TÜRK YOĞUN BAKIM DERGİSİ

TURKISH JOURNAL OF INTENSIVE CARE

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

E-ISSN: 2602-2974

CİLT / VOLUME 20
SAYI / ISSUE 2
HAZIRAN / JUNE 2022

ÖZGÜN ARAŞTIRMALAR / ORIGINAL RESEARCHES

OLGU SUNUMLARI / CASE REPORTS

galenos yayınevi

TURKISH JOURNAL
OF INTENSIVE CARE

CİLT / VOLUME 20
SAYI / ISSUE 2
HAZIRAN / JUNE 2022

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

TÜRK
YOĞUN
BAKIM
DERGİSİ

Yazışma Adresi / Correspondence Address
Türk Yoğun Bakım Derneği
İnönü Cad., Işık Apt., No: 53 Kat: 4 Gümüşsuyu, 34437 Taksim, İstanbul, Türkiye
Tel.: +90 212 292 92 70
Faks: +90 212 292 92 71
E-posta: dergi@yogunbakim.org.tr - info@yogunbakim.org.tr
URL: http://www.yogunbakimderg.com

galenos yayınevi

Galenos Publishing House
Owner and Publisher
Derya Mor
Erkan Mor

Publication Coordinator
Burak Sever

Web Coordinators
Fuat Hocalar
Turgay Akpınar

Graphics Department
Ayda Alaca
Çiğdem Birinci
Gülay Saday
Gülşah Özgül

Finance Coordinator
Sevinç Çakmak
Emre Kurtulmuş

Project Coordinators
Aysel Balta
Duygu Yıldırm
Gamze Aksoy
Gülay Akın
Hatice Sever
Melike Eren
Özlem Çelik Çekil
Pınar Akpınar
Rabia Palazoğlu
Sümeyye Karadağ

Research&Development
Melisa Yiğitoğlu
Nihan Karamanlı

Digital Marketing Specialist
Ümit Topluoğlu

Yayınevi İletişim/Publisher Contact
Adres/Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Türkiye
Telefon/Phone: +90 (212) 621 99 25
Faks/Fax: +90 (212) 621 99 27
E-posta/E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr
Yayıncı Sertifika No/Publisher Certificate Number: 14521
Online Yayınlanma Tarihi/Online Publication Date: Haziran 2022/June 2022
E-ISSN: 2602-2974

Üç ayda bir yayımlanan süreli yayındır.
International scientific journal published quarterly.

TURKISH JOURNAL
OF INTENSIVE CARE

CİLT / VOLUME 20
SAYI / ISSUE 2
HAZIRAN / JUNE 2022

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

TÜRK
YOĞUN
BAKIM
DERGİSİ

AMAÇ VE KAPSAM

Türk Yoğun Bakım Dergisi (eski adı Türk Yoğun Bakım Derneği Dergisi ISSN: 2146-6416), Türk Yoğun Bakım Derneği'nin süreli yayın organı olup yoğun bakım içerikli, yayın dili Türkçe ve İngilizce olan, bağımsız ve önyargısız hakemlik ilkelerine dayanan ulusal, periyodik bir dergidir. Türk Yoğun Bakım Dergisi Mart, Haziran, Eylül, Aralık aylarında olmak üzere yılda dört sayı çıkar. Ayrıca yılda bir kez özel sayı yayınlanır.

Türk Yoğun Bakım Dergisi'nin hedefi nitelikli, sürekli ve yoğun bakım konusunda özgün bir periyodik olarak klinik ve bilimsel açıdan en üst düzeyde derlemeler, olgu sunumları ve araştırmalar yayınlamaktır. Dergi, yoğun bakım alanı ile ilgili olan hekimler, anestezistler, cerrahlar, pediatristler ve bu alanla ilgili diğer uzmanlara yöneliktir.

Türk Yoğun Bakım Dergisi, **Emerging Sources Citation Index (ESCI), ProQuest Health & Medical Complete, EBSCO Database, Gale, Index Copernicus, CINAHL, Tübitak/Ulakbim, Türk Tıp Dizini, Türkiye Atıf Dizini, Hinari, GOALI, ARDI, OARE, AGORA, J-Gate, IdealOnline** ve **Türk Medline**'da indekslenmektedir.

Açık Erişim Politikası

Dergide açık erişim politikası uygulanmaktadır. Açık erişim politikası Budapest Open Access Initiative (BOAI) http://www.budapestopenaccessinitiative.org/ kuralları esas alınarak uygulanmaktadır.

Açık Erişim, "[hakem değerlendirmesinden geçmiş bilimsel literatürün], İnternet aracılığıyla; finansal, yasal ve teknik engeller olmaksızın, serbestçe erişilebilir, okunabilir, indirilebilir, kopyalanabilir, dağıtılabilir, basılabilir, taranabilir, tam metinlere bağlantı verilebilir, dizinlenebilir, yazılıma veri olarak aktarılabilir ve her türlü yasal amaç için kullanılabilir olması"dır. Çoğaltma ve dağıtım üzerindeki tek kısıtlama yetkisi ve bu alandaki tek telif hakkı rolü; kendi çalışmalarının bütünlüğü üzerinde kontrol sahibi olabilmeleri, gerektiği gibi tanınmalarının ve alıntılanmalarının sağlanması için, yazarlara verilmelidir.

Abone İşlemleri

Türk Yoğun Bakım Dergisi, Türk Yoğun Bakım Derneği'ne üye olan ve tüm ilgili öğretim elemanlarına ücretsiz olarak dağıtılmaktadır. Derginin tüm sayılarına ücretsiz olarak www.yogunbakim.org.tr adresinden tam metin ulaşılabilir. Dergiye abone olmak isteyen kişiler Türk Yoğun Bakım Derneği'ne başvurmalıdır.

Adres: İnönü Cad. Işık Apt. No: 53 Kat: 4, 34437 İstanbul, Türkiye

Tel. : +90 212 292 92 70

Faks : +90 212 292 92 71

Web sayfası: www.yogunbakim.org.tr

E-posta: dergi@yogunbakim.org.tr - info@yogunbakim.org.tr

Baskı İzinleri

Editör: Prof. Dr. Perihan Ergin Özcan

Adres: İnönü Cad. Işık Apt. No: 53 Kat: 4, 34437 İstanbul, Türkiye

Tel.: +90 212 292 92 70

Faks: +90 212 292 92 71

Web sayfası: www.yogunbakimderg.com

E-posta: dergi@yogunbakim.org.tr - info@yogunbakim.org.tr

Reklam

Reklam ile ilgili başvurular Türk Yoğun Bakım Derneği'ne yapılmalıdır.

Adres: İnönü Cad. Işık Apt. No: 53 Kat: 4, 34437 İstanbul, Türkiye

Tel.: +90 212 292 92 70

Faks: +90 212 292 92 71

Web sayfası: www.yogunbakimderg.com

E-posta: dergi@yogunbakim.org.tr - info@yogunbakim.org.tr

Yayınevi Yazışma Adresi

Galenos Yayınevi Tic. Ltd. Şti.

Adres: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Türkiye

Tel.: +90 212 621 99 25

Faks: +90 212 621 99 27

E-posta: info@galenos.com.tr

Web sayfası: www.galenos.com.tr

Yazarlara Bilgi

Yazarlara Bilgi dergi sayfalarında ve www.yogunbakimderg.com web sayfasında yayınlanmaktadır.

Materyal Sorumluluk Reddi

Türk Yoğun Bakım Dergisi'nde yayınlanan tüm yazılarda görüş ve raporlar yazar(lar)ın görüşüdür ve Editör, Editörler Kurulu ya da yayıncının görüşü değildir; Editör, Editörler Kurulu ve yayıncı bu yazılar için herhangi bir sorumluluk kabul etmemektedir.

TURKISH JOURNAL
OF INTENSIVE CARE

CİLT / VOLUME 20
SAYI / ISSUE 2
HAZIRAN / JUNE 2022

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

TÜRK
YOĞUN
BAKIM
DERGİSİ

AIMS AND SCOPE

Turkish Journal of Intensive Care (formerly called Journal of the Turkish Society of Intensive Care ISSN: 2146-6416) is the periodical of the "Turkish Society of Intensive Care" and it covers subjects on intensive care, being published in Turkish and English languages, and is an independent national periodical based on unprejudiced peer-review principles. Turkish Journal of Intensive Care is regularly published four times a year; in March, June, September and December In addition, an annual special issue is published.

The aim of the Turkish Journal of Intensive Care is to publish original periodic research papers of highest scientific and clinical value on intensive care, reviews, case reports. It is directed towards for interested in intensive care, physicians, anesthesists, surgeons, pediatricians, and any other specialists concerned with these fields.

Turkish Journal of Intensive Care is indexed in **Emerging Sources Citation Index (ESCI), ProQuest Health & Medical Complete, EBSCO Database, Gale, Index Copernicus, CINAHL, Tübitak/Ulakbim Turkish Medical Database, Turkiye Citation Index, Hinari, GOALI, ARDI, OARE, AGORA, J-Gate, IdealOnline** and **Turk Medline**.

Open Access Policy

This journal provides immediate open access to its content on the principle that making research freely available to the public supports a greater global exchange of knowledge.

Open Access Policy is based on rules of Budapest Open Access Initiative (BOAI) http://www.budapestopenaccessinitiative.org/. By "open access" to [peer-reviewed research literature], we mean its free availability on the public internet, permitting any users to read, download, copy, distribute, print, search, or link to the full texts of these articles, crawl them for indexing, pass them as data to software, or use them for any other lawful purpose, without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. The only constraint on reproduction and distribution, and the only role for copyright in this domain, should be to give authors control over the integrity of their work and the right to be properly acknowledged and cited.

Subscription

The Turkish Journal of Intensive Care is sent free of charge to the subscribers and to relevant academic members. All published volumes in full text can be reached free of charge through the web site www.yogunbakim.org.tr. Requests for subscription should be addressed to Turkish Society of Intensive Care.

Address: İnönü Cad. Işık Apt. No: 53 Kat: 4, 34437 İstanbul, Turkey

Phone : +90 212 292 92 70

Fax : +90 212 292 92 71

Web page: www.yogunbakim.org.tr

E-mail: dergi@yogunbakim.org.tr - info@yogunbakim.org.tr

Print Permissions

Editor: Prof. Dr. Perihan Ergin Özcan

Address: İnönü Cad. Işık Apt. No: 53 Kat: 4, 34437 İstanbul, Turkey

Phone: +90 212 292 92 70

Fax: +90 212 292 92 71

Web page: www.yogunbakimderg.com

E-mail: dergi@yogunbakim.org.tr - info@yogunbakim.org.tr

Advertisement

Applications for advertisement should be addressed to Turkish Society of Intensive Care.

Address: İnönü Cad. Işık Apt. No: 53 Kat: 4, 34437 İstanbul, Turkey

Phone: +90 212 292 92 70

Fax: +90 212 292 92 71

Web page: www.yogunbakimderg.com

E-mail: dergi@yogunbakim.org.tr - info@yogunbakim.org.tr

Publisher Corresponding Address

Galenos Yayınevi Tic. Ltd. Şti.

Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Turkey

Phone: +90 212 621 99 25

Fax: +90 212 621 99 27

Web page: www.galenos.com.tr

E-mail: info@galenos.com.tr

Instructions to Authors

Instructions to authors are published in the journal and on the web page www.yogunbakimderg.com.

Material Disclaimer

The author(s) is (are) responsible from the articles published in the Turkish Journal of Intensive Care. The editor, editorial board and publisher do not accept any responsibility for the articles.

TURKISH JOURNAL
OF INTENSIVE CARE

CİLT / VOLUME 20
SAYI / ISSUE 2
HAZIRAN / JUNE 2022

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

TÜRK
YOĞUN
BAKIM
DERGİSİ

YAZARLARA BİLGİ

Türk Yoğun Bakım Dergisi, Türk Yoğun Bakım Derneği'nin yayın organıdır. Dergi dört ayda bir (Nisan, Ağustos, Aralık) yayınlanan bağımsız, uluslararası hakemli bir dergidir.

Türk Yoğun Bakım Dergisi'ne gönderilen yazılar çift-kör hakemliğe tabi tutulur. Dergi Türkçe ve İngilizce dillerinde makaleler yayınlar.

Türk Yoğun Bakım Dergisi'nin kısa adı "Turk J Intensive Care"dir. Kaynaklarda kullanılırken bu şekilde belirtilmelidir.

Yoğun bakım alanına ilişkin özgün deneysel ve klinik araştırmaları, olgu sunumlarını, yayın kurulu kararı ile istenmiş derlemeleri, editöryal yorumları, editöre mektupları ve ulusal yoğun bakım kongrelerinde sunulan bildiri özetlerini yayımlar. Dergide yayınlanacak yazıların seçimine temel teşkil eden hakem heyeti, dergide belirtilen danışmanlar ve gerekirse yurt içi/dışı otörler arasından seçilir.

Türkçe yazılarda Türk Dil Kurumu'nun Türkçe Sözlüğü ve Yazım Kılavuzu temel alınmalıdır.

Yazıların Gönderilmesi

Türk Yoğun Bakım Dergisi makale başvuru ücreti ve ya makale işlem ücreti uygulamamaktadır.

Yazılar sadece online olarak kabul edilmektedir. Yazarların makale gönderebilmesi için web sayfasına (http://www.journalagent.com/tybdd/) kayıt olup şifre almaları gereklidir. Bu sistem online yazı gönderilmesine ve değerlendirilmesine olanak tanımaktadır.

Makale gönderimi yapılırken sorumlu yazarın ORCID (Open Researcher and Contributor ID) numarası belirtilmelidir. http://orcid.org adresinden ücretsiz olarak kayıt oluşturabilir.

Bu sistem ile toplanan makaleler International Committee of Medical Journal Editors (ICMJE), Index Medicus (Medline/PubMed) ve Ulakbim-Türk Tıp Dizini kurallarına uygun olarak sisteme alınmakta ve arşivlenmektedir.

Yayına kabul edilmeyen yazılar, sanatsal resimler hariç geriye yollanmaz.

Editör veya yardımcıları tarafından, etik kurul onayı alınması zorunluluğu olan klinik araştırmalarda onay belgesi (etik onay numarası ile birlikte), talep edilmektedir. Yazıların içeriğinden ve kaynakların doğruluğundan yazarlar sorumludur.

Yazarlar, gönderdikleri çalışmanın başka bir dergide yayınlanmadığı ve/veya yayınlanmak üzere incelemede olmadığı konusunda garanti vermelidir. Daha önceki bilimsel toplantılarda 200 kelimeyi geçmeyen özet sunumlarının yayınları, durumu belirtilmek koşulu ile kabul edilebilir. Tüm otörler bilimsel katkı ve sorumluluklarını bildiren toplu imza ile yayına katılmalıdırlar.

Hastalar mahremiyet hakkına sahiptirler. Belirleyici bilgiler, hasta isimleri ve fotoğraflar, bilimsel olarak gerekli olmayan durumlarda ve hasta (ebeveyn veya koruyucu) tarafından yayınlanmasına yazılı olarak bilgilendirilmiş bir onay verilmediği sürece yayınlanmamalıdır.

Bu amaçla, bilgilendirilmiş onay, hastanın yayınlanacak belirli bir taslağı görmesini gerektirir. Eğer gerekli değilse hastanın belirleyici detayları yayınlanmayabilir. Tam bir gizliliği yakalamak oldukça zordur ancak eğer bir şüphe varsa, bilgilendirilmiş onay alınmalıdır. Örneğin, hasta fotoğraflarında göz bölgesini maskelemek, yetersiz bir gizlilik sağlanmasıdır.

Yazarlar, takip edilen standartların, insan deneylerinden sorumlu komitenin (kurumsal ve ulusal) etik standartlarına ve 2013'de gözden geçirilmiş 1964 Helsinki Beyannamesine uygun olduğunu belirtmelidirler. Deney hayvanı ile olan çalışmalarda, yazarlar takip edilen standartların hayvan haklarına (laboratuvar hayvanlarının bakım ve kullanımı için rehber www.nap.edu/catalog/5140.html) uygun olduğunu ve hayvan etik komitesinin onayını aldıklarını belirtmelidirler. Etik kurul onayı ve bilgilendirilmiş onam formu alındığı araştırmanın "Gereç ve Yöntem" bölümünde belirtilmelidir.

Yazıların bilimsel ve etik sorumlulukları yazarlara, telif hakkı ise Türk Yoğun Bakım Dergisi'ne aittir. Yazıların içeriğinden ve kaynakların doğruluğundan yazarlar sorumludur. Yazarlar, yayın haklarının devredildiğini belirten onay belgesini (Yayın Hakları Devir Formu) yazıları ile birlikte göndermelidirler. Bu belgenin tüm yazarlar tarafından imzalanarak dergiye gönderilmesi ile birlikte yazarlar, gönderdikleri çalışmanın başka bir dergide yayınlanmadığı ve/veya yayınlanmak üzere incelemede olmadığı konusunda garanti vermiş, bilimsel katkı ve sorumluluklarını beyan etmiş sayılırlar.

Makale Değerlendirmesi

Dergiye yayımlanmak üzere gönderilen tüm yazılar 'iThenticate' programı ile taranarak intihal kontrolünden geçmektedir. İntihal taraması sonucuna göre yazılar red ya da iade edilebilir.

Tüm yazılar, editör ve ilgili editör yardımcıları ile en az iki danışman hakem tarafından incelenir. Yazarlar, yayına kabul edilen yazılarda, metinde temel değişiklik yapmamak kaydı ile editör ve yardımcılarının düzeltme yapmalarını kabul etmiş olmalıdırlar.

Makalelerin formatı Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication (http://www.icmje.org/) kurallarına göre düzenlenmelidir.

İncelemeye sunulan araştırmada olası bir bilimsel hata, etik ihlal şüphesi veya iddiasıyla karşılaşılırsa, bu dergi verilen yazıyı destek kuruluşların veya diğer yetkililerin soruşturmasına sunma hakkını saklı tutar. Bu dergi sorunun düzgün biçimde takip edilmesi sorumluluğunu kabul eder ancak gerçek soruşturmayı veya hatalar hakkında karar verme yetkisini üstlenmez.

Yayın Politikası ve Makale Yazım Kuralları aşağıda belirtilen maddeler "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" (2016, http://www.icmje.org/) temel alınarak hazırlanmıştır.

Araştırma makalelerinin hazırlığı, sistematik derleme, meta-analizleri ve sunumu ise uluslararası kılavuzlara uygun olmalıdır.

Randomize çalışmalar için; CONSORT (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285:1987-91) (http://www.consort-statement.org/).

Sistematik derleme ve meta-analizlerin raporlamaları için; PRISMA [Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097] (http://www.prisma-statement.org/).

Tanısal değerli çalışmalar için; STARD (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4) (http://www.stard-statement.org/).

Gözlemsel çalışmalar için; STROBE (http://www.strobe-statement.org/).

Meta-analizleri ve gözlemsel çalışmaların sistematik derlemeleri için; MOOSE [Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting "Meta-analysis of observational Studies in Epidemiology" (MOOSE) group. JAMA 2000; 283: 2008-12].

YAZI ÇEŞİTLERİ

Özgün Araştırmalar

Yazının tümünün 5000 kelimeden az olması gerekmektedir. İlk sayfa hariç tüm yazıların sağ üst köşelerinde sayfa numaraları bulunmalıdır. Yazıda, konunun anlaşılmasında gerekli olan sayıda ve içerikte tablo ve şekil bulunmalıdır.

Başlık sayfası, kaynaklar, şekiller ve tablolar ile ilgili kurallar bu dergide basılan tüm yayın türleri için geçerlidir.

1) Başlık Sayfası (Sayfa 1)

Yazı başlığının, yazar(lar)ın bilgilerinin, anahtar kelimelerin ve kısa başlıkların yer aldığı ilk sayfadır.

TURKISH JOURNAL
OF INTENSIVE CARE

CİLT / VOLUME 20
SAYI / ISSUE 2
HAZIRAN / JUNE 2022

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

TÜRK
YOĞUN
BAKIM
DERGİSİ

YAZARLARA BİLGİ

Türkçe yazılarda, yazının İngilizce başlığı da mutlaka yer almalıdır; yabancı dildeki yayınlarda ise yazının Türkçe başlığı da bulunmalıdır.

Türkçe ve İngilizce anahtar sözcükler ve kısa başlık da başlık sayfasında yer almalıdır.

Yazarların isimleri, hangi kurumda çalıştıkları ve açık adresleri belirtilmelidir. Yazışmaların yapılacağı yazarın adresi de ayrıca açık olarak belirtilmelidir. Yazarlarla iletişimde öncelikle e-posta adresi kullanılacağından, yazışmaların yapılacağı yazara ait e-posta adresi belirtilmelidir. Buna ek olarak telefon ve faks numaraları da bildirilmelidir.

Çalışma herhangi bir bilimsel toplantıda önceden bildirilen koşullarda tebliğ edilmiş ya da özeti yayınlanmış ise bu sayfada konu ile ilgili açıklama yapılmalıdır.

Yine bu sayfada, dergiye gönderilen yazı ile ilgili herhangi bir kuruluşun desteği sağlanmışsa belirtilmelidir.

2) Özet (Sayfa 2)

İkinci sayfada yazının Türkçe ve İngilizce özetleri (her biri için en fazla 200 sözcük) ile anahtar sözcükler belirtilmelidir.

Özet bölümü; Amaç, Gereç ve Yöntem, Bulgular, Sonuç şeklinde alt başlıklarla düzenlenir. Derleme, olgu sunumu ve eğitim yazılarında özet bölümü alt başlıklara ayrılmaz. Bunlarda özet bölümü, 200 kelimeyi geçmeyecek şekilde amaçlar, bulgular ve sonuç cümlelerini içermelidir.

Özet bölümünde kaynaklar gösterilmemelidir. Özet bölümünde kısaltmalardan mümkün olduğunca kaçınılmalıdır. Yapılacak kısaltmalar metindekilerden bağımsız olarak ele alınmalıdır.

3) Metin (Özetin uzunluğuna göre Sayfa 3 veya 4'den başlayarak)

Metinde ana başlıklar şunlardır: Giriş, Gereç ve Yöntem, Bulgular, Tartışma.

Giriş bölümü, çalışmanın mantığı ve konunun geçmişi ile ilgili bilgiler içermelidir. Çalışmanın sonuçları giriş bölümünde tartışılmamalıdır.

Gereç ve Yöntem bölümü, çalışmanın tekrar edilebilmesi için yeterli ayrıntılar içermelidir. Kullanılan istatistik yöntemler açık olarak belirtilmelidir.

Bulgular bölümü de çalışmanın tekrar edilebilmesine yetecek ayrıntıları içermelidir.

Tartışma bölümünde, elde edilen bulguların doğru ve ayrıntılı bir yorumu verilmelidir. Bu bölümde kullanılacak literatürün, yazarların bulguları ile direkt ilişkili olmasına dikkat edilmelidir.

Teşekkür mümkün olduğunca kısa tutulmalıdır. Her türlü çıkar çatışması, finansal destek, bağış ve diğer editöryal (istatistik analiz, İngilizce/Türkçe değerlendirme) ve/veya teknik yardım var ise metnin sonunda sunulmalıdır.

Metinde fazla kısaltma kullanmaktan kaçınılmalıdır. Tüm kısaltılacak terimler metinde ilk geçtiği yerde parantez içinde belirtilmelidir. Özette ve metinde yapılan kısaltmalar birbirinden bağımsız olarak ele alınmalıdır. Özet bölümünde kısaltması yapılan kelimeler, metinde ilk geçtiği yerde tekrar uzun şekilleri ile yazılıp kısaltılmalıdırlar.

4) Kaynaklar

Kaynakların gerçekliğinden yazarlar sorumludur.

Kaynaklar metinde geçiş sırasına göre numaralandırılmalıdır. Kullanılan kaynaklar metinde parantez içinde belirtilmelidir.

Kişisel görüşmeler, yayınlanmamış veriler ve henüz yayınlanmamış çalışmalar bu bölümde değil, metin içinde şu şekilde verilmelidir: [isim(ler), yayınlanmamış veri, 19...].

Kaynaklar listesi makale metninin sonunda ayrı bir sayfaya yazılmalıdır. Altıdan fazla yazarın yer aldığı kaynaklarda 6. isimden sonraki yazarlar için "et al" ("ve ark") kısaltması kullanılmalıdır. Dergi isimlerinin kısaltmaları Index Medicus'taki stile uygun olarak yapılır. Tüm referanslar Vancouver sistemine göre aşağıdaki şekilde yazılmalıdır.

a) Standart Makale: Intiso D, Santilli V, Grasso MG, Rossi R, Caruso I. Rehabilitation of walking with electromyographic biofeedback in foot-drop after stroke. Stroke 1994;25:1189-92.

b) Kitap: Getzen TE. Health economics: fundamentals of funds. New York: John Wiley & Sons; 1997.

c) Kitap Bölümü: Porter RJ, Meldrum BS. Antiepileptic drugs. In: Katzung BG, editor. Basic and clinical pharmacology. 6th ed. Norwalk, CN: Appleton and Lange; 1995. p. 361-80.

Birden fazla editör varsa: editors.

d) Toplantıda Sunulan Makale: Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Reinhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. p. 1561-5.

e) Elektronik Formatta Makale: Morse SS. Factors in the emergence of infectious disease. Emerg Infect Dis [serial online] 1995 1(1):[24 screens]. Available from:s URL:http://www/cdc/gov/ncidoc/EID/eid.htm. Accessed December 25, 1999.

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

5) Tablolar, Grafikler, Şekiller, Resimler

Tüm tablolar, grafikler veya şekiller ayrı bir kağıda basılmalıdır. Her birine metinde geçiş sırasına göre numara verilmeli ve kısa birer başlık yazılmalıdır. Kullanılan kısaltmalar alt kısımda mutlaka açıklanmalıdır. Özellikle tablolar metni açıklayıcı ve kolay anlaşılır hale getirme amacı ile hazırlanmalı ve metnin tekrarı olmamalıdır. Başka bir yayından alıntı yapılıyorsa yazılı baskı izni birlikte yollanmalıdır. Fotoğraflar parlak kağıda basılmalıdır. Çizimler profesyonellerce yapılmalı ve gri renkler kullanılmamalıdır.

Özel Bölümler

1) Derlemeler: Dergiye derlemeler editörler kurulu daveti ile kabul edilmektedir. Derginin ilgi alanına giren derlemeler editörlerce değerlendirilir.

2) Olgu Sunumları: Nadir görülen ve önemli klinik deneyimler sunulmalıdır. Giriş, olgu ve tartışma bölümlerini içerir.

3) Editöre Mektuplar: Bu dergide yayınlanmış makaleler hakkında yapılan değerlendirme yazılarıdır. Editör gönderilmiş mektuplara yanıt isteyebilir. Metnin bölümleri yoktur.

Yazışma Adresi

Tüm yazışmalar dergi editörlüğünün aşağıda bulunan posta veya e-posta adresine yapılabilir.

Türk Yoğun Bakım Derneği

Adres: İnönü Cad. Işık Apt. No: 53 Kat: 4, 34437 İstanbul, Türkiye

Tel.: +90 212 292 92 70

Faks: +90 212 292 92 71

Web sayfası: www.yogunbakimderg.com

E-posta: dergi@yogunbakim.org.tr

info@yogunbakim.org.tr

TURKISH JOURNAL
OF INTENSIVE CARE

CİLT / VOLUME 20
SAYI / ISSUE 2
HAZIRAN / JUNE 2022

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

TÜRK
YOĞUN
BAKIM
DERGİSİ

INSTRUCTIONS TO AUTHORS

Turkish Journal of Intensive Care is the periodical of the Turkish Society of Intensive Care. The journal is an independent, peer-reviewed international, published quarterly in April, August, December.

Submitted manuscripts to Turkish Journal of Intensive Care are subjected for double-blind peer-review. The journal publishes articles in Turkish and English languages.

The abbreviation of the Turkish Journal of Intensive Care is "Turk J Intensive Care". It should be denoted as it when referenced.

It publishes original experimental and clinical researches, case reports, invited reviews, editorial comments, letters to editor on topics related to intensive care, and poster abstracts presented in national intensive care congresses/meetings. The scientific board guiding the selection of the papers to be published in the journal consists of elected experts of the journal and if necessary, selected from national and international authorities.

Turkish Language Institution dictionary and orthography guide should be taken as basic for literary language for Turkish manuscripts.

Submission of Manuscripts

Turkish Journal of Intensive Care does not charge any article submission or processing charges.

Manuscripts can only be submitted electronically through the web site http://www.journalagent.com/tybdd/ after creating an account. This system allows online submission and review.

The ORCID (Open Researcher and Contributor ID) number of the correspondence author should be provided while sending the manuscript. A free registration can be done at http://orcid.org

The manuscripts are archived according to International Committee of Medical Journal Editors (ICMJE), Index Medicus (Medline/PubMed) and Ulakbim-Turkish Medicine Index rules. Rejected manuscripts, except artwork are not returned.

In clinical trials in which the approval ethics committee is prerequisite, the certificate of approval (including approval number) will be requested by the editor/assistant editors.

The authors should guarantee that their manuscript has not been published and/or is under consideration for publication in any other periodical. Only those data presented at scientific meetings in form of abstracts that does not exceed 200 words could be accepted for consideration if notification of the scientific conference is made. The signed statement of scientific contributions and responsibilities of all authors, and statement on the absence of conflict of interests are required.

Patients have a right to privacy. Identifying information, including the patients' names should not be published in written descriptions, and photographs, unless the information is scientifically essential and the patient (or parent or guardian) gives written informed consent for publication.

Identifying the patient details should be omitted if they are not essential. Complete anonymity is difficult to achieve, however, informed consent should be obtained if there is any doubt. For example, covering eyes with a band in the photographs is not sufficient to ensure confidentiality.

Authors should indicate in manuscript that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, revised 2013. In experimental animal studies the authors should indicate that the procedures followed were in accordance with animal rights (Guide for the care and use of laboratory animals. www.nap.edu/catalog/5140.html) and obtain animal ethics committee approval. The approval of the ethics committee and the fact that informed consent was given by the patients should be indicated in the Materials and Methods section.

The scientific and ethical liability of the manuscripts belongs to the authors and the copyright of the manuscripts belongs to the Turkish Journal of Intensive Care. Authors are responsible for the contents of the manuscript and accuracy of the references. All manuscripts submitted for publication must be accompanied by the Copyright Transfer Form [copyright transfer]. Once this form, signed by all the authors, has been submitted, it is understood that neither the manuscript nor the data it contains have been submitted elsewhere or previously published and authors declare the statement of scientific contributions and responsibilities of all authors.

The Review Process

All manuscripts submitted to the Turkish Journal of Intensive Care are screened for plagiarism using the 'iThenticate' software. Results indicating plagiarism may result in manuscripts being returned or rejected.

All manuscripts are reviewed by editor, related associate editor and at least two experts/referees. The authors of the accepted manuscript for publication should be in consent of that the editor and the associate editors can make corrections without changing the main text of the paper.

Manuscripts format should be in accordance with Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication (available at http://www.icmje.org/)

In case of any suspicion or claim regarding scientific shortcomings or ethical infringement, the Journal reserves the right to submit the manuscript to the supporting institutions or other authorities for investigation. The Journal accepts the responsibility of initiating action but does not undertake any responsibility for an actual investigation or any power of decision.

The Editorial Policies and General Guidelines for manuscript preparation specified below are based on "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (2016, archived at http://www.icmje.org/).

Preparation of research articles, systematic reviews and meta-analyses must comply with study design guidelines:

CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285: 1987-91) (http://www.consort-statement.org/);

PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

MANUSCRIPT TYPES

Original Researches

Manuscript should not exceed 5000 words. All pages of manuscript should be numbered at right top corner except the title page. In order to be comprehensible, papers should include sufficient number of tables and figures.

TURKISH JOURNAL
OF INTENSIVE CARE

CİLT / VOLUME 20
SAYI / ISSUE 2
HAZIRAN / JUNE 2022

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

TÜRK
YOĞUN
BAKIM
DERGİSİ

INSTRUCTIONS TO AUTHORS

The style for title page, references, figures and tables should be unique for all kind of articles published in this journal.

1) Title Page (Page 1)

This page should include the titles of the manuscript, knowledge about author(s), key words and running titles.

English title should take place for every article in the title page. Likely, Turkish title should be mentioned for articles in foreign language.

Turkish and English key words and running titles should also be included in the title page.

The names and full postal addresses (including institutions addresses) of authors and the author to whom correspondence is to be addressed should be indicated separately. Especially as e-mail addresses will be used for communication, e-mail address of the corresponding author should be stated. In addition, telephone and fax numbers must be notified.

If the content of the paper has been presented before, the time and place of the conference should be denoted.

If there are any grants and other financial supports by any institutions or firms for the study, information must be provided by the authors.

2) Summary (Page 2)

In the second page, Turkish and English summaries of the manuscript (maximum 200 words for each), and the key words should take place.

The summary consists of the following sections separately: Objective, Materials and Methods, Results, Conclusion. Separate sections are not used in the summaries for the review articles, case reports and educational articles. For these articles, the summaries should not exceed 200 words and briefly present the scope and aims of the study, describe the salient findings and give the conclusions.

The references should not be cited in the summary section. As far as possible, use of abbreviations are to be avoided. If any abbreviations are used, they must be taken into consideration independently of the abbreviations used in the text.

3) Text (According to the length of the summaries Page 3 or 4 and etc.)

The typical main headings of the text are as follows: Introduction, Materials and Methods, Results, Discussion.

The introduction, part should include the rationale for investigation and the background of the present study. Results of the present study should not be discussed in introduction part. Materials and methods section should be presented in sufficient detail to permit the repetition of the work. The statistical tests used should be stated. Results should also be given in detail to allow the reproduction of the study.

Discussion section should provide a thorough interpretation of the results. It is recommended that citations should be restricted to those which relate to the findings of the authors.

Acknowledgements should be as brief as possible. Any technical or financial support or editorial contributions (statistical analysis, English/Turkish evaluation) towards the study should appear at the end of the article.

The excessive use of abbreviations is to be avoided. All abbreviations should be defined when first used by placing them in brackets after the full term. Abbreviations made in the abstract and text are separately taken into consideration. Abbreviations of the full terms that are made in the abstract must be re-abbreviated after the same full term in the text.

4) References

Accuracy of reference data is the author's responsibility. References should be numbered according to the consecutive citation in the text. References should be indicated by parenthesis in the text.

Personal communications, unpublished observations, and submitted manuscripts must be cited in the text as "(name(s), unpublished data, 19...)".

The reference list should be typed on a separate page at the end of the manuscript and if there are more than 6 authors, the rest should be written as 'et al' or 've ark.' Journal titles should be abbreviated according to the style used in the Index Medicus. All the references should be written according to the Vancouver system as follows:

a) Standard Journal Article: Intiso D, Santilli V, Grasso MG, Rossi R, Caruso I. Rehabilitation of walking with electromyographic biofeedback in foot-drop after stroke. Stroke 1994;25:1189-92.

b) Book: Getzen TE. Health economics: fundamentals of funds. New York: John Wiley & Sons; 1997.

c) Chapter of a Book: Porter RJ, Meldrum BS. Antiepileptic drugs. In: Katzung BG, editor. Basic and clinical pharmacology, 6th ed. Norwalk, CN: Appleton and Lange; 1995. p. 361-80.

If more than one editor: editors.

d) Conference Papers: Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Reinhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. p. 1561-5.

e) Journal on the Internet (e-Publishing): Morse SS. Factors in the emergence of infectious disease. Emerg Infect Dis [serial online] 1995 1(1):[24 screens]. Available from:s URL: http://www/cdc/gov/ncidoc/EID/eid.htm. Accessed December 25, 1999.

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

5) Tables, Graphics, Figures, and Pictures

All tables, graphics or figures should be presented on a separate sheet. All should be numbered consecutively and a brief descriptive caption should be given. Used abbreviations should be explained further in the figure's legend. Especially, the text of tables should be easily understandable and should not repeat the data of the main text. Illustrations that already published are acceptable if supplied by permission of authors for publication. Photographs should be printed on glossy paper. Figures should be done professionally and no gray colors be used.

Special Parts

1) Reviews: The reviews within the scope of the journal will be taken into consideration by the editors; also the editors may solicit a review related with the scope of the journal from any authorized person in the field.

2) Case Reports: Case reports should present important and unique clinical experience. It consists of the following parts: Introduction, case, discussion.

3) Letters to the Editor: Views about articles published in this journal. The editor invites responses to letters as appropriate. Letters may be shortened or edited. There are no separate sections in the text.

Address for Correspondence

All correspondences can be done to the following postal address or to the following e-mail address, where the journal editorial resides:

Türk Yoğun Bakım Derneği

Address: İnönü Cad. Işık Apt. No: 53 Kat: 4, 34437 İstanbul, Turkey

Phone: +90 212 292 92 70

Fax: +90 212 292 92 71

Web page: www.yogunbakimderg.com

E-mail: dergi@yogunbakim.org.tr

info@yogunbakim.org.tr

TURKISH JOURNAL
OF INTENSIVE CARE

CİLT / VOLUME 20
SAYI / ISSUE 2
HAZIRAN / JUNE 2022

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

TÜRK
YOĞUN
BAKIM
DERGİSİ

İÇİNDEKİLER/CONTENTS

Turk J Intensive Care 2022;20:65-71
DOI: 10.4274/tybd.galenos.2021.29392

ÖZGÜN ARAŞTIRMA / *ORIGINAL RESEARCH*

Nihal Akçay,
Ülkem Koçoğlu Barlas,
Esra Deniz Papatya Çakır,
Mey Talip Petmezci,
Hasan Serdar Kıhtır,
Osman Yeşilbaş,
Bedir Akyol,
Esra Şevketoğlu

Dilate Kardiyomiyopatinin Tedavi Edilebilir Nedeni, Raşitizm; İki Yıllık Deneyim

Treatable Cause of Dilated Cardiomyopathy, Rickets; Two Years' Experience

Geliş Tarihi/Received : 28.04.2020
Kabul Tarihi/Accepted : 25.01.2021

Nihal Akçay, Ülkem Koçoğlu Barlas, Mey Talip Petmezci, Hasan Serdar Kıhtır, Osman Yeşilbaş, Esra Şevketoğlu
Sağlık Bilimleri Üniversitesi, İstanbul Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi, Çocuk Yoğun Bakım Kliniği, İstanbul, Türkiye

Esra Deniz Papatya Çakır
Sağlık Bilimleri Üniversitesi, İstanbul Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi, Çocuk Endokrinoloji Kliniği, İstanbul, Türkiye

Bedir Akyol
Sağlık Bilimleri Üniversitesi, İstanbul Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi, Çocuk Kardiyoloji Kliniği, İstanbul, Türkiye

Uzm. Dr. Nihal Akçay (✉),
Sağlık Bilimleri Üniversitesi, İstanbul Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi, Çocuk Yoğun Bakım Kliniği, İstanbul, Türkiye

E-posta : drnihalakcay@gmail.com
Tel. : +90 212 414 73 29
ORCID ID : orcid.org/0000-0002-8273-2226

ÖZ *Amaç:* Dilate kardiyomiyopati (DK), bir ya da her iki ventrikülün dilatasyonu ve sistolik disfonksiyonu sonucu ortaya çıkan bir durumdur. Raşitizm, DK'nin çok nadir bir nedenidir. Bu makalede, raşitizme bağlı DK gelişen ve başarılı şekilde tedavi edilen hasta serisi sunulacaktır.
Gereç ve Yöntem: Hastanemiz çocuk yoğun bakım ünitesinde (YBÜ) DK'ye bağlı kalp yetmezliği tanılarıyla takip edilmiş olan hastalar geriye dönük olarak tarandı. Hipokalsemi ve D vitamini düşüklüğü dışında kalp yetmezliğine neden olacak başka bir hastalığı olan hastalar çalışmaya alınmadı.
Bulgular: Raşitizm ile ilişkili kalp yetmezliği gelişen altı hasta çalışmaya dahil edildi. Hastaların yaş ortalaması 6,4±3,2 aydı. Tüm hastalarda büyüme gelişme geriliği mevcuttu. En sık solunum sıkıntısı nedeniyle hastaneye getirilmiş olmalarına rağmen, hepsinde ilk muayene sırasında konjestif kalp yetmezliği bulguları tespit edildi. D vitamini düzeyleri tüm hastalarda düşük saptandı. Hastalarımızın tedavi öncesi ejeksiyon fraksiyonu ortalamaları %35,16 (±10,66) iken tedavi sonrası %55 (±9,83) olarak saptandı. Tedavi sonrasında sol ventrikül fonksiyonunda belirgin iyileşme tespit edildi.
Sonuç: YBÜ'ye kalp yetmezliği tanısı ile yatırılan hastalarda raşitizm akla gelmeli ve D vitamini eksikliği, kardiyomiyopati ve kardiyak fonksiyon bozukluğu dahil diğer birçok komplikasyona neden olabileceğinden mutlaka tedavi edilmelidir.
Anahtar Kelimeler: D vitamini eksikliği, kardiyomiyopati, raşitizm

ABSTRACT *Objective:* Dilated cardiomyopathy (DC) results from dilatation of one or both ventricles and is caused by systolic dysfunction. Rickets are a rare cause of DC. Here, we present a case series of DC due to rickets, which was successfully treated.
Materials and Methods: Patients were followed-up at paediatric intensive care unit (ICU) with the diagnosis of DC-related heart failure, which was retrospectively evaluated. Patients with a disease other than hypocalcaemia and low vitamin D levels, which can cause heart failure, were excluded from this study.
Results: Six patients who developed rickets-related heart failure were included in this study. The mean age of the patients was 6.4±3.2 months. All patients had growth developmental delay. Although most of the patients were admitted to the hospital due to respiratory distress, congestive heart failure findings were detected at the first examination of all the patients. The vitamin D levels of all patients were low. While the pre-treatment mean ejection fraction (EF) of the patients was 35.16% (±10.66), the post-treatment mean EF was found to be 55% (±9.83). Significant improvement in left ventricular function was observed post-treatment.
Conclusion: In patients admitted to the ICU due to the diagnosis of heart failure, rickets should be considered and treated, considering that it can cause many other complications, including vitamin D deficiency, cardiomyopathy and cardiac dysfunction.
Keywords: Vitamin D deficiency, cardiomyopathy, rickets

Giriş

Dilate kardiyomiyopati (DKMP), bir ya da her iki ventrikülün dilatasyonu ve sistolik disfonksiyonu sonucu ortaya çıkan durumdur. Sistolik disfonksiyon, ejeksiyon fraksiyonunun (EF)<%50'nin altında olması olarak tanımlanır. DKMP'nin en sık nedenleri idiyopatik (%35-40), ailesel (%20 -35) ve akut miyokarditttir (%12). Viral enfeksiyonlar, endokrin bozuklukları, metabolik hastalıklar, kardiyotoksik ilaçlar ve bazı sistemik hastalıklar da DKMP'ye neden olabilir. Raşitizme bağlı hipokalsemi, DKMP'nin çok nadir bir nedenidir (1,2). Kalsiyum, miyokard kasının uyarılması ve kasılmasında önemli bir rol oynar. Bundan dolayı hipokalsemili hastalarda miyokard kontraktilitesi düşebilir (3). Hipokalsemi ile ilişkili geri dönüşümlü DKMP ile ilgili çok sayıda olgu raporları yayınlanmıştır (4-7). Raşitik hipokalsemik kardiyomiyopati; D vitamini eksikliği olan annelerden doğan ve emzirilen bebekler arasında artan bir toplum sağlığı sorunudur. Ayrıca yaşamı tehdit eden ciddi bir komplikasyondur (8). Ülkemizde yapılan çalışmalar hipokalseminin önemli bir nedeni olan raşitizmin ciddi bir sağlık sorunu olmaya devam ettiğini ve DKMP'ye neden olabileceğini göstermektedir (9-11). Bu çalışmada, şiddetli raşitizme ikincil kardiyomiyopati ve konjestif kalp yetmezliği olan hastaların klinik ve laboratuvar özellikleri değerlendirildi.

Gereç ve Yöntem

Çalışmamızda Kasım 2016-Aralık 2018 tarihleri arasında 16 yataklı üçüncü düzey çocuk yoğun bakım biriminde DKMP'ye bağlı kalp yetmezliği tanılarıyla takip edilmiş olan hastalar geriye dönük olarak tarandı. Bu olgular içinden hipokalsemi ve D vitamini düşüklüğü saptanan olgular çalışmaya dahil edildi. DKMP tanısı klinik, radyolojik ve ekokardiyografik bulgularla çocuk kardiyoloji uzmanı tarafından, raşitizm tanısı çocuk endokrin uzmanı tarafından kesinleştirildi. Hipokalsemi ve D vitamini düşüklüğü dışında kalp yetmezliğine neden olacak başka bir hastalığı olan hastalar çalışmaya alınmadı. Olguların yaş, cinsiyet, sosyoekonomik özellikleri, beslenme öyküleri, D vitamini replasmanı alıp almadıkları, önceki enfeksiyon öyküleri, aile anamnezi (ani kardeş ölüm öyküsü) ile birlikte fizik muayene bulguları (kraniyotabes, fontanel genişlikleri ve diğer raşitizm bulguları), pediatrik mortalite riski (PRISM) III skorları, organ yetmezlik indeksi (OFI) skorları, diğer tanıları ve hastane yatış süreleri, radyolojik ve laboratuvar sonuçları derlendi. Kardiyomiyopatiye neden olacak etiyolojiler açısından tetkik edilen hastaların; elektrokardiyogram, ekokardiyografi (EKO), akciğer grafisi, kan gazı analizi, sepsis taraması, böbrek ve karaciğer fonksiyon testleri, kalsiyum, iyonize kalsiyum, inorganik fosfat ve alkalin fosfataz dahil serum elektrolitleri, parathormon ve D vitamini seviyesi, serum kan aminoasitleri, idrar organik asitleri, metabolik hastalık tarama testi, viral solunum paneli (influenza, parainfluenza, rinovirüs, koranavirüs, respiratuar sinsityal virüs, adenovirüs, bocavirüs, enterovirüs, parechovirus, *Mycoplasma pneumoniae*), hepatit A, B ve C, Epstein-Barr virüsü, sitomegalovirüs, herpes simpleks virüs ve parvovirüs için gönderilen sonuçları derlendi. Tüm hastalara supin pozisyonda Terason 3200 smart cihazı ile hasta başı ekokardiyografik inceleme yapıldı. Ölçülen sol ventrikül fonksiyonu ve sol ventrikül sistolik sonu ve diyastol sonu çapları kaydedildi. Tüm olgular çocuk endokrinoloji ve çocuk kardiyoloji hekimlerinin önerileri dikkate alınarak çocuk yoğun bakım uzmanı tarafından takip ve tedavi edildi. Hastaların başvuru, taburculuk ve 1 ay sonra kontrole gelmek suretiyle EKO, D vitamini, kalsiyum, inorganik fosfat, alkalen fosfataz, magnezyum ve parathormon düzeylerine bakıldı. Çalışma Helsinki Deklarasyonu İlkeleri'ne uygun olarak yapıldı ve Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu'ndan 2019/131 protokol kodu ile onay alındı (karar no: 2019-06-11, tarih: 18.03.2019). Çalışmaya katılan hastaların ebeveynlerinden onam alındı.

İstatistiksel Analiz

Sürekli değişkenler ortalama ± standart sapma olarak ifade edilirken, kategorik değişkenler n (%) olarak ifade edildi. İstatistiksel hesaplamalar için Statistical Package for Social Science (SPSS) for Windows sürüm 24 kullanıldı.

Bulgular

Raşitizm ile ilişkili şiddetli hipokalsemi sonucu kalp yetmezliği gelişen altı hasta çalışmaya dahil edildi. Hastaların yaş ortalaması 6,4±3,2 aydı. Anne yaşı ortalaması 22,5±5,50 yıl idi. Doğum sırası dört hastada ikinci, iki hastada ilk doğumdu. Tüm hastalarda büyüme gelişme geriliği mevcuttu. Hastaların ortalama yoğun bakım yatış süresi 26,8±18,86 gündü. Hastaların PRISM III skoru ortalaması 12,8±6,61, OFI skor ortalaması 1,67±0,51 idi. D vitamini düzeyleri tüm hastalarda düşük, ortalama 7,28±3,00 saptandı. Hastaların beş tanesinde entübasyon ve mekanik ventilasyon (%83,3) ihtiyacı oldu. Olguların yatış ve tedavi sonrası laboratuvar verileri Tablo 1'de sunulmuştur.

Tablo 1. Hastaların demografik verileri, tedavi öncesi ve sonrası laboratuvar sonuçları

	Olgular							
	1	2	3	4	5	6	Ortalama	SS
Cinsiyet	Kız	Erkek	Kız	Erkek	Erkek	Erkek		
Yaş (ay) (%)	11,13	9,23	6,57	3,03	4,23	4,20	6,40	±3,20
Boy (cm)	65 (<3p)	62 (<3p)	62 (<3p)	58 (10-25p)	60 (3-10p)	60 (3-10p)	61,16	±2,40
Kilo (gr)	7000 (3-10p)	6060 (<3p)	6200 (3-10p)	5000 (3-10p)	6000 (3-10p)	5000 (<3p)	5970	±820
Anne yaşı (yıl)	33	18	24	20	20	20	22,50	±5,50
PRISM III	16	18	23	7	10	13	12,83	±6,62
OFI	1	2	2	2	2	1	1,67	±0,52
YBÜ yatış (gün)	10	53	46	13	28	11	26,83	±18,86
Kalsiyum (mg/dL) TÖ	5,00	4,80	5,30	5,50	6,10	6,40	5,51	±0,62
Kalsiyum (mg/dL) TS	10,20	11,30	9,50	9,70	10,50	10,20	10,23	±0,63
İyonize Ca (mmol/L) TÖ	0,76	0,64	0,54	0,79	0,72	0,80	0,70	±0,10
İyonize Ca (mmol/L) TS	1,22	1,26	1,14	1,16	1,21	1,12	1,18	±0,05
Fosfor (mg/dL) TÖ	2,7	4,2	11,1	3,8	4,9	2,5	4,86	±3,18
Fosfor (mg/dL) TS	7,58	5,19	5,35	4,65	4,60	3,80	5,19	±1,28
Magnezyum (mg/dL) TÖ	1,8	1,8	2,4	1,9	2,2	3,2	2,22	±0,52
Magnezyum (mg/dL) TS	2,06	1,62	2,16	2,65	1,64	1,61	1,93	±0,36
Alkalen fosfataz (U/L) TÖ	579	892	1017	2185	1107	489	1044,83	±608,92
Alkalen fosfataz (U/L) TS	515	926	275	697	288	727	571,33	±259,64
Parathormon (pg/mL) TÖ	1041	144	820	527	555	1141	704,66	±370,16
Parathormon (pg/mL) TS	134	29	65	42	46	39	59,16	±38,51
25-(OH)D_3 (ng/mL) TÖ	4,7	7,4	9,7	7,9	11	3	7,28	±3,00
25-(OH)D_3 (ng/mL) TS	31	35	30	38	36	37,5	34,58	±3,35
Anne 25-(OH)D_3 vitamini	7	12	7	7,2	9,2	7	8,23	±2,03
Pro BNP (ng/L)	4890	35000	35000	14465	16500	4737	18432	±13796
Entübasyon ihtiyacı	-	+	+	+	+	+		

BNP: Beyin natriüretik peptid, OFI: organ yetmezlik indeksi, PRISM III: pediatrik mortalite riski, TÖ: tedavi öncesi, TS: tedavi sonrası, SS: standart sapma, YBÜ: yoğun bakım ünitesi, 25-(OH)D_3: 25-hidroksivitamin D_3; Ca: kalsiyum

Tüm hastalar anne sütü alıyor olmalarına rağmen D vitamini replasmanı almıyorlardı. En sık solunum sıkıntısı nedeniyle hastaneye getirilmiş olmalarına rağmen, hepsinde ilk muayene sırasında konjestif kalp yetmezliği bulguları tespit edildi. Tüm hastalarda temel başvuru şikayeti solunum sıkıntısıydı. Hastalarımızın tedavi öncesi EF ortalamaları %35,16 (±10,66) iken tedavi sonrası %55 (±9,83) olarak saptandı. Tedavi sonrasında sol ventrikül fonksiyonunda belirgin iyileşme tespit edildi (Şekil 1A). Tüm hastalara milrinon infüzyonu, iki hastamızda hipotansiyon, dolaşım bozukluğu ve şok tablosu olduğundan adrenalin infüzyonu da tedaviye eklendi. Hastalarımızın başvuru şikayetleri, özgeçmiş, fizik muayene, raşitizm bulguları ve başlangıç tedavileri Tablo 2'de gösterilmiştir. Hastaların yatış ve taburculuk kardiyotorasik indeksleri (KTİ) değerlendirildiğinde belirgin olarak gerileme olduğu görüldü (Şekil 1B, Şekil 2). Etiyoloji açısından incelendiğinde tüm hastaların viral serolojik ve metabolik taramaları normaldi. Klinik iyileşmeden sonra tüm hastalar kardiyak fonksiyonları iyileşerek taburcu edildi.

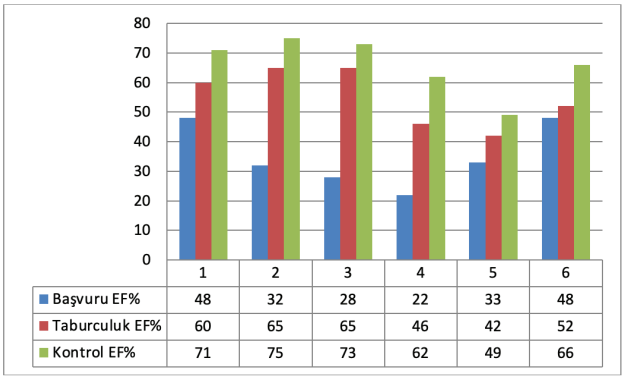
Tartışma

DKMP, ağırlıklı olarak, sol ventrikül sistolik disfonksiyon ile karakterizedir. Etkilenen bireyler kalp yetmezliği belirti ve bulgularını gösterir. Çocuklarda emerken yorulma, beslenme zorluğu, solunum sıkıntısı, kilo kaybı, taşikardi, gallo ritmi,

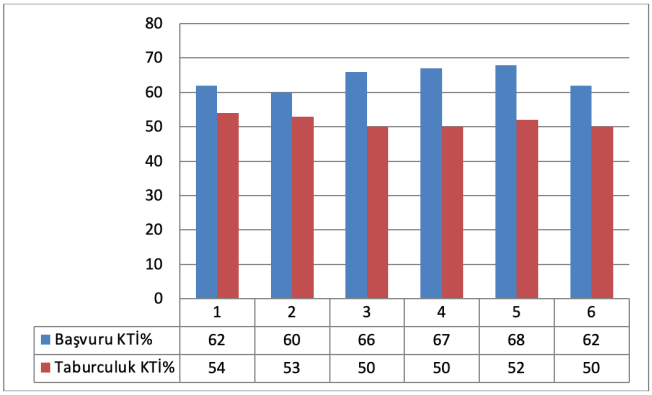
Tablo 2. Hastaların klinik özellikleri ve başlangıç tedavileri

Olgu no	Başvuru şekli	Özgeçmiş	FM	Raşitizm bulgusu	Tedavi
1	Solunum sıkıntısı, öksürük, ateş	Anne sütü ilk 6 ay almış. İlk 2 ay D vitamini takviyesi almış.	Gelişim geriliği, taşipne, suprasternal, interkostal retraksiyon, ekspiryum uzunluğu, 1/6 sistolik üfürüm, taşikardi, hepatomegali	Kaput quadratum, genis ön fontanel, el bileğinin genişlemesi	Milrinon, aspirin, furosemid kalsiyum ve D vitamini replasmanı
2	Nöbet geçirme, solunum sıkıntısı	Dört ay anne sütü, sonrasında inek sütü kullanmış, ek D vitamini kullanım öyküsü yok.	Subkostal ve interkostal retraksiyon, takipneik dispneik, bradikardik, 2/6 sistolik üfürüm, hepatomegali, KDZ>2 sn, hipotansiyon	Raşitik rozari kraniyotabes, el bileğinin genişlemesi	Milrinon, aspirin, adrenalin furosemid kalsiyum ve D vitamini replasmanı
3	Solunum sıkıntısı, kusma	Anne sütü ve inek sütü alıyor. Ek D vitamini öyküsü yok.	Subkostal ve interkostal retraksiyon, yaygın krepitan ral, 2/6 sistolik üfürüm, hepatomegali, KDZ>2 sn, hipotansiyon, alacalı deri görünümü	Kaput quadratum, raşitik rozari, geniş ön fontanel, el bileğinin genişlemesi	Milrinon, aspirin, adrenalin furosemid kalsiyum ve D vitamini replasmanı
4	Emmeme, solunum sıkıntısı, ateş	Anne sütü alıyor. Ek D vitamini öyküsü yok.	Taşipneik, subkostal retraksiyon, solda solunum sesleri azalmış, krepitan ral, 1/6 sistolik üfürüm, taşikardi, hepatomegali	Geniş ön fontanel, el bileğinin genişlemesi	Milrinon, aspirin, furosemid kalsiyum ve D vitamini replasmanı
5	Huzursuzluk, öksürük, solunum sıkıntısı	Anne sütü alıyor, ek D vitamini öyküsü yok	Bilateral, krepitan ral, 2/6 sistolik üfürüm, taşikardi, hepatomegali	Kaput quadratum, geniş ön fontanel	Milrinon, aspirin, furosemid, kalsiyum ve D vitamini replasmanı
6	Beslenememe, halsizlik, solunum sıkıntısı	Anne sütü alıyor, ek D vitamini öyküsü yok	Yaygın krepitan ral, 2/6 sistolik üfürüm, taşikardi, hepatomegali	Geniş ön fontanel, el bileğinin genişlemesi	Milrinon, aspirin, furosemid, kalsiyum ve D vitamini replasmanı

KDZ: Kapiller dolum zamanı, FM: fizik muayene

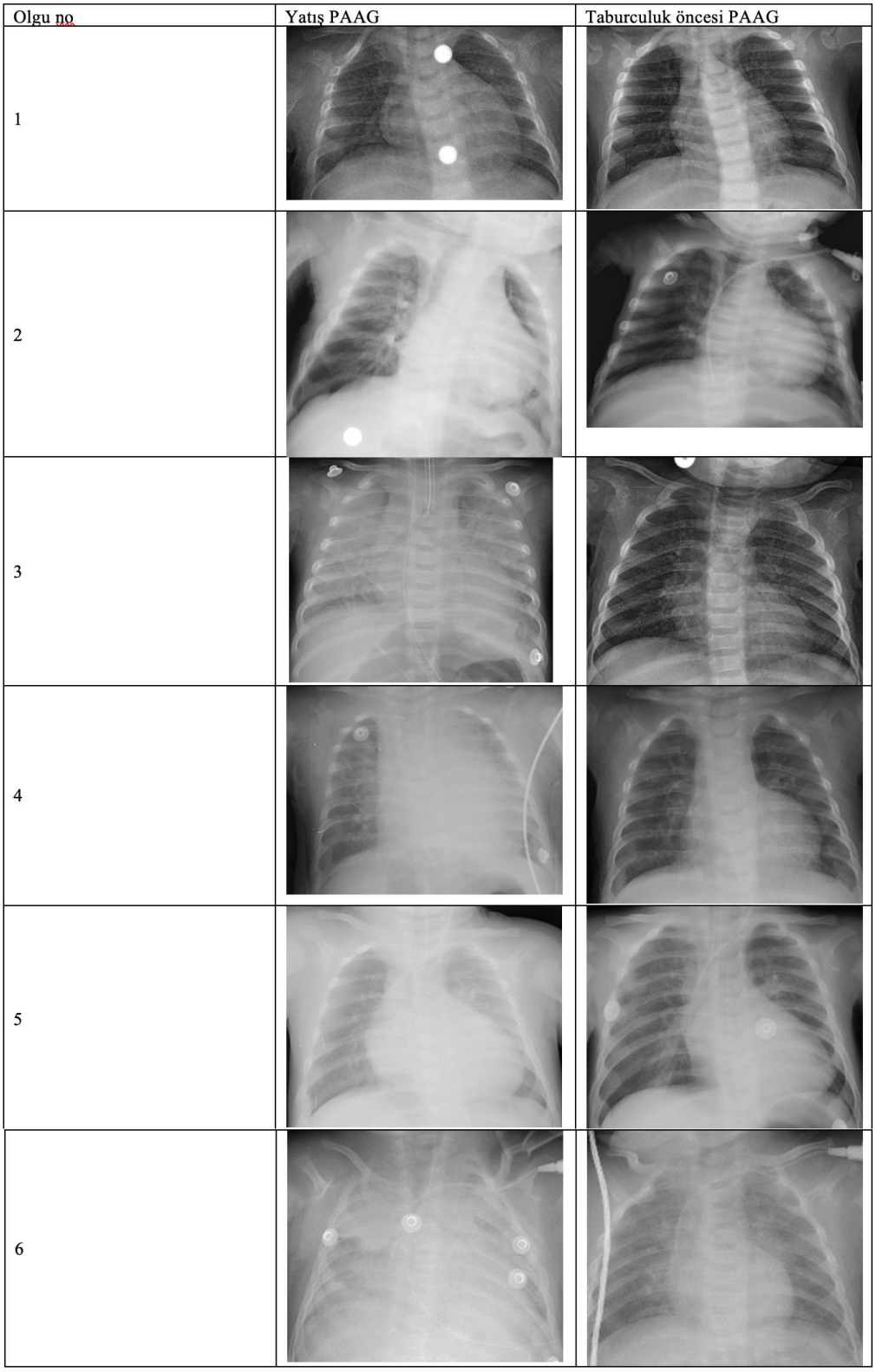


Şekil 1A. Başlangıç ve takipteki kardiyotorasik indeks ve ejeksiyon fraksiyonları. Başvuru, taburculuk ve kontrol ejeksiyon fraksiyon değerleri
EF: Ejeksiyon fraksiyon



Şekil 1B. Başvuru ve taburculuk kardiyotorasik indeks bulguları
KTİ: Kardiyotorasik indeks

juguler venöz distansiyon, solukluk, soğuk el ve ayaklar, hepatomegali ve mitral kapak yetersizliğine bağlı üfürüm görülebilir (12). Raşitik hipokalsemik kardiyomiyopati; kalp yetmezliği, aritmi, kardiyojenik şok ve ölüme neden olabileceği için D vitamini eksikliğinin en ciddi komplikasyonudur. Raşitizm ve DKMP sıklıkla bir arada bulunsa da, özellikle hastalar bütünsel olarak araştırılmazsa ve semptomlar subklinik ise gözden kaçabilir (13). Bizim çalışmamızda



Şekil 2. Hastaların tedavi öncesi ve sonrası akciğer grafileri
PAAG: Akciğer grafisi

yoğun bakıma başvuran hastaların tümünde başvuru şikayeti solunum sıkıntısı olmasına rağmen tüm hastalarda inotrop tedavisi gerektiren kalp yetmezliği saptandı. Bu hastaların yoğun bakım hastalık ağırlık skoru olarak PRISM değerleri orta derecede yüksek olup, OFI değerleri büyük çoğunluğunda iki organ yetmezliğini göstermekteydi (akciğer-kalp). Kalp yetmezliği etiyolojisi tarandığında hepsinde belirgin D vitamini yetmezliği, laboratuvar ve klinik bulguları saptanarak tedavi edildi ve hepsinde kalp yetmezliği ve solunum bulguları düzeldi. Serimizde, tüm hastalarımızın tedavi öncesi ile karşılaştırıldığında tedavi sonrası EF'sinde anlamlı artış, KTİ'de anlamlı azalma saptandı. Brown ve ark.'nın (2) 4-10 aylıkken tanı alan raşitizm ile ilişkili DKMP bulguları olan dört hastada inotropik ve antikonjestif tedavilerin yanı sıra kalsiyum ve D vitamini desteği ile tüm hastalar tedaviye yanıt verdiğini bildirmişlerdir. Benzer bir şekilde, 1999 ve 2012 yılları arasında Yilmaz ve ark. (10) raşitizm ilişkili hipokalsemi nedeniyle DKMP ve konjestif kalp yetmezliği gelişen sekiz hastada antikonjestif tedavilerin yanı sıra kalsiyum ve D vitamini desteği ile konjestif kalp yetmezliği belirtileri ortadan kalktığı ve kalp fonksiyonlarında belirgin iyileşme saptandığını göstermişlerdir. Literatürdeki çalışmalarda EF değerinde artış açısından değerlendirilmesine rağmen KTİ açısından değerlendirilmemiştir. KTİ ile değerlendirme deneyimli personel olmadığında tedaviye cevabı değerlendirmede kullanılabilir olduğunu düşünmekteyiz. Hipokalsemik DKMP tedavisinde; uzun süreli yoğun bakım ve inotrop desteği, serum kalsiyumunu hızla normalleştirmek için intravenöz kalsiyum infüzyonları ve oral alfakalsidol (veya kalsitriol), dekonjestif tedavi, ventilasyon ve bazen ekstrakorporeal membran oksijenasyonu (ECMO) tedavisi kullanılabilir (13). Bizim hastalarımızda bütün bu tedaviler uygulanmış, mekanik ventilasyon ihtiyacı olmuş ama ECMO ihtiyacı olan hasta olmamıştır.

Birinci olgumuzun annesi dışında tüm annelerin gebelik takiplerine gitmediği ve vitamin preparatı kullanmadıkları tespit edildi. Birinci olgumuzun sadece ilk 2 ay D vitamini tedavisi aldığı öğrenildi diğer hastalarımızın hiçbiri ek D vitamini kullanmamışlardı. Ülkemizde 2005 yılından itibaren D vitamini yetersizliğinin önlenmesi ve kemik sağlığının korunması projesi dahilinde tüm bebeklere 400 ünite/gün dozunda D vitamini ücretsiz verilmektedir (14). Yine 2011 yılında gebelere D vitamini destek programında D vitamininin kullanılamayacağı durumlar haricinde kalan bütün gebelere, gebeliğin 12. haftasından itibaren ve doğum sonrası annelere 6 ay D vitamini desteği (1200 ünite/gün) verilmesi önerilmektedir (15). Bu nedenle gebelerin D vitamini ve kullanımının önemi konusunda ayrıntılı bilgilendirilmesi gerekmektedir. Serimizde tüm hastalarda ve annelerinde D vitaminin düşüklüğüne eşlik eden hipokalsemi olduğu görüldü. Bebeklere D vitamini doğumdan hemen sonra başlanmalı ve erken bebeklik dönemindeki hipokalsemi olgularında D vitamini eksikliği düşünülmelidir.

Sonuç

Yoğun bakıma solunum yetmezliği ile birlikte hayatı tehdit eden kardiyomiyopati tanısı ile yatan hastalarda raşitizm tanısı akılda tutulmalı ve hastalar bu açıdan mutlaka değerlendirilmelidir. Zamanında teşhis ve tedavi ile raşitik kardiyomiyopatide prognoz yüz güldürücüdür. Raşitizmi önleme projelerine rağmen raşitik kardiyomiyopati olgularına ülkemizde hala rastlanmakta olup, bu durum risk faktörlerinin ve takip stratejilerinin daha kapsamlı bir şekilde ele alınması gerektiğini göstermektedir.

Etik

Etik Kurul Onayı: Çalışma Helsinki Deklarasyonu ilkelerine uygun olarak yapıldı ve Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi Etik Kurulu'ndan 2019/131 protokol numarası ile onay alındı (karar no: 2019-06-11, tarih: 18.03.2019).

Hasta Onamı: Çalışmaya katılan hastaların ebeveynlerinden onam alındı.

Hakem Değerlendirmesi: Editörler kurulu tarafından değerlendirilmiştir.

Yazarlık Katkıları

Cerrahi ve Medikal Uygulama: E.D.P.Ç., M.T.P., B.A., Konsept: Ü.K.B., O.Y., E.Ş., Dizayn: Ü.K.B., M.T.P., E.Ş., Veri Toplama veya İşleme: N.A., H.S.K., Analiz veya Yorumlama: N.A., H.S.K., O.Y., E.Ş., Literatür Arama: N.A., H.S.K., Yazan: N.A.

Çıkar Çatışması: Yazarlar tarafından çıkar çatışması bildirilmemiştir.

Finansal Destek: Yazarlar tarafından finansal destek almadıkları bildirilmiştir.

Kaynaklar

1. Akman I, Omeroglu RE, Dindar A. Can myocarditis and dilated cardiomyopathy be differentiated from each other in pediatric patients? Arch Turk Soc Cardiol 1994;22:38-42.
2. Brown J, Nunez S, Russell M, Spurney C. Hypocalcemic rickets and dilated cardiomyopathy: case reports and review of literature. Pediatr Cardiol 2009;30:818-23.
3. Ringer S. A further Contribution regarding the influence of the different Constituents of the Blood on the Contraction of the Heart. J Physiol 1883;4:29-42.3.
4. Amirlak I, Al Dhaheri W, Narchi H. Dilated cardiomyopathy secondary to nutritional rickets. Ann Trop Paediatr 2008;28:227-30.
5. Carlton-Conway D, Tulloh R, Wood L, Kanabar D. Vitamin D deficiency and cardiac failure in infancy. J R Soc Med 2004;97:238-9.
6. Gillor A, Groneck P, Kaiser J, Schmitz-Stolbrink A. Kongestive Herzinsuffizienz bei Vitamin D-Mangel-Rachitis [Congestive heart failure in rickets caused by vitamin D deficiency]. Monatsschr Kinderheilkd 1989;137:108-10.
7. Kim BG, Chang SK, Kim SM, Hwang JS, Jung JW. Dilated cardiomyopathy in a 2 month-old infant: a severe form of hypocalcemia with vitamin d deficient rickets. Korean Circ J 2010;40:201-3.
8. Elidrissy AT, Munawarah M, Alharbi KM. Hypocalcemic rachitic cardiomyopathy in infants. J Saudi Heart Assoc 2013;25:25-33.
9. Ozkan B, Doneray H, Karacan M, Vançelik S, Yildirim ZK, Ozkan A, et al. Prevalence of vitamin D deficiency rickets in the eastern part of Turkey. Eur J Pediatr 2009;168:95-100.
10. Yilmaz O, Olgun H, Ciftel M, Kilic O, Kartal I, Iskenderoglu NY, et al. Dilated cardiomyopathy secondary to rickets-related hypocalcaemia: eight case reports and a review of the literature. Cardiol Young 2015;25:261-6.
11. Ari H, Ari S, Koca V, Bozat T. Geri dönüşümlü dilate kardiyomiyopatinin nadir bir nedeni: Hipokalsemi [A rare cause of reversible dilated cardiomyopathy: hypocalcemia]. Turk Kardiyol Dern Ars 2009;37:266-8.
12. Jefferies JL, Towbin JA. Dilated cardiomyopathy. Lancet 2010;375:752-62.
13. Högler W. Complications of vitamin D deficiency from the foetus to the infant: One cause, one prevention, but who's responsibility? Best Pract Res Clin Endocrinol Metab 2015;29:385-98.
14. TC Sağlık Bakanlığı. Bebeklerde D vitamini Yetersizliğinin Önlenmesi ve Kemik Sağlığının Geliştirilmesi Programı. Erişim tarihi: 1 Ocak 2005. Erişim Linki: http.//www.saglik.gov.tr/TR/belge/1-11576/bebeklerde-d-vitamini-yetersizliginin-onlenmesi-ve-kemik-htlm.
15. TC Sağlık Bakanlığı. Gebelere D Vitamini Destek Programı. Erişim tarihi: 1 Ocak 2011. Erişim Linki: http://www.saglik.gov.tr/TR/belge/1-12656/gebelere-d-vitamini-destek-programi.

Turk J Intensive Care 2022;20:72-78
DOI: 10.4274/tybd.galenos.2021.42103

ÖZGÜN ARAŞTIRMA / *ORIGINAL RESEARCH*

Kezban Akçay,
Hatice Ayhan,
Burcu Kelleci Çakır,
Osman Abbasoğlu

Beslenme Tedavisi Alan Hastalarda Hipofosfatemiye Neden Olan Faktörler

The Factors That Cause Hypophosphatemia in Patients Receivig Clinical Nutrition Treatment

Geliş Tarihi/Received : 05.11.2020
Kabul Tarihi/Accepted : 26.02.2021

Kezban Akçay
Hacettepe Üniversitesi Erişkin Hastanesi, Klinik Beslenme Birimi, Ankara, Türkiye

Hatice Ayhan
Sağlık Bilimleri Üniversitesi, Gülhane Hemşirelik Fakültesi, Cerrahi Hastalıkları Hemşireliği Anabilim Dalı, Ankara, Türkiye

Burcu Kelleci Çakır
Hacettepe Üniversitesi Eczacılık Fakültesi, Klinik Eczacılık Anabilim Dalı, Ankara, Türkiye

Osman Abbasoğlu
Hacettepe Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Ankara, Türkiye

Burcu Kelleci Çakır (✉),
Hacettepe Üniversitesi Eczacılık Fakültesi, Klinik Eczacılık Anabilim Dalı, Ankara, Türkiye

E-posta : burcukelleci@hacettepe.edu.tr
Tel. : +90 535 610 97 84
ORCID ID : orcid.org/0000-0003-2547-8919

Sunulan: Çalışma 12. KEPAN Kongresi'nde poster olarak sunulmuştur (CSN supplement kitapçığında sayfa 69: PS-44 The Factors That Cause Hypophosphatemia in Patients Receiving Clinical Nutrition Treatment).

ÖZ *Amaç:* Beslenme tedavisi başlanan hastalarda dikkat edilmesi gereken en önemli konulardan biri, ilk dört gün içinde gelişebilen yeniden beslenme sendromudur (YBS). Hipofosfatemi, YBS'nin erken dönemde görülen en önemli belirtilerindendir ve serum fosfor düzeyinin <2,5 mg/dL olması olarak kabul edilmiştir. Bu çalışmanın amacı, deneyimli bir klinik beslenme ekibinin (KBE) bir yıllık izlem sonuçlarının değerlendirilmesi, beslenme tedavisi alan farklı hasta gruplarında hipofosfatemi görülme oranının ve hipofosfatemiye neden olan faktörlerin incelenmesidir.
Gereç ve Yöntem: Çalışma Ocak 2018-Ocak 2019 tarihleri arasında KBE tarafından izlenen 18 yaş üzeri hastaların verilerinin retrospektif olarak incelenmesi ile gerçekleştirilmiştir. Hastaların demografik özellikleri, beslenme öncesi klinik durumları, beslenme özellikleri ile serum fosfat düzeyleri incelenmiştir. Belirlenen bu parametreler ile hipofosfatemi arasında bir ilişki olup olmadığı araştırılmıştır.
Bulgular: Çalışmaya dahil edilen 622 hastanın %11'inde hipofosfatemi görülmüştür. Hipofosfatemi görülen hastaların 39'unun (%51,3) erkek, ortanca (minimum-maksimum) yaşın 66 (21-95) olduğu belirlenmiştir. İkili grupların karşılaştırılması ile elde edilen sonuçlara bakıldığında yaş (p=0,04), beslenme şekli (p=0,01), ameliyat öyküsü (p=0,03), parenteral beslenmede hedefe ulaşma durumu (p=0,04) ve ek hastalık varlığının (p=0,02) hipofosfatemi gelişmesi ile istatistiksel olarak anlamlı bir ilişkisinin olduğu tespit edilmiştir. Çok değişkenli regresyon analizinde ileri yaş (p=0,03, Exβ=1,01) ve ameliyat olma durumunun (p=0,009 , Exβ=2) hipofosfatemi riskini artırdığı görülmüştür.
Sonuç: İleri yaş ve ameliyat olma durumunun hipofosfatemi gelişme riskini artırdığı ve bu hastalarda beslenme tedavisinin planlanması ve takibi sürecinde daha dikkatli olunması gerektiği sonucuna varılmıştır.
Anahtar Kelimeler: Hipofosfatemi, klinik beslenme ekibi, yeniden beslenme sendromu

ABSTRACT *Objective:* One of the most important issues to be considered in patients who are started on nutritional therapy is refeeding syndrome (RS), which can occur within the first four days. Hypophosphatemia (serum phosphorus level <2.5 mg/dL) is an early symptom of refeeding syndrome. This study aimed to evaluate the rate of hypophosphatemia in different patient groups receiving nutritional therapy. This has been undertaken to examine the one-year follow-up results of an experienced clinical nutrition team (CNT) and the factors that cause hypophosphatemia.
Materials and Methods: In this retrospective study, patients over 18 years of age and followed up by the CNT between January 2018-January 2019 were included. Patients' characteristics, nutritional characteristics, serum phosphate levels and the relationship between these parameters and hypophosphatemia were evaluated.
Results: Out of 622 patients who were included in the study, 11% showed hypophosphatemia. It was determined that 51.3% of the patients with hypophosphatemia were male (n=39), the median age was 66 years (range 21-95). The development of hypophosphatemia was ascertained to have a significant relationship with age (p=0.04), diet (p=0.01), surgery history (p=0.03), the status of reaching the target in parenteral nutrition (p=0.04) and the presence of additional disease (p=0.02). The multivariate regression analysis showed advanced age (p=0.03, Exβ=1.01) and surgery status (p=0.009, Exβ=2) increased the risk of hypophosphatemia.
Conclusion: The advanced age and surgery, along with other already known factors, seem to increase the risk of hypophosphatemia, and therefore, more attention should be given to the clinical nutrition treatment in these patients.
Keywords: Hypophosphatemia, clinical nutrition team, refeeding syndrome

Giriş

Malnütrisyonu olan hastaların beslenmesi oral yoldan sağlanamadığında, beslenme tedavisinin enteral ya da parenteral yol ile sağlanması gerekmektedir. Beslenme tedavisi başlanan hastalarda dikkat edilmesi gereken en önemli konulardan biri, ilk dört gün içinde gelişebilen yeniden beslenme sendromudur (YBS) (1). YBS ile ilgili ilk bilgiler 1950'lerde, yetersiz beslenen savaş esirlerinin beslenmeye başlamasından sonra gelişen kardiyolojik ve nörolojik bulguların gözlemlenmesi ile ortaya çıkmıştır (2-4). Fizyolojik bir reaksiyon olmasına rağmen, YBS erken fark edilmediği ve uygun şekilde tedavi edilmediğinde yüksek morbidite ve mortalite oranları nedeniyle oldukça önemli ve dikkat edilmesi gereken bir konu olarak bilinmektedir (5,6).

Yetersiz beslenen hastalarda karbonhidrat alımının azalmasına bağlı olarak insülin salınımı azalmakta, enerji üretimi yağ ve protein depolarından sağlanmaktadır. Hastanın yeniden beslenmeye başlamasını takiben insülin salınımı ile birlikte elektrolitler de (fosfat, potasyum, magnezyum) hücre içine geçmektedir (6,7). Ancak laboratuvar testlerinde serum fosfat konsantrasyonları normal düzeyde görünse de hücre içi fosfat depolarının tüketilmiş olabileceği unutulmamalıdır.

Hipofosfatemi YBS'nin en önemli erken uyarı belirtisidir. Yapılan çalışmalarda hipofosfatemi tanısı koyabilmek için farklı serum fosfat değerleri dikkate alınmıştır. Hastalarda klinik belirti vermeden, hafif düzeyde hipofosfatemi bulgusu gözlenebilir (8-11). Biyokimyasal bozukluğun şiddetine göre bulgular bulantı, kusma ve laterjiden, deliryum, solunum yetmezliği, kalp yetmezliği ve ani ölüme kadar gidebilir (6). YBS'nin evrensel olarak geçerli bir tanımı olmaması nedeni ile görülme sıklığı da net olarak bilinmemektedir (12,13). Ancak hasta gruplarına göre farklı oranlarda gözlenmektedir. İç hastalıkları bölümünde yatan hastalarda %8 (14), geriatrik hastalarda %14 (15), ameliyat sonrası dönemde %44 (16), onkoloji hastalarında %25 (17) ve psikiyatri hastalarında (özellikle anoreksiya nevroza durumunda) %28'e varan oranlar bildirilmiştir (18).

Yoğun iş yükü, beslenme tedavisi hakkındaki bilgi eksikliği, biyokimyasal parametrelerdeki kritik düzeyde olmayan azalmalar ve klinik semptomların her zaman görülmemesi gibi sebeplere bağlı olarak çoğu zaman YBS, sağlık hizmeti verenlerin gözünden kaçabilmektedir. Deneyimli klinik beslenme ekipleri, beslenme tedavisini planlarken hastanın uzun süren açlık döneminin ardından yeniden beslendiğinde, gelişebilecek komplikasyonları öngörebilmekte, biyokimyasal bulgulardaki anormallikler ile hastanın kliniğini yorumlayabilmektedir. Beslenme tedavisinin deneyimli bir ekip tarafından planlanması ve izlenmesinin, hipofosfatemiyi fark etme, önleme ve geliştiği durumlarda gerekli tedaviyi sağlama becerileri ile beslenme tedavisinin başarısını artırdığı vurgulanmakta ve beslenme tedavisinin ekip tarafından verilmesi önerilmektedir (3,16,19). Bununla birlikte beslenme ekiplerinin izlem sonuçlarını ve deneyimlerini ortaya koyan çalışmaların da az sayıda olduğu görülmektedir.

Bu çalışmanın amacı, deneyimli bir klinik beslenme ekibinin (KBE) bir yıllık izlem sonuçlarının değerlendirilmesi, beslenme tedavisi alan farklı hasta gruplarında hipofosfatemi görülme oranının ve hipofosfatemiye neden olan faktörlerin incelenmesidir.

Gereç ve Yöntem

Araştırmanın Tasarımı

Araştırma kesitsel bir çalışmadır. Ocak 2018-Ocak 2019 tarihleri arasında, Türkiye'de bir üniversite hastanesinin KBE tarafından izlenen erişkin hastaların verilerinin retrospektif incelenmesi ile gerçekleştirildi. Etik kurul onayı Hacettepe Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'ndan alındı (karar no: 2019/04-33, tarih: 05.02.2019). Çalışmanın gerçekleştirildiği üniversite hastanesinde, nütrisyon tedavisi, hekim, hemşire, diyetisyen ve eczacıdan oluşan deneyimli bir KBE tarafından yürütülmektedir. Bu ekip tarafından beslenme tedavisi düzenlenmekte, takip edilmekte, oluşturulmuş protokollere göre tedavi ve bakım sürdürülmektedir. Protokoller, Amerikan Parenteral ve Enteral Beslenme Derneği (*American Society for Parenteral* and *Enteral Nutrition*), Avrupa Klinik Nütrisyon ve Metabolizma Derneği (*European Society for Clinical Nutrition* and *Metabolism*-ESPEN) ve Ulusal Sağlık ve Bakım Mükemmelliği Enstitüsü (*The National Institute for Healthand Care Excellence*-NICE) rehberlerine uygun şekilde hazırlanmıştır. YBS'nin önlenmesi ve yönetilebilmesi için geliştirilen protokol gereği enteral ve parenteral nütrisyon tedavisi alan tüm hastaların plazma elektrolitleri, glikoz düzeyi, böbrek fonksiyonları, trigliseritler, magnezyum, fosfor, kolesterol, trombositler, karaciğer fonksiyon testleri rutin tedavinin bir parçası olarak KBE tarafından izlenmektedir. Her hasta için tedaviye başlamadan önce kontrol edilen bu değerler özellikle YBS riski olan hastalarda tedavi süresince ilk 7 gün günlük olarak, devamındaki haftada günaşırı olacak şekilde takip edilmiştir (20,21). Protokole göre hastanın

hipofosfatemi (<2,5 mg/dL), hipopotasemi (<3,5 mEq/L) ve hipomagnezemisi (1,8 mg/dL) varsa beslenme tedavisine başlamadan önce primer hekimi tarafından replasman yapılması istenmektedir. Beslenme tedavisinin düzenlenmesi sırasında hastanın oral, enteral ve parenteral yollardan alabildiği enerjinin tamamı göz önünde bulundurulmaktadır. Tablo 1'de yer alan risk grubu hastalarda enerji 10 kcal/kg/gün ile başlanarak yavaş yavaş hedeflenen doza çıkılacak şekilde artırılmaktadır. Parenteral beslenme solüsyonları hastane eczanesinde temiz oda koşullarında, eczacı denetiminde sağlık teknisyenleri tarafından dolum yapılarak hazırlanmaktadır. Solüsyonların içeriğini karbonhidrat %50-60, yağ %30-40 ve protein %15-20 oranında olacak şekilde KBE diyetisyeni belirlemektedir. Klinik eczacının önerisi ile vitamin ve eser elementler, gerektiğinde torbanın stabilitesini koruyacak dozlarda fosfat 0,2-0,5 mmol/kg/gün, potasyum 1-2,2 mmol/kg/gün, magnezyum 0,3-0,4 mmol/kg/gün eklenmektedir (22). Hastanın fosfat ve diğer elektrolitleri normal sınırlara ulaştığında beslenme dozu kademeli olarak artırılmaktadır.

Örneklem Büyüklüğü

Çalışmada bir yıllık sürede KBE ekibi tarafından takip edilen 681 hastanın verileri geriye dönük incelendi, 622 (%91,3) hasta çalışmaya dahil edilirken, beslenmeye başlanmadan önceki fosfat değeri düşüklüğü veya böbrek fonksiyon bozukluğu olan 59 hasta çalışma dışında bırakıldı.

Verilerin Toplanması

Verilerin toplanmasında bu çalışma için araştırmacılar tarafından literatür taraması sonucu geliştirilen "Veri Toplama Formu" kullanıldı (6,10-12,20,21,23,24). Form içeriğinin belirlenmesinde NICE 2006 ve ESPEN 2017 Klinik Nütrisyonda Tanımlar ve Terminoloji Rehberi'nde YBS için belirtilen risk faktörleri (Tablo 1) de dikkate alındı (23). Form, hastaların demografik özelliklerini (yaş, cinsiyet), tedavi öncesi klinik özelliklerini [beslenme öncesi prealbümin değeri, açlık gün sayısı, vücut kitle indeksi (VKİ), Nutritional Risk Screening 2002 (NRS 2002) puanı, son bir ay içinde ameliyat olma durumu, ek hastalık varlığı], beslenme özelliklerini (enteral veya parenteral beslenme şekli, beslenme hedefine ulaşma durumu) ve serum fosfor düzeyini içermekteydi.

Her bir hasta için veriler, Nütrisyon Hemşire İzlem Formu, hastaların hastane sisteminde kayıtlı bulunan laboratuvar sonuçları ve elektronik hasta dosyalarında bulunan klinik bilgilerden faydalanılarak Veri Toplama Formu'na kayıt edildi. Beslenme hedefine ulaşma, hastanın ihtiyacı olarak hesaplanan enerji miktarının en az %80'ine ulaşılması olarak belirlendi (24,25). YBS belirteci olarak, beslenmeye başladıktan sonraki ilk dört günlük süre içinde hipofosfatemi gelişmesi alındı (1). Hipofosfatemi, serum fosfor değerlerinde araştırmanın yapıldığı kurum laboratuvarının kabul ettiği normal serum fosfor değerinin <2,5 mg/dL olarak kabul edildi. Formda yer alan değişkenler ile hipofosfatemi arasında bir ilişki olup olmadığı araştırıldı.

İstatistiksel Analiz

Verilerin analizinde IBM SPSS Version 23.0 (Armonk, NY: IBM Corp.) programı kullanıldı. Tanımlayıcı istatistik olarak sayısal değişkenlerde ortalama ve standart sapma ya da ortanca ve en küçük-en büyük değerler, kategorik değişkenlerde ise sayı ve yüzde değerleri verildi. Parametrik test varsayımlarından normallik varsayımı Shapiro-Wilks testi ve grafik gösterimleri ile incelendi. Grup karşılaştırması için parametrik test varsayımları sağlanamadığı için Mann-Whitney U ve Pearson ki-kare testi kullanıldı. Farklılık yaratan grup/grupları belirlemede Bonferroni düzeltmesi uygulandı. Gruplar arası karşılaştırma sonuçlarında $p<0,05$ değeri anlamlı olarak kabul edildi.

Bulgular

Çalışmaya dahil edilen 622 hastanın 76'sında (%11) hipofosfatemi görüldü. Hipofosfatemi görülen hastaların 39'u (%51,3) erkekti. Ortanca yaş 66 (sınırlar 21-95), ortanca

Tablo 1. YBS için risk faktörleri (22)

En az birinin varlığı YBS için risk faktörü	En az ikisinin varlığı YBS için risk faktörü
VKİ <16 kg/m^2	VKİ <18,5 kg/m^2
Son 3-6 aylık dönemde istemsiz olarak %15'ten fazla kilo kaybı	Son 3-6 aylık dönemde istemsiz olarak %10'dan fazla kilo kaybı
On günden fazla yetersiz beslenme veya hiç besin alamama	Beş günden fazla yetersiz beslenme veya hiç besin alamama
Beslenmeye başlamadan önce potasyum, fosfat ve magnezyum seviyelerinin düşük olması	Alkol bağımlılığı, insülin, kemoterapi, antiasitler veya diüretik içeren ilaçların kullanımı

YBS: Yeniden beslenme sendromu, VKİ: vücut kitle indeksi

VKİ 23 kg/m^2 (sınırlar 11,70 kg/m^2-42 kg/m^2) olarak bulundu (Tablo 2). Hipofosfatemi olup olmaması ile prealbümin düzeyi, açlık gün sayısı, VKİ ve NRS 2002 değerleri arasında bir ilişki bulunamadı. Ancak yaş (p=0,04), ameliyat öyküsü (p=0,03), beslenme şekli (p=0,01), parenteral beslenmede hedefe ulaşma durumu (p=0,04) ve ek hastalık varlığının (p=0,02) hipofosfatemi olup olmaması ile istatistiksel olarak anlamlı bir ilişkisinin olduğu tespit edildi. Bu ilişkinin tam olarak hangi gruptan kaynaklandığını tespit edebilmek için çok değişkenli regresyon analizi yapıldı. Hipofosfatemi görülen hastalar beslenme şekline göre karşılaştırıldığında, enteral beslenen hastalarda (%52) parenteral beslenen hastalara göre (%47,4) hipofosfateminin anlamlı derecede fazla olduğu saptandı (p=0,01). Beslenme şekline bakılmaksızın son bir ay içinde ameliyat olan hastaların %46,1'inde hipofosfatemi geliştiği belirlendi (p=0,03). Hipofosfatemi gözlenen hastaların enteral beslenmede %40'ının, parenteral beslenmede ise yalnızca %22,2'sinin hedeflenen enerji miktarına ulaşabildiği tespit edildi. Planlanmış olan enerji miktarına ulaşma ile beslenme şekli arasında anlamlı bir fark bulundu (p=0,01). Çok değişkenli regresyon analizinde ileri yaş (p=0,03, Exβ=1,01) ve ameliyat olma durumunun (p=0,009, Exβ=2) hipofosfatemi riskini artırdığı görüldü. Tablo 1'de verilen YBS risk faktörlerinden VKİ, kilo kaybı, 10 günden fazla yetersiz beslenme ile hipofosfatemi arasında istatistiksel olarak anlamlı bir ilişki tespit edilemedi (p>0,05).

Tartışma

Çalışmamızda KBE tarafından izlenen ve değerlendirmeye alınan tüm hastalarda hipofosfatemi görülme oranı %11 olarak bulunmuştur. Martinez ve ark. (16) tarafından yapılan prospektif bir çalışmada ameliyat sonrası, hipofosfatemi prevelansının %44 olduğu, erken dönemde fark edildiği için hipofosfateminin, hafif-orta düzeyde iken tedavi edilebildiği ve ekip izleminin gerekliliği belirtilmiştir. Friedli ve ark.'nın (26), hastanede yatan ve malnütrisyonu olan hastalarda beslenme tedavisinin etkisini inceleyen çok merkezli, randomize kontrollü bir çalışmasında ise, YBS'nin fosfat, potasyum, magnezyum düzeyleri ile birlikte klinik bulgular ve hastanın öyküsü de dikkate alınarak tanımlanmasına rağmen, YBS görülme oranı %14,6 olarak tespit edilmiştir. Bu çalışmada hipofosfatemi oranının literatüre göre daha düşük bulunmasında, hastaların laboratuvar sonuçları ve klinik durumunun hastanın primer hekimi ile birlikte bir ekip tarafından, protokole göre izlenmesi ve erken dönemde fark edilerek tedavi edilmesinin etkili olduğu düşünülebilir.

Bu çalışmada hipofosfatemi gözlenen hastaların %64,5'inin ek bir hastalığının olduğu tespit edilmiştir. Literatürdeki yayınlarda YBS gelişiminde ek hastalık durumu pek tartışılmamıştır. Çalışmanın retrospektif tasarımı sebebiyle ek hastalıkların hangileri olduğu bilgisine bütün hastalarda ulaşılamamıştır fakat ulaşılabilen hastalarda ek hastalıklar kapsamında hipertansiyon, diabetes mellitus, koroner arter hastalığı, kronik obstrüktif akciğer hastalığı, kronik böbrek yetersizliği, konjestif kalp yetersizliği tespit edilmiştir.

Tablo 2. Hastaların tanımlayıcı bilgileri, klinik ve beslenme özellikleri

		Hipofosfatemi var n=76	Hipofosfatemi yok n=546	p-değeri
Yaş		66 (21-95)	63 (18-96)	0,04*
Cinsiyet	Kadın	37 (48,7)	235 (43,0)	0,35
	Erkek	39 (51,3)	311 (57)	
Tedavi öncesi klinik özellikler	Prealbümin (g/L) ortanca (min-maks)	12,6 (4,8-27)	14,4 (0,64-45,6)	0,87
	Geçirilmiş ameliyat, var n (%)	35 (46,1)	185 (33,9)	0,03*
	Aç kalma günü ortanca (min-maks)	0 (0-15)	0 (0-13)	0,06
	VKİ ortanca (min-maks)	23 (11,7-42)	23,1 (13-46)	0,70
	NRS-2002 ortanca (min-maks)	5 (3-6)	5 (3-6)	0,64
	Ek hastalık varlığı, var n (%)	49 (64,5)	276 (50,5)	0,02*
Beslenme şekli	EN n (%)	40 (52,6)	203 (37,5)	0,01*
Planlanan enerji miktarına ulaşabilme	EN hedefe ulaşılmış n (%)	16 (40,0)	117 (56,5)	0,05
	PN hedefe ulaşılmış n (%)	8 (22,2)	83 (30,9)	0,04*

*p<0,05, VKİ: vücut kitle indeksi, min: minimum, maks: maksimum, NRS: Nutritional Risk Screening, EN: enteral beslenme, PN: parenteral beslenme

Bu çalışmada literatür ile uyumlu olarak hipofosfateminin en çok görüldüğü grup, enteral beslenme tedavisi alan hastalar olarak belirlenmiştir. Kanser hastalarında yapılan bir çalışmada benzer olarak enteral beslenen hasta grubunda hipofosfateminin daha fazla olduğu bildirilmiştir (17). Retrospektif başka bir çalışmada da aynı şekilde enteral beslenen hastalarda hipofosfateminin daha yüksek oranda olduğu bulunmuştur (27). Bu durum oral ve enteral yolla alınan glukozun insülin salınımını intravenöz yolla alınan glukoza göre daha fazla uyarması (inkretin etki) ile açıklanmıştır (27,28). İnsülin glikojen, yağ ve protein sentezini uyarır. Bu süreçte fosfat ve magnezyum gibi mineraller de senteze katılacağından hücre içine geçiş artar ve serum fosfat düzeyi düşer (12).

Bu çalışmada hipofosfatemi gözlenip gözlenmemesi ile ilişkili bir diğer parametrenin hedeflenen enerji miktarına ulaşma durumu olduğu görülmüştür. Hipofosfatemi gözlenen hastaların enteral beslenmede %40'ında, parenteral beslenmede %22,2'sinde hedeflere ulaşılabildiği görülmüştür. Enteral beslenmede hipofosfateminin fazla görülmesine rağmen hedeflenen enerji miktarına parenteral beslenmeye göre daha yüksek oranda görülmesi, parenteral beslenmenin diğer komplikasyonlarını düşündürmektedir. Parenteral beslenme sırasında YBS dışında gelişebilen hiperglisemi, hipernatremi gibi diğer metabolik komplikasyonların yanı sıra, flebit, tromboz, kateter enfeksiyonu, kateterin yerinden çıkması ya da tıkanması gibi erişim yolu komplikasyonları da hedeflenen enerji miktarına ulaşmayı engelleyebilmektedir. Hastada YBS veya diğer komplikasyonları düşündüren herhangi bir bulgu görüldüğünde, parenteral beslenme solüsyonunun içeriği tamamen KBE kontrolünde olduğundan, yeniden düzenlenebilmekte ve gerektiğinde KBE tarafından kalori dozu azaltılmakta ya da beslenmeye ara verilebilmektedir. Ayrıca parenteral beslenme tedavisinde periferik erişim yolundan hastanın belli oranlarda beslenme ihtiyacı karşılanabilmekte, yüksek kalori ve protein ihtiyacı olan hastalara santral venöz erişim yolu gerekmektedir. Parenteral beslenme tedavisi alan her hastaya santral venöz erişim yolu sağlanamadığından hedeflenen enerji miktarına, enteral beslenme tedavisi alan hastalara göre daha az oranda ulaşılabildiği düşünülebilir. Enteral beslenen hastaların tamamı KBE tarafından yönetilmemekte, ekibin önerileri dışında hipofosfatemi veya diğer komplikasyonlara rağmen beslenme hızı artırılarak hedeflenen enerji miktarına ulaşıldığı görülebilir. Yapılan çalışmalar ve fikir birlikleri beslenme tedavisine başlanırken ihtiyacın en fazla %50'si ile başlanması gerektiğini belirtmektedir. Kritik hastalarda kalori kısıtlamasını inceleyen 339 hastanın dahil edildiği randomize kontrollü bir çalışmada hastanın ihtiyacı olan kalorinin altında kısıtlı bir şekilde beslenme tedavisinin başlanmasının hastalar için olumsuz bir sonuç oluşturmadığı aksine riskli gruplarda YBS gelişiminin önüne geçildiği belirtilmiştir (12,29).

Çok değişkenli regresyon analizinde hipofosfatemi riskini artıran parametrelerden biri yaş olarak tespit edilmiştir. Yaşın ilerlemesinin hipofosfatemi görülme olasılığını yaklaşık bir kat artırdığı tespit edilmiştir (Exβ=1,01). Literatürde ileri yaşlı hastalarda beslenme tedavisi sırasında hipofosfatemi gelişmesi ile ilgili yapılan bir olgu kontrol çalışmasında, hipofosfatemi görülme oranı %14 olarak bildirilmiştir (15). Klinik olarak hipofosfatemi bulgularının gözden kaçabilmesi buna ek olarak hipofosfatemi bulgularının yaşlı ve kırılgan hasta grubunda var olan güçsüzlük, konfüzyon ve hareketlerde zayıflık gibi bulgularla benzer olması, hipofosfateminin fark edilememesine ve tedavi edilememesine neden olmaktadır (10).

Çalışmamızda hipofosfatemi riskini artıran bir diğer risk faktör ise ameliyat olma olarak bulunmuştur. Beslenme şekline bakılmaksızın son bir ay içinde ameliyat olan hastaların %46,1'inde hipofosfatemi gelişmiş ve ameliyat olma durumunun hipofosfatemi görülme olasılığını yaklaşık iki kat artırdığı tespit edilmiştir (Exβ=2). Cerrahi yoğun bakımda enteral beslenme tedavisi alan hastaların retrospektif incelendiği bir çalışmada hipofosfatemi oranı %39 olarak belirtilmiştir (9). Ameliyat sonrası parenteral beslenme tedavisi alan hastalarla yapılan prospektif bir çalışmada ise hipofosfatemi oranı %44 olarak bulunmuş ve cerrahi hasta gruplarında hipofosfatemi gelişme riskinin yüksek olduğu bildirilmiştir (16). Ameliyat sonrası erken dönemde hastalar YBS'ye bağlı hipofosfatemi dışında da, metabolik ve elektrolitik bozukluklara yatkındır. Ameliyat öncesi ve sonrası uzun süren açlık dönemi, bağırsak emiliminin azalması, fosfor bağlayıcı antasitlerin kullanımı, diyabetik ketoasidoz, sepsis gibi durumların hipofosfatemiye neden olduğu ifade edilmektedir (30). Açık kalp ameliyatı sonrası hastaların fosfat düzeylerinin incelendiği bir çalışmada, hipofosfatemi görülme insidansı %52,5 olarak bulunmuş ve durumun intraoperatif hipotermi döneminde böbreklerden fosfat atılması ve hastanın ısıtılma işlemi sırasında fosfatın hücre içine geçişine bağlı olarak gelişebileceği belirtilmiştir. Ayrıca hipofosfatemi üzerinde ekstrasellüler sıvı artışı, diüretik kullanımı, dopamin infüzyonu, kortikosteroid ve epinefrin

uygulanması ile solunum alkolozu gibi faktörlerin de etkili olduğu vurgulanmıştır (31).

Bu çalışmada YBS risk faktörlerinden VKİ, kilo kaybı, 10 günden fazla yetersiz beslenme ile hipofosfatemi arasında bir ilişki tespit edilememiştir. Beslenmeye başlamadan önce potasyum, fosfat ve magnezyum seviyelerinin düşük olması da YBS için bir risk faktörüdür ancak KBE tarafından beslenmeye başlamadan önce potasyum, fosfat ve magnezyum seviyeleri düşük olan hastaların elektrolit düzeyleri normal seviyeye getirildikten sonra beslenme tedavisi başlandığı için, bu grupta yer alan hastalar baştan çalışma dışı bırakılmıştır. Bu nedenle çalışmada bu risk faktörü elenmiştir. Diğer risk faktörleri olan insülin, kemoterapi, antiasitler veya diüretik içeren ilaçlarla ilgili retrospektif olan bu çalışmada yeterli bilgiye ulaşılamadığı için bu risk faktörleri değerlendirilememiştir ve çalışmanın kısıtlılıkları arasında yer almıştır. NICE tarafından risk faktörü olarak belirtilmemiş olan ileri yaş ve ameliyat olma durumları bu çalışmada hipofosfatemi ile istatistiksel olarak ilişkili bulunması dikkat çekmektedir. Bu durum NICE'nin yayımladığı risk faktörlerinin değerlendirilmesinin yanı sıra diğer faktörlerin de göz önünde bulundurulması gerektiğini göstermektedir.

Sonuç

Bu çalışmada hipofosfatemi YBS'nin en önemli erken uyarı belirtisi olarak ele alınmış ve farklı hasta gruplarında hipofosfatemi görülme oranları incelenmiştir. Hastanın primer hekimi ve deneyimli bir KBE iş birliği ile düzenlenen ve yürütülen beslenme tedavisinde hipofosfatemi görülme oranının literatüre göre daha düşük olduğu görülmüştür. Ancak ileri yaş ve ameliyat olma durumu gibi faktörlerin göz önünde bulundurulması gerektiği düşünülmüştür.

Etik

Etik Kurul Onayı: Etik kurul onayı Hacettepe Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'ndan alındı (karar no: 2019/04-33, tarih: 05.02.2019).

Hasta Onamı: Retrospektif çalışma.

Hakem Değerlendirmesi: Editörler kurulu dışında olan kişiler tarafından değerlendirilmiştir.

Yazarlık Katkıları

Konsept: K.A., H.A., O.A., Dizayn: K.A., H.A., O.A., Veri Toplama veya İşleme: K.A., H.A., Analiz veya Yorumlama: K.A., B.K.Ç., Literatür Arama: K.A., H.A., B.K.Ç., Yazan: K.A., H.A., B.K.Ç., O.A.

Çıkar Çatışması: Yazarlar tarafından çıkar çatışması bildirilmemiştir.

Finansal Destek: Yazarlar tarafından finansal destek almadıkları bildirilmiştir.

Kaynaklar

1. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr 2017;36:49-64.
2. SCHNITKER MA, MATTMAN PE, BLISS TL. A clinical study of malnutrition in Japanese prisoners of war. Ann Intern Med 1951;35:69-96.
3. Hearing SD. Refeeding syndrome. BMJ 2004;328:908-9.
4. Khan LU, Ahmed J, Khan S, Macfie J. Refeeding syndrome: a literature review. Gastroenterol Res Pract 2011;2011:410971.
5. Crook MA, Hally V, Panteli JV. The importance of the refeeding syndrome. Nutrition 2001;17:632-7.
6. Friedli N, Stanga Z, Culkin A, Crook M, Laviano A, Sobotka L, et al. Management and prevention of refeeding syndrome in medical inpatients: An evidence-based and consensus-supported algorithm. Nutrition 2018;47:13-20.
7. Boateng AA, Sriram K, Meguid MM, Crook M. Refeeding syndrome: treatment considerations based on collective analysis of literature case reports. Nutrition 2010;26:156-67.
8. Coşkun R, Gündoğan K, Baldane S, Güven M, Sungur M. Refeeding hypophosphatemia: a potentially fatal danger in the intensive care unit. Turk J Med Sci 2014;44:369-74.
9. Fuentes E, Yeh DD, Quraishi SA, Johnson EA, Kaafarani H, Lee J, et al. Hypophosphatemia in Enterally Fed Patients in the Surgical Intensive Care Unit. Nutr Clin Pract 2017;32:252-7.
10. Aubry E, Friedli N, Schuetz P, Stanga Z. Refeeding syndrome in the frail elderly population: prevention, diagnosis and management. Clin Exp Gastroenterol 2018;11:255-64.
11. Olthof LE, Koekkoek WACK, van Setten C, Kars JCN, van Blokland D, van Zanten ARH. Impact of caloric intake in critically ill patients with, and without, refeeding syndrome: A retrospective study. Clin Nutr 2018;37:1609-17.
12. Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. BMJ 2008;336:1495-8.
13. McKnight CL, Newberry C, Sarav M, Martindale R, Hurt R, Daley B. Refeeding Syndrome in the Critically Ill: a Literature Review and Clinician's Guide. Curr Gastroenterol Rep 2019;21:58.
14. Kraaijenbrink BV, Lambers WM, Mathus-Vliegen EM, Siegert CE. Incidence of refeeding syndrome in internal medicine patients. Neth J Med 2016;74:116-21.
15. Kagansky N, Levy S, Koren-Morag N, Berger D, Knobler H. Hypophosphataemia in old patients is associated with the refeeding syndrome and reduced survival. J Intern Med 2005;257:461-8.
16. Martínez MJ, Martínez MA, Montero M, Campelo E, Castro I, Inaraja MT. Hypophosphatemia in postoperative patients with total parenteral nutrition: influence of nutritional support teams. Nutr Hosp 2006;21:657-60.
17. González Avila G, Fajardo Rodríguez A, González Figueroa E. Incidencia de síndrome de realimentación en enfermos con cáncer que reciben tratamiento nutricio artificial [The incidence of the refeeding syndrome in cancer patients who receive artificial nutritional treatment]. Nutr Hosp 1996;11:98-101.
18. Ornstein RM, Golden NH, Jacobson MS, Shenker IR. Hypophosphatemia during nutritional rehabilitation in anorexia nervosa: implications for refeeding and monitoring. J Adolesc Health 2003;32:83-8.
19. Crook MA. Refeeding syndrome: problems with definition and management. Nutrition 2014;30:1448-55.
20. Kirkland LL, Kashiwagi DT, Brantley S, Scheurer D, Varkey P. Nutrition in the hospitalized patient. J Hosp Med 2013;8:52-8.
21. da Silva JSV, Seres DS, Sabino K, Adams SC, Berdahl GJ, Citty SW, et al. ASPEN Consensus Recommendations for Refeeding Syndrome. Nutr Clin Pract 2020;35:178-95.
22. Sobotka L, editor. Basics in clinical nutrition. 5th ed. Prague: Galen; 2019.
23. National Institute for Health and Care Excellence (NICE). (2006). Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition. NICE Clinical Guideline No. 32. February 2006.
24. Tresley J, Sheean PM. Refeeding syndrome: recognition is the key to prevention and management. J Am Diet Assoc 2008;108:2105-8.
25. Berger MM, Soguel L, Charrière M, Thériault B, Pralong F, Schaller MD. Impact of the reduction of the recommended energy target in the ICU on protein delivery and clinical outcomes. Clin Nutr 2017;36:281-7.
26. Friedli N, Baumann J, Hummel R, Kloter M, Odermatt J, Fehr R, et al. Refeeding syndrome is associated with increased mortality in malnourished medical inpatients: Secondary analysis of a randomized trial. Medicine (Baltimore) 2020;99:e18506.
27. Zeki S, Culkin A, Gabe SM, Nightingale JM. Refeeding hypophosphataemia is more common in enteral than parenteral feeding in adult in patients. Clin Nutr 2011;30:365-8.
28. Güçlü M, İmamoğlu Ş. Incretins and usage in clinical practice. Turkiye Klinikleri J Int Med Sci 2007;3:53-60.
29. Doig GS, Simpson F, Heighes PT, Bellomo R, Chesher D, Caterson ID, et al. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. Lancet Respir Med 2015;3:943-52.
30. Dwyer K, Barone JE, Rogers JF. Severe hypophosphatemia in postoperative patients. Nutr Clin Pract 1992;7:279-83.
31. Taşöz R. Oğuz M. Eryılmaz S. Akalın H. Açık kalp cerrahisi sonrası hipofosfatemi gelişim ve solunum problemleri ile ilişkisi. GKD Cer Derg 1996;1:31-5.

Turk J Intensive Care 2022;20:79-85
DOI: 10.4274/tybd.galenos.2021.52523

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Nurdan Çobaner,
Birgül Yelken,
Nilüfer Erkasap,
Mete Özkurt,
Ezgi Bektur

Investigation of the Anti-inflammatory Effects of Astaxanthin on Liver Tissue in Lipopolysaccharide-induced Sepsis in Rats

Sıçanlarda Lipopolisakkarit ile Oluşturulmuş Sepsis Modelinde Astaksantinin Karaciğer Dokusunda Anti-enflamatuvar Etkilerinin Araştırılması

Received/Geliş Tarihi : 15.11.2020
Accepted/Kabul Tarihi : 26.02.2021

Nurdan Çobaner, Birgül Yelken,
Eskişehir Osmangazi University Faculty of Medicine, Department of Anaesthesiology and Reanimation, Divison of Intensive Care, Eskişehir, Turkey

Nilüfer Erkasap, Mete Özkurt
Eskişehir Osmangazi University Faculty of Medicine, Department of Physiology, Eskişehir, Turkey

Ezgi Bektur
Atılım University Faculty of Medicine, Department of Histology and Embryology, Ankara, Turkey

Nurdan Çobaner MD (✉),
Eskişehir Osmangazi University Faculty of Medicine, Department of Anaesthesiology and Reanimation, Divison of Intensive Care, Eskişehir, Turkey

E-mail : nurdancobaner@hotmail.com
Phone : +90 507 488 14 16
ORCID ID : orcid.org/0000-0003-3948-8819

ABSTRACT *Objective:* Corticosteroids are one of the treatment methods used to prevent inflammation in sepsis. This study aimed to determine the anti-inflammatory activity of astaxanthin in sepsis and compare it with dexamethasone.
Materials and Methods: After approval of the local ethics committee, 40 Sprague-Dawley male rats were randomly assigned to the control group (n=8), lipopolysaccharide group (n=8), astaxanthin group (n=8), astaxanthin + lipopolysaccharide group (n=8) and dexamethasone + lipopolysaccharide group (n=8). On day 1, these groups were given dimethyl sulfoxide, *Salmonella typhimurium* lipopolysaccharide, astaxanthin dissolved in dimethyl sulfoxide, astaxanthin and lipopolysaccharide and dexamethasone and lipopolysaccharide, respectively. After 24 hours, rats underwent laparotomy, and liver and blood samples were taken. GraphPad Prism 6 was used for statistical analysis. P values less than 0.05 were considered significant.
Results: Nuclear factor-kappa B levels in both treatment groups significantly decreased when compared with the lipopolysaccharide group. Apoptotic cells and reaction severity decreased significantly in the treatment groups compared with the lipopolysaccharide group.
Conclusion: This study revealed that the use of astaxanthin had a positive effect on liver tissue undergoing treatment for sepsis. Moreover, despite some differences, measurement values were comparable when dexamethasone was administered.
Keywords: Astaxanthin, dexamethasone, anti-inflammatory, liver

ÖZ *Amaç:* Kortikosteroidler enflamasyonu önlemek için sepsiste kullanılan tedavi yöntemlerinden biridir. Çalışmamızda astaksantinin sepsiste anti-enflamatuvar aktivitesini göstermeyi ve deksametazon ile karşılaştırmayı amaçladık.
Gereç ve Yöntem: Yerel etik komitenin onayından sonra, 40 Sprague-Dawley erkek sıçan randomize olarak kontrol grubu (n=8), lipopolisakkarit grubu (n=8), astaksantin grubu (n=8), astaksantin + lipopolisakkarit grubu (n=8) ve deksametazon + lipopolisakkarit grubu (n=8) olarak belirlendi. İlk gün bu gruplara sırasıyla dimetil sülfoksit, Salmonella typhimurium lipopolisakkariti, dimetil sülfoksit içinde çözünmüş astaksantin, astaksantin ve lipopolisakkarit ve deksametazon verildi. Yirmi dördüncü saatin sonunda sıçanlara laparotomi yapılarak karaciğer ve kan örnekleri alındı. İstatistiksel analiz için GraphPad Prism6 programı kullanıldı. 0,05'ten küçük p değerleri anlamlı kabul edildi.
Bulgular: Lipopolisakkarit grubu ile karşılaştırıldığında, her iki tedavi grubunda da nükleer faktör-kappa B seviyelerinde istatistiksel olarak anlamlı bir düşüş vardı. Tedavi gruplarında lipopolisakkarit grubuna göre apoptotik hücreler ve reaksiyon şiddeti anlamlı olarak azaldı.
Sonuç: Astaksantin kullanımının, karaciğer dokusunda sepsis tedavisi konusunda olumlu bir etkisi olduğunu bulduk. Farklılıklar olmasına rağmen, deksametazon uygulamasına kıyasla benzer ölçüm değerleri elde edildi.
Anahtar Kelimeler: Astaksantin, deksametazon, anti-enflamatuvar, karaciğer

Introduction

Today, sepsis is defined as life-threatening organ dysfunction caused by the impaired host response to infection (1) and has been accepted as a result of an uncontrolled inflammatory response (2). Medical advances, increased use of immunosuppressive drugs, and the age of the population contribute to the increase in the incidence of sepsis (3,4).

In sepsis, tumor necrotizing factor-alpha (TNF-alpha) is the first released proinflammatory cytokine, and the release of interleukin-1 (IL-1), IL-6 and IL-8 occur. TNF-alpha and IL-1 are the most important pro-inflammatory cytokines in sepsis. They are biologically closely related to each other, act synergistically and are largely responsible for the clinical manifestations of sepsis (5,6).

In experimental sepsis models, various pro-inflammatory mediators such as lipopolysaccharide (LPS) and TNF-alpha have been shown to cause apoptosis in endothelial and various other cell types (7,8). LPS is a commonly used agent in sepsis model animal studies.

Although corticosteroid treatments are considered to have suspicious benefits in mortality in sepsis, corticosteroids have been used in sepsis treatments in various doses for more than 50 years (9). The anti-inflammatory effect of dexamethasone (DEX) is a known property. DEX may interfere with specific glucocorticoid receptors and suppress many proinflammatory mediator expressions, such as a cytokine, chemokine, and adhesion molecules (10-12).

Astaxanthin (AST) is one of the most common carotenoids and is found in shellfish and the red pigment of salmon (13). It has various pharmacological properties such as antioxidant, antitumor, anti-inflammatory, antidiabetic, hepatoprotective, and immunomodulatory effects (13-15). Moreover, one of the characteristic features is that it is highly safe (14). It has been shown that AST induces reactive oxygen radicals and reduces inflammation by inhibiting nuclear factor kappa B (NF-kB) activation (16). AST has also therapeutic properties that protect mononuclear cells produced in special cultures from inflammation and oxidative stress induced by LPS (17). Many studies are showing the anti-inflammatory efficacy of AST, but studies on anti-inflammatory activity in liver tissue in the sepsis model are limited.

In this study, we aimed to determine whether AST has anti-inflammatory activity in sepsis and to compare the efficacy of AST with DEX which has anti-inflammatory activity.

Materials and Methods

We conducted this study after the approval of Eskişehir Osmangazi University Animal Experiments Local Ethics Committee dated 25.01.2018 and numbered 409-4. The experimental animals used in our study were obtained from the Medical and Surgical Experimental Research Center (TICAM). Forty male Sprague-Dawley rats weighing 260-320 grams were randomly divided into 5 equal groups (n=8). The rats were kept alive in the rooms whose temperature (20-22 °C) and humidity (45%-50%) were adjusted automatically with 12-hour light-dark illumination during the experiment. In this process, all rats were kept in transparent cages, fed with standard rat feed (pellet feed) and tap water. All subjects were fasted 12 hours before the experiment and allowed to drink only water.

The subjects included in the study were divided into five groups as the control (C) group (n=8), LPS group (n=8), AST group (n=8), AST+LPS group (n=8) and DEX+LPS group (n=8). On the first day, group C was given 0.2 mL of dimethyl sulfoxide intraperitoneally; group LPS was given *Salmonella typhimurium* LPS at a dose of 200 µg/0.2 mL intradermally; group AST was given AST dissolved in dimethyl sulfoxide at a dose of 100 mg/kg in a volume of 0.2 mL intraperitoneally; the AST+LPS group was given AST and LPS the same doses as the other groups; DEX+LPS group was given 1 mg/kg DEX in a volume of 0.2 mL intraperitoneally.

At the end of the 24th hour, after anesthesia was provided intraperitoneally with thiopental sodium 50 mg/kg, rats underwent laparotomy in a supine position. The right lobe of the liver and 2 mL of intracardiac blood were collected for sampling. After the procedure, euthanasia was performed by decapitation.

Some of the tissue samples were stored in 10% formaldehyde solution for immunohistochemical analysis, some were frozen in liquid nitrogen for polymerized chain reaction (PCR) analysis and then stored at -80 °C for a long time.

Six sections with 4 µm thickness were taken from paraffin blocks belonging to each group. To determine apoptotic cells in the sections, "terminal deoxynucleotidyl transferase-mediated dUTP nick and labeling" (TUNEL) method was applied. The sections were evaluated by a single histologist who did not know the distribution of the groups. Ten different areas were examined randomly in each section. The number of apoptotic cells in each area examined was evaluated by computer-assisted Olympus BX51 microscope

and BAB Bs200pro software. The number of apoptotic cells and the reaction intensity in the randomly selected areas were determined as a percentage (%).

Statistical Analysis

GraphPad Prism6 program was used for statistical analysis. The groups were first analyzed using the Shapiro-Wilk normality test to see if they had a normal distribution. Normally distributed data were evaluated by One-Way ANOVA test and differences between groups were evaluated by Tukey test. After the non-normal distribution of data was evaluated by the Kruskal-Wallis test, the differences between the groups were evaluated by the Dunn test. P values less than 0.05 were considered significant. Results were expressed as mean ($\dot{x}$), ± standard error (±SE).

Results

Biochemical Findings

TNF-alpha Levels

There was a statistically significant decrease in TNF-alpha levels in DEX+LPS group when compared with LPS group ($p<0.05$); although there was a decrease in the other treatment group (AST+LPS), it was not found to be statistically significant ($p>0.05$). When the AST+LPS and DEX+LPS groups were compared, decrease in the DEX+LPS group was found to be statistically significant ($p<0.05$). TNF-alpha values and their comparisons are shown in Tables 1 and 2.

PCR Findings

TNF-alpha Levels

When the groups were evaluated in terms of TNF-alpha levels; There was a statistically significant decrease in both treatment groups (AST+LPS and DEX+LPS) when compared with the LPS group ($p<0.05$). No statistically significant difference was found between the treatment groups ($p>0.05$). PCR TNF-alpha values and comparisons are shown in Tables 3 and 4.

IL-6 Levels

In terms of IL-6 levels; compared with the LPS group, a decrease was observed in both treatment groups (AST+LPS and DEX+LPS) but was not statistically significant ($p>0.05$). There was no significant difference between the treatment groups ($p>0.05$). IL-6 values and comparisons are shown in Tables 5 and 6.

NF-kB Levels

When the groups were evaluated in terms of NF-kB level; there was a statistically significant decrease in both treatment groups (AST+LPS and DEX+LPS) when compared

Table 1. Mean, standard deviation and standard error values of TNF-alpha measurements (biochemical findings)

	$\dot{x}$ (mean ± SD)	SEM
C	35.47±4.53	2.02
LPS	38.44±7.95	3.24
AST	24.42±1.72	0.77
AST+LPS	33.96±4.39	1.66
DEX+LPS	25.05±4.24	1.60

C: Control, LPS: lipopolysaccharide, AST: astaxanthin, AST+LPS: astaxanthin + lipopolysaccharide, DEX+LPS: dexamethasone + lipopolysaccharide, mean: mean value, SD: standard deviation, SEM: standard error values, TNF-alpha: tumor necrotizing factor-alpha

Table 2. Comparison of the groups in terms of TNF-alpha (p-value) (biochemical findings)

Groups	p-value
C vs LPS	0.8642
C vs AST	0.0150
C vs AST+LPS	0.9853
C vs DEX+LPS	0.0129
LPS vs AST	0.0009
LPS vs AST+LPS	0.5112
LPS vs DEX+LPS	0.0006
AST vs AST+LPS	0.0259
AST vs DEX+LPS	0.9995
AST+LPS vs DEX+LPS	0.0219

C: Control, LPS: lipopolysaccharide, AST: astaxanthin, AST+LPS: astaxanthin + lipopolysaccharide, DEX+LPS: dexamethasone + lipopolysaccharide, TNF-alpha: tumor necrotizing factor-alpha

Table 3. Mean, standard deviation and standard error values of TNF-alpha measurements (PCR findings)

	$\dot{x}$ (mean ± SD)	SEM
C	1.25±1.18	0.48
LPS	13.33±7.65	3.82
AST	0.94±0.54	0.22
AST+LPS	5.99±4.92	2.01
DEX+LPS	2.64±1.89	0.66

C: Control, LPS: lipopolysaccharide, AST: astaxanthin, AST+LPS: astaxanthin + lipopolysaccharide, DEX+LPS: dexamethasone + lipopolysaccharide, mean: mean value, SD: standard deviation, SEM: standard error values, PCR: polymerized chain reaction, TNF-alpha: tumor necrotizing factor-alpha

with the LPS group ($p<0.05$). No significant difference was found between the treatment groups ($p>0.05$). NF-kB values and comparisons are shown in Tables 7 and 8.

Immunohistochemical Findings

TUNEL negative reaction was observed in tissue samples belonging to group C, whereas apoptotic cells that showed positive reaction were observed in the LPS group. In the AST+LPS and DEX+LPS groups, apoptotic cell and reaction intensity decreased significantly compared to the LPS group. Apoptotic cells were not found in the AST group. The percentage of apoptotic cells was evaluated as 0% in the C group, 36.32% in the LPS group, 12.10% in the AST+LPS group, and 9.36% in the DEX+LPS group. The immunohistochemical appearance of apoptotic cells is shown in Figure 1.

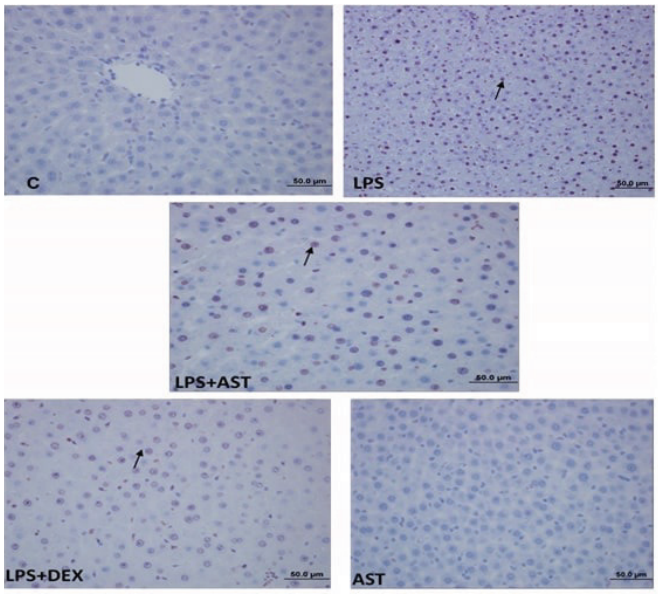


Figure 1. Apoptotic cells identified by TUNEL reaction (400x, ⟶) C: Control, LPS: lipopolysaccharide, LPS+AST: lipopolysaccharide + astaxanthin, LPS+DEX: lipopolysaccharide + dexamethasone, AST: astaxanthin

Discussion

Most treatment methods in sepsis include supportive and symptomatic approaches. Sepsis is a multifactorial pathophysiological pathway that intervenes in the progression of the process by blocking any step. Experimental studies have continued to determine the changes in these physiopathological processes. In this study, we aimed to investigate the effects of AST which we think may have an anti-inflammatory effect on inflammatory cytokines that play a role in one of these processes. The liver is known as a mechanical and immunological filter for the portal system, as well as an important source of cytokines (8). Today, subclinical liver damage is defined as dangerous diseases. In addition to these reasons, the liver being an easily accessible organ by laparotomy can be considered as one of the main reasons for our study.

TNF-alpha, one of the cytokines whose increase was detected in many studies examining the sepsis process, was evaluated in our study. Zhou et al. (18) examined the protective effects of AST against multiple organ damage in sepsis model-induced rats and administered AST orally for 7 days before cecal ligation and wounding surgery to be a peritonitis model. They found that TNF-alpha levels increased at the first hour and maximum at the third hour, and there was a less increase in the TNF-alpha level in the peritonitis-induced group after AST administration in our study, TNF-alpha levels in the DEX+LPS group were found to be significantly lower than those in the AST+LPS group. However, the effect of AST in lowering TNF-alpha levels in the presence of LPS was not as effective as DEX. In the study conducted by Ohgami et al. (13) using intradermal LPS injection method, TNF-alpha levels in humor aqueous induced by LPS tended to decrease in AST groups depending on AST dose. The same results as the TNF-alpha levels in the prednisolone-treated group with proven anti-inflammatory activity were also achieved in the intravenous AST-treated group. In our study, plasma TNF-alpha levels were measured by ELISA and TNF-alpha levels in liver cells were evaluated

Table 4. Comparison of the groups in terms of TNF-alpha (p-value) (PCR findings)

Groups	p-value
C vs LPS	0.0002
C vs AST	0.9999
C vs AST+LPS	0.1930
C vs DEX+LPS	0.9525
LPS vs AST	0.0002
LPS vs AST+LPS	0.0330
LPS vs DEX+LPS	0.0006
AST vs AST+LPS	0.1473
AST vs DEX+LPS	0.9058
AST+LPS vs DEX+LPS	0.4511

C: Control, LPS: lipopolysaccharide, AST: astaxanthin, AST+LPS: astaxanthin + lipopolysaccharide, DEX+LPS: dexamethasone + lipopolysaccharide, PCR: polymerized chain reaction, TNF-alpha: tumor necrotizing factor-alpha

Table 5. Mean, standard deviation and standard error values of IL-6 measurements		
	ẋ (mean ± SD)	SEM
C	0.33±0.19	0.09
LPS	0.29±0.15	0.06
AST	0.22±0.19	0.06
AST+LPS	0.10±0.06	0.02
DEX+LPS	0.017±0.21	0.08

C: Control, LPS: lipopolysaccharide, AST: astaxanthin, AST+LPS: astaxanthin + lipopolysaccharide, DEX+LPS: dexamethasone + lipopolysaccharide, mean: mean value, SD: standard deviation, SEM: standard error values, IL-6: interleukin-6

Table 6. Comparison of the groups in terms of IL-6 (p-value)	
Groups	p-value
C vs LPS	0.9970
C vs AST	0.8636
C vs AST+LPS	0.2912
C vs DEX+LPS	0.5897
LPS vs AST	0.9650
LPS vs AST+LPS	0.4142
LPS vs DEX+LPS	0.7582
AST vs AST+LPS	0.6970
AST vs DEX+LPS	0.9692
AST+LPS vs DEX+LPS	0.9605

C: Control, LPS: lipopolysaccharide, AST: astaxanthin, AST+LPS: astaxanthin + lipopolysaccharide, DEX+LPS: dexamethasone + lipopolysaccharide, IL-6: interleukin-6

Table 7. Mean, standard deviation and standard error values of NF-kB measurements		
	ẋ (mean ± SD)	SEM
C	1.03±0.27	0.09
LPS	1.03±0.27	0.11
AST	0.50±0.08	0.02
AST+LPS	0.02±0.01	0.005
DEX+LPS	0.024±0.023	0.008

C: Control, LPS: lipopolysaccharide, AST: astaxanthin, AST+LPS: astaxanthin + lipopolysaccharide, DEX+LPS: dexamethasone + lipopolysaccharide, mean: mean value, SD: standard deviation, SEM: standard error values, NF-kB: nuclear factor-kappa B

by PCR. Plasma TNF-alpha levels were significantly lower in AST and DEX+LPS groups compared to control group C. When the TNF-alpha levels in the liver by PCR method were evaluated, a significant increase was found in LPS group compared to C group. TNF-alpha levels in AST+LPS and DEX+LPS groups were significantly lower than the LPS group. However, there was no significant difference between

Table 8. Comparison of groups in terms of NF-kB (p-value)	
Groups	p-value
C vs LPS	>0.9999
C vs AST	<0.0001
C vs AST+LPS	<0.0001
C vs DEX+LPS	<0.0001
LPS vs AST	<0.0001
LPS vs AST+LPS	<0.0001
LPS vs DEX+LPS	<0.0001
AST vs AST+LPS	<0.0001
AST vs DEX+LPS	<0.0001
AST+LPS vs DEX+LPS	>0.9999

C: Control, LPS: lipopolysaccharide, AST: astaxanthin, AST+LPS: astaxanthin + lipopolysaccharide, DEX+LPS: dexamethasone + lipopolysaccharide, NF-kB: nuclear factor-kappa B

DEX+LPS group and AST+LPS group, while there was a significant difference in plasma between two groups, DEX and AST activity were not found to be similar in the liver of LPS rats. Considering that the liver is the first organ in which protein synthesis occurs, AST activity may reach a similar level to DEX in plasma similar to that in the liver over 24 hours.

In our study, we evaluated the IL-1 alpha level which is known to be effective in the liver inflammatory process by Western blot method. In the study of Zhou et al. (18), serum IL-1 beta levels were evaluated by ELISA method and it was found that serum IL-1 beta increased significantly in the peritonitis-induced and the AST-treated group increased significantly less than in the peritonitis-treated but untreated group. In our study, IL-1 alpha level was slightly decreased in the DEX+LPS group compared to the LPS group. However, there was no decrease in AST+LPS group. In this context, we found that DEX was more effective on IL-1 alpha in the sepsis model than AST.

In a study conducted by Izumi-Nagai et al. (19), the anti-inflammatory effects of AST as a preventive of choroidal neovascularization was investigated, and they concluded that IL-6 levels decreased in endothelial cells in the AST-treated group. In our study, no significant difference was found between the groups in terms of IL-6 levels in liver tissue evaluated by PCR technique.

NF-kB is a transcription factor composed of heterodimers or homodimers and is adhered to inhibitory kB proteins and is seen as sequestered in the cytoplasm. TNF-alpha, IL-1 and many other cytokines induce NF-kB synthesis and initiate

and maintain their cascades (20). In a study by Izumi-Nagai et al. (19), they examined the effects of AST *in vivo* and *in vitro* and found that NF-kB levels were lower in the AST-treated group *in vivo* study. In our study, the levels of NF-kB measured by PCR in liver cells were significantly lower in AST+LPS and DEX+LPS groups. However, there was no significant difference between the two groups. According to these results, it can be said that AST and DEX have a similar effect on NF-kB levels.

It is known that there is an increase in apoptosis and loss of immune system cells in the process of sepsis (18). In the study of Otsuka et al. (14), apoptosis was evaluated by TUNEL method in retinal cells damaged by excessive light after the administration of AST and it was found that apoptosis was less than 28%. In the study of Zhang et al. (21), they induced subarachnoid hemorrhage and administrated intracerebroventricular AST and they evaluated the effects of AST on early brain injury. They found that there was a decreased apoptosis rate in response to different doses by TUNEL method. In our study, the negative reaction was observed in C and AST groups in liver samples examined by TUNEL staining method, whereas apoptotic cells that showed a positive reaction in the LPS group were observed. In the AST+LPS and DEX+LPS groups, apoptotic cell and reaction intensity decreased significantly compared to the LPS group. Based on these findings, DEX, and AST significantly reduced apoptosis and anti-inflammatory applications in sepsis were thought to be beneficial. Because it is an *in vivo* study, it can be considered as a promising result in clinical practice.

Our study was an experimental study and a limited number of experimental animals were used. However, some parameters related to sepsis were studied and some parameters used in clinical trials could not be evaluated. The administration of AST as a single dose and examination of tissue and blood samples after 24 hours does not reveal the long-term effects of AST on sepsis.

Conclusion

In our study, we evaluated the anti-inflammatory activity of AST, which we think may have therapeutic efficacy in sepsis; In an LPS-induced sepsis model and we evaluated various inflammatory cytokine levels and apoptosis in liver tissue and plasma of rats. We found that the use of AST had positive effects on TNF-alpha in plasma and IL-1 alpha, IL-6, TNF-alpha, NF-kB levels in liver tissue. We also obtained similar measurement values, although there were differences when compared to DEX administration. When apoptosis cell ratios were evaluated, we concluded that AST had a significant effect. Because of the complex interaction of inflammatory and anti-inflammatory agents involved in the pathogenesis of sepsis, well-standardized studies with a large number of factors and recordings are required for a healthy evaluation of the molecules and AST thought to be effective in this process.

Publication: This article was designed as Dr Nurdan Çobaner's specialization thesis.

Ethics

Ethics Committee Approval: We conducted this study after the approval of Eskişehir Osmangazi University Animal Experiments Local Ethics Committee dated 25.01.2018 and numbered 409-4.

Informed Consent: An animal experiment.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.Ç., M.Ö., Concept: N.Ç., B.Y., N.E., Design: N.Ç., B.Y., N.E., Data Collection and Process: N.Ç., M.Ö., E.B., Analysis or Interpretation: N.Ç., B.Y., N.E., M.Ö., E.B., Literature Search: N.Ç., Writing: N.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This study was funded by Eskişehir Osmangazi University Scientific Research Project Committee (project code: 2015-770).

References

1. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A,et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:762-74.
2. Zanotti-Cavazzoni SL, Dellinger RP, Parillo JE. Ciritical Care Medicine. In:Dellinger RP, Parillo JE, editors. Severe sepsis and Multiple Organ Dysfuction 4th ed. Philadephia Elsevier Saunders: 2014.p.365-78.
3. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003;348:1546-54.
4. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001;29:1303-10.
5. Irwin RS, Rippe JM. Sepsis yönetimi (çeviri: S. Çakar Turhan). Tulunay M, Cuhruk H, editors. Yoğun Bakım Tıbbı. Ankara, Güneş tıp kitabevleri: 2014.p.1855-69.
6. Zanotti S, Kumar A, Kumar A. Cytokine modulation in sepsis and septic shock. Expert Opin Investig Drugs 2002;11:1061-75.
7. Giamarellos-Bourboulis EJ, Routsi C, Plachouras D, Markaki V, Raftogiannis M, Zervakis D, et al. Early apoptosis of blood monocytes in the septic host: is it a mechanism of protection in the event of septic shock? Crit Care 2006;10:R76.
8. Hotchkiss RS, Osmon SB, Chang KC, Wagner TH, Coopersmith CM, Karl IE. Accelerated lymphocyte death in sepsis occurs by both the death receptor and mitochondrial pathways. J Immunol 2005;174:5110-8.
9. Annane D, Bellissant E, Bollaert PE, Briegel J, Confalonieri M, De Gaudio R, et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. JAMA 2009;301:2362-75.
10. Li L, Whiteman M, Moore PK. Dexamethasone inhibits lipopolysaccharide-induced hydrogen sulphide biosynthesis in intact cells and in an animal model of endotoxic shock. J Cell Mol Med 2009;13:2684-92.
11. Korhonen R, Lahti A, Hämäläinen M, Kankaanranta H, Moilanen E. Dexamethasone inhibits inducible nitric-oxide synthase expression and nitric oxide production by destabilizing mRNA in lipopolysaccharide-treated macrophages. Mol Pharmacol 2002;62:698-704.
12. Lasa M, Brook M, Saklatvala J, Clark AR. Dexamethasone destabilizes cyclooxygenase 2 mRNA by inhibiting mitogen-activated protein kinase p38. Mol Cell Biol 2001;21:771-80.
13. Ohgami K, Shiratori K, Kotake S, Nishida T, Mizuki N, Yazawa K, et al. Effects of astaxanthin on lipopolysaccharide-induced inflammation in vitro and in vivo. Invest Ophthalmol Vis Sci 2003;44:2694-701.
14. Otsuka T, Shimazawa M, Nakanishi T, Ohno Y, Inoue Y, Tsuruma K, et al. Protective effects of a dietary carotenoid, astaxanthin, against light-induced retinal damage. J Pharmacol Sci 2013;123:209-18.
15. Uchiyama K, Naito Y, Hasegawa G, Nakamura N, Takahashi J, Yoshikawa T. Astaxanthin protects beta-cells against glucose toxicity in diabetic db/db mice. Redox Rep 2002;7:290-3.
16. Lee SJ, Bai SK, Lee KS, Namkoong S, Na HJ, Ha KS, et al. Astaxanthin inhibits nitric oxide production and inflammatory gene expression by suppressing I(kappa)B kinase-dependent NF-kappaB activation. Mol Cells 2003;16:97-105.
17. Franceschelli S, Pesce M, Ferrone A, De Lutiis MA, Patruno A, Grilli A, et al. Astaxanthin treatment confers protection against oxidative stress in U937 cells stimulated with lipopolysaccharide reducing O2- production. PLoS One 2014;9:e88359.
18. Zhou L, Gao M, Xiao Z, Zhang J, Li X, Wang A. Protective effect of astaxanthin against multiple organ injury in a rat model of sepsis. J Surg Res 2015;195:559-67.
19. Izumi-Nagai K, Nagai N, Ohgami K, Satofuka S, Ozawa Y, Tsubota K, et al. Inhibition of choroidal neovascularization with an anti-inflammatory carotenoid astaxanthin. Invest Ophthalmol Vis Sci 2008;49:1679-85.
20. Suzuki Y, Ohgami K, Shiratori K, Jin XH, Ilieva I, Koyama Y, et al. Suppressive effects of astaxanthin against rat endotoxin-induced uveitis by inhibiting the NF-kappaB signaling pathway. Exp Eye Res 2006;82:275-81.
21. Zhang XS, Zhang X, Zhou ML, Zhou XM, Li N, Li W, et al. Amelioration of oxidative stress and protection against early brain injury by astaxanthin after experimental subarachnoid hemorrhage. J Neurosurg 2014;121:42-54.

Turk J Intensive Care 2022;20:86-92
DOI: 10.4274/tybd.galenos.2021.38039

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Burhan Sami Kalın,
İhsan Solmaz

Effects of Red Blood Cell Distribution Width on the Outcomes of Patients with Sepsis in Intensive Care Unit: A Retrospective Study

Yoğun Bakım Ünitesinde Septik Hastaların Sonuçları Üzerine Kırmızı Kan Hücresi Dağılım Genişliğinin Değerlendirilmesi: Retrospektif Bir Çalışma

Received/Geliş Tarihi : 20.12.2020
Accepted/Kabul Tarihi : 04.03.2021

Burhan Sami Kalın
University of Health Sciences Turkey, Diyarbakır Gazi Yaşargil Training and Research Hospital, Clinic of Internal Medicine, Division of Critical Care, Diyarbakır, Turkey

İhsan Solmaz
University of Health Sciences Turkey, Diyarbakır Gazi Yaşargil Training and Research Hospital, Clinic of Internal Medicine, Diyarbakır, Turkey

Burhan Sami Kalın MD (✉),
University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital, Clinic of Internal Medicine, Division of Critical Care, Diyarbakır, Turkey

E-mail : bskalin@windowslive.com
Phone : +90 538 978 71 80
ORCID ID : orcid.org/0000-0003-2624-6175

ABSTRACT *Objective:* This study aimed to determine the prognostic value of red cell distribution width (RDW) in patients with sepsis in intensive care unit (ICU).
Materials and Methods: This single centre study includes a retrospective analysis of critically ill patients with sepsis. Patients' demographic data; comorbidities; RDW values upon ICU admission, day 3 (RDW3) and day 7 (RDW7); Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score; need for haemodialysis and invasive mechanical ventilation (IMV) were compared between survivors and non-survivors. In addition, patients were divided into the following two groups: high RDW (>14.5%) and normal RDW (≤14.5%). Logistic regression analysis was performed to determine independent risk factors for ICU mortality.
Results: A total of 102 patients with sepsis were included. Survivors had lower RDW than non-survivors (p<0.05 for RDW values upon ICU admission, RDW3 and RDW7). The APACHE-II score, presence of septic shock on ICU admission, need for IMV and mortality rate were higher in patients in the high RDW group than those in patients in the normal RDW group (for all p<0.05). In this study, the presence of septic shock on ICU admission, RDW3 value and need for IMV were found to be independent risk factors for mortality.
Conclusion: In this study, RDW3 value was significantly associated with mortality in critically ill patients with sepsis and has an important value in predicting the prognosis of patients with sepsis in ICU.
Keywords: Sepsis, septic shock, intensive care unit, red blood cell distribution width

ÖZ *Amaç:* Bu çalışmanın amacı yoğun bakım ünitesinde (YBÜ) bulunan septik hastalarda eritrosit dağılım genişliğinin (RDW) prognostik değerini belirlemektir.
Gereç ve Yöntem: Bu tek merkezli çalışmada, kritik olan sepsis hastalarının retrospektif bir analizi yer almaktadır. Hastaların demografik verileri, komorbiditeleri, YBÜ'ye kabuldeki RDW, 3. gün (RDW3) ve 7. gün RDW (RDW7) değerleri, Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II (APACHE-II) skoru, hemodiyaliz ve invaziv mekanik ventilasyon (IMV) ihtiyacı sağ kalanlar ve vefat edenler arasında karşılaştırıldı. Ayrıca hastalar yüksek (>%14,5) ve normal (≤%14,5) RDW olarak iki gruba ayrıldı. YBÜ mortalitesi için bağımsız risk faktörlerini belirlemek üzere lojistik regresyon analizi yapıldı.
Bulgular: Yüz iki septik hasta çalışmaya dahil edildi. Sağ kalanlar, vefat edenlere kıyasla daha düşük RDW'ye sahipti (YBÜ'ye kabuldeki RDW, RDW3 ve RDW7 değerleri, tümü için p<0,05). Yüksek RDW grubundaki hastalar normal RDW grubundaki hastalara göre daha yüksek APACHE-II skoruna, YBÜ'ye kabulde daha yüksek oranda septik şok varlığına, daha yüksek IMV ihtiyacına ve mortalite oranına sahipti (tümü için p<0,05). Bu çalışmada YBÜ'ye kabulde septik şok varlığı, RDW3 değeri ve IMV ihtiyacı mortalite için bağımsız risk faktörleri olarak bulundu.
Sonuç: Bu çalışmada RDW3 değeri, kritik septik hastalarda mortalite ile anlamlı olarak ilişkili bulunmuştur ve YBÜ septik hastalarının prognozunu öngörmede önemli bir değere sahiptir.
Anahtar Kelimeler: Sepsis, septik şok, yoğun bakım ünitesi, kırmızı kan hücresi dağılım genişliği

Introduction

Sepsis is a life-threatening organ dysfunction caused by dysregulated host response to infection and septic shock is defined as a circulatory and metabolic disorder associated with a higher risk of mortality (1,2). Sepsis and septic shock are important healthcare problems which are affecting quite a lot of people in the world (3). The progression of severity is associated with rised mortality with insufficiency in multiple organ systems and most oftenly quantified by the Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score which can predict the severity and outcome depending on different organ functional status (4). It would be advantageous to identify a rapid, cheap and easily applicable biomarker associated with the severity of sepsis. Red cell distribution width (RDW) is an index of complete blood count (CBC) analysis which is commonly measured among patients. RDW is specified as a numeric percentage which is calculated as red blood cell (RBC) volume divided by the mean corpuscular volume (MCV) and multiplied by 100 (5). RDW is an indicator of anisocytosis as a part of CBC analysis to determine the heterogeneity of erythrocytes. Throughout the years, RDW has been typically utilized in combination with the MCV and mean corpuscular hemoglobin (MCH) to differentiate the etiology of anemia (6). RDW is a component of CBC which is calculated by flow cytometry machine. Normal limits of RDW is oftenly accepted between 11.5% and 14.5%. Except the assessment of anemia etiology, studies have notified that RDW may be associated with outcome in patients with heart failure, acute myocardial infarction, thrombolysis used during ischemic stroke, pulmonary thromboembolism, pneumonia and cardiopulmonary arrest (7-12). Elevation in RDW is also known to be associated with elevated inflammatory marker tests such as IL-6 and TNF-α. It is a known mechanism that proinflammatory cytokines could lead suppression on RBC maturation, which may result as an elevation in RDW. Even though there are some hypothesis, the precise pathophysiological situation underlying changes in RDW and clinical conclusions are not elucidated clearly yet (13,14). There are only few studies investigating the correlation between sepsis and RDW. The main purpose of this study was to appreciate the relation among RDW and outcome and to determine it's prognostic significance in critically septic patients.

Materials and Methods

This single center retrospective analysis was conducted in a tertiary medical intensive care unit (ICU) at hospital, Department of Internal Medicine, Division of Critical Care between January 2015 and January 2020. The study protocol was approved by the University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital Ethics Committee (decision no: 487, date: 12.06.2020). One hundred two patients older than 18 years followed up with sepsis were included in the study. The identifiaction of sepsis and/or septic shock was described according to the International Sepsis Definitions Conference criteria (1). Patients with blood product transfusion in last two weeks, active major bleeding, history of diseases which may affect RDW such as leukemia, bone marrow infiltration, transplantation, agranulocytosis, recently received chemotherapy, radiotherapy and drugs that significantly effect RDW measurements were excepted. Demographic and laboratory data were collected from hospital electronic records and patient file archives. Patient age, gender, APACHE-II score, need for invasive mechanical ventilation (IMV), lenght of stay (LOS) in ICU, comorbid conditions (cardiovascular, renal, endocrinological, respiratory and neurological diseases), need for hemodialysis, presence of septic shock on ICU admission and mortality status were recorded. APACHE-II score was calculated within the parameters of first 24 hours after admission to ICU. C-reactive protein (CRP), procalcitonin, RDW, white blood cell (WBC), hemoglobin (Hb), MCH, MCV and platelet (PLT) values were measured on ICU admission. Also, RDW3 and RDW7 values were noted. Haematological parameters were determined using analyser. The analyser calculates MCV, MCH and MCHC based on measurements of Hb. The reference range for RDW in our laboratory was 11.5-14.5%.

Statistical Analysis

Preliminarily, patients were divided in two separate groups as survivors and non-survivors, normal and high RDW values and also septic shock and non-septic shock. Continuous variables were tested using Kolmogorov-Smirnov test for normality and datas are expressed as median and interquartile range or mean ± standard deviation. Mann-Whitney U test was performed to compare distinctions for non-normally distributed variables. Student t-test was performed to compare distinctions for normally distributed variables. Categorical variables were analyzed with a

chi-square test or Fisher's Exact test and expressed as numbers (percentages). Binary logistic regression analysis was performed to determine the independent risk factors for mortality. The outcomes of the regression analyses were expressed as odds ratio (OR) and 95% confidence interval (CI). The receiver operator characteristics (ROC) curve was formed and the area under the curve (AUC) was computed to understand the strength of RDW on mortality. A p-value less than 0.05 were presumed statistically significant. Statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS), version 22.0 software (SPSS Inc.,Chicago, IL, USA).

Results

Fifty-two (51%) were female of 102 septic patients participated in this study. The median age was 72 (62-80) years. Median RDW value on admission to the ICU was 16.8 (15.3-18.8). Mortality rate was 59.8%. LOS in ICU was 6 (4-12) days. In this study, 46 (45.1%) patients had cardiovascular disease, 39 (38.2%) patients had renal disease and 25 (24.5%) patients had endocrinological disease. The frequency of comorbidities was not different between survivors and non-survivors. The need for IMV was 62 (60.8%). APACHE-II score was 20 (17-28). The number of patients undergoing hemodialysis was 49 (48%). Sixty-six (64.7%) of the patients was diagnosed as septic shock on ICU admission. Survivors had lower RDW value on admission to the ICU [15.8 (14.1-18) versus 17.4 (16.2-19.3), p=0.001], RDW3 value [15.8 (14.6-17.5) versus 17.4 (16.2-19.3), p=0.002] and RDW7 value [15.8 (14.8-17.5) versus 17.5 (16.1-19.8), p=0.003] as compared to non-survivors. The patients with RDW value >14.5% on admission to the ICU was more higher in non-survivors than in survivors and was statistically significant [56 (91.8) versus 30 (73.2), p=0.011]. Non-survivors had higher CRP [127 (82-178) versus 87 (33-188), p=0.05], procalcitonin [3.3 (1.2-8.7) versus 0.9 (0.3-2.8), p=0.001) and APACHE-II score [24 (19-32) versus 17 (15-20), p=0.001] as compared in survivors. The need for hemodialysis were higher in non-survivors than in survivors [35 (57.4) versus 14 (34.1), p=0.02]. There were no significant difference WBC, MCV, MCH, Hb and PLT values between these two groups. Detailed demographic characteristics were described in Table 1. Patients were divided in two groups as a high RDW (>14.5%) and a normal RDW (≤14.5%). The high RDW group had higher APACHE-II score [22 (17-28) versus 18 (13-23), p=0.05], septic shock rate on ICU admission [62 (72.1) versus 4 (25), p=0.001], need for hemodialysis [46 (53.5) versus 3 (18.8), p=0.011] and mortality rate [56 (65.1) versus 5 (31.3), p=0.011] as compared to normal RDW group. There were no significant difference in LOS in ICU and need for IMV between normal and high RDW groups. Detailed demographic characteristics were described in Table 2. Patients with septic shock had higher RDW value on admission to the ICU [17.3 (16-19.5) versus 15.4 (13.8-17.1), p=0.001], RDW3 value [17.3 (16.1-19.1) versus 15 (14.1-17.2), p=0.001] and RDW7 value [17.5 (16-18.8) versus 15.4 (14.2-17.2), p=0.004] as compared in patients without septic shock. Detailed demographic characteristics were described in Table 3. In the binary logistic regression analysis, presence of septic shock on ICU admission, need for IMV and RDW3 value were found to be independent risk factors for mortality [OR: 9.469 (1.964-45.646), p=0.005, OR: 9.231 (2.118-40.234), p=0.003, OR: 2.227 (1.083-4.580), p=0.029], respectively (Table 4). As shown in Figure 1, AUC of the receiver operating characteristic for prediction of mortality was 0.701 (95% CI: 0.586-0.815) for RDW3 value. Based on ROC curve for RDW3 shows a cut-off value of 16 with a sensitivity of 78.9% and a specificity of 56.1% (95% CI: 0.586-0.815, p=0.002).

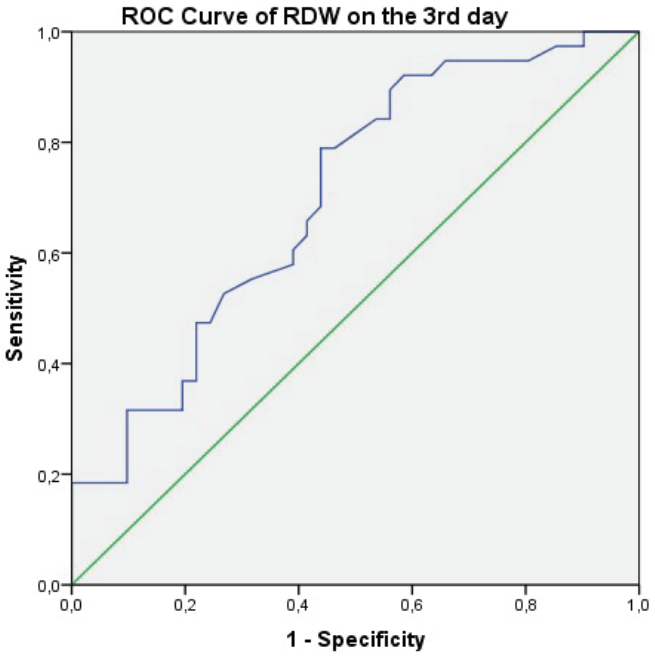


Figure 1. Receiving operator curve analysis of RDW3 value in predicting mortality
ROC: Receiver operator characteristics, RDW: red cell distribution width

Table 1. Baseline characteristics of the patients				
Variables	**Total n=102**	**Survivors n=41**	**Non-survivors n=61**	**p**
Age, (y)	72 (62-80)	69 (57-83)	72 (62-79)	0.785
Male, n (%)	50 (49)	20 (48.8)	30 (49.2)	0.968
APACHE-II score	20 (17-28)	17 (15-20)	24 (19-32)	0.001
Septic shock in ICU, n (%)	66 (64.7)	15 (36.6)	51 (83.6)	0.001
Comorbidity, n (%)				
Cardiovascular disease	46 (45.1)	19 (46.3)	27 (44.3)	0.836
Renal insufficiency	39 (38.2)	17 (41.5)	22 (36.1)	0.582
Endocrinological disease	25 (24.5)	12 (29.2)	13 (21.3)	0.379
Respiratory disease	29 (28.4)	11 (26.8)	18 (29.5)	0.769
Neurological disease	16 (15.6)	6 (14.6)	10 (16.4)	0.799
Laboratory parameters on admission				
CRP (mg/L)	109 (68-179)	87 (33-188)	127 (82-178)	0.05
Procalcitonin (ng/mL)	1.93 (0.5-5.5)	0.9 (0.3-2.8)	3.3 (1.2-8.7)	0.001
Hb (g/dL)	10.1±2.18	10.5±2.03	9.9±2.3	0.266
WBC (10^3/μL)	10.9 (7.1-16.3)	10 (7.1-15)	12 (6.8-17.3)	0.609
MCV (fL)	85.9±7.5	86.9±7.4	85.2±7.5	0.254
MCH (pg)	28 (27-30)	29 (27-30)	28 (26-29)	0.112
PLT (10^3/μL)	174±105	191±100	164±108	0.192
RDW value on admission to the ICU, %	16.8 (15.3-18.8)	15.8 (14.1-18)	17.4 (16.2-19.3)	0.001
High RDW value on admission to the ICU, n (%)	86 (84.3)	30 (73.2)	56 (91.8)	0.011
RDW3 value, %	16.8 (15-18.1)	15.8 (14.6-17.5)	17.4 (16.2-19.3)	0.002
High RDW3 value, n (%)	69 (67.6)	33 (80.5)	36 (59)	0.09
RDW7 value, %	16.4 (15.1-18.2)	15.8 (14.8-17.5)	17.5 (16.1-19.8)	0.003
High RDW7 value, n (%)	60 (58.8)	29 (70.7)	31 (50.8)	0.137
Need for hemodialysis, n (%)	49 (48)	14 (34.1)	35 (57.4)	0.02
Need for IMV, n (%)	62 (60.8)	13 (31.7)	49 (80.3)	0.001
LOS in ICU days	6 (4-12)	6 (4-10)	7 (3-15)	0.673

n: Number, y: year, p: probability, APACHE-II: Acute Physiologic and Chronic Health Evaluation-II, ICU: intensive care unit, Hb: hemoglobin, RDW: red cell distribution width, WBC: white blood cell, CRP: C-reactive protein, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, PLT: platelet, IMV: invasive mechanical ventilation, LOS: length of stay

Discussion

Sepsis is a major problem with high morbidity and mortality rates, especially for ICU patients. Most biochemical markers indicating sepsis related inflammation are expensive and not easily available, which is the point, RDW seems to have an advantage. Although RDW is not a definite indicator for sepsis, in recent years, it has been emphasized that the high RDW value is in relation with mortality in septic patients (15,16). Elevated RDW presumably reflects the presence of elevated proinflammatory cytokines in sepsis and septic shock. In a retrospective analysis of patients with sepsis and septic shock, RDW was remarkably higher in non-survivors as compared in survivors (17). In this present study, RDW was also found significantly higher in non-survivor septic patients when compared to survivors, which is compatible with literature data. In previous studies, positive association was detected between RDW and mortality rates in neonatal, pediatric and adult patient groups according to cox proportional hazards model. Ellahony et al. (18) indicated an evident association of RDW with mortality in neonatal patients (OR, 1.31; 95% CI, 1.241-1.399). Mahmood et al.

Table 2. Baseline characteristics of the patients according to RDW value

Variables	Total n=102	High RDW n=86	Normal RDW n=16	p
Age, (y)	72 (62-80)	72 (63-79)	57 (52-79)	0.665
Male, n (%)	50 (49)	39 (45.3)	11 (68.8)	0.086
APACHE-II score	20 (17-28)	22 (17-28)	18 (13-23)	0.05
Septic shock in ICU, n (%)	66 (64.7)	62 (72.1)	4 (25)	0.001
Need for hemodialysis, n (%)	49 (48)	46 (53.5)	3 (18.8)	0.011
Need for IMV, n (%)	62 (60.8)	53 (61.6)	9 (56.3)	0.686
LOS in ICU days	6 (4-12)	6 (4-12)	7 (3-12)	0.879
Mortality, n (%)	61 (59.8)	56 (65.1)	5 (31.3)	0.011

n: Number, y: year, p: probability, APACHE-II: Acute Physiologic And Chronic Health Evaluation-II, ICU: intensive care unit, RDW: red cell distribution width, IMV: invasive mechanical ventilation, LOS: length of stay

Table 3. RDW values of the patients according to situation of septic shock

Variables	Total n=102	Patients with septic shock n=66	Patients without septic shock n=36	p
RDW value on admission to the ICU, %	16.8 (15.3-18.8)	17.3 (16-19.5)	15.4 (13.8-17.1)	0.001
RDW3 value, %	16.8 (15-18.1)	17.3 (16.1-19.1)	15 (14.1-17.2)	0.001
RDW7 value, %	16.4 (15.1-18.2)	17.5 (16-18.8)	15.4 (14.2 -17.2)	0.004

n: Number, p: probability, ICU: intensive care unit, RDW: red cell distribution width

Table 4. Multivariable binary logistic regression modeling of parameters for mortality

Variables	OR (95% CI)	p
Septic shock in ICU	9.469 (1.964-45.646)	0.005
Need for IMV	9.231 (2.118-40.234)	0.003
RDW3 value, %	2.227 (1.083-4.580)	0.029
Need for hemodialysis	1.656 (0.418-9.368)	0.549
High RDW on admission to the ICU	1.287 (0.088-18.782)	0.854
APACHE-II score	0.993 (0.834-1.652)	0.798
RDW7 value, %	1.355 (0.482-1.687)	0.299
RDW value on admission to the ICU, %	0.586 (0.132-1.289)	0.134
Procalcitonin	1.095 (0.852-1.406)	0.479

OR: Odds ratio, CI: confidence interval, p: probability, ICU: intensive care unit, IMV: invasive mechanical ventilation, RDW: red cell distribution width, APACHE-II: Acute Physiologic and Chronic Health Evaluation-II

(19), demonstrated that RDW value ≥16 was an independent risk factor for mortality in the septic patients. Sadaka et al. (20) performed, RDW was assigned to be an independent risk factor for mortality occurring both in the critical care unit and hospital in patients with sepsis and septic shock. In another studies demonstrated that RDW value on admission to the ICU were valuable for predicting 28-day mortality (21). Ramby et al. (22) could not be established between mortality and RDW in pediatric septic patients. Zhang et al. (23) RDW were found to be independent risk factor for mortality in patients with severe acute pancreatitis. Similarly, in this study, RDW value on admission to the ICU and RDW7 values were not found to be independent risk factors for mortality but RDW3 value was a risk factor. Ku et al. (24) performed that 72 hours of RDW could be an indicator for all reasons mortality in patients with Gram-negative bacterial sepsis as similar to the results of this study. Severe sepsis and/or septic shock patients received massive or goal directed fluid resuscitation and appropriate empiric antibiotic therapy in the first hours of treatment and because of this reasons, the number of reported deaths in the first 24 hours was lower among our septic patients. Although the value of RDW was higher on admission to ICU, it could not be associated with mortality. Also the lack of an association between RDW value on admission to the ICU and mortality may be attributable to the relatively small number of patients, high incidence of comorbidities, life-threatening conditions of the patients on admission to ICU (such as need for hemodialysis and acute renal failure etc.), high APACHE-II score, high rate of septic shock and the increased use of IMV. Increased

mortality rate after three days with high RDW3 values were easily associated. Another study showed that RDW values on 1, 4, and 8 days were associated with prognosis in septic patients. Non-survivors septic patients had higher RDW than survivors in the first week of ICU stay and RDW during the first week was associated with mortality (25). Chan and his colleagues reported that rise in RDW values during the first 72 h after admission to hospital was associated with a higher mortality ratio in septic patients (26). In our study, non-survivor group had higher RDW values (on admission to the ICU, RDW3 and RDW7) than survivors. This result intended that dynamic observation of RDW values appeared to be more valuable than one single result in clinical practice. Also patients with septic shock had higher RDW value on admission to the ICU, RDW3 value and RDW7 value as compared in patients without septic shock (for all $p<0.05$). Lakshmi and Palanisamy (27) showed in a sepsis study as similar results to our study that the subjects with sepsis had a mean RDW of 15.92, with severe sepsis had a mean RDW of 16.73 and with septic shock had a mean RDW of 18.06. There are studies have notified that RDW may be associated a worse prognosis in patients with life-threatening illnesses such as congestive heart failure, acute myocardial infarction, thrombolysis used during ischemic stroke, pulmonary embolism, pneumonia, critical illness and cardiac arrest (7-12). The association between RDW and mortality or severity in sepsis and septic shock is uncertain. It is thought that proinflammatory cytokines may cause depression in the maturation of RBC and decrease the half-life of RBCs. Therefore, inflammatory situations could cause elevation in RDW (28). There were several limitations in our study. This was a single-center study with a small sample size. In addition, RDW may be affected by nutritional status, iron, folate, total cholesterol values, hepatic or renal dysfunction, cancer, thyroid disease, acute or chronic inflammatory response, use of some medications, albumin and vitamin B12 values. This is a retrospective analysis and we did not involve the nutritional status or any of the vitamin and hormonal values of the patients. Also, in a much wider patient population or different disease subgroups, the results related to RDW may differ.

Conclusion

Although RDW value on admission to the ICU was not a risk factor for mortality, RDW3 value was found as an independent risk factors for mortality. Accordingly the follow-up of patient's RDW value in the days after admission to the ICU can be valuable. RDW which has the low cost and universal availability can be used as an adjunct factor for predicting mortality in septic patients along with other prognostic values. Also, the RDW values (on admission to the ICU, RDW3 and RDW7) were higher especially in septic shock patients compared to sepsis patients without septic shock. Further studies are necessary to verify the act of RDW in sepsis and septic shock patients as a predictive marker in the ICU.

Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital Ethics Committee (decision no: 487, date: 12.06.2020).

Informed Consent: Patient consent was waived because no patient identifiers were disclosed and the diagnosis and management of patients would not be affected.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: B.S.K., İ.S., Design: B.S.K., İ.S., Data Collection and Process: B.S.K., İ.S., Analysis or Interpretation: B.S.K., İ.S., Literature Search: B.S.K., İ.S., Writing: B.S.K., İ.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:775-87.
2. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:762-74.
3. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001;29:1303-10.
4. Qiao Q, Lu G, Li M, Shen Y, Xu D. Prediction of outcome in critically ill elderly patients using APACHE II and SOFA scores. J Int Med Res 2012;40:1114-21.
5. Morris M, Davey FR, Henry JB. Basic examination of blood. In Clinical diagnosis and management by laboratory methods. 20th edition. Philadelphia: WB Saunders Company; 2001.
6. Demir A, Yarali N, Fisgin T, Duru F, Kara A. Most reliable indices in differentiation between thalassemia trait and iron deficiency anemia. Pediatr Int 2002;44:612-6.
7. Felker GM, Allen LA, Pocock SJ, Shaw LK, McMurray JJ, Pfeffer MA, et al. Red cell distribution width as a novel prognostic marker in heart failure: data from the CHARM Program and the Duke Databank. J Am Coll Cardiol 2007;50:40-7.
8. Zorlu A, Bektasoglu G, Guven FM, Dogan OT, Gucuk E, Ege MR, et al. Usefulness of admission red cell distribution width as a predictor of early mortality in patients with acute pulmonary embolism. Am J Cardiol 2012;109:128-34.
9. Dabbah S, Hammerman H, Markiewicz W, Aronson D. Relation between red cell distribution width and clinical outcomes after acute myocardial infarction. Am J Cardiol 2010;105:312-7.
10. Braun E, Domany E, Kenig Y, Mazor Y, Makhoul BF, Azzam ZS. Elevated red cell distribution width predicts poor outcome in young patients with community acquired pneumonia. Crit Care 2011;15:R194.
11. Kim J, Kim K, Lee JH, Jo YH, Rhee JE, Kim TY, et al. Red blood cell distribution width as an independent predictor of all-cause mortality in out of hospital cardiac arrest. Resuscitation 2012;83:1248-52.
12. Turcato G, Cappellari M, Follador L, Dilda A, Bonora A, Zannoni M, et al. Red Blood Cell Distribution Width Is an Independent Predictor of Outcome in Patients Undergoing Thrombolysis for Ischemic Stroke. Semin Thromb Hemost 2017;43:30-5.
13. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med 2009;133:628-32.
14. Bazick HS, Chang D, Mahadevappa K, Gibbons FK, Christopher KB. Red cell distribution width and all-cause mortality in critically ill patients. Crit Care Med 2011;39:1913-21.
15. Wang F, Pan W, Pan S, Ge J, Wang S, Chen M. Red cell distribution width as a novel predictor of mortality in ICU patients. Ann Med 2011;43:40-6.
16. Hu ZD, Lippi G, Montagnana M. Diagnostic and prognostic value of red blood cell distribution width in sepsis: A narrative review. Clin Biochem 2020;77:1-6.
17. Jo YH, Kim K, Lee JH, Kang C, Kim T, Park HM, et al. Red cell distribution width is a prognostic factor in severe sepsis and septic shock. Am J Emerg Med 2013;31:545-8.
18. Ellahony DM, El-Mekkawy MS, Farag MM. A Study of Red Cell Distribution Width in Neonatal Sepsis. Pediatr Emerg Care 2017;36:378-83.
19. Mahmood NA, Mathew J, Kang B, DeBari VA, Khan MA. Broadening of the red blood cell distribution width is associated with increased severity of illness in patients with sepsis. Int J Crit Illn Inj Sci 2014;4:278-82.
20. Sadaka F, O'Brien J, Prakash S. Red cell distribution width and outcome in patients with septic shock. J Intensive Care Med 2013;28:307-13.
21. Kim YC, Song JE, Kim EJ, Choi H, Jeong WY, Jung IY, et al. A Simple Scoring System Using the Red Blood Cell Distribution Width, Delta Neutrophil Index, and Platelet Count to Predict Mortality in Patients With Severe Sepsis and Septic Shock. J Intensive Care Med 2019;34:133-9.
22. Ramby AL, Goodman DM, Wald EL, Weiss SL. Red blood cell distribution width as a pragmatic marker for outcome in pediatric critical illness. PLoS One 2015;10:e0129258.
23. Zhang FX, Li ZL, Zhang ZD, Ma XC. Prognostic value of red blood cell distribution width for severe acute pancreatitis. World J Gastroenterol 2019;25:4739-48.
24. Ku NS, Kim HW, Oh HJ, Kim YC, Kim MH, Song JE, et al. Red blood cell distribution width is an independent predictor of mortality in patients with gram-negative bacteremia. Shock 2012;38:123-7.
25. Lorente L, Martín MM, Abreu González P, Solé-Violán J, Ferreres J, Labarta L, et al. Red blood cell distribution width during the first week is associated with severity and mortality in septic patients. PloS One 2014;9:e105436.
26. Kim CH, Park JT, Kim EJ, Han JH, Han JS, Choi JY, et al. An increase in red blood cell distribution width from baseline predicts mortality in patients with severe sepsis or septic shock. Crit Care 2013;17:R282.
27. Lakshmi K, Palanisamy B. Clinical significance of red cell distribution width (rdw) and circulating neutrophil – lymphocyte count ratio (nlcr) as prognostic markers in sepsis. International Journal of Current Research 2018;10:75155-60.
28. Pierce CN, Larson DF. Inflammatory cytokine inhibition of erythropoiesis in patients implanted with a mechanical circulatory assist device. Perfusion 2005;20:83-90.

Turk J Intensive Care 2022;20:93-101
DOI: 10.4274/tybd.galenos.2021.09709

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Ceyda Ulusaloğlu,
İlkay Ceylan,
Nermin Kelebek Girgin,
Remzi İşçimen,
Ferda Şöhret Kahveci

A Retrospective Analysis of Causes for Readmission to Hospital and Intensive Care Unit in Patients Discharged from Intensive Care Units

Yoğun Bakımdan Taburcu Edilen Hastaların Yoğun Bakıma ve Hastaneye Yeniden Başvurularının Geriye Dönük İncelenmesi

Received/Geliş Tarihi : 11.08.2020
Accepted/Kabul Tarihi : 26.04.2021

Ceyda Ulusaloğlu
Bursa Gürsu State Hospital, Clinic of Anesthesiology and Reanimation, Bursa, Turkey

İlkay Ceylan
University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Bursa, Turkey

Nermin Kelebek Girgin, Remzi İşçimen, Ferda Şöhret Kahveci
Bursa Uludağ University Faculty of Medicine, Department of Anesthesiology and Reanimation, Bursa, Turkey

İlkay Ceylan MD (✉),
University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Bursa, Turkey

E-mail : ceylanilkay@yahoo.com
Phone : +90 533 631 31 13
ORCID ID : orcid.org/0000-0003-3306-3107

Presented in: This manuscript has been published as a poster at 21st International Critical Care Symposium in İstanbul 2017.

ABSTRACT *Objective:* Intensive care unit (ICU) readmission is a common and unwanted situation. Mortality rates, length of stay in ICU and treatment expenses are also higher in readmitted patients. This study aimed to examine the hospital/ICU readmission rates and risk factors among patients discharged from the ICU.

Materials and Methods: Patients older than 18 years who were hospitalised in the ICU between January 1, 2012 and October 31, 2016 and were re-admitted to the hospital/ICU within 30 days after discharge were retrospectively analysed.

Results: A total of 510 patients met the inclusion criteria, of whom 91 (17.84%) patients were readmitted to the ICU. The average age was higher (p=0.002) among the readmitted patients. The acute physiology and chronic health evaluation-II and sequential organ failure assessment scores at admission and discharge, stability and workload index for transfer (SWIFT) scores at discharge and comorbid disease rates were higher among readmitted patients (p<0.05 for all). Patients discharged with mechanical ventilation support had higher readmission rates (p=0.041). In our risk analysis model, factors that increased the risk of readmission were identified as age [odds ratio (OR), 1.02; 95% confidence interval (CI), 1.01-1.03] and presence of renal disease (OR, 5.72; 95% CI, 2.81-11.65) among patient-related reasons.

Conclusion: High acute physiology and chronic health evaluation and SWIFT scores during discharge as well as presence of comorbidities can predict hospital/ICU readmission.

Keywords: SWIFT score, intensive care, readmission, acute physiology and chronic health evaluation-II score

ÖZ *Amaç:* Yoğun bakım ünitesine (YBÜ) yeniden başvuru yaygın ve istenmeyen bir durumdur. Mortalite oranları, YBÜ'de kalış süresi ve tedavi giderleri yeniden yatırılan hastalarda daha yüksektir. Bu çalışmada, YBÜ'den taburcu edilen hastalarda hastane/YBÜ'ye yeniden başvuru oranlarının ve buna neden olan risk faktörlerinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: 1 Ocak 2012 ve 31 Ekim 2016 tarihleri arasında YBÜ'de yatmış ve taburculuk sonrası hastaneye/YBÜ'ye 30 gün içinde yeniden başvuran 18 yaşından büyük hastalar üzerinde retrospektif bir analiz yapıldı.

Bulgular: Toplam 510 hasta çalışmaya dahil edildi. Bunların 91'i (%17,84) YBÜ'ye yeniden başvurdu. YBÜ'ye ilk başvuru ve taburculuk sırasında hesaplanan akut fizyoloji ve kronik sağlık değerlendirmesi-II ve sıralı organ yetmezliği değerlendirmesi skorları ile taburculuk sırasında hesaplanan stabilite ve iş yükü indeksi (SWIFT) skoru ve komorbid hastalık oranları yeniden başvuran hastalarda daha yüksekti (p<0,05). Yeniden başvuran hastaların yaş ortalaması daha yüksekti (p=0,002). Mekanik ventilasyon desteği ile taburcu edilen hastaların tekrar başvuru oranı daha yüksekti (p=0,041). Risk analizi modelimizde yaş [olasılık oranı (OR), 1,02; %95 güven aralığı (CI), 1,01-1,03] ve böbrek hastalığı varlığı (OR, 5,72; %95 CI, 2,81-11,65) yeniden yatış riskini artıran faktörler olarak belirlendi.

Sonuç: Taburculuk sırasında hesaplanan yüksek akut fizyolojik skorlar ile SWIFT skoru ve komorbid hastalıkların varlığı hastaneye/YBÜ'ye yeniden yatışı öngörebilir.

Anahtar Kelimeler: SWIFT skoru, yoğun bakım, yeniden başvuru, APACHE-II skoru

Introduction

Readmission to the intensive care unit (ICU) after prior treatment in the ICU is a common and an unwanted situation (1). Approximately 4%-6.3% of patients discharged from the ICU are known to be readmitted to the same hospital (2). One argument claims that there is a 1.5- to 10-fold increase in mortality rates and a minimum of a 2-fold increase in hospitalisation duration among patients' readmission to the ICU after being discharged compared with those who have not been hospitalised (3).

The ICU team generally determines which patients are ready to be discharged from the ICU (4). These determinations are based on personal/subjective decisions, and the high demand for ICU beds might cause some patients to be prematurely discharged. Due to the concerns regarding the early discharge of patients without (the possibility of developing) permanent solutions to their problems, determining the risk factors for the readmissions of critical patients to the ICU or hospital after being previously discharged is crucial (4). At the same time, determining the patients' risk factors can also contribute to a better evaluation of an appropriate ICU discharge time. The studies conducted in this respect revealed that the most common diagnoses related to readmission to ICU are heart failure, gastrointestinal bleeding, bacterial pneumonia and chronic obstructive pulmonary disease (3). Furthermore, researchers have claimed that factors concerning the patient and initial time as an in-patient such as age, comorbid diseases, physiological anomalies during ICU discharge, haemodialysis, mechanical ventilation (MV) applications and the initial time spent in the ICU might impact the reapplication for ICU admission (5). In addition, other components are involved such as the insufficiency of ICU bed capacities, limited ICU resources and institutional factors like night-weekend transfer influential on ICU reapplications (3,6).

Some scores used in intensive care are thought to be effective in predicting readmission. Disease severity scores [acute physiology and chronic health evaluation (APACHE) and sequential organ failure assessment (SOFA)] measured during the first application for admission to the ICU and at the time of discharge were found to be higher in patients readmitted to the ICU. Each increase in standard deviation reflected on the readmission risk by 43% (7). The stability and workload index for transfer (SWIFT) score developed by Gajic et al. (8) was shown as a potential tool for determining readmissions to the ICU.

Within the scope of our study, the main objectives were to examine readmission to the ICU as well as risk factors for readmission by evaluating critical patients sent to the clinic or their homes after their treatments.

Materials and Methods

The study was approved by the Medical Research Ethics Board on 28 November 2016 (decision no: 2016-19/15) from the Bursa Uludağ University. No informed consent was obtained from the patients because our research was retrospective and descriptive in nature. The study included adult patients over the age of 18 years who were discharged to the clinic, another ICU or home following their treatment that lasted longer than 24 hours between 1 January 2012 and 31 October 2016 with invasive or noninvasive MV support in the ICU. Our ICU has 19 beds, which accept surgical and medical patients, and is managed by the Department of Anaesthesiology and Reanimation at the Bursa Uludağ University, Faculty of Medicine. Patient information was retrospectively obtained from archived registry files and hospital information management system.

The exclusion criteria were determined as follows: being under 18 years of age, death, admission to the ICU for less than 24 hours and absence of MV support.

The following data were recorded: demographic information of the patients, ICU admission diagnoses, comorbid diseases, ICU treatments [vasoactive medications, renal replacement, extracorporeal membrane oxygenation (ECMO), plasmapheresis], presence of ICU-sourced diagnosed infections, durations of endotracheal intubation-tracheostomy, length of stay in ICU or hospital, APACHE-II and SOFA scores during the initial ICU admission and discharge, need for MV support during discharge, SWIFT scores, time of discharge (working hours, weekdays or weekends outside of working hours) and readmission to the ICU or hospital. The APACHE-II and SOFA scores were recalculated for the patients' readmission to the hospital/ICU, and the outcomes of patients (death/discharge) were recorded.

Readmission was defined as admission to the emergency room within 30 days after discharge from the hospital, demand for prompt ICU consultation during treatment at the clinic and unexplained death within 1 week after discharge. Information of the patients who were discharged to home was obtained from the death declaration system of the Directorate-General for Public Health of the Republic of Turkey Ministry of Health.

Statistical Analysis

Averages, standard deviations, medians, minimum and maximum values, interquartile ranges, frequencies and ratio values were used as the descriptive statistics for the data. The distribution of variables was calculated using the Kolmogorov-Smirnov test, and for the analysis of quantitative independent data, quantitative dependent data and qualitative independent data and in cases in which chi-squared test conditions were not fulfilled, Mann-Whitney U test, Wilcoxon test, chi-squared test and Fisher Exact test were used, respectively. A multiple logistic regression analysis was performed to determine the risks of readmission. The statistical analyses were performed using SPSS 22. A $p<0.05$ was considered to be statistically significant.

Results

A total of 1,437 patients were admitted to the ICU between 1 January 2012 and 31 October 2016. Of these patients, 615 died despite treatment and 11 were still being treated during the study period. There were 811 patients who were discharged after their treatments. According to the study protocol criteria, 301 patients were excluded, thereby leaving 510 patients to be evaluated (Figure 1).

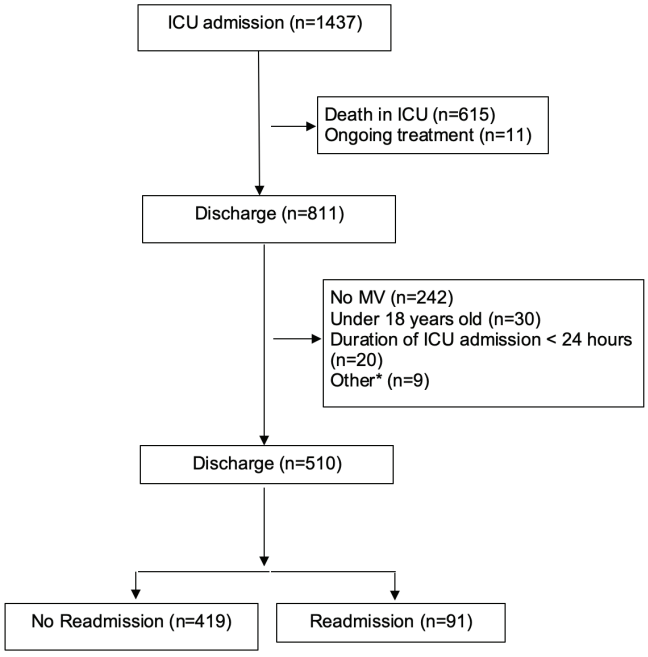


Figure 1. Flow diagram
ICU: Intensive care unit, MV: mechanical ventilation

The demographic data regarding the cases, presence of comorbid diseases, ICU admission diagnoses, airway management, treatments, times and places of discharge and length of stay in the ICU/hospital are shown in Tables 1 and 2.

Included in the study were 194 (38%) female and 316 (62%) male patients. The age average of the patients was calculated as 51.8 years; 70% of the patients had comorbid diseases, of which the most common comorbid diseases were hypertension and cardiac diseases (32.34%).

The most frequent diagnoses for ICU admission among the patients were respiratory system diseases (36.7%), followed by trauma and neurological diseases. Approximately 37.1% of the patients were admitted to the ICU from the hospital ward, 34.3% from the emergency room, 12.2% from the external centre, 12.2% from other ICUs within the hospital and 4.3% from the operating room following urgent surgeries.

In the ICU, 95.7% of the patients had invasive MV support through endotracheal intubation-tracheostomy and 4.3% of the patients had noninvasive MV support. Furthermore, 55.5% of patients underwent one or more of the following treatments: vasoactive medications, renal replacement therapy (RRT), ECMO and plasmapheresis. ICU-related infection was detected at least once among 55.5% of the patients.

After their treatments in the ICU, 397 patients were referred to a ward in the hospital, 81 were sent home, 19 were referred to other surgical and medical ICUs within the hospital and 12 were discharged to the external centre. A total of 306 patients were discharged during working hours, whereas 204 patients were discharged during the weekend or outside of working hours.

A total of 91 patients were readmitted to the ICU and hospital after being discharged. The readmission rate was calculated as 17.8%. There were 37 patients readmitted to the emergency room, 26 patients accepted to the ICU, 14 were ICU consultations demanded from clinics, and 14 were unexplained deaths within 1 week.

The age average of patients readmitted to the ICU/hospital was 58.2 years, and they were older than those who were not readmitted ($p=0.002$). A total of 60 readmitted patients were men, and 31 were women. Sex was not a determining factor in the readmissions ($p>0.05$). The comorbid disease rate among patients applying for rehospitalisation and readmission to the ICU after being discharged was higher ($p=0.049$) (Table 3).

Table 1. Demographic data and clinical characteristics of cases	
Age (Avg ± SD) (min-max)	51.8±19.8 (18-93)
Sex (F/M) (n, %)	194 (38.0)/316 (62.0)
Co-morbid disease (yes/no) (n, %)	357 (70.0)/153 (30.0)
ICU admission diagnosis (n, %)	
Respiratory diseases	187 (36.7)
Trauma	93 (18.2)
Neurological diseases	69 (13.5)
Sepsis/septic shock	55 (10.8)
Post-CPR care	45 (8.8)
Cardiac disease	19 (3.7)
Other	67 (13.1)
Place of ICU admission (n, %)	
Ward	189 (37.1)
Emergency room	175 (34.3)
Postoperative urgent surgery	22 (4.3)
External centre	62 (12.2)
Other ICU	62 (12.2)
Airway (n, %)	
Endotracheal intubation/tracheostomy	488 (95.7)
Non-invasive MV (n, %)	22 (4.3)
ICU treatments (n, %)	
None	232 (45.5)
Vasoactive medication	213 (41.8)
Renal replacement treatment	117 (22.9)
ECMO	19 (3.7)
Plasmapheresis	31 (6.1)
Place of discharge (n, %)	
Ward	397 (77.8)
Home	81 (15.9)
Other ICU	19 (3.7)
External centre	12 (2.4)
Time of discharge (n, %)	
During working hours	306 (60)
Weekend-outside working hours	204 (40)
Length of stay in ICU (days) (avg ± SD) (min-max)	31.7±31.9 (2-155)
Length of stay in hospital (days) (avg ± SD) (min-max)	48.6±38.2 (3-212)

Avg: Average, SD: standard deviation, F: female, E: male, ICU: intensive care unit, MV: mechanical ventilation, ECMO: extra-corporeal membrane oxygenation, min: minimum, max: maximum, CPR: cardiopulmonary resuscitation

Table 2. Co-morbid diseases of patients	
Co-morbid diseases	**n (%)**
Cardiac disease	196 (32.34%)
Endocrine disease	120 (19.80%)
Asthma/COPD	70 (11.55%)
Neurological disease	62 (10.23%)
Renal disease	50 (8.25%)
Malignancy	48 (7.92%)
Psychiatric disease	24 (3.96%)
GIS disease	22 (3.63%)
Rheumatic disease	14 (2.31%)

COPD: Chronic obstructive pulmonary disease, GIS: gastrointestinal system

Readmitted patients had significantly higher APACHE-II and SOFA scores at the first admission and discharge (p=0.000 for all). The average scores among patients readmitted to the hospital/ICU were as follows: Glasgow coma scale, 10.53; APACHE-II, 18.19; and SOFA, 5.83. The SWIFT score during the first discharge from the ICU was found to be significantly higher among readmitted patients (p=0.01) (Table 4).

When compared with patients who were not readmitted to the hospital/ICU, the length of stay in the ICU and hospital and MV support were significantly longer among the patients who were not readmitted (p=0.019, p=0.002, p=0.018, respectively). The time of first discharge (within and outside of working hours/weekends) was not a contributing factor in readmission (Table 3).

The rates of ICU-related infections and airway management (intubation/tracheostomy) among the readmitted patients were not found to be significantly different in comparison with those who were not readmitted. However, the readmission rate for the hospital/ICU were higher among the patients discharged with MV support (p=0.041) (Table 5).

The comparison of age, duration of MV support, length of stay in ICU, APACHE and SOFA scores, SWIFT scores, renal disease rates, neurological disease rates, traumas, sepsis/septic shock, vasoactive medication use and RRT made based on the univariate model for the differentiation of readmission showed that all of the parameters were statistically significant with a ratio of p<0.05. The multivariate analysis model for the differentiation of readmission demonstrated that APACHE-II and SOFA scores as well as renal disease are independent factors (Table 6).

Table 3. Demographic data, co-morbid diseases, ICU admissions, mechanical ventilation and hospital admission durations of patients readmission/no readmission to ICU or hospital

	No readmission	Readmission	p
Age (avg ± SD)	50.4±19.5	58.2±20.1	0.002
Sex (F/M) (n, %)	163 (38.9)/256 (61.1)	31 (34.1)/60 (65.9)	0.457
Co-morbid disease (Y/N) (n, %)	285 (68)/134 (32)	72 (79.1)/19 (20.9)	0.049
Length of stay in ICU (day)	30.0±30.8	39.6±35.7	0.019
Duration of MV (day)	26.7±31.0	37.3±36.7	0.018
Length of stay in hospital (day)	46.5±38.3	58.3±36.5	0.002
Time of discharge (n, %)			
During working hours	259 (61.8)	48 (52.7)	0.138
Weekend-outside working hours	160 (38.2)	43 (47.3)	

Avg: Average, SD: standard deviation, F: female, M: male, Y: yes, N: no, ICU: intensive care unit, MV: mechanical ventilation

After excluding the deceased (n=14), 62 (80.5%) of the readmitted patients were discharged from the ICU, while 15 (19.5%) patients died during their second stay in the ICU.

Discussion

In our study that examined the readmission to hospital and ICU after ICU discharge, the readmission rate in 30 days after discharge was 17.8%. The readmitted patients were older, and the comorbid disease rates among these patients were higher. They were also supported with MV for more days while staying longer in the hospital. Furthermore, the high initial and second ICU admission and discharge scores (APACHE-II, SOFA and SWIFT) and high discharge rate with MV were determined as contributing factors that increased the risk of readmission.

Readmission to the ICU is considered a crucial measure for the safety and the quality of ICUs (6,9). However, the argument that readmission rates are signs of low-quality health care is controversial because insufficient ICU bed capacity, the occupancy of clinic beds and the absence of sufficient directives for patient transfer are also influential on early discharge and readmission (6).

Woldhek et al. (10) analysed the data of 19,750 patients treated in a period of 14 years in a single-centre retrospective study and revealed that the readmission rate to the same

Table 4. ICU admission and discharge scores of cases (n=510)

		No readmission (n=419)	Readmission (n=91)	p
GCS	Admission	8.3±3.9	7.5±3.8	0.109
	Discharge	13.2±2.9	12.8±3.2	0.235
APACHE-II	Admission	18.0±6.3	21.9±7.8	<0.001
	Discharge	8.9±5.7	13.1±6.2	<0.001
SOFA	Admission	6.0±4.7	8.1±3.9	<0.001
	Discharge	2.1±1.7	3.3±2.2	<0.001
SWIFT		21.8±12.1	25.9±11.8	0.010

GCS: Glasgow coma scale, APACHE-II: acute physiology and chronic health evaluation-II, SOFA: sequential organ failure assessment, SWIFT: stability and workload index for transfer

Table 5. Relationship between discharge and ICU related infections, airway management, and mechanical ventilation support (IMV and NIMV)

	No readmission	Readmission	p
ICU-related infection (n, %)			
Yes	225 (53.7)	57 (62.6)	0.150
No	194 (46.3)	34 (37.4)	
Airway management (n, %)			
IMV	402 (95.9)	86 (94.5)	0.743
NIMV	17 (4.1)	5 (5.5)	
Discharged with MV support			
Yes	89 (21.2)	29 (31.9)	0.041
No	330 (78.8)	62 (68.1)	

ICU: Intensive care unit, NIMV: non-invasive mechanical ventilation, IMV: invasive mechanical ventilation, MV: mechanical ventilation

ICU after being discharged was 7%. Another multicentre study examined 263,082 patients, of whom 105 were in the ICU, and the study found that the readmission rate was 6.3% (6). The readmission rate was calculated as 5.7% in a compilation document in which 24 studies published as of February 2014 were quantitatively analysed (1). There is no fixed time interval for readmission. Although the quality standards in Turkey designate this interval as the first 48 hours following the initial discharge from the ICU, studies in the literature consider the first 1-30 days as the time interval for readmission (11). We took 30 day period because we aimed to evaluate the reasons of readmissions in a wider perspective.

The reason why the readmission rates were higher (17.8%) in our study might be that in addition to the admission to the same ICU within 30 days after being

Table 6. Risk analysis for readmission

	Univariate model			Multivariate model		
	OR	95% CI	p	OR	95% CI	p
Age	1.02	1.01-1.03	0.002	1.02	1.01-1.03	0.016
Sex	0.82	0.49-1.38	0.450			
Co-morbid disease	1.76	0.97-3.20	0.062			
Duration of MV	1.01	1.00-1.02	0.011			
Length of stay in ICU	1.01	1.00-1.01	0.016			
Discharged with MV support	0,58	0.34-1.00	0,052			
ICU-related Infection	0.68	0.41-1.13	0.135			
GCS	0.94	0.88-1.01	0.090			
APACHE-II	1.09	1.05-1.13	<0.001	1.06	1.02-1.10	0.007
SOFA	1.09	1.02-1.16	0.007	4.28	1.99-9.23	<0.001
SWIFT	1.03	1.01-1.05	0.008			
Co-morbid disease						
Cardiac disease	0.92	0.55-1.53	0.744			
Endocrine disease	1.66	0.96-2.87	0.068			
Respiratory disease	1.24	0.62-2.47	0.543			
Neurological disease	0.82	0.37-1.82	0.622			
Renal disease	5.72	2.81-11.65	<0.001	1.02	1.00-1.03	0.027
Malignancy	1.62	0.75-3.47	0.218			
GIS disease	2.41	0.88-6.65	0.088			
Psychiatric disease	0.50	0.11-2.20	0.357			
Rheumatic disease	0.92	0.20-4.28	0.914			
ICU admission diagnosis						
Cardiac disease	1.89	0.58-6.19	0.294			
Respiratory disease	1.32	0.79-2.20	0.293			
Neurological disease	0.38	0.16-0.92	0.032			
Trauma	0.45	0.21-0.99	0.047			
Sepsis/septic shock	2.80	1.32-5.93	0.007			
Post-resuscitation care	1.74	0.81-3.76	0.157			
ICU treatment						
Vasoactive medication	1.94	1.18-3.21	0.009			
RRT	3.13	1.85-5.31	<0.001			
ECMO	0.65	0.14-2.92	0.572			
Plasmapheresis	1.16	0.38-3.57	0.796			

GCS: Glasgow coma scale, ICU: intensive care unit, APACHE-II: acute physiologic and chronic health evaluation score-II, SOFA: sequential organ failure assessment score, SWIFT: stability and workload index for transfer, GIS: gastrointestinal system, RRT: renal replacement therapy, ECMO: extracorporeal membrane oxygenation, MV: mechanical ventilation, OR: odds ratio, CI: confidence interval

discharged, we included readmissions to the emergency room, additional ICU consultations for patients sent to the wards and unexplained death within 1 week. When we exclude the additional readmission criteria and calculate, like other studies, the readmission rate seems to be similar to that of other studies (5.09%).

Many risk factors were proposed for readmission to the ICU after discharge. While patient-related factors such as age, comorbid diseases, ICU treatments and disease severity scores are effective, institutional factors like limited ICU capacity and resources are also significant (3,6,12-14). Elliott et al. (15) found out that patients readmitted to the ICU after being discharged tend to be older than those who are not readmitted. The authors claimed that the ageing process contributes to the rise of comorbid disease and functional disorder incidences and that age, therefore, will continue to be a risk factor for readmission. Another study detected that readmission rates increase up until the age of 80 and decline afterwards (3). We also revealed in our study that age is influential on readmission and that patients reapplying to the ICU are older than those who do not (p=0.002) (Table 3).

Sex has also been proposed as a contributing factor for readmission to the ICU after discharge. Jo et al. (4) found that in their single-centre study conducted in their medical ICU, male patients have a higher risk for readmission. Contradicting this study, many others have demonstrated that sex is not influential on readmission (8,13,14). Despite the high rate of male patients among the readmitted patients in our study, no statistical significance was detected.

Comorbid diseases are another risk factor for ICU readmission. Studies comparing readmitted patients and non-readmitted patients have shown that many comorbid diseases pose a risk factor in the former group of patients (3,6,12,15). Hua et al. (12) examined the reasons behind the early and late unplanned hospital readmissions of critical patients, and they reported that metastatic cancer and final stage kidney disease were risk factors for readmission. Another study demonstrated that the presence of diabetes mellitus increased the risk of readmission to the ICU (4). Our study also found that the readmission rate among patients with comorbid diseases was significantly higher than those without comorbid diseases. The most common comorbid diseases were hypertension/other cardiac diseases, endocrine diseases and renal diseases in that order. In addition, we learned that the presence of renal diseases increased the risk of readmission [odds ratio (OR), 5.72; 95% confidence interval (CI) 2.81-11.65].

The location of the patient prior to the initial ICU

admission (clinic, another hospital or the emergency room) is asserted to have a relationship with readmission (6,8,14,15). The prospective cohort study including 4,684 patients conducted by Rosenberg et al. (16) detected that patients transferred from another hospital or admitted to the ICU from the hospital ward have higher rates of readmission after discharge compared with patients admitted directly from the emergency room. Another study revealed that readmission rates are higher among patients who are transported to the ICU from the operating room and the emergency room (3). Our study did not find a significant relationship between the initial place of admission to the ICU and readmission. The differences between patient admission policies of hospitals might have affected this outcome. The working procedure of our hospital is as follows: If there are available beds in the ICU, patients are accepted from clinics within the hospital, from other ICUs within the hospital and from the emergency room. There are only two beds reserved for patients in the early postoperative period in our unit.

In ICUs, patients are frequently supported with MV. The choice of airway management depends on a wide range of factors such as the patient's respiratory and neurological function impairment. A retrospective study conducted by Hua et al. (12) evaluated 492,653 critical patients and found that patients undergoing tracheostomy and MV have higher rehospitalisation rates compared with those not supported with MV. Another study examined deceased patients after being discharged from the ICU and reported that prolonged MV support is correlated with mortality (17). Yet, a study by Woldhek et al. (10) found that patients supported with MV during their stay in the ICU have lower ICU readmission rates. The authors argued that the fact that more than 50% of the patients included in their study had limited disease severity and elective cardiac surgery might have affected this outcome. Our study showed no effect of airway management (endotracheal intubation or tracheostomy) during the initial ICU admission on readmission. However, we found a correlation between prolonged MV support and readmission.

During the stay in the ICU, ECMO treatments are administered in patients with organ failure. The relationship between ICU treatments and readmission is commonly evaluated although the number of studies focusing on renal replacement treatment is higher (3,4,6,10,12). An examination of a patient's readmission to the medical ICU by Jo et al. (4) revealed that only continuous renal replacement treatment correlated with readmission to the ICU. Similarly, our study found a relationship between renal replacement treatment in the ICU and readmission.

Studies have shown that discharge during the night or outside of working hours is an independent risk factor as far as ICU readmission is concerned (9). Night-time discharge is often thought to be a sign of insufficient bed capacity (18). Our study showed no difference between patients discharged during working hours or outside of working hours/weekends in terms of readmission (Table 3).

It is well recognised that prolonged ICU admission is influential on readmission to ICU/hospital (3,6,10,13,15). In a multicentred study by Kramer et al. (3), 229,961 critical patients were examined, and 6.1% of these patients were readmitted to the ICU. The authors stated that prolonged admission is influential on the initial ICU application and that the readmission rate is directly proportional to the duration of admission. This might be caused by complications such as ICU-related infections that occur when a patient stays in the ICU for a long time and their treatments. In our study, we also detected a correlation between prolonged length of ICU stay and readmission. However, we did not find a significant relationship between ICU-related infections and readmission.

According to several researchers, readmission to hospital/ICU admission is determined by the patient's physiological state at the end of ICU treatment (16). Studies have demonstrated a relationship between disease severity scores showing the physiological anomaly level at the time of discharge from the ICU and readmission (1,3,13,16,17). In addition, a meta-analysis examined 11 research studies on this subject and concluded that the time of physiological measurements (admission or discharge) and evaluated scores, regardless of the type of ICU disease severity, increase the risk for readmission to the ICU (7). Certain researchers have claimed that there is a valid point in calculated scores to help differentiate between patients who can be discharged to the ward or to a lower ICU unit and those who require additional ICU treatment (19). Acute physiological scores calculated at the time of discharge from the ICU posed a greater risk for ICU readmission compared with the scores calculated during the initial admission (3). However, the studies used different disease severity scores. In our study, having high disease severity scores (APACHE-II, SOFA) at the time of initial admission and discharge is a risk factor for death or readmission after being discharged

from the ICU (OR, 1.06; 95% CI, 1.02-1.1; OR, 4.28; 95% CI, 1.99-9.23). This finding is consistent with outcomes in several studies (10,13,20).

Using the tools or scores based on objective data might help us decide whether a patient can be safely discharged or whether special supervision after ICU treatment is necessary. The SWIFT score, which is developed to measure the workload within the context of intensive care, can differentiate between the patients who apply to the ICU and those who do not (21). SWIFT scores were employed in a prospective cohort study evaluating patients at a medical-surgical ICU in Europe, and its validity was proven (50% sensitivity, 85% specificity) (20). Being one of these statistical models, the SWIFT score was also calculated in our study based on the data regarding the time of discharge. We observed that the score was significantly higher among the readmitted patients.

As palliative care system is still developing in Turkey, after intensive care treatments, some patients are sent home to continue their treatments using home-type mechanical ventilators. Patients discharged in this manner were found to have higher readmission rates. The inability to use home care services due to short-staffed units and insufficiently trained patients' relatives might be contributing factors in this respect.

The primary limitation of our study is that we were not able to obtain data on patients who could not be admitted to the ICU after being sent home or discharged to the service and who were referred to another centre due to some type of shortage within the system. Furthermore, as the readmission period was set at 30 days, applications made at different times such as on the 2nd, 3rd or 7th days after discharge were not included in the study. Finally, our results cannot be generalised since the study was conducted within a single centre in a certain period.

Conclusion

In conclusion, on examining patients' readmission to the hospital/ICU after being discharged, we found that the patients' acute physiological problems, comorbid diseases and durations of RRT and MV increased their risk of readmission. As readmission prolongs the length of stay in hospital/ICU, entails moral burdens to the patient and their relatives as well as medical personnel and increases medical costs, we concluded that protocols must be created to determine and prevent the risk factors for readmission.

Ethics

Ethics Committee Approval: The study was approved by the Medical Research Ethics Board on 28 November 2016 (decision no: 2016-19/15) from the Bursa Uludağ University.

Informed Consent: No informed consent was obtained from the patients because our research was retrospective and descriptive in nature.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: İ.C., N.K.G., Design: C.U., N.K.G., Data Collection and Process: C.U., İ.C., Analysis or Interpretation: C.U., İ.C., N.K.G., Literature Search: C.U., İ.C., R.İ., F.Ş.K., Writing: C.U., İ.C., N.K.G., R.İ., F.Ş.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Wong EG, Parker AM, Leung DG, Brigham EP, Arbaje AI. Association of severity of illness and intensive care unit readmission: A systematic review. Heart Lung 2016;45:3-9.e2.
2. Hosein FS, Roberts DJ, Turin TC, Zygun D, Ghali WA, Stelfox HT. A meta-analysis to derive literature-based benchmarks for readmission and hospital mortality after patient discharge from intensive care. Crit Care 2014;18:715.
3. Kramer AA, Higgins TL, Zimmerman JE. Intensive care unit readmissions in U.S. hospitals: patient characteristics, risk factors, and outcomes. Crit Care Med 2012;40:3-10.
4. Jo YS, Lee YJ, Park JS, Yoon HI, Lee JH, Lee CT, et al. Readmission to medical intensive care units: risk factors and prediction. Yonsei Med J 2015;56:543-9.
5. Kramer AA, Higgins TL, Zimmerman JE. Can this patient be safely discharged from the ICU? Intensive Care Med 2016;42:580-2.
6. Kramer AA, Higgins TL, Zimmerman JE. The association between ICU readmission rate and patient outcomes. Crit Care Med 2013;41:24-33.
7. Frost SA, Alexandrou E, Bogdanovski T, Salamonson Y, Davidson PM, Parr MJ, et al. Severity of illness and risk of readmission to intensive care: a meta-analysis. Resuscitation 2009;80:505-10.
8. Gajic O, Malinchoc M, Comfere TB, Harris MR, Achouiti A, Yilmaz M, et al. The Stability and Workload Index for Transfer score predicts unplanned intensive care unit patient readmission: initial development and validation. Crit Care Med 2008;36:676-82.
9. Rhodes A, Moreno RP, Azoulay E, Capuzzo M, Chiche JD, Eddleston J, et al. Prospectively defined indicators to improve the safety and quality of care for critically ill patients: a report from the Task Force on Safety and Quality of the European Society of Intensive Care Medicine (ESICM). Intensive Care Med 2012;38:598-605.
10. Woldhek AL, Rijkenberg S, Bosman RJ, van der Voort PH. Readmission of ICU patients: A quality indicator? J Crit Care 2017;38:328-34.
11. Elliott M, Worrall-Carter L, Page K. Intensive care readmission: a contemporary review of the literature. Intensive Crit Care Nurs 2014;30:121-37.
12. Hua M, Gong MN, Brady J, Wunsch H. Early and late unplanned rehospitalizations for survivors of critical illness*. Crit Care Med 2015;43:430-8.
13. Campbell AJ, Cook JA, Adey G, Cuthbertson BH. Predicting death and readmission after intensive care discharge. Br J Anaesth 2008;100:656-62.
14. Santamaria JD, Duke GJ, Pilcher DV, Cooper DJ, Moran J, Bellomo R, et al. Readmissions to Intensive Care: A Prospective Multicenter Study in Australia and New Zealand. Crit Care Med 2017;45:290-7.
15. Elliott M, Worrall-Carter L, Page K. Intensive care readmission: a contemporary review of the literature. Intensive Crit Care Nurs 2014;30:121-37.
16. Rosenberg AL, Hofer TP, Hayward RA, Strachan C, Watts CM. Who bounces back? Physiologic and other predictors of intensive care unit readmission. Crit Care Med 2001;29:511-8.
17. Lee J, Cho YJ, Kim SJ, Yoon HI, Park JS, Lee CT, et al. Who Dies after ICU Discharge? Retrospective Analysis of Prognostic Factors for In-Hospital Mortality of ICU Survivors. J Korean Med Sci 2017;32:528-33.
18. Priestap FA, Martin CM. Impact of intensive care unit discharge time on patient outcome. Crit Care Med 2006;34:2946-51.
19. Kastrup M, Powollik R, Balzer F, Röber S, Ahlborn R, von Dossow-Hanfstingl V, et al. Predictive ability of the stability and workload index for transfer score to predict unplanned readmissions after ICU discharge. Crit Care Med 2013;41:1608-15.
20. Ouanes I, Schwebel C, Français A, Bruel C, Philippart F, Vesin A, et al. A model to predict short-term death or readmission after intensive care unit discharge. J Crit Care 2012;27:422.e1-9.
21. Oakes DF, Borges IN, Forgiarini Junior LA, Rieder Mde M. Assessment of ICU readmission risk with the Stability and Workload Index for Transfer score. J Bras Pneumol 2014;40:73-6.

Turk J Intensive Care 2022;20:102-105
DOI: 10.4274/tybd.galenos.2022.66587

CASE REPORT / *OLGU SUNUMU*

Hatice Feray Arı,
Berna Kırhan,
Murat Arı

Successfully Treated Severe Colchicine Intoxication in an Adolescent

Başarıyla Tedavi Edilmiş Ciddi Kolşisin Zehirlenmesi Olan Bir Adölesan

Received/Geliş Tarihi : 01.02.2022
Accepted/Kabul Tarihi : 07.04.2022

Hatice Feray Arı
Şanlıurfa Training and Research Hospital, Clinic of Pediatrics, Division of Pediatric Intensive Care, Şanlıurfa, Turkey

Berna Kırhan
Şanlıurfa Training and Research Hospital, Clinic of Pediatrics, Şanlıurfa, Turkey

Murat Arı
Aydın Adnan Menderes University Health Sciences Institute, Department of Medical Biochemistry, Aydın, Turkey

Hatice Feray Arı MD (✉),
Şanlıurfa Training and Research Hospital, Clinic of Pediatrics Division of Pediatric Intensive Care, Şanlıurfa, Turkey

E-mail : dr.hferayyavas@gmail.com
Phone : +90 505 685 49 23
ORCID ID : orcid.org/0000-0002-2208-2524

ABSTRACT The contain is extracted from the autumn crocus plant, colchicine that an anti-inflammatory drug. The use of colchicine impairs mobilization and activation of neutrophil and supporting treating from some rheumatological diseases especially in childhood as familial mediterranean fever. Colchicine poisoning is rare but severe drug intoxication that can cause life-threatening multiorgan failure at high doses. In this report, a girl who 15-year-old and has Familial Mediterranean fever was admitted to a hospital for ingesting 0.47 mg/kg colchicine. We treated her successfully receiving plasmapheresis and dialysis. The case of colchicine intoxication is a life-threatening problem requiring close monitoring. All the colchicine intoxication cases should be treated in the pediatric intensive care.
Keywords: Colchicine, adolescent, intoxication, pediatric intensive care

ÖZ İçeriği sonbahar çiğdem bitkisinden elde edilen kolşisin, anti-enflamatuvar bir ilaçtır. Kolşisin kullanımı, nötrofil mobilizasyonunu ve aktivasyonunu bozmaktadır ve özellikle çocukluk çağında Ailevi Akdeniz ateşi (AAA) gibi bazı romatolojik hastalıkların tedavisinde kullanılmaktadır. Yüksek dozlarda alındığında kolşisin zehirlenmesi, hayatı tehdit eden çoklu organ yetmezliğine neden olabilen nadir fakat ciddi bir ilaç intoksikasyonudur. Bu olguda, 15 yaşında AAA tanılı bir kız çocuğu 0,47 mg/kg kolşisin alması nedeniyle hastaneye yatırılmıştır. Plazmaferez ve diyaliz ile hasta başarılı bir şekilde tedavi edildi. Kolşisin intoksikasyonu olgusu, yakın takip gerektiren ve yaşamı tehdit eden bir durumdur. Kolşisin intoksikasyon olgularının tamamı çocuk yoğun bakımda tedavi edilmelidir.
Anahtar Kelimeler: Kolşisin, adölesan, zehirlenme, çocuk yoğun bakım

Introduction

The contain is extracted from the autumn crocus plant, colchicine that an anti-inflammatory drug. The use of colchicine is impairing mobilization and activation of neutrophil and supporting to treat from some rheumatological diseases especially in childhood as Familial Mediterranean fever (FMF) (1,2). Colchicine poisoning has severe complications that can occur after ingestion. Accidentally or suicidally using overdose, must be closely monitoring and treatment in intensive care unit because of high risk of mortality (3). In our case report, we present successfully treated severe colchicine intoxication ingested in fatal dosages with observed all phases of intoxication.

Case Report

A previously diagnosed FMF patient 15-year-old and 60-kg-weight girl was admitted to the pediatric emergency department after ingesting 56 of her colchicine tablets which each of the 0.5 mg. After questions about her medical history, it has been learned that she ingested these tablets before 24 hours. At the time of admission, she had a nausea and stomach ache and her heart rate was 102/min, respiratory rate 12/min, blood pressure 102/57(69) mmHg. Glasgow coma scale was 15. Her body temperatures were 36.5 °C, oxygen saturation 100% in room air, capillary refill time was under 2 seconds (sec). There was no abnormal finding in her skin, extremities, chest and abdomen. Arterial blood gas examination, pH: 7.30, pCO_2: 32, HCO_3: 16.3, lactate: 3.6 and additional blood test results were as follows: her complete blood count white blood cell was 19,600×10^3/mm^3, her haemoglobin was 9.4 g/dL, total platelet count was 156×10^3/mm^3; serum urea/creatinine was 44/1.11 mg/dL, serum sodium/potassium was 139/3.9 mEq/L, aspartate transaminase/alanine aminotransferase was 49/36 U/L, glucose was 150 mg/dL, international normalized ratio: 2.6, prothrombin time: 29 sec, activated plasma thromboplastin time: 46.7 sec, creatine kinase: 560U/L and lactate dehydrogenase: 3600 U/L. The patient was admitted to pediatric intensive care unit (PICU) for close monitoring and treatment. Because of the fatal dosage of colchicine tablets ingestion (0.42 mg/kg), we planned high volume plasmapheresis and then beginning continuous veno venousus hemodiafiltration (CVVHDF). In the 40th hour of CVVHDF, anemia, neutropenia and thrombocytopenia were developed and excessive menstrual bleeding occurred. Appropriate blood product support was provided and prophylactic broad-spectrum antibiotics were started. Daily intermittent hemodialysis was begun for four days. On the 7th day of admission agitation, hypertension, and then seizure was occurred. Her brain computed tomography was normal but her magnetic resonance (MR) scanning reported that bilateral asymmetrical cortical-subcortical pathological signal changes are observed in the bilateral posterior parietal and occipital regions. It was evaluated in favor of posterior reversible encephalopathy syndrome (PRES) (The remarkable appearance of the lesions is detected on her cranial MR imaging scanning in Figures 1 and 2). Antiepileptic and antihypertensive treatment were begun. On the 12th day admitted to PICU, her coagulopathy, renal and hepatic failure, bone marrow suppression findings and neurological symptoms completely healed, but alopecia developed, she was given to general pediatrics. The patient informed consent form was obtained from her parents.

Discussion

Colchicine poisoning is a rare but severe drug intoxication because of fatality. It can cause life-threatening multiorgan failure at high doses. Especially who had a treatment for their rheumatological diseases are used colchicine and suicidally ingested. The half-life of colchicine has a 9-16-hour and the therapeutic index is narrow (4).

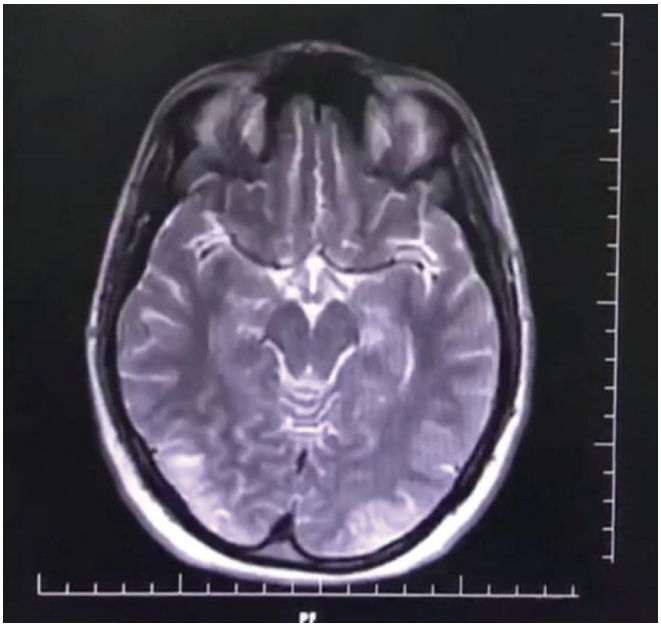


Figure 1. T2W scanning

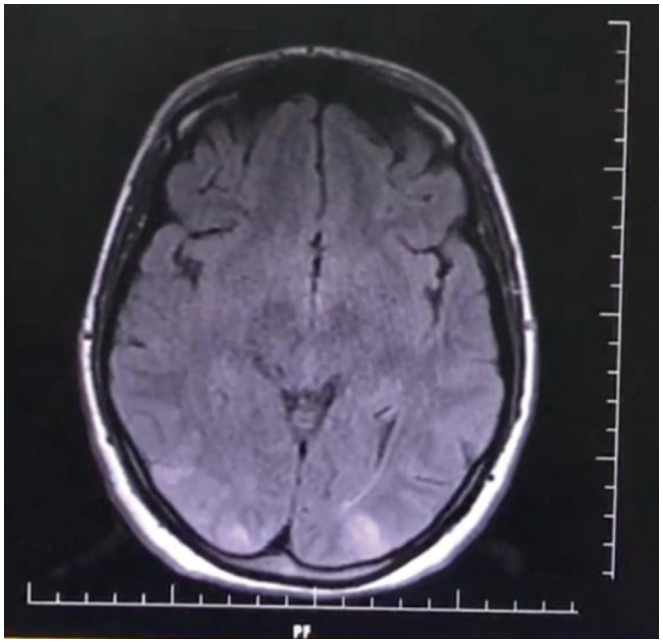


Figure 2. FLAIR scanning, the remarkable appearance of the lesions is detected on cranial magnetic resonance scanning, bilateral asymmetrical cortical and subcortical T2W/FLAIR pathological signal changes are observed in the bilateral posterior parietal and occipital regions

In literaturally, it has been reported, minor toxicity like mild gastrointestinal system symptoms developed with <0.5 mg/kg. The dosage from 0.5 to 0.8 mg/kg results of oral intake has a major toxicity with myelosuppression and multiorgan failure, so >0.8 mg/kg can be lethal (4,5). Mortality is correlated with the timing of drug ingestion and admission time of hospital (6). The prognosis of colchicine intoxication is associated with ingestion dose and the admission time after ingestion. In the adults studies was reported that, under 0.5 mg/kg ingestion dose patients can be recovered 100%. On the other hand in the literature, the children who ingested 0.37 and 0.6 have died (2,7). Our patient ingested 0.47 mg/kg colchicine 24 hours before admission and she had severe effects on organs during all the phases of intoxication. Although these effects we treated her successfully without any persistent disease.

Acute colchicine poisoning has three clinical phases which are likely to include all the clinical phases of our patient. The 1st phase which in first 24 hours after drug ingestion includes: gastrointestinal symptoms, hypovolemia, hypotension and leukocytosis. In the 2nd phase, (1-7 days) multiple organ failure occur (cardiac, neurological, repiratory and renal). In this phase unconsciousness, hematologic problems and disseminated intravasculary coagulopathy, ion imbalances, metabolic acidosis, dysrhythmias, and systemic collapse can be seen. The supportive management is important for the good outcomes. After second phase, if the patient lives, in the third phase is observed getting better of organ failure in 3 to 4 weeks from ingestion of colchicine (8).

The case of colchicine intoxication is a life-threatening problem requiring close monitoring. All of the colchicine intoxication cases should be treated in the PICU. Because of not having effective antidote, supportive treatment is recommended. Gastric lavage and activated char coal administration is recommended in the first 60 min from ingestion. If shock and multiorgan failure are developed, it can be given fluid resuscitation and inotropic agents (5). Although hemodialysis and hemoperfusion treatments are ineffective because of extensive volume distribution, if it is necessary, plasma exchange and CVVHDF can be initiated (2,9). In our case report, although she was late for elimination treatment because of the late hospital admission time, we treated her successfully with plasmapheresis, continuous hemodiafiltration, and then intermittent hemodialysis.

PRES is a clinical and radiological diagnose with acute neurological symptoms like headache, epileptic/nonepileptic seizures and some different neurological deficits (10). It is reported that the mechanism of that is a problem of dysregulated perfusion. Many studies suggest up to 55% of these have renal failure and hypertension (11). Our case had a FMF before intoxication and this disease may be caused proteinuria and cellular renal effects, but we did not have any data certainly which can trigerred secondary hypertension. The aim of initiating plasmapheresis, CVVHDF and intermittent hemodialysis in this case was drug elimination, there was no sign and symptoms about new developed and/or past history of renal failure.

Colchicine poisoning is a rare but high mortality drug intoxication. It can cause life-threatening multiorgan failure at high doses. Mortality is correlated with the timing of drug ingestion and admission time of hospital. Although hemodialysis and hemoperfusion treatments are ineffective because of extensive volume distribution, if it is necessary, plasma exchange and CVVHDF can be initiated.

Ethics

Informed Consent: The patient informed consent form was obtained from her parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.F.A., B.K., Concept: H.F.A., M.A., Design: H.F.A., M.A., Data Collection and/

or Processing: B.K., Analysis and/or Interpretation: B.K., Literature Search: M.A., Writing: H.F.A., M.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Wasserscheid K, Backendorf A, Michna D, Mallmann R, Hoffmann B. Long-term outcome after suicidal colchicine intoxication in a 14-year-old girl: case report and review of literature. Pediatr Emerg Care 2013;29:89-92.
2. Kısaarslan AP, Yel S, Yılmaz K, Akyıldız BN, Düşünsel R, Gündüz Z, et al. Colchicine Intoxication in Children: Four Case Reports. Arch Rheumatol 2015;30:67-70.
3. Karakaya ZY. Colchicine Intoxication. Clinical Toxicology in Emergency In: Satar S, editör. Clinic Toxicology in Emergency. Adana: Nobel Company; 2009. p. 397-9.
4. Finkelstein Y, Aks SE, Hutson JR, Juurlink DN, Nguyen P, Dubnov-Raz G, et al. Colchicine poisoning: the dark side of an ancient drug. Clin Toxicol (Phila) 2010;48:407-14.
5. Ozdemir R, Bayrakci B, Teksam O. Fatal poisoning in children: acute colchicine intoxication and new treatment approaches. Clin Toxicol (Phila) 2011;49:739-43.
6. Polat E, Tuygun N, Akca H, Karacan CD. Evaluation of the Colchicine Poisoning Cases in a Pediatric Intensive Care Unit: Five Year Study. J Emerg Med 2017;52:499-503.
7. Ataş B, Caksen H, Tuncer O, Kirimi E, Akgün C, Odabaş D. Four children with colchicine poisoning. Hum Exp Toxicol 2004;23:353-6.
8. Yakut HI, Ayar G, Sahin S, Gündüz RC, Kalkan G. Retrospective Evaluation of Cases of Colchicine Toxicity ın a Pediatric Intensive Care Unit. Nobel Med 2015;11:24-8.
9. Demirkol D, Karacabey BN, Aygun F. Plasma exchange treatment in a case of colchicine intoxication. Ther Apher Dial 2015;19:95-7.
10. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. N Engl J Med 1996;334:494-500.
11. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. Lancet Neurol 2015;14:914-25.

Turk J Intensive Care 2022;20:106-109
DOI: 10.4274/tybd.galenos.2022.08831

CASE REPORT / *OLGU SUNUMU*

Mehmet Turan İnal,
Dilek Memiş,
Pervin Hancı,
Gökhan Günbay,
Samet Keleş,
Habibe Tülin Elmaslar Mert,
Rüveyde Garip,
Selis Gülseven Güven,
Emre Hocaoğlu,
Banu Tütüncüler

Mucormycosis in a Patient with Uncontrolled Diabetes Mellitus

Kontrolsüz Diabetes Mellituslu Hastada Mukormikoz

Received/Geliş Tarihi : 21.02.2022
Accepted/Kabul Tarihi : 09.05.2022

Mehmet Turan İnal, Dilek Memiş, Gökhan Günbay, Samet Keleş,
Trakya University Faculty of Medicine, Department of Anesthesiology and Reanimation, Division of Intensive Care, Edirne, Turkey

Pervin Hancı
Trakya University Faculty of Medicine, Department of Chest Diseases, Edirne, Turkey

Habibe Tülin Elmaslar Mert
Trakya University Faculty of Medicine, Department of Infectious Diseases, Edirne, Turkey

Rüveyde Garip
Trakya University Faculty of Medicine, Department of Ophthalmology, Edirne, Turkey

Selis Gülseven Güven
Trakya University Faculty of Medicine, Department of Otorhinolaryngology, Edirne, Turkey

Emre Hocaoğlu
Trakya University Faculty of Medicine, Department of Plastic and Reconstructive Surgery, Edirne, Turkey

Banu Tütüncüler
Trakya University Faculty of Medicine, Department of Neurosurgery, Edirne, Turkey

Mehmet Turan İnal Prof. MD (✉),
Trakya University Faculty of Medicine, Department of Anesthesiology and Reanimation, Division of Intensive Care, Edirne, Turkey

E-mail : mehmetturaninal@yahoo.com
Phone : +90 284 235 76 41
ORCID ID : orcid.org/0000-0001-8462-4299

ABSTRACT Mucormycosis; is a rapidly progressive fungal infection due to filamentous fungi of the mucoraceae family. In this case report, we aimed to present the diagnosis and treatment modalities of a patient who developed rhinoorbital mucormycosis. A 54-year-old patient with a history of hypertension applied to the emergency department with a complaint of wound in the mouth that started four days ago. In the examinations performed here, the patient was diagnosed with diabetic ketoacidosis. In the examination of the patient, it was found that there was a necrotic wound on the left hard palate, a necrotic wound extending from the left inferior turbinate to the nasopharynx, and hyphae in the nasal passage. The patient underwent an aggressive debridement operation on the third day, due to the growth in the fungal culture. In the following clinical examination of the patient, ketone in the urine became negative, and his acidosis status improved. On the same day, the patient was treated with a positive coronavirus disease-2019 (COVID-19) polymerase chain reaction. After 15 days of treatment, the patient died due to COVID-19 pneumonia. Mucormycosis should be doubtful in patients presenting with uncontrolled diabetes mellitus and severe sino-orbital infection. All physicians following diabetic ketoacidosis should be vigilant against this rapidly progressing disease with high mortality.
Keywords: Mucormycosis, diabetic ketoacidosis, mortality

ÖZ Mukormikoz mucoraceae familyasının filamentli mantarlarına bağlı hızla ilerleyen bir mantar enfeksiyonudur. Bu olgu sunumunda rinoorbital mukormikoz gelişen bir hastanın tanı ve tedavi yöntemlerini sunmayı amaçladık. Elli dört yaşında hipertansiyon öyküsü olan hasta, dört gün önce başlayan ağızda yara şikayeti ile acil servise başvurdu. Burada yapılan tetkiklerde hastaya diyabetik ketoasidoz tanısı konuldu. Hastanın muayenesinde sol sert damakta nekrotik yara, sol alt konkadan nazofarenkse kadar uzanan nekrotik yara ve burun pasajında hifa tespit edildi. Üçüncü gün mantar kültüründe üreme olması üzerine hastaya agresif debridman operasyonu uygulandı. Hastanın sonraki klinik muayenesinde idrarda keton negatif çıktı ve asidoz durumu düzeldi. Aynı gün hasta pozitif koronavirüs hastalığı-2019 (COVID-19) polimeraz zincir reaksiyonu ile tedavi edildi. On beş günlük tedaviden sonra hasta COVID-19 pnömonisi nedeniyle eksitus kabul edildi. Kontrolsüz diabetes mellitus ve şiddetli sino-orbital enfeksiyon ile başvuran hastalarda mukormikozdan şüphelenilmelidir. Diyabetik ketoasidoz sonrası tüm hekimler hızla ilerleyen ve mortalitesi yüksek olan bu hastalığa karşı dikkatli olmalıdırlar.
Anahtar Kelimeler: Mukormikoz, diyabetik ketoasidoz, mortalite

Introduction

Mucormycosis; it is a rapidly progressive fungal infection due to filamentous fungi of the mucoraceae class of fungi and is frequently seen in people who have diabetes mellitus, corticosteroid use, hematological malignancies such as lymphoma and leukemia, neutropenia, undergoing solid organ/allogeneic stem cell transplant operation, kidney failure, treated with immunosuppressants, cirrhosis, burns, protein energy malnutrition and AIDS (1-3). Depending on organ involvement, mucormycosis can be seen as rhinocerebral, rinoorbital, pulmonary, cutaneous, gastrointestinal or disseminated. The rhinocerebral form is the most common form (1-3). Rhinoorbital infection begins as a result of inhalation of fungal spores and invasion of the nasal mucosa, by invading the arteries, this fungus forms thrombi that reduce blood flow in blood vessels and cause necrosis of hard and soft tissues. Orbital involvement occurs when the fungus infection moves from the paranasal sinuses to the orbital wall. Pain in and around the eye, redness of the eye, decreased vision and proptosis can be seen in patients (1,4,5).

Despite advances in diagnosis and treatment, mucormycosis is still a disease with high mortality (6).

In this case report, we aimed to present the diagnosis and treatment modalities of a patient who developed rhinoorbital mucormycosis.

Case Report

The 54-year-old patient with a history of hypertension applied to the emergency department with a complaint of wound in the mouth that started four days ago. In the examinations performed here, fasting blood sugar was found to be 686 mg/dL and pH 7.30 in arterial blood gas, and ketone was detected in the urine. The patient was diagnosed with diabetic ketoacidosis (DKA) and was hospitalized in the intensive care unit. In the examination of the patient, it was found that there was a necrotic wound on the left hard palate, a necrotic wound extending from the left inferior turbinate to the nasopharynx, and hyphae in the nasal passage. Orbital computed tomography (CT) was performed for the patient whose sample was taken from here, and no pathology was detected in the orbita. Amphotericin B treatment was started on the same day. After one day, the swelling and redness of the left eye increased, and endoscopic debridement was performed. The patient underwent an aggressive debridement operation on the third day, due to the growth in the fungal culture. Maxillectomy, anterior ethmoidectomy, left orbital bone excision, left eye exenteration, and skull base debridement adjacent to the frontal sinus were performed. In the following clinical examination of the patient, ketone in the urine became negative, and his acidosis status improved. On the same day, the patient was started to treated with a positive coronavirus disease-2019 (COVID-19) polymerase chain reaction. The patient was followed up in the intensive care unit for 15 days due to COVID-19 pneumonia. The patient was considered exitus on the 15th day.

Approve was taken from the patient's relatives for this case presentation.

Discussion

In this case report, rhinoorbital mucormycosis in a uncontrolled diabetes mellitus patient was reported.

Although opportunistic fungal infections such as mucormycosis usually occur in immunocompromised individuals, they can also be seen in healthy individuals (5,6). Predisposing factors for mucormycosis are uncontrolled diabetes (especially in patients with ketoacidosis), malignancies such as lymphoma and leukemia, chronic corticosteroid use, immunosuppressive therapy, kidney failure, cirrhosis, burns, previous organ transplant, protein energy malnutrition, and AIDS (1-3). In the study of Yohai et al. (7) on 145 patients, diabetes mellitus was found to be the most common predisposing factor. Gumral et al. (8) also reported that diabetes mellitus was the predisposing factor in 32 of 79 mucormycosis cases and hematological pathologies in 32 of them. The authors also reported that diabetes is newly diagnosed in 16% of patients (9), similarly to our patient. Our patient had uncontrolled diabetes, which is a frequently reported predisposing factor for mucormycosis. Our patient had high blood sugar at the time of admission to the hospital. We think that the patient continued his life with high blood sugar, even though there was no diagnosis of diabetes mellitus in the patient's history.

While the rhinocerebral form is the most common form, the sino-orbital form seen in our patient is seen in only 15% of the cases (2,6). When the fungi are inhaled, the spores turn into hyphae, causing tissue necrosis and thrombosis of blood vessels (2,9). Although the reason why fungi are more common in diabetic patients is not fully explained, fungal microvascular disease has been reported to be

associated with greater tissue destruction and spread in diabetic patients (6). The dysfunction in phagocytic cells due to hyperglycemia and acidosis is an facilitating factor. It has been shown to increase the availability of free iron, which is a requirement for fungal survival, by impairing the binding of iron to transferrin in acidosis, which is also seen in DKA (6). In addition, the fact that some fungal species have a special enzyme system that can increase fungal growth in acidic and hyperglisemic conditions, as in diabetic ketoasidosiz, is also considered as a reason (2).

Mucormycosis should be diagnosed quickly and treatment should be started quickly. While the survival rate was found to be 76-81% in patients who started the treatment within the first 6 days, the survival rate was reported as 36-42% in the case of starting treatment after 12 days (1). Our patient had a complaint of sores in the mouth that started 4 days ago, but we had no idea about the duration of the high blood sugar since the patient was not diagnosed with diabetes.

Although magnetic resonance imaging is more sensitive than CT in the diagnosis of sinus mucormycosis, both results have been reported to be negative (2,6). Therefore, mucosal biopsy and surgical exploration should be considered in cases with high clinical suspicion. Due to the high mortality of the disease, it is recommended to start treatment as fast as possible (2,6). In our patient the treatment was started quickly. Amphotericin B treatment was started initially.

Control of hyperglycemia and ketoacidosis is important in treatment. Combined surgery and antifungal therapy provides better survival (70%) than surgery (57%) and antifungals alone (61%) (2). In the rhinocerebral form, while the mortality rate was 70% in patients using only antifungals, it decreased to 14% in patients treated with antifungal therapy and surgery (9,10). In our patient, endoscopic debridement was performed one day after hospitalization, but surgical exploration was performed the next day because the necrotic area continued to grow.

Clinical differential diagnosis of the lesion should include chronic granulomatous infection such as squamous cell carcinoma, tuberculosis, syphilis, and other fungal infections (11).

In conclusion, mucormycosis should be considered in patients presenting with uncontrolled diabetes mellitus and severe sino-orbital infection. All physicians following DKA should be vigilant against this rapidly progressing disease with high mortality.

Ethics

Informed Consent: Approve was taken from the patient's relatives for this case presentation.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.T.İ., D.M., P.H., G.G., S.K., H.T.E.M., R.G., S.G.G., E.H., B.T., Concept: M.T.İ., G.G., S.K., Design: M.T.İ., Data Collection and/or Processing: G.G., S.K., Analysis and/or Interpretation: M.T.İ., Literature Search: M.T.İ., Writing: M.T.İ.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Karadeniz Uğurlu Ş, Selim S, Kopar A, Songu M. Rhino-orbital Mucormycosis: Clinical Findings and Treatment Outcomes of Four Cases. Turk J Ophthalmol 2015;45:169-74.
2. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 2005;41:634-53.
3. Tabarsi P, Khalili N, Pourabdollah M, Sharifynia S, Safavi Naeini A, Ghorbani J, et al. Case Report: COVID-19-associated Rhinosinusitis Mucormycosis Caused by Rhizopus arrhizus: A Rare but Potentially Fatal Infection Occurring After Treatment with Corticosteroids. Am J Trop Med Hyg 2021;105:449-53.
4. Leitner C, Hoffmann J, Zerfowski M, Reinert S. Mucormycosis: necrotizing soft tissue lesion of the face. J Oral Maxillofac Surg 2003;61:1354-8.
5. Pogrel MA, Miller CE. A case of maxillary necrosis. J Oral Maxillofac Surg 2003;61:489-93.
6. Saul SR, Aleksic S, Magnotti M. A Patient with Newly Diagnosed Diabetes Presenting with Sino-Orbital Mucormycosis. AACE Clinical Case Rep 2016;2:e41-5.
7. Yohai RA, Bullock JD, Aziz AA, Markert RJ. Survival factors in rhino-orbital-cerebral mucormycosis. Surv Ophthalmol 1994;39:3-22.
8. Gumral R, Yildizoglu U, Saracli MA, Kaptan K, Tosun F, Yildiran ST. A case of rhinoorbital mucormycosis in a leukemic patient with a literature review from Turkey. Mycopathologia 2011;172:397-405.
9. Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev 2005;18:556-69.
10. Perlroth J, Choi B, Spellberg B. Nosocomial fungal infections: epidemiology, diagnosis, and treatment. Med Mycol 2007;45:321-46.
11. Afroze SN, Korlepara R, Rao GV, Madala J. Mucormycosis in a Diabetic Patient: A Case Report with an Insight into Its Pathophysiology. Contemp Clin Dent 2017;8:662-6.