWD is accepted as a marker of prolonged interatrial and intraatrial conduction times and atrial arhytmias.[9] In previous studies, Association between ASA and atrial tachyarrhythmias has been suggested.[5] Janion and Kurzawski showed that P-wave dispersion was higher in interatrial septal aneurysm patients than in the control subjects and it is believed that this may be related to the more frequent occurrence of atrial arrhythmia in these patients.[16]

In the present study; we have demonstrated that PWD, which is a non-invasive technique providing an estimation for the risk of atrial arrhythmia, was significantly longer in pregnant

women with ASA than the control subjects. PWD may be a predictor of structural atrial anomaly or atrial arrhythmia so we suggest that more attention should be paid to the evaluation of electrocardiographic findings in all pregnant women and PWD should be utilized as a non invasive method to identify pregnant women with structural heart disease and at risk of atrial arrhythmia. At least, pregnant women with prolonged PWD should be taken under detailed cardiac examination even if they don't have any other clinical risk factor or cardiac symptom. This finding would contribute to the improvement of the follow up strategy during pregnancy.

CONCLUSIONS: Consistent with other studies demonstrating the relationship between arrhythmia and ASA, this study indicated that the PWD and max P-wave duration were prolonged in pregnant women with ASA. As a result of our study, PWD which is a non-invasive, cheap, accessible and simple technique may be a pre-determinative for atrial structural anomalies or atrial arrytmias in pregnancy and this non invasive method should be used to predict pregnant women with cardiac risk at the beginning of pregnancy.

Declaration of Interest: The author declares no conflicts of interest.

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RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

The efficacy of new treatment methods in HCV patients: a single center study

HCV hastalarında yeni tedavi yöntemlerinin etkinliği: tek merkezli bir çalışma

Derya Demirtaş[1], Hilmi Erdem Sümbül[1], Erdinc Gülümsek[1], Adnan Taş[2], Banu Kara[2], Tayyibe Saler[1]

[1] Department of Internal Medicine, University of Health Sciences - Adana Health Practice and Research Center, Adana, Turkey.

[2] Department of Gastroenterology, University of Health Sciences - Adana Health Practice and Research Center, Adana, Turkey.

Corresponding Author: Derya Demirtas

Address: University of Health Sciences - Adana Health Practice and Research Center, Department of Internal Medicine,

E-mail: deryademirtas83@gmail.com

Phone: + (90) 530 521 87 01

ORCID

Derya Demirtaş, https://orcid.org/0000-0001-9449-8759

Hilmi Erdem Sümbül, https://orcid.org/0000-0002-7192-0280

Erdinc Gülümsek, https://orcid.org/0000-0003-0026-2396

Adnan Taş, https://orcid.org/0000-0002-5706-2136

Banu Kara, https://orcid.org/0000-0003-4278-6593

Tayyibe Saler https://orcid.org/0000-0001-5588-5609

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ABSTRACT

Aim: Achieving sustained virologic response (SVR) is critical in patients with chronic hepatitis C virus (HCV) infection. Over the last few years, many developments have been made in HCV infection treatment with the evaluation of direct-actinga antivirals (DAAs). Treatment with DAAs resulted in high rates of SVR among patients with chronic HCV infection. The aim of our study aim to compare the treatment efficacy between different DAA regimens in patients with HCV.

Methods: In our study 290 patients were evaluated retrospectively with regard to the effects related to the use of DAAs and its effects on HCV-RNA. The primary end point was a SVR at 12 weeks after the end of the DAA therapy.

Results: In our study included 290 patients who were treated with DAA. The rate of SVR was 99% (98%; 95

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confidence interval [CI], 96 to 100) with 12 weeks of ledipasvir plus sofosbuvir (LDV+SOF), 96% (97.9%; 95% CI, 94 to 99) with 12 weeks of sofosbuvir plus ribavirin (SOF+RBV), and 90% (98.9%; 95% CI, 95 to 99) with 12 weeks of ombitasvir/paritaprevir/ritonavir plus dasabuvir (PrOD). In comparing LDV+SOF, SOF+RBV and PrOD, the chance of having SVR between these three DAA regimens was not significantly different.

Conclusion: DAA treatment regimens should be preferred in the first line drug for the treatment of chronic HCV infection because of the their significant clinical benefits.

Key words: Chronic Hepatitis C, direct-acting antiviral, sustained virologic response.

ÖZET

Amaç: Sürekli virolojik yanıtın (SVR) elde edilmesi, kronik hepatit C virüsü (HCV) enfeksiyonu olan hastalarda kritik öneme sahiptir. Geçtiğimiz birkaç yıl boyunca, HCV enfeksiyonu tedavisinde, direkt etkili antivirallerin (DAA) değerlendirilmesi ile birçok gelişme kaydedilmiştir. DAA' lar ile tedavi, kronik HCV enfeksiyonu olan hastalarda yüksek oranda SVR ile sonuçlandı. Çalışmamızın amacı, HCV' li hastalarda farklı DAA rejimleri arasındaki tedavi etkinliğini karşılaştırmaktır.

Yöntem: Çalışmamızda, 290 hasta DAA kullanımı ve HCV-RNA üzerindeki etkileri ile ilgili retrospektif olarak değerlendirildi. Birincil sonlanım noktası, DAA tedavisinin bitiminden 12 hafta sonraki SVR idi.

Bulgular: Çalışmamıza DAA ile tedavi edilen 290 hasta alındı. 12 hafta boyunca ledipasvir + sofosbuvir (LDV + SOF) ile SVR oranı %99 (%98; 95 güven aralığı [CI], 96-100), sofosbuvir + ribavirin (SOF + RBV) ile %96 (%97.9; %95 CI, 94-99), ve ombitasvir / paritaprevir / ritonavir + dasabuvir (PrOD) ile %90 (%98.9; %95 CI, 95-99) SVR oranı %99 idi. LDV + SOF, SOF + RBV ve PrOD' un karşılaştırılmasında, bu üç DAA rejimi arasında SVR elde etme şansı önemli ölçüde farklı değildi.

Sonuç: Kronik HCV enfeksiyonunun birinci basamak tedavisinde önemli klinik yararları nedeniyle DAA tedavi rejimleri tercih edilmelidir.

Anahtar kelimeler: Kronik Hepatit C, direkt etkili antiviral, sürekli virolojik yanıt.

INTRODUCTION:

The World Health Organization(WHO) have estimated the national and global rates of chronic hepatitis C virus (HCV) infection to be approximately 185 million people and also 360 000 people die each year from HCV related liver complications.[1, 2]. Chronic HCV is a major cause of cirrhosis, hepatocellular carcinoma and end-stage liver disease that require liver transplantation. Therefore, early diagnosis and initial treatment are very important to improve long-term health outcomes in patients with chronic HCV.[1] HCV shows high genetic heterogeneity, and it is classified into six major genotypes. Specifically, genotypes 1, 2, and 3 are found worldwide, with subtype 1a is predominant in the USA and subtype 1b is predominant in Europe, China and Japan. The response to treatment of each genotype varies, genotype 1 is most difficult to treat.[3, 4]

To reduce associated mortality and improve health-related quality of life for HCV patients, achievement of sustained virological response (SVR) is a surrogate endpoint for these goals.[5, 6] For the traditional treatment of chronic HCV, peginterferon alfa plus ribavirin (pegIFN/RBV) has been used. However, pegIFN/RBV achievement is limited and only has SVR rates of 40%-50% and is associated with lots of adverse events (Aes).[7, 8]

HCV infections treatment has significantly improved in the past few years with the development of direct-acting antiviral agents (DAAs). These new DAAs can be combined with or without pegIFN/RBV and could improve the SVR compared to pegIFN/RBV alone.[9] To the best our knowledge there were no evidence from randomized controlled trials that compare directly the different DAAs regimens and pegIFN/RBV. Therefore, our study was aimed to compare the clinical outcomes and efficacy of three new DAAs such as sofosbuvir plus ribavirin (SOF+RBV), ledipasvir plus sofosbuvir (LDV+SOF) and ombitasvir/paritaprevir/ritonavir plus dasabuvir (PrOD) in patients with HCV infection.

METHODS

Patients

In this study, 290 patients were evaluated retrospectively with regard to the effects related to the use of DAAs and its effects on HCV-RNA. The treatment results were collected and evaluated in our Internal Medicine and Gastroenterology Department between June 2018 and December 2018.

Patients eligible for our study were 18 years of age and above with different genotypes of HCV infection with or without cirrhosis, treatment-experienced or naive, were retrospectively followed and treated with LDV+SOF, SOF+RBV, and PrOD for 12 weeks. In patients with chronic HCV, cirrhosis was defined as a liver-biopsy specimen revealing evidence of cirrhosis (Metavir stage F4 [on a scale of F0 to F4, with higher stages indicating a greater degree of fibrosis] or Ishak score of 5 or 6 [on a scale of 0 to 6, with higher scores indicating a greater degree of fibrosis]).

Our exclusion criteria were: suspected or documented hepatocellular carcinoma and other solid organ or hematologic malignancies, decompensated liver cirrhosis (including a history of hepatic encephalopathy, ascites, or bleeding varices), human immunodeficiency virus coinfection, severe chronic kidney disease.

Study Design

This retrospectively study included 290 individuals with 3 different treatment regimens; LDV+SOF for 12 weeks, SOF+RBV for 12 weeks and PrOD for 12 weeks according to the therapeutic protocol. The patients were stratified according to genotype, naive or response to previous treatment and presence or absence of cirrhosis.

Subjects included in the study were grouped as:

Group 1: The patients who received LDV+SOF regimen. These patients were taken a combination tablet containing 90 mg of ledipasvir and 400 mg of sofosbuvir, administered orally once daily.

Group 2: The patients who received SOF+RBV regimen. These patients were taken 400 mg of sofosbuvir administered orally once daily along with ribavirin administered orally twice daily, with doses determined according to body weight (1000 mg daily in patients with a body weight of <75 kg, and 1200 mg daily in patients with a body weight of ≥75 kg). The dose of ribavirin could be decreased or discontinued according to the product label to manage hemoglobin reductions.

Group 3: The patients who received PrOD regimen. These regimen contains paritaprevir 75 mg boosted with ritonavir 50 mg and ombitasvir 12.5 mg 2 tablets in a single daily dose, and dasabuvir twice-daily administration.

Study Assessments

In the screening assessments, the serum HCV RNA level of all the patients was measured, in addition to other clinical tests and standard laboratory. The serum HCV RNA level of all patients was measured with the use of the COBAS TaqMan HCV Test, version 2.0, Roche Molecular Systems, which has a lower limit of quantification of 25 IU per milliliter. Versant HCV Genotype INNO-LiPA 2.0 assay (Siemens Healthcare Diagnostics) was used to determine the HCV genotype and subtype.

Standard laboratory testing, serum HCV RNA level measurement, vital signs, electrocardiography, and physical examinations were made during the treatment assessments

End Points

The primary efficacy end point was the rate of SVR, defined as the absence of HCV-RNA in serum (<25 IU per milliliter), at 12 weeks after the end of DAAs treatment among all the patients with chronic HCV who received treatment. The rate of SVR in each of the three DAAs treatment groups was compared in the primary efficacy analysis.

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Study Oversight

The study was conducted according to the recommendations of the Declaration of Helsinki, Good Clinical Practice guidelines, about biomedical research involving human subjects and the protocol was approved by the institutional ethics committee. Our study was firstly designed according to the protocol by the academic investigators and then conducted. These investigators collected the data and performed the statistical analyses. All the authors of our study had access to the data and assume responsibility for the integrity and completeness of the all reported data. All the authors affirm that the study was conducted with fidelity to the protocol. The manuscript was written by the first and second author with input from all coauthors.

Statistical Analysis

All analyses were performed with SPSS 20.0 (Chicago, IL, USA) statistical software package. The variables were divided into two groups as categorical and continuous variables. The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. The continuous variables in the group were expressed as mean ± standard deviation while categorical variables are given in numbers and percentages. Continuous variables that showed normal distribution were compared using the Student t-test and ANOVA, whereas the Mann-Whitney U test and Kruskal-Wallis test were used for non normally distributed samples. The statistical details between the groups are indicated on the tables. Chi-square ($\chi 2$) test was used to compare categorical variables. The efficacy analysis examined data concerning the total patient population. A p value less than 0.05 was considered statistically significant.

RESULTS

Our study data were compared by dividing the patients in 3 different treatment groups as LDV+SOF, SOF+RBV, and PrOD.

Clinical, demographic and laboratory findings of the study groups

Of the 428 patients who were initially screened, 290 patients received treatment. There were 50 females and 61 males in the group 1 who received LDV+SOF regimen, 43 females and 45 males in the group 2 who received SOF+RBV regimen, whereas there were 41 females and 50 males in the group 3 who received PrOD regimen. Follow-up data at post-treatment week 4 and week 12 were available for 290 patient. Most of the patients were male. The baseline and demographic data and

clinical characteristics of the eligible patients were generally balanced among the three treatment groups except for treatment experienced patient, HCV genotypes and cirrhosis (Table 1a-b).

Treatment experienced patient was common in group 1. Genotype 1a and 1b were common in group 1 and 3 except for group 2 where genotype 2 and 3 were the most common instead (Table 1a-b). The prevalence of cirrhosis was found to be 31%, 5.1%, 6.5% in patients with group 1, 2 and 3, respectively. There is no statistically significant difference was detected in laboratory values. There were 32 patient with diabetes mellitus in group 1, whereas there were 10 and 12 patient with diabetes mellitus in group 2 and 3, respectively (Table 1a-b).

Efficacy

The criterion for the primary end point was met in all three treatment groups, with rates of SVR that were superior to the adjusted historical control rate of 60% (P<0.001 for all comparisons). The rates of SVR 12 weeks after the end of treatment were as follows: among 101 patients who was taken 12 weeks of LDV+SOF, 99 had a SVR (98%; 95% confidence interval [CI], 96 to 100); among 98 who was taken 12 weeks of SOF+RBV, 96 had a SVR (97.9%; 95% CI, 94 to 99); among 91 who was taken 12 weeks of PrOD, 90 had a SVR (98.9%; 95% CI, 95 to 99) (Table 2).

Overall at the end of treatment, 5 of the 290 patients (1%) had a no virologic response: 1 of 101 patients (1%) in the group 1, 2 of 98 (2%) in the group 2 and 1 of 91 patients (1%) in the group 3, whereas the patient with virologic breakthrough did not.

DISCUSSION

This study evaluated the effectiveness of second generation DAAs such as LDV+SOF, SOF+RBV and PrOD in HCV infected patients with or without cirrhosis, no significant alteration was observed in sustained virologic response. This trial showed that a 12-week regimen of second generation DAAs, constitutes effective treatment for patients who have HCV similar to COSMOS, OPTIMIS and ALLY clinical trials real-life studies.[10-12]

In the literature, there are previous systematic review articles that recommended DAA plus pegIFN/RBV regimens.[13, 14] However, the prior studies about the HCV treatment did not apply network meta-analysis in order to address the efficacy between the different DAA plus pegIFN/RBV regimens and pegIFN/RBV alone. Therefore, our study did not compare HCV treatment regimens with or without pegIFN/RBV. The response rates to interferon-based therapy, including protease-inhibitor–containing therapies, have been low in patients with cirrhosis.[15-20] The

low rates of response among patients with cirrhosis reflect both an unidentified effect of cirrhosis on responsiveness to treatment and an increased risk of interferon-related side effects.[21]

In the literature, previous studies suggested that the first generation of DAA (i.e. telaprevir, boceprevir) could improve the chance of having SVR in treatment-naive HCV. However, both boceprevir and telaprevir significantly increased the risk of adverse drug events (e.g. rash and anemia) and have an issue of pill burden.[22] The bocepravir and telaprevir treatments are no longer recommended as the first choice in the guidelines. For that reasons, the first generation DAA was not included in our study.

In the study of Welzel et al.[23] with 1017 patients, patients with genotype 1 and 4 were included. In this study ombitasvir/paritaprevir/ritonavir (OBV/PTV/r)±dasabuvir (DSV)±ribavirin (RBV) regimen was evaluated. In this study, it was found that SVR 12 was 96% in genotype 1 and 100% in genotype 4. We found in our study that SVR 12 was 98.9%. In the study conducted by Welzel et al., 1.5% of patients quited medications because of side effects but in our study, there were no patients that discontinued treatment.

In the study conducted by Deterding et al.[24] patients with genotype 1 were given 6 weeks LDV and SFV treatment. 22 patients were included in this study and SVR 12 was 100%. No side effects were seen in any of the patients. As a result of this study, 6 weeks of LDV+SFV treatment was found to be effective. Also, similar results were found in our study. In our study, SVR 12 was found to be 99% and no side effects were observed.

Feld et al.[25] evaluated ombitasvir / paritaprevir / ritonavir (OBV / PTV / r) ± dasabuvir (DSV) ± ribavirin (RBV) in patients with genotype 1 infection who had not received prior treatment and had no cirrhosis. 12 weeks of treatment was given and SVR was determined as 96.2%. Patients with no virologic response rate in patients infected with genotype 1a was 0.2% and genotype 1b was 1.5%. In our study, patients with no virologic response was 1%.

In our country, there is not enough study with DAAs. In a study conducted by Bayan K et al.[26] (OBV / PTV / r) ± dasabuvir (DSV) ± ribavirin (RBV) treatment was evaluated in 57 patients. 80.7% of the patients were genotype 1b. In our study, 72.5% of patients receiving (OBV/PTV/r)±dasabuvir (DSV)±ribavirin (RBV) treatment was genotype 1 b. In the study performed Bayan K et al., SVR 12 was 100% and the rate of discontinuation of medication was 1.7% but in our study, SVR 12 was found to be 99% and no patient discontinued treatment.

CONCLUSION

In our study, there was no discontinuation of treatment due to reasons such as side effects and we found that the rates of sustained virologic response in all three treatment groups were 94% or higher in the groups treated for 12 weeks. Our single center study showed that 12 weeks of the LDV+SOF, SOF+RBV, PrOD were a highly effective treatment for patients with chronic HCV infection with a different genotype. The duration of treatment was not seen the need to extend to 24 weeks.

Conflicts of Interest: There is no conflict of interest.

Table 1a. Comparison of general characteristics.

Characteristic	**LDV+SOF (n: 101)**	**SOF+RBV (n: 98)**	**PrOD (n:91)**	**p Value**
Age (mean±SD)	64.3±12.7	62.5± 12.3	60±15.3	**<0.01**
Female, n, (%)	50 (49.5)	43 (43.8)	41 (45)	.085
Treatment experienced, n, (%)	51 (50.5)	8 (8.2)	8 (8.8)	**0.01**
Comorbidities, n, (%)	34 (33.6)	14 (14.2)	13 (14.2)	**<0.01**
Diabetes mellitus	32(31.6)	10 (10.2)	12 (13)	**<0.01**
CAD	2 (2)	4 (4)	1 (1)	.12
Hb (g/dl±SD)	12.65±1.8	13.13± 1.31	11.33±1.53	0.260
AST (U/l±SD)	98.25±50.2	95.75±69.7	101.5±75.2	.95
ALT (U/l±SD)	95.0±46.0	86.5±69.1	98.6±69.2	.45
Platelets (1000/мl±SD)	145.24±8.2	142.75±4.5	148.62±2.6	.98
Albumin, g/dL (mean±SD)	4.02±0.8	4.01±0.6	4.05±0.4	.94
Total bilirubin, mg/dL (mean±SD)	1.08±0.42	1.05±0.6	1.2±0.4	.38

INR (mean±SD)	1.17±0.24	1.12±0.5	1.18±0.32	.15
HCV-RNA log10 IU/mL, mean±SD	6.21±0.62	6.23±0.54	6.25±0.70	.697

p <0.05, Statistically Significant

Table 1b. Comparison of general characteristics.

Characteristic	**LDV+SOF (n: 101)**	**SOF+RBV (n: 98)**	**PrOD (n:91)**	**p Value**
HCV Genotype:				
Genotype 1	1 (1)	0 (0)	2 (2.2)	.32
Genotype 1a	5 (5)	0 (0)	16 (17.6)	**<0.01**
Genotype 1b	86 (85.1)	0 (0)	66 (72.5)	**<0.01**
Genotype 2	0 (0)	25 (25.5)	0 (0)	**<0.01**
Genotype 2b	0 (0)	1 (1)	0 (0)	.37
Genotype 2c	0 (0)	1 (1)	0 (0)	.37
Genotype 3	0 (0)	65 (66.3)	0 (0)	**<0.01**
Genotype 3a	0 (0)	2 (2)	0 (0)	.13
Genotype 4	4 (4)	0 (0)	5 (5.5)	.07
Genotype 5a	1 (1)	0 (0)	0 (0)	.39
Genotype 2_3	0 (0)	4 (4.1)	0 (0)	.01
Genotype 2_4	1 (1)	0 (0)	0 (0)	.39
Genotype 3_4	2 (2)	0 (0)	0 (0)	.15
Genotype 1b_4	0 (0)	0 (0)	2 (2.2)	.11
Genotype 1a_2b	1 (1)	0 (0)	0 (0)	.39
Cirrhosis (%)	31 (31)	5 (5.1)	6 (6.5)	**<0.01**
HAI, mean±SD	8.93±2.97	7.02±2.30	7.39±2.61	**<0.01**
Fibrosis. mean±SD	3.29±1.41	1.97±0.89	2.25±0.97	**<0.01**

p <0.05, Statistically Significant

Table 1a-b. LDV+SOF: Ledipasvir Plus Sofosbuvir, SOF+RBV: Sofosbuvir Plus Ribavirin, PrOD: Ombitasvir/Paritaprevir/Ritonavir Plus Dasabuvir, CAD: Coronary Artery Disease, Hb: Hemoglobin, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, INR: International Normalized Ratio, HAI: Histological Activity Index.

Table 2. Response after 4- and 12-week treatment.

Response	**LDV+SOF (n: 101)**	**SOF+RBV (n: 98)**	**PrOD (n:91)**
HCV-RNA<25 IU/ml			
At 4 week At 12 week	95 (94) 99 (98)	94 (95.9) 96 (97.9)	88 (96.7) 90 (98.9)
Virologic breakthrough during treatment regimen	0	0	0
Patients with no virologic response	2(1)	2 (2)	1 (1)

LDV+SOF: Ledipasvir plus sofosbuvir, SOF+RBV: sofosbuvir plus ribavirin, PrOD: ombitasvir/paritaprevir/ritonavir plus dasabuvir.

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REVİEW ARTİCLE / DERLEME

5 Saat ve Üzeri Uçuşlarda Kompresyon Çorabı Giyilmesi ile Derin Ven Trombozu Oluşumunun Önlenmesi

Preventing Deep Vein Thrombosis with Compression Stockings in 5 Hours and Above Flights

Ayşe Çevirme[1], Tuğçe Ertürk[2]

[1]Sakarya Üniversitesi, Sağlık Bilimleri Fakültesi, Hemşirelik Bölümü/Halk Sağlığı Hemşireliği Anabilim Dalı, Sakarya, Türkiye

[2]Karapürçek Toplum Sağlığı Merkezi, Sakarya, Türkiye

Corrresponding Author: Ayşe Çevirme

Sakarya Üniversitesi, Tıp Fakültesi Dekanlık Binası, Halk Sağlığı Hemşireliği Anabilim Dalı, Esentepe Kampüsü, 54050 Serdivan/SAKARYA

Tel: +905363237836

Email: acevirme@sakarya.edu.tr

ORCID

Ayşe Çevirme, https://orcid.org/0000-0001-7116-2523

Tuğçe Ertürk https://orcid.org/0000-0002-4089-821X

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ÖZET

Bu çalışmada, 5 saat ve üzeri uçuşlarda kompresyon çorabı giyilmesi ile derin ven trombozunun oluşmasının önlenmesi hakkında ulusal ve uluslararası literatür taraması amaçlanmıştır. Literatürde süresi 3 saatten 7-8, hatta 12 saate varan uçuşlarda derin ven trombozu (DVT) proflaksisinin incelendiği çalışmalar mevcuttur. DVT epidemiyolojisine bakıldığında, daha çok uzun mesafeli uçuşlarda gözlendiğinden çalışmamızda ortalama bir süre olarak 5 saat ve üzeri çalışmalara yer verilmiştir. Çalışmada Cochrane, PubMed ve Google Akademik, Science Direct veritabanından ‘’deep vein thrombosis’’ ve ‘’compression stockings’’flights’’, ‘’derin ven trombozu’’ ve ‘’uçuş’’ anahtar kelimeleri kullanılarak 2000 yılı Ocak ayından 2019’a kadar olan 60’ı yabancı 74 çalışma taranmıştır. Anahtar kelimeler yoluyla özetlerini taradığımız 74 çalışmadan 44’ünün tam metinlerine ulaşılmıştır. Tam metinlerine ulaştığımız çalışmalar hem kaynak hemde tablo oluşturulması amacıyla

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değerlendirilmiştir. DVT-uçuş-kompresyon çorabı ilişkisini inceleyen 6 randomize kontrollü çalışma saptanmıştır. Tablo aşamasında bu çalışmalardan yararlanılmıştır. İncelenen 6 randomize kontrollü çalışmada toplam 2482 katılımcı değerlendirilmiştir. Tüm katılımcılarda toplam 48 derin ven trombozu (DVT) vakası bildirilmiştir (%1.93). Kontrol gruplarındaki toplam 1234 katılımcıdan 35'ünde DVT bildirilmiştir (%2.83). Kompresyon çorabı giydirilen 1248 katılımcıdan 13'ünde DVT bildirilmiştir (%1.04). Yalnızca bir çalışmada DVT vakası bildirilmemiş olup, diğer çalışmalarda kompresyon çorabının DVT insidansını azalttığı söylenebilir. Konu ile ilgili yapılmış çoğu çalışmanın sonucuna göre 5 saat ve üzeri uçuşlarda kompresyon çorabının giyilmesi ile derin ven trombozu oluşumu önlenebilir. Son 16 yıldır uzun mesafeli uçuşlarda kompresyon çoraplarının etkisinin değerlendirildiği randomize kontrollü çalışma yapılmamıştır. Yüksek kanıt temelli çalışmalar olan randomize kontrollü çalışmaların önemi düşünüldüğünde, önerimiz bu konuda güncel çalışmaların yapılması gerektiğidir.

Anahtar Sözcükler: Derin ven trombozu, kompresyon çorabı, uçuş

ABSTRACT

The aim of this study is to present a national and international literature on the prevention of the formation of deep vein thrombosis by wearing compression stockings in flights of 5 hours or more. In the literature, there are studies investigating the prophylaxis of deep vein thrombosis (DVT) in flights ranging from 3 hours to 7-8 or even 12 hours. When the epidemiology of DVT is observed, it is mostly observed in long-distance flights. In this study, 74 studies has been surveyed from 2000 years January to 2019 including 60 foreign based studies by using the keywords ''deep vein thrombosis'', ''flights'' and ''compression stocking'' in the Cochrane, PubMed, Science Direct and Google Scholar database. The full texts of 44 of the 74 studies that we have searched for keywords and abstracts have been reached. Six randomized controlled trials investigating the relationship between DVT-flight-compression stockings were obtained. These studies were utilized in the table stage. A total of 2482 participants were evaluated in 6 randomized controlled trials. A total of 48 cases of deep vein thrombosis (DVT) were reported in all participants (1.89%). Of the total 1234 participants in the control group, 35 had DVT (2.83%). DVT was reported in 13 out of 1248 participants wearing compression stockings (1.04%). No DVT cases were reported in only one study, and in other studies the compression stockings were found to reduce the incidence of DVT. In this study, it is shown that the formation of deep vein thrombosis can be prevented by wearing compression stockings in flights of 5 hours or more. Individuals traveling 5 hours or more should wear compression stockings during the flight.

Key words: Deep vein thrombosis, compression stockings, flight

Giriş

Hızlı ve güvenli seyahat etmek isteyenlerin tercihi havayolu ulaşımı, son yıllarda en çok tercih edilen seyahat tiplerinden biri haline gelmiştir. Büyük ölçüde büyüme görülen hava taşımacılığında son 1 yıl raporları incelendiğinde Türkiye'de iç hat uçuşlarında 60 milyon,

dış hat seferlerinde ise 45 milyon yolcunun uçuş gerçekleştirdiği görülmektedir. Hava taşımacılığında ve dış hatlar seyahatinde görülen artış ile birlikte uzun mesafeli uçuşlarda da büyük oranda artış izlenmiştir[1]. Clarke ve arkadaşlarının (2016) sistematik derlemesinde, Amerikan Göğüs Hekimleri Koleji Kanıta Dayalı Klinik Uygulama Kılavuzlarının 9. baskısından hareketle 5 saat ve üzeri uçuşlar için derin ven trombozu için artmış risk bildirilmiştir. Özellikle 5 saat ve üzeri uçuşlarda bireysel ve seyahate özgü risk faktörleri birleştiğinde birçok sorun ortaya çıkabilmektedir. Bu sorunların başında derin ven trombozu (DVT) oluşumu gelmektedir. Homans, 1954 yılında uzun mesafeli uçuşlardan sonra venöz tromboz vakası bildiren ilk kişi olmuştur[2]. Daha sonra uçakla yolculuğun ardından DVT, pulmoner emboli (PE), inme ve arteriyel tromboz saptanan pek çok olgu bildirilmiştir. Bu durum, ilk kez 1977'de Symington ve Stack tarafından "ekonomi sınıfı sendromu" olarak tanımlanmış olmakla birlikte, uzun süreli hareketsizliğe neden olan araba ve otobüs seyahatlerinden sonra da görülebildiğinden, "yolculuk trombozu" deyiminin daha uygun olabileceği önerilmektedir. Bu durum son yıllarda basında da geniş yer almakta ve yolculuğun bir risk faktörü olup olmadığı üzerinde durulmaktadır[3,4]. Derin ven trombozu venöz sisteminin herhangi bir yerinde görülebilecek önemli bir sağlık sorunudur. %90 oranında alt ekstremite venöz sisteminde ortaya çıkmaktadır[5,6]. Derin ven trombozunun ortaya çıkmasında Virchow triadı (kan akımı değişiklikleri, damar duvarı değişiklikleri ve koagülasyon bozuklukları) olarak adlandırılan hipotezin bir veya daha fazla faktörü etkendir[7,8,9]. Derin ven trombozunun insana ve seyahate özgü risk faktörleri bulunmaktadır. Uçak kabin basıncında ani değişimler, koltuk aralarının dar olmasına bağlı hareketsizlik, az su tüketimi, yolculuk sırasında çay- kahve gibi idrar söktürücü özelliği olan içeceklerin tüketilmesi, az nemli ortam damarda bulunmak pıhtılaşmaya meyli arttıran etkenlerdir. Pıhtının sonuçları da en basit olarak yüzeysel venlerde oluştuğunda kızarıklık ve ağrı ile seyreden ‘’tromboflebit’’, en ağır olarak da ‘’pulmoner emboli’’dir[4,10].

Derin Ven Trombozu Risk Faktörleri

Derin ven trombozu, çok faktörlü bir hastalıktır. Bireyin mevcut trombotik risk faktörlerine yeni risk faktörlerinin eklenmesi, trombozun gelişip gelişmeyeceğini belirlemektedir[11]. Tromboembolik Risk Faktörleri Konsensüs grubunun (Thromboembolic Risk Factors (THRIFT) Consensus Group) 1992'de hazırladığı risk faktörleri Amerikan Göğüs Hekimleri Derneği (American College of Chest Physicians-ACCP) tarafından 2008 yılında

güncellenmiştir[12]. Buna göre insana özgü tromboembolik risk faktörleri; artan yaş, immobilite (72 saatten fazla), parezi, venöz tromboemboli öyküsü, kanser ve/veya tedavisi, cerrahi travma (majör ya da alt esktremite), obezite, santral venöz kateter, inflamatuar bağırsak hastalığı, nefrotik sendrom, hamilelik, doğum sonrası dönem, östrojen tedavisi, östrojen içeren oral kontraseptifleri kullanma, kalp ya da solunum yetmezliği olmasıdır[6,13,14]. Hava yolu uçuşlarındaki seyahate özgü risk faktörleri; yeteri kadar sıvı almaması (dehidrasyon), havadaki nemin azlığı, ekonomi sınfında koltuk aralarının dar olması, uzun süre koltukta otururak seyahat edilmesi şeklinde sıralanmaktadır[15]. Yolculuk sırasında yetersiz sıvı alımı dehidratasyon nedeniyle tromboza eğilimi arttırmaktadır. Ayrıca uçak yolculukları sırasında alınan alkollü içecekler diüretik etkileri ile dehidratasyonu arttırdıkları gibi vazodilatör etkileri ile venöz stazı da arttırırlar. Bir çalışmada sağlıklı insanlarda sekiz saat uçak yolculuğu sonrası plazma ve idrar osmolaritesinin arttığı gösterilmiştir[16]. Buna karşılık, bir çalışmada ise dehidrasyon ile seyahatle ilişkili derin ven trombozu arasında bir ilişki olduğuna dair hiçbir kanıt bulunamamıştır. Buna göre hidrasyonun zararlı olması muhtemel değildir, fakat trombozun önlenmesi için şiddetle tavsiye edilememektedir[11]. Uçuş süresi ile artmış DVT riski arasında güçlü bir ilişki bulunmaktadır. 4 saat ve üzeri uçuşlarda, uçuş sırasında hareketsizlik ve cam kenarı koltuk (özellikle obez kişiler için) DVT riskini arttırmaktadır[17]. Her 2 saatlik ilave seyahat için %18 oranında artmış DVT riski vardır. En güçlü risk 8–10 saatlik seyahatle ilişkilidir[18]. Uçak yolculuğunda popliteal venlerin koltuk tarafından uzun süre kompresyonu, venöz staza yol açmaktadır. En az bir saat oturma pozisyonunda kalındığında, venöz stazla birlikte kan akışı azalmaktadır. Bacak venlerindeki kanda protein, hematoktrit ve viskozite artmaktadır. Daha uzun süreli aralıksız oturmalarda ise mikrotravmalar sonucu damar duvarının direkt hasarı ile trombüs için zemin oluşmaktadır. Böylece uzun süreli oturur pozisyonda kalmak Virchow triadını oluşturan; staz, hiperkoagülasyon ve damar duvarı hasarının meydana gelmesine neden olmaktadır[16]. Koridor tarafındaki koltuklar, ortadaki ve cam kenarındaki koltuklara kıyasla hareket alanı sağlamaktadır. Amerikan Göğüs Hekimleri Koleji, uzun mesafeli seyahatlerde DVT 'yi azaltmaya yönelik kılavuz ilkeler arasında sık sık ambulasyon, baldır ve bacak egzersizleri, koridorda oturma, kompresyon çoraplarını önermektedir. Bireysel risk faktörlerine sahip yüksek riskli yolcular için koruyucu önlemlerin bireysel olarak planlanmalıdır[18]. Atmosferin bazı fiziksel özellikleri gökyüzünde yükseldikçe değişmektedir. Uçuş sırasında yükseklik arttıkça ısı, atmosferik basınç ve parsiyel oksijen düzeyi düşmektedir. 8000 feet'te solunan

havadaki oksijen %21'den %15.1-17.1 düzeyine inmektedir. Bireyin fizyolojik özelliklerine göre değişmekle birlikte, 8000 feet'te sağlıklı insanlarda bile kandaki oksijen saturasyonu %85-91 civarına inmektedir. Hipoksi vücutta fibrinolitik aktiviteyi azaltır. Bunun sonucunda oluşan vazodilatasyon venöz stazı arttırarak tromboz için zemin hazırlamaktadır. Hiçbir tromboz riski taşımayan olgularda da uzun uçuşlar sonucu DVT gelişebileceği bildirilmiştir[16]. Bu durum da uçuşlarda kompresyon çorabı giyilmesinin önemini yansıtmaktadır.

Dünya Sağlık Örgütü yüksek riskli gruplarda uzun süreli uçak yolculuğu ile tromboz arasında bir ilişki olabileceğini kabul etmektedir[4]. Tromboz oluşumunda yolculuğun mesafesi ve süresi önemli bir risk faktörü olup, hem uçak hem de araba yolculuklarından sonra görülebilmektedir. Literatürde süresi 3 saatten 7-8, hatta 12 saate varan uçuşlarda DVT proflaksisinin incelendiği çalışmalar mevcuttur. DVT epidemiyolojisine bakıldığında, daha çok uzun mesafeli uçuşlarda gözlendiğinden çalışmamızda ortalama bir süre olarak 5 saat ve üzeri çalışmaların önemine değinilmiştir. Havayolu ulaşımındaki artış düşünüldüğünde, bu konudaki güncel yüksek kanıtlı randomize kontrollü çalışmalarının varlığı önemlidir. Bu çalışmada uzun mesafeli havayolunda kompresyon çorabının DVT'yi önleyip önlemediğinin yanı sıra literatürdeki yüksek kanıtlı çalışmaların güncelliğini incelemek hedeflenmiştir. Böylelikle literatürdeki DVT-uçuş-kompresyon çorabı ilişkisi hakkındaki güncel randomize çalışma açığı ortaya konulabilecektir.

Gereç-Yöntemler

Çalışmada Cochrane, PubMed ve Google Akademik veritabanından ''deep vein thrombosis'' ve ''compression stockings'', ''flights'', ''derin ven trombozu'' ve ''uçuş'' anahtar kelimeleri kullanılarak 2000 yılı ocak ayından 2019'a kadar olan bütün çalışmaların başlıkları tarafımızca taranmıştır. Tarama yaparken dil sınırı konulmamıştır. Başlıklarında ''kompresyon çorabı'', ''uçuş'', ''havayolu yolcuları'', ''derin ven trombozu'' kelimelerini içeren çalışmaların özet kısımları değerlendirilip farklılıkları tartışılmıştır. Anahtar kelimeler yoluyla özetlerini taradığımız 74 çalışmadan 44'ünün tam metinlerine ulaşılmıştır. 44 çalışmanın 6'sı Türkçe, 22'si İngilizce olmak üzere 28'i derleme türündedir. Derleme olan çalışmaların 10'undan yararlanılmıştır. Kalan 12 çalışma ya bilgilerin tekrarı niteliğindeydi ya da konu olarak çalışmamızın dışındaydı. Sistematik derleme türünde 3 İngilizce çalışmadan yararlanılmıştır. Yararlanılan 2 vaka kontrol türündeki 2 İngilizce çalışmadan

yararlanılmıştır. 1977 yılındaki Symington ve arkadaşlarının vaka kontrol çalışmasına Aksu'nun (2003) çalışmasındaki referans yoluyla ulaşılmıştır. Çalışmalardan biri orijinal makaledir ve dili İngilizcedir. Bu çalışmalardan metin içi kaynakça olarak yararlanılmıştır. Bulgular bölümünde tabloda yararlanmak üzere konumuzla ilgili çalışmalardan erişebildiğimiz randomize kontrollü çalışmalar taranmıştır. Kanıt temelli olması açısından 2000 yılından 2019'a kadar olan ve tam metnine erişilebilen randomize kontrollü çalışmalar değerlendirilmiştir. Seçim kriteri olarak hava yolunda kompres çorabının kullanımını içeren çalışmalar veya hava yolunda DVT proflaksisinde kullanılan herhangi bir yöntemin arka planında kompresyon çorabının etkinliğini araştıran çalışmaların kullanılması sağlanmıştır. Her iki çalışma grubunun sonuçları bu derlemede birleştirilmiştir. İngilizce 4 meta analiz çalışmasından ikisi tabloda yer alan aynı randomize kontrollü çalışmaları incelediği için yararlanılmamıştır. Diğer iki çalışma ise çalışmamızın içeriğine uygun olmaması sebebiyle yararlanılmamıştır. Ulaşılan 6 randomize kontrollü çalışma 2001-2003 yılları arasındadır ve çalışmaların ana bulguları bulgular kısmında tablo halinde sunulmuştur.

Bulgular

Kompresyon çoraplarının hava yolu ile seyahat sonrası DVT riski üzerindeki etkisini değerlendirmek için toplam 6 randomize çalışma değerlendirilmiştir. Bu çalışmaların ana bulguları Tablo 1'de yer almaktadır. Çalışmalardan Scurr ve arkadaşlarının 2001'de gerçekleştirdiği çalışma hariç tümü, tek bir araştırmacı grubu tarafından yürütülmüştür. Değerlendirilen çalışmalarda 5 saat ve üzeri kesintisiz süren havayolu uçuşlarında random olarak kompresyon çorabı giydirilen katılımcılar ile giydirilmeyenler karşılaştırılmıştır. Bu derlemede yer alan altı çalışmada tüm çoraplar diz altı kompresyon çoraplarıdır. Çalışmaların üçünde sıkıştırma gücü ayak bileğinde 20-30 mm Hg iken, diğer üç çalışmada 10-20 mm Hg basınç sağladığı bildirilmiştir. Bulgular uçuş sonrasında ultrasonografi ile değerlendirilen semptomatik ve asemptomatik DVT; yüzeyel ven trombozu, ödem, pulmoner emboli ve ölüm gibi komplikasyonlar açısından değerlendirilmiştir. Bütün çalışmalar benzer bir tasarıma sahipti: sayıları 200'den 833'e kadar değişen uzun mesafeli hava yolcuları (>7 saat) kontrol grubuna veya müdahale grubuna randomize edildi. Tüm yolcular, uçuş sonrasında ultrasonografi ile asemptomatik DVT açısından rutin olarak tarandı (maksimum 48 saat içerisinde). Katılımcıları seçim yöntemi ve çalışma grubu ve sonuçları değerlendirenlerin müdahale grubu için kör olup olmadığı belirsizdir. Tüm katılımcılara uçuş sırasında yeterli

sıvı almaları ve hafif egzersiz yapmaları önerilmiştir. Değerlendirilen 6 çalışmadan 4'ü istatiksel olarak anlamlı olarak bildirilmiştir[19,20,21,22]. Scurr ve arkadaşlarının (2001) çalışmasında ayak bileğinde 20-30 mmHg basınç sağlayan elastik kompresyon çoraplarının etkisi en az 8 saat uçuş yapan 231 havayolu yolcusunda değerlendirilmiştir[19]. Elastik kompresyon çorabı grubuna randomize edilen 100 yolcunun hiçbiri DVT geliştirmezken, kontrol grubundaki 100 yolcunun 12'sinde (%12) asemptomatik DVT saptanmıştır. Belcaro ve arkadaşlarının (2001) çalışmasında elastik kompresyon çoraplarının etkisi 12.4 saatte tamamlanan bir uçuşta, DVT açısından riskli 833 yolcudan 422'sinde değerlendirilmiştir[20]. Uçuştan 6-10 saat önce ayak bileğinde 25 mmHg basınç sağlayan kompresyon çorabı giyen 422 yolcudan uçuş sonrasında 1 katılımcıda (%0.2) DVT bildirilmiştir. Kontrol grubunda ise 421 katılımcıdan 19'unda (%4.5) DVT gözlenmiştir. Belcaro ve arkadaşlarının (2002) 7-12 saatlik iki uçuşta yaptığı çalışmada düşük riskli 629 yolcu değerlendirilmiştir[21]. Ayak bileğinde 20-30 mmHg basınç sağlayan kompresyon çorabını giyen 315 yolcuda DVT görülmemiştir (%0). Kontrol grubunda 314 yolcudan 7'sinde (%2.2) DVT bildirilmiştir. Cesarone ve arkadaşlarının (2003) çalışmasında, düşük-orta riskli 341 yolcudan 172'sine ayak bileğinde 12-18 mmHg basınç sağlayan kompresyon çorabı giydirilmiştir. 7-8 saat süren uçuşun sonunda hiçbir katılımcıda DVT bildirilmemiştir[23]. Cesarone ve arkadaşlarının (2003) çalışmasında düşük-orta riskli 274 yolcudan 136'sına uçuştan 6-10 saat önce kompresyon çorabı giydirilmiştir (14-17 mmHg). 7-8 saatlik uçuşun sonunda kompresyon çorabı giyen grupta DVT görülmezken, kontrol grubundaki 138 katılımcının 2'sinde (%1.4) DVT bildirilmiştir[24]. Belcaro ve arkadaşlarının (2003) çalışmasında artmış riskli 205 katılımcıdan 103'ün uçuştan 3-4 saat önce kompresyon çorabı giydirilmiştir (14-17 mmHg)[21]. 11,5-12 saat süren uçuşun sonunda kompresyon çorabı giyen grupta 1(%0) katılımcıda, kontrol grubundaki 102 yolcunun 6'sında (%5.9) DVT bildirilmiştir[22]. İncelenen 6 randomize kontrollü çalışmada toplam 2482 katılımcı değerlendirilmiştir. Tüm katılımcılarda toplam 48 derin ven trombozu (DVT) vakası bildirilmiştir (%1.93). Kontrol gruplarındaki toplam 1234 katılımcıdan 35'inde DVT bildirilmiştir (%2.83). Kompresyon çorabı giydirilen 1248 katılımcıdan 13'ünde DVT bildirilmiştir (%1.04). Yalnızca bir çalışmada DVT vakası bildirilmemiş olup, diğer çalışmalarda kompresyon çorabının DVT insidansını azalttığı söylenebilir.

İncelenen çalışmalarda semptomatik DVT, pulmoner emboli ya da ölüm vakası bildirilmemiştir. Bu nedenle kompresyon çoraplarının bu vakalar için koruyucu etkisi belirsizdir.

Belcaro ve arkadaşlarının (2003) çalışmasında katılımcı sayısına ilişkin karar, önceden örneklem büyüklüğü hesaplamasına dayanmalıdır. Gecikmiş DVT, yüzeyel ven trombozu ve pulmoner emboli oluşumunu değerlendirmek için uzun gözlem süreleri gerekebilir. Tekrarlanan ölçümler değerli olabilir[22].

Havayolu yolcuları tarafından kullanılacak kompresyon çoraplarının optimal sıkıştırma basıncı incelenmelidir. Cevaplanması gereken sorular arasında, hangi katılımcı gruplarında uçuşla ilişkili trombozun önlenmesinde hangi sıkıştırma baskısının en etkili olduğu ve kompresyon çorabı uygulamasından hangi risk grubu hastalardan yararlanabileceği yer almaktadır.

Hiçbir çalışmada kompresyon çorabının giyilmesine bağlı olası sorunlar hakkında rapor bildirmemişlerdir. Yalnızca bazı çalışmalarda çorapların sorunsuzca tolere edildiği söylenmiştir.

Çalışmanın Sınırlılıkları

Çeşitli veritabanlarından anahtar kelimeler yardımıyla 2000-2019 yılları arasında geniş bir literatür taraması yapılmasına karşın ulaşılan randomize kontrollü çalışmaların en yenisi 2003 yılına aittir. Bu sonuç, güncel bir konu olan uçuşlarda DVT proflaksisine çok önem verilmediğini ve literatürde boşluk olduğunu göstermektedir.

Sonuç ve Tartışma

Clarke ve arkadaşlarının (2016) sistematik derlemesinde bildirdiği yüksek kalitedeki kanıtlar, uzun mesafeli uçuşlarda (en az dört saat süren) havayolu yolcularının kompresyon çoraplarını giymesinin asemptomatik DVT insidansını azalttığını göstermektedir[15]. Derlememizdeki incelenen çalışmalarda gösterildiği gibi, havayolu yolcularının seyahat öncesinden itibaren kompresyon çorapları giymesi ile asemptomatik DVT olgularında önemli bir düşüş beklenebilmektedir. Ancak bu çalışmada çorapların etkisinin ölümler, pulmoner emboli veya semptomatik DVT olgularında proflaktik etki sağlayamadığı, çünkü hiç olgu saptanmadığı belirtilmiştir. Tabloda yer alan çalışmaların tasarımları benzerdir. Çeşitliliği artırmak için diğer araştırmacılar tarafından ek çalışmalara ihtiyaç vardır. Gözlemci yanlılığını önlemek için ek çaba gösterilmeli ve sonuçların değerlendirilmesinde çift kör değerlendirme tekniği ugulanmalıdır. Kompresyon çoraplarının diğer önleyici tedbirlere göre maliyet etkinlik ve diğer avantajlarına dayanarak üstünlüğünü desteklemek

için daha fazla kanıt gereklidir. Antitrombotik ilaçlar gibi diğer önlemlerin profilaksisi ile kıyaslandığında kompresyon profilaksisini değerlendirmek için daha ileri çalışmalara ihtiyaç vardır. Kompresyon çoraplarının profilaktik etkisinin, diğer önleyici tedbirlerle birleştirildiğinde arttırılıp arttırılamayacağına ilişkin soruların da cevaplanması gerekmektedir. Konu ile ilgili yapılmış çoğu çalışmanın sonucuna göre 5 saat ve üzeri uçuşlarda kompresyon çorabının giyilmesi ile derin ven trombozu oluşumu önlenebilir. Son 16 yıldır uzun mesafeli uçuşlarda kompresyon çoraplarının etkisinin değerlendirildiği randomize kontrollü çalışma yapılmamıştır. Yüksek kanıt temelli çalışmalar olan randomize kontrollü çalışmaların önemi düşünüldüğünde, önerimiz bu konuda güncel çalışmaların yapılması gerektiğidir.

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Tablo 1. Randomize Kontrollü Çalışmalar

Birinci Yazar/ Yayınlanma Tarihi	Uçuş Süresi ve Uçuş Sayısı	Kompresyon Çorabı Giyme Başlangıcı	Kompresyon Çorabı Basıncı (mmHg)	Basıncın oluştuğu yer	Katılımcılar	Müdahale	DVT Görülen Katılımcılar (%)
Scurr /2001[19]	8 saat ve üzeri 2 uçuş	Uçuş başlamadan önce	20–30 mmHg	Ayak Bileği	200 rastgele seçilmiş yolcu	Kompres Çorabı Giymeyen:100	0 (0)
						Giyen:100	12 (12)
Belcaro /2001[20]	12.4 saatlik 1uçuş	Uçuştan 6-10 saat önce	25 mmHg	Ayak Bileği	*DVT açısından Riskli 833 yolcu	Kompres Çorabı Giymeyen:411	19 (4.5)
						Giyen:422	1(0.2)
Belcaro /2002[21]	7–8 ve 11-12 saatlik 2 uçuş	Uçuştan 2-3 saat önce	20-30 mmHg	Ayak Bileği	Düşük riskli 629 yolcu	Kompres Çorabı Giymeyen:314	7 (2.2)
						Giyen:315	0(0)
Cesarone/2003[23]	7–8 saatlik 1 uçuş	Uçuştan 3-4 saat önce	12-18 mmHg	Ayak Bileği	Düşük-orta riskli 341 yolcu	Kompres Çorabı Giymeyen:169	0(0)
						Giyen:172	0(0)
Cesarone/2003[24]	7-8 saatlik 1 uçuş	Uçuştan 6-10 saat önce	14-17 mmHg	Ayak Bileği	Düşük-orta riskli 274 yolcu	Kompres Çorabı Giymeyen: 138	2 (1.4)
						Giyen:136	0(0)
Belcaro /2003[22]	11,5-12 saatlik 1 uçuş	Uçuştan 3-4 saat önce	14-17 mmHg	Ayak Bileği	Artmış riskli 205 yolcu	Kompres Çorabı Giymeyen:102	6(5.9)
						Giyen:103	1(0)

*DVT: Derin ven trombozu.

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CASE REPORT / OLGU SUNUMU

A Rare Cause Of Ascites, Pancreatic Ascites, And Successful Treatment With Endoscopic Transpapillary Stenting

Asitin Nadir Bir Nedeni Pankreatik Asit; Endoskopik Transpapiller Stent İle Başarılı Tedavisi

Tezcan Kaya[1], Nesibe Altay[2], Sultan Seçil Ersoy[2]

[1] Sakarya University Faculty of Medicine, Department of Internal Medicine

[2] Sakarya University Faculty of Medicine

Corresponding author: Tezcan Kaya, MD, Associate Professor

Sakarya University Faculty of Medicine, Department of Internal Medicine

54100 Sakarya, Turkey.

Tel: +90- 264 8884077, Fax: +90- 264 275 91 92,

E-mail: tezcankaya@gmail.com

ORCID

Tezcan Kaya, https://orcid.org/0000-0003-0483-2333

Nesibe Altay, https://orcid.org/0000-0002-6461-7961

Sultan Seçil Ersoy https://orcid.org/0000-0002-1506-284X

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ABSTRACT

Pancreatic ascites is one of the rare cause of ascites. It usually occurs due to a complication of chronic pancreatitis, pancreatic trauma, or damage to the ducts during surgical procedures. There are case reports in the literature about the treatment of pancreatic ascites and different approaches have been reported. The main recommended methods of treatment for pancreatic ascites are conservative management, transpapillary stenting, and surgery. In this report, we describe a case with pancreatic ascites that treated successfully with endoscopic transpapillary stenting.

Keywords: Ascites, Endoscopic retrograde cholangiopancreatography, Pancreatic ascites, Pancreatitis

ÖZ

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Pankreatik asit nadir bir asit nedenidir. Genellikle kronik pankreatitin bir komplikasyonu, pankreatik travma veya cerrahi sırasında pankreatik kanallarda hasarlanma sonucu oluşur. Pankreatik asit tedavisi ile ilgili literatürde olgu sunumları mevcuttur ve farklı yaklaşımlar bildirilmiştir. Pankreatik asitin tedavisinde başlıca önerilen yöntemler konservatif tedavi, transpapiller stent yerleştirilmesi ve cerrahidir. Bu bildiride Pankreatik asiti olan ve endoskopik transpapiller stent yerleştirilmesi ile başarılı bir şekilde tedavi edilen bir olgu sunduk.

Anahtar sözcükler: Asit, Endoskopik retrograd kolanjiyopankreatografi, Pankreatik asit, Pankreatit

INTRODUCTION

Ascites is defined as the excessive accumulation of fluid in the abdominal cavity. At the more than 80% of patients with ascites the cause is liver cirrhosis.[1] Other common causes are portal hypertension, malignancy, heart failure, infections such as tuberculosis, and kidney diseases such as nephrotic syndrome. [1] Pancreatic ascites is one of the rare cause of ascites. [2, 3] It usually occurs due to a complication of chronic pancreatitis, pancreatic trauma, or damage to the ducts during surgical procedures.[2, 3] In this report, we describe a case with pancreatic ascites that treated successfully with endoscopic transpapillary stenting.

CASE REPORT

An 86-year-old female patient presented with a two months history of abdominal distention. Sonography revealed large amount of free fluid in the abdomen. Liver, spleen, and pancreas were normal. The patient was hospitalized to investigate the etiology of fluid in the abdomen. Her past medical history included type 2 diabetes and she had been using only insulin. She was not using any other drug or alcohol. Abdominal examination revealed findings of ascites. Her laboratory values were as follows: creatinine 1.3 mg/dl, amylase 637 U/L (20-160), lipase 53 U/L (8-78), C-reactive protein 82 mg/L (0-5). Complete blood count, thyroid stimulating hormone, aspartate transaminase, alanine transaminase, bilirubin, urine, and other laboratory tests were normal. Echocardiography and clinical evaluation revealed no signs of heart

failure. Abdominal computed tomography revealed free fluid at the perihepatic area, perisplenic area, and the midline of the abdomen **(Figure 1)**. The macroscopic appearance of the ascitic fluid was red-colored and slightly turbid **(Figure 2)**. Biochemical analysis results of ascitic fluid were as follows: amylase >6554 U/L (normally less than half of the serum amylase value) and serum ascites albumin gradient 0.9 g/dL. Ascitic fluid culture was negative and the cytology was benign. The level of adenosine deaminase in the ascitic fluid was normal. The patient hadn't chronic alcohol use, no previous hospitalization for pancreatitis, but had intermittent abdominal pain and dyspeptic symptoms suggesting chronic pancreatitis. Serum lipase levels were normal in the follow-up period and serum amylase levels were continuously high at 300-400 U/L levels. Our patient with pancreatic ascites underwent conservative medical treatment including total parenteral nutrition, octreotide, and diuretic. The amount of ascites and complaints did not change. Persistent high levels of amylase suggested internal pancreatic fistula. The patient was consulted with gastroenterologist and endoscopic retrograde cholangiopancreatography (ERCP) was performed. In ERCP, the duodenal papilla was fibrotic, biliary sphincterotomy was performed, the pancreatic duct was imaged but no major pancreatic leakage was observed. Pancreatic sphincterotomy was performed considering the clinical status of the patient. A plastic stent was inserted into the pancreas duct, extending to the tail. At the clinical follow-up of the patient, serum amylase levels decreased to 170 U/L and the amount of ascites decreased. Patient was discharged with regression of her initial complaints. The final diagnosis was pancreatic ascites secondary to the chronic pancreatitis.

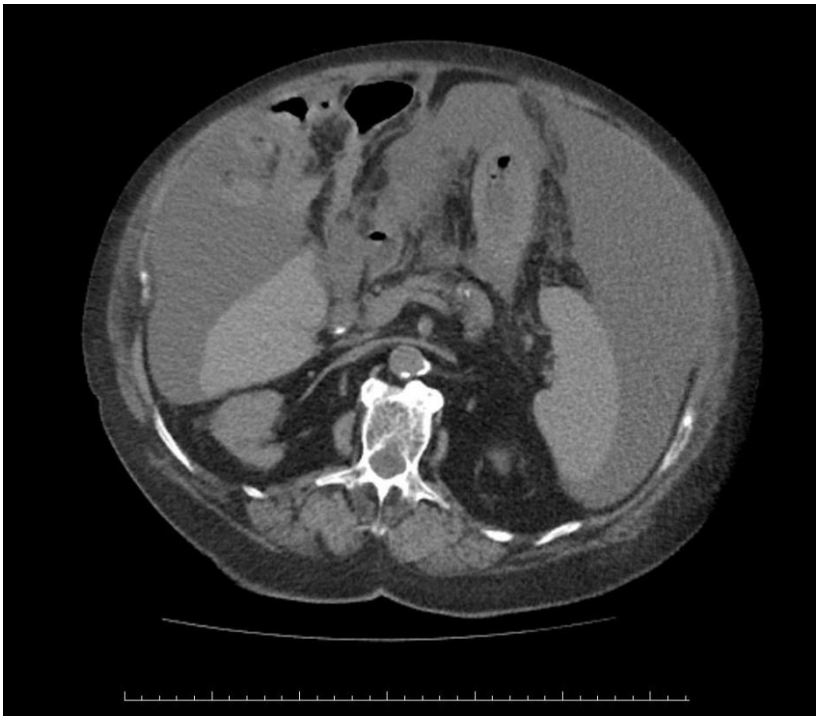

Figure 1: Abdominal CT scan demonstrates free peritoneal fluid.

Figure 2: Macroscopic appearance of the pancreatic ascites.

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DISCUSSION

Diagnosis of the disease causing ascites is important in terms of determining the treatment method. Pancreatic ascites is one of the rare cause of ascites.[2, 3] It is usually caused by pancreatic fluid passing into the peritoneal cavity as a result of damage in the pancreatic ducts. The amylase level of pancreatic ascites is generally higher than 1000 U/L and the serum-ascites albumin gradient is below 1.1 g/dL. The most common cause of pancreatic ascites is chronic pancreatitis with approximately 80% and occurs in approximately 4% of patients with chronic pancreatitis.[2, 3] It may also develop after acute pancreatitis, trauma, and pancreatic/peripancreatic surgery.[2, 3]

The main recommended methods of treatment for pancreatic ascites are conservative management, transpapillary stenting, and surgery.[3-5] In the first stage of treatment, oral nutrition is discontinued and total parenteral nutrition is recommended. This may reduce pancreatic exocrine secretions and ascites. In addition, somatostatin or octreotide treatment can also be used to reduce pancreatic secretions. ERCP is also recommended to detect leakage from pancreatic ducts in patients.[3-5] Stenting of the pancreatic ducts can also be performed when necessary with ERCP. Surgical management may be required in patients who do not respond to medical treatment. However, the mortality rate of surgical interventions may be high. Surgical managements are consisting of partial pancreatic resection, cystogastrostomy, or cystojejunostomy.[4,5]

In patients with pancreatic ascites, ERCP can be used both for the detection of pancreatic fistula and for treatment. In our case, pancreatic fistula could not be demonstrated in ERCP. However, this does not rule out the pancreatic fistula. Failure to find the fistulas may result from inadequate contrast agent and the location of fistula. Bracher et al. reported that transpapillary pancreatic duct stent was placed in the treatment of 8 patients with pancreatic

ascites.[6] In this case series, pancreatic ascites resolved in 7 of 8 patients.[6] Shaikh et al. and Karlapudi et al. reported the treatment of two pancreatic ascites cases secondary to chronic pancreatitis.[7, 8] Both cases were successfully managed with endoscopic transpapillary stenting.[7, 8] In our case, it was successfully treated with a similar method. Surgical treatment was performed in another pediatric case of pancreatic acid secondary to chronic pancreatitis.[9]

In conclusions, chronic pancreatitis may rarely cause pancreatic ascites. It should be kept in mind that the etiology of ascites may also be pancreatic ascites. In addition, endoscopic transpapillary stenting is an alternative treatment option to surgical treatment in the patients with pancreatic ascites.

Conflict of Interests: The authors declare no conflict of interests.

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