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About the Journal

Bagcilar Medical Bulletin (Bağcılar Tıp Bülteni) (BMB) is periodical scientific publishing of Health Sciences University Turkey, İstanbul Bağcılar Training and Research Hospital. This editorially independent, unbiased, international journal periodically publishes peer-reviewed work in the all medical fields on an international scientific basis. Publication language is English for full text and Turkish and English for abstracts. The journal is published in English since December issue of 2016 as an e-journal.

The journal is published quarterly in March, June, September and December.

Original clinical and experimental articles,interesting case studies, and literature reviews made from relevant authors in their branches will be accepted for evaluation in BMB.

The editorial policies are based on the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (2017, archived at http://www.icmje.org/) rules.

Bagcilar Medical Bulletin is indexed in **TÜBİTAK/ULAKBİM, EBSCO, Gale, Turk Medline, Turkey Citation Index, Index Copernicus, ProQuest, J-Gate, EuroPub** and **ScopeMed**.

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Bağcılar Tıp Bülteni/Bagcilar Medical Bulletin, (BTB) Sağlık Bilimleri Üniversitesi, İstanbul Bağcılar Eğitim ve Araştırma Hastanesinin süreli bilimsel yayınıdır. Uluslararası, hakem değerlendirmeli, İngilizce ve açık erişim olarak yılda 4 sayı(Mart, Haziran, Eylül, Aralık) olarak yayınlanan bilimsel bir dergi olup, tıbbın tüm alanlarındaki bilgi birikiminin uluslararası bilimsel platformda yayılabilmesini amaçlamaktadır. Bu amaçla tıbbın her alanında yapılmış orijinal klinik ve deneysel çalışmalar ve ilginç olgu sunumları ile konusunda uzman yazarların yaptığı literatür derlemeleri yayın için değerlendirmeye alınır.

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Yayın politikaları "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" (2016, http://www.icmje.org/) temel alınarak hazırlanmıştır.

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T.C.Sağlık Bakanlığı Sağlık Bilimleri Üniversitesi, İstanbul Bağcılar Eğitim ve Araştırma Hastanesi adına Hastane Yöneticisi Ahmet Yaser Müslümanoğlu, Prof. M.D (Türkiye Cumhuriyeti Sağlık Bakanlığı Sağlık Bilimleri Üniversitesi, İstanbul Bağcılar Eğitim ve Araştırma Hastanesi, Üroloji Kliniği, İstanbul, Türkiye).

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Description

Bagcilar Medical Bulletin is a peer reviewed English journal aiming to publish original research, current review articles, case reports and letters related to all medical fields. The journal is currently published quarterly as online publication. The articles will become freely available to all readers in pdf format as soon as they have been accepted after peer review. Accepted articles will immediately appear as a part of the issue belonging to that publication period. The journal is currently published by Galenos Publishing House. The journal is using online manuscript submission, review and tracking systems.

Editorial Policies and Review Process

Publication Policy

Bagcilar Medical Bulletin considers for publication papers in the following categories:

- Original researches,
- Brief researches,
- Case reports,
- Reviews,
- Letters to the editor

The journal gives high priority to original studies in publication because of aiming to add the findings of searches in Turkey to international scientific knowledge, to share them within the international science milieu and to constitute the introduction of Turkish scientists. The review articles to be published in the journal are authorized by the editor to the relevant authors working on the subject.

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Papers that have not been published before or under evaluation by other publications are accepted for evaluation by the journal, if approved by each of the author. Publication board may amend manuscripts upon informed consent of authors. Editors and redactors are fully empowered to correct mistakes related to orthography, citation as given in National Library of Medicine MEDLINE/PubMed Resources.

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All submissions must be original, unpublished (including as full text in conference proceedings), and not under the review of any other publication synchronously. Each manuscript is reviewed by one of the editors and at least two referees under double-blind peer review process. We reserve the right to use plagiarism detecting software to screen submitted papers at all times. We check for plagiary and fraudulent data; falsification (fabrication or manipulation of research data, tables, or images) and improper use of humans or animals in research. All manuscripts not in accordance with these standards will be removed from the publication. This also contains any possible malpractice discovered after the publication. In accordance with the code of conduct we will report any cases of suspected plagiarism or duplicate publishing.

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Biomedical Research-revised in 2006 http://www.wma.net/en/30publications/10policies/a18/

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The language of the Bagcilar Medical Bulletin is American English. In addition, abstracts of the articles are published in both English and Turkish, and abstracts in both languages are requested from the authour(s).

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All correspondence will be sent to the first-named author unless otherwise specified. Papers should be accompanied by a cover letter indicating that the paper is intended for publication and specifying for which section of the Journal it is being submitted (i.e., original research article,brief research article, review article, case report or letter to the editor). In addition, a Copyright Transfer Form, Author Contribution Form and ICJME Form for Disclosure of Potential Conflicts of Interest must be submitted. Authors will be notified of the receipt of their paper and the number assigned to it. The number should be included in all further correspondence. All parts of the manuscript, including case reports, quotations, references, and tables, must be double-spaced throughout. All four margins must be at least 2.5 cm. The manuscript should be arranged in the following order, with each item beginning a new page: 1) title page, 2) abstract, 3) text, 4) acknowledgement 5) references, and 6) tables and/or figures. All pages must be numbered consecutively.

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Manuscript Types

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Original research articles report substantial and original scientific results within the journal scope. Original research articles comprised of Abstract, Key Words, Introduction, Material and Methods, Results, Discussion, Conclusion, References and Table/Figures. The abstract should be structured as the following.

Abstract

The abstract should be no longer than 500 words and structured as follows: objective, method, results, and conclusions. Objective -the primary purpose of the article; Material and Method(s) -data sources, design of the study, patients or participants, interventions, and main outcome measures; Results -key findings; Conclusions -including direct clinical applications.

Key Words

Up to 3-10 key words in English and in Turkish should be in accordance with National Library of Medicine's Medical Subjects Subheadings (MeSH).

Introduction

This section should contain a clear statement of the general and specific objectives as well as the hypotheses which the work is designed to test. It should also give a brief account of the reported literature. The last sentence should clearly state the primary and secondary purposes of the article. Only, the actual references related with the issues have to be indicated and data or findings related with the current study must not be included in this section.

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This section should contain explicit, concise descriptions of all procedures, materials and methods used in the investigation to enable the reader to judge their accuracy, reproducibility, etc. This section should include the known findings at the beginning of the study and the findings during the study must be reported in results section. Ethics Committee Approval of the research and written Informed Consent obtained from the participants should be indicated.

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Discussion

The findings of the study, the findings and results which support or do not support the hypothesis of the study should

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Conclusions derived from the study should be stated. For experimental studies, it is useful to begin the discussion by summarizing briefly the main findings, then explore possible mechanisms or explanations for these findings, compare and contrast the results with other relevant studies, state the limitations of the study, and explore the implications of the findings for future research and for clinical practice. The conclusions should be linked with the goals of the study but unqualified statements and conclusions not adequately supported by the data should be avoided. New hypotheses should be stated when warranted, but should be labeled clearly as such.

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Tables, graphics and illustrations should be numbered in Arabic numerals in the text. The places of the illustrations should be signed in the text. Detailed information is under the related heading in below.

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Brief researches are similar to original research in that they follow the same format and guidelines, but they consider small-scale research or research that is in early stages of development. These may include preliminary studies that has a simple research design or a small sample size and that have produced limited pilot data and initial findings that indicate need for further investigation. Brief researches are much shorter than manuscripts associated with a more advanced, larger-scale research project. They are not meant to be used for a short version of an article about research that would otherwise qualify for a full original research manuscript or for publishing material on research that lacks significance, is not rigorous or, if expanded, would not qualify for a full article or for research.

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Review articles are written by individuals who have done substantial work on the subject or are considered experts in the field. The Journal invites authors to write articles describing, evaluating and discussing the current level of knowledge regarding a specific subject in the clinical practice.

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Original papers and reviews have no specific word limitation. A case report must be strictly limited to 1000 words excluding abstract and have minimal figures, tables, and references. Letters to the Editor (maximum of 500 words, including references; no tables or figures) will be considered if they include the notation "for publication." A letter must be signed by all of its authors. Letters critical of an article published in the journal must be received within 12 weeks.

Preparation of Manuscripts

The "Bagcilar Medical Bulletin'' follows the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (International Committee of Medical Journal Editors - http://www.icmje.org/). Upon submission of the manuscript, authors are to indicate the type of trial/research and provide the checklist of the following guidelines when appropriate:

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 for 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 /),

INSTRUCTIONS TO AUTHORS

STROBE statement-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).

CARE guidelines are designed to increase the accuracy, transparency, and usefulness of case reports. (Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D; the CARE Group. The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development.) (http://www.care-statement.org /

References

Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. Readers should therefore be provided with direct references to original research sources whenever possible. On the other hand, extensive lists of references to original work on a topic can use excessive space on the printed page. Small numbers of references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently. Using abstracts as references should be avoided.

References to papers accepted but not yet published should be designated as “in press” or “forthcoming”; authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication. Information from manuscripts submitted but not accepted should be cited in the text as “unpublished observations” with written permission from the source. Citing a “personal communication” should be avoided unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text. For scientific articles, written permission and confirmation of accuracy from the source of a personal communication must be obtained.

Reference Style and Format

The Uniform Requirements style for references is based largely on an American National Standards Institute style adapted by the National Library of Medicine for its databases. Authors should consult NLM’s Citing Medicine (http://www.nlm.nih.gov/bsd/uniform_requirements.html) for information on its recommended formats for a variety of reference types. References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses. References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used in the list of Journals in National Library of Medicine sources. In addition the list should be obtained in the web address of http://www.nlm.nih.gov. Accuracy of citation is the author’s responsibility. All references should be cited in text. Type references in the style shown below. If there are more than 6 authors, list them followed by et al. Abbreviations of journal names should conform to the style used in National Library of Medicine. If a journal is not indexed in National Library of Medicine’s MEDLINE/PubMed, it should not be abbreviated.

Examples for References:

1. For articles in journals:

For the published article from the journal which placed and abbreviated in MEDLINE:

Crow SJ, Peterson CB, Swanson SA, Raymond NC, Specker S, Eckert ED, et al. Increased mortality in bulimia nervosa and other eating disorders. Am J Psychiatry 2009;166(12):1342-1346.

For the published article from the journal which is not placed and is not abbreviated in MEDLINE:

Sevinçer GM, Konuk N. Emotional eating. Journal of Mood Disorders 2013;3(4):171-178.

2. For the supplement:

For the published article from the journal which placed and abbreviated in MEDLINE:

Sharan P, Sundar AS. Eating disorders in women. Indian J Psychiatry 2015:57(Suppl 2):286-295.

For the published article from the journal which is not placed and is not abbreviated in MEDLINE:

Maner F. Yeme bozukluklarının tedavisi. Anadolu Psikiyatri Dergisi 2009;10(Ek 1):55-56.

3. For articles in press:

Cossrow N, Pawaskar M, Witt EA, Ming EE, Victor TW, Herman BK, et al. Estimating the prevalence of binge eating disorder in a community sample from the United States: comparing DSM-IV-TR and DSM-5 criteria. J Clin Psychiatry, 2016. (in press).

4. For the citations from books:

Books edited by one editor:

McKnight TL. Obesity Management in Family Practice. 1st ed., NewYork: Springer, 2005:47-51.

INSTRUCTIONS TO AUTHORS

For the citation from a section of book edited by editor(s):

Jebb S, Wells J. Measuring body composition in adults and children. In Clinical Obesity in Adults and Children, Copelman P, Caterson I, Dietz W (editors). 1st ed., London: Blackwell Publishing, 2005:12-18.

If the authors of the cited section are the editors of the book:

Eckel RH (editor). Treatment of obesity with drugs in the new millennium. In Obesity Mechanisms and Clinical Management. First ed., Philadelphia: Lippincott Williams & Wilkins, 2003:449-476.

For the citation from a translated book:

McGuffin P, Owen MJ, Gottsman II. Psikiyatri Genetiği ve Genomiği. Abay E, Görgülü Y (Çevirenler) 1st ed., Istanbul: Nobel Tıp Kitabevleri, 2009:303-341.

5. For the citation from thesis:

Keçeli F. Yeme bozukluğu hastalarında obsesif kompulsif bozukluk ve kişilik bozukluğu. Thesis, T.C. Sağlık Bakanlığı Bakırköy Prof. Dr. Mazhar Osman Ruh Sağlığı ve Sinir Hastalıkları Eğitim ve Araştırma Hastanesi, Istanbul:2006.

6. For the citation from posters:

Akbaş Öncel D, Akdemir A. Üniversite öğrencilerinde diyet, beden algısı ve kendilik algısı arasındaki ilişkiler. 47. Ulusal Psikiyatri Kongresi Özet Kitabı, 26-30 Ekim 2011, Antalya, 2011:102.

7. Online Article:

Kaul S, Diamond GA. Good enough: a primer on the analysis and interpretation of noninferiority trials. Ann Intern Med [Internet]. 2006 Jul 4 [cited 2007 Jan 4];145(1):62-9. Available from:http://www.annals.org/cgi/reprint/145/1/62.pdf

SUBMISSION TO JOURNAL

All new manuscripts must be submitted through the Bagcilar Medical Bulletin online manuscript submission and peer review system. Complete instructions are available at the website (). A cover letter should accompany with manuscripts, including the knowledge of:

•The findings of previous same studies should be informed and should be cited. The copies of previous same studies should be sent with manuscripts that might help to the editor in the decision process.

•The knowledge of "all authors have read and accepted the study in its form, all authors meet the criteria for being in authorship" should be stated.

•All helpful things for editorial ship should be stated: The comments of previous editor/reviewers and the response of authors should be added if the manuscript has been sent to another journal for consideration, previously. The editor requested this information to accelerate the publication process.

SUBMISSION CHECKLIST

It is hoped that this list will be useful during the final checking of an article prior to sending it to the journal's editor for review. Please consult this Guide for Authors, for further details of any item.

Ensure that the following items are present:

- Cover letter to the editor
  - The category of the manuscript
  - Acknowledgement of "the paper is not under consideration for publication in another journal"
  - Disclosure of any commercial or financial involvement
  - Reviewing the statistical design of the research article
  - Last control for fluent English
- Copyright Transfer Form
- Author Contribution Form
- ICJME Form for Disclosure of Potential Conflicts of Interest
- Permission of previous published material if used in the present manuscript
- Acknowledgement of the study "in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of in 2000.
- Statement that informed consent was obtained after the procedure(s) had been fully explained.
- Indicating whether the institutional and national guide for the care and use of laboratory animals was followed as in "Guide for the Care and Use of Laboratory Animals".
- Title page
  - The title of the manuscript both in Turkish and in English
  - All authors and their affiliations
  - All authors' e-mail address, full postal address, GSM phone, business telephone and fax numbers
- Abstracts (400-500 words) Both in Turkish and in English
- Key words: 3 to 10 words (in Turkish and in English)
- Body text
- Acknowledgement
- Reference
- All tables (including title, description, footnotes)

YAZARLARA BİLGİ

Derginin Tanımı

Bağcılar Tıp Bülteni (Bagcilar Medical Bulletin), tıbbın her alanında araştırma makalelerini, güncel derleme yazılarını, olgu sunumlarını ve editöre mektupları İngilizce tam metin ve Türkçe özle yayınlayan hakemli bir dergidir. Dergi online olarak yılda 4 sayı yayınlanmaktadır. Tüm makaleler kabul edilir edilmez, online olarak pdf formatında bu web sitesinde, o dönemdeki sayının bir makalesi olarak yer alacaktır. Dergi Galenos Yayınevi tarafından yayımlanmaktadır.

Editoryal Politikalar ve Hakem Süreci

Yayın Politikası

Bağcılar Tıp Bülteni, yayınlanmak üzere gönderilen yazıları aşağıda belirtilen şekillerde kabul eder:

- Orijinal araştırmalar,
- Kısa araştırmalar,
- Olgu sunumları,
- Derlemeler,
- Editöre mektup

Dergi, Türkiye'de yapılan araştırmaların uluslararası bilim arenasına duyurulması, uluslararası bilim çevrelerince paylaşılması ve bu bağlamda Türkiye'nin tanıtılmasına katkıda bulunmayı misyon edindiğinden özellikle orijinal araştırma niteliğindeki yazıları yayınlamaya öncelik vermektedir. Dergide yayınlanacak derleme türündeki yazılar editör tarafından konu ile ilgili çalışan yetkin kişilere hazırlatılmaktadır.

Genel İlkeler

Daha önce yayınlanmamış ya da yayınlanmak üzere başka bir dergide halen değerlendirmede olmayan ve her bir yazar tarafından onaylanan makaleler dergide değerlendirilmek üzere kabul edilir. Yayın kurulu, yazarların iznini alarak yazıda değişiklikler yapabilir. Editör ve dil editörleri dil, imlâ ve kaynakların National Library of Medicine MEDLINE/PubMed Resources'da belirtildiği gibi yazılmasında ve ilgili konularda tam yetkilidir.

Eğer makalede daha önce yayınlanmış alıntı yazı, tablo, resim vs. mevcut ise makale yazarı, yayın hakkı sahibi ve yazarlarından yazılı izin almak ve bunu makalede belirtmek zorundadır. Gerekli izinlerin alınıp alınmadığından yazar(lar) sorumludur.

Bilimsel toplantılarda sunulan özet bildiriler, makalede belirtilmesi koşulu ile kaynak olarak kabul edilir. Editör, dergiye gönderilen makale biçimsel esaslara uygun ise, gelen yazıyı yurtiçinden ve/veya yurtdışından en az iki hakemin değerlendirmesinden geçirtir, hakemler gerek gördüğü takdirde yazıda istenen değişiklikler yazarlar tarafından yapıldıktan sonra yayınlanmasına onay verir. Makale yayınlanmak üzere dergiye gönderildikten sonra yazarlardan hiçbirinin ismi, tüm yazarların yazılı izni olmadan yazar listesinden silinemez ve yeni bir isim yazar olarak eklenemez ve yazar sırası değiştirilemez. Yayına kabul edilmeyen makale, resim ve fotoğraflar yazarlara geri gönderilmez.

Yazarların Sorumluluğu

Makalelerin bilimsel ve etik kurallara uygunluğu yazarların sorumluluğundadır. Yazar makalenin orijinal olduğu, daha önce başka bir yerde yayınlanmadığı ve başka bir yerde, başka bir dilde yayınlanmak üzere değerlendirmede olmadığı konusunda teminat sağlamalıdır. Uygulamadaki telif kanunları ve anlaşmaları gözetilmelidir. Telife bağlı materyaller (örneğin tablolar, şekiller veya büyük alıntılar) gerekli izin ve teşekkürle kullanılmalıdır. Başka yazarların, katkıda bulunanların çalışmaları ya da yararlanılan kaynaklar uygun biçimde kullanılmalı ve referanslarda belirtilmelidir.

Gönderilen makalede tüm yazarların akademik ve bilimsel olarak doğrudan katkısı olmalıdır, bu bağlamda "yazar" yayınlanan bir araştırmanın kavramsallaştırılmasına ve desenine, verilerin elde edilmesine, analizine ya da yorumlanmasına belirgin katkı yapan; yazının yazılması ya da bunun içerik açısından eleştirel biçimde gözden geçirilmesinde görev yapan; yazının yayınlanmak üzere nihai halini onaylayan ve çalışmanın herhangi bir bölümünün doğruluğuna ya da bütünlüğüne ilişkin soruların uygun şekilde soruşturulduğunun ve çözümlendiğinin garantisini vermek amacıyla çalışmanın her yönünden sorumlu olmayı kabul eden kişi olarak görülür. Fon sağlanması, ya da araştırma grubunun genel süpervizyonu tek başına yazarlık hakkı kazandırmaz. Yazar olarak gösterilen tüm bireyler sayılan tüm ölçütleri karşılamalıdır ve yukarıdaki ölçütleri karşılayan her birey yazar olarak gösterilebilir. Çok merkezli çalışmalarda grubun tüm üyelerinin yukarıda belirtilen şartları karşılaması gereklidir. Yazarların isim sıralaması ortak verilen bir karar olmalıdır. Tüm yazarlar yazar sıralamasını Telif Hakkı Devir Formunda imzalı olarak belirtmek zorundadırlar. Yazarların tümünün ismi yazının başlığının altındaki bölümde yer almalıdır.

Yazarlık için yeterli ölçütleri karşılamayan ancak çalışmaya katkısı olan tüm bireyler teşekkür (acknowledgement) kısmında sıralanmalıdır. Bunlara örnek olarak ise sadece teknik destek sağlayan, yazıma yardımcı olan ya da sadece genel bir destek sağlayan kişiler verilebilir. Finansal ve materyal destekleri de belirtilmelidir.

Yazıya materyal olarak destek veren ancak yazarlık için gerekli ölçütleri karşılamayan kişiler "klinik araştırıcılar" ya da "yardımcı araştırıcılar" gibi başlıklar altında toplanmalı ve bunların işlevleri ya da katılımları "bilimsel danışmanlık yaptı", "çalışma önerisini gözden geçirdi", "veri topladı" ya da "çalışma hastalarının bakımını üstlendi" şeklinde belirtilmelidir. Teşekkür (acknowledgement) kısmında belirtilen bu ifadeler için bu bireylerden de yazılı izin alınması gerekmektedir.

Bütün yazarlar, araştırmanın sonuçlarını ya da bilimsel değerlendirmeyi etkileyebilme potansiyeli olan finansal

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ilişkiler, çıkar çatışması ve çıkar rekabetini beyan etmelidirler. Bir yazar kendi yayınlanmış yazısında belirgin bir hata ya da yanlışlık tespit ederse, bu yanlışlıklara ilişkin düzeltme ya da geri çekme için yayın yönetmeni ile hemen temasa geçme ve işbirliği yapma sorumluluğunu taşır. Yazarların katkısını belirten Yazar Katkı Formu ve çıkar çatışması olup olmadığını belirten ICMJE Potansiyel Çıkar Çatışması Beyan Formu makale ile birlikte gönderilmelidir. Yazarların görevleri ve sorumlulukları konusunda aşağıdaki kaynağa bakabilirsiniz; http://www.icmje.org/recommendations/browse/roles-and-responsibilities/

Editör ve Hakem Sorumlulukları ve Değerlendirme Süreci

Editörler, makaleleri, yazarların etnik kökeninden, cinsiyetinden, cinsel yöneliminden, uyruğundan, dini inancından ve siyasi felsefesinden bağımsız olarak değerlendirirler. Yayına gönderilen makalelerin adil bir şekilde çift taraflı kör hakem değerlendirmesinden geçmelerini sağlarlar. Gönderilen makalelere ilişkin tüm bilginin, makale yayınlanana kadar gizli kalacağını garanti ederler. Editörler içerik ve yayının toplam kalitesinden sorumludurlar. Gereğinde hata sayfası yayınlamalı ya da düzeltme yapmalıdırlar.

Genel Yayın Yönetmeni; yazarlar, editörler ve hakemler arasında çıkar çatışmasına izin vermez. Hakem atama konusunda tam yetkiye sahiptir ve Bağcılar Tıp Bülteni'nde yayınlanacak makalelerle ilgili nihai kararı vermekle yükümlüdür. Yayın etiği konusunda COPE kaynağına bakabilirsiniz. https://publicationethics.org/files/u7141/1999pdf13.pdf

Hakemler makaleleri, yazarların etnik kökeninden, cinsiyetinden, cinsel yöneliminden, uyruğundan, dini inancından ve siyasi felsefesinden bağımsız olarak değerlendirirler. Araştırmayla ilgili, yazarlarla ve/veya araştırmanın finansal destekçileriyle çıkar çatışmaları olmamalıdır. Değerlendirmelerinin sonucunda tarafsız bir yargıya varmalıdırlar. Hakemler yazarların atıfta bulunmadığı konuyla ilgili yayınlanmış çalışmaları tespit etmelidirler. Gönderilmiş yazılara ilişkin tüm bilginin gizli tutulmasını sağlamalı ve yazar tarafında herhangi bir telif hakkı ihlali ve intihal fark ederlerse Genel Yayın Yönetmeni'ne raporlamalıdırlar. Hakem, makale konusu hakkında kendini vasıflı hissetmiyor ya da zamanında geri dönüş sağlaması mümkün görünmüyorsa, Genel Yayın Yönetmeni'ne bu durumu bildirmeli ve hakem sürecine kendisini dahil etmemesini istemelidir.

Editör makalelerle ilgili bilgileri (makalenin alınması, içeriği, gözden geçirme sürecinin durumu, hakemlerin eleştirileri ya da varılan sonuç) yazarlar ya da hakemler dışında kimseyle paylaşmaz.

Değerlendirme sürecinde editör hakemlere gözden geçirme için gönderilen makalelerin, yazarların özel mülkü olduğunu ve bunun imtiyazlı bir iletişim olduğunu açıkça belirtir. Hakemler ve yayın kurulu üyeleri topluma açık bir şekilde makaleleri tartışamazlar. Hakemlerin kendileri için makalelerin kopyalarını çıkarmalarına izin verilmez ve editörün izni olmadan makaleleri başkasına veremezler. Hakemler gözden geçirmelerini bitirdikten sonra makalenin kopyalarını yok etmeli ya da editöre göndermelidirler. Dergimiz editörü de reddedilen ya da geri verilen makalelerin kopyalarını imha etmelidir.

Yazarın ve editörün izni olmadan hakemlerin gözden geçirmeleri basılamaz ve açıklanamaz. Hakemlerin kimliğinin gizli kalmasına özen gösterilmelidir. Bazı durumlarda editörün kararıyla, ilgili hakemlerin makaleye ait yorumları aynı makaleyi yorumlayan diğer hakemlere gönderilerek hakemlerin bu süreçte aydınlatılması sağlanabilir. Değerlendirme süreciyle ilgili olarak COPE kaynağına bakabilirsiniz: http://publicationethics.org/files/Peer review guidelines.pdf

Açık Erişim İlkesi

Açık erişimli bir yayın olan Bağcılar Tıp Bülteni dergisinin tüm içeriği okura ya da okurun dahil olduğu kuruma ücretsiz olarak sunulur. Okurlar, yayıncı ya da yazardan izin almadan dergi makalelerinin tam metnini okuyabilir, indirebilir, kopyalayabilir, dağıtabilir, basabilir, arayabilir ve link sağlayabilir.

Yayın Etiği

İlke ve Standartlar

Bağcılar Tıp Bülteni yayın etiğinde en yüksek standartlara bağlıdır ve Committee on Publication Ethics (COPE), Council of Science Editors (CSE), World Association of Medical Editors (WAME) ve International Committee of Medical Journals (ICJME) tarafından geliştirilen yayın etiği ilkelerini ve tavsiyelerini gözetir.

Gönderilen tüm makaleler orijinal, yayınlanmamış (konferans bildirilerindeki tam metinler de dahil) ve başka bir dergide değerlendirme sürecinde olmamalıdır. Her bir makale editörlerden biri ve en az iki hakem tarafından çift kör değerlendirmeden geçirilir. Gönderilen makaleleri intihal yazılımı ile denetleme hakkımız haklıdır. İntihal, veride hile ve tahrif (araştırma verisi, tabloları ya da imajlarının manipülasyonu ve asılsız üretimi), insan ve hayvanların araştırmada uygun olmayan kullanımı konuları denetimden geçmektedir. Bu standartlara uygun olmayan tüm makaleler yayından çıkarılır. Buna yayından sonra tespit edilen olası kuraldışı, uygunsuzluklar içeren makaleler de dahildir. Yayın etiği kurallarına bağlı olarak, intihal şüphesini ve duplikasyon durumlarını rapor edeceğimizi belirtiriz. Olası bilimsel hatalı davranışları ve yayın etiği ihlali vakalarını ele alırken COPE Ethics Flowcharts http://publicationethics.org/resources/flowcharts izlenir.

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İnsan ve Hayvan Hakları, Bilgilendirilmiş Olur, Çıkar Çatışması

Bağcılar Tıp Bülteni, yayınladığı makalelerin ticarî kaygılardan uzak ve konu ile ilgili en iyi etik ve bilimsel standartlarda olması şartını gözetmektedir. Makalelerin etik kurallara uygunluğu yazarların sorumluluğundadır.

Bağcılar Tıp Bülteni, 1975 Helsinki Deklarasyonu'nun 2004 yılında revize edilen Ethical Principles for Medical Research Involving Human Subjects'e http://www.wma.net/en/30publications/10policies/b3/index.html ve 2006 yılında revize edilen WMA Statement on Animal Use in Biomedical Research'e http://www.wma.net/en/30publications/10policies/a18/uymayı prensip edinmiştir. Bu yüzden dergide yayınlanmak üzere gönderilen yazılarda, klinik deneylere katılan denekler ile ilgili olarak yukarıda belirtilen etik standartlara uyulduğunun mutlaka belirtilmesi gerekmektedir. Ayrıca deneyin türüne göre gerekli olan yerel veya ulusal etik komitelerden alınan onay yazıları yazı ile birlikte gönderilmelidir. Bununla birlikte deneye katılan kişi/hastalardan, hastalar eğer temyiz kudretine sahip değilse vâsilerinden yazılı bilgilendirilmiş onam alındığını belirten bir yazı ile beraber tüm yazarlar tarafından imzalanmış bir belgenin editöre gönderilmesi gerekmektedir.

Hastalardan izin alınmadan mahremiyet bozulamaz. Hastaların ismi, isimlerinin baş harfleri ya da hastane numaraları gibi tanımlayıcı bilgiler, fotoğraflar ve soy ağacı bilgileri vb. bilimsel amaçlar açısından çok gerekli olmadıkça ve hasta (ya da anne-baba, ya da vâsisi) yazılı bilgilendirilmiş onam vermedikçe basılmazlar. Özellikle olgu bildirimlerinde, çok gerekli olmadıkça hasta ile ilgili tanımlayıcı ayrıntılar çıkarılmalıdır. Örneğin, fotoğraflarda göz bölgesinin maskelenmesi kimliğin gizlenmesi için yeterli değildir. Eğer veriler kimliğin gizlenmesi için değiştirildiyse yazarlar bu değişikliklerin bilimsel anlamı etkilemediği konusunda güvence vermelidirler. Olgu sunumlarında yer verilen hastalardan bilgilendirilmiş onam alınmalıdır. Bilgilendirilmiş onam alındığı da makalede belirtilmelidir.

Bu tip çalışmaların varlığında yazarlar, makalenin YÖNTEM(LER) bölümünde bu prensiplere uygun olarak çalışmayı yaptıklarını, kurumlarının etik kurullarından ve çalışmaya katılmış insanlardan "bilgilendirilmiş onam" aldıklarını belirtmek zorundadırlar.

Çalışmada "hayvan" kullanılmış ise yazarlar, makalenin YÖNTEM(LER) bölümünde "Guide for the Care and Use of Laboratory Animals" (www.nap.edu/catalog/5140.html) doğrultusunda çalışmalarında hayvan haklarını koruduklarını ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadırlar. Hayvan deneyleri rapor edilirken yazarlar, laboratuvar hayvanlarının bakımı ve kullanımı ile ilgili kurumsal ve ulusal rehberlere uyup uymadıklarını yazılı olarak bildirmek zorundadırlar.

Editör ve yayıncı, reklâm amacı ile dergide yayınlanan ticari ürünlerin özellikleri ve açıklamaları konusunda hiçbir garanti vermemekte ve sorumluluk kabul etmemektedir. Eğer makalede doğrudan veya dolaylı ticarî bağlantı veya çalışma için maddî destek veren kurum mevcut ise yazarlar; kaynak sayfasında, kullanılan ticarî ürün, ilaç, ilaç firması v.b. ile ticari hiçbir ilişkisinin olmadığını veya varsa nasıl bir ilişkisinin olduğunu (konsültan, diğer anlaşmalar) bildirmek zorundadır. Bağcılar Tıp Bülteni, WAME'nin çıkar çatışması tanımını benimser http://www.wame.org/about/wame-editorial-on-coi

Buna göre, yazar, hakem ya da editör sorumluluklarını aşırı düzeyde ve/veya haksızlığa yol açabilecek düzeyde etkileyebilecek ya da etkileyebileceği olası bir çıkar rekabeti içindeyse, çıkar çatışması söz konusudur ve bunun açıklanması gerekir. Açıklanması öngörülen çıkar çatışması tipleri, finansal bağlar, akademik taahhütler, kişisel ilişkiler, politik ya da dini inançlar, kurumsal bağlantılardır. Çıkar çatışması söz konusuysa bu makalede açıklanmalıdır.

Dil

Bağcılar Tıp Bülteni'nin yayın dili Amerikan İngilizcesi'dir, ayrıca makalelerin özleri hem İngilizce, hem Türkçe yayınlanır. Her iki dildeki özler yazarlardan istenir.

Yazıların Hazırlanması

Aksi belirtilmedikçe gönderilen yazılarla ilgili tüm yazışmalar ilk yazarla yapılacaktır. Gönderilen yazılar, yazının yayınlanmak üzere gönderildiğini ve Bağcılar Tıp Bülteni'nin hangi bölümü (Orijinal Araştırma, Kısa Araştırma, Olgu Sunumu, Derleme, Editöre Mektup) için başvurulduğunu belirten bir mektup, yazının elektronik formunu içeren Microsoft Word 2003 ve üzerindeki versiyonları ile yazılmış elektronik dosya ile tüm yazarların imzaladığı 'Telif Hakkı Devir Formu', Yazar Katkı Formu ve ICMJE Potansiyel Çıkar Çatışması Beyan Formueklenerek gönderilmelidir. Yazıların alınmasının ardından yazarlara makalenin alındığı, bir makale numarası ile bildirilecektir. Tüm yazışmalarda bu makale numarası kullanılacaktır. Makaleler sayfanın her bir kenarından 2,5 cm kenar boşluğu bırakılarak ve çift satır aralıklı yazılmalıdır. Makalelerde aşağıdaki sıra takip edilmelidir ve her bölüm yeni bir sayfa ile başlamalıdır: 1) başlık sayfası, 2) öz, 3) metin, 4) teşekkür / 5) kaynaklar ve 6) tablo ve/veya şekiller. Tüm sayfalar sırayla numaralandırılmalıdır.

Başlık

Başlık sayfasında, yazarların adları, akademik ünvanları ve yazışılacak yazarın tam adres, telefon ve faks numaraları ile e-mail adresi mutlaka bulunmalıdır. Yazıların Türkçe özlerinde mutlaka Türkçe başlık da yer almalıdır.

Öz ve Anahtar Sözcükler

Makalenin İngilizce başlığı İngilizce özde, Türkçe başlığı da

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Türkçe özde yer almalıdır. Bütün makaleler öz ve anahtar kelime içermelidir. Özler bir makalenin birçok elektronik veri tabanında yer alan en belirgin kısmı olduğundan, yazarlar özün makalenin içeriğini doğru olarak yansıttığından emin olmalıdır. Öz çalışmanın temeliyle ilgili bilgi vermeli ve çalışmanın amacını, temel prosedürleri (olguların ya da laboratuvar hayvanlarının seçimi, gözlemsel ve analitik yöntemler), ana bulguları (mümkünse özgül etki büyüklüklerini ve istatistiksel anlamlılıklarını vererek) ve temel çıkarımları içermelidir. Çalışmanın ya da gözlemlerin yeni ve önemli yönleri belirtilmelidir. Anahtar sözcükler, her türlü yazıda Türkçe ve İngilizce özlerin altındaki sayfada 3-10 adet verilmelidir. Anahtar sözcük olarak National Library of Medicine'ın Tıbbi Konu Başlıkları'nda (Medical Subject Headings, MeSH) yer alan terimler kullanılmalıdır. MeSH'de yer alan terimlerin Türkçe karşılıklarına Türkiye Bilim Terimleri'nden http://www.bilimterimleri.com erişilebilir.

Makale Türleri

Orijinal Araştırma

Orijinal araştırma makaleleri derginin kapsamına uygun konularda önemli, özgün bilimsel sonuçlar sunan araştırmaları raporlayan yazılardır. Orijinal araştırma makaleleri, Öz, Anahtar Kelimeler, Giriş, Yöntem ve Gereçler, Bulgular, Tartışma, Sonuçlar, Kaynaklar bölümlerinden ve Tablo, Grafik ve Şekillerden oluşur. Öz bölümü araştırma yazılarında aşağıda belirtilen formatta yapılandırılmış olmalıdır.

Öz

Araştırma yazılarında Türkçe ve İngilizce özler en fazla 500 kelime olmalı ve şu şekilde yapılandırılmalıdır: Amaç/Objective: Yazının birincil ve asıl amacı; Yöntem ve Gereçler/Material and Method(s): Veri kaynakları, çalışmanın iskeleti, hastalar ya da çalışmaya katılanlar, görüşme/değerlendirmeler ve temel ölçümler; Bulgular/Results: Ana bulgular; Sonuç(lar)/Conclusion(s):Doğrudan klinik uygulamalar, çıkartılacak sonuçlar belirtilmelidir.

Anahtar Kelimeler

National Library of Medicine'ın Tıbbi Konu Başlıkları'nda (MedicalSubjectHeadings, MeSH) yer alan terimler kullanılmalıdır, en az üç anahtar kelime belirtilmelidir.

Giriş

Giriş/Introduction bölümünde konunun önemi, tarihçe ve bugüne kadar yapılmış çalışmalar, hipotez ve çalışmanın amacından söz edilmelidir. Hem ana hem de ikincil amaçlar açıkça belirtilmelidir. Sadece gerçekten ilişkili kaynaklar gösterilmeli ve çalışmaya ait veri ya da sonuçlardan söz edilmemelidir.

Yöntem ve Gereçler

Yöntem ve Gereçler/Material and Methods bölümünde, veri kaynakları, hastalar ya da çalışmaya katılanlar, ölçekler, görüşme/değerlendirmeler ve temel ölçümler, yapılan işlemler ve istatistiksel yöntemler yer almalıdır. Yöntem bölümü, sadece çalışmanın planı ya da protokolü yazılırken bilinen bilgileri içermelidir; çalışma sırasında elde edilen tüm bilgiler bulgular kısmında verilmelidir. Yöntem ve Gereçler bölümünde olguların seçimi ve tanımlanması hakkında bilgi, teknik bilgi ve istatistik hakkında bilgi yer almalıdır. Araştırmanın Etik Kurul Onayı ve katılımcılardan alınan yazılı Bilgilendirilmiş Onam belirtilmelidir.

Olguların Seçimi ve Tanımlanması

Gözlemsel ya da deneysel çalışmaya katılanların (hastalar, hayvanlar, kontroller) seçimi, kaynak popülasyon, çalışmaya alınma ve çalışmadan dışlanma ölçütleri açıkça tanımlanmalıdır. Yaş ve cinsiyet gibi değişkenlerin çalışmanın amacıyla olan ilişkisi her zaman açık olmadığından yazarlar çalışma raporundaki kullanımlarını açıklamalıdır; örneğin yazarlar niçin sadece belli bir yaş grubunun alındığını ya da neden kadınların çalışma dışında bırakıldığını açıklamalıdır. Çalışmanın niçin ve nasıl belli bir şekilde yapıldığı açık bir şekilde belirtilmelidir. Yazarlar etnisite ya da ırk gibi değişkenler kullandıklarında bu değişkenleri nasıl ölçtüklerini ve geçerliklerini açıklamalıdır.

Teknik Bilgi

Diğer çalışmacıların sonuçları yineleyebilmesi için yöntem ve kullanılan araçlar (üretici firma ve adres paragraf içinde belirtilerek) ayrıntılı bir şekilde belirtilmelidir. Önceden kullanılan bilinen yöntemler için (istatistiksel yöntemler dahildir) kaynak gösterilmeli, basılmış ama iyi bilinmeyen bir yöntem için kaynak verilmeli ve yöntem açıklanmalıdır. Aynı şekilde yeni ya da belirgin olarak modifiye edilmiş yöntemler tanımlanmalı ve kullanılma nedenleri belirtilip kısıtlılıkları değerlendirilmelidir. Kullanılan tüm ilaç ve kimyasallar doğru olarak tanımlanıp jenerik isimleri, dozları ve kullanım biçimleri belirtilmelidir. Gözden geçirme yazısı gönderen yazarlar veriyi bulma, seçme, ayırma ve sentezleme yöntemlerini belirtmelidir. Bu yöntemler aynı zamanda özde de yer almalıdır.

İstatistik

İstatistiksel yöntem, orijinal veriye erişebilecek bilgili bir okuyucunun rapor edilen sonuçları onaylayabileceği bir ayrıntıda belirtilmelidir. Mümkünse, bulgular niceliksel hale getirilmeli ve hata ölçümleri (güvenlik aralıkları gibi) sunulmalıdır. Etki büyüklüğünü vermeyen, p değerlerinin kullanımı gibi, salt istatistiksel hipotez sınamasına dayanılmamalıdır. Çalışma deseni ve istatistiksel yönteme dair kaynaklar sayfalar belirtilerek mümkün olduğu sürece standart kaynaklar olmalıdır. İstatistiksel terimler, kısaltmalar ve semboller tanımlanmalıdır. Kullanılan bilgisayar programı belirtilmelidir.

Bulgular

Ana bulgular istatistiksel verilerle desteklenmiş olarak eksiksiz

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verilmeli ve bu bulgular uygun tablo, grafik ve şekillerle görsel olarak da belirtilmelidir. Bulgular yazıda, tablolarda ve şekillerde mantıklı bir sırayla önce en önemli sonuçlar olacak şekilde verilmelidir. Tablo ve şekillerdeki tüm veriyi yazıda vermemeli, sadece önemli noktaları vurgulanmalıdır. Ekstra materyal ve teknik bilgi ek kısmında verilerek yazının akışının bozulmaması sağlanmalı, alternatif olarak bunlar sadece elektronik versiyonda yer almalıdır.

Tartışma

Tartışma/Discussion bölümünde o çalışmadan elde edilen veriler, kurulan hipotez doğrultusunda hipotezi destekleyen ve desteklemeyen bulgular ve sonuçlar irdelenmeli ve bu bulgu ve sonuçlar literatürde bulunan benzeri çalışmalarla kıyaslanmalı, farklılıklar varsa açıklanmalıdır. Çalışmanın yeni ve önemli yanları ve bunlardan çıkan sonuçları vurgulanmalıdır. Giriş ya da sonuçlar kısmında verilen bilgi ve veriler tekrarlanmamalıdır.

Sonuçlar

Sonuçlar/Conclusions bölümünde çalışmadan çıkarılan sonuçlar sıralanmalıdır. Deneysel çalışmalar için tartışmaya sonuçları kısaca özetleyerek başlamak, daha sonra olası mekanizmaları ya da açıklamaları incelemek ve bulguları önceki çalışmalarla karşılaştırmak, çalışmanın kısıtlılıklarını özetlemek, gelecekteki çalışmalar ve klinik pratik için uygulamalarını belirtmek faydalıdır. Varılan sonuçlar çalışmanın amacıyla karşılaştırılmalı, ancak elde edilen bulgular tarafından yeterince desteklenmeyen çıkarımlardan kaçınılmalıdır. Yazarlar, eğer elde ettikleri veriler ekonomik veri ve analizler içermiyorsa, ekonomik çıkar ya da faydalarla ilgili yorumlardan özellikle kaçınılmalıdır. Gerektiğinde yeni hipotezler ortaya konmalı, ancak bunların yeni hipotezler olduğu belirtilmelidir.

Tablo, Grafik ve Şekiller

Yazı içindeki grafik, şekil ve tablolar Arap sayıları ile numaralandırılmalıdır. Şekillerin metin içindeki yerleri belirtilmelidir. Ayrıntılı bilgi aşağıda ilgili başlık altında yer almaktadır.

Kısa Araştırma

Kısa Araştırma makaleleri tarz ve format açısından Orijinal Araştırma makaleleri gibidir; ancak daha küçük ölçekli araştırmaları ya da geliştirme çalışmasının erken aşamalarında olan araştırmaları ele alır. Basit araştırma tasarımı kullanan ön çalışmalar, sınırlı pilot veri sağlayan küçük örnek kitle ile yapılan çalışmalar, ileri araştırma gereksinimine işaret eden başlangıç bulguları bu tür araştırmalar kapsamında sayılabilir. Kısa Araştırma makaleleri, büyük ölçekli gelişkin araştırma projelerini konu alan Orijinal Araştırma makalelerinden daha kısadır. Ancak Kısa Araştırma, Orijinal Araştırma makalesi olabilecek kalitede bir araştırma makalesinin kısa versiyonu olarak anlaşılmamalıdır; önem derecesi düşük, titizlikle yapılmamış bir araştırma hakkında bir yayın malzemesi hazırlamak için kullanılmamalıdır ya da genişletildiğinde Orijinal Araştırma makalesi ya da araştırma niteliği kazanmayacak bir içeriği değerlendirecek bir makale türü olarak anlaşılmamalıdır.

Olgu Sunumu

Olgu sunumu makaleleri özgün vakaları rapor eden yazılardır. Derginin kapsamına giren konulara ilişkin bir problemin üstesinden gelen tedaviyle ilgili, yeni araçlar, teknikler ve metotlar göstererek okuyucular için bilgilendirme sağlamalıdır. Olgu sunumu yazıları Öz (özün araştırma makalesinde olduğu gibi belli bir formatta yapılandırılmış olması gerekmiyor), Anahtar Kelimeler, Giriş, Olgu Sunumu, Tartışma, Referanslar, gerekirse Tablo ve açıklayıcı bilgilerden oluşur. Olgu sunumunda yazılı bilgilendirilmiş onam alınmalı ve makalede belirtilmelidir.

Derleme

Derleme makaleleri alanında zengin birikime ve atıf alan çalışmalara sahip uzman kişilerce yazılan yazılardır. Klinik pratiğe ilişkin bir konuda mevcut bilgiyi tanımlayan, değerlendiren ve tartışan; geleceğe ilişkin çalışmalara yol gösteren derleme yazıları yazmaları için dergi belirlediği yazarlara davet gönderir. Derleme makaleleri, Öz (özün, araştırma makalesinde olduğu gibi belli bir formatta yapılandırılmış olması gerekmiyor), Anahtar Kelimeler, Giriş, Sonuç bölümlerinden oluşur. Derleme makale gönderen yazarların, makalede kullandıkları verinin seçimi, alınması, sentezi için kullandıkları yöntemleri tanımlayan bir bölüme de makalede yer vermeleri gerekir. Bu yöntemler Öz bölümünde de belirtilmelidir.

Editöre Mektup

Editöre Mektup, kısa ve net görüş bildiren yazılardır. Dergide daha önce yayınlanmış olan makalelerle ilgili olarak ya da dergide ifade edilmiş görüşlerle ilgili olarak yazılmış olması tercih edilir. Editöre Mektup yazıları, daha sonra yeni bir yazı ile geçerlilik ispatı gerektirebilecek ön görüş bildiren yazılar olmamalıdır.

Tablolar

Tablolar bilgileri etkin bir şekilde gösterir ve ayrıca bilginin istenen tüm ayrıntı seviyelerinde verilmesini sağlar. Bilgileri metin yerine tablolarda vermek genelde metnin uzunluğunu kısaltır.

Her tablo ayrı bir sayfaya çift aralıklı olarak basılmalıdır. Tablolar metindeki sıralarına göre numaralanıp, her birine kısa bir başlık verilmelidir. MS Word 2003 ve üstü versiyonlarında otomatik tablo seçeneğinde “tablo klasik 1” ya da “tablo basit 1” seçeneklerine göre tablolar hazırlanmalıdır. Başlık satırı ve tablo alt üst satırları dışında tablonun içinde başka dikey ve yatay çizgiler kullanılmamalıdır. Her sütuna bir başlık verilmelidir. Yazarlar açıklamaları başlıkta değil, dipnotlarda yapmalıdır.

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Dipnotlarda standart olmayan tüm kısaltmalar açıklanmalıdır. Dipnotlar için sırasıyla şu semboller kullanılmalıdır: (*,†,‡,§,ǁ,¶,**,††,‡‡).

Varyasyonun standart sapma ya da standart hata gibi istatistiksel ölçümleri belirtilmelidir. Metin içinde her tabloya atıfta bulunulduğuna emin olunmalıdır. Eğer yayınlanmış ya da yayınlanmamış herhangi başka bir kaynaktan veri kullanılıyorsa izin alınmalı ve onlar tam olarak bilgilendirilmelidir. Çok fazla veri içeren tablolar, çok yer tutar ve sadece elektronik yayınlar için uygun olabilir ya da okuyuculara yazarlar tarafından doğrudan sağlanabilir. Böyle bir durumda uygun bir ifade metne eklenmelidir. Bu tip tablolar, hakem değerlendirmesinden geçmesi için makaleyle beraber gönderilmelidir.

Şekiller

Şekiller ya profesyonel olarak çizilmeli ve fotoğraflanmalı ya da fotoğraf kalitesinde dijital olarak gönderilmelidir. Şekillerin basıma uygun versiyonlarının yanı sıra JPEG ya da GIF gibi elektronik versiyonlarda yüksek çözünürlükte görüntü oluşturacak biçimlerde elektronik dosyaları gönderilmeli ve yazarlar göndermeden önce bu dosyaların görüntü kalitelerini bilgisayar ekranında kontrol etmelidir.

Röntgen, CT, MRI filmleri ve diğer tanısal görüntülemeler yüksek kalitede basılmış olarak gönderilmelidir. Bu nedenle şekillerin üzerindeki harfler, sayılar ve semboller açık ve tüm makalede eşit ve yayın için küçültüldüklerinde bile okunabilecek boyutlarda olmalıdır. Şekiller mümkün olduğunca tek başlarına anlaşılabilir olmalıdır. Fotomikrografik patoloji preparatları iç ölçekler içermelidir. Semboller, oklar ya da harfler fonla kontrast oluşturmalıdır. Eğer insan fotoğrafı kullanılacaksa, ya bu kişiler fotoğraftan tanınmamalıdır ya da yazılı izin alınmalıdır (Etik bölümüne bakınız).

Şekiller metinde geçiş sıralarına göre numaralandırılmalıdır. Eğer önceden yayınlanmış bir şekil kullanılacaksa, yayın hakkını elinde bulunduran bireyden izin alınmalıdır. Toplum alanındaki belgeler hariç yazarlığa ve yayıncıya bakılmadan bu izin gereklidir. Basılacak bölgeyi gösteren ek çizimler editörün işini kolaylaştırır. Renkli şekiller editör gerekli gördüğünde ya da sadece yazar ek masrafı karşılarsa basılır.

Şekillerin Dipnotları

Ayrı bir sayfadan başlayarak şekiller için tablo başlıkları ve dipnotları tek aralıklı olarak ve Arap sayıları ile hangi şekle karşı geldikleri belirtilerek yazılmalıdır. Semboller, oklar, sayılar ya da harfler şeklin parçalarını belirtmek için kullanıldığında, dipnotlarda her biri açıkça tanımlanmalıdır. Fotomikrografik patoloji preparatlarında iç ölçek ve boyama tekniği açıklanmalıdır.

Ölçüm Birimleri

Uzunluk, ağırlık ve hacim birimleri metrik (metre, kilogram, litre) sistemde ve bunların onlu katları şeklinde rapor edilmelidir. Sıcaklıklar Celsius derecesi, kan basıncı milimetre civa cinsinden olmalıdır. Ölçü birimlerinde hem lokal hem de Uluslararası Birim Sistemleri (International System of Units, SI) kullanılmalıdır. İlaç konsantrasyonları ya SI ya da kütle birimi olarak verilir, alternatif olarak parantez içinde de verilebilir.

Kısaltmalar ve sembollerde sadece standart kısaltmalar kullanılmalıdır, standart olmayan kısaltmalar okuyucu için çok kafa karıştırıcı olabilir. Başlıkta kısaltmadan kaçınılmalıdır. Standart bir ölçüm birimi olmadıkça kısaltmaların uzun hali ilk kullanılışlarında açık, kısaltılmış hali parantez içinde verilmelidir.

Teşekkür(ler)

Yazının sonunda kaynaklardan önce yer verilir. Bu bölümde kişisel, teknik ve materyal yardımı gibi nedenlerle yapılacak teşekkür ifadeleri yer alır.

Kelime Sayısı Sınırlandırması

Türkçe ve İngilizce özler en fazla 500 kelime olmalıdır. Orijinal makaleler ve derleme yazılarında özel bir kelime sayısı sınırlandırması yoktur. Olgu Sunumları Öz hariç 1000 kelime ile sınırlandırılmalı ve en az sayıda şekil, tablo ve kaynak içermelidir. Editöre mektuplar (en fazla 1000 kelime, tablosuz ve şekilsiz) olmalı ve mektup, tüm yazarlar tarafından imzalanmış olmalıdır. Bağcılar Tıp Bülteni'nde yayınlanmış olan bir yazı ile ilgili eleştiri ya da değerlendirme niteliğindeki mektuplar sözü edilen yazının yayınlanmasından sonraki 12 hafta içinde alınmış olmalıdır.

Makale Hazırlığı :

"Bağcılar Tıp Bülteni", Tıp Dergilerinde Bilimsel Çalışmaların Yürütülmesi, Raporlanması, Düzenlenmesi ve Yayınlanmasına İlişkin yönergeleri takip eder "(Uluslararası Tıp Dergisi Editörleri Komitesi - http://www.icmje.org/). Makalenin sunulması üzerine, yazarlar deneme/araştırma türünü belirtmeli ve uygun olduğunda aşağıdaki kuralların kontrol listesini sağlamalıdır:

Randomize çalışmalar için CONSORT açıklaması (CONSORT Grubu için Moher D, Schultz KF, Altman D. CONSORT beyanı paralel grup randomize çalışmaların raporlarının kalitesini iyileştirmek için önerileri gözden geçirdi. JAMA 2001; 285: 1987-91) (http: //www.consort-statement.org /),

Sistematik gözden geçirmeler ve meta-analizler için tercih edilen raporlama maddeleri için PRISMA (Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Grubu. Sistematik İncelemeler ve Meta-Analizler için Tercih Edilen Raporlama Maddeleri: PRISMA Beyanı. PLoS Med 2009; 6 (7): e1000097.) (Http:// www.prisma-statement.org /),

Tanısal doğruluk çalışmalarının raporlanması için STARD kontrol listesi (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, vd, STARD Grubu için. Teşhis doğruluğu çalışmalarının eksiksiz ve doğru raporlanmasına yönelik: STARD girişimi, Ann Intern Med 2003; 138: 40-4.) (http://www. stard-statement.org /),

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STROBE gözlemsel çalışma raporlarında yer alması gereken maddelerin kontrol listesi (http://www.strobe-statement.org /),

Gözlemsel çalışmaların meta-analizi ve sistemik incelemeleri için MOOSE yönergeleri (Stroup DF, Berlin JA, Morton SC, vd.) Epidemiyolojideki gözlemsel çalışmaların meta-analizi: Epidemiyoloji (MOOSE) grubundaki gözlemsel çalışmaların Meta-analizini bildirme önerisi JAMA 2000; 283: 2008-12).

CARE kuralları, vaka raporlarının doğruluğunu, şeffaflığını ve kullanışlılığını artırmak için tasarlanmıştır. (Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D; CARE Grubu. CARE Yönergeleri: Konsensüs Tabanlı Klinik Vaka Raporlama Rehberinin Geliştirilmesi.) (Http://www.care-statement.org /

Kaynaklar

Kaynaklarla İlgili Genel Konular

Gözden geçirme yazıları okuyucular için bir konudaki kaynaklara ulaşmayı kolaylaştıran bir araç olsa da, her zaman orijinal çalışmayı doğru olarak yansıtmaz. Bu yüzden mümkün olduğunca yazarlar orijinal çalışmaları kaynak göstermelidir. Öte yandan, bir konuda çok fazla sayıda orijinal çalışmanın kaynak gösterilmesi yer israfına neden olabilir. Birkaç anahtar orijinal çalışmanın kaynak gösterilmesi genelde uzun listelerle aynı işi görür. Ayrıca günümüzde kaynaklar elektronik versiyonlara eklenebilmekte ve okuyucular elektronik literatür taramalarıyla yayınlara kolaylıkla ulaşabilmektedir.

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MEDLINE'da yer almayan ve kısaltması olmayan dergi makalesi için: Sevinçer GM, Konuk N. Emotional eating. Journal of Mood Disorders 2013;3(4):171-178.

2. Ek sayı için:

MEDLINE'da yer alan ve kısaltması MEDLINE'a göre yapılan dergi makalesi için: Sharan P, Sundar AS. Eating disorders in women. Indian J Psychiatry 2015:57(Suppl 2):286-295.

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3. Baskıdaki makale için:

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4. Kitaptan alıntılar:

Tek yazarlı kitaptan alıntı için:

McKnight TL. Obesity Management in Family Practice. 1st ed., New York:Springer, 2005:47-51.

Kitaptan bir bölüm için, editör(ler) varsa:

Jebb S, Wells J. Measuring body composition in adults and children. In Clinical Obesity in Adults and Children, Copelman P, Caterson I, Dietz W (editors). 1st ed., London: Blackwell Publishing, 2005:12-18.

Editörler aynı zamanda kitabın içindeki metin ya da metinlerin yazarı ise: Önce alınan metin ve takiben kitabın ismi yine kelimeler büyük harfle başlatılarak yazılır.

Eckel RH (editor). Treatment of obesity with drugs in the new millennium. In Obesity Mechanisms and Clinical Management. 1st ed., Philadelphia: Lippincott Williams & Wilkins, 2003:449-476.

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Çeviri Kitaptan Alıntı için:

McGuffin P, Owen MJ, Gottsman II. Psikiyatri Genetiği ve Genomiği. Abay E, Görgülü Y (translation editors) 1st ed., Istanbul: Nobel Tıp Kitabevleri, 2009:303-341.

5. Tezden alıntı için:

Keçeli F. Yeme bozukluğu hastalarında obsesif kompulsif bozukluk ve kişilik bozukluğu. Thesis, T.C. Sağlık Bakanlığı Bakırköy Prof. Dr. Mazhar Osman Ruh Sağlığı ve Sinir Hastalıkları Eğitim ve Araştırma Hastanesi, Istanbul:2006.

6. Kongre bildirileri için:

Akbaş Öncel D, Akdemir A. Üniversite öğrencilerinde diyet, beden algısı ve kendilik algısı arasındaki ilişkiler. 47. Ulusal Psikiyatri Kongresi Özet Kitabı, 26-30 Ekim 2011, Antalya, 2011:102.

7. Online Makale:

Kaul S, Diamond GA. Good enough: a primer on the analysis and interpretation of noninferiority trials. Ann Intern Med [Internet]. 4 Temmuz 2006 [Atıf tarihi:4 Ocak 2007];145(1):62-9. Erişim adresi:http://www.annals.org/cgi/reprint/145/1/62.pdf

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REVIEW

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Review of a Challenging Clinical Issue: Acute Biliary Pancreatitis During Pregnancy

Zorlu Bir Klinik Sorunun Gözden Geçirilmesi: Gebelikte Akut Biliyer Pankreatit

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Abstract

Acute pancreatitis is an inflammatory condition of the pancreas most commonly caused by gallstone. Approximately 70% cases of acute pancreatitis during pregnancy are secondary to gallstones or sludge. Acute pancreatitis is a rare complication with a reported incidence of one per 1.500-4.500 pregnancies. Gallstones cause bile duct obstruction and pancreatic hyperstimulation. These processes lead to increased hydrostatic pressure, trypsin reflux and activation of digestive enzymes within the pancreas and cause autodigestion of pancreas, followed by local inflammation. During pregnancy, the steroid hormones of pregnancy affect the gallbladder motility and bile content. Progesterone induces gallbladder smooth muscle relaxation and estrogens increase bile cholesterol level, enhancing bile stasis. The clinical symptoms include pain in the right upper abdominal area and/or epigastric area, which can radiate to the right flank, scapula and shoulder, anorexia, nausea, vomiting, dyspepsia, low-grade fever and sinus tachycardia, hyperventilation and smell of acetone in the breath. The diagnosis of acute pancreatitis in pregnancy is confirmed by laboratory investigations and imaging methods. The management of acute biliary pancreatitis during pregnancy is similar on a large scale.

Keywords: Acute biliary pancreatitis, pancreatitis, pancreatitis during pregnancy

Öz

Akut pankreatit, en yaygın olarak safra taşının neden olduğu pankreasın iltihaplı bir durumudur. Hamilelik sırasında akut pankreatit olgularının yaklaşık %70'i safra taşı veya çamura ikincildir. Akut pankreatit, 1,500-4,500 gebelikte bir bildirilen insidansı ile nadir bir komplikasyondur. Safra taşları safra kanalı tıkanıklığına ve pankreas hiperstimülasyonuna neden olur. Bu süreçler, hidrostatik basıncı, tripsin geri akışını ve pankreas içindeki sindirim enzimlerinin aktivasyonunu artırarak pankreasın kendi kendine sindirilmesine ve ardından lokal iltihaplanmaya neden olur. Hamilelik sırasında, hamileliğin steroid hormonları safra kesesi hareketliliğini ve safra içeriğini etkiler. Progesteron safra kesesi düz kas gevşemesine neden olur ve östrojenler safra kolesterol seviyesini yükselterek safra stazını artırır. Klinik semptomlar arasında sağ üst karın bölgesinde ve/veya epigastrik bölgede ağrı, sağ flank, skapula ve omuza yayılabilen ağrı, iştahsızlık, bulantı, kusma, dispepsi, düşük dereceli ateş ve sinüs taşikardisi, hiperventilasyon ve nefesin aseton kokusu yer alır. Gebelikte akut pankreatit tanısı, laboratuvar incelemeleri ve görüntüleme yöntemleri ile doğrulanır. Gebelik sırasında akut biliyer pankreatitin yönetimi büyük ölçüde benzerdir.

Anahtar kelimeler: Akut bilier pankreatit, gebelik sırasında pankreatit, pankreatit

Introduction

The prevalence rate of gallstones varies with ethnicity. The incidence is higher in Native American Indians, Mexicans and Latin Americans but lower in Asia and Africa (1).

Gallbladder disease is closely related to the metabolic syndrome. Pregnancy is an important risk factor for gallbladder disease. Hormonal changes and weight gain are major risk factors for biliary sludge and gallstone formation during pregnancy (2).

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Acute pancreatitis is a rare complication with a reported incidence of one per 1.500-4.500 pregnancies (3,4). Acute pancreatitis is a dangerous disease with high maternal and fetal mortality rates. Over the past decade, the maternal and fetal mortality rates were 37% and 11 to 37%, respectively. However, maternal mortality declined to <1% and perinatal mortality was nearly 18% in recent studies. Approximately 70% of cases of acute pancreatitis during pregnancy are secondary to gallstones or sludge (5).

Pathogenesis

Gallstones cause bile duct obstruction and pancreatic hyperstimulation. These processes lead to increased hydrostatic pressure, trypsin reflux and activation of digestive enzymes within the pancreas and cause autodigestion of pancreas, followed by local inflammation (6).

The reasons for the association of pregnancy and biliary tract disease include increased volume of the gallbladder and decreased flow of bile (7). During pregnancy, the steroid hormones of pregnancy affect the gallbladder motility and bile content. Progesterone induces gallbladder smooth muscle relaxation and estrogens increase bile cholesterol level, enhancing bile stasis (8).

High parity is a risk factor for gallstones; however, it remains unclear (9). Pre-pregnancy body mass index (BMI) is a strong predictor factor of gallbladder diseases. Obesity (BMI>30 kg/m^2) is strongly associated with gallbladder diseases. However, weight gain during pregnancy is conversely associated with the risk of incident gallbladder diseases (10).

Insulin resistance increases the risk of gallstones and sludge, which is another situation associated with obesity (11). Some studies report that women gain more weight during pregnancy and this weight could contribute to insulin resistance (10).

Serum leptin level is another predictive factor of gallbladder disease. Leptin is a hormone which is secreted by the adipose tissue and closely correlated with body fat mass. Leptin levels are increased during pregnancy. Leptin affects biliary cholesterol elimination and may cause gallstone formation and gallbladder disease (12,13).

Clinical Presentation

The symptoms of acute pancreatitis due to the gallbladder disorders in pregnancy are non-specific. The symptoms of gallbladder disease can be present before the clinical presentation of acute pancreatitis. The symptoms include the classic colicky or stabbing pain in the right upper abdominal area and/or epigastric area, which can radiate to the right flank, scapula and shoulder in about 40% of cases. Other symptoms are anorexia, nausea, vomiting, dyspepsia, low-grade fever and sinus tachycardia, hyperventilation and smell of acetone in the breath. Abdominal pain due to the acute pancreatitis could be mild to severe with abdominal tenderness, muscle rigidity, jaundice, paralytic ileus and hypoxemia. The symptoms can occur at any time of pregnancy but increase with gestational age. The duration of symptoms may change from 24 hours up to 3 weeks.

Diagnosis

The diagnosis of acute pancreatitis in pregnancy is confirmed by laboratory investigations and imaging methods. Serum amylase and lipase levels could be elevated three times over upper limit of normal value. Serum glucose, bilirubin and liver enzyme activities could be normal or increased. Leukocytosis may be present (14).

Abdominal ultrasound scan with no radiation to the fetus is an initial, safe and inexpensive imaging technique for the detection of gallstones, which are a potential cause of acute pancreatitis in pregnancy (15).

Magnetic resonance cholangiopancreatography (MRCP) provides multi-planar large field with excellent soft-tissue contrast and images of bilio-pancreatic duct systems. MRCP does not require contrast medium and radiate ionizing radiation to mother and fetus. The sensitivity of MRCP to the diagnosis of common bile duct stones is over 90% (15). It could also specify their numbers and locations but small gallstones located in the distal common bile duct could be missed by MRCP (16). The other advantage of MRCP is also its facilitating endoscopic retrograde cholangiopancreatography (ERCP) and laparoscopic cholecystectomy (17).

Endoscopic ultrasonography (EUS) has higher specificity than MRCP in detecting suspected small common bile duct stones (≤2 mm) or sludge. However, EUS requires general anesthesia and expensive equipment, and depends on the operator's experience (18).

Although computed tomography is the most commonly used imaging technique in the diagnosis of acute pancreatitis among adults, it is not recommended in pregnant patients because of the fear of radiation exposure of the fetus (19).

ERCP is used for both diagnostic and therapeutic options in selected acute biliary pancreatitis cases when other

imaging techniques fail to demonstrate small gallstones or sludge in the common bile duct (20). ERCP with endoscopic sphincterotomy is useful in extracting small gallstones and ensuring the drainage of the infected bile in severe acute biliary pancreatitis (21). A major concern for this procedure has been radiation exposure of the fetus. Therefore, before performing therapeutic ERCP, MRCP or EUS helps to identify patients who require ERCP (22).

Treatment

The management of acute biliary pancreatitis during pregnancy is similar on a large scale. The pregnant women should be admitted to an intensive care unit. Intravenous fluid and nutritional therapy are required. Parenteral nutrition outcomes are successful in obstetric patients. However, the frequency of central venous catheter- related complications are higher in pregnant than in non-pregnant patients (23). Naso-jejunal enteral nutrition is preferable to total parenteral nutrition in severe acute pancreatitis during pregnancy. Enteral nutrition has lower frequency of infectious complications than parenteral nutrition (24).

The first decision is a choice of which procedure to clear gallstones in common bile duct. The second decision is cholecystectomy time (25). The presence or absence of common bile duct dilatation, cholangitis, obstructive jaundice, peritonitis, severity of acute pancreatitis and trimester of pregnancy affect the treatment modalities. Although symptomatic biliary tract diseases are managed conservatively, 50% of patients receiving conservative treatment have recurrent episodes of biliary pancreatitis during pregnancy (4). Acute biliary pancreatitis patients could be evaluated for cholecystectomy to prevent recurrence during pregnancy. Laparoscopic cholecystectomy is a safe procedure for both the mother and the fetus in all trimesters (26). It cannot be performed at late gestation weeks because uterus is too big and it makes difficult to evaluate the surgical area for laparoscopic approach. The main advantages of laparoscopic cholecystectomy are earlier mobilization, shorter hospitalization time, lower dose of narcotic and analgesic use, lower risk of wound infections and thromboembolism (27). Uterine injuries during trocar placement, preterm delivery and fetal acidosis are the main complications of laparoscopic cholecystectomy (28).

ERCP is another safe and alternative diagnostic and therapeutic procedure in acute biliary pancreatitis during pregnancy. Sphincterotomy and clearance of bile duct stones by ERCP are indicated in patients with severe acute pancreatitis, cholangitis and persistent biliary obstruction (29). Biliary sphincterotomy with ERCP may be more suitable than cholecystectomy in acute biliary pancreatitis during pregnancy (30).

Conclusion

Acute pancreatitis is a dangerous disease with high maternal and fetal mortality rates. The diagnosis of acute pancreatitis in pregnancy is confirmed by laboratory investigations and imaging methods. The management of acute biliary pancreatitis during pregnancy is similar on a large scale.

Ethic

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: Y.C., Design: B.A., Data Collection or Processing: Y.C., Analysis or Interpretation: B.A., Literature Search: B.A., Writing: Y.C.

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ORIGINAL RESEARCH

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Does the Coraco-acromial Angle Contribute to the Diagnosis of Impingement Syndrome?

Korako-akromial Açının İmpingement Sendromu Tanısına Katkısı Var Mı?

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Abstract

Objective: The aim of the present study is to investigate the contribution of the coraco-acromial angle to the diagnosis of impingement syndrome.

Method: The magnetic resonance images of the shoulder of 159 patients (96 females, 63 males) with impingement syndrome and 201 control cases (113 females, 88 males) from 2017 to 2019 were retrospectively evaluated. On the sagittal plane T2-weighted images, the shortest distances of humeral head to the acromion and the coracoid process, and the angle between longitudinal axis of the coraco-acromial ligament and longitudinal axis of the acromion were measured. To evaluate intra-observer reliability, all measurements were repeated two weeks later.

Results: The mean values of coraco-humeral distance, acromio-humeral distance and coraco-acromial angle were 8.39±5.97 mm, 8.07±4.00 mm and 123.45±11.10°, respectively, in the patient group, and 10.32±2.52 mm, 10.69±2.19 mm and 124.75±6.95°, respectively, in the control group. While there was a significant difference between the patient and control groups in terms of coraco-humeral and acromio-humeral distances ($p<0.05$), there was no significant difference in terms of coraco-acromial angle ($p>0.05$). Elsewise, no correlation was found between impingement syndrome and coraco-acromial angle, since there were moderately negative correlations in terms of coraco-humeral and acromio-humeral distances.

Conclusion: Unlike the coraco-humeral and acromio-humeral distances, there was no correlation between coraco-acromial angle and impingement syndrome.

Keywords: Coraco-acromial angle, impingement syndrome, magnetic resonance imaging

Öz

Amaç: Bu çalışmanın amacı korako-akromial açının sıkışma sendromu tanısına katkısını araştırmaktır.

Yöntem: 2017-2019 yılları arasında sıkışma sendromlu 159 hastanın (96 kadın, 63 erkek) ve 201 kontrol olgusunun (113 kadın, 88 erkek) omuz manyetik rezonans görüntüleri geriye dönük olarak değerlendirildi. Sagittal düzlem T2 ağırlıklı görüntülerde, humerus başı ile akromion ve korakoid proçesin en kısa mesafeleri ve korako-akromial ligamentin uzunlamasına ekseni ile akromionun uzunlamasına ekseni arasındaki açı (korako-akromial açı) ölçüldü. Gözlemci içi güvenilirliği değerlendirmek için, tüm ölçümler iki hafta sonra tekrarlandı.

Bulgular: Ortalama korako-humeral mesafe, akromio-humeral mesafe ve korako-akromial açı değerleri hasta grubunda sırasıyla 8,39±5,97 mm, 8,07±4,00 mm ve 123,45±11,10° iken, kontrol grubunda 10,32±2,52 mm, 10,69±2,19 mm 124,75±6,95° idi. Hasta ve kontrol grubu arasında korako-humeral ve akromio-humeral mesafeler açısından anlamlı fark varken ($p<0,05$), korako-akromial açı açısından anlamlı fark yoktu ($p>0,05$). Korako-humeral ve akromio-humeral mesafeler ile sıkışma sendromu arasında orta derecede negatif korelasyonlar mevcut iken korako-akromial açı ile sıkışma sendromu arasında bir ilişki saptanmadı.

Sonuç: Korako-humeral ve akromio-humeral mesafelerden farklı olarak, korako-akromial açı ile sıkışma sendromu arasında bir ilişki saptanmadı.

Anahtar kelimeler: Korako-akromial açı, manyetik rezonans görüntüleme, sıkışma sendromu

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Introduction

Impingement syndrome is one of the most common causes of shoulder pain in the subacromial region. A leading cause of this syndrome is the compression of the supraspinatus tendon and long head of biceps brachi muscle between the humeral head and coraco-acromial ligament (1). Shoulder impingement syndrome was first described by Neer (2). He explained this syndrome as a mechanical compression of the rotator cuff tendons under the antero-inferior part of the acromion in the forward flexion and internal rotation position of the shoulder (3).

The superior border of the subacromial space is formed by one third anterior part of acromion, coraco-acromial ligament, coracoid process, acromio-clavicular joint and acromio-clavicular ligament. The lower border is formed by humeral head and tuberculum majus (4). In impingement syndrome, the rotator cuff tendons are compressed in subacromial space due to the pathologies of the anatomic structures that limit this space. Impingement of the tendons may occur due to internal and external causes (5). Among the external causes, the morphological structure of acromion and acromio-clavicular joint pathologies, which causes narrowing of the subacromial space, is the most common (6). Acromion variations are also considered among the causes of impingement and might lead to rotator cuff rupture (7). Internal causes of impingement are tendon degenerations due to decreased vascularity and recurrent loads in rotator cuff tendons (8). The rotator cuff tendons provide the dynamic stabilization of the shoulder joint along with the long head of biceps brachi, pectoralis major, latissimus dorsi and serratus anterior musles, while the joint capsule, glenoidal labrum, glenohumeral ligaments and negative joint pressure ensure the static stabilization. Although the diagnosis of impingement syndrome is made through clinical examination, imaging methods are helpful for an accurate diagnosis.

Magnetic resonance imaging (MRI) is widely used in musculoskeletal imaging due to its high soft tissue resolution. Shoulder MRI can help to evaluate the pathological condition causing compression, the condition of the tendon exposed to compression and possible additional findings (6,7). The main parameters used for the diagnosis of impingement syndrome on MRI are the reduction of coraco-humeral distance (CHD) and acromio-humeral distance (AHD). However, the reduction of these distances is not always compatible with clinical findings. We think that the addition of new anatomical data may increase the clinico-radiologic compliance. Therefore, we investigated whether there was a correlation between the coraco-acromial angle (CAA) and impingement syndrome, in addition to AHD and CHD.

Materials and Methods

Approval was obtained from the University of Aydın Adnan Menderes Ethics Committee for non-interventional clinical trials within our institution (protocol no: 2019/175). Since it was designed retrospectively and only MRI images of the patients were evaluated, no “voluntary consent form” was obtained from the patients.

Patient Selection

From May 2017 to May 2019, shoulder MRIs of patients older than 18 years were scanned retrospectively. Among patients referred to our clinic for shoulder MRI with a pre-diagnosis of impingement syndrome, those whose MRI results were compatible with impingement syndrome were identified. Patients with history of trauma, rheumatologic disease or severe glenohumeral arthrosis, and tumors, those who had previous operations and those with poor MRI quality were excluded from the study. Consequently, 159 patients (96 females, 63 males) diagnosed with impingement syndrome were included in the study. Two hundred-one cases (113 females, 88 males) with a similar age distribution to the patient group without clinical pre-diagnosis of impingement syndrome and with normal shoulder MRI report were defined as the control group.

MRI Evaluation

All MRI examinations were obtained with a 1.5 Tesla MR device (Philips Achieva, Philips Medical Systems, Nederland BV) using an 8-channel superficial shoulder coil. As a standard shoulder MRI scan, T1 and T2-weighted series in the sagittal oblique plan, T2-weighted fat-suppressed series in the coronal oblique plan, and T2-weighted series in the axial plane were obtained. All measurements were made on T2-weighted sections in the sagittal oblique plane.

AHD and CHD measurements were made from the section where the distance between the humeral head-acromion and humeral head-coracoid process was the shortest, respectively. CAA was measured between the longitudinal axis of the coraco-acromial ligament and the line tangent to the inferior surface of the acromion (Figure 1). For intra-observer reliability analysis, all measurements were repeated after two weeks.

Acromion shapes of all cases were evaluated on sagittal plane T2-weighted MR images, based on the morphological

classification of Bigliani et al (9). Accordingly, acromion types were divided into three groups: type 1=flat, type 2=anteriorly curved, type 3=hooked.

Statistical Analysis

SPSS 22.0 program was used for the statistical analysis. The normality analysis of the obtained data was evaluated with the Kolmogorov-Smirnov test. The Student's t-test was used for the analysis of normally distributed data, and the Mann-Whitney U test for non-normally distributed data, with a significance level of α=0.05. For the correlation analysis, the Pearson and Spearman correlation tests was used for normally and non-normally distributed data, respectively.

Results

One hundred and fifty-nine patients (96 females, 63 males) and 201 (113 females, 88 males) controls were included in our study. The average age of the patient group was 55.1±12.4 years in females and 52.4±14.3 years in males. The mean age of the control group was 47.4±10.5 years in females and 40.2±13.5 years in males. The average age of the patient group was higher than that of the control group for both males and females (p<0.05).

The mean values of CHD, AHD and CAA were 8.39±5.97 mm, 8.07±4.00 mm and 123.45±11.10°, respectively, in patients with impingement syndrome, and 10.32±2.52 mm, 10.69±2.19 mm and 124.75±6.95°, respectively, in the control group. While there was a significant difference between the two groups in terms of CHD (p=0.001) and AHD (p=0.001), there was no significant difference in CAA (p=0.182). The statistical analyses of patients according to their gender, the distribution of age, CHD, AHD and CAA values by groups were summarized in Table 1, 2.

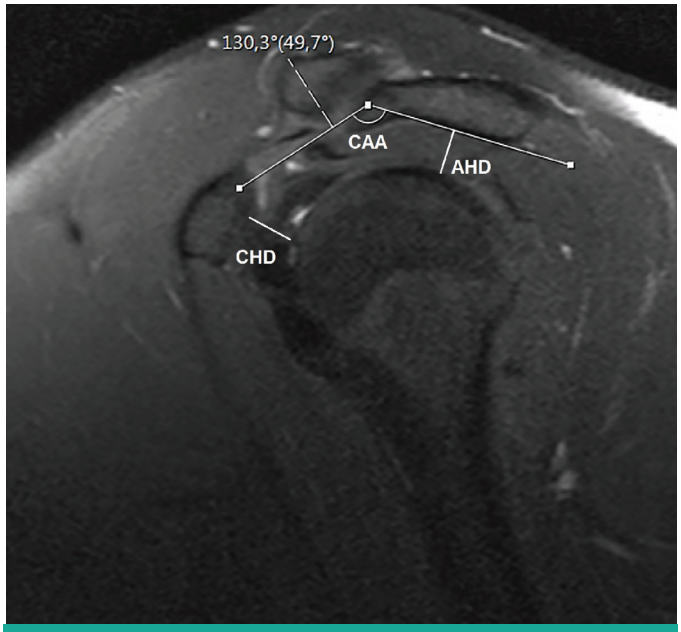

Figure 1. The measurements of acromio-humeral distance (AHD), coraco-humeral distance (CHD) and coraco-acromial angle (CAA) on sagittal plane T2-weighted magnetic resonance imaging

In terms of acromion types of males, 37 were type I and 26 were type II in the patient group and 70 were type I and 18 were type II in the control group. While 54 of the female patients had type I and 42 had type II, 69 women had type I and 44 had type II acromion in the control group. We did not determine type III acromion in any group. In males, type II acromion was significantly higher in the patient group compared to the control group (p=0.002). We did not find a significant difference between the patient and control groups in women.

When the effect of gender was evaluated, there was a significant difference between men and women in the control group in terms of AHD (p=0.04), CHD (p=0.00), CAA (p=0.01) and acromion types (p=0.01). There was no significant difference between the female and male patients in term of acromion type in the patient group (p>0.05).

Correlation analysis indicated moderately negative correlation between impingement syndrome and CHD (r=0.455) and AHD (r=0.590). There was also a moderate negative correlation between the age and CHD (r=0.320) and AHD (r=0.169). In addition, a moderately positive

Table 1. Measurement results of females in the patient and control groups

Female	Patient group (n=96)	Control group (n=113)	p
Age	55.1±12.4	47.4±10.5	0.001
Acromio-humeral distance (mm)	8.0±4.9	10.4±2.1	0.001
Coraco-humeral distance (mm)	8.1±7.4	9.8±2.3	0.031
Coraco-acromial angle (°)	122.9±13.5	123.6±6.9	0.637

Table 2. Measurement results of males in the patient and control groups

Male	Patient group (n=63)	Control group (n=88)	p
Age	52.4±14.3	40.2±13.5	0.001
Acromio-humeral distance (mm)	8.1±2.1	11.0±2.3	0.001
Coraco-humeral distance (mm)	8.7±2.5	10.9±2.6	0.001
Coraco-acromial angle (°)	124.4±5.7	126.2±6.8	0.083

correlation was found between impingement syndrome and age parameter (r=0.357).

In the intra-observer reliability analysis, there was a high correlation between both measurements in terms of CHD, AHD and CAA (r=0.860, 0.869 and 0.922, respectively) (Table 3).

Discussion

In the shoulder impingement syndrome, the subacromial space is contracted due to internal or external factors, and tendons are compressed in this interval during joint movements. Although the diagnosis of the syndrome is usually based on clinical findings, in most cases, radiological imaging methods are used for confirmation or to reveal the etiology. In order to diagnose impingement radiologically, the narrowing in AHD and CHD distances is considered. However, contraction of these distances is not always consistent with clinical symptoms and signs. Therefore, we thought that adding new anatomical data to existing radiological diagnostic criteria for the diagnosis of impingement might increase clinico-radiologic compliance.

In the current study, we investigated the contribution of the CAA to the diagnosis of impingement syndrome in addition to the distances between humeral head with coracoid process and acromion. According to our findings, AHD and CHD decreased significantly in impingement syndrome compared to the control group, in parallel to the literature (10,11). In contrast, CAA decreased slightly in impingement syndrome, but no significant difference was observed between the patient and the control groups.

In our study, AHD and CHD were measured at the shortest distance on the sagittal plane MRI. However, there is no clear consensus on the method of measuring CHD and AHD in the literature. Some researchers made their measurements from MR images in the sagittal plane, some in the coronal plane, some in axial or combined (10-14). In spite of this, in most of these studies, measurements were made at the level where these distances were the shortest. Unlike measuring in different planes, some researchers made measurements from different locations to evaluate the effect of the measurement site on diagnosis (12,14). Park et al. (12) measured AHD on three different points, as medial, lateral and central of the acromion, on the sagittal plane MRI of 56 male and 24 female patients with impingement. They stated that AHD measurements taken from the lateral and center of the acromion decreased in correlation with the impingement syndrome and that AHD measurements made from the medial of the acromion did not show a significant difference between the groups.

Table 3. Intra-observer reliability measurement results

	r	p
Acromio-humeral distance	0.922	0.001
Coraco-humeral distance	0.869	0.001
Coraco-acromial angle	0.860	0.001

Despite the high correlation between impingement syndrome and CHD-AHD, the unsatisfactory clinico-radiologic correlation leads researchers to different searches (15,16). We performed CAA measurements that we thought might be useful for diagnosis for this purpose, but we did not find a significant difference between the patient and control groups in terms of CAA measurements. Similar to our study, Cay et al. (15) measured AHD, CHD and CAA of 40 patients who underwent shoulder arthroscopy due to rotator cuff rupture and 28 healthy cases on the sagittal plane MRI. They stated that AHD, CHD and CAA were significantly decreased in patients compared to the control group. McGinley et al. (16) retrospectively evaluated the MRI of 89 impingement cases. In their study, they measured acromion angles on MRI in the coronal plane and divided the patients into two groups as those with an acromion angle higher and lower than 7.5°. They also compared the two groups by measuring the distance between coraco-acromial ligament and humeral head. As a result, they found that this distance was significantly shorter in the group with low acromion angle.

In our study, we also examined the relationship between acromion types and impingement syndrome. In male cases, a significant difference was observed between the patient and control groups in terms of acromion types, while we could not find any significant difference in women. We think that the reason for this was the absence of type III acromion in our study. This condition may also have contributed to the fact that females' AHD and CHDs are less than those of males. There are studies in the literature comparing acromion type with CHD or AHD in patients with impingement syndrome. Duymuş et al. (17) compared acromion types and AHD in 38 male and 62 female patients with impingement syndrome retrospectively. In their study, they classified the acromion into 4 groups according to their morphology (type I: flat, type II: parallel to the caput humerale; type III: hook-shaped; type IV: convex bottom surface). As a result, they found that there was no significant difference between acromion types and AHD

measurements in men, whereas AHD was shorter in type III acromion than in other types in female patients. Asal and Şahan (11) divided the coracoid process of 200 patients (87 males and 113 females) with subcoracoid impingement syndrome into three groups: type I flat, type II osteophytic and type III hooked. In their measurements on the MRI in the axial plane, they found that the CHD in the type III group was significantly shorter than in the type I group.

In accordance with the literature, we found that the mean age of both male and female patients was higher than that of the control group, due to aging-related ligamentous laxity and structures degenerative changes (decreased vascularity, etc.) in the subacromial space (12,17).

Our study showed that women in the control group had lower AHD, CHD and CAA values than men in the control group. But there was no significant difference between male and female patient groups in terms of AHD, CHD and CAA values. This condition may be attributed to the anatomical structure difference between men and women. Unlike our study, Duymuş et al. (17) examined 100 patients with impingement syndromes (38 men, 62 women) and found AHD to be shorter in women than in men.

Study Limitations

Our study has some limitations. The most important limitation was the lack of clinical examination data due to the retrospective nature of the study. Making the measurements by a single researcher can be considered as a limitation. However, the measurements of all cases were repeated after two weeks and a high correlation was found in the intra-observer reliability analyses. Another limitation may be the lack of etiological classification in the patient group, which may reveal different anatomical signs.

Conclusion

As a result, the findings in our study revealed a significant decrease in the CHD and AHDs in impingement syndrome, while there was no significant difference in the CAA values. However, studies with extended study groups and different measurement techniques are needed for a better understanding of impingement syndrome and etiological causes.

Ethics

Ethics Committee Approval: Approval was obtained from the University of Aydın Adnan Menderes Ethics Committee for non-interventional clinical trials within our institution (protocol no: 2019/175).

Informed Consent: Since it was designed retrospectively and only MRI images of the patients were evaluated, no "voluntary consent form" was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.E., Z.S.K., Design: E.E., Z.S.K., Data Collection or Processing: E.E., Z.S.K., Analysis or Interpretation: E.E., Z.S.K., Literature Search: E.E., Z.S.K., Writing: E.E., Z.S.K.

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ORIGINAL RESEARCH

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Comparison of the Effect of Different Anesthesia Maintenance on Hemodynamics in Coronary Artery Bypass Grafting Surgery: A Retrospective Cohort Study

Koroner Arter Baypas Greftleme Cerrahisinde Farklı Anestezi İdamesinin Hemodinami Üzerine Etkisinin Karşılaştırılması: Retrospektif Bir Kohort Çalışması

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Abstract

Objective: General anesthesia management in coronary artery bypass graft surgery (CABGC) should preserve myocardial function, prevent ischemic damage, and maintain stable hemodynamics. There is not a universally accepted technique for anesthetic management during CABGC. Drugs or drug combinations and maintenance of infusions are decided based on the pathophysiological condition of the patient and the individual preference and experience of the anesthesiologist (1). Although there are many studies about an anesthesia induction in CABGC, studies about anesthetic maintenance are very limited. In this study, we compared the hemodynamic effects of three different methods that were used in anesthetic maintenance in CABGC.

Method: The retrospective records of 108 patients in ASA II-III group who underwent elective CABGC were divided into 3 groups according to their anesthetic maintenance methods. Group I was maintained with 1-3% sevoflurane and fentanyl 4 mcg/kg/hour infusion, group II with propofol 1.5-4 mg/kg/hour and fentanyl 4 mcg/kg/hour infusion, and group III with propofol 1.5-4 mg/kg/hour and remifentanil infusion of 0.03 mg/

Öz

Amaç: Koroner arter baypas greft cerrahisinde (KABGC) genel anestezi yönetimi miyokard fonksiyonunu korumalı, iskemik hasarı önlemeli ve stabil hemodinamiyi sağlamalıdır. KABGC sırasında anestezi yönetimi için evrensel olarak kabul edilmiş olan tek bir teknik bulunmamaktadır. Kullanılan ilaçlar ve ilaç kombinasyonları, idame infüzyonları hastanın patofizyolojik durumu ile anesteziyoloji ve reanimasyon uzmanının bireysel tercihi ile deneyimine dayanır. KABGC'sinde anestezi indüksiyonu ile ilgili çok sayıda çalışma olsa da anestezi idamesi ile ilgili çalışmalar kısıtlıdır. Bu çalışmada, retrospektif olarak KABGC'sinde anestezi idamesinde kullanılmış 3 farklı yöntemin hemodinami üzerine etkileri karşılaştırıldı.

Yöntem: Elektif KABGC uygulanmış olan ASA II-III grubu 108 hastanın kayıtları anestezi idame yöntemlerine göre 3 gruba ayrılmıştır. Grup 1 %1-3 sevofluran ve fentanil 4 mcg/kg/saat infüzyonu, grup 2 propofol 1,5-4 mg/kg/saat ve fentanil 4 mcg/kg/saat infüzyonu, grup 3 propofol 1,5-4 mg/kg/saat ve remifentanil 0,03 mg/kg/saat infüzyonu ile idame edilmişti. İndüksiyon sonrası (T0), sternotomi sonrası (T1), perikardiyotomi sonrası (T2), CPB sonrası beşinci dakikada (T3), toraks kapatılırken (T4)

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Abstract

kg/hour. Systolic blood pressure, diastolic blood pressure, mean arterial pressure (MAP) and heart rate (HR) were measured and recorded after induction (T0), after sternotomy (T1), after pericardiotomy (T2), 5 minutes after cardiopulmonary bypass (CPB) (T3), after thorax closure (T4), at the end of the operation (T5). The vasodilator requirements in the time period before CBP and the inotropic agent requirements after CPB were noted.

Results: Data of 108 patients (88 men/20 women) were analyzed. Demographic characteristics of the patients were similar in all the groups. Statistical analysis was made among the groups depending on coronary artery bypass graft number, cross-clamp time, total fluid administration, total blood transfusion, total urine volume, inotropic agent requirement after CPB, postoperative central venous pressure, and pre- and postoperative lactate levels; however, there was no statistical difference. There was not change more than 20-25% in MAP and HR in group I than the others.

Conclusion: Better hemodynamic results were achived with sevoflurane and fentanyl in the anesthetic maintenance of CABGC.

Keywords: Cardiovascular anesthesia, hemodynamics, inhalation, intravenous

Öz

ve operasyon bitiminde (T5) olmak üzere sistolik kan basıncı (SKB), diyastolik kan basıncı, ortalama arter basıncı (OAB), kalp hızı (nabız) kaydedilmişti. Kardiyopulmoner baypas (KBP) öncesi dönemde kullanılan vazodilatatör ilaç ihtiyacı ile KPB sonrasında kullanılmış olan inotropik ajan miktarları hesaplandı.

Bulgular: Yüz sekiz hastadan (88 erkek/20 kadın) elde edilen veriler analiz edildi. Hastaların demografik özellikleri her üç grupta da benzerdi. Koroner arter baypas greft sayısı, kros klemp süresi, toplam sıvı, toplam kan transfüzyonu, toplam idrar hacmi, KPB sonrası inotropik ajan gereksinimi, ameliyat sonrası santral venöz basınç, ameliyat öncesi ve sonrası laktat ve laktat artışı açısından gruplar arasında istatistiksel olarak fark yoktu. Grup 1'de diğer gruplara göre, OAB ve nabızda %20-25'ten fazla değişiklik yoktu.

Sonuç: KABGC'de sevofluran ve fentanil ile anestezi idamesi daha stabil hemodinami sağladı.

Anahtar kelimeler: Hemodinami, inhalasyon, intravenöz, kardiyovasküler anestezi

Introduction

Purpose of coronary artery bypass graft surgery (CABGS) anesthesia is to provide hemodynamic stability in patients who do not have sufficient cardiac reserve (1). Coronary artery disease patients with limited cardiac reserves are highly sensitive to the factors that increase myocardial oxygen demand such as blood pressure increase, myocardial contractility, and systemic and pulmonary vascular resistance. These patients are also more vulnerable in events that reduce coronary perfusion, such as hypotension. These factors lead to increase in current ischemia with an increase in the incidence of perioperative myocardial infarction (MI) (2). Therefore, the selection of anesthetic agents is very important in anesthetic induction and maintenance.

There is no accepted technique for CABGS anesthesia. Preferred drug combinations and maintenance of drug infusions may vary depending on the pathophysiological condition of the patient and the personal experience and preference of the anesthesiologist (3,4). Although there are many studies on CABGS anesthesia induction, studies on anesthetic maintenance seem to be insufficient (2-4).

In our study, we compared the hemodynamic effects of different anesthesia maintenance methods from the records of patients who underwent anesthesia induction with the combination of opioids and benzodiazepines. Our aim is to determine the most stable hemodynamic anesthetic method during CABGS and to share its advantages over other methods with the readers.

Materials and Methods

As of the approval of the Ethics Committee (59491012-604.01.02), retrospectively 108 patients in the ASA II-III group, who underwent elective CABGS between September 2018 and September 2020, were included in our study. Exclusion criteria were recorded as emergency surgery, history of drug allergy, body mass index (BMI) >30 kg/m², presence of unregulated hypotension or hypertension, ejection fraction <25%, preoperative intraaortic balloon pump requirement, history of neurological or psychiatric disease, peripheral vascular disease, hepatic or renal dysfunction, presence of uncontrolled arrhythmia and heart valve surgery in addition to CABGS. The records of re-operation and development of serious postoperative complications (cardiac arrest, pulmonary embolism, pneumonia, sepsis, septic shock, need for postoperative intraaortic balloon pump, postoperative cerebral embolism) were determined as exclusion criteria as well.

Anesthesia procedure: Thirty minutes before starting the surgery, 1 mg of intravenous midazolam was administered each patient. Five-channel electrocardiography, peripheral oxygen saturation (SpO_2), and invasive arterial blood pressure monitoring were performed. Before anesthesia

induction, preoxygenation was performed with 100% oxygen for 3 minutes. Standard anesthesia induction was applied to all patients with midazolam 0.2 mg/kg, fentanyl 10 mcg/kg, and rocuronium 1 mg/kg. A central venous catheter was placed in the right internal jugular vein. A probe was placed in the esophagus for body temperature measurement. Anesthetic maintenance was provided with 1-3% sevoflurane and fentanyl 4 mcg/kg/hour infusion in group I, with propofol 1.5-4 mg/kg/hour and fentanyl 4 mcg/kg/hour infusion in group II, and with propofol 1.5-4 mg/kg/hour and remifentanil 0.03 mg/kg/hour in group III. All patients have routinely received rocuronium 10 mg/hour infusion. No inhalation anesthesia had been used in the patients in group II and III. Three hundred ml colloid was infused when the mean arterial pressure (MAP) fell below 70 mmHg and central venous pressure (CVP) was less than 12 mmHg in the pre-cardiopulmonary bypass (CPB) period. When the cause of hypotension did not require fluid infusion, dopamine infusion (3-8 mcq/kg/min) was started. Moderate hypothermia (28-32 °C) was applied to the patients during CPB. MAP was stabilized between 50 and 80 mmHg using vasopressors (norepinephrine) or vasodilators (nitroglycerin). The doses of anesthetic drugs were reduced in all groups during CBP (sevoflurane 1%, propofol 2 mg/kg/h, fentanyl 3 mcg/kg/hour, remifentanil 0.03 mg/kg/hour). The previous doses were resumed when the patient warmed up. In addition, intravenous dormicum 3 mg was administered to all patients during warming up. Inotropic support was provided so that the MAP was 70 mmHg at the weaning of CPB. Arterial blood gas analysis was evaluated at thirty-minute intervals during the operation. At the end of the operation, the patients were transferred to the intensive care unit (ICU).

Outcome measures: The demographic data of the patients (age, gender, BMI), the number of coronary bypasses, the duration of the cross-clamp period, the duration of CPB, the duration of the operation, the total amount of fluid administered during the surgery, bleeding, transfusion of blood and products, the CVP value at the beginning and the end of the operation and lactate levels in arterial blood gas were recorded. T0 (after induction of anesthesia), T1 (after sternotomy), T2 (after pericardiotomy), T3 (5^{th} minute after CPB), T4 (after thorax closure), and T5 (at the end of the operation) were six moments that systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, heart rate (HR) were recorded. The need for vasodilators before CBP and the number of inotropic agents used after CPB were recorded as well.

Statistical Analysis

SPSS v21.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Normality was assessed by using the Shapiro-Wilk test and descriptive statistics. Continuous variables were presented as mean ± standard deviation or median (minimum-maximum), and categorical variables were presented as frequency and percentage. The chi-square test or Fisher Exact test was used to analyze categorical variables. Comparison of continuous variables was performed by using one-way Mann-Whitney U test or Kruskal-Wallis test, where appropriate. A p-value <0.05 was accepted for statistical significance.

Results

Data of 108 patients (88 men/20 women) were analyzed. Demographic characteristics of the patients were similar in all three groups. There was no statistical difference between the groups in terms of number of CABG, cross clamp duration, total fluid, total blood transfusion, total urine volume, inotropic agent requirement after CPB, CVP after operation, lactate before and after operation and increase in lactate. The mean operative duration of group I, II, and III were 6±1, 6±1 and 5±1, respectively. The mean operation duration of group I was significantly lower than that of the other groups (p=0.001). The CPB duration was also significantly lower in group III (p=0.001). The mean total blood loss of group III was 1.293±475 and significantly more than the other groups (p<0.001). Inotropic requirement before CPB was different among groups (p=0.021). Increase in CVP was higher (32%±42%) in group II (p=0.008) (Table 1).

The systolic arterial pressure, diastolic arterial pressure, MAP and HR of the groups were compared every mentioned moment (T0-T5). The HR of group III was lower than that of group II in T4 and both groups in T5 (p=0.013, p<0.001, respectively). SBP was different at all times except T4 (p=0.221). SBP of group III was higher than group II in T0 and T2 and both groups in T3 but lower than group I in T5 (p=0.003, p=0.011, p=0.030, respectively). SBP in T1 was significant but there was no statistical significance in pair wise comparisons. DBP was different in T3-T5 among groups. DBP of group II was lower than that of group III in T3 and both groups in T4 and T5 (p=0.015, p=0.003, p<0.001, respectively). The MAP was different at all times except T1 and T2. MAP of group III was higher than that of group II in T0 and T3 (p=0.024, p=0.006, respectively). MAP of group II was lower than that of group I in T4 and both groups in T5 (p=0.031, p=0.009, respectively) (Table 2).

Discussion

There is no universally accepted anesthetic method for cardiac surgery, and differences can be observed even among doctors in the same clinic (1). Anesthetic management is preferred according to the degree of ventricular dysfunction, accompanying diseases and physiological and pharmacological effects of drugs on the particular patient (2,3). In every stage of cardiac surgery, the depth of anesthesia should be adjusted according to the level of surgical stress. At the same time, systemic hypotension should be prevented, adequate intravascular volume should be provided, the continuity of sinus rhythm and the protection of myocardial oxygen demand balance should be aimed (4). Recent literature has referred that inhalational anesthesia technique might be associated with lower mortality (5). The American College of Cardiology/ American Heart Association Guidelines recommends that inhalational anesthesia is superior than Total Intra Venous Anesthesia (TIVA) in CABGS (6).

In this study, nitroglycerin requirement before CBP was more in group III than the others. Nitroglycerin improves coronary arterial blood flow intraoperatively (7) and its use for prophylaxis is very common in high risk patients to reduce the incidence of perioperative MI (8). On the other hand, there is no evidence from randomized controlled trials (RCTs) (9). Before CBP, the mean MAP values were higher in group III than the others. Remifentanil reduces blood pressure and provides stable hemodynamics, it is used in combination with propofol in cardiac surgery (10); however, these effects

Table 1. Demographic data and clinical parameters of the groups

	Group I (n=35)	Group II (n=36)	Group III (n=37)	p
Age (years)	63 (39-82)	60 (40-72)	60 (38-81)	0.334[a]
Gender (male)	28 (80)	33 (92)	27 (73)	0.116[b]
Weight (kg)	79±10	80±15	78±11	0.777[c]
Height (cm)	167±7	170±7	168±7	0.495[c]
BMI (kg/m^2)	27.8±4.1	27.4±3.9	27.6±4	0.948[c]
Number of CABG	3±1	3±1	3±1	0.153[a]
Duration of operation (hour)	6±1	6±1	5±1	**0.001**[a,III]
Cross clamp duration (min)	80±27	81±27	69±21	0.088[a]
CPB duration (min)	118±35	116±30	94±24	**0.001**[c,III]
Total fluid (mL)	2.176±603	2097±591	1.939±360	0.135[a]
Total blood transfusion (mL)	891±397	765±249	895±347	0.326[a]
Total blood loss (mL)	771±258	712±402	1.293±475	**<0.001**[a,III]
Total urine volume (mL)	1.448±495	1.550±567	1.305±621	0.083[a]
Vasodilatator agent requirement before CPB				**0.021**[d]
No requirement	17 (49)	17 (47)	10 (27)	-
Nitroglycerin	15 (43)	19 (53)	27 (73)	-
Inotropic agent requirement after CPB				0.943[d]
No requirement	4 (11)	6 (17)	7 (19)	-
1 (dopamine)	25 (71)	25 (69)	24 (65)	-
2 (dopamine + adrenaline)	6 (17)	5 (14)	5 (14)	-
3 (dopamine + adrenaline + dobutamine)	0	0	1 (3)	-
CVP before CPB (mmHg)	11±3.7	9±3.3	11±3.5	**0.041**[a,ϕ]
CVP after CPB (mmHg)	11±1.9	11±2.2	11±1.5	0.740[c]
Increase in CVP (%)	11±39	32±42	7±31	**0.008**[c,II]
Lactate before operation	1.2±0.5	1.1±0.5	1±0.4	0.212[c]
Lactate after operation	2.8±1.8	2.6±1.5	2.1±1	0.203[c]
Increase in lactate (%)	147±123	149±142	123±86	0.882[c]

BMI: Body mass index, CABG: Coronary artery bypass graft, CPB: Cardiopulmonary bypass, CVP: Central venous pressure, [a]: One-Way ANOVA test, [b]: Chi-square test, [c]: Kruskal-Wallis test, [d]: Fisher's Exact test, [ϕ]: No statistical significance in pairwise comparisons, [II]: P-value is significantly different in group II, [III]: P-value is significantly different in group III

are dose-depended (11). The first limitation of our study was not able to monitorize the depth of anesthesia with bispectral index (BIS). Our findings may be related to inadequate level of anesthesia in group III. Conversely, Lehmann et al. (12) declared that the different levels of BIS values had no influence on hemodynamics or the need of catecholamines in the pre-CPB period. Yet, MAP was also higher in group III than in group II. Kapoor et al. (13) also reported that their patients in the TIVA group had higher MAPs on weaning off CPB and lower inotropic support.

MAP was lower in group II than in group I. The reason for the low MAP values especially after CBP in our patients who underwent TIVA with propofol and fentanyl, in intravascular volume loss of propofol, it may be secondary to venodilation with dose-dependent hypotension effect (14,15). Hypotension associated with propofol is also related to the increase in systemic vascular resistance. 2 mg/kg propofol administered into the venous line during CPB reduces SVR. In addition, propofol increases arterial compliance and decreases afterload (16).

While shorter durations were found with remifentanil in early extubation studies, it was also observed that it might cause bradycardia. In CABGS with remifentanil, the hemodynamic response to skin incision and sternotomy occurs with lower HRs (17). Even though remifentanil is used instead of fentanyl during perioperative period, some authors argue that it may not be suitable for hemodynamically unstable patients (18).

Although we did not have the power to detect a serious hemodynamic difference due to the low number of patients in the groups, which is one of the other limitations of our study, we observed that more stable hemodynamics were achieved in patients who used sevoflurane and fentanyl, among the three different methods we used in CABGS, for anesthesia maintenance, especially in the post-CPB period. However, we found that the other two groups did not have serious negative effects on hemodynamics. It is observed that hemodynamic stability does not change more than 20-25% in MAP and HR (19). In classical literature knowledge, inhalational anesthesia was better than intravenous anesthesia in the CABG (20-22). Straarup et al. (23) declared that inhalational anesthesia should be the first option comparing TIVA in CABGS. Ren et al. (24) meta-analyzed that TIVA and inhalational anesthesia had similar results on cardioprotection, renal injury, complications (pulmonary, neurological, postoperative

Table 2. Blood pressure and HR data of the patients

	T0	T1	T2	T3	T4	T5
SAP (mmHg)						
Group I	123±19	133±17	108±14	101±21	110±13	107±10
Group II	119±19	125±15	105±11	105±12	105±10	102±7
Group III	133±17	124±17	114±14	114±15	106±17	99±13
P-value	**0.003$^{a,I-III}$**	**0.031$^{\phi}$**	**0.011^{II-III}**	**0.001^{III}**	0.221	**0.030^{I-III}**
DAP (mmHg)						
Group I	67±12	71±13	64±9	58±7	60±7	57±7
Group II	64±14	72±12	64±12	56±8	55±7	53±5
Group III	69±9	67±10	66±10	60±8	62±13	60±8
P-value	0.098	0.228^{a}	0.520	**0.015^{II-III}**	**0.003^{II}**	**<0.001^{II}**
MAP (mmHg)						
Group I	86±14	92±13	79±10	73±9	77±8	74±7
Group II	82±15	90±12	78±11	72±8	72±6	69±4
Group III	90±10	86±10	82±9	78±9	77±11	73±8
P-value	**0.024$^{a,II-III}$**	0.141	0.155^{a}	0.006^{II-III}	0.031^{I-II}	0.009^{II}
HR (bpm)						
Group I	80±15	78±12	75±9	88±14	90±11	90±10
Group II	76±13	78±13	76±14	89±11	93±10	94±9
Group III	77±13	75±12	74±10	85±11	85±15	81±13
P-value	0.602	0.478^{a}	0.638^{a}	0.239	**0.013^{II-III}**	**<0.001^{III}**

SAP: Systolic arterial pressure, DAP: Diastolic arterial pressure, MAP: Mean arterial pressure, HR: Heart rate, ^{a}: One-Way ANOVA test, $^{\phi}$:No statistical significance in pairwise comparisons, ^{II}: P-value is significantly different in group II, ^{III}: P-value is significantly different in group III

bleeding, mechanical ventilation support), ICU and hospital stay and mortality. Moreover, inhalational agents have a cerebral vasodilatory effect, and as sevoflurane is a cerebroprotective during CBP. It decreases cerebral metabolic rate (25). Inhalational anesthetics also induce myocardial protection from ischemia reperfusion injury (26).

Conclusion

The use of sevoflurane inhalation and fentanyl infusion was superior to TIVA for CABGS anesthesia maintenance in our study. For clarifying this issue, further high-quality large RCTs are still needed.

Ethics

Ethics Committee Approval: As of the approval of the Ethics Committee (59491012-604.01.02), retrospectively 108 patients in the ASA II-III group, who underwent elective CABGS between September 2018 and September 2020, were included in our study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.Y.A., Y.Ö., M.A.Y., Z.S., Design: H.Y.A., M.Y., İ.H., Data Collection or Processing: H.Y.A., M.Y., Z.S., M.A.Y., Analysis or Interpretation: H.Y.A., Z.S., Y.Ö., İ.H., Literature Search: H.Y.A., K.E., Y.Ö., Writing: H.Y.A., M.Y., K.E., M.A.Y., Manuscript Review and Revisation: H.Y.A, K.E., İ.H.

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ORIGINAL RESEARCH

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The Effect of Vitamin D Deficiency on Vital Parameters in Myofascial Pain Syndrome

Miyofasiyal Ağrı Sendromunda D Vitamini Eksikliğinin Yaşamsal Parametreler Üzerindeki Etkisi

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Abstract

Objective: It is known that in vitamin D deficiency, people suffer extensive musculoskeletal pain. In this study, the relationship between vitamin D deficiency and myofascial pain syndrome (MPS) and the effect of vitamin D on pain, disability, quality of life, sleep and psychological condition were examined.

Method: In this study, 180 cases were examined. Of the cases, 120 were patients, and 60 were in the control group. The cases were compared in terms of 25(OH)D level and quality of life. The patients were also divided into two subgroups based on their 25(OH)D levels. Their scores on the visual pain scale, the neck pain and disability scale, the short form-36 (SF-36) quality of life index, Pittsburgh sleep quality index, Beck anxiety inventory and Beck depression inventory, which were tested for validity and reliability in Turkish, were recorded.

Results: The average 25(OH)D level of the patient group was 12.8±7.3 ng/mL, while that of the control group was 22.8±14.3 ng/mL, and there was a significant difference. Physical parameters of SF-36 quality of life index were higher in the control group than in the patient group. In the patient group with a deficiency in 25(OH)D levels, depression and anxiety levels were significantly higher and the mental parameters of the SF-36 quality of life index were significantly lower.

Conclusion: In our study, 25(OH)D levels were significantly lower in the patients diagnosed with MPS compared to the healthy people in the control group, and vitamin D deficiency was shown to have a negative effect on mental functions and mood.

Keywords: Mood, myofascial pain syndrome, quality of life, quality of sleep, 25(OH)D

Öz

Amaç: D vitamini eksikliğinde yaygın kas iskelet ağrısı olduğu bilinmektedir. Bu çalışmada D vitamini eksikliği ile myofasiyal ağrı sendromu (MAS) arasındaki ilişki ve D vitamininin ağrı, özürlülük, yaşam kalitesi, uyku ve psikolojik durum üzerindeki etkisi değerlendirilmiştir.

Yöntem: Çalışmada 120'si hasta ve 60'ı kontrol olmak üzere 180 olgu değerlendirildi. Olgular 25(OH)D düzeyi ve yaşam kalitesi yönünden karşılaştırıldı. Aynı zamanda hastalar 25(OH)D düzeyine göre iki alt gruba ayrılarak, vizuel ağrı skalası, Türkçe geçerlilik ve güvenilirlik çalışmaları yapılmış boyun ağrısı ve özür göstergesi, kısa form-36 (SF-36) yaşam kalitesi kısa formu, Pittsburgh uyku kalitesi indeksi, Beck anksiyete ölçeği ve Beck depresyon ölçeği skorları kaydedildi.

Bulgular: Hasta grubun 25(OH)D düzeyi 12,8±7,3 ng/mL iken kontrol grubunun 22,8±14,3 ng/mL olup, anlamlı farklılık vardı. Kontrollerde SF-36 yaşam kalitesi indeksinin fiziksel parametreleri hasta grubuna göre yüksek düzeyde idi. Hastaların 25(OH)D düzeyine göre eksikliği olan grupta depresyon ve anksiyete düzeyleri anlamlı daha yüksek ve SF-36 yaşam kalitesi indeksinin mental parametreleri anlamlı düşük idi.

Sonuç: Çalışmamızda MAS tanılı hastalarda sağlıklı kontrollere göre 25(OH)D düzeyi anlamlı düşük saptanmıştır ve D vitamini eksikliğinin mental fonksiyonlar ve duygu durumu üzerinde olumsuz etki oluşturduğu gösterilmiştir.

Anahtar kelimeler: Duygu durumu, miyofasiyal ağrı sendromu, uyku kalitesi, yaşam kalitesi, 25(OH)D

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Introduction

Myofascial pain syndrome (MPS) is a clinical picture characterized by pain, muscle spasms, stiffness, limitation of movement, weakness and sometimes autonomic disorder characterized by myofascial trigger points in taut bands formed in skeletal muscles and fascia (1,2). The frequency of the disease in the society is 12%, and its frequency in the patient population presenting to clinics due to pain is 30-31% (1,2). Because there is not any specific laboratory test or imaging method for MPS, the diagnosis is made through anamnesis and physical examination. The primary symptom in patients is pain. At the trigger point in the taut band in the affected muscle, the pain reflected in the particular area related to that muscle is felt. However, autonomic findings such as abnormal sweating, increase in body secretions and redness in the skin may also occur in addition to symptoms such as contraction, hypersensitivity, stiffness, limitation of movement, weakness, headache, dizziness, depression and sleep disorders (1-3).

Vitamin D is one of the most important physiological regulators of calcium (Ca), phosphorus (P) and bone metabolism (4). Its deficiency can have negative consequences on many organs and systems, especially on bone metabolism. It causes an increase in balance disorder and fall risk by creating myopathy, which is pronounced in the proximal muscles of the musculoskeletal system (5).

Our aim in this study was to examine the relationship between vitamin D deficiency and MPS and to examine the effect of vitamin D deficiency on clinical parameters such as pain, disability, quality of life, sleep and mood.

Materials and Methods

Our study began after the approval of the Local Ethics Committee. The study included 120 patients (95 females and 25 males) presenting to our Physical Therapy Outpatient Clinic between June 2015 and January 2017, who were diagnosed with MPS and whose 25(OH)D levels were checked, and 60 healthy cases (47 females and 13 males) as the control group. Healthy controls were selected from hospital staff.

Medical records of the patients were examined retrospectively. The group of people with MPS was examined separately in itself as 2 subgroups depending on their levels of 25(OH)D. The 2011 Endocrine Guideline Report identified 25(OH)D levels less than 20 ng/mL as deficiency, between 20 and 29 ng/mL as insufficiency and between 30 and 100 ng/mL as sufficiency (6). In our study, any value less than 20 ng/mL was accepted to be a deficiency.

Patients aged between 18 and 65 years, who were diagnosed with MPS based on the criteria defined by Travel and Simons, and who had at least one trigger point and/or a taut band in at least one of the neck and back muscles accompanying neck and/or back pain, were included in the study, and healthy subjects without any complaints of pain were included as the control group (2). Patients who had been diagnosed with fibromyalgia syndrome (FMS), who had any systemic disease (neurological disorders, chronic kidney, heart or liver diseases, or rheumatological diseases), who had distinct cervical disc lesions, cervical radiculopathy or myelopathy, who had undergone neck or shoulder surgery within the past year, who were pregnant, who would not cooperate, who had cognitive dysfunction, and those who used drugs or had any diseases affecting their 25(OH)D level were excluded from the study.

The patients' ages, genders, body mass indices (BMIs), sunbathing levels, clothing styles, pain durations, 25(OH) D, Ca and parathormone (PTH) levels, and their scores on the visual pain scale (VAS), neck pain and disability scale (NPDS), short form quality of life (SF-36), Pittsburgh sleep quality index (PSQI), Beck anxiety inventory (BAI) and Beck depression inventory (BDI), which were tested for validity and reliability in Turkish, were recorded (7-12). 25(OH)D, Ca, PTH and sunbathing levels and clothing styles of the healthy volunteers who did not have any complaints of pain and their scores on the short form-36 (SF-36) quality of life were recorded for the control group.

Visual Analog Scale (VAS)

Visual analog scale is used to evaluate the severity of pain. The severity of pain is scored between 0 and 10. 0 shows no pain, 1-3 mild, 4-7 moderate, 8-10 severe pain, and 10 points indicate intolerable pain (7).

Neck Pain and Disability Scale (NPDS)

Neck Pain and Disability scale is used to evaluate neck pain and disability. It consists of 20 items and each item is scored from 0 to 5. Summing of 20 item points gives the total score. The higher scores indicate elevated severity of pain and disability (8).

Short form-36 (SF-36)

SF-36 is used to appraise the quality of life. It contains 36 health-related items and assesses eight dimensions of physical and mental health. Eight dimensions are physical

functioning (PF), physical role (RP), vitality (VT), general health (GH), bodily pain (BP), emotional role (RE), social functioning (SF), mental health (MH), mental component summary (MCS), physical component summary (PCS). The score of each domain is 0 and 100 and high scores indicate greater health status. SF-36 was tested and proven to be a valid evaluation tool of health quality in Turkey (9).

Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a 19-item, self-reported, questionnaire-based assessment of sleep patterns to measure subjective sleep quality. It has been widely used by various researchers to monitor and evaluate insomnia among patients. The contents of the PSQI include subjective sleep duration, sleep quality, sleep latency, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction. Total score ranges from 0 to 21 and scores above 5 indicate poor sleep quality (10).

Beck Anxiety Inventory (BAI)

BAI is used to evaluate anxiety severity. It includes 21 questions that are scored from 0 to 3. The total score ranges from 0 to 63. High scores indicate a high severity of anxiety (11).

Beck Depression Inventory (BDI)

BDI consists of 21 questions, with each question scored between 0 and 3. Total score range between 0 and 63. High scores indicate a high severity of depression (12).

Statistical Analysis

The behavior of quantitative variables was expressed using centralization and variance measures: Mean ± standard deviation. To show the behavioral differences of group averages, the ANOVA t-test was used when normality and uniformity assumptions were met, and the Mann-Whitney U test (number of groups=2) non-parametric method was used when not. Statistical significance was determined as p=0.05 for all cases. Statistical analysis was provided by IBM SPSS (Statistics Package for Social Sciences for Windows, Version 21.0, Armonk, NY, IBM Corp.) package program.

Results

There was no significant difference between the groups in terms of sunbathing levels, clothing styles and demographic data in the study. The duration of pain was 8.53 months on average. The average 25(OH)D level of the patient group was 12.8±7.3 ng/mL, while that of the control group was 22.8±14.3 ng/mL, and a significant difference was found (p<0.001). Besides that, there was no significant difference between Ca and PTH levels.

Statistically significant differences were found between the patient group and the control group in the RP, BP and PCS parameters based on the SF-36 quality of life index parameters (p<0.05) (Table 1). Based on NPDS, 88.3% of the patients in the patient group had varying degrees of disability due to neck pain, and 14.2% of them had severe pain. Moreover, 57.5% of the patients had anxiety, 40.8% had depression, and 80.8% had sleep disorders.

In the analysis of subgroups conducted according to the 25(OH)D levels of the patient group, no statistically significant difference was found in terms of pain duration, VAS score, and NPDS and PSQI parameters (p<0.05). However, BAI and BDI scores were significantly higher in the group with vitamin D deficiency (p<0.05) (Table 2).

Significant differences were found in the parameters of GH, SF, MH and MCS in the comparison made according to SF-36 quality of life index parameters (p<0.05) (Table 3).

The correlation analysis showed that among the patients with MPS, 25(OH)D levels were negatively correlated with their scores on VAS (r=-0.155, p=0.091), NPDS (r=-0.026, p=0.780), BAI (r=-0.200, p=0.028), BDI (r=-0.219, p=0.016), PSQI (r=-0.139, p=0.129) and BMI (r=-0.047, p=0.528), and positively correlated with their scores on SF-36 quality of life index PCS (r=0.141, p=0.059) and MCS (r=0.088,

Table 1. Comparison of the MPS and control groups by SF-36 parameters

	MPS (n=120)	Control (n=60)	p
PF	69.5±22.0	74.5±22.8	0.089
RP	49.1±41.4*	67.5±36.0*	0.004*
BP	51.0±20.0**	65.9±22.1**	<0.001**
GH	59.2±18.6	59.8±17.0	0.933
VT	50.0±20.6	50.6±17.4	0.919
SF	64.9±24.2	68.7±25.7	0.272
MH	54.2±39.5	59.7±39.6	0.384
RE	65.7±16.4	68.3±13.3	0.423
PCS	60.4±19.0*	66.9±17.9*	0.002*
MCS	59.7±19.1	61.8±18.2	0.341

*Statistically significant at the p<0.05 level, **Statistically significant at the p<0.001 level.

MPS: Myofascial pain syndrome, SF-36: Short form-36, PF: Physical functioning, RP: Physical role, BP: Bodily pain, GH: General health, VT: Vitality, SF: Social functioning, MH: Mental health, RE: Emotional role, PCS: Physical component summary, MCS: Mental component summary

Table 2. Comparison of demographic and clinical parameters of MPS patients based on 25(OH)D levels

	25(OH)D <20ng/mL (98)	25(OH)D ≥20ng/mL (22)	p
25(OH)D	10.08±4.69**	24.93±4.06**	<0.001**
Duration	8.36±8.37	9.64±8.37	0.381
	Median (minimum-maximum)		**p**
BAI	11 (0-44)*	6.5 (0-22)*	0.019*
BDI	7.5 (0-41)*	3.5 (0-16)*	0.035*
NPDI	48 (6-91)*	48 (18-84)*	0.943
PSQI total	7 (0-17)	5.5 (2-15)	0.089
VAS	6 (1-10)	5 (3 10)	0.225
Age	36.5 (18-58)	43.5 (21-57)	0.158

*Statistically significant at the p<0.05 level, **Statistically significant at the p<0.001 level.

MPS: Myofascial pain syndrome, BAI: Beck anxiety inventory, BDI: Beck depression inventory, NPDI: Neck Pain and Disability index, PSQI: Pittsburgh sleep quality index, VAS: Visual pain scale

Table 3. Comparison of MPS1 and MPS2 groups by SF-36 parameters

	MPS1 (n=98)	MPS2 (n=22)	p
PF	69.4±22.0	70.0±22.5	0.935
RP	47.4±41.1	56.8±43.0	0.284
BP	49.9±19.9	55.9±20.0	0.253
GH	57.7±17.9*	66.2±20.4*	0.024*
VT	49.6±21.0	52.0±19.0	0.641
SF	62.9±24.3*	73.7±22.1*	0.044*
MH	50.4±38.9*	71.0±38.9*	0.026*
RE	65.4±17.4	66.9±11.0	0.911
PCS	56.1±18.6	62.2±19.1	0.086
MCS	57.1±19.8*	65.9±16.8*	0.033*

*Statistically significant at the p<0.05 level, **Statistically significant at the p<0.001 level.

MPS: Myofascial pain syndrome, SF-36: Short form-36, PF: Physical functioning, RP: Physical role, BP: Bodily pain, GH: General health, VT: Vitality, SF: Social functioning, MH: Mental health, RE: Emotional role, PCS: Physical component summary, MCS: Mental component summary

p=0.240). Based on the correlation analysis, 25(OH)D levels were found to have a significant correlation with BAI and BDI (p<0.05).

Discussion

In our study, we examined the relationship between MPS and vitamin D. The average 25(OH)D level of the patient group was 12.8±7.3 ng/mL, while that of the control group was 22.8±14.3 ng/mL. There was a statistically significant difference between the patient and control groups. In the analysis of subgroups conducted according to the 25(OH) D levels of the patient group, BAI and BDI scores were significantly higher in the group with vitamin D deficiency. Finally, significant differences were found in the parameters of GH, SF, MH and MCS in the comparison made according to SF-36 quality of life index parameters.

As with many tissues and cells, musculoskeletal tissues have vitamin D receptors (13). In vitamin D deficiency, a clinical picture called vitamin D myopathy is observed, which is mostly characterized by proximal muscle weakness and neuromuscular coordination disorder, and causes the risk of imbalance, frequent falls and increased fractures in the affected elderly, difficulty in standing up and walking in affected children (14,15). Moreover, non-specific musculoskeletal pain, chronic widespread pain, and lower back pain can also be seen in vitamin D deficiency (15,16). Gerwin (17) have reported that low levels of vitamin D cause persistent FMS and MPS and recommended that vitamin D levels be checked in chronic FMS and MPS patients. Plotnikkof and Quigley (5) found vitamin D deficiency in 93% of patients with chronic non-specific pain, severe hypovitaminosis D in 28% of patients (≤8 ng/mL) and vitamin D levels below the detectable level in 5 patients, and they reported that the widespread pain felt by these patients could be caused by low levels of vitamin D. A significant relationship was found also in our study between vitamin D deficiency and MPS development. The average 25(OH)D level of the patient group was 12.8±7.3 ng/mL, while that of the control group was found to be 22.8±14.3 ng/mL. A significant difference was found between the 25(OH)D levels of both groups according to the results of the statistical analyses (p<0.001).

There are studies showing the chronic pain and vitamin D relationship (18,19). Yener (20) examined the FMS and vitamin D relationship, and Canpolat Erkan (21) examined the soft tissue rheumatism and vitamin D relationship. In both studies, significant differences were found between the control group and patient groups in terms of VAS. However, there was no significant difference between VAS scores in subgroup analyses depending on low and high vitamin D levels. Similarly, our study showed no difference between VAS and the NPDS scores in subgroup analyses based on vitamin D levels in patients with MPS (p>0.005).

Evidence has been found in recent years that the central pain mechanism plays a role in MPS (22). Similarly, there is evidence that vitamin D affects the brain and nervous system (23-25). Armstrong et al. (26) reported

that patients with vitamin D deficiency and insufficiency had higher levels of anxiety and depression than those in control groups. A study in healthy volunteers found that vitamin D improved the positive effect and reduced the negative effect during the winter months (27). Berk et al. (28) reported vitamin D deficiency in patients with FMS as being associated with anxiety and depression. Our study also showed that in line with the literature, vitamin D statistically significantly correlated negatively with anxiety and depression in our patient group (BAI: r=-0.20, p=0.028 and BDI: r=-0.219, p=0.016). Additionally, in subgroup analyses based on vitamin D levels, depression and anxiety scores were significantly higher in the group with vitamin D deficiency (p=0.035, p=0.019, respectively). In light of these results, it should be borne in mind that deficiency of vitamin D may also be a significant factor in changes in mood that is seen in patients with MPS and has been linked mainly to chronic pain to date.

Soft tissue rheumatism in relation to chronic pain may bring about changes in quality of life. Sahin et al. (29) examined SF-36 parameters in patients with MPS and found that RP, BP and VT scores were significantly lower. Irnich et al. (30) found a decrease in RP and BP parameters in patients with chronic neck pain. In our study, the SF-36 quality index physical scores of the patient group with MPS (RP, p=0.004; BP, p=0.000; and PCS, p=0.002) were significantly lower than those of the control group. Besides that, vitamin D deficiency along with MPS can have negative consequences on quality of life (31,32). Feng et al. (31) conducted a study on 686 patients between the ages of 60 and 89 years. They showed that PF, RP, BP and GH scores decreased gradually with the decrease of vitamin D in their grouping according to vitamin D levels. In addition, they showed that the group with vitamin D deficiency scored worse on SF, VT and MH, which are some of the mental health-related parameters, compared to the group with sufficient vitamin D. Similarly, in subgroup analyses, we found that SF (p=0.044), MH (p=0.026) and MCS (p=0.033) scores, which are some of the mental parameters, and GH (p=0.024) scores, which are a physical parameter, were significantly lower in the group with low vitamin D (p<0.05). These results support that vitamin D deficiency impairs the quality of life by causing deterioration in MH in patients with chronic muscle pain, as well as aggravating anxiety and depression.

Conclusion

Vitamin D deficiency was found to be more common in MPS patients compared to the normal population. And this was found to have a significant effect on depression and anxiety and negatively alter the quality of life, especially by influencing cognitive functions.

Ethics

Ethics Committee Approval: This study was approved by the Ethical Committee Faculty of Medicine Namık Kemal University (date: 25.05.20I7, number: 2017154105/03).

Informed Consent: Consent was obtained from the volunteers.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: İ.C., A.B.S., Design: İ.C., A.B.S., Data Collection or Processing: İ.C., A.Y.G., Analysis or Interpretation: İ.C., A.Y.G., Literature Search: İ.C., A.B.S., Writing: İ.C., Manuscript review and revisation: A.B.S., A.Y.G.

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ORIGINAL RESEARCH

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Evaluation of the Morphometric Measurements of Main Mediastinal Vascular Structures with Multi-detector Computed Tomography in Healthy Children

Sağlıklı Çocuklarda Mediastinal Ana Vasküler Yapıların Multi-dedektör Bilgisayarlı Tomografi ile Değerlendirilmesi

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Abstract

Objective: In this study, we aimed to evaluate the feasibility of the main pulmonary artery (MPA)/ascending aorta (AA) ratio measurement, which is 1:1 in adults, using the multi-detector computed tomographt in pediatric patients also.

Method: The study was approved by the Institutional Review Board (number: 09.2016.014, approval date: 08.01.2016) and informed consent was waived since the study was retrospective. IV contrast-enhanced pulmonary computed tomography images of 487 pediatric patients (0-18 years), which had been performed between January 2015 and February 2016 in our center, were retrospectively evaluated. The diameters of the AA, MPA, right and left pulmonary arteries, and thoracic aorta were measured separately.

Results: A positive correlation was determined between the diameters of mediastinal vascular structures and the patient age. The MPA/AA ratio was higher in the pediatric group when compared to adults, and this ratio was found to be higher than 1 in all pediatric cases.

Conclusion: The higher diameter of MPA when compared to AA in pediatric cases is thought to be responsible for MPA/AA ratio being greater than 1, and that should not be considered as pulmonary hypertension. We suggest a threshold of 1.06 for the MPA/AA ratio regarding the diagnosis of PH.

Keywords: Aorta, child, hypertension, pulmonary artery, tomography

Öz

Amaç: Çalışmada multi-dedektör bilgisayarlı tomografi kullanarak, erişkin yaş grubunda 1:1 olan ana pulmoner arter (APA)/asendan aorta (AA) oranının pediyatrik yaş grubunda uygulanabiliyor olup olmadığını araştırmayı amaçladık.

Yöntem: Çalışma için, Klinik Araştırmalar Etik Kurulu tarafından 08.01.2016 tarihinde 09.2016.014 sayılı yazı ile onay verilmiştir. Ocak 2015 ile Şubat 2016 tarihleri arasında hastanemize başvuran ve kontrastlı akciğer bilgisayarlı tomografisi çekilen pediyatrik yaş grubundan (0-18 yaş) 487 olgunun görüntüleri retrospektif olarak değerlendirilmiştir. AA, APA, sağ pulmoner arter, sol pulmoner arter, torasik aorta ve torasik vertebra çapları ayrı ayrı ölçülmüştür.

Bulgular: Ölçülen mediastinal vasküler yapı çapları ve hasta yaşı arasında pozitif korelasyonun varlığı tespit edilmiştir. APA/AA oranının, pediyatrik yaş grubunda erişkin yaş grubuna göre anlamlı olarak yüksek olduğu tespit edilmiştir. Çalışmamızda bu oran tüm pediyatrik yaş grupları arasında 1'in üzerinde bulunmuştur.

Sonuç: Pediyatrik yaş grubunda APA'nın AA çapından daha geniş olması nedeniyle APA/AA oranının 1'in üzerinde olan tüm olgularda pulmoner hipertansiyon ön tanısında bulunulmamalıdır. Bu oranın eşik değerinin 1,06 olarak kabul edilebileceğini önermekteyiz.

Anahtar kelimeler: Aorta, çocuk, hipertansiyon, pulmoner arter, tomografi

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Introduction

Pulmonary hypertension (PH) is a rare disorder with significant morbidity and mortality rates in newborns, infants, and children. In most of the pediatric patients, PH is either idiopathic or associated with congenital heart disease; rarely, it may be associated with other conditions such as connective tissue diseases and thromboembolic disorders (1).

Multi-detector computed tomography (MDCT) has been increasingly used for the evaluation of congenital and postoperative cardiac disorders in the pediatric age group. When the radiation dose used is particularly taken into consideration, obtaining most of the information through diagnostic screening as far as possible is important regarding patient care. The complete assessment of all structures observed on tomography carries critical importance whether they are related to the clinical indication or not. For example, the diameters of the mediastinal vascular structures (MVS) observed on computed tomography (CT) should be a part of the routine evaluation of the cardiomediastinal structures. The measurement and determination of these main vessels on MDCT have a high degree of reconciliation among different independent observers. Moreover, the measurements obtained through right heart catheterization, which is considered as the reference for the assessment of the pulmonary arterial tree, show a good correlation with the diameters of the vascular structures observed on CT (2,3).

As seen in MDCT, the ratio of the diameter of the main pulmonary artery (MPA) to the diameter of the ascending aorta (AA) has been generally considered as equal to or less than 1 in healthy adults. The MPA/AA ratios over 1 suggest the presence of PH. In children, PH has been clinically defined using the criteria also used in adults: The mean pulmonary artery pressure greater than 25 mmHg (4).

Patients with PH may be relatively asymptomatic or may manifest normal findings on physical examination (5). However, this disorder might have various underlying causes, and the manifestations might be delayed in the clinical course due to its non-specific findings and symptoms (dyspnea, syncope, chest pain, fatigue) (1,6,7).

MDCT has been used for the exclusion of secondary causes that might lead to PH in children diagnosed with PH (8). Meanwhile, it can also be used for the identification of asymptomatic patients who have not been diagnosed with PH. This information carries importance regarding the referral of the patient to the clinician. The treatment and follow-up of the patient can be initiated when the findings of hypertension are identified. Thus, the use of proper MPA/AA ratio in pediatric patients, which is determined based on the findings in MDCT performed for other reasons, has critical importance for the identification of high-risk pediatric patients.

In our study, it was aimed to determine the ratio of the MPA diameter to the diameter of the AA based on the morphometric measurements of main mediastinal vascular structures using the MDCT in healthy children.

Materials and Methods

The contrast-enhanced pulmonary CT images of 487 patients in pediatric age group (0-18 years), who had been admitted to our hospital between January 2015 and February 2016, were evaluated retrospectively. The study was approved by the Institutional Review Board (ethics committee no: 09.2016.014, approval date: 08.01.2016) and informed consent was waived since the study was retrospective.

Patients with disorders that could be considered to change the MPA/AA ratio, such as parenchymal pulmonary disease, congenital lung malformation (pulmonary hypoplasia, congenital diaphragmatic hernia), mediastinal mass, pulmonary parenchymal mass, the presence of significant artifacts that might have led to faulty measurement of MVS, and non-contrast investigations, were excluded from the study.

Four hundred eighty-seven cases were classified into four different age groups: 0-24 months, 2-6 years, 7-11 years, and 12-18 years. A different number of cases were present in each group. 64.5% of the cases were male and 35.5% were female.

The MDCT investigations of the patients were performed by the 256-detector MDCT (Siemens, the Somatom Definition Flash, Germany) equipment. The contrast agent was then administered through the antecubital vein at a dose equivalent to the patient's age and speed of 0.5-1 mL/sec using an automated syringe. Detector collimation of 128x0.6 mm, tube voltage of 120 KV, a gantry rotation of 0.28 sec., tube current of 50-148 mA, and the pitch value of 3.2 were used as the imaging parameters during tomographic examination in pediatric cases with body weight up to 30 kg. In pediatric cases having a body weight over 30 kg, detector collimation of 32x1.2 mm, tube voltage of 120 kV, a gantry rotation of 0.5 sec, tube current of 50-148 mA, and the pitch value of 1.4 were used. The obtained MDCT images were sent to the workstation through the network.

The images were reconstructed at a thickness of 3 mm and with a reconstruction interval of 3 mm.

The CT images were retrospectively evaluated by two radiologists, one with more than 10 years experience and the other with one-year experience in thoracic radiology. All measurements were performed using the contrast-enhanced images and at the axial plane. The AA, the MPA, the right and left pulmonary arteries, the thoracic aorta (TA), and the thoracic vertebra (TV) at the same level were measured. AA and TA were measured transversely at the level of the right pulmonary artery. MPA was measured at its widest point, perpendicular to its longitudinal axis, and at the distal level of the postvalvular segment (Figure 1). The right and left pulmonary arteries were measured at their widest points and perpendicular to the longitudinal axis. The anteroposterior (AP) corpus diameter of the TV was measured at the cross-sectional level that the pulmonary bifurcation was observed.

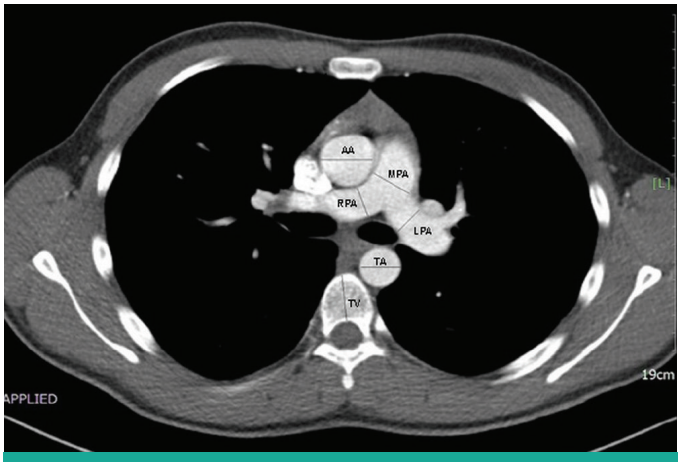

Figure 1. The measurement levels of the mediastinal vascular structures

Statistical Analysis

SPSS 21.0 software was used for statistical analysis. During the evaluation of the study data, the Kolmogorov-Smirnov normality test was used for the identification of the descriptive statistical methods (frequency, percentage, mean, standard deviation) together with conformity with a normal distribution. For comparison of qualitative data, the Pearson chi-square and Fisher's Exact tests were used. For quantitative data and comparison of the parameters between two groups, the Mann-Whitney U test was used. For the comparison of quantitative data among more than two groups of parameters which were not in conformity with a normal distribution, the Kruskal-Wallis test was used. The results were evaluated within the confidence interval of 95% and at a significance level of $p<0.05$.

Results

In our study, contrast-enhanced MDCT images of a total of 487 cases were evaluated. The mean age of the patients was 118.5±64 (1-216) months. Of the patients, 314 (64.5%) were male and 173 (35.5%) were female. Twenty six (5.3%) patients were in the 0-24 months age group, 146 (30%) were in the 2-6 years age group, 105 (21.6%) were in the 7-11 years age group, and 210 (43.1%) were in the 12-18 years age group.

The distributions of the MDCT measurements together with the MPA/AA and MVS/TV ratios according to gender were shown in Table 1 and Figures 2 and 3. The measurement results of MPA, AA, right and left pulmonary arteries, TA, and TV were found to be statistically significantly higher in males compared to females ($p<0.05$). The MPA/AA was determined to be significantly higher in females compared to the males ($p<0.05$).

Table 1. The distributions of the measurements of the patients according to gender

	Male (n=314)					Female (n=173)					
	Mean	Median	Standard deviation	Minimum	Maximum	Mean	Median	Standard deviation	Minimum	Maximum	p
MPA (mm)*	20.04	20.00	4.06	10.40	33.00	18.76	18.70	3.83	8.10	28.50	**0.002**
AA (mm)	19.26	19.50	3.93	9.00	30.00	17.53	17.50	3.65	8.10	27.70	**<0.001**
Right pulmonary artery (mm)	12.30	12.00	2.78	6.50	22.80	11.21	11.00	2.50	4.50	17.00	**<0.001**
Left pulmonary artery (mm)	12.67	12.50	2.70	6.00	20.00	11.42	11.00	2.46	5.50	19.00	**<0.001**
Thoracic aorta (mm)	15.15	15.40	3.46	6.50	25.40	13.16	13.00	3.03	6.00	23.00	**<0.001**
Thoracic vertebra AP (mm)	19.90	20.00	3.75	9.30	28.50	17.75	17.80	3.21	7.00	26.00	**<0.001**
MPA*/AA† ratio	1.05	1.04	0.13	0.65	1.54	1.08	1.08	0.13	0.70	1.46	**0.006**

*MPA: Main pulmonary artery, †AA: Ascending aorta, AP: Anteroposterior

When all cases were taken into consideration, the calculated mean MPA/AA ratio was 1.06 and was 1.07 (±0.11) in 0-24 months age group, 1.09 (±0.13) in the 2-6 years age group, 1.06 (±0.12) in the 7-11 years age group, and 1.03 (±0.13) in the 12-18 years age group. The distributions of the MDCT measurements together with the MPA/AA (Figure 4) and MVS/TV ratios according to the age groups were shown in Table 2. No statistically significant differences were found to be present between the 0-24 months age group and the 2-6 years age group ($p>0.05$), the other age groups were statistically significantly different from each other regarding AA, right and left pulmonary arteries, and TA ($p>0.05$). All age groups were different from each other regarding MPA and TV ($p<0.05$). The 2-6 years age group was found to be statistically significantly different when compared to the 7-11 years age group; the differences among other groups were not statistically significant regarding MVS/TV ($p>0.05$).

When the relationships between gender and age groups were analyzed, it was found that in males that the 2-6 years and 12-18 years age groups were statistically significantly different from each other ($p<0.05$), and the differences among the other age groups were not significant ($p>0.05$) regarding MPA/AA ratio. No significant differences were present between the 0-24 months age group and the 2-6 years age group ($p>0.05$), the other age groups were statistically significantly different from each other regarding the MPA, AA, right and left pulmonary arteries, TA, and TV ($p<0.05$). The 2-6 years age group was significantly different from the 7-11 years age group regarding the MVS/TV ratio ($p<0.05$), the differences between the other age groups were not statistically significant ($p>0.05$).

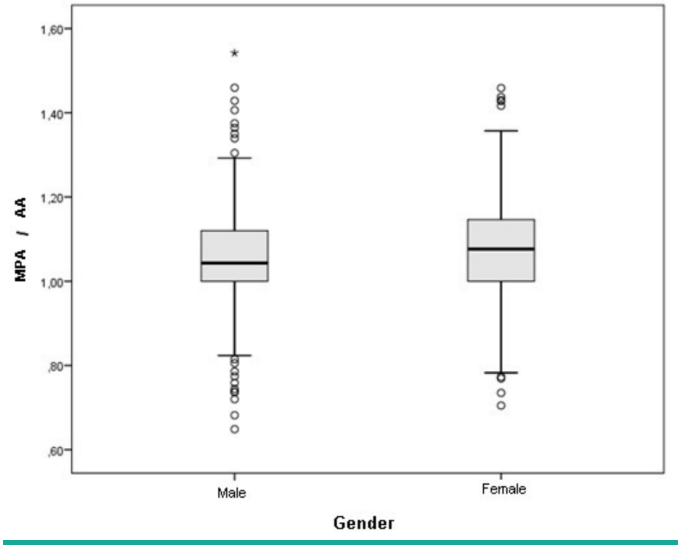

Figure 2. The distribution of the MPA/AA ratio according to gender

MPA: Main pulmonary artery, AA: Ascending aorta

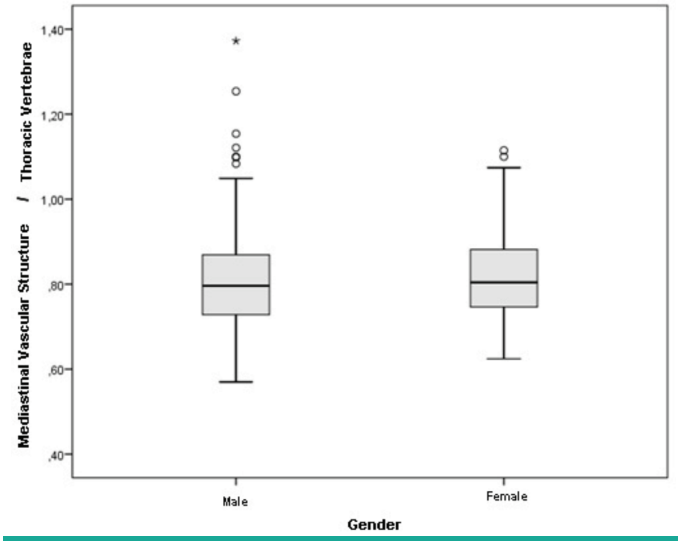

Figure 3. The distribution of the MVS/TV ratio according to gender

MVS: Mediastinal vascular structures, TV: Thoracic vertebrae

Table 2. The distributions of the measurements of the patients according to the age groups

	0-24 months		2-6 years		7-11 years		12-18 years	
	Mean	±	Mean	±	Mean	±	Mean	±
MPA (mm)*	13.39	3.58	16.57	2.36	20.01	2.73	22.23	3.20
AA (mm)†	12.50	3.15	15.26	2.07	18.95	2.40	21.61	2.65
Right pulmonary artery (mm)	7.85	2.05	9.83	1.57	12.04	1.96	13.79	2.14
Left pulmonary artery (mm)	8.27	2.31	10.04	1.53	12.46	1.71	14.12	2.02
Thoracic aorta (mm)	8.97	2.17	11.43	1.62	14.50	1.98	17.19	2.38
TV AP (mm)	12.82	2.42	16.10	1.76	18.77	1.95	22.23	2.49
MPA/AA ratio	1.07	0.11	1.09	0.13	1.06	0.12	1.03	0.13
MVS‡ /TV§ ratio	0.80	0.12	0.79	0.11	0.83	0.09	0.81	0.10

‡MVS: Mediastinal vascular structures, §TV: Thoracic vertebrae, *MPA: Main pulmonary artery, †AA : Ascending aorta, AP: Anteroposterior

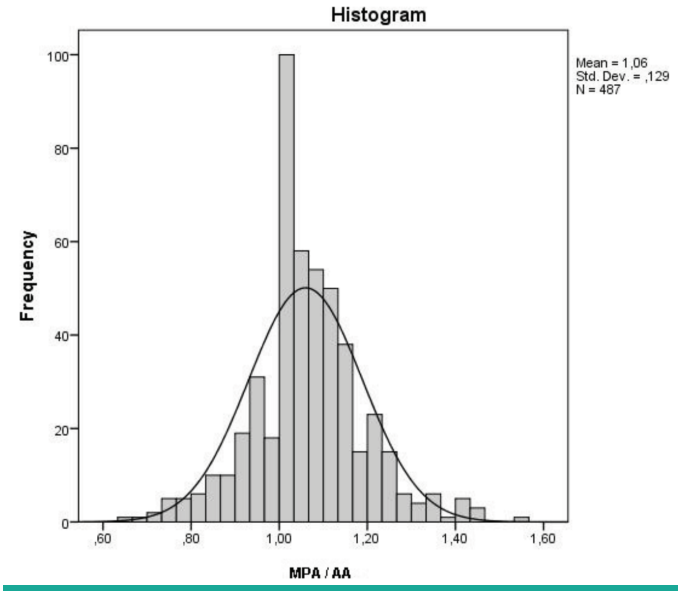

Figure 4. The distribution of the calculated MPA/AA ratio in all cases included in the study

MPA: Main pulmonary artery, AA: Ascending aorta

In females, no significant differences were found to be present among the age groups regarding the MPA/AA ratio (p>0.05). There was no difference between the 7-11 years and the 12-18 years age groups (p>0.05), the other age groups were different from each other regarding MPA (p<0.05). There were no differences between the 7-11 years and 12-18 years age groups and between the 0-24 months and 2-6 years age groups regarding AA (p>0.05), the other age groups were different from each other (p<0.05). No significant differences were present between the 0-24 months and 2-6 years age groups (p>0.05), the other age groups were found to be different from each other (p<0.05) regarding the right and left pulmonary arteries, TA, and TV. A statistically significant difference was found between the 0-24 months and the 7-11 years age groups (p<0.05), the other age groups were not different from each other (p>0.05) regarding the MVS/TV ratio.

In patients within the 0-24 months age group, no differences were found between males and females regarding MPA, AA, right and left pulmonary arteries, TA, TV, the MPA/AA and MVS/TV ratios (p>0.05). In patients within the 2-6 years age group, no differences were found between males and females regarding MPA, AA, right and left pulmonary arteries, the MPA/AA and MVS/TV ratios (p>0.05). The TA and TV measurements were found to be statistically significantly higher in males when compared to females (p<0.05). In patients within the 7-11 years age group, no differences were found between males and females regarding MPA, AA, right pulmonary artery, the MPA/AA and MVS/TV ratios (p>0.05). The left pulmonary artery, TA and TV measurements were found to be statistically significantly higher in males when compared to females (p<0.05). In patients within 12-18 years age group, no differences were found between males and females regarding the MPA/AA and MVS/TV ratios (p>0.05). The measurements of MPA, AA, the right and left pulmonary arteries, TA, and TV were found to be statistically significantly higher in males when compared to females (p<0.05).

A negative significant correlation at a level of 22.6% was determined between age and MPA/AA ratio (r=-0,226, p=0,001). No significant relationship was determined between age and the MVS/TV ratio (p>0.05). A significant positive correlation at a level of 81.1% was determined between age and the AA (r=0.811, p<0.001). A significant positive correlation at a level of 70.9% was present between age and the MPA (r=0.709, p<0.001). A significant positive correlation at a level of 73.6% was present between age and the right pulmonary artery (r=0.736, p<0.001). A significant positive correlation at a level of 75.6% was determined between age and the left pulmonary artery (r=0.756, p<0.001). A significant positive correlation at a level of 85.3% was present between age and the TA (r=0.853, p<0.001). A significant positive correlation at a level of 85.6% was found between age and the TV AP (r=0.856, p<0.001).

Discussion

One of the most significant contributions of MDCT in the pediatric age group is the assessment of the cardiovascular system. In this age group, motion artifacts and administration of low-dose contrast agent are among the limitations of CT angiography. However, with the invention of MDCT, these problems have been overcome. Therefore, in infancy and pediatric age group, MDCT has become one of the first investigations for the diagnosis of cardiovascular pathologies (9). In the newborn period, MPA may be wider than AA. Since the pulmonary arterial pressure is high due to the physiologic circulation of the fetus, an increase in the diameter of MPA may be observed.

In our study, we aimed to demonstrate the presence of a negative correlation between MPA/AA ratio and increasing age in the pediatric age group. Also, we aimed to calculate the mean values of thoracic vascular structures, together with the positive correlations of these values with increasing age and the inter-gender variations. In none of the cases included in our study, a suspicious finding regarding PH was identified in computed tomographic images. To our

knowledge, the relationships between pediatric age groups, the mean values of thoracic vascular structures and MPA/AA ratio have not been discussed in the literature.

Truong et al. (10), in the study that they conducted on 3.171 adult cases in 2011, aimed to determine a reference value for the MPA/AA ratio and verified this value as 0.9. In another study conducted by Edwards et al. (3), it was concluded that the increase in MPA diameter was not correlated with age increase. However, the patient ages in their study group ranged between 11 years and 90 years, and few patients were in the pediatric age group. On the other hand, in our study, a significant correlation for the MPA / AA ratio was determined in the pediatric age group, contrary to the results of the study conducted by Edwards et al. (3).

In our study, the mean MPA/AA ratio was found to be 1.06, and in all age groups this ratio was above 1 (in the 0-24 months age group, 1.07 (±0.11), in the 2-6 years age group, 1.09 (±0.13), in the 7-11 years age group, 1.06 (±0.12), in the 12-18 years age group 1.03 (±0.13). The results obtained in our study suggest that the statement related to adults that the MPA/AA ratio should be 1 or less than 1 is not valid for the pediatric age group.

Ichida et al. (11), in their study related to echocardiography in pediatric age group, determined that the MPA/AA ratio decreased with increasing age. The results revealed a significant relationship between the MPA/AA ratio and age. Compton et al. (4), in measurements of 200 healthy children that they performed with MDCT in 2015, calculated the MPA/AA ratio to be greater than 1 and close to 1.09 in all pediatric age groups. We calculated this ratio as over 1 and obtained similar results. Compton et al. (4), Fitzgerald et al. (12), and Akay et al. (2), in their studies, stated that no statistically significant difference was present between the MPA/AA ratio and gender. However, in our study conducted with 487 cases, we determined that this ratio was statistically significantly higher in females when compared to males ($p<0.05$) (1.08 in females vs. 1.05 in males).

When we investigated the relationship between the MPA/AA and age groups, we determined that this ratio was statistically significantly higher in the 2-6 years age group when compared to the 12-18 years age group. No other significant difference was determined among the other age groups. Akay et al. (2), in their study conducted on the pediatric age group in 2009, in accordance with our study, showed the presence of a positive correlation between AA, MPA, right and left pulmonary arteries, TA, TV, and age ($p<0.001$). We also determined that these vascular structures were positively correlated with age ($p<0.001$). On the other hand, Akay et al. (2) in their study, found no statistically significant difference in these vascular structures related to gender. On the contrary, in our study, we determined that the diameters of MPA, AA, right and left pulmonary arteries, TA, and TV were significantly higher in males compared to females ($p<0.05$).

When we investigated the changes related to age in both genders, we determined in males that no significant differences were present between the 0-24 months age group and the 2-6 years age group regarding the diameters of MPA, AA, right and left pulmonary arteries, TA, and TV. The other age groups were found to be different from each other. On the other hand, in females, no significant differences were present between the 0-24 months and 2-6 years age groups regarding the diameters of right and left pulmonary arteries, TA, and TV. The other age groups were different from each other ($p<0.05$). The study conducted by Fitzgerald et al. in the pediatric age group revealed that TA and the TV width measured at the level of pulmonary artery bifurcation increased with age (12). Also in our study, it was found that TA and TV AP diameters increased consistently with increasing age ($p<0.001$).

Our study had a limitation. Since PH could not be excluded in the cases included in our study, a negative MPA/AA ratio could not allow us to rule out the absence of PH. However, when our criteria for exclusion from the study are taken into consideration, we have the opinion that we have excluded many conditions that could be predisposing factors for PH.

In previously conducted studies, the mean MPA/AA ratio was determined by measuring the MPA and AA for the prediction of PH. In the adult age group, the limit value for MPA/AA has been determined as 1. The values greater than 1 for this ratio has been suggested to create suspicion for PH. However, this ratio should not be used in the pediatric age group. In our study, it was determined that this ratio was greater than 1 in healthy children, contrary to the adult age group. Also, even though the MPA/AA ratio was negatively correlated with age, the threshold value was calculated to be 1.06 in all age groups.

Conclusion

We do not favor using MDCT for an investigation when PH is suspected in the pediatric age group. On the other hand, we have the opinion that the changes determined in the MPA/AA ratio should take place in the radiology reports for enabling appropriate patient monitoring. We suggest that

cases with MPA/AA ratio 1.06 and over in MDCT should be evaluated regarding PH.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Review Board (ethics committee no: 09.2016.014, approval date: 08.01.2016).

Informed Consent: Informed consent was waived since the study was retrospective.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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ORIGINAL RESEARCH

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The Results of Adjuvant and Salvage Radiotherapy Following Radical Prostatectomy

Radikal Prostatektomi Sonrası Adjuvan ve Kurtarma Radyoterapi Sonuçları

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Abstract

Objective: The aim of the study is to evaluate the contribution of postoperative adjuvant radiotherapy (ART) and salvage radiotherapy (SRT) to oncological outcomes and side effects related to treatment in prostate cancer patients with adverse prognostic factors.

Method: Between January 2000 and January 2020, 105 patients who received the diagnosis of prostate cancer and underwent ART or SRT in our clinic after open or robotic-assisted radical prostatectomy were evaluated retrospectively and 93 patients whose follow-ups were still ongoing were included in the study. Fifty-two patients received ART and 41 patients received SRT. External beam radiotherapy (EBRT) was applied to prostate bed (PB) with a median EBRT of 70 Gy (66-72 Gy) and/or pelvic lymphatics with 50 Gy. Biochemical relapse-free survival (bRFS) and treatment-related acute and late gastrointestinal (GI) and genitourinary (GU) toxicities were evaluated. The Mann-Whitney U and chi-square tests were used for univariate analysis to analyze clinicopathological variables associated with biochemical relapse-free and overall survival and to evaluate side effects. Logistic regression model was used for multivariate analysis to investigate the risk factors associated with toxicities.

Results: The median age of the patients included in the study was 64 (50-82) years. The median follow-up period of the entire patient population was 30 months (range, 3-234 months). Adjuvant RT was applied to 52 patients with adverse pathological features such as postoperative surgical margin positivity, extracapsular extension and seminal vesicle involvement, while SRT was applied to 41 patients with a prostate-specific antigen level ≥0.2 ng/mL detected during follow-up and considered to have biochemical relapse. bRFS rates at 3 years were detected as 100% in the ART and 97.4% in the SRT arm. Acute and late side effects were

Öz

Amaç: Çalışmanın amacı, advers prognostik faktörlere sahip prostat kanserli hastalarda postoperatif adjuvan radyoterapi (ART) ve salvage radyoterapinin (SRT) onkolojik sonuçlara katkısını ve tedaviye bağlı yan etkileri değerlendirmektir.

Yöntem: Ocak 2000-Ocak 2020 yılları arasında prostat kanseri tanısı alan ve açık veya robotic-assisted radikal prostatektomi sonrası kliniğimizde ART veya SRT uygulanan 105 hasta retrospektif olarak değerlendirilmiş ve takipleri devam eden 93 hasta çalışmaya dahil edilmiştir. Elli iki hastaya ART ve 41 hastaya da SRT tedavisi uygulanmıştır. Eksternal RT prostat yatağı medyan 70 Gy (66-72 Gy) ± pelvik lenfatiklere 50 Gy olacak şekilde uygulandı. Biyokimyasal nükssüz sağkalım (bPFS) ve tedaviye bağlı akut ve geç gastrointestinal (GI) ve genitoüriner (GU) toksisiteler değerlendirildi. bPFS ve tüm sağkalım ile ilişkili klinopatolojik değişkenleri analiz etmek ve yan etkileri değerlendirmek için Mann-Whitney U ve tek değişkenli analiz için ki-kare testi kullanıldı. Toksisite ile ilişkili risk faktörlerini araştırmak amacıyla çok değişkenli analiz için lojistik regresyon modeli kullanıldı.

Bulgular: Çalışmaya dahil edilen hastaların medyan yaşı 64 (50-82) yıl idi. Tüm hasta popülasyonu için medyan takip süresi 30 ay (3-234 ay) idi. Postoperatif olarak cerrahi sınır pozitif, ekstrakapsüler ve seminal vesikül tutulumu olan advers patolojik özelliklere sahip 52 hastaya adjuvan RT uygulanırken, takip esnasında prostata özgü antijen düzeyi ≥0,2 ng/mL olan ve biyokimyasal nüks kabul edilen 41 hastaya SRT uygulandı. Üç yıllık bPFS ART kolunda %100 ve SRT kolunda %97,4 olarak tespit edildi. Akut ve geç yan etkiler Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer sistemine göre değerlendirildi ve ART ve SRT uygulanan hastalarda akut ve geç GI ve GU yan etkiler benzer bulundu. Akut toksisite gelişmesini predikte

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Abstract

evaluated according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer system, and acute and late GI and GU side effects were found to be similar in patients who underwent ART or SRT. In the multivariate logistic regression analysis in which the factors predicting the development of acute toxicity were investigated, the risk of developing acute toxicity was found to be higher in patients with lymph node involvement (p=0.047) and those who underwent whole pelvic RT (WPRT) compared to those who received RT applied only to PB (p= 0.002). When the patients who received WPRT using volumetric arc therapy (VMAT) were compared with those who had radiotherapy delivered only to PB, grade ≥2 acute GI side effects were detected in 4.2% and 1.4% of the patients, respectively (p=0.002). On the other hand, grade ≥2 acute GU side effects were found in 12.5% and 5.7% of the patients, respectively. When WPRT vs only PB was compared, any statistically significant difference was not found in terms of late toxicity.

Conclusion: Postoperative radiotherapy improves biochemical relapse-free survival in patients with adverse prognostic factors. Despite low incidence of side effects, postoperative pelvic radiotherapy results in significant increases in the acute gastrointestinal toxicity rates. Advanced treatment techniques such as VMAT should be considered in pelvic radiotherapy so as to reduce the incidence of these side effects. It should be noted that in order to improve the quality of life of the patients, timely administration of early SRT showed comparable cancer control rates while reducing potential overtreatment toxicity.

Keywords: Adjuvant radiotherapy, adverse prognostic factors, prostate cancer, salvage radiotherapy

Öz

eden faktörlerin araştırıldığı çok değişkenli lojistik regresyon analizinde lenf nodu tutulumu olan (p=0,047) ve pelvik RT (WPRT) uygulanan hastalarda akut toksisite gelişme riski sadece prostat yatağı (PB) RT uygulananlara göre daha yüksek bulundu (p=0,002). Volümetrik arc tekniği kullanılarak (VMAT) uygulanan WPRT vs PB RT uygulanan hastalar karşılaştırıldığında, ≥grade 2 akut GI yan etki sırasıyla %4,2 ve %1,4 olarak tespit edilirken, ≥ grade 2 akut GU yan etki ise %12,5 ve %5,7 olarak bulundu (p=0,002). WPRT vs PB karşılaştırıldığında geç toksisite açısından istatistiksel olarak anlamlı bir fark bulunmadı.

Sonuç: Postoperatif radyoterapi, kötü prognostik faktörü olan hastalarda bPFS'yi artırır. Postoperatif pelvik radyoterapiye bağlı yan etkilerin görülme sıklığı az olsa da, GI toksisite oranı belirgin derecede artmaktadır. VMAT gibi ileri tedavi teknikleri pelvik radyoterapinin yan etkilerini azaltmak için uygulanmalıdır. Hastaların hayat kalitesini artırmak için, zamanında uygulanan erken kurtarma radyoterapisi tedaviye bağlı yan etkileri azaltırken hastalık kontrolünü de artırır.

Anahtar kelimeler: Adjuvan radyoterapi, kurtarma radyoterapisi, olumsuz prognostik faktörler, prostat kanseri

Introduction

As curative treatment alternatives, radiotherapy (RT) and radical prostatectomy (RP) are prevalently accepted and used as therapeutic options in the treatment of localized prostate cancer (PCa). Post-treatment outcomes of these treatment alternatives are comparable; however, vast majority of patients who previously underwent RP will ultimately undergo immediate (adjuvant) or delayed (salvage) RT (1). As demonstrated in several studies, nearly one-third of the patients undergoing RP will develop postoperative biochemical relapse following RP (2). For high-risk postprostatectomy patients with positive surgical margins (PSM), seminal vesicle involvement (SVI), extracapsular (EC) involvement, high pathologic T-stage or higher Gleason score (GS), ART is often signified depending on postoperative pathologic findings. In PCa patients with adverse pathologic features following RP, ART reduces the biochemical failure by improving clinical outcomes (3). SRT is also used in the treatment of cases with biochemical relapse detected during follow-up. The presence of two rising PSA levels ≥0.2 ng/mL is considered as postoperative biochemical relapse (4). Controversial opinions have been put forth regarding the application of ART or SRT due to an increase in PSA levels. However, RT is directed at the prostatic fossa and/or pelvic lymph nodes (PLNs) related to the pathologic adverse factors which may be combined with androgen deprivation therapy (ADT) (5,6). Application of ART and elective RT targeting pelvic nodes in clinically node-negative patients without any risk of developing potential recurrences in the future remains to be a debatable issue. Indeed, due to its potential GU and GI side effects, RT may be an unnecessary treatment modality for these patients (7).

Biochemical progression-free survival (bPFS) or overall survival (OS) rates, and the increasing of side effects related to ART vs SRT have not been conclusively determined yet.

Three large randomized controlled trials (EORTC 22911, SWOG 8794 and ARO 96-02) enrolling more than 1.700 patients compared ART to watchful waiting and all of these studies revealed a significant benefit favoring ART in terms of biochemical recurrence-free survival (bRFS) rates, while only one of these trials also demonstrated an increase in OS rates in the ART arm (8-10). However, in the ART arm, grade ≥2 GI and GU toxicities were observed (11).

Unfortunately, any randomized studies have not compared ART with SRT. Biochemical and OS benefits of SRT in

a subgroup of patients have been revealed in many retrospective series (12,13). In numerous studies, significant differences have not been detected between safety profiles of postoperatively administered ART and SRT (14,15).

Even if the most advanced techniques have been used, relatively higher doses of the pelvic field RT delivered outside the prostate bed increased incidence rates of GI and GU side effects. Indeed, an increased rate of toxicity following WPRT was reported previously (16). There are no data available on patients treated with elective WPRT compared with PB-RT not targeting pelvic fields.

Therefore, the choice between RP plus ART or SRT with or without ADT depends on their treatment-related toxicity and personal preferences.

The objective of this study is to compare the oncological results and treatment-related toxicity with the diagnosis of PCa patients treated with ART or SRT after RP performed in a single center.

Materials and Methods

Between January 2000 and January 2020, 105 patients who were treated with ART or SRT after RP in the Radiation Oncology Clinic of University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital were retrospectively evaluated. Patient information was obtained from patient files and hospital data system. Twelve patients were excluded from the study because they were lost to follow-up. Ninety-three patients with completed data, who had surgical margin (SM) positivity, SV or EC involvement, regardless of tumor stage, or biochemical recurrence at follow-up, were included in the study.

Preoperatively, all patients were evaluated based on medical history, clinical assessment, serum PSA and testosterone levels, transrectal ultrasound and abdominopelvic computed tomography (CT)/magnetic resonance imaging (MRI) and bone scintigraphy findings. The ART group consisted of patients with postoperative PSA ≤0.2 ng/mL whose RT was initiated within 6 months after surgery. The SRT group consisted of patients with a postoperative PSA level ≥0.2 ng/mL during follow-up and considered to have biochemical recurrence. ART was applied to 52 and SRT to 41 patients.

Patients with positive pelvic nodes or carrying a risk (>15%) of pelvic node involvement defined according to the Roach formula underwent pelvic RT (17).

None of the patients underwent hormonal therapy before prostatectomy. ADT consisting of gonadotropin-releasing hormone agonists or antiandrogen therapy was administered in the presence of adverse pathologic features including T3/4 stage, EC extension (ECE), and SVI, GS ≥7, PSA >20 ng/mL before surgery, relapse or lymph node involvement.

Patients were treated using the volumetric arc therapy (VMAT) technique delivered by a linear accelerator (Varian RapidArc, Palo Alto, CA, USA). All patients underwent CT simulation with a full bladder and empty rectum in the supine position placed in an appropriate fixation device with knee and foot support. CT data sets were sent for contouring on the Eclipse treatment planning system (VarianMedical System, Palo Alto, CA, USA) and then using DICOM RT (digital imaging and communication in medicine) format, they were exported directly to the treatment with the trilogy linear accelerator. For all patients, clinical target volume 1 (CTV 1) included prostate bed and the seminal vesicles bed, and CTV2, obturator, presacral, external and internal lymph nodes below the aortic bifurcation. The CTV1 was contoured using the Radiation Therapy Oncology Group consensus guidelines modified according to surgical and pathologic findings (18). The planning target volume1 (PTV1) was defined as CTV 1 with an additional margin of 1 cm in all directions except 6 mm posteriorly so as to reduce the risk of rectal toxicity. PTV2 was achieved adding a 7 mm isotropic margin to CTV2. The rectum, bladder, femoral heads, large and small bowel, and penile bulb were outlined as organs at risk. The course of RT consisted of 33-36 fractions of 2 Gy daily for a total dose of 66-72 Gy to PTV1. If pelvic nodes were to be irradiated, a total dose of 50 Gy in 25 fractions with a single fractional dose of 2 Gy was delivered.

Follow-up and Toxicity Evaluation

Patients were observed for 4 weeks after the completion of RT, then every 3-6 months with physical examination, PSA measurements, and assessments of toxicity. Acute toxicities were retrospectively graded based on physicians' notes taken during the treatment and within 6 months after RT using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) guidelines (19). Late toxicities were defined as those occurring 6 months after RT and scored using the RTOG and EORTC scale (Table 1).

Primary endpoints were acute and late toxicities. Secondary endpoints were bRFS and OS. This retrospective data

analysis was approved by the ethics committee of our hospital. All patients signed a written informed consent.

Statistical Analyses

The prognostic factors such as age, comorbidity, disease stage, GS, baseline pre-RT and post-RT PSA levels, status of SM, ADT and RT technique and dose were comparatively analyzed between ART and SRT using SPSS v21 (IBM Inc. USA) program. For categorical variables, the numbers and percentages, and for continuous variables median and range values were reported. The Mann-Whitney U test, chi-square test or Fisher's Extact test were used to compare intergroup differences. Logistic regression models were used in order to investigate the risk factors associated with toxicities. An overall p-value of less than 0.05 was considered to have statistical significance.

Results

Patient Characteristics

The median age of the patients included in the study was 64 (50-82) years. Comorbid disease was present in 52.7% of the patients who underwent RT after RP, and frequently hypertension (36.96%) and diabetes mellitus (16.30%) were found. The median follow-up of the entire patient population was 30 months (3-234) following RT.

Fifty-two patients were treated with ART and 41 with SRT. RT was initiated within postoperative 1-6 months (median 4 months) in the ART group. While SRT was maintained for 6-194 months (median 37 months) following prostatectomy. Pre-RT median PSA values were 0.016 ng/mL (0.001-1.90 ng/mL) in the ART and 0.60 ng/mL (0.21-12.01 ng/mL) in the SRT group.

Seventy-two patients had open RP and 21 had robot-assisted prostatectomy. Lymph node dissections were performed in a total of 41 patients, and the median number of 7 (1-24) lymph nodes were removed. The most frequent SM positivity was detected in the posterior lobe (36.11%) and apex (15.28%) of the prostate.

ART vs SRT

A higher percentage of patients treated with SRT had a GS of 8-10 (26.8% vs 19.2%) and more frequently had adverse pathologic factors compared to those receiving ART. Median values for rates of ECE positivity (48.1% and 34.1%, p=0.033), SVI (15.4% and 19.5%, p=0.783), SM positivity (92.6% and 53.7%, p<0.0001), and lymph node involvement (23.5% and 26.8%, p=0.850) were determined in the ART and SRT groups, respectively (Table 2).

In the ART and SRT groups of patients, PLNs were irradiated in 13 (25%) and 11(26.8%) patients, while only PB-RT was

Table 1. RTOG acute and RTOG/EORTC late radiation morbidity scoring criteria

	Acute		Late	
Organ tissue	**Lower gastrointestinal**	**Genitourinary**	**Lower gastrointestinal**	**Genitourinary**
Grade 0	No change	No change	None	None
Grade 1	Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics	Frequency of urination or nocturia twice pretreatment habit/dysuria, urgency not requiring medication	Mild diarrhea, mild cramping, bowel movement 5 times daily, slight rectal discharge or bleeding	Slight epithelial atrophy, minor telangiectasia (microscopic hematuria)
Grade 2	Diarrhea requiring parasympatholytic drugs (e.g., diphenoxylate/mucus discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics	Frequency of urination or nocturia at longer than hourly intervals Dysuria, urgency, bladder spasm requiring local anesthetic (e.g., pyridium)	Moderate diarrhea and colic, bowel movement >5 times daily, excessive rectal mucus or intermittent bleeding	Moderate urinary frequency, generalized telangiectasia, intermittent macroscopic hematuria
Grade 3	Diarrhea requiring parenteral support/severe mucous or blood discharge necessitating sanitary pads/abdominal distention (plain abdominal radiograph demonstrates distended bowel loops)	Urinary frequency with urgency and nocturia at hourly or more frequent intervals/dysuria, pelvic pain, or bladder spasm requiring regular, frequent narcotic analgesics/gross hematuria with/without clot passage	Obstruction or bleeding, requiring surgery	Severe frequency and dysuria, severe telangiectasia frequent hematuria, reduction in bladder capacity
Grade 4	Acute or subacute obstruction, fistula or perforation, gastrointestinal bleeding requiring transfusion, abdominal pain or tenesmus requiring tube decompression or bowel diversion	Hematuria requiring transfusion/ acute bladder obstruction not secondary to clot passage, ulceration, or necrosis	Necrosis/perforation fistula	Necrosis/contracted bladder(reduced bladder capacity)

EORTC: European Organization for Research and Treatment of Cancer, RTOG: Radiation Therapy Oncology Group

delivered in 39 (75%) and 30 (73.2%) patients, respectively. In patients who underwent pelvic field RT and postoperative PB-RT, the median pre-RT PSA values were 0.147 ng/mL (0.001-7.710) and 0.134 (0.003-12.010), respectively.

Hormonal therapy (HT) was used in 61.5% and 56.1% of the patients undergoing ART and SRT, respectively. The median duration of HT was 12 months (6-36 months) in the ART and SRT groups. RT doses <70 Gy were administered to 29.4% and 36.6%, and ≥70 Gy were administered to 70.6% and 63.4% of the patients in the ART, and SRT groups, respectively

At the time of analysis, only one patient had a biochemical relapse in the SRTgroup (2.43%) following previous RT after 36 months and received hormone therapy.

Treatment-related Toxicities

Acute GI side effects were not observed in 88.5% and 85.4% of the patients in the ART and SRT groups, respectively. In only one patient in both ART, and SRT groups, grade 2, and 3 side effects were observed (p=0.527).

Acute GU system side effects were not observed in 50%, and 53.7% of the patients in the ART and SRT groups, respectively. Grade 2 and 3 side effects were seen in 5.8% vs 7.3%, and 0% vs 2.4% of the patients in the ART and SRT groups, respectively (p=0.628) (Table 3).

Grade 2 and 3 late GI side effects were detected at the rates of 1.9% and 1.9% in the ART group, and 4.9% and 0% in the SRT group, while they were not observed in 94.2% and 95.1% of the patients, respectively (p=0.532). Late GU side effects were not observed in 76.9% and 82.9% of the patients, while grade 2 GU side effects were observed in 1.9% vs 2.4% and grade 3 in 9.6% vs 4.9% of the patients in the ART and SRT groups, respectively (p=0.829) (Table 3).

In the multivariate logistic regression analysis in which the factors affecting the development of acute toxicity were investigated, the risk of developing acute toxicity was found to be higher in patients who underwent pelvic RT compared to those who did not (p=0.002) (Table 4). In addition, the risk of developing acute toxicity was found

Table 2. Patient characteristics in the SRT and ART groups

Characteristics	SRT n=41	ART n=52	p
Age, year, median (range)	66 (53-82)	64 (50-76)	0.100
≤64, year n (%)	17 (41.5)	30 (57.7)	0.146
>64, year, n (%)	24 (58.5)	22 (42.3)	
Comorbidity, n (%)	24 (58.5)	25 (48.1)	0.403
Pre-RT PSA, median (range)	**0.60 (0.21-12.01)**	**0.016 (0.001-1.90)**	**<0.0001**
Post-RT PSA, median (range)	**0.06 (0.003-9.59)**	**0.008 (0.003-0.29)**	**<0.0001**
RT dose, n (%)	-	-	0.158
<70 Gy	15 (36.6)	15 (29.4)	
≥70 Gy	26 (63.4)	36 (70.6)	
Surgical margin positivity n (%)	**22 (53.7)**	**50 (96.2)**	**<0.0001**
SV Involvement n (%)	8 (19.5)	8 (15.4)	0.783
ECE, positivity n (%)	**14 (34.1)**	**25 (48.1)**	**0.033**
Gleason score, n (%)	-	-	0.069
6	13 (31.7)	9 (17.3)	-
3+4	9 (22.0)	25 (48.1)	-
4+3	8 (19.5)	8 (15.4)	-
8-10	11 (26.8)	10 (19.2)	-
Hormonal therapy n (%)	23 (56.1)	32 (61.5)	0.673
Duration of hormonal therapy, months, median (range)	12 (6-30)	12 (6-36)	0.849
Lymph node involvement, n (%)	11 (26.8)	12 (23.5)	0.850
RT field	-	-	0.158
Whole pelvic fields	11 (26.8)	13 (25.0)	-
Prostate bed	30 (73.2)	39 (75.0)	-

SV: Seminal vesicle, ECE: Extracapsular invasion, RT: Radiotherapy, ART: Adjuvant radiotherapy, SRT: Salvage radiotherapy, PSA: Prostate-specific antigen

to be higher in patients with lymph node involvement (p=0.047). When the factors affecting the development of late toxicity were investigated, any statistically significant factor was not found (Table 5).

Table 3. Side effects

				p
ACUTE	**GI. N (%)**	**SRT**	**ART**	0.527
	Absent	35 (85.4)	46 (88.5)	-
	Grade 1	5 (12.2)	5 (9.6)	-
	Grade 2	0 (0.0)	1 (1.9)	-
	Grade 3	1 (2.4)	0 (0.0)	-
	GU. n (%)	**SRT**	**ART**	0.628
	Absent	22 (53.7)	26 (50.0)	-
	Grade 1	15 (36.6)	23 (44.2)	-
	Grade 2	3 (7.3)	3 (5.8)	-
	Grade 3	1 (2.4)	0 (0.0)	-
LATE	**GI. n (%)**	**SRT**	**ART**	0.532
	Absent	39 (95.1)	49 (94.2)	-
	Grade 1	0 (0.0)	1 (1.9)	-
	Grade 2	2 (4.9)	1 (1.9)	-
	Grade 3	0 (0.0)	1 (1.9)	-
	GU. n (%)	**SRT**	**ART**	0.829
	Absent	34 (82.9)	40 (76.9)	-
	Grade 1	4 (9.8)	6 (11.5)	-
	Grade 2	1 (2.4)	1 (1.9)	-
	Grade 3	2 (4.9)	5 (9.6)	-

GI: Gastrointestinal, SRT: Salvage radiotherapy ART: Adjuvant radiotherapy, GU: Genitourinary

Table 4. Factors affecting acute side effects

Characteristics		HR	95% CI	p
Age		1.04	0.98-1.10	0.259
DM		0.69	0.28-1.66	0.405
HPT		1.14	0.58-2.25	0.702
Post-op PSA		1.12	0.91-1.38	0.297
Pre-RT PSA		1.01	0.87-1.18	0.856
Surgical margin positivity		0.59	0.23-1.57	0.293
Hormonal therapy		1.69	0.83-3.44	0.149
WPRT		4.17	1.72-10.00	0.002*
Gleason score ≥8-10		1.75	0.78-3.83	0.164
Lymph node involvement		2.63	1.01-7.14	0.047*
Type of surgery	Open (ref)	1	-	-
	Robotic	1.05	0.42-2.65	0.912
Type of RT	ART (ref)	1	-	-
	SRT	0.48	0.21-1.08	0.075

DM: Diabetes mellitus, HPT: Hypertension, RT: Radiotherapy, WPRT: Whole pelvic radiotherapy, PSA: Prostate-specific antigen, CI: Confidence interval, HR: Hazard ratio

Discussion

This study evaluated the effectiveness of local and pelvic RT in PCa patients with adverse pathologic features following RP, acute and late GI and GU toxicity profiles.

The American Urological Association (AUA) and the American Society for Radiation Oncology (ASTRO) have recommended ART in patients with SVI, PSM and ECE while the application of SRT is suggested for the treatment of the patients with biochemical relapse described as two rising PSA levels ≥0.2 ng/mL following RP (20,21).

Three randomized controlled trials (EORTC22911, SWOG8794, ARO96-02/AUO-AP09/95) with long-term follow-up results demonstrated improvement in bPFS (p<0.00001) with ART to the prostatic bed vs watchful waiting in the patients with adverse pathologic features such as PSM, SVI or ECE (8-10). Only SWOG 8.794 trial demonstrated an improvement in OS (9). In the observational arms, approximately 40% of patients never had recurrences,thus indicating the possibility of overtreatment with ART in this group of patients. However, the number of treatment-related side effects increased, which was associated with improper patient selection. ART was associated with higher toxicity levels when compared with the observational arm (grade ≥2 GI toxicities: 2% vs 1% and grade ≥2 GU toxicities: 17% vs 10%) in these trials (22).

Table 5. Factors affecting late side effects

Characteristics		HR	95% CI	p
Age		1.02	0.95-1.10	0.524
DM		0.12	0.01-1.07	0.057
HPT		1.15	0.44-3.00	0.776
Post-op PSA		0.78	0.42-1.52	0.493
Pre-RT PSA		1.03	0.81-1.29	0.834
Surgical margin positivity		0.36	0.11-1.16	0.087
Hormonal therapy		0.95	0.35-2.58	0.913
Pelvic RT		3.33	0.90-12.50	0.070
Gleason score ≥8-10		2.00	0.61-6.55	0.256
Lymph node involvement		1.79	0.44-7.14	0.419
Type of surgery	Open (ref)	1	-	-
	Robotic	1.77	0.57-5.48	0.323
Type of RT	ART (ref)	1	-	-
	SRT	0.42	0.14-1.24	0.116

DM: Diabetes mellitus, HPT: Hypertension, RT: Radiotherapy, ART: Adjuvant radiotherapy, SRT: Salvage radiotherapy, CI: Confidence interval, PSA: Prostate-specific antigen, HR: Hazard ratio

Application of postoperative ART or SRT is still controversial in the patient group with high risk of biochemical relapse after surgery while very recently three randomized studies GETUG-AFU 17, RAVES and RADICALS have been evaluated in a systematic review and meta-analysis that will enable us to decide the appropriate time of RT after surgery (23-25). This prospectively designed meta-analysis has revealed that ART does not improve PSA-related event-free survival but urinary and intestinal adverse effects were observed with a higher rate in patients who underwent ART (26). Our data have shown that the patients receiving SRT had very low biochemical relapse rates (97.57%) with acceptable side effects. It should be noted that in order to improve the patients' quality of life, timely administration of early SRT ensures comparable cancer control rates while reducing potential overtreatment toxicity.

Jereczek-Fossa et al. (27) applied ART in 258 patients, and SRT in 173 patients using conformal technique, and did not observe any difference between both treatment modalities as for acute and late GI toxicities. However, higher rates of grade 3-4 acute urinary toxicities were reported in the ART group (27). In multivariate analysis performed for the pooled multi-institutional trials have shown side effects in late GU and GI in postprostatectomy patients undergoing ART or SRT, higher rates of grade ≥2 GU toxicity were detected in the ART group (28). Although modern RT techniques including intensity- modulated radiation therapy (IMRT) were not used and 2-dimensional (2-D) or 3-dimensional (3-D) conformal RT (CRT) treatment planning was employed in these studies, there was no difference in GI and GU side effects between the two groups. In our study, as in the study of Jereczek-Fossa et al. (27), no statistical difference was observed between the ART and SRT groups in terms of GI side effects, while it was determined that late grade 3 GU side effects were more frequently seen in the ART arm rather than SRT arm without any statistically significant intergroup difference.

Some authors have considered lower PSA levels (<0.01 ng/mL) as an indicative of subclinical disease. Abugharib et al. (29) explored the best timing of SRT following RP based on the lowest levels of PSA and observed that PSA levels detected before SRT strongly correlated with bRFS. Higher PSA levels before SRT (0.01-0.2, 0.2-0.5 and >0.5 ng/mL) predicted worse 10-year bRFS (62%, 44% and 27%, respectively). There was a significant benefit in OS rates (29). In our study, we found higher pre-RT PSA levels in the SRT group. The most important reason for this is delayed referral of the majority of the patients to the radiation oncology department for SRT despite explicit AUA and ASTRO guidelines.

However, the role of ADT in combination with ART or SRT remains debatable. GETUG 17 phase III, multicenter trial randomized the patients into two groups of postoperatively initiated RT after BCR versus RT plus 6-months of goserelin treatment. Five-year follow-up results demonstrated that SRT plus ADT had been associated with higher BCR-free survival rates as compared to RT alone without any difference in late toxicity (23). In contrast, in a retrospective study that compared RT alone vs RT plus hormone therapy, no benefit was observed in terms of OS or metastasis- free survival rates (30).We found that in the ART and SRT groups, 61.5% vs 56.1% of patients received hormone therapy without any statistically significant intergroup difference in terms of bDFS and side effects.

It has been shown in randomized studies that increasing the external RT dose improves oncological outcomes in localized PCa (31). Nevertheless, appropriate dose of postoperative RT to be delivered is debatable. Even though doses of >70 Gy potentially increase biochemical control rates, the treatment -related toxicities increase even with the use of advanced RT techniques such as IMRT or VMAT.

Riou et al. (32) compared CRT and IMRT, which they applied 68 Gy dose to the PB and observed rectum and bladder doses significantly decreased by IMRT planning without any grade >2 acute and late toxicities. In phase III trial SAKK 09/10, the patients with biochemical relapse but without any macroscopic disease were grouped as 64 vs 70 Gy RT. The patients were treated with 3-D CRT or IMRT, and acute GI and GU side effects were not seen between both groups while urinary symptoms worsened in the patients whom were applied 70 Gy (33). In most radiation oncology clinics, especially for SRT, total RT dose of 65-70.2 Gy is applied. In this study, the RT doses between 66 and 72 Gy were used, and higher number of patients received RT ≥70 Gy in the whole cohort; without any intergroup difference in terms of bPFS or side effects. However, it is encouraging that despite higher doses, with IMRT/VMAT techniques, frequencies of late GI and GU side effects decreased.

Recently performed randomized studies have revealed that compared with RT targeted at prostate bed only, irradiation of PLNs during extended field RT can yield more improved treatment outcomes. Although only few studies have compared the toxicities of both treatment modalities so far, extended field RT has yielded better bPFS in patients with adverse pathologic features (6,34). Deville et al. (35) stated

that WPRT enhanced the toxicity profile, while the acute GI side effects were increasing, there was no difference in GU or late GI side effects compared with PBRT. They reported 61% grade ≥2 acute GI and 22% GU toxicities, and 28% grade ≥2 late GU and 3% GI side effects in their patients (35). Van Praet et al. (16) reported on toxicity of postoperative high-dose WPRT with ADT for PCa patients with lymph node metastases using IMRT technique in the ART and SRT settings. Incidence rates of acute and late GI toxicities were higher following WPRT compared to PB-RT ($p \leq 0.041$) despite comparable GU toxicity rates (16). In this study where RT was applied with VMAT technique, any statistically significant difference was not detected between WPRT vs PB-RT -only groups in terms of bPFS, but acute GI side effects were observed more frequently in the WPRT group.

Study Limitations

Our study's limitation is its retrospective, non-randomized planning applied to a mixed group of patients who were applied ART or SRT, with short-term or long-term ADT. Among the ART and SRT patients, some characteristics may differ especially in the time elapsed between surgery and RT application and the inclusion of patients with a higher pre-RT PSA levels >0.5 ng/mL at the time of SRT.

A further limitation of this study is that treatment allocation (PB-RT versus WBRT) was not randomized; however, predefined risk-dependent criteria were used to allocate patients to the respective treatment modalities.

Conclusion

We present a comparison of oncologic outcomes and treatment-related side effects with adverse pathologic features in patients applied ART vs SRT. In patients with rising PSA, SRT was effective and applicable treatment modality with reduced toxicity. However, in high risk patients SRT results were as effective as ART outcomes. Serum PSA levels should be monitorized closely before treatment and taken consideration of administring early SRT would also delay the onset of treatment-related adverse events among these patients. As revealed in our study, clinical manifestations of treatment-related side effects could be reduced by using advanced treatment techniques like IMRT or VMAT.

Ethics

Ethics Committee Approval: This retrospective data analysis was approved by the ethics committee of our hospital (date: 20.11.2018, number: 1048).

Informed Consent: All patients signed a written informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.D., Ç.N., E.M., Design: S.D., M.H.A., E.M., M.D., Data Collection or Processing: S.D., Ç.N., Analysis or Interpretation: M.H.A., E.M., Ç.N., Literature Search: S.D., M.D., M.H.A., Writing: S.D., M.D.

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ORIGINAL RESEARCH

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Transverse Abdominis Plane Block-based Multimodal Analgesia Protocol Reduces Tramadol Need After Cesarean Section

Transvers Abdominis Plan Bloğu Tabanlı Multimodal Analjezi Protokolü, Sezaryen Sonrası Tramadol İhtiyacını Azaltır

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Abstract

Objective: Various strategies of multimodal analgesia exist for pain control following caesarean section, aiming to improve analgesia, reduce opioid requirement, and therefore decrease the incidence of opioid related side effects. This study aimed to compare the analgesic quality and reduction in tramadol need across four different multimodal analgesia strategies after caesarean section with general anesthesia.

Method: A total of 160 patients that underwent elective cesarean section under general anesthesia were retrospectively included in one of the following groups: only tramadol-based patient-controlled analgesia, tramadol-based patient-controlled analgesia plus diclofenac suppository, tramadol-based patient-controlled analgesia plus diclofenac suppository plus paracetamol, and tramadol-based patient-controlled analgesia plus diclofenac plus transverse abdominis plane block. Visual analogue scale scores and tramadol use were monitored and recorded at 2nd, 4th, 8th, 12th, and 24th hours.

Results: At 2nd, 4th and 8th hours, tramadol-based patient-controlled analgesia-only group had significantly higher visual analogue scale scores than all other groups ($p<0.05$). At 24th hour, transverse abdominis plane block group had lower scores than both tramadol-based patient-controlled analgesia-only group and tramadol-based patient-controlled analgesia plus diclofenac group ($p<0.01$ and $p=0.014$). Tramadol-based patient-controlled analgesia-only group had the highest and transverse abdominis plane block group had the lowest cumulative tramadol dose at all time points ($p<0.05$), the remaining two groups were similar ($p>0.05$).

Conclusion: Tramadol-based patient-controlled analgesia alone does not seem to provide effective pain control following caesarean section under general anesthesia. Multimodal analgesia including transverse abdominis plane block distinguishes itself with its most marked opioid-

Öz

Amaç: Sezaryen sonrası postoperatif ağrı tedavisinde, opioid ihtiyacını azaltmayı ve dolayısıyla opioidle ilişkili yan etkilerin insidansını azaltmayı amaçlayan çeşitli multimodal analjezi stratejileri mevcuttur. Bu çalışma, genel anestezi ile sezaryen olan hastalarda uygulanan dört farklı multimodal analjezi stratejisinde, tramadol ihtiyacındaki azalmayı ve analjezi kalitesini karşılaştırmayı amaçladı.

Yöntem: Genel anestezi altında elektif sezaryen yapılan toplam 160 hasta geriye dönük olarak şu gruplardan birine dahil edildi: sadece tramadol bazlı hasta kontrollü analjezi, tramadol bazlı hasta kontrollü analjezi artı diklofenak fitil, tramadol bazlı hasta- kontrollü analjezi artı diklofenak fitil artı parasetamol ve tramadol bazlı hasta kontrollü analjezi artı diklofenak artı transversus abdominis plan bloğu. Görsel analog skala skorları ve tramadol kullanımı 2., 4., 8., 12. ve 24. saatlerde izlenerek kaydedildi.

Bulgular: İkinci, 4. ve 8. saatlerde, sadece tramadol kullanılan hasta kontrollü analjezi grubu diğer tüm gruplardan anlamlı olarak daha yüksek görsel analog skala puanlarına sahipti ($p<0,05$). Yirmi dördüncü saatte, transversus abdominis plan bloğu grubu, hem tramadol bazlı hasta kontrollü analjezi grubu hem de tramadol bazlı hasta kontrollü analjezi artı diklofenak grubundan daha düşük skorlara sahipti ($p<0,01$ ve $p=0,014$). Kümülatif tramadol tüketimi, tramadol temelli hasta kontrollü analjezi alan grupta en yüksek, transversus abdominis plan bloğu grubunda ise tüm zaman noktalarında en düşük düzeyde olarak görülürken ($p<0,05$), kalan iki grubun tüketimleri benzerdi ($p>0,05$).

Sonuç: Tramadol bazlı hasta kontrollü analjezi tek başına genel anestezi altında sezaryen sonrası etkili ağrı kontrolü sağlamamaktadır. Transversus abdominis plan bloğu tabanlı multimodal analjezi protokolü, en belirgin opioid koruyucu etkiye sahipken, parasetamol ek fayda sağlamıyor gibi görünmektedir.

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Abstract

sparing effect, while paracetamol does not appear to provide additional benefits.

Keywords: Cesarean section, diclofenac, paracetamol, patient-controlled analgesia, tramadol, transverse abdominis plane block

Öz

Anahtar kelimeler: Diklofenak, hasta kontrollü analjezi, parasetamol, sezaryen, tramadol, transversus abdominis plan bloğu

Introduction

Proper management of postoperative pain caused by cesarean section results in improved patient satisfaction, early mobilization, and better bonding between the mother and infant. Despite many proposed management strategies, multimodal approach forms the cornerstone of the current treatment (1).

Patient controlled analgesia (PCA) with intravenous (IV) opiates is a well-established component of postoperative pain management following caesarean section or labor, particularly for patients receiving single dose spinal anesthesia or general anesthesia during the procedure. However, systemic use of high dose opiates is associated with adverse effects ranging from pruritis, nausea, and vomiting to sedation and respiratory depression (2,3). Tramadol, on the other hand, is a central analgesic with mixed opioid and non-opioid activity that has been reported to be associated with lower rates of neonatal respiratory depression as compared to other narcotics (4). Tramadol administration via IV PCA or continuous infusion provides effective early postoperative analgesia in patients undergoing caesarean section (5). Therefore, IV tramadol use for PCA not only provides satisfactory pain control, but also is preferred owing to its advantages in terms of respiratory depression, sedation, and intestinal motility (5). Nevertheless, high dose tramadol is known to be potentially associated with seizures as well as nausea/vomiting (6).

The objective of multimodal analgesia is to augment the analgesic effect, reduce the opioid dosage required for pain relief, and therefore decrease the incidence of opioid related side effects (7). Non-steroid anti-inflammatory drugs (NSAIDs) and paracetamol are among the main constituents of this approach and contribute to postoperative analgesia by significantly reducing morphine use (8). Furthermore, supplementary use of NSAIDs after caesarean section/labor is particularly valuable due to their ability to alleviate pain caused by uterine contractions (9,10). Transversus abdominis plane (TAP) block represents one of the abdominal field block techniques used for the treatment of postoperative pain after lower abdominal surgery. TAP-block has been most commonly used after caesarean section for postoperative pain control and to reduce the need for analgesia and incidence of side effects (11).

This study aimed to compare different analgesia strategies added on top of patient-controlled analgesia (PCA) with IV tramadol, in terms of their analgesic outcomes as well as tramadol sparing effects, in patients that undergoing cesarean section with general anesthesia.

Materials and Methods

Patients

A total of 160 patients with American Society of Anesthesiologists physical status of I-II undergoing elective caesarean section under general anesthesia were included. Subjects who received PCA with tramadol between 2014 and 2019 were screened. The following four multimodal treatment groups were defined and retrospectively 40 patients were included in each group: Only PCA with tramadol (TrPCA), TrPCA plus diclofenac suppository, TrPCA plus diclofenac suppository plus paracetamol, and TrPCA plus TAP-block. The study protocol was approved by the local ethics committee.

Anesthesia Management

Prior to general anesthesia, an 18G IV cannula was used to gain venous access for physiological saline infusion. In all three patient groups, induction was achieved with propofol 2 mg/kg (Propofol 1%, Fresensius Kabi, Istanbul, Turkey), followed by curarization with rocuronium bromide 0.6 mg/kg (Esmeron, Merck Sharp & Dohme, Istanbul, Turkey), intubation, and mechanical ventilation. After caesarean section and delivery were completed, all patients received fentanyl 1.5 mg/kg (Fentanyl 0.05 mg/mL, Johnson and Johnson, Istanbul, Turkey) as a part of the anesthesia protocol. Also, based on the discretion of the obstetrician, 10 IU oxytocin was administered intravenously to support uterine contractions.

Postoperative Analgesia Protocols

PCA with tramadol was administered to all patients undergoing caesarean section under general anesthesia. Following the completion of surgery and at the discretion of the attending anesthesiologist, one of the four main postoperative analgesia protocols of our unit was administered just prior to the termination of general anesthesia. The first protocol involved PCA with tramadol alone. The second group received additional diclofenac 100 mg as a suppository, followed by a second dose after 12 hours. The third group received additional diclofenac suppository plus paracetamol 0.5 mg IV every 6 hours, with the first dose being given just before the termination of anesthesia. The fourth group received additional diclofenac suppository plus transverse abdominis plane block via 20 cc 0.25% bupivacaine injection to both sides, performed under ultrasound guidance just prior to the termination of anesthesia. In all groups, tramadol (Contramal, Abdi Ibrahim, Istanbul, Turkey) administered via PCA comprised the main component of the postoperative pain treatment protocol. Before patients regained consciousness, a bolus 0.5 mg/kg dose of tramadol was administered in all groups. PCA was scheduled with 10-minute lock time and 20 mg bolus doses. The 4-hour limit was not used. The control button of the PCA device was supplied to patients after the completion of the recovery from anesthesia.

Assessments

Sedation scores, visual analogue scale (VAS) scores, and tramadol use were monitored for 24 hours and recorded at 2^{nd}, 4^{th}, 8^{th}, 12^{th}, and 24^{th} hours using the PCA follow-up form. Also, side effects such as nausea, vomiting, pruritis, or atony were recorded. VAS scores were measured using a 10 cm visual scale. For sedation, the following scoring was used: 1) conscious, 2) occasional drowsiness, 3) frequent drowsiness, 4) sleeping but easily awakened, 5) sleeping but awakened with difficulty. A score of >2 recorded at any time-point during the 24-h observation period was considered sedation, while nausea or vomiting was considered to occur if at least one episode was recorded.

Statistical Analysis

For data analysis, SPSS (Statistical Package for Social Sciences) version 21 software was used. Hypothesis tests and graphical methods were used to test normality. Between-group comparisons of continuous variables were done using One-Way analysis of variance (ANOVA) or the Kruskal-Wallis test, depending on data distribution. The Pearson chi-square test was used for the between-group comparison of categorical variables. Two-Way ANOVA test for repeated measurements was used to examine the significance of changes and differences between the groups in VAS scores and cumulative tramadol doses over time. Between-subject comparisons at different time points were done using the Kruskal-Wallis test and post hoc tests were done using built-in pairwise comparisons of the Kruskal-Wallis test. Two-sided p-values <0.05 were considered as the indication of statistical significance.

Results

Patients

Table 1 shows preoperative demographical and clinical characteristics. The only parameter that the groups differed was the duration of cesarean section (p<0.001). TrPCA plus diclofenac plus TAP-block group had significantly longer duration when compared to all other groups (p<0.001 for all comparisons).

Table 1. Preoperative patient characteristics

Characteristics	TrPCA only	TrPCA + diclofenac	TrPCA + diclofenac + paracetamol	TrPCA + diclofenac + TAP-block	p
Age, y	31.2±4.6	31.4±4.5	31.1±4.3	31.0±4.3	0.964*
BMI, kg/m^2	27.2±4.1	27.2±3.6	27.0±3.1	27.0±1.1	0.975*
SBP, mmHg	126.5±8.6	126.0±8.4	125.8±9.3	124.8±9.6	0.663*
DBP, mmHg	75.3±7.0	74.8±6.6	75.5±6.7	75.3±6.8	0.945*
MAP, mmHg	90.6±6.8	90.1±6.5	90.5±6.6	90.0±6.8	0.978*
Heart rate, beats/min	75.2±9.4	75.7±10.2	75.9±10.5	76.3±10.9	0.972†
Gestational age, weeks	38.4±0.8	38.5±0.8	38.5±0.9	38.5±0.9	0.973*
CS duration, min.	41.5±7.5	42.3±7.8	43.9±9.0	55.1±8.4	**<0.001***
Multiparity, n (%)	20 (50.0%)	21 (52.5%)	20 (50.0%)	20 (50.0%)	0.995‡

Unless otherwise stated, data presented as mean ± standard deviation. PCA: Patient-controlled analgesia with tramadol, TAP-block: Transversus abdominis plane block, BMI: Body mass index, SBP: Systolic blood pressure; DBP: Diastolic blood pressure, MAP, mean arterial pressure; CS: Cesarean sectio, TrPCA: Patient-controlled analgesia with tramadol. Each group has 40 patients. P-values are from Kruskall-Wallis (*), One-Way ANOVA (†), or Pearson's chi-square test

Changes in VAS Scores

Figure 1 shows the changes in mean VAS scores over time. There was a significant difference between the groups in terms of changes in VAS score over time (p<0.001). At 2nd, 4th and 8th hours, TrPCA group had significantly higher scores than all other groups (p<0.05 for all), but at 12th hour, the groups had similar scores. At 24th hour, TrPCA plus diclofenac plus TAP-block group had lower scores than both TrPCA and TrPCA plus diclofenac groups (p<0.001 and p=0.014).

Changes in Tramadol Requirement

Figure 2 shows the changes in cumulative tramadol dose over time. There was a significant difference between the groups in terms of changes in cumulative tramadol dose over time (p<0.001). TrPCA group had the highest and TrPCA plus diclofenac plus TAP-block group had the lowest cumulative tramadol dose at all time points (p<0.05 for all); however, the remaining two groups had similar cumulative doses over time (p>0.05 for all). At 24th hour, cumulative tramadol doses for the groups were as follows: TrPCA, 357.0±58.3 mg, TrPCA plus diclofenac, 289.0±54.7 mg, TrPCA plus diclofenac plus paracetamol, 261.0±41.5 mg, and TrPCA plus diclofenac plus TAP-block, 203.0±33.5 mg. Thus, TrPCA plus diclofenac plus TAP-block resulted in 43%, 30%, and 22% reduction in cumulative dose when compared to TrPCA, TrPCA plus diclofenac, and TrPCA plus diclofenac plus paracetamol group, respectively.

Side Effects

Table 2 shows the distribution of side effects across the groups. The differences of the frequencies of sedation,

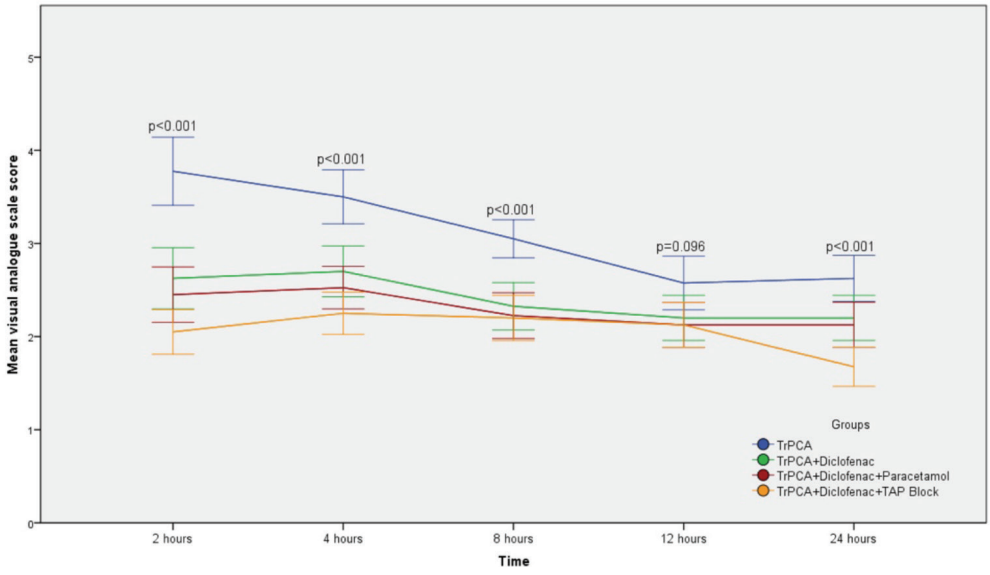

Figure 1. Changes in mean VAS scores over time. Error bars indicate 95% confidence intervals. p-value for Two-Way ANOVA for repeated measurements is <0.001, indicating a significant difference between groups in terms of changes in VAS score over time. p-values on the figure indicates significance of overall differences between groups at specific time points, which were obtained from Kruskal-Wallis test. To avoid confusion, p-values for pairwise comparisons at each time point is given in the text.

TrPCA: Patient-controlled analgesia with tramadol, TAP-block: Transversus abdominis plane block, VAS: Visual analog scale

Table 2. Frequencies of side effects

Side effect	PCA only	PCA + diclofenac	PCA + diclofenac + paracetamol	PCA + diclofenac + TAP-block	p*
Sedation*	1 (2.5%)	0	0	0	0.389
Nausea/vomiting	6 (15.0%)	2 (5.0%)	2 (5.0%)	2 (5.0%)	0.229
Pruritis	3 (7.5%)	1 (2.5%)	3 (7.5%)	2 (5.0%)	0.730
Uterine atony	1 (2.5%)	1 (2.5%)	1 (2.5%)	0	0.797
Any side effect	10 (25.0%)	4 (10.0%)	6 (15.0%)	4 (10.0%)	0.195

*Defined as >2 sedation score. Data presented as n (%). PCA: Patient-controlled analgesia with tramadol, TAP-block: Transversus abdominis plane block, CS: Cesarean each group has 40 patients. *p-values are from Pearson's chi-square test*

nausea/vomiting, pruritis, uterine atony as well as the frequency of any side effect did not reach statistical significance. However, when the groups were combined, the frequency of any side effect was higher in patients that received PCA only when compared to other patients that had add-on treatments (25.0% vs. 11.7%, p=0.041). On the other hand, the frequency of any side effect was not significantly different in the TrPCA plus diclofenac plus TAP-block group when compared to the rest of the patients (p=0.306).

Discussion

The findings of our study suggest that PCA with tramadol only was unable to provide adequate postoperative pain control in patients undergoing caesarean section under general anesthesia and that a management strategy based on multimodal analgesia may allow better pain control and reduced need for tramadol. To the best of our knowledge, this is the first study to examine such a high number of multimodal analgesia strategies in patients who underwent caesarean section with general anesthesia and received tramadol based IV PCA.

Opiates are administered via IV PCA following caesarean section to provide analgesia. However, it is important to limit postoperative need for opiates due to their well-established side effects such as sedation, nausea, and vomiting (2,3,12). Furthermore, opiates may also have adverse effects on the newborns (13). Therefore, not only the choice of suitable agents, but also reducing the need for opiates are clinically important considerations with respect to mother and infant health in this setting.

Tramadol, which has been shown to be quite effective for postoperative analgesia with synergistic effects when combined with non-opioid analgesics, has also been reported to be effective and safe when used for caesarean section (5,14,15). Its effects on the cardiovascular and respiratory systems are less pronounced as compared to equivalent doses of other opioids (16,17), which renders this agent suitable for multimodal analgesia. However, tramadol may still be associated with some opioid-type side effects. For instance, in the study by Mitra et al. (18) comparing diclofenac/tramadol and diclofenac/acetaminophen for pain management after caesarean section, both treatments were found to be effective, although there was a higher incidence of postoperative nausea among patients who received diclofenac/tramadol. Furthermore, tramadol may be associated with seizures (6) and shows limited efficacy in severe pain (1). Therefore, improving multimodal analgesia with non-opiate and opiate combinations including

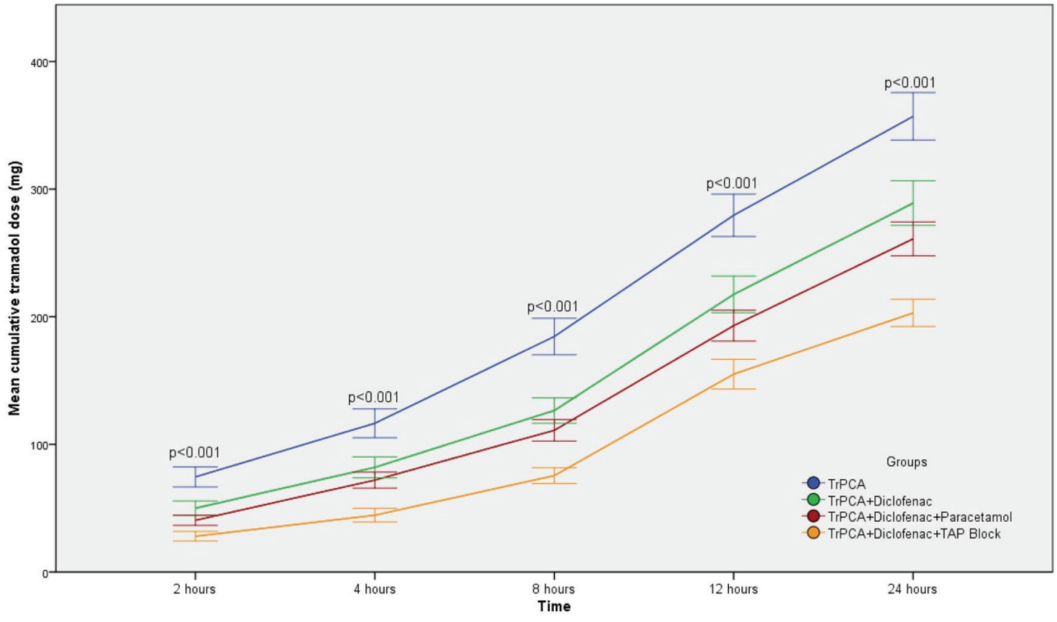

Figure 2. Changes in cumulative tramadol dose over time. Error bars indicate 95% confidence intervals. p-value for Two-Way ANOVA for repeated measurements is <0.001, indicating a significant difference between groups in terms of changes in cumulative tramadol dose over time. p-values on the figure indicates significance of overall differences between groups at specific time points, which were obtained from Kruskal-Wallis test. p-values for pairwise comparisons at each time point is given in the text. To avoid confusion, p-values for pairwise comparisons at each time point is given in the text.

TrPCA: Patient-controlled analgesia with tramadol, TAP-block: Transversus abdominis plane block

regional analgesia strategies such as local anesthetic-based TAP-block, and/or other analgesic agents may represent a key for ideal postoperative analgesia.

TAP-block is the administration of local anesthetics into the anatomic neuro-fascial space between the internal oblique and transversus abdominus muscles in the antero-lateral abdomen, to block the anterior branches of thoracic inter-costal (T7-T12) and first lumbar nerves. As shown in multiple studies, this allows safe and effective blockade of the nerves responsible for the transmission of pain sensation from the area of intervention in caesarean section (19,20). Although local anesthetic concentrations exceeding the safety limits have been detected in systemic circulation, systematic reviews have concluded that TAP-block is a relatively safe procedure (20). It has also been proposed that ultrasound-guided TAP-block may even be more effective and provide a means for more accurate nerve block, negating some of the side effects (19). Erbabacan et al. (21) observed comparable efficacy between TAP-block and IV PCA in patients undergoing lower abdominal surgery. However, these authors stated that when compared to IV PCA, TAP-block was preferable due to its ability to avoid systemic effects of morphine and due to more rapid onset of analgesic effects (21). Jadon et al. (22) in their double-blind randomized study concluded that ultrasound-guided TAP-block reduced the pain due to caesarean section with spinal anesthesia, prolonged the time to first request of analgesia, and decreased the need for additional opioids when used as a component of a multimodal analgesia strategy (22). Although superior analgesia was reported by Kanazi et al. (23) for subarachnoid morphine administered as compared to ultrasound-guided TAP block as a part of multimodal analgesia, the former method was also found to be associated with some serious side effects including nausea/vomiting and pruritus. In many other studies, TAP-block was reported to provide safe analgesia, improve patient comfort, and reduce the need for tramadol in patients undergoing caesarean section (9,11,24). In line with these findings, inclusion of TAP-block into multimodal strategy resulted in better analgesia and opioid-sparing effect in the present study.

NSAIDs are effective for the management of visceral pain caused by uterine contractions, which are an important factor for postoperative pain after caesarean section (9,25). Diclofenac is one of the most important inhibitors of the cyclooxygenase enzyme. Although its analgesic effect is primarily based on peripheral inhibition of prostaglandin synthesis, it is also known to exert central effects (26,27). Although NSAIDs have been associated with a slightly prolonged increase in bleeding time when used for postoperative pain management, this is not clinically significant (28). Olofsson et al. (9) showed that diclofenac at a dose of 150 mg administered over a 24-hour period as a part of multimodal analgesia strategy was associated with significantly reduced opiate use and improved analgesia quality in patients undergoing caesarean section, thus avoiding systemic side effects of opiates. Our findings also suggest that diclofenac may have a role in multimodal analgesia approach following cesarian section.

The analgesic activity of paracetamol, which also has antipyretic effects, is thought to occur via central anti-nociceptive mechanisms due to inhibition of cyclooxygenase-3, a purported variant of cyclooxygenase-1 (29). Paracetamol has a well-established efficacy and safety record and is considered a first-choice agent for the treatment of pain in pregnant or lactating women (30). Several studies have reported that paracetamol used in combination with tramadol following caesarean section may provide safe and effective analgesia and reduce the need for tramadol (31). On the other hand, Siddik et al., in their study investigating the effect of diclofenac and/or propacetamol on morphine doses administered via PCA, found that concurrent use of diclofenac with morphine based PCA improved analgesia quality, in addition to significantly reducing the need for morphine as compared to propacetamol and placebo (8). These authors showed that propacetamol itself, alone or in combination with diclofenac, did not contribute to the reduction in morphine requirement (8). Again, in the present study, while diclofenac was able to reduce tramadol use via PCA and to improve the quality of analgesia, paracetamol had no additional effects.

Pain after surgical procedures results from the direct trauma on neural structures as well as the stimulation of nociceptors. The roles of certain receptors, mediators, and neurotransmitters involved in central and peripheral sensitization after surgical incision have been relatively elucidated (32). When planning multimodal analgesia, these complex mechanisms and the involved receptors, mediators, and neurotransmitters should be taken into consideration as well as the need to prevent the development of chronic pain after surgery. Based on our results, TAP-block administered in conjunction with the peripherally acting diclofenac and centrally acting tramadol appears to provide the most effective analgesia together with minimized side effects.

Conclusion

Tramadol administered through PCA alone only does not seem to provide effective pain control following caesarean section under general anesthesia. Multimodal analgesia targeting multiple pain mechanisms not only contributes to the quality of analgesia, but also reduces the need for tramadol. Among different approaches tested, multimodal analgesia including TAP-block distinguishes itself with its most marked opioid-sparing effect, while paracetamol does not appear to provide additional benefits.

Ethics

Ethics Committee Approval: It was approved by Demiroğlu Science University Clinical Research Ethics Committee (2020/9-7).

Informed Consent: It was a retrospective study.

Peer-review: Internally peer-reviewed.

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

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ORIGINAL RESEARCH

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Immunohistochemical Analysis of 1.25-dihydroxyvitamin D3 Receptor Expression in Endometrial Cancer

Endometrium Kanserinde 1,25-dihidroksivitamin D3 Reseptör Ekspresyonunun İmmünohistokimyasal Analizi

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Abstract

Objective: This study aimed to immunohistochemically investigate the expression of 1.25-dihydroxyvitamin-D3-receptors (VDR) in benign and malignant lesions of the endometrial tissue.

Method: The cases were divided into two groups as benign (n=10) and endometrioid adenocarcinoma (n=17) according to their endometrial pathology results. The expression of VDR was examined by immunohistochemical method in endometrial tissues of participants (n=27). Then, VDR expression levels were compared between the groups. The intensity of expression, extent of staining and overall scores were determined for the semi-quantitative evaluation of VDR expression. Demographic data of the patients were also recorded.

Results: There was no significant difference between the groups in terms of demographic data (p>0.05) except age (p<0.001). VDR expression level in the malignant group was significantly higher than in the benign group (p<0.001). It was observed that when the tumor grade increased, the expression level of VDR also increased significantly (r=0.888, p<0.001). Similarly, VDR expression increased significantly as the stage progressed (r=0.639, p=0.006) but there was no statistically significant correlation between tumor size (p=0.645), estrogen receptor positivity, PR positivity and presence of lymphovascular invasion on VDR expression (p>0.05).

Conclusion: The expression of VDR was increased in endometrial cancer when compared to normal endometrial tissue. As the tumor behavior became aggressive, VDR expression also increased. As a result, increased VDR level may be associated with endometrial cancer development and stage of disease.

Keywords: Endometrial cancer, vitamin D, vitamin D receptor

Öz

Amaç: Bu çalışma, endometrial dokunun benign ve malign lezyonlarında 1,25-dihidroksi-vitamin-D3-reseptörlerinin (VDR) ekspresyonunu immünohistokimyasal olarak araştırmak için tasarlandı.

Yöntem: Olgular endometrial patoloji sonuçlarına göre benign (n=10) ve endometrioid adenokarsinom (n=17) olarak iki gruba ayrıldı. Olgulara (n=27) ait olan endometrial dokulardaki VDR ekspresyonu immünohistokimyasal yöntemlerle incelendi ve gruplar arasında VDR ekspresyon seviyeleri karşılaştırıldı. VDR ekspresyonunun yarı nicel değerlendirilmesi için ekspresyon yoğunluğu, boyanma dansitesi ve genel skorlar belirlendi. Hastalara ait demografik veriler kaydedildi.

Bulgular: Gruplar arasında, yaş dışındaki (p<0,001) demografik verilerde anlamlı fark yoktu (p>0,05). Malign grupta VDR ekspresyon düzeyi benign gruba göre anlamlı olarak daha yüksekti (p<0,001). Tümör derecesi arttığında VDR ekspresyon seviyesinin de önemli ölçüde arttığı gözlendi (r=0,888, p<0,001). Benzer şekilde, VDR ekspresyonu da evre ilerledikçe önemli ölçüde artmıştı (r=0,639, p=0,006). Ancak tümör boyutu, (p=0,645), östrojen reseptörü pozitifliği, PR pozitifliği ve lenfovasküler invazyon varlığı ile VDR ekspresyonu arasında istatistiksel olarak anlamlı bir ilişki bulunamadı (p>0,05).

Sonuç: VDR ekspresyonu, normal endometrial doku ile karşılaştırıldığında endometrial kanserde artmaktadır. Tümör davranışı agresif hale geldiğinde, VDR ekspresyonunun da arttığı gözlendi. Sonuç olarak, artan VDR seviyesi, endometrial kanser gelişimi ve hastalık evresi ile ilişkili olabilir.

Anahtar kelimeler: Endometrial kanser, vitamin D, vitamin D reseptörü

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Introduction

Endometrial cancer (EC) is the most common gynecological cancer in developed countries (1). Risk factors for EC are obesity, nulliparity, older age, unopposed estrogen therapy, and diabetes mellitus. There are two main subtypes of EC, known as endometrioid and non-endometrioid. Endometrioid type is well differentiated and estrogen dependent tumor seen at a younger age. In contrast, the non-endometrioid type (clear cell, serous) is known to be estrogen-independent and more aggressive tumors seen at older ages (2).

At the present times, low vitamin D levels are suggested as an important risk factor for many types of cancer. It has been reported that vitamin D may achieve its anti-carcinogenic effect via inhibition of cellular proliferation, enhancement of differentiation, apoptosis and modulation of calcium metabolism (3,4). Besides the anti-carcinogenic properties of vitamin D, it also has positive effects on cardiovascular disease and diabetes mellitus (5,6).

Vitamin D active form (1.25-dihydroxyvitamin-D3) achieves all these effects via 1.25-dihydroxyvitamin-D3-receptors (VDR). VDR belongs to the nuclear receptor group and is located on the long arm of the 12th chromosome. VDR has been shown to be found in 30 different tissues in the body, including the endometrium. VDR is known to regulate gene expression by interacting with retinoic acid (RXR) transcription factor after combining with vitamin D active form (7,8). A recent study has reported that the RXR receptor and VDR are overexpressed in mutation of BRCA1 in breast cancer cases and predicted overall survival (9). VDR expression has been demonstrated in many types of cancer, including EC. This situation strengthens the possibility of VDR to play a role in cancer etiology (10). Since studies investigating the relationship between EC and VDR are quite limited in the literature (11,12), we aimed to investigate the vitamin D receptor expression in EC cells in the present study.

Materials and Methods

Tissue samples were obtained from İstanbul University Cerrahpaşa-Cerrahpaşa Pathology Laboratory between January 2017 and January 2018. Demographic data of the patients were recorded. The cases were divided into two groups as benign (n=10) and endometrioid adenocarcinoma (n=17) according to their endometrial pathology results. The expression of VDR was immunohistochemically (IHC) investigated in endometrial tissues of participants (n=27) and VDR expression levels were compared between the groups. The intensity of expression, staining density and overall scores were determined for the semi-quantitative evaluation of VDR expression.

The material was archival formalin-fixed, paraffin-embedded tissue from routine histopathological work-ups. Tumor blocks of paraffin-embedded tissue were selected by experienced pathologist, evaluating the routine H&E stained sections. Tissue samples used for immunohistochemistry were proliferative and secretory phase endometrium and endometrioid adenocarcinoma

IHC Analysis

The immunostaining was carried out at the room temperature using DAKO Autostainer Universal Staining System (Autostainer Link 48 DAKO, Glostrup, Denmark). At the first step, sections obtained from selected paraffin embedded blocks in 4-mm thickness were put on positively charged slides. Then, all the sections were deparaffinized in xylene and dehydrated through a graded series of ethanol solution. At the third stage, antigen retrieval was performed at 96 °C (10 mM/L citrate buffer, pH 6) for 40 min in a thermostatic bath (PT link). The sections were incubated with anti-GC (primary VDR antibody cat. no: #12550, Cell signaling technology, inc. dilution of 1:200) for 60 min at the room temperature. Positive and negative controls were added for antibody. A streptavidin-biotin enhanced immunoperoxidase technique (K8000 Envision Flex, DAKO, Glostrup, Denmark) in an automated system was used to show immunoreactions. The sections were incubated with DAB and counterstained lightly with hematoxylin to demonstrate binding. Finally, the sections were dehydrated and mounted onto the slides. The positively immunostained slides were used as positive controls. Normal rabbit serum IgG was used to replace primary antibody as a negative control.

Evaluation of the Immunostaining

All the sections were examined under light microscope (Olympus BX53 Olympus Co., Tokyo, Japan). Image Analysis Software (DP-BSW Microscope digital camera software program) was used for assessing the samples. For each section, five areas of similar grade were analyzed semiquantitatively for the fraction of cells staining. The intensity of VDR expression evaluated microscopically was graded on a scale of 0 to 3+ (0, no staining; 1+, mildly intense; 2+, moderately intense; 3+, severely intense). The extent of staining was quantified as the percentage of cells staining positive for VDR antibody, as follows: 0= no

staining; 1= positive staining in <25% of the sample; 2= positive staining in 25%-50% of the sample; 3= positive staining in >50% of the sample. Intensity score (0 to 3+) was multiplied by the density score (0-3) to give an overall score of 0-9. The overall score for each specimen was then categorically assigned to one of the following groups: 0 score, negative expression; 1-2 scores, weak expression; 3-6 scores, moderate expression; 7-9 score, strong expression (Table 1) (13).

Statistical Analysis

Whether the distributions of continuous variables were normal or not was determined with the Shapiro-Wilk test. The assumption of homogeneity of variances was examined by the Levene test. Descriptive statistics were expressed as mean ± standard deviation, median (minimum-maximum) or number of cases and (%), where appropriate. While the mean differences between the groups were compared using the Student's t-test, the Mann-Whitney U test was applied for the comparisons of the variables which did not meet the parametrical test assumptions. In both 2x2 and also RxC contingency tables to compare categorical variables, the Fisher's Exact or Fisher Freeman Halton test was used when ¼ or more of the cells had an expected frequency of 5 or less. Spearman's rank order correlation coefficients were calculated to determine degrees of association between tumor size, tumor grade, and stage with overall expression scores. Data analysis was performed using IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY, USA). A p-value less than 0.05 was considered as statistically significant.

Results

Comparisons of demographic and clinical characteristics of benign (control) and malignant (study) groups are shown in Table 2. The mean age of the case group was statistically significantly higher than that of the control group (p<0.001). Among the groups, there was no statistically significant difference in terms of body mass index, parity, education level, hypertension, diabetes mellitus and smoking history (p>0.05).

Other clinical parameters of endometrioid cancer cases are shown in Table 3.

The intensity, extent of staining and overall median expression scores of the study group were statistically significantly higher than those of the control group (p=0.005, p<0.001 and p<0.001) (Figure 1).

Table 3 shows the correlation levels between tumor grade, tumor diameter and stage and overall staining score within the study group. Accordingly, as the tumor grade increased, the overall expression score increased significantly (r=0.888,

Table 1. Immunohistochemical evaluation of vitamin D receptors

Score	Intensity expression (X)	Staining density (Y)	Overall score (XxY)
0	No staining	No staining	Negative expression
+1	Mildly intense	<25% of the sample	1-2: weak expression
+2	Moderately intense	25-50% of the sample	3-6: moderate expression
+3	Severely intense	>50% of the sample	7-9: strong expression

Table 2. Demographic and clinical data of the groups

	Control group (n=10)	Study group (n=17)	p
Age (year)	48.0±4.0	58.9±7.4	**<0.001†**
BMI (kg/m²)	27.2±4.0	29.6±5.6	0.253†
Parity	3 (2-5)	2 (0-5)	0.287‡
Education	-	-	0.773¶
Primary school	9 (90.0%)	13 (76.5%)	-
High school	1 (10.0%)	2 (11.8%)	-
University	0 (0.0%)	2 (11.8%)	-
Hypertension	4 (40.0%)	9 (52.9%)	0.695¥
Diabetes mellitus	3 (30.0%)	8 (47.1%)	0.448¥
History of smoking	2 (20.0%)	4 (23.5%)	>0.999¥
Intensity expression scores	1 (1-3)	2 (1-3)	**0.005‡**
Staining density scores	1 (0-1)	2 (1-3)	**<0.001‡**
Overall scores	1 (0-2)	4 (1-9)	**<0.001‡**

†Student's t-test, ‡Mann-Whitney U test, ¶Fisher-Freeman-Halton test, ¥Fisher's Exact test, BMI: Body mass index

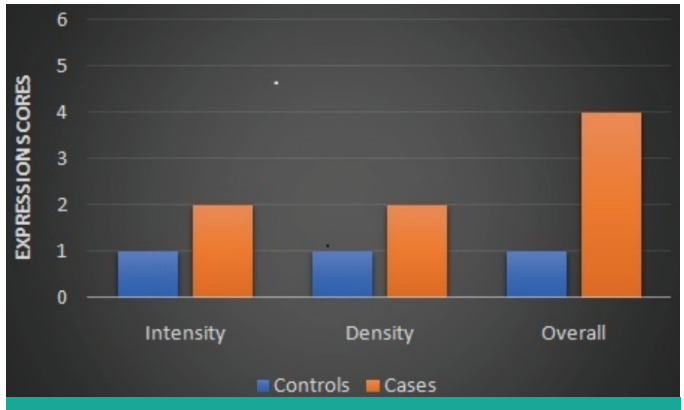

Figure 1. The distribution of VDR expression scores (intensity, density and overall) in the endometrial tissue according to the groups

VDR: 1.25-dihydroxyvitamin-D3-receptors

p<0.001). While there was no statistically significant correlation between tumor diameter and overall expression (p=0.645), as the stage progressed, the overall expression score also increased significantly (r=0.639, p=0.006).

Table 3. Other clinical findings of the cases within the study group

	n=17
Grade of tumor	
I	6 (35.3%)
II	8 (47.1%)
III	3 (17.6%)
Tumor diameter (cm)	3.5 (0.5-5.0)
ER +	10 (58.8%)
PR +	10 (58.8%)
Myometrial invasion	
Less than ½	14 (82.4%)
More than ½	3 (17.6%)
Lymphovascular invasion	4 (23.5%)
Intraperitoneal fluid	
Benign	14 (93.3%)
Malignant	1 (6.7%)
Stage	
A1	13 (76.5%)
B1	1 (5.9%)
B2	2 (11.8%)
4	1 (5.9%)

ER: Estrogen receptor, PR: Progesterone receptor

In Table 4, the comparisons made in terms of overall staining scores according to the other clinical findings of the cases within the case group are included. Accordingly, there was no statistically significant effect of ER positivity, PR positivity and LVI on overall expression scores (p>0.05). On the other hand, overall staining scores of those with more than ½ were statistically significantly higher than those with myometrial invasion level less than ½ (p=0.012).

IHC Results of the VDR

VDR Expression in Normal Endometrium

The VDR immunoreactivity in the proliferative and secretory phase endometrium was weak nuclear staining in the glandular epithelium compared to the surrounding stroma. Some of the normal endometrial glands revealed weak nuclear immunoreactivity for VDR, while the remaining cases were VDR negative (Figure 2).

VDR Expression in Endometrioid Adenocarcinoma

The VDR immunostaining of an endometrioid adenocarcinoma revealed moderate-strong immunostaining of endometrial cells. The intensity of VDR immunostaining and the number of VDR positive cells were both up-regulated in endometrioid adenocarcinoma cells as compared to control endometrium. In respect of the vitamin D receptor in grade III endometrioid adenocarcinoma, its expression was more increased compared to normal endometrial glands. It

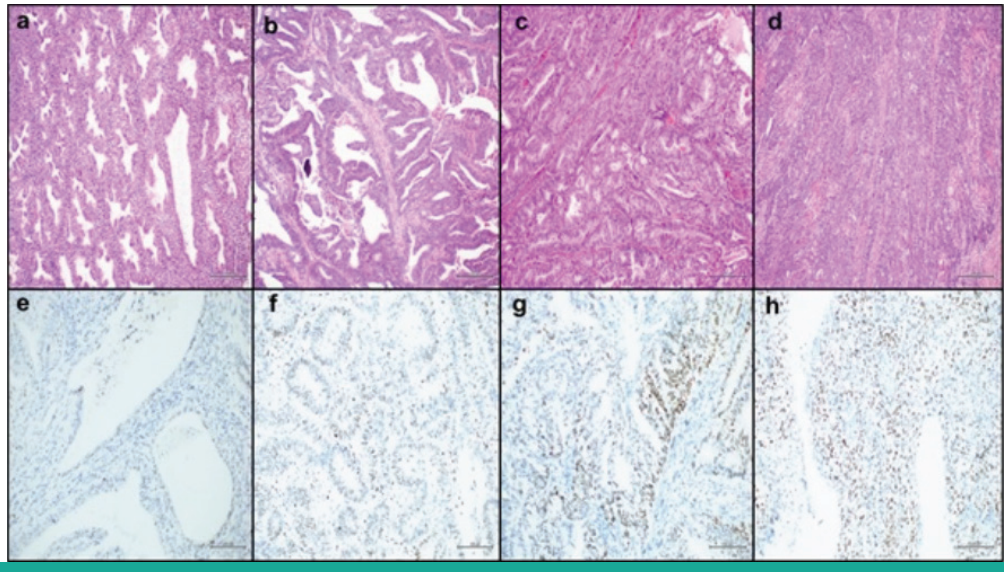

Figure 2. Expression of VDR in normal endometrial tissue and endometrioid adenocarcinoma. H-E staining (a,b,c,d) and immunohistochemical VDR expression (e,f,g,h) in normal endometrial tissue (a,e), grade I (b,f), grade II (c,g) and grade III (d,h). Original magnification of H-E and VDR immunostaining at x200 (scale bar 100 µm). Notice strong immunoreactivity for VDR that is upregulated in grade III endometrioid adenocarcinoma compared to normal endometrial tissue

VDR: 1.25-dihydroxyvitamin-D3-receptors

was shown that the VDR immunoreactivity was upregulated in cancer cells (Figure 2).

Discussion

Currently, the relationship between vitamin D and cancers is being studied more. However, most of these studies consist of epidemiological studies (13,14). Although the relationship between vitamin D and many cancer types has been shown, the studies on the relationship between EC and vitamin D are quite limited in the literature. In an ecological study, it was shown that ultraviolet-B decreased the incidence of EC by increasing vitamin D level. On the contrary, it was emphasized in a meta-analysis that no significant relationship was found between vitamin D intake and EC. These conflicting and limited results suggest that this issue should be investigated further.

Studies on vitamin D receptors at the tissue receptor level are very limited in the literature, especially in EC (11,12). Therefore, we chose to investigate vitamin D receptor expression in EC tissue.

In the systematic review by Deuster et al. (10), it was reported that VDR expression increased in all gynecological cancers. In addition, it was reported that *VDR* gene polymorphism was associated with increased risk of breast, prostate, and bowel cancer in studies other than gynecological cancers (15-17). This information supports the possibility that VDR may play a role in the development of EC.

It is known that estrogen is an important risk factor in the development of EC (2). It was reported in a previous study that VDR was a mediator of estrogen-dependent pathways (18). In our study, there was no statistically significant effect of ER positivity and PR positivity on overall expression scores ($p>0.05$) in endometrioid adenocancer cases. We think that further studies at molecular level are needed in the future regarding the relationship between estrogen and VDR.

Table 4. Correlation coefficients and significance levels between tumor grade, tumor diameter and stage and overall staining score within the study group

	Correlation coefficients	p†
Tumor grade	0.888	**<0.001**
Tumor diameter	-0.121	0.645
Stage	0.639	**0.006**

†Spearman's rank order correlation analysis

There were very few studies in the literature similar to our study. In the study conducted by Agic et al. (11) in only five EC cases, VDR expression was found to be higher in the EC group compared to the benign group. These findings were not compatible with those of Bergada et al. (12). Yabushita et al. (19) observed that VDR expression decreased when 1.25-dihydroxyvitamin D3 was added to EC live cell cultures for six days. In our study, VDR expression was found to be higher in the EC group (n=17) compared to the benign group. This situation may be explained by the increase in VDR due to low vitamin D level in EC. Since our study was designed retrospectively, serum vitamin D levels could not be measured simultaneously.

In our study, in accordance with the findings of Bergada et al. (12), it was observed that VDR expression increased significantly as the grade of tumor tissue increased in EC cases ($r=0.888$, $p<0.001$). In addition, as the stage progressed, the overall expression score also increased statistically significantly ($r=0.639$, $p=0.006$) but there was no statistically significant correlation between tumor diameter and overall expression ($p=0.645$). Similarly, overall staining scores of those with more than ½ were statistically significantly higher than those with myometrial invasion level less than ½ ($p=0.012$). This indicates that VDR expression increases as the tumor grade and stage increases. There was information that VDR expression increased as vitamin D level decreased. (19). VDR is a nuclear receptor and it is not clear how to work. In a molecular study on VDR, it was reported that VDR interacts with transcription factors such as RXR and exerts its anticarcinogenic effects by regulating gene expression (8). In this way, it may be possible for VDR to affect grade and stage of tumors.

There was no significant difference in demographic data except age. This difference may be related to the fact that EC cases are seen at older ages. Moreover, simultaneous serum vitamin D levels could not be measured because our study was not designed prospectively. In addition, the inhomogeneity of the number of the groups, low number of cases and not investigating the relationship between histological subtypes and VDR expression can be counted among the limitations of this study.

Conclusion

As a result, increased VDR expression in endometrial tissue may be closely related to the development of EC. Prospective studies are needed on this subject.

Ethics

Ethics Committee Approval: The study protocol was approved by the local ethics committee of our institution (09/12/2020-E.63807).

Informed Consent: Written informed consent was obtained.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: Ö.D.T., N.K.Ç., Design: Ö.D.T., N.K.Ç., Data Collection or Processing: Ö.D.T., N.K.Ç., Literature Search: Ö.D.T., N.K.Ç., Analysis or Interpretation: Ö.D.T., N.K.Ç., Writing: Ö.D.T., N.K.Ç.

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ORIGINAL RESEARCH

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Multiple Primary Tumors of the Gastrointestinal Tract: Our Six-year Results

Gastrointestinal Sistemin Çoklu Primer Tümörleri: Altı Yıllık Sonuçlarımız

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Abstract

Objective: Multiple primary tumors (MPTs) are tumors that develop simultaneously or at different times in the same or different organs. They are divided into two groups as synchronous and metachronous tumors. Genetic instability, gene mutation, immunodeficiency, prolongation of life span with chemotherapy, radiotherapy and target treatments are among the reasons that increase the development of the second primary tumor. In our study, we aimed to present cases with MPTs accompanying gastrointestinal system (GIS) tumors with clinicopathological features.

Method: The cases having the criteria of MPT among the cases diagnosed with primary tumor discussed in the GIS councils of our hospital between 2014 and 2019 were included in our study.

Results: A total of 162 cases (4.7%) with a diagnosis of MPT were detected. While 52 of the cases were in the synchronous tumor group and 110 were in the metachronous tumor group. Most of the patients in both groups were male (59.9%). The most common MPT groups observed in men were left colon-prostate and rectum-right colon tumors, and stomach-breast and left colon-breast tumors in women. The second primary tumors accompanying GIS tumors in the synchronous and metachronous tumor groups belonged to the GIS and urogenital system. Survival rates were lower in cases with metachronous tumors than in cases with synchronous tumors, but the intergroup difference was not statistically significant. The survival rate in cases of GIS malignancy originating from the stomach was lower compared to cases with other GIS malignancies with a statistically significant difference.

Conclusion: In terms of GIS tumors, prostate and colon tumors in men and breast tumors in women may be risk factors for the development of MPTs.

Keywords: Gastrointestinal system, metachronous, multiple primary tumor, synchronous

Öz

Amaç: Çoklu primer tümörler (ÇPT) eş zamanlı ya da farklı zamanda aynı ya da farklı organlarda gelişen tümörlerdir. Senkron ve metakron tümör olarak iki gruba ayrılmaktadırlar. Genetik instabilite, gen mutasyonu, immün yetmezlik, kemoterapi, radyoterapi ve hedef tedavileri ile yaşam süresinin uzaması ikinci primer tümör gelişimini artıran nedenler arasında sayılmaktadır. Çalışmamızda gastrointestinal sistem (GİS) tümörleri ile birliktelik gösteren ÇPT'li olguları klinikopatolojik özellikleriyle birlikte sunmayı amaçladık.

Yöntem: Çalışmamıza 2014-2019 yılları arasında hastanemiz GİS konseylerinde tartışılan primer tümör tanısı almış olgular içinden ÇPT kriterleri taşıyan olgular dahil edildi.

Bulgular: ÇPT tanılı 162 olgu (%4,7) saptandı. Olguların 52'si senkron, 110'u metakron tümör grubundaydı. Her iki grupta olguların çoğu erkekti (%59,9). Erkeklerde en sık izlenen çoklu primer tümör grubu sol kolon-prostat ve rektum-sağ kolon iken, kadınlarda mide-meme ve sol kolon-memeydi. Senkron ve metakron tümör grubunda GİS tümörlerine eşlik eden ikinci primer tümörler GİS ve ürogenital sisteme aitti. Sağkalım oranları metakron tümörlü olgularda senkron tümörlü olgulara göre daha düşük saptandı, ancak aradaki fark istatistiksel olarak anlamlı değildi. GİS malignitesi mide kaynaklı olgularda sağkalım oranı, diğer GİS malignitesi olan olgularla karşılaştırıldığında daha düşüktü ve istatistiksel olarak anlamlıydı.

Sonuç: GİS tümörleri açısından erkeklerde prostat ve kolon, kadınlarda ise meme tümörleri ÇPT gelişimi için risk faktörü olabilir.

Anahtar kelimeler: Çoklu primer tümör, gastrointestinal sistem, metakron, senkron

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Introduction

Multiple primary tumors (MPTs) are tumors that develop simultaneously or at different times in the same or different organs. Three features should be present in these tumors; each tumor should be proven to be malignant, histologically different, and should not be the recurrence or metastasis of another tumor (1). MPTs are divided into two groups as synchronous and metachronous tumors. If the second tumor is detected 6 months after the diagnosis of the first tumor, it is called metachronous, and if detected within 6 months, it is called synchronous tumor.

It has been reported that the risk of developing a second tumor for each individual increases 1.1 times for each month after the diagnosis of the first primary tumor (2). Different factors such as genetic instability, gene mutation, immunodeficiency and persistent environmental carcinogens can also trigger the development of multiple tumors (3). In addition, prolongation of life span with chemotherapy, radiotherapy, chemoradiotherapy and target treatments are among the reasons that increase the development of the second primary tumor (4,5).

In our study, we aimed to present the cases with MPTs that we detected among the cases discussed in the gastrointestinal system (GIS) council of our hospital, together with their clinicopathological features, in the light of literature information.

Materials and Methods

The cases with MPT criteria (1) among the cases diagnosed with primary tumor discussed for treatment and follow-up at the GIS councils held in our hospital between 2014 and 2019 were included in our study. Ethical approval for this study was obtained from Ethics Committee (06.30.2020/288).

In the council files, the primary tumor located in the GIS and tumors secondary to previously detected primary tumor were grouped as synchronous and metachronous tumors, respectively, according to their date of diagnosis. In addition to the demographic characteristics (age, gender of the cases and family history) obtained from the council files, from the pathology and hospital archives including the localization and histopathological diagnosis of MPTs, the diagnostic intervals of synchronous and metachronous tumors (in months according to their occurrence before or after the development of GIS tumor), and from the files of the cases, follow-up times (in months) were retrieved.

Statistical Analysis

Continuous variables were presented as median (interquartile range) or mean ± standard deviation, according to their normality of distribution. Categorical variables were presented as numbers and percentages. The compliance of the numerical values to the normal distribution was examined using histograms or analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk test). The Student's t-test was used to compare the means between the groups. The chi-square or Fisher's Exact test, where appropriate, was used to compare proportions between the groups. Survival data were evaluated using the Kaplan-Meier analysis and compared using the Log-rank test. An overall p-value less than 0.05 was considered as statistically significant. Statistical analyses were performed using the SPSS software v22 (IBM Inc, USA).

Results

Clinical features of the cases

Among the 3.546 cases discussed in the GIS council between 2014 and 2019, 162 cases (4.7%) had a diagnosis of MPTs. While 65 (40.1%) of the cases were female, 97 (59.9%) were male. There were 52 (32.1%) cases in the synchronous tumor group and 110 (67.9%) cases in the metachronous tumor group. The mean age at diagnosis was 64.58±9.71 years in the synchronous tumor group and 65.39±11.25 years in the metachronous tumor group. Most of the cases in the synchronous and metachronous tumor groups were over 50 years old (92.3% vs 90.9%). Both tumor groups were more common in males (67.3% vs 56.4%). The mean time interval between the diagnoses of two primary tumors in the metachronous tumor group was 60 months (24-123 months). In this group, the first primary tumor detected in five patients was of GIS origin. In the other 105 cases, the GIS originated tumor was the second primary tumor. Time elapsed between the diagnoses of two primary tumors was 60 months (18-72 months) when GIS originated tumors were the first primary tumors, and 72 months (24-132 months) when the second primary tumor developed.

Cases with a family history of cancer were more numerous in the metachronous tumor group compared to the synchronous tumor group (9.6% vs 20%), without a statistically significant intergroup difference (p=0.098). Left colon and stomach tumors were frequently observed among GIS tumors, while breast and prostate tumors were more common as the second primary tumors.

Although the ratio of female to male patients was equal in 14 cases diagnosed with multiple tumors under the age of 50 years, female cases were more numerous in the metachronous tumor group than in the synchronous tumor group. The second primary tumors were mostly of lower GIS origin and more frequently observed in the metachronous tumor group. Relevant family history was found only in two cases in the metachronous tumor group.

The clinical features of all cases are presented in Table 1, and the clinical features of the cases in the group under 50 years of age are included in Table 2.

Distribution of GIS tumors and their relationship with the second primary tumor group

The most common locations of GIS tumors were the stomach (28.4%), rectum (25.9%), left colon (21.6%) and right colon (12.9%) in order of their frequencies. Locations in the esophagus (5.6%), appendix (2.5%), transverse colon (1.9%) and anal canal (1.2%) were observed less frequently. The most common tumor locations in males were the rectum (28.9%) and stomach (26.8%). In women, most frequently, tumors were seen in the stomach (30.8%) and left colon (23.1%). The most common MPT groups in males were left colon-prostate (0.06%) and rectum-right colon tumors (0.06%), whereas in females they were stomach-breast (0.2%) and left colon-breast tumors (0.11%).

The second primary tumors accompanying GIS tumors in the synchronous and metachronous tumor groups belonged to the GIS (13% vs 11.7%) and the urogenital system (6.8% vs 16.7%). Colorectal tumor (9.9% vs 9.3%) was most frequently detected in the GIS group, and prostate cancer (3.1% vs 10.5%) was most often detected among urogenital system tumors. When tumor localizations were evaluated separately, it was found that GIS tumors were mostly accompanied by breast (20.4%) and prostate (13.6%) tumors. The most common accompanying gastric tumors among GIS tumors were breast (28.3%) and prostate tumors (10.9%).

The distribution of synchronous and metachronous GIS tumors according to their localizations is given in Table 3, and the distribution of GIS tumors and second primary tumors according to their localizations is given in Table 4.

Histopathological findings of the cases

The most common histological type of GIS malignancies was adenocarcinoma (83.3%). Signet ring cell carcinoma (4.9%), gastrointestinal stromal tumor (GIST) (3.1%), squamous cell carcinoma (3.1%), neuroendocrine tumor (2.5%), mucinous carcinoma (2.5%) and high-grade B-cell lymphoma (0.6%) were other detected histological types. The majority of synchronous and metachronous tumors had morphologic features of adenocarcinoma (73.8% vs. 88.2%).

Table 1. Clinical characteristics of MPTs

	Synchronous (n, %)	Metachronous (n, %)	Total (n, %)	p
No. of patients	52 (32.1)	110 (67.9)	162	-
Age. mean ± SD	64.58±9.71	65.39±11.25	-	0.654
Median interval. mo	-	72 (24-132) (for second tumor from GIS)	-	-
		60 (18-72) (for first tumor from GIS)	-	-
Gender				0.185
Male	35 (67.3)	62 (56.4)	97 (59.9)	
Female	17 (32.7)	58 (43.6)	65 (40.1)	
Age at diagnosis of primary tumor				1
<50	4 (7.7)	10 (9.1)	14 (8.6)	
≥50	48 (92.3)	100 (90.9)	148 (91.4)	
Family history				0.098
Yes	5 (9.6)	22 (20)	27 (16.7)	
No	47 (90.4)	88 (80)	137 (83.3)	
First degree	3 (5.8)	18 (16.4)	21 (13)	
Second degree	2 (3.8)	4 (3.6)	6 (3.7)	

MPT: Multiple primary tumor, mo: Month, GIS: Gastrointestinal system, SD: Standard deviation

GIST, which is among the special diagnoses, was in four cases in the synchronous tumor group and in one case in the metachronous tumor group. It was located in the stomach in four cases and in the right colon in one case. Three of the accompanying secondary primary tumors were GIS tumors, and two of them originated from the breast and all of them had adenocarcinoma morphology. Neuroendocrine tumor detected in four cases was in the synchronous tumor group. All four cases were localized in the appendix. The second primary accompanying tumors were located in the GIS and one in the uterus (endometrium) which had adenocarcinoma morphology. High-grade B-cell lymphoma was also in the synchronous tumor group and was located in the right colon. The accompanying second primary tumor was located in the liver and was diagnosed as hepatocellular carcinoma.

The distribution of histopathological diagnoses of GIS tumors is given in Table 5.

Survival

The mean follow-up period of all cases was 16 months (7.75-31 months) from the time of diagnosis. The median survival time of cases with synchronous tumors was 44 months [95% confidence interval (CI), 33.8-54.2%], and the median survival time of cases with metachronous tumors was 22 months (95% CI, 18.8-25.2%). While 1, 3 and 5-year survival rates were 79.4%, 58.3% and 42.7% in cases with synchronous tumors, they were 89.1%, 35.9% and 33.3% in cases with metachronous tumors, respectively. Although survival rates were found to be lower in cases with metachronous tumors than in cases with synchronous tumors, the intergroup difference was not statistically significant (p=0.086) (Figure 1A). During the follow-up period, 21 (40.4%) of 52 cases in the synchronous tumor group and 55 (50%) of 110 cases in the metachronous tumor group died.

The survival rate of cases with GIS malignancy originating from the stomach was lower compared to cases with other GIS malignancies, and this result was statistically significant (p=0.002) (Figure 1B).

The median survival time for cases in the group under 50 years old was 22 months (95% CI, 8.4-35.7 months). The survival times of two patients with a relevant family history was significantly lower than those without an associated family history (p=0.008) (Figure 2). Though not statistically

Table 2. Characteristics of the patients aging under fifty years

	Synchronous (n, %)	Metachronous (n, %)	Total (n, %)
No. of patients	4 (28.6)	10 (71.4)	14
Median interval. mo	-	54 (21-99) (second tumor from GIS)	-
Gender			
Male	3 (75)	4 (40)	7 (50)
Female	1 (25)	6 (60)	7 (50)
Age at diagnosis of primary tumor			
≤45	2 (50)	3 (30)	5 (35.7)
≥45	2 (50)	7 (70)	9 (64.3)
Family history			
Yes	0 (0)	2 (20)	2 (14.3)
No	4 (100)	8 (80)	12 (85.7)
First degree	-	2 (80)	2 (14.3)
Second degree	-	0 (0)	0 (0)
Second tumor			
Upper GIS	0 (0)	3	3
Lower GIS	4	7	11
Follow-up, mo	16 (8.75-50.25)	15.5 (6.5-29)	16 (7-29)
Final state			
Alive	3 (75)	5 (50)	8 (57)
Ex	1 (25)	5 (50)	6 (43)

MPT: Multiple primary tumor, mo: Month, GIS: Gastrointestinal system

significant, the survival times of the female cases were lower than those of male patients (p=0.091), and both cases with a relevant family history were women. In this group, there was no difference in survival rates between cases with synchronous and metachronous tumors (p=0.492).

Discussion

The incidence of MPTs varies between 0.5% and 11.7% in the literature (5,6). Among these tumors, the frequency of synchronous tumors is reported to be 30-55 % (4,7). Our rate of MPTs in our study was 4.7%. Synchronous tumors were detected in 32.1% of the cases. These findings seem to be compatible with the literature. However, our study included only GIS tumors. This rate would have been lower if all system tumors had been included.

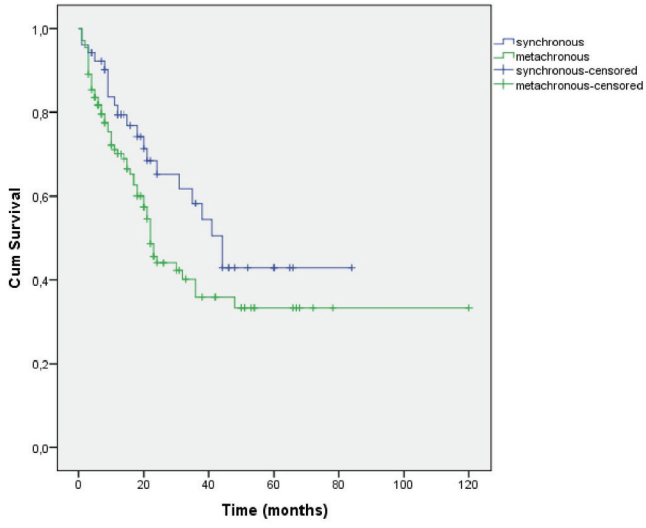

Figure 1A. Survival curve between synchronous and metachronous tumors

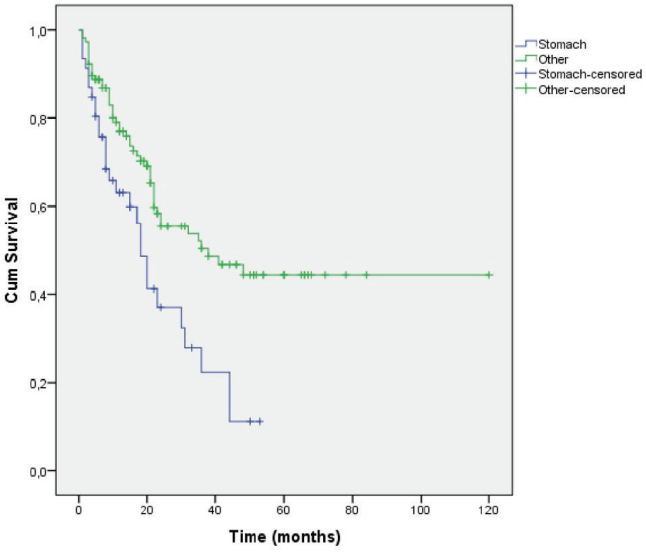

Figure 1B. Survival curve between stomach and other tumors

Although MPTs can be seen at any age, they are more common in patients at 50 years of age or older (8). In our study, most of the patients in the synchronous and metachronous tumor groups were over 50 years old (>64.5 years). Smaller number of cases were included in the group under 50 years of age, still more than half of these cases were observed in the metachronous tumor group. This finding was also compatible with the literature data (5).

MPTs are more common in men than in women. The male/female ratio reported in the literature varies between 0.9 and 3.5/1 (7,9,10). In our study, this rate was 1.5 which was consistent with the literature data. In our study, the mean time interval between the diagnoses of two primary tumors in the metachronous tumor group was 60 months. In the literature, this period varies between 60 months in cases with colorectal tumors and between 42 and 46.9 months in cases with gastric tumors (4,11). This highlights the fact that the follow-up of cases with the diagnosis of primary tumor should be at least five years.

Among the reasons why synchronous tumors are observed more frequently in neighboring organs in MPTs, the concept of ''field cancerization'' can be mentioned. The upper respiratory tract, colorectal region, and lower

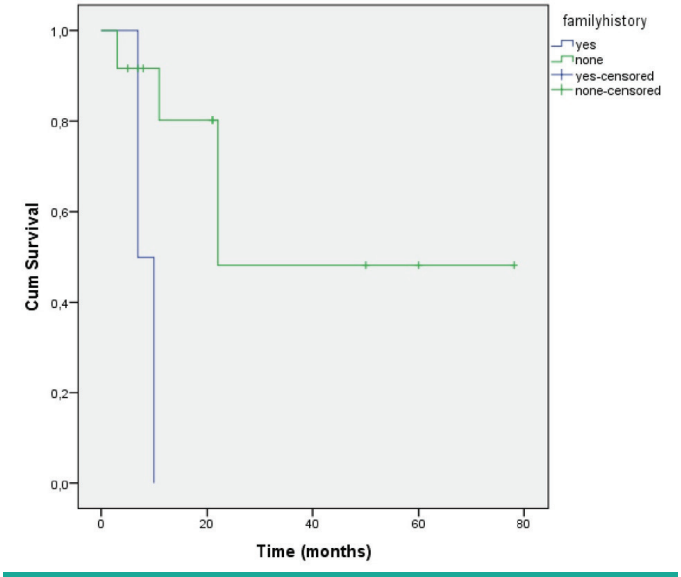

Figure 2. Survival curve of patients under 50 years of age with and without family history

Table 3. The distribution of synchronous and metachronous tumors

	Synchronous		Metachronous		
Location	**Male (n, %)**	**Female (n, %)**	**Male (n, %)**	**Female (n, %)**	**Total (n, %)**
Esophagus	1 (0.6)	1 (0.6)	5 (3.1)	2 (1.2)	9 (5.6)
Stomach	9 (5.6)	6 (3.7)	17 (10.5)	14 (8.6)	46 (28.4)
Right colon	5 (3.1)	3 (1.9)	7 (4.3)	6 (3.7)	21 (12.9)
Transverse colon	0	0	0	3 (1.9)	3 (1.9)
Left colon	6 (3.7)	4 (2.5)	14 (8.6)	11 (6.8)	35 (21.6)
Rectum	11 (6.8)	2 (1.2)	17 (10.5)	12 (7.4)	42 (25.9)
Anal canal	0	0	2 (1.2)	0	2 (1.2)
Appendix	3 (1.9)	1 (0.6)	0	0	4 (2.5)
Total	35 (21.6)	17 (10.5)	62 (38.3)	48 (39.6)	162 (100)

Table 4. The distribution of GIS tumors and second primary tumors according to their localizations

Location	**Eso**	**Stom**	**RC**	**TC**	**LC**	**Rec**	**AC**	**App**	**Sync Tm**	**Met Tm**	**Total (n, %)**
GIS (n)											
Esophagus	-	-	-	-	-	1	-	-	1	-	1 (0.6)
Stomach	1	2	-	-	1	1	1	-	2	4	6 (3.7)
Small bowel	-	1	-	-	-	1	-	-	2	-	2 (1.2)
Appendix	-	-	-	-	-	-	-	-	-	-	0
Colorectal	1	6	6	1	5	9	-	3	16	15	31 (19.1)
Anal canal	-	-	-	-	-	-	-	-	-	-	0
Breast (n)	3	13	4	2	7	4	-	-	5	28	33 (20.4)
US (n)											
Prostate	2	5	3	-	6	5	1	-	5	17	22 (13.6)
Kidney	-	-	1	-	2	1	-	-	3	1	4 (2.5)
Bladder	-	3	-	-	1	4	-	-	3	5	8 (4.9)
Testis	-	2	-	-	-	2	-	-	-	4	4 (2.5)
H & N (n)											
Brain	-	-	2	-	-	-	-	-	1	1	2 (1.2)
Thyroid	-	2	-	-	1	1	-	-	-	4	4 (2.5)
SG	-	1	-	-	-	-	-	-	1	-	1 (0.6)
RS (n)											
Lung	1	1	-	-	4	4	-	-	5	5	10 (6.2)
Larynx	-	2	1	-	1	1	-	-	1	4	5 (3.1)
FGS (n)											
Cervix uteri	-	1	-	-	-	-	-	-	-	1	1 (0.6)
Uterus	-	1	1	-	1	4	-	1	2	6	8 (4.9)
Ovary	-	1	-	-	3	2	-	-	2	4	6 (3.7)
HS (n)											
Liver	-	2	1	-	-	-	-	-	3	-	3 (1.9)
Pancreas	-	-	-	-	1	-	-	-	-	1	1 (0.6)
Biliary tract	-	-	1	-	-	1	-	-	-	2	2 (1.2)
Hemato. S (n)	1	3	1	-	1	-	-	-	-	6	6 (3.7)
Skin (n)	-	-	-	-	1	1	-	-	-	2	2 (1.2)
Total (n)	9	46	21	3	35	42	2	4	52	110	162 (100)

Eso: Esophagus, Stom: Stomach, RC: Right colon, TC: Transverse colon, LC: Left colon, Rec: Rectum, AC: Anal canal, App: Appendix, Sync Tm: Synchronous tumor, Met Tm: Metachronous tumor, GIS: Gastrointestinal system, US: Urogenital system, H&N: Head&neck, SG: Salivary gland, RS: Respiratory system, FGS: Female genital system, HS: Hepatobiliary system, Hemato.S: Hematopoietic system

Table 5. Histopathologic characteristics of MPTs

Histologic type of GIS malignancy	Synchronous (n, %)	Metachronous (n, %)	Total (n, %)
Adenocarcinoma	38 (73.8)	97 (88.2)	135 (83.3)
Signet ring cell carcinoma	3 (5.8)	5 (4.5)	8 (4.9)
Gastrointestinal stromal tumor	4 (7.7)	1 (0.9)	5 (3.1)
Squamous cell carcinoma	1 (1.9)	4 (3.6)	5 (3.1)
Neuroendocrine tumor	4 (7.7)	0	4 (2.5)
Mucinous carcinoma	1 (1.9)	3 (2.7)	4 (2.5)
High grade B-cell lymphoma	1 (1.9)	0	1 (0.6)

MPT: Multiple primary tumor, GIS: Gastrointestinal system

urinary tract are the locations where this effect is frequently observed (10). The presence of similar genetic changes can be counted among the reasons (5). In addition, advanced endoscopic and radiological examinations can enable simultaneous recognition of tumors in neighboring organs more easily (10). The results we obtained in our study also supported these possibilities. Indeed, the second primary tumors in the synchronous tumor group originated from the digestive and the urogenital system.

Family history of cancer is among the reasons that increase the probability of developing a second primary tumor. Positive family history has been reported, especially in cases with breast and ovarian tumors (12). In a study, it was observed that approximately half of the patients with MPTs had gastric tumors in their first and second-degree relatives (13). In our story family history of cancer was detected in 2 cases in the group of patients aged less than 50 years. While colon and gastric tumors were prominent among GIS tumors, breast and prostate tumors were found to be the second most common accompanying primary tumors.

In our study, the second primary tumors in the patients under 50 years of age were mostly originated from lower GIS. In cases with a relevant family history and under 50 years of age diagnosed with GIS malignancy, *mismatch repair* genes, APC and TP53 mutations are genetic tests recommended for those developing colorectal cancers (13,14). As in our study, genetic analysis including these mutations may be included in screening methods for metachronous lower GIS tumors that may occur especially in young cases.

According to the SEER database in which cancer-related data are published, prostate-colorectal tumors in men and breast-colorectal tumors in women are the most common MPTs (15,16). In our study, an association of left colon-prostate and rectum-right colon tumors was observed in males, whereas an association of tumors in the stomach-breast and left colon-breast was observed in females. Especially, the more frequent detection of breast and colorectal tumors can be attributed to the use of improved screening methods (16).

In our study, gastric tumors ranking on top among GIS tumors were most frequently accompanied with breast and prostate tumors. In the literature, it has been observed that stomach tumors are more often accompanied by colorectal tumors (17,18).

Hormonal treatment applied after the diagnosis of breast tumor may increase the risk of developing a second primary tumor also invading the stomach.

In addition, a strong relationship between hereditary gastric cancers and lobular breast tumors was mentioned (16). These data may explain the higher frequency of stomach-breast tumor association that we found in our study. Tumors of the rectum were the second most frequently seen tumors in our study, and they were accompanied by the right colon and prostate tumors. This result was compatible with the literature (15,18).

In our study, the most common histological type found in GIS malignancies was adenocarcinoma. Special diagnoses included GIST, neuroendocrine tumor and high- grade B-cell lymphoma. GIST is the most frequently diagnosed mesenchymal tumor of GIS. It can be detected together with other GIS malignancies as a synchronous and a rare metachronous tumor (19,20). It often accompanies stomach and esophageal carcinomas. It has been reported in the literature that cases with MPTs, including GIST, show a worse prognosis (5). In our study, it was localized in the stomach in four cases, and in two of these cases, it was synchronously associated with gastric carcinoma. Two cases with GİST localized in the stomach died during the follow-up.

In the literature, it has been reported that synchronous or metachronous second primary tumors can be observed in 35% of the cases with appendiceal tumors (21). In addition, approximately half of neuroendocrine tumors can be observed in association with second primary tumors in the appendix (22). In our study, all four cases of neuroendocrine tumor were located in the appendix. The most common

organ with extranodal lymphoma involvement is GIS. However, association of lymphoma and GIS malignancy is extremely rare. A case with synchronous hepatocellular carcinoma with diffuse large B-cell lymphoma located in the lymph node has been reported in the literature (23). In our study, high-grade B-cell lymphoma with synchronously diagnosed hepatocellular carcinoma was located in the right colon.

MPTs have a worse prognosis than a single primary tumor. In particular, the synchronous tumor group shows a worse clinical picture in terms of survival (5,24). In our study, unlike the literature, the survival time, though not statistically significant, was shorter in patients with metachronous tumors compared to patients with synchronous tumors. This may lead us to the conclusion that the follow-up times and examinations of our patients diagnosed with primary tumor are not sufficient. In addition, the survival rate of patients with gastric GIS malignancies in our study was lower compared to the patients with other GIS malignancies. In the literature, the 5-year survival rate for cases with primary gastric tumor is reported as less than 30% (25). The most important cause of poor prognosis in these tumors is diagnosis made at an advanced stage of the disease. It is important to detect gastric tumors at an early stage in order to increase survival rates. For this purpose, methods similar to screening methods used for breast and colorectal tumors can also be applied for gastric tumors.

Conclusion

In terms of GIS tumors, prostate and colon tumors in men and breast tumors in women may be risk factors for the development of MPTs. In cases with gastrointestinal tumors, the gastrointestinal and urogenital system, where detection of a second primary tumor is likely, can be monitored more closely. In addition, studies for genetic analysis of metachronous tumors that may develop in patients with primary tumors at a young age can be included in screening methods. In addition to these, since the life span of the patients has increased, in cases with primary tumors, it is important to complete all necessary tests and examinations, and to keep follow-up periods much longer.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from Ethics Committee (06.30.2020/288).

Informed Consent: Consent was obtained.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: S.Ş.E., S.T.D., Design: S.Ş.E., S.T.D., A.A., Data Collection or Processing: S.Ş.E., S.T.D., A.A., E.U., Literature Search: S.Ş.E., S.T.D., E.U., Analysis or Interpretation: S.Ş.E., S.T.D., A.A., E.U., Writing: S.Ş.E., S.T.D., E.U.

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

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ORIGINAL RESEARCH

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Citation Analysis of the Articles Published in the Bagcilar Medical Bulletin Between December 2016 and June 2020

Bağcılar Tıp Bülteni'nde Aralık 2016 ve Haziran 2020 Tarihleri Arasında Yayımlanan Makalelerin Atıf Analizlerinin Değerlendirilmesi

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Abstract

Objective: To describe publication characteristic and citation analysis of Bagcilar Medical Bulletin (BMB) since its first publication time to January 2020 using bibliometric methods.

Method: Researched articles published in the BMB between December 2016 and June 2020 have been analyzed. The journal database was evaluated according to study type (original research, review, case report, letter to the editor), related scientific subspecialty and the geographical origin. We also calculated the rates of citation by dividing the total number of citations received by all papers by the total number of papers.

Results: A total of 88 articles were included in the study. The articles about neurosurgery, anesthesia and pediatrics were in the top three (27.27%, 13.63% and 11.36%, respectively). Citation rates of the original article, case report and review were 15.7%, 10.3% and 0%, respectively. Most of the articles (81.81%) were published from Marmara Region in Turkey. Of the articles, 4 (4.5%) were international papers submitted from 2 different countries. All international papers were preclinical subspecialties like pharmacology, microbiology and physiology.

Conclusion: Our study provides an opportunity to compare the citation numbers and characteristics before and after indexing of the journal in TUBITAK/ULAKBIM, in near future.

Keywords: Articles, Bagcilar Medical Bulletin, citation

Öz

Amaç: Bağcılar Tıp Bülteni (BMB) Dergisi'nin ilk yayın tarihi olan Aralık 2016'dan Haziran 2020'ye kadar olan yayın özelliklerini ve atıf analizini bibliyometrik yöntemler kullanarak tanımlamak.

Yöntem: Aralık 2016-Haziran 2020 yılları arasında BMB'de yayınlanan makaleler analiz edildi. Dergi veritabanı yazıların tipine (orijinal makale, derleme, olgu sunumu, editöre mektup), makalenin ilgili branşına ve coğrafik orijinine göre değerlendirildi. Ayrıca toplam atıf miktarının toplam yayınlanmış makale sayısına bölünmesi suretiyle atıf oranı da hesaplandı.

Bulgular: Toplam 88 makale çalışmaya dahil edildi. Yayınlanan makalelerde ilk 3 sırayı sırasıyla nöroşirurji, anestezi ve reanimasyon ve pediyatri (%27,27, %13,6 ve %11,36) bölümleri aldı. Atıf oranları sırasıyla orijinal makale, olgu sunumu ve derleme olacak şekilde %15,7, %10,3 ve %0 olarak hesaplandı. Makalelerin birçoğu Türkiye'de Marmara Bölgesi'nden yayınlandı (%81,81). İki farklı yabancı ülkeden yayınlanan makale sayısı 4 (%4,5) olarak hesaplandı. Bütün yabancı makaleler farmakoloji, mikrobiyoloji ve fizyoloji gibi preklinik branşlara aitti.

Sonuç: Çalışmamız, yakın gelecekte derginin TÜBİTAK/ULAKBİM'de indekslenmesinden önceki ve sonraki atıf sayılarını ve özelliklerini karşılaştırma fırsatı sunmaktadır.

Anahtar kelimeler: Atıflar, Bağcılar Tıp Bülteni, makaleler

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Introduction

Bagcilar Medical Bulletin (BMB) is periodical scientific publishing of University of Health Sciences Turkey, Bagcilar Training and Research Hospital. The journal has been published since December issue of 2016 as an e-journal. The journal is published quarterly in March, June, September and December, and it is indexed in EBSCO, Gale, Turk Medline, Turkey Citation Index, Index Copernicus, ProQuest, J-Gate, EuroPub and ScopeMed. However, in Turkey, indexing a journal in TUBITAK/ULAKBIM scientific database is more important, especially for authors in terms of academic advancements. In this regard, journals indexing in TUBITAK/ULAKBIM are more popular for the authors who attend to submit their works. Starting on June 2020, the journal, BMB, has been indexed in TUBITAK/ULAKBIM and has become a suitable option for medical authors.

In this study, we aimed to describe publication characteristic and citation analysis of BMB since its first publication time to June 2020, acceptance time of TUBITAK/ULAKBIM database, using bibliometric methods.

Materials and Methods

Researched articles published in the BMB between December 2016 and June 2020 have been analyzed. Extracted characteristics of published articles were collected from the journal database (http://www.behmedicalbulletin.org/archives.com/eng/archive) according to study type (original research, review, case report, letter to the editor), related scientific subspecialty and the geographical origin. Citation rates were extracted from the Google Scholar citation database (https://scholar.google.com.tr), which is a meta-database of scholarly journals and books. We also categorized the citations as national and international. Citation rates were calculated by dividing the total number of citations received by all papers by the total number of papers according to article types (such as original research, review, etc.), related scientific subspecialty of articles and intuitional regions of the authors during the period of 2016-2020. Impact factor (IF) could not be determined yet because of the restricted citation numbers of the journal.

Statistical Analysis

No statistics have been made in this article, so the title of statistics is not included.

Results

A total of 88 articles were included in the study. The types of the published articles consisted of original articles, review articles and case reports. Details are presented in Table 1. The greater number of the papers were original research articles (64.77%). Most of the articles (81.81%) were published from Marmara Region in Turkey. Of the articles, 4 (4.5%) were international papers submitted from 2 different countries. All international papers were preclinical subspecialties like pharmacology, microbiology and physiology. Among the published articles, articles about neurosurgery, anesthesia and pediatrics were in the top three, respectively (27.27%, 13.63% and 11.36%, respectively). The total citation number was established as 12. International papers had received 6 citations up to June 2020. Overall citation rate was 26%. Citation rates of the original articles and case reports were 15.7 % and 10.3%, respectively. Interestingly review articles had not been cited yet. The top cited articles were about pharmacology and microbiology subspecialties. The detailed information about citation characteristics for article types and subspecialties are shown in Table 1 and 2, respectively.

Discussion

The term bibliométrie was first used by Paul Otlet in 1934 (1). Bibliometric analysis is used for statistical evaluation of published scientific articles and it is an effective method to measure the influence of publication in the scientific area (2-5). Widely used bibliometric tools are citation analysis and IF in the evaluation of research performance (6). The IF of an academic journal is a scientometric index that reflects the yearly average number of citations that articles published in the last two years in a given journal have received (7,8). It is reported by Foster that there is a correlation between IF and journal prestige (9). Tsay has underlined that IF is a significant measure of importance that could be used for journal selection (10).

There are many factors that can affect the citation characteristics of a publication. In the medical sciences,

Table 1. The types of the articles published in the BMB

Article type	Citation count	Article count	Citation rate
Original research article	9	57	0.157
Review	0	2	0
Case report	3	29	0.103
Total	12	88	0.260

BMB: Bagcilar Medical Bulletin

previous studies have for instance analyzed the effect of study design (e.g., case report, randomized controlled trial, or meta-analysis), article type (i.e., brief report or full-size article), and article length (6). In our study, we investigated the differences in article type, region and subspecialty of article for citation characteristics.

BMB is periodical scientific publishing of University of Health Sciences Turkey, Bagcilar Training and Research Hospital since December 2016 and it is indexed in TUBITAK/ULAKBIM since June 2020. In the present study, we performed a comprehensive evaluation of the articles published in the BMB and we calculated the number of citations before being indexed in TUBITAK/ULAKBIM. We found that articles published in the field of pharmacology and microbiology had higher citation rates compared to other subspecialties. The most published three articles were about neurosurgery (n=24), anesthesia (n=12) and pediatric (n=10) but there were only 3 citations with these 46 articles and all of them were cited in neurosurgery. We think that relatively young nature of the journal and poor indexing characteristics might have played a role as a reason of it. Most cited articles were in preclinical subspecialties and submitted from foreign countries. These data demonstrate that more published international papers provide more citation numbers and high IF.

Table 2. Citation counts according to the subspecialties

Article type	Citation count	Article count
Neurosurgery	3	24
Anesthesia	0	12
Pediatrics	0	10
Cardiovascular surgery	1	4
Orthopedics	1	2
Urology	0	3
Emergency	0	6
General surgery	1	3
Otolaryngology/head and neck surgery	0	4
Gynecology and obstetrics	0	4
Aesthetic and plastic surgery	0	2
Internal medicine	0	3
Cardiology	0	1
Physical therapy and rehabilitation	0	1
Nuclear medicine	0	1
Neurology	0	2
Pharmacology	4	2
Microbiology	2	1
Physiology	0	1
Radiology	0	1
Total	12	88

Study Limitations

Our study has some limitations. The major one is the lack of the determination of the IF. However, this was not suitable for the limited number of citations. In future, with the increase in published articles, further studies may help in reduction of this issue. The second limitation is that we could not perform any comparison on citation characteristics. Similarly, as mentioned above, further studies can compare the citation characteristics with increased published articles after indexing in TUBITAK/ULAKBIM database.

Conclusion

We think that joining the TUBITAK/ULAKBIM will increase the bibliometric characteristics of the journal. Our study provides an opportunity to compare the citation numbers and characteristics before and after indexing of the journal in TUBITAK/ULAKBIM, in near future.

Ethics

Ethics Committee Approval: Since this article is a bibliography article that evaluates the properties of articles until June 2020 in Bagcilar Medical Journal, no patient data were used. Therefore, ethical consent and patient consent were not required.

Informed Consent: Since this article is a bibliography article that evaluates the properties of articles until June 2020 in Bagcilar Medical Journal, no patient data were used. Therefore, ethical consent and patient consent were not required.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: M.Z.T., A.S., E.K., A.Ç., Design: M.Z.T., A.S., E.K., Data Collection or Processing: İ.H., S.Z.S., R.Ö.Y., Literature Search: İ.H., S.Z.S., R.Ö.Y., Analysis or Interpretation: İ.H., S.Z.S., R.Ö.Y., Writing: A.Ç., E.K., M.Z.T., Manuscript Review and Revisation: A.Ç., E.K., A.S.

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

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ORIGINAL RESEARCH

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A Clinical Experience: Endoscopic and Surgical Management of Bezoars

Klinik Bir Deneyim: Bezoarların Endoskopik ve Cerrahi Yönetimi

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Abstract

Objective: This study aims to evaluate the cases treated for gastrointestinal obstruction due to bezoar in terms of clinical-radiological-endoscopic features and treatment methods.

Method: Among the patients treated for acute mechanical intestinal obstruction (AMIO) in our hospital between January 2014 and December 2019, 33 patients with bezoar-related AMIO were included in the study. The cases were examined in terms of the presence of comorbidity, tomography and endoscopy features, and treatment modalities.

Results: A history of intraabdominal surgery was found in 82% of patients (n=27) and a history of upper gastrointestinal surgery in 60% (n=20). DM accompanied in 27% of the patients (n=9) and psychiatric disorder in 18% (n=6). With computered tomography, gastric dilatation was observed in 9 patients, jejunal in 9 patients, jejunoileal in 9 patients, and dilatation in all bowel segments in 6 patients. Endoscopy was performed in 12 patients; 9 had peptic ulcers, 3 were normal. Seventeen cases were treated with laparotomy, 9 cases with a laparoscopic enterotomy, and 3 cases with endoscopic procedures. 4 cases were treated with a Coca-Cola injection from a nasogastric catheter, which was successful.

Conclusion: It is difficult to diagnose bezoar-related AMIO with clinical findings. Radiological and endoscopic methods are important in diagnosis. Although endoscopic methods are also used successfully for therapeutic purposes, surgical methods are used in distal locations and complicated cases.

Keywords: Acute mechanical intestinal obstruction, bezoar, endoscopy, gastrointestinal surgery

Öz

Amaç: Bu çalışmada bezoara bağlı gastrointestinal obstrüksiyon nedeniyle tedavi edilen olguların klinik-radyolojik-endoskopik özellikler ve tedavi yöntemleri açısından değerlendirilmesi amaçlanmıştır.

Yöntem: Ocak 2014-Aralık 2019 tarihleri arasında hastanemizde akut mekanik intestinal obstrüksiyon (AMİO) tedavisi gören hastalardan bezoar ilişkili AMİO'su olan 33 hasta çalışmaya dahil edildi. Olgular, komorbidite varlığı, tomografi ve endoskopi özellikleri ve tedavi modaliteleri açısından incelendi.

Bulgular: Hastaların %82'sinde (n=27) intraabdominal cerrahi öyküsü; %60'ında üst gastrointestinal cerrahi öyküsü vardı (n=20). DM hastaların %27'sine (n=9), psikiyatrik bozukluk hastaların %18'ine (n=6) eşlik etmekteydi. Bilgisayarlı tomografi ile 9 hastada mide dilatasyonu, 9 hastada jejunal, 9 hastada jejunoileal ve 6 hastada tüm bağırsak segmentlerinde dilatasyon görüldü. On iki hastaya endoskopi yapıldı; 9'unda peptik ülser vardı, 3'ü normaldi. On yedi olgu laparotomi, 9 olgu laparoskopik enterotomi ve 3 olgu endoskopik işlemlerle tedavi edildi. Dört olgu nazogastrik kateterden Coca-Cola enjeksiyonu ile tedavi edildi ve başarılı oldu.

Sonuç: Bezoar ilişkili AMİO'su klinik bulgularla teşhis etmek zordur. Tanıda radyolojik ve endoskopik yöntemler önemlidir. Endoskopik yöntemler de tedavi amaçlı olarak başarıyla kullanılsa da distal bölgelerde ve komplike olgularda cerrahi yöntemler kullanılmaktadır.

Anahtar kelimeler: Akut mekanik intestinal obstrüksiyon, bezoar, endoskopi, gastrointestinal cerrahi

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Introduction

Acute mechanical intestinal obstructions (AMIO) constitute 20% of all emergency abdominal surgical procedures (1). In all age groups, the most common cause of AMIO is adhesions secondary to abdominal surgery, although obstructions due to malignancy should be ruled out in older patients (2). Bezoars formed by the precipitation of non-digestible materials anywhere in the gastrointestinal tract (GIS) are among the rare causes of mechanical intestinal obstruction (0.4% to 4%) (3). They are named in different ways (phytobezoar, trichobezoar, pharmacobezoar, lactobezoar) according to the component they contain (4,5).

Conditions such as advanced age, DM, hypothyroidism, decreased GIS motility, feeding on fiber-poor food, dental or psychiatric disorders, not chewing food, vegetarian diet, dehydration, gastric emptying dysfunctions, and digestive difficulties. Methods such as partial gastrectomy, vagotomy, and gastric bypass in obesity surgery also increase the risk of developing bezoars (6,7). Although the symptoms vary depending on the content and localization, they can cause non-specific complaints such as epigastric tenderness, abdominal pain, and constipation. The most important complication is intestinal obstruction. In this case, patients usually apply to the emergency room with AMIO symptoms such as nausea-vomiting, and abdominal pain. The first imaging method to be used in the diagnosis is standing upright abdomen X-ray (8). Although it cannot be directly displayed with plain radiography, they may cause suspicion due to the calcification they contain and the air-liquid levels due to the AMIO they cause (9). Abdominal tomography (CT) is the most commonly used method for AMIO imaging in terms of showing the level, degree, and cause of obstruction (10). In the selection of the treatment modality, as bezoar provides information on localization, the degree of obstruction and dilatation is guiding in terms of operation indication and timing as it also shows complication findings such as accompanying intraabdominal air-fluid (11). Nevertheless, endoscopic methods continue to be the preferred method in the diagnosis of bezoar as it provides simultaneous treatment (12).

In this article, we discussed the series of 33 cases treated in our clinic in terms of clinical-radiological-endoscopic features and treatment methods due to bezoar, which is a rare entity in intestinal obstruction.

Materials and Methods

Patients who were operated on or treated conservatively in our hospital between January 2014 and December 2019 were retrospectively reviewed. Thirty three cases with GIS obstruction due to bezoars were included in the study. The cases were evaluated in terms of demographic features, symptomatology, presence of comorbidity, and history of previous abdominal operation. All patients underwent standing upright abdominal X-ray and abdominal CT examination. Bezoar localization-count and additional findings were evaluated through CT. The patients were also evaluated in terms of radiological imaging and endoscopy findings, treatment methods, hospital stay, and morbidity/mortality rates.

Statistical Analysis

Data were presented as mean ± standard deviation (SD). As the overall number of cases was relatively small, no inferential statistical analysis was undertaken.

Results

Patients diagnosed with AMIO between January 2014 and December 2019 were retrospectively screened. The etiology of 33 of 593 patients with AMIO was bezoar. The type in all of them was phytobezoar. The age range of the patients included in the study was 46-81 years (mean: 68 y). Twenty-three of the patients were male and 10 were female. The interval between the onset of symptoms and admission to the hospital ranged from 4 to 10 days (7.4±2.0). Common symptoms in all patients were abdominal pain, nausea, and vomiting. 27% of patients had DM and 18% had psychiatric disorders.

History of intra-abdominal surgery was available in 82% of patients (27/33) (11 cases with peptic ulcer operation, 5 cases with Nissen fundoplication, 1 case with Heller myotomy for achalasia, 2 cases with obesity surgery, others with appendectomy, cholecystectomy, umbilical herniorrhaphy, primary raffia due to perforation) and 60% (20/33) had a history of upper GIS operation.

With CT, gastric dilatation was observed in 6 patients, jejunal in 14 patients, ileal in 7 patients, and dilatation in all small bowel segments in 8 patients. Bezoar could only be visualized in 2 patients (two patients with a gastric band in the stomach due to obesity surgery) (Figure 1). Intra-abdominal free fluid was detected in 2 patients and pathological intestinal wall thickening in 1 patient.

After CT, 12 patients underwent endoscopy. 9 had peptic ulcers; 3 of them were normal. Bezoars were seen and removed with endoscopy in 3 cases (Figure 2, 3).

Seventeen patients were treated with laparotomy (11 patients with gastrotomy and/or enterotomy, 4 patients with milking, 2 patients with segmental bowel resection), 9 patients with laparoscopic enterotomy, and 3 patients with endoscopic procedures. Pineapple juice was given to 3 patients after endoscopy. Four cases were treated with a carbonated drink with caffeine injection from a nasogastric catheter, which was successful.

The length of hospital stay of the patients ranged from 1 to 9 days (mean ± SD: 5.2±3.0). Thirty patients were discharged without any problem. In one case, we removed the migrated gastric band and bezoar, anastomosis leak was detected on the post-op 5th day. The leak was treated with a conservative approach. In another patient who underwent laparoscopic enterotomy, intraabdominal infection developed. Intra-abdominal abscess was drained with the help of a percutaneous catheter. One patient developed lung infection. He was treated with antibiotics. Wound infection developed in only one patient. No mortality was detected in our series.

Details on comorbid diseases, previous abdominal surgeries, abdominal CT findings, procedures, and complications are shown in Table 1.

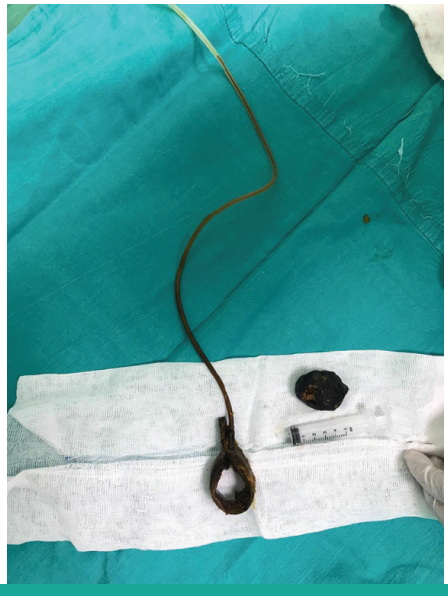

Figure 1. Gastric band migrated into the stomach

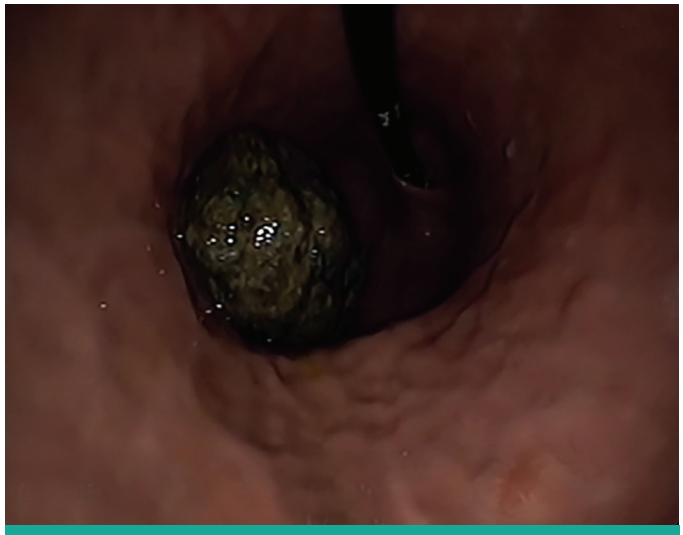

Figure 2. Bezoar seen on endoscopy

Discussion

Previous gastric surgical operations prepare the ground for bezoar formation due to the hypomotility and hypoacidity they cause. In patients operated on for peptic ulcer, vagotomy accompanied by partial gastrectomy (antrectomy) has been identified as the most important risk factor for bezoar formation (13). Vagotomy decreases gastric acidity and interferes with chemical digestion; whereas, with antrectomy, mechanical digestion is negatively affected (14,15). In a study conducted by Kement et al. (14), it was reported that gastric surgery operations were the most common predisposing factor in bezoar formation with a high rate of 48%. According to Krausz et al.'s (15) and Bowden et al.'s (16) studies, these rates vary from 20% to 93%. In our series, the history of intra-abdominal operation was 82%, and the upper GIS operation history was 55%, which was in accordance with the literature. Consistent with the literature, 33% of these cases were operated due

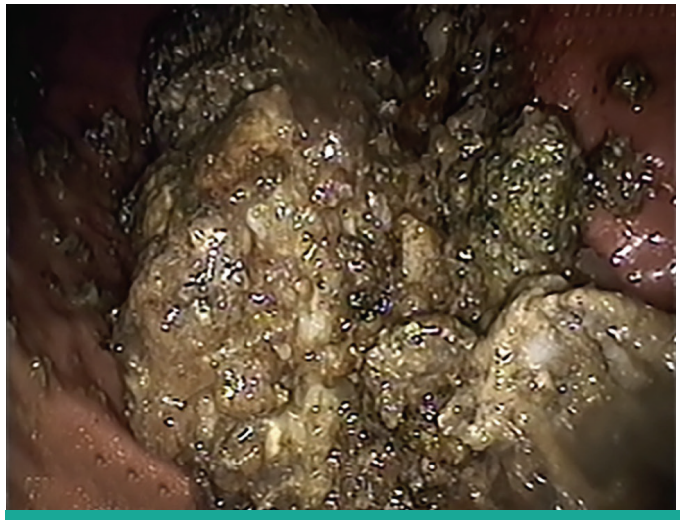

Figure 3. View of fragmented bezoar

Table 1. Preoperative characteristics of patients, treatment, and complications

Case	GIS operation history	CT findings	Gastroscopy	Localization	Applied operation	Complication
1	-	Dilated small bowel segments	Normal	Jejunum	Carbonated drink with caffeine delivery to the nasogastric tube	None
2	Nissen fundoplication	Dilated stomach	Ulcer in the bulbous, reflux esophagitis	Duodenum	The bezoar without laparotomy-enterotomy was disintegrated by hand and distal to the ileocecal valve.	None
3	Umbilical hernia	Dilated ileal segments proximal to the middle ileum	Normal	Stomach and jejunum	Removal of bezoar by laparotomy-Gastrotomy and enterotomy	None
4	Cholecystectomy	Dilated jejunal segments	None	Jejunum	Laparotomy - bezoar without enterotomy was disrupted by hand and distal to the ileocecal valve	Lung infection
5	Peptic ulcus operation (Truncal Vagotomy + Billroth 2)	Intraabdominal free fluid, dilated small bowel segments	Gastritis	Ileum	Laparotomy- Removal of bezoar by enterotomy	None
6	Peptic ulcus operation (Truncal Vagotomy + Billroth 2)	Dilated ileal segments proximal to the middle ileum, intestinal wall thickness increase	Normal	Jejunum	Laparotomy- Removal of bezoar by small bowel resection	Wound infection
7	Primary therapy due to stomach perforation	Dilated jejunal segments	Healed ulcer scar in the bulbous	Jejunum	Laparotomy- Removal of bezoar by enterotomy	None
8	-	Dilated stomach	5 cm stomach bezoar, ulcer in a small curvature	Stomach	Endoscopic bezoar removal	None
9	Appendectomy	Dilated stomach	Pyloric stenosis healed ulcer area in the bulb, reflux esophagitis	Stomach	Endoscopic bezoar rupture	None
10	Nissen fundoplication and cholecystectomy	Dilated ileal segments proximal to the middle ileum	None	Distal ileum	Removal of bezoars by laparoscopic-assisted enterotomy	None
11	Gastric tape implantation due to obesity	Dilated jejunal segments bezoar and migrate gastric band in the small bowel	None	Stomach	Laparotomy - Removal of bezoar by gastrotomy, migrate gastric band removal by enterotomy	Leak on the 5th day from the enterotomy line wound infection
12	Peptic ulcus operation (Truncal Vagotomy + Billroth 2)	Dilated ileal segments proximal to the middle ileum	None	Ileum	Laparotomy- Removal of bezoar by enterotomy	None
13	Peptic ulcus operation (Truncal Vagotomy + Billroth 2)	Dilated jejunal segments	None	Jejunum	Removal of bezoars by laparoscopic enterotomy	Intraabdominal abscess
14	Peptic ulcus operation (subtotal gastrectomy RNY gastrojejunostomy)	Dilated ileal segments proximal to the middle ileum	ulcer in the stomach fundus,	Ileum	Laparotomy - bezoar without enterotomy was disrupted by hand and distal to the ileocecal valve.	None
15	-	Dilated ileal segments proximal to the middle ileum	None	Stomach, ileum	Removal of bezoar by laparotomy-Gastrotomy and enterotomy	None
16	Appendectomy	Dilated small bowel segments	None	Ileum	Laparotomy - bezoar without enterotomy was disrupted by hand and distal to the ileocecal valve.	None

Table 1. Continued

Case	GIS operation history	CT findings	Gastroscopy	Localization	Applied operation	Complication
17	Heller myomtomy-door fundoplication	Dilated jejunal segments	None	Jejunum	Removal of bezoars by laparoscopic enterotomy	None
18	Gastric tape implantation due to obesity	Dilated ileal segments proximal to the middle ileum	None	Ileum	Removal of bezoars by laparoscopic enterotomy	None
19	Peptic ulcus operation (Truncal Vagotomy + Billroth 2)	Dilated stomach	4 cm stomach bezoar, ulcer in a small curvature	Stomach	Endoscopic bezoar rupture	None
20	Peptic ulcus operation (Truncal Vagotomy + Billroth 2)	Dilated jejunal segments	None	Jejunum	Removal of bezoars by laparoscopic enterotomy	None
21	Peptic ulcus peration (Truncal Vagotomy + Gastrojejunostomy-Brown anastomosis)	Dilated jejunal segments	Ulcer in the bulbous	Jejunum	Removal of bezoars by laparoscopic-assisted enterotomy	None
22	Peptic ulcus operation (subtotal gastrectomy RNY gastrojejunostomy)	Dilated small bowel segments	Ulcer in the bulbous, reflux esophagitis	Ileum	Laparotomy- Removal of bezoar by enterotomy	None
23	Nissen fundoplication	Dilated jejunal segments	Recurrent hiatal hernia, reflux esophagitis	Jejunum	Removal of bezoars by laparoscopic enterotomy	None
24	Umbilical hernia	Dilated small bowel segments	None	Ileum	Carbonated drink with caffeine delivery to the nasogastric tube	None
25	Appendectomy	Dilated stomach and jejunal segments	None	Jejunum	Laparotomy- Removal of bezoar by enterotomy	None
26	-	Dilated jejunal segments	None	Jejunum	Laparotomy- Removal of bezoar by enterotomy	None
27	Nissen fundoplication	Dilated jejunal segments	Ulcer in the bulbous	Jejunum	Removal of bezoars by laparoscopic enterotomy	None
28	Peptic ulcus operation (Truncal Vagotomy + Billroth 2)	Dilated jejunal segments	None	Jejunum	Removal of bezoars by laparoscopic-assisted enterotomy	None
29	Appendectomy	Dilated jejunal segments	None	Jejunum	Laparotomy- Removal of bezoar by enterotomy	None
30	Nissen fundoplication	Dilated small bowel segments	Ulcer in the bulbous	Ileum	Carbonated drink with caffeine delivery to the nasogastric tube	None
31	-	Dilated stomach and jejunal segments	None	Jejunum	Laparotomy- Removal of bezoar by enterotomy	None
32	-	Dilated small bowel segments	None	Ileum	Carbonated drink with caffeine delivery to the nasogastric tube	None
33	Peptic ulcus operation (Truncal Vagotomy + Billroth 2)	Intraabdominal free fluid, dilated small bowel segments	None	Ileum	Laparotomy- Removal of bezoar by enterotomy	None

to peptic ulcers. Thanks to the proton pump inhibitors commonly used in the treatment of peptic ulcers, these rates are significantly reduced. On the other hand, with the proliferation of obesity surgery, the increase in gastric band, sleeve gastrectomy or gastric bypass operation rates also leads to an increase in the incidence of bezoar, since it affects both mechanical and chemical digestion (6,7). In our study, two patients had gastric band operation due to obesity and the bezoar was localized to the small bowel.

One of the most important medical conditions affecting intestinal motility is diabetes. Diabetic gastroparesis

develops with the neuropathy caused by many years and GIS motility in these cases slows down significantly and prepares the ground for bezoar formation. In literature studies, the relationship between diabetes and bezoar has been well defined (13,17,18). In our series, diabetes rate was found to be associated with the development of bezoars at a high rate of 27%. Apart from this, psychiatric diseases have been reported among frequent etiologies due to both changes in eating habits and anticholinergic drugs used in treatment slowing the GIS motility (19,20). In our series, psychiatric disorders accompanied in 17% of our cases, which is compatible with the literature.

Pyloroplasty performed in peptic ulcer surgery generally accelerates the migration of bezoars into the small intestine (13,14). However, it can also occur primarily in conditions such as stricture, diverticulum, and tumor that affect the mechanical passage of the small intestine (14,21). Additionally, previous intra-abdominal surgical operations create brid AMIO and a tendency to intestinal bezoar development. They almost always present with the symptoms of intestinal obstruction. The majority of the intestinal bezoars are located in the distal-terminal ileum, 50-75 cm of the ileocecal valve, the narrowest segment of the small intestine (22). In our cases, the rate of intestinal bezoars was higher than gastric bezoars and 80% of these cases had a history of GIS operation 82% intraabdominal-60% upper GIS). However, contrary to expectations, only 25% of intestinal bezoars were located in the distal ileum (13). We think that this is due to the fact that adhesions developing secondary to previous intraabdominal operations lead to more proximal obstruction.

The treatment of bezoars varies according to localization, size, the degree of AMIO caused, and complications. Chemical solvents such as carbonated drink with caffeine, cellulose, acetylcysteine, and endoscopic approaches and conservative methods are preferred in the treatment of bezoars located in the gastric and proximal intestine (23). Endoscopic methods are generally the preferred methods since they provide simultaneous diagnosis and treatment (13). In the treatment of gastric bezoar, lavage or dissolution, fragmentation, and/or retrieval are successful methods that can be applied endoscopically. In cases unresponsive to these procedures, open or laparoscopic surgical treatments can be applied in large-sized or distally located bezoars, and complicated AMIO (14). The most common method applied surgically is the manual fragmentation of the bezoar and milking method towards the cecum (1,2,22). In case of failure, bezoar should be removed by enterotomy. In the presence of gangrenous intestine, segmental resection-anastomosis can be performed (1,2). In our series, 12 patients underwent endoscopic intervention, but only 3 of them were localized to the stomach endoscopically. In other cases, endoscopy was inadequate due to distal location, and a surgical operation was needed.

During surgery, the presence of accompanying bezoars in different localizations should be investigated because in one-third of the cases, there are multiple bezoars (23). Laparoscopy is preferred more than open procedures because of the shorter length of hospital stay and its being more comfortable for patients, but it requires experience for the manipulation of dilated and fragile segments. Radiological follow-up of the cases is also required after treatment, as it may lead to secondary complications (24-26). Recurrence rates are very low as long as the underlying factors are regulated by appropriate prophylactic medications that increase motility (1).

Conclusion

Bezoars should be kept in mind in the differential diagnosis of AMIO, especially in the case of concomitant diabetes or previous intraabdominal surgery. In its treatment, firstly, medical and conservative methods should be tried, and surgical options should be used in cases of obvious AMIO and complications.

Ethics

Ethics Committee Approval: The study protocol was approved by local ethics committee (date: 07.01.2021 no: 2575).

Informed Consent: Patients were not required to give their informed consent for inclusion in this retrospective study because we used anonymous clinical data and individual could not be identified according to the data present.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: S.S.U., N.G., A.K.Z., Y.Z.E., Design: S.S.U., N.G., A.K.Z., Y.Z.E., Data Collection or Processing: D.E.T.Ş., S.S.U., Analysis or Interpretation: S.S.U., D.E.T.Ş., Writing: S.S.U., D.E.T.Ş., A.K.Z., Y.Z.E., N.G.

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ORIGINAL RESEARCH

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Can HIF-1 Alpha (Hypoxia- inducible factor-1 alpha) be a New Cardiac Hypoxia Marker in Acute Coronary Ischemia?

HIF-1 Alfa (Hypoxia- inducible factor-1 alpha) akut Koroner İskemide Yeni Bir Kardiyak Hipoksi Belirteci Olabilir Mi?

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Abstract

Objective: Hypoxia- inducible factor-1 alpha (HIF-1 alpha) is a gene protein whose activation is a primary defensive mechanism against tissue hypoxia. It is the main regulator of cellular oxygen delivery and consumption. HIF-1 alpha activity is increased in tissue ischemia and this induces the angiogenic growth factor release that is needed for vascular remodeling and collateral formation, and contributes to improvement in cardiac functions. In this study, it was aimed to measure HIF-1 alpha levels in acute cardiac ischemia, to evaluate its relationship with inflammatory and biochemical parameters, and to investigate HIF-1 alpha as a possible cardiac hypoxia marker.

Method: First 31 patients who were admitted to coronary ICU with Acute Coronary syndrome (ACS) diagnosis in March 2018 were included in the study and 22 (14 female, 8 male) age-gender-matched healthy control group were included in the study. In both case (coronary ICU patient) and control groups), after 12-hour hunger, venous blood samples were taken to measure HIF-1 alpha, biochemical parameters [glucose, urea, creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT)], hemoglobin, platelets, platelet parameters [mean platelet volume (MPV), procalcitonin (PCT), platelet distribution width (PDW)], inflammatory parameters [C-reactive protein (CRP), neutrophil/lymphocyte ratio] and homocysteine levels. Results were evaluated using SPSS 22.0 program.

Results: Thirty one patients in the case group and 22 patients in the control group, totally 53 patients, were included in the study. The mean age was 68.2±14.3 years in the case group and 63.6±9.6 years in the control group. Age and gender distribution, glucose, AST, ALT, PLT, MPV, PCT, PDW and homocysteine levels did not show any significant difference in the case and control groups (p>0.05). Urea, creatinine, uric

Öz

Amaç: Hipoxia- inducible factor-1 alfa (HIF-1 alfa) bir gen proteini olup, aktivasyonu, dokudaki hipoksiye karşı primer defansif mekanizmadır. Dokudaki oksijen dağıtımında ve kullanımında başlıca düzenleyicidir. Doku iskemisinde artan HIF-1 alfa aktivitesi vasküler remodeling ve kollateral oluşumu için gerekli anjiyogenik büyüme faktörü salınımını uyarır ve kardiyak fonksiyonların düzeltilmesine katkı sağlar. Bu çalışmada akut kardiyak iskemide HIF-1 alfa düzeyine bakılıp, biyokimyasal ve enflamatuvar parametreler ile olan ilişkisi değerlendirilerek, HIF-1 alfanın kardiyak hipoksi göstergesi olarak araştırılması amaçlanmıştır.

Yöntem: Çalışmaya koroner yoğun bakım ünitesine Mart 2018'de akut koroner sendrom tanısıyla yatırılan ilk 31 hastayla, yaş ve cinsiyet uyumlu 22 sağlıklı kontrol grubu alındı. Katılımcıların yaş ve cinsiyetleri kaydedildi. Yoğun bakıma alınan hastalardan yatış sonrası ilk 12 saat içinde ve kontrol grubundan 12 saat açlık sonrası alınan venöz kan örneklerinden HIF-1 alfa düzeyi, biyokimyasal parametreler [glukoz, üre, kreatinin, ürik asit, aspartat aminotransferaz (AST), alanin aminotransferaz (ALT), gama-glutamil transferaz (GGT)], hemoglobin, trombositler, trombosit parametreleri [ortalama trombosit hacmi (MPV), prokalsitonin (PCT), trombosit dağılım genişliği (PDW)], enflamatuvar parametreler [C-reaktif protein (CRP), nötrofil/lenfosit oranı) ve homosistein bakıldı. Olgu ve kontrol gruplarının her ikisinde HIF-1 alfa düzeyi ve diğer araştırma parametreleri arasındaki ilişki SPSS 22.0 analiz programı ile değerlendirildi.

Bulgular: Çalışmaya 15 kadın, 16 erkek olmak üzere toplam 31 akut koroner sendrom tanılı hasta ile 14 kadın, 8 erkek olmak üzere toplam 22 sağlıklı kontrol grubu alındı. Yaş ortalaması olgu grubunda 68,2±14,3 yıl ve kontrol grubunda 63,6±9,6 yıl idi. Olgu ve kontrol grubunda hastaların yaşları ve cinsiyet dağılımı anlamlı (p>0,05) farklılık göstermedi. Olgu ve kontrol grubunda AKŞ değeri, AST değeri, ALT değeri, PLT değeri, MPV

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Abstract

acid, GGT, CRP, hemoglobin, and N/L levels were significantly higher in the case group when compared to the control group (p<0.05). Although HIF-1 alpha level was higher in the case group when compared to the control group, it was not statistically significant.

Conclusion: There are studies showing the role of HIF-1 alpha in myocardial remodeling, angiogenesis and cardiac function improvement. In hypoxic conditions, increase in HIF-1 alpha improves tissue oxygenation. Same adaptive mechanism was not observed in our study. We think the reasons underlying this situation could be that in our patients, ischemia was localized but not generalized like in hypoxia, medical therapy was started immediately after admission (e.g.oxygen, nitrates, acetyl salicylic acid, heparin), the patients were normotensive under treatment, they did not have anemia, and they were given specific medications (e.g. ACE inhibitors, ARB) that could decrease oxidative distress.

New treatment modalities to protect the heart from ischemic damage will be available when our knowledge about cardiac functions at different oxygen levels and factors affecting them increases. Then, HIF-1 alpha might be re-evaluated as a potential cardiac hypoxia marker.

Keywords: Coronary ischemia, HIF-1 alpha, hypoxia

Öz

değeri, PCT değeri, PDW değeri ve homosistein değeri anlamlı (p>0,05) farklılık göstermedi. Olgu grubunda üre değeri, kreatinin değeri, ürik asit değeri, GGT değeri, CRP değeri, Hgb değeri ve N/L değeri kontrol grubundan anlamlı (p<0,05) olarak daha yüksek bulundu. Olgu grubunda HIF-1 alfa değeri, kontrol grubundan daha yüksek olmakla birlikte sonuç istatistiksel olarak anlamlı değildi.

Sonuç: HIF-1 alfanın artmış doku oksijenasyonu yoluyla kardiyak fonksiyonu düzeltmede etkisi olduğuna dair çok sayıda çalışma mevcuttur, ama aynı adaptif mekanizma çalışmamızda gözlenmemiştir. Sadece lokalize iskeminin varlığı, medikal tedavinin hemen başlanması, hipertansiyon veya anemi bulunmaması bu farklılık için açıklayıcı faktörler olabilir. Farklı oksijen konsantrasyonlarındaki kardiyak fonksiyonlar ve bunu etkileyen faktörler hakkında bilgimiz arttıkça, kalbi iskemik hasardan koruyacak yeni tedavi modalitelerinin de önü açılacaktır. O zaman HIF-1 alfa potansiyel bir kardiyak hipoksi belirteci olarak yeniden değerlendirilebilir.

Anahtar kelimeler: HIF-1 alfa, hipoksi, koroner iskemi

Introduction

Hypoxia- inducible factor-1 alpha (HIF-1 alpha) is a gene protein whose activation is a primary defensive mechanism against tissue hypoxia. It is the main regulator of cellular oxygen delivery and consumption. HIF-1 alpha activity is increased in tissue ischemia and this induces the angiogenic growth factor release that is needed for vascular remodeling and collateral formation and contributes to improvement in cardiac functions (1-5).

HIF pathway has a major role in most aspects of cardiovascular development and control. The principle of therapeutic modulation of HIF pathway has two components: Its pharmacological activation can enhance protective responses during cardiac ischemia or if it is applied prior to the cardiac event, it can moderate ischemic injury by pre-conditioning the tissue and protecting it from the distress (6,7). Thus, HIF-1 alpha is suggested as a potential novel diagnostic and therapeutic tool in cardiac events (8).

In this study, it was aimed to measure HIF-1 alpha levels in acute cardiac ischemia, to evaluate its relationship with inflammatory and biochemical parameters, and to investigate HIF-1 alpha as a potential cardiac hypoxia marker.

Materials and Methods

This study was designed as a prospective, case-control study. First 35 patients who were admitted to coronary ICU with Acute Coronary syndrome (ACS) diagnosis in March 2018 were included in the study. For the case group, inclusion criteria were age of 18 years or older, diagnosis of ACS, admission to coronary intensive care unit after emergency room evaluation and exclusion criteria were the presence of active malignancy or malignancy history and transfer from another hospital or ward. Four patients with active malignancy/malignancy history were excluded. In the same month, age-gender-matched 22 patients were randomly chosen from the internal medicine out-patient clinic as the healthy control group. For the control group, inclusion criteria were age of 18 years or older, age-gender match with the case group, internal medicine visit with any reason other than chronic diseases and exclusion criterion was the presence of any chronic disease history. Demographic features of both groups and accompanying diseases of the case group were recorded.

In the case group, the day after the admission, and in the control group, the day after outpatient clinic visit, venous blood samples were taken from antecubital vein after 12-hour hunger. All blood work was finished within 24 hours after the ACS diagnosis in the case group. HIF-1 alpha, biochemical parameters [glucose, urea, creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT)], haemoglobin, platelets, platelet parameters [mean platelet volume (MPV), procalcitonin (PCT), platelet distribution width (PDW)], inflammatory parameters

[C-reactive protein (CRP), neutrophil/lymphocyte ratio] and homocysteine levels were measured. Synergy HT device was used to measure HIF-1 alpha level with ELISA method and Beckman Coulter AU 2700 plus (Beckman Coulter, Inc., Fullerton, USA) autoanalyzer was used to measure other parameters with spectrophotometric method. Results were evaluated using SPSS 22.0 program.

The study was conducted according to the Helsinki 1964 Declaration. Informed consent was obtained from all patients. Ethical approval was obtained from University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethical Committee (1875/14.06.2019).

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 for Windows program. Three types of descriptive statistics were used: Measures of frequency (frequency, percentage), measures of central tendency (mean, median), and measures of dispersion or variation (standard deviation, minimum, maximum). A measure of frequency is used for the categorical data while others were used for quantitative data. Distribution of variables was tested with the Kolmogorov-Smirnov test. Quantitative independent data analysis was made with the Mann-Whitney U test and qualitative independent data analysis with the chi-square test. The statistical significance level was regarded as $p<0.05$.

Results

Thirty one cases (15 female, 16 male) and 22 controls (14 female, 8 male), totally 53 patients, were included in the study. The mean age was 68.2±14.3 years in the case group and 63.6±9.6 years in the control group. In the case group, 3 patients (9.6%) had no accompanying diseases, 3 patients (9.6%) had only one accompanying disease, and 25 patients (80.6%) had 2≥ accompanying diseases. The most common accompanying diseases included diabetes mellitus (n=13, 41.9%), hypertension (n=18,58%), chronic heart failure (n=10, 32.2%), chronic renal failure (n=6,19%), ischemic heart disease (n=14, 45%), and atrial fibrillation (n=6,13%). Age and gender distribution did not show any significant difference in the case and control groups ($p>0.05$). Fasting blood glucose, AST, ALT, PLT, MPV, PCT, PDW and homocysteine levels did not show any significant difference in the case and control groups ($p>0.05$) (Table 1).

Urea, creatinine, uric acid, GGT, CRP, Hb, and N/L levels were significantly higher in the case group when

Table 1. The analysis of the searched parameters for the case and control groups

		Case group		Control group		p
		Mean ± SD/n-%	Median	Mean ± SD/n-%	Median	
Age		68.2±14.3	70.0	63.6±9.6	68.0	0.102[m]
Gender	**Female**	15±48.4%	-	14±63.6%	-	0.272[x²]
	Male	16±51.6%	-	8±36.4%	-	
HIF-1 A		3.0±3.0	1.9	2.0±1.8	1.4	0.470[m]
FBG		152.8±77.8	144.0	104.5±16.8	104.0	0.093[m]
Urea		63.6±36.1	49.0	33.4±8.5	34.5	**0.003**[m]
Creatinine		1.22±0.54	1.06	0.75±0.14	0.72	**0.000**[m]
Uric acid		8.3±2.7	7.9	4.8±1.3	4.5	**0.000**[m]
AST		39.0±51.4	23.0	25.4±16.2	21.0	0.671[m]
ALT		21.5±18.3	17.0	22.6±10.9	21.5	0.282[m]
GGT		51.4±50.0	33.5	25.5±12.0	22.0	**0.047**[m]
CRP		4.8±5.2	3.2	0.2±0.3	0.2	**0.000**[m]
Hgb		11.8±1.9	11.9	13.6±1.6	13.7	**0.002**[m]
N/L		5.5±4.3	4.2	1.6±0.4	1.4	**0.000**[m]
Plt		231.1±65.7	230.0	252.2±57.3	254.0	0.236[m]
MPV		10.5±1.2	10.3	10.7±0.9	10.7	0.541[m]
PCT		0.24±0.06	0.24	0.27±0.06	0.27	0.117[m]
PDW		15.5±16.3	12.4	13.2±1.8	13.0	0.296[m]
Homocysteine		17.4±7.0	15.3	15.9±3.8	14.6	0.704[m]

[m]:Mann-Whitney U test, [x²]: Chi-square test, SD: Standard deviation, HIF-1 A: Hypoxia-inducible factor-1 alpha, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, CRP: C-reactive protein, MPV: Mean platelet volume, PCT: Procalcitonin, PDW: Platelet distribution width

compared to the control group ($p<0.05$). Although HIF-1 alpha level was higher in the case group when compared to the control group, it was not statistically significant (Table 1).

Discussion

Cardiovascular diseases are the first main cause of mortality worldwide. 17.9 million people lose their lives from cardiovascular diseases each year, which is estimated to be 31% of all deaths (9). Coronary artery disease is a major part of this group of diseases. It is shown that ischemic heart disease affects around 126 million people worldwide, which is almost 1.72% of the world's population. 70% of individuals who are at-risk for ischemic heart disease have multiple cardiac risk factors and only 2-7% of the general population have no cardiac risk factors (10). Our study population consisted of ACS patients as a sample of this important global problem.

Despite impressive new developments in preventing and treating cardiovascular diseases, disease mortality did not change or decrease in most parts of the world (11). Thus, new approaches to detect cardiac disease risk factors/presence with simple methods are needed urgently. HIF-1 alpha seems to be a promising candidate to achieve this goal.

HIF-1 is a known transcriptional activator. It is oxygen-sensitive and it has a specific effect on several homeostatic responses in the presence of hypoxia (12,13). It activates the transcription of several multiple hypoxia-inducible genes' transcription. Vascular endothelial growth factor, lactate dehydrogenase A, erythropoietin, main glycolytic enzymes, inducible nitric oxide synthase and heme oxygenase-1 are examples of those genes which are important components of cell survival, vascularization, adaptation, tissue homeostasis, anaerobic metabolism, cytokine production and immune reaction. Also, HIF-1 has a key role in physiological system development in both fetal and postnatal lives. It is also a critical mediator of cardiovascular diseases, lung diseases, kidney diseases, and cancer (13,14).

HIF-1 consists of alpha and beta subunits. The alpha subunit is distinctive to HIF-1 but beta subunit can combine with other bHLH-PAS proteins to form a dimer. HIF-1 alpha protein levels are increased in the presence of anemia or hypoxia (13). Nitric oxide inhibits hypoxia-induced HIF-1 alpha expression (15). Because of its relationship with hypoxia, HIF-1 alpha is searched as a possible biomarker in different diseases (16-19) and we searched it with the same purpose in ACS patients.

HIF-1 alpha controls O_2 delivery and utilization to regulate O_2 homeostasis. When arterial stenosis causes ischemia or tissue hypoxia, HIF-1 activity is induced. This is needed to produce angiogenic growth factors and to trigger vascular remodeling. Consequently, blood flow in collateral vessels is increased. In people with advanced age or chronic diseases, this response of HIF-1 alpha is impaired. Ischemic preconditioning is described as repeated short episodes of ischemia and reperfusion to protect the myocardium against injury caused by prolonged ischemia. HIF-1 alpha also has a role in this heart protective action. Increased cardiac adenosine levels are efficient for cardioprotection and HIF-1 is involved in adenosine production, too. Also, it reduces reactive oxygen species to contribute to metabolic reprogramming for preventing myocardial injury caused by prolonged ischemia-reperfusion (20).

Same adaptive mechanism was not observed in our study. Although HIF-1 alpha level was increased in the case group when compared to the control group, the difference was not statistically significant. We think there might be several reasons underlying this situation. First of all, ischemia was localized but not generalized in our patients, medical therapy was started immediately after admission (e.g. oxygen, nitrates, acetyl salicylic acid, heparin), the patients were normotensive under treatment, they did not have anemia, and they were given specific medications (e.g. ACE inhibitors, ARB) that could decrease oxidative distress. Also, renal function tests, inflammatory markers and uric acid levels were higher in the case group. This was attributed to accompanying diseases and acute inflammation related to acute coronary ischemia in the case group.

There have been several studies presenting how HIF-1 alpha favors in acute cardiac ischemia. Ong et al. (21) showed that HIF-1 alpha reduced cardiac ischemia-reperfusion injury in mice and murine. Ockaili et al. (22) also pointed out that HIF-1 had a newly presented anti-inflammatory role in ischemia-reperfusion injury. Similarly, Kido et al. (23) found that HIF 1-alpha reduced infarction and attenuated further cardiac damage after myocardial infarction in their mouse study. Several studies found similar results. Thus, HIF-1 alpha was suggested as a therapeutic target for heart diseases that could be used in the near future (24).

Conclusion

In hypoxic conditions, increase in HIF-1 alpha favors to tissue oxygenation. Although the same adaptive mechanism could not be mimicked in our study, there are several studies demonstrating the role of HIF-1 alpha in myocardial remodeling, angiogenesis and cardiac function improvement. New treatment modalities to protect the heart from ischemic damage will be available when our knowledge about cardiac functions at different oxygen levels and factors affecting them increases. Then, HIF-1 alpha might be re-evaluated as a potential cardiac hypoxia marker and it can be used in a broader prospect both for the diagnosis and the treatment part of ischemic heart diseases.

The study group included 31 people and the control group included 22 people. More accurate results could have been obtained if the number of both groups had been equal and both groups had had more patients. However, unfortunately, limited HIF test kit availability did not allow us to increase the numbers.

Ethics

Ethics Committee Approval: The study was conducted according to the Helsinki 1964 Declaration. Ethical approval was obtained from University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethical Committee (1875/14.06.2019).

Informed Consent: Informed consent was obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: F.A., H.U.A., Design: F.A., H.U.A., M.E.P., Data Collection or Processing: F.A., H.U.A., Literature Search: F.A., M.E.P., Analysis or Interpretation: F.A., H.U.A., M.E.P., Writing: F.A., H.U.A., M.E.P.

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

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ORIGINAL RESEARCH

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The Effect of Prehospital Fluid Resuscitation on Mortality and Post-trauma Recovery Time in Trauma Patients

Travma Hastalarında Hastane Öncesi Sıvı Resusitasyonunun Mortalite ve Post-travma İyileşme Süresine Etkisi

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Abstract

Objective: It was aimed to evaluate the effect of pre-hospital fluid resuscitation on serum lactate level, mortality, radiological imaging, and late post-trauma recovery (PRT) in patients with trauma, who were admitted to the emergency department.

Method: In this study, 532 patients over the age of 18 years, who were admitted to the emergency department due to trauma between January 1, 2016, and December 31, 2017, were included. The average age of the patients was 37.19±13.91 years, 378 (71%) were male and 154 (29%) were female. The demographic characteristics, fluid resuscitation, and serum lactate levels, trauma patterns, mortality, and PRT results of these patients were evaluated retrospectively.

Results: PRT duration was shorter (22.48±7.17 days) in patients who underwent prehospital fluid resuscitation and longer (26.85±7.58 days) in those who did not receive it. Also, lactate levels were significantly lower in liquid areas (2.18±1.05 mmol/L) compared to those that did not take it (2.61±1.40 mmol/L). PRT time was 24.20±7.34 days in the group without mortality, and 33.43±12.87 days in the group with mortality. Serum lactate level was 2.29±1.10 mmol/L in the group without mortality, and 5.51±1.87mmol/L in the group without mortality. Serum lactate levels were 2.29±1.10 mmol/L in liquid areas and 5.51±1.87 mmol/L in those who did not receive it. Types of trauma were associated with fluid resuscitation and radiological imaging methods (p=0.001). These parameters showed a moderate and/or strong positive correlation among themselves, as well as in terms of lactate, PRT duration, and mortality. ROC curve analysis was performed to predict the development of mortality. The rates of lactate and PRT were over 45% with a sensitivity of 97.7% and a specificity of 94.3% and with a sensitivity of 89.7% and a specificity of 83.6%, respectively.

Öz

Amaç: Acil servise başvuran travmalı hastalarda, hastane öncesi sıvı resusitasyonunun serum laktat düzeyi, mortalite, radyolojik görüntüleme ve geç post-travma iyileşmesine (PRT) etkisi amaçlandı.

Yöntem: Bu çalışmaya, 1 Ocak 2016-31 Aralık 2017 tarihleri arasında acil servisine travma nedeniyle başvuran 18 yaşından büyük 532 hasta dahil edildi. Hastaların yaş ortalaması 37,19±13,91/yıl, 378'i (%71) erkek, 154'ü (%29) kadındı. Bu hastaların demografik özellikleri, sıvı resusitasyonu ve serum laktat düzeyleri, travma şekilleri, mortalite ve PRT sonuçları retrospektif olarak değerlendirildi.

Bulgular: Hastane öncesi sıvı resusitasyonu yapılan hastalarda PRT süresi kısa (22,48±7,17 gün), almayanlarda daha uzundu (26,85±7,58 gün). Ayrıca laktat düzeyi sıvı alanlarda (2,18±1,05 mmol/L), almayanlara (2,61±1,40 mmol/L) göre anlamlı olarak düşük bulundu. Mortalite gözlenmeyen grupta PRT süresi 24,20±7,34 gün, gözlenen grupta ise 33,43±12,87 gün olduğu tespit edildi. Serum laktat düzeyi mortalite gözlenmeyen grupta 2,29±1,10 mmol/L, gözlenmeyen grupta 5,51±1,87 mmol/L olarak saptandı. Serum laktat düzeyi sıvı alanlarda 2,29±1,10 mmol/L, almayanlarda 5,51±1,87 mmol/L olarak saptandı. Travma çeşitleri, sıvı resusitasyonu ve radyolojik görüntüleme yöntemleriyle ilişkiliydi (p=0,001). Bu parametreler kendi aralarında, ayrıca laktat, PRT süresi, mortalite açısından, orta ve/veya güçlü pozitif yönlü bir ilişki sergiledi. Mortalitenin gelişimini tahmin etmek için ROC curve analize yapıldı. Laktat %97,7 duyarlılık ve %94,3 özgüllük, PRT %89,7 duyarlılık ve %83,6 özgüllük ile %45'in üzerinde bulunmuştur.

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Abstract

Conclusion: Mortality and morbidity rates can be reduced by early detection of trauma cases with multidisciplinary understanding, adjustment of fluid and lactate levels, and early decision-making on the procedures to be performed.

Keywords: Fluid resuscitation, lactate, mortality, post-trauma recovery, trauma

Öz

Sonuç: Travma olgularının erken multidisipliner bir anlayışla saptanması, sıvı ve laktat düzeyinin ayarlanması ve yapılacak işlemlerin kararının erken verilmesi ile mortalite ve morbidite oranları düşürülebilir.

Anahtar kelimeler: Laktat, mortalite, post-travma iyileşme, sıvı resusitasyonu, travma

Introduction

Trauma is one of the most important causes of young age deaths and causes serious disabilities (1). Despite technological developments and measures taken, 5.8 million people are lost in the world every year due to various injuries. This constitutes 10% of all deaths in the world (2). Trauma-related deaths are divided into three groups: pre-hospital, emergency, and intensive care. According to the reports of the World Health Organization, when all age groups are evaluated, traffic accidents rank 10th among the most common causes of death in the world and constitute 2.1% of all deaths (3). According to estimates, if the number of injured continues to increase rapidly, trauma will be ranked 3rd among ''Causes of Death in the World'' in 2020 (2).

Bleeding, the preventable cause of death that occurs in the first 24 hours after trauma, is responsible for 30-40% of trauma-related mortality (4). The general approach is to perform an intravenous fluid replacement, which begins at the site of the trauma and during the patient's transfer. However, some publications contain evidence that this practice may not be the right approach in all trauma patients (5). In some studies, there are opinions that as patients' time to reach the hospital increases, the risk of death due to intravenous route opening and fluid replacement application at the scene and during transfer also increases (6,7). It has been reported that prehospital fluid administration in penetrating trauma can increase bleeding and mortality, so delaying fluid resuscitation may be appropriate in these patients. For patients with blunt trauma, studies on this subject remain limited (8).

The markers we will use to decide the adequacy of resuscitation in patients with trauma should also be a reliable parameter in the follow-up of tissue hypoxia. In practice, keeping vital parameters such as blood pressure, urine output, and heart rate within normal limits is used to evaluate the effectiveness of the resuscitation, but it is a fact that these criteria are not sufficient alone in the resuscitation of critically ill patients. In this respect, two markers commonly used today to evaluate the effectiveness of resuscitation are base deficit and lactate. Base deficit and lactate level measured for the first time after trauma can be used as early indicators in determining the prognosis of shock. Early identification of patients prone to shock after trauma and effective resuscitation of these patients are also very important in terms of prognosis. Therefore, centers dealing with trauma prefer blood gas analysis and base deficit values, the results of which can be obtained immediately, to manage the treatment (9). Lactate measurements in arterial blood gas can be used as a predictor of post-traumatic tissue hypoxia and metabolic acidosis. Serial lactate measurements may be useful in predicting mortality in trauma patients (10).

In parallel with the resuscitation and stabilization efforts in the first hour, which is called the ''golden hour'', it is of great importance to start radiological examinations to have an idea about the extent of trauma in patients before treatment. Initial radiological examinations to be performed on patients with polytrauma are divided into 4 groups: First, X-ray examinations to be performed in trauma patients include direct and contrast-enhanced examinations. Second, ultrasonographic examinations are inexpensive, practical, non-invasive applications that can be used safely in determining free fluid in the abdomen with significant parenchymal damage in hemodynamically unstable patients. Thirdly, while computed tomographic examinations can display all body parts, high accuracy data can be obtained regarding the functions of most organs with the contrast agents given. Therefore, some advocate the use of head, thorax, abdomen, and extremity computed tomography (CT) as a non-invasive, more advantageous, and highly accurate method in patients with initial polytrauma. Finally, there are advanced radiological examinations. Advanced radiological modalities (such as magnetic resonance imaging and angiography) are carried out under the supervision of a specialist radiologist and generally adhering to the routine trauma protocol. Since most of the devices with advanced radiological examinations are

not located directly adjacent to the trauma room, it should be ensured that the patient's condition is stable before transport (11).

Materials and Methods

In our study, we aimed to investigate the effects of pre-hospital fluid support on early radiological imaging and serum lactate levels on mortality and post-trauma recovery time.

Study Design and Population

In this retrospective study, 532 patients over the age of 18 years, who were admitted to the emergency department due to trauma between 1 January and 31 December 2017, were included. Patients with minor home accidents and cuts, patients who did not undergo the necessary examination and treatment in the emergency service, those with isolated head and neck trauma, and extremity trauma after the first 24 hours were excluded from the study. Demographic characteristics, trauma types, radiological images, organ injuries, fluid resuscitation, serum lactate levels, and blood results were evaluated.

In the study, patients were divided into two groups according to fluid resuscitation therapy. Data on whether these patients received fluid resuscitation were obtained from hospital automation and patient file records. Trauma patients were followed up retrospectively for three months with an automation system after they were discharged. Patients who did not visit hospital during this period were called by phone and the recovery period was questioned. Diagnoses, admission dates, contact information, demographic, clinical, and laboratory data are included in the registry system of our hospital. As a result, recovery levels three months after discharge were obtained from the patients and/or relatives and/or hospital records.

Traumas were divided into three general groups as falls (low and high), traffic accidents (inside and outside the vehicle), and penetrating (penetrating, cutting, and firearm injuries) injuries.

Post-traumatic recovery time (PRT) described the period of recovery and mobilization after the trauma patient was discharged. Patients who recovered and became active after discharge described those with mobilization who had extremity rest due to fractures, dislocations, and injuries and/or immobile patients after surgical operation after recovery. Patients in good general condition described those whose vital signs were defined as stable, conscious, not life-threatening, oriented and cooperative after they were evaluated in the emergency department. Patients with no complaints described those who were brought to the emergency service after trauma, whose general condition and physical examination were normal, and who needed to be followed up.

Apart from these, two groups were formed according to the presence or absence of thoracic vertebra, lumbar vertebra, thorax, and intraabdominal injuries. Two groups were evaluated considering whether or not fluid resuscitation was performed and whether there was mortality.

Laboratory Design

Arterial blood gas, lactate level, hemogram, and biochemical blood analyses of the patients were evaluated on admission to the emergency service.

Arterial blood gas; The lactate levels of the patients were obtained from arterial blood gas analysis using the Acobas® b221 Blood Gas system (Roche, Basel, Switzerland). Arterial blood gas results were analyzed in 5-10 minutes.

Hemogram blood analysis was performed using Sysmex DI-60 CBC Analyzer (Istanbul, Turkey). Biochemistry blood was analyzed by Beckman Coulter Automated AU-680 (Beckman Coulter, Inc., Fullerton, CA, USA). Hemogram and biochemistry results were studied in 45-60 minutes.

Radiological Design

Patients whose general condition was good had no complaints but they were brought to the emergency room for trauma and they were followed up in the emergency observation unit for a certain period. X-rays were not taken for them unless necessary. X-rays of patients with a good general condition, no thoracic and abdominal trauma, bruises, simple fractures, and dislocations were taken. Ultrasonography (USG) was planned in two ways. First, patients with good general conditions and stable vital signs were taken to the radiology unit. The other group included patients with the poor general condition and bad vital signs. Patient-Focused Assessment Sonography for Trauma was applied to these patients. CT, non-contrast, and/or contrast CT scans were performed for patients who could go to the radiology unit due to the general condition of thoracic and/or lumbar vertebral fracture, thoracic injury, abdominal organ injury, or bleeding. Multiple imaging was applied to patients with polytrauma. Resuscitation measures were taken in these patients and filming was performed in the presence of a physician. All USG and CTs were analyzed jointly with radiology, emergency, and related specialists.

The study was conducted according to the Helsinki Declaration on human research, after getting approval from the local Ethics Board (2019-12/22).

Statistical Analysis

The data obtained from this study were analyzed with SPSS 20 (SPSS Inc., Chicago, IL, USA) package program. The Kolmogorov-Smirnov test was used while investigating the normal distributions of the variables. Descriptive statistics were presented as mean ± standard deviation or median (minimum-maximum) for continuous variables and as the number of cases and percentage (%) for nominal variables. When examining the differences between the groups, the Mann-Whitney U test was used because the variables did not come from the normal distribution. The chi-square analysis was used when examining the relationships between the groups of nominal variables. The Pearson's correlation analysis was used for assessing the linear relationship between variables. Receiver operating characteristic (ROC) curve analysis was performed to predict the development of mortality. When interpreting the results, values below the significance level of 0.05 were considered statistically significant.

Results

The average age of the patients was 37.19±13.91 years, 378 (71%) were male and 154 (29%) were female. When the patients were evaluated in terms of biochemical, hematological, and arterial blood gas parameters, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, blood sugar, hematocrit values were not found to be significant in terms of trauma types. White blood cell was 10.45±3.90 mg/dL (p=0.019) and the lactate level in blood gas was 2.37±1.23 mmol/L (p=0.001) and it was significant. In addition, in the mortality group, lactate was found higher than in those living with 5.51±1.87 mmol/L (p=0.001) and PRT 33.43±12.87 days (p=0.004). PRT was found to be 22.48±7.17 days and lactate level was 2.18±1.05 mmol/L (p=0.001) in patients who underwent prehospital fluid resuscitation, which was significantly lower than in those who did not take fluid (Table 1).

There was no statistically significant difference in the distribution of trauma types by gender (p=0.410). Mortality was detected more in falls and traffic accidents with 6 (1.1%) patients and penetrating injuries (p=0.003). Thoracic injuries were detected in 183 (22.2%) and abdominal traumas in 25 (4.7%) falls (p=0.001). In 10 (1.9%) of the thoracic vertebra and 30 (5.6%) of the lumbar vertebra injuries, the rate of a traffic accident was the highest (p=0.001). Fluid resuscitation was given in falls in 244 (45.9%) patients (p=0.016). X-ray, USG, and CT imaging were most frequently performed in falls. While 58 (10.9%) of the traffic accident cases were performed CT imaging, it was found that none of the penetrating traumas was X-rayed (p=0.001, Table 2).

A variable analysis of prehospital fluid resuscitation was not found to be significant in terms of gender, thoracic, and lumbar vertebral injuries. In the group receiving fluid resuscitation, mortality was high in 12 patients (2.3%), 13 patients with thoracic vertebrae (2.4%), and 40 patients with abdominal trauma (7.5%). Multiple radiological imaging was performed in the group of 38 (7.1%) patients who did not receive fluid resuscitation. However, all other images were performed in the fluid resuscitation group (p=0.001, Table 3).

No relationship was found in the analysis of radiological images in terms of gender (p=0.203). Mortality was associated with multiple imaging in 10 (1.9%), abdominal injuries in 47 (8.8%), thoracic injuries in 16 (3%), and lumbar vertebral injuries in 26 (4.9%) patients. On the other hand, thoracic injuries were detected mostly on CT imaging in 157 (29.5%) patients (p=0.001, Table 4).

In the correlation analysis of the variables with radiological imaging, types of trauma and fluid resuscitation, a relationship between age and gender in all three parameters could not be determined. Considering trauma types, a moderate and/or strong positive correlation was observed with radiological imaging (r=0.405, p=0.001), fluid resuscitation (r=0.115, p=0.008), plasma lactate level (r=0.311, p=0.001), PRT (r=0.105, p=0.015), and mortality (r=0.177, p=0.001). Considering fluid resuscitation, a strong positive relationship was found with radiological imaging (r=0.097, p=0.025), plasma lactate level (r=0.174, p=0.001), PRT (r=0.284, p=0.001), and mortality (r=0.135, p=0.002). Considering radiological imaging, a moderate and/or strong positive correlation was found with plasma lactate level (r=0.677, p=0.001), PRT (r=0.390, p=0.001) and mortality (r=0.216, p=0.001). Correlation analysis of other parameters are given in Table 5.

''The ROC curve analysis'' of mortality is shown in Figure 1. According to this analysis, the rates of lactate and PRT optimal cut-off value to predict the development of mortality were above 45%, with a sensitivity of 97.7% and specificity of 94.3% for lactate [area under the curve (AUC):

0.947, 95% confidence interval: 0.908-0.986], and with a sensitivity of 89.7% and specificity of 83.6% for PRT (AUC: 0.724, 95% confidence interval: 0.570-0.879).

Discussion

Trauma triage guidelines are typically based on the injury mechanism, detected injuries, and reported vital signs (5-8). Vital signs and physical examination findings vary individually and may cause patients with serious injuries to be overlooked. Standard parameters that give results within minutes that can be used in the initial evaluation of trauma patients are required. Serum lactate measurement, in addition to pre-hospital clinical evaluation, is a marker that has the potential to guide triage and further treatment decision-making (9-11). Ter Avest et al. (12), in their study on 156 trauma patients, showed that prehospital lactate levels correlated with the severity of trauma and the need for resuscitative in-hospital care. Similar results were obtained in previous multi-center studies, which stated that serum

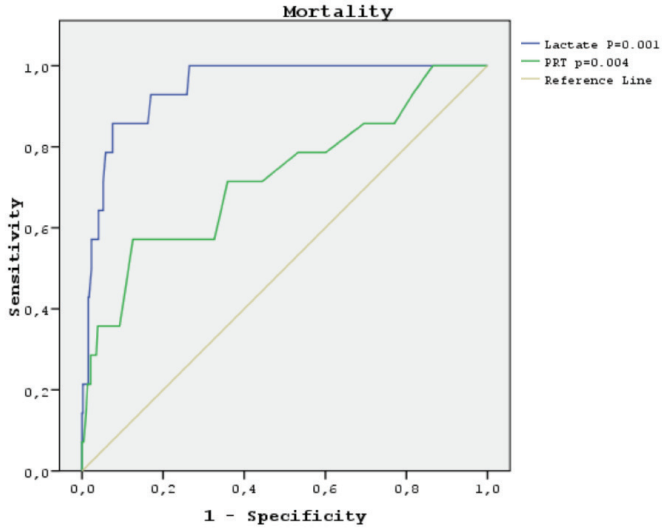

Figure 1. ROC curve analysis according to the mortality relationship between lactate and post-trauma recovery time of trauma patients

Table 1. Baseline characteristics and laboratory variables of the types of trauma

		All patients	Types of trauma			p
			Fall	Traffic accident	Penetrating	
Baseline characteristics		**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	
Age, yr		37.19±13.91	36.92±13.80	38.52±14.03	35.40±17.76	0.415
Sex, female/male		154/378	134/300	29/69	1/9	0.410
PRT, day		24.44±7.66	24.05±7.47	25.87±8.10	27.30±10.03	0.095
Laboratory finding						
Biochemistry	BS, mg/dL	120.11±31.12	119.56±32.00	123.06±26.36	114.70±37.42	0.075
	BUN, mg/dL	20.48±9.01	20.62±9.29	19.73±7.41	22.01±10.82	0.826
	Krea, mg/dL	0.92±0.29	0.93±0.30	0.89±0.26	0.98±0.31	0.557
	ALT, mg/dL	31.99±23.87	31.85±24.84	32.28±19.91	35.26±18.56	0.525
	AST, mg/dL	30.70±26.28	30.86±27.55	29.35±20.53	37.20±21.71	0.353
	ALP, mg/dL	10.56±55.08	102.94±57.48	101.10±42.75	100.90±62.97	0.704
Hemogram	WBC, mg/dL	10.45±3.90	10.25±3.91	11.40±3.86	9.77±2.23	**0.019**
	Hb, g/dL	14.08±1.91	14.10±1.86	14.01±2.04	14.24±2.72	0.877
	Hct, %	42.36±7.18	42.30±7.15	42.51±7.18	43.26±8.66	0.723
Lactate, mmol/L		2.37±1.23	2.19±1.07	3.02±1.42	3.88±2.31	**0.001**
		Mortality				
		No		**Yes**		
PRT, day		24.20±7.34		33.43±12.87		**0.004**
Lactate, mmol/L		2.29±1.10		5.51±1.87		**0.001**
		Fluid resuscitation				
		No		**Yes**		
PRT, day		26.85±7.58		22.48±7.17		**0.001**
Lactate, mmol/L		2.61±1.40		2.18±1.05		**0.001**

SD: Standard deviation, Yr: Year, PRT: Posttraumatic recovery time, BS: Blood sugar, BUN: Blood urea nitrogen, Krea: Creatinine, ALT: Alanine aminotransferase, AST: Aspartate aminotransfersez, ALP: Alkaline phosphates, WBC: White blood cell, Hb: Hemoglobin, Hct: Hematocrit

Table 2. Analysis of types of trauma with variables

		Types of trauma			
		Fall n (%)	Traffic accident n (%)	Penetrating n (%)	p
Gender	**Female**	124 (23.3)	29 (5.5)	1 (0.2)	0.410
	Male	300 (56.4)	69 (13)	9 (1.7)	
Mortality	**No**	418 (78.6)	92 (17.3)	8 (1.5)	**0.003**
	Yes	6 (1.1)	6 (1.1)	2 (0.4)	
Thorax	**No**	306 (57.5)	15 (2.8)	1 (0.2)	**0.001**
	Yes	118 (22.2)	83 (15.6)	9 (1.7)	
Thoracic vertebra	**No**	418 (78.6)	88 (16.5)	9 (1.7)	**0.001**
	Yes	6 (1.1)	10 (1.9)	1 (0.2)	
Lumbar vertebra	**No**	411 (77.3)	68 (12.8)	7 (1.3)	**0.001**
	Yes	13 (2.4)	30 (5.6)	3 (0.6)	
Abdominal	**No**	399 (75)	74 (13.9)	6 (1.1)	**0.001**
	Yes	25 (4.7)	24 (4.5)	4 (0.8)	
Fluid resuscitation	**No**	180 (33.8)	51 (9.6)	8 (1.5)	**0.016**
	Yes	244 (45.9)	47 (8.8)	2 (0.4)	
Radiological imaging	**No**	56 (10.5)	3 (0.6)	0	**0.001**
	X-ray	125 (23.9)	9 (1.7)	0	
	USG	120 (22.6)	3 (0.6)	1 (0.2)	
	BT	102 (19.2)	58 (10.9)	5 (0.9)	
	Multiple	21 (3.9)	25 (4.7)	4 (0.8)	

Table 3. Analysis with variables according to pre-hospital fluid resuscitation

		Fluid resuscitation		
		No n (%)	Yes n (%)	p
Gender	**Female**	78 (14.7)	76 (14.3)	0.090
	Male	161 (30.3)	217 (40.8)	
Mortality	**No**	227 (42.7)	291 (54.7)	**0.002**
	Yes	12 (2.3)	2 (0.4)	
Thorax	**No**	145 (27.3)	177 (33.3)	0.951
	Yes	94 (17.7)	116 (21,8)	
Thoracic vertebra	**No**	226 (42.5)	289 (54.3)	**0.008**
	Yes	13 (2.4)	4 (0.8)	
Lumbar vertebra	**No**	213 (40)	273 (51.3)	0.098
	Yes	26 (4.9)	20 (3.8)	
Abdominal	**No**	199 (37.4)	280 (52.6)	**0.001**
	Yes	40 (7.5)	13 (2.4)	
Radiological imaging	**No**	22 (4.1)	37 (7)	**0.001**
	X-ray	58 (10.9)	768 (14.3)	
	USG	59 (11.1)	65 (12.2)	
	BT	62 (11.7)	103 (19.4)	
	Multiple	38 (7.1)	12 (2.3)	

lactate levels could be an effective criterion in guiding the initial evaluation and resuscitative treatment of trauma patients. They also suggested that the lactate level could be used to predict trauma mortality and morbidity (13-16). In the study, high lactate level was found in patients who did not undergo prehospital fluid resuscitation. In this case, it was determined that there was an increase in mortality in the acute period and a prolongation in post-traumatic recovery in the late period. We think that pre-hospital fluid resuscitation in trauma patients will be an important indicator in terms of shortening the late PRT. Also, the fact that a significant difference was found in terms of mortality may be an important parameter in terms of fluid resuscitation and serum lactate level in future studies.

Lactate formation in body metabolism occurs as a result of anaerobic glycolysis by causing bleeding, insufficient ventilation, hypovolemia, hypoxemia, and end-organ hypoperfusion following a traumatic injury (17,18). However, in the last decade, it has become clear that accelerated aerobic glycolysis (beta adrenergically mediated) also contributes significantly to lactate formation under a variety of conditions. Intense adrenergic discharge increases lactate formation in trauma patients (19).

Intense sympathetic activation and adrenergic stimulation occur in trauma patients for hypovolemic compensation secondary to possible bleeding and due to pain and stress (17). In some studies, it is aimed to control lactate production by modifying beta-adrenergic stimulation

with different treatment regimens (13,14). Of course, since these treatments do not affect pre-hospital lactate levels, they do not restrict the use of lactate measurement as a prognostic marker for end-organ hypoperfusion and morbidity. In their study, Kruse et al. (20) suggested that the results obtained by blood lactate monitoring and especially serial lactate sampling were valuable in predicting in-hospital mortality in the risk assessment of patients who were acutely admitted to the hospital. In this study, it has been recommended that all patients with lactate above 2.5 mm on admission require close clinical follow-up, and serial lactate samples should be taken in patients with lower lactate levels (20). In the study, pre-hospital fluid resuscitation has a significant relationship with lactate and recovery, as well as in-hospital mortality. Also, radiological imaging was found to be easier and faster in patients with fluid intake in terms of hemodynamic stability. This resulted in mortality, length of hospital stay, better hemodynamic parameters, and rapid transport of the patients to be operated on.

The type of trauma or mechanism of tissue damage is associated with lactate levels. In previous studies, it was observed that pulse fullness, heart rate, systolic blood pressure, shock index, oxygen saturation, and end-tidal carbon dioxide levels were correlated with plasma lactate levels (12,16). Pain and/or stress experienced by trauma patients contributes to prehospital lactate levels. In our study, the relationship between pain and lactate could not be directly evaluated. However, it was observed that prehospital fluid supplementation decreased lactate levels. It is well known that fluid administration and adequate analgesia dull the physiological stress response and limit endogenous catecholamine release, resulting

Table 4. Analysis of radiological imaging methods with variables

		Radiological imaging					
		No n (%)	X-ray n (%)	USG n (%)	BT n (%)	Multiple n (%)	p
Gender	**Female**	14 (2.6)	47 (8.8)	28 (5.3)	49 (9.2)	16 (3)	0.203
	Male	45 (8.5)	87 (16.4)	96 (18)	116 (21.8)	34 (6.4)	
Mortality	**No**	59 (11.1)	134 (25.2)	122 (22.9)	163 (30.6)	40 (7.5)	**0.001**
	Yes	0	0	2 (0.4)	2 (0.4)	10 (1.9)	
Thorax	**No**	59 (11.1)	125 (23.5)	123 (23.1)	8 (1.5)	7 (1.3)	**0.001**
	Yes	0	9 (1.7)	1 (0.2)	157 (29.5)	43 (8.1)	
Thoracic vertebra	**No**	59 (11.1)	134 (25.2)	124 (23.3)	164 (30.8)	34 (6.4)	**0.001**
	Yes	0	0	0	1 (0.2)	16 (3)	
Lumbar vertebra	**No**	59 (11.1)	134 (25.2)	124 (23.3)	145 (27.3)	24 (4.5)	**0.001**
	Yes	0	0	0	20 (3.8)	26 (4.9)	
Abdominal	**No**	59 (11.1)	133 (25)	123 (23.1)	161 (30.3)	3 (0.6)	**0.001**
	Yes	0	1 (0.2)	1 (0.2)	4 (0.8)	47 (8.8)	

Table 5. Correlation analysis of radiological imaging methods, types of trauma and fluid resuscitation with variables

	Radiological imaging		Types of trauma		Fluid resuscitation	
	r	p	r	p	r	p
Radiological imaging	**1**		**0.405**	**0.001**	**0.097**	**0.025**
Types of trauma	**0.405**	**0.001**	**1**		**0.115**	**0.008**
Fluid resuscitation	**0.097**	**0.025**	**0.115**	**0.008**	**1**	
Lactate	**0.677**	**0.001**	**0.311**	**0.001**	**0.174**	**0.001**
PRT	**0.390**	**0.001**	**0.105**	**0.015**	**0.284**	**0.001**
Age	0.056	0.195	0.028	0.521	0.003	0.952
Gender	-0.008	0.856	0.029	0.511	-0.073	0.091
Mortality	**0.216**	**0.001**	**0.177**	**0.001**	**0.135**	**0.002**
Thorax	**0.749**	**0.001**	**0.456**	**0.001**	-0.003	0.951
Lumbar vertebra	**0.403**	**0.001**	**0.376**	**0.001**	0.072	0.098
Thoracic vertebra	**0.296**	**0.001**	**0.192**	**0.001**	**0.115**	**0.008**
Abdominal	**0.511**	**0.001**	**0.277**	**0.001**	**0.204**	**0.001**

in a decrease in glycolysis rate (21). In our study, lactate and mortality were found to be higher in trauma type of penetrating injuries. Also, the significant correlation of trauma causes with fluid resuscitation, radiological imaging, mortality, and lactate should be considered. In similar studies, the number of studies showing that the effect of fluid resuscitation increases mortality in patients with penetrating trauma has increased in recent years (22-25). However, since the mechanism of penetrating trauma and the mechanism of blunt trauma are different from each other, it may be expected that fluid resuscitation may be beneficial in patients with blunt trauma (26). Mizushima et al. (23) stated that limited fluid resuscitation may be beneficial. On the other hand, it has been predicted that the aggressive administration of pre-hospital intravenous fluid therapy may lead to the opening of clots formed as a result of increasing blood pressure and causing recurrent bleeding (25,26). Therefore, limited fluid therapy is recommended only in hypotensive patients.

These factors may be the reason for the different results obtained in studies with lactate measurements. In the evaluation of lactate levels, not only pre-hospital and initial evaluation results but also serial laboratory measurements will provide enlightening and correlated results in the evaluation of organ damage and comorbidities, and shed light on advanced treatment methods.

Study Limitations

There were some limitations in our study. The most important of these is that it is single-center and retrospective. Also, difficulties in accessing hospital records, patients, and/or patients' relatives by phone were other important limitations.

Conclusion

Lactate levels that give rapid results in trauma patients are a parameter associated with the type of injury, treatment at the scene, and final organ perfusion and oxygenation rates, which also show the effect of many factors that cannot be measured. Lactate values also need to be taken into account in the application of clinical algorithms to guide prehospital triage or treatment.

Ethics

Ethics Committee Approval: The study was conducted according to the Helsinki Declaration on human research, after getting approval from the local Ethics Board (2019-12/22).

Informed Consent: Patient consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: F.T.T., A.C., Design: F.T.T., A.C., Data Collection or Processing: F.T.T., A.C., Analysis or Interpretation: F.T.T., A.C., Writing: F.T.T.

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ORIGINAL RESEARCH

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The Evaulation of Risk Scorings in Non-variceal Upper Gastrointestinal Bleedings

Varis Dışı Üst Gastrointestinal Kanamalarda Risk Skorlamalarının Değerlendirilmesi

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Abstract

Objective: Upper gastrointestinal (GI) bleeding is a major reason of mortality and morbidity today, and patients' follow-up and treatment costs are still high. In our study, the values of risk scorings of the patients with upper GI bleeding in estimation of mortality and morbidity were evaluated.

Method: One hundred sixty-nine patients who were admitted to emergency internal medicine in University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital Clinic of Internal Medicine due to the diagnosis of upper GI bleeding were reviewed retrospectively between January 2015 and January 2016 in the study. Patients with upper GI bleeding due to varices (esophageal and gastric) endoscopically were excluded from the study. Forrest scoring's classification was made according to the endoscopic findings. Classification of bleeding ulcers according to their appearance is as follows; Forrest 1a; "gushing active bleeding", Forrest 1b; "oozing active bleeding", Forrest 2a; "visible non-bleeding vein", Forrest 2b; "adherent clot", Forrest 2c; "flat pigmented lesion", Forrest 3; "no evidence of bleeding". Rockall scoring's classification uses clinical criteria (pulse, age, systolic blood pressure, comorbidity) in addition to endoscopic findings (diagnosis, hemorrhage). Accordingly, a score less than 3 carries good prognosis. Glasgow-Blatchford scoring's classification was calculated according to the situation of urea nitrogen, hemoglobin, systolic blood pressure, pulse, melena occurrence, syncope, and hepatic or cardiac problems. In this scoring, patients may be in the range of 0-23 points and the need for endoscopic intervention increases according to rising in the score.

Results: The average age of the participants in the study was 57.39±19.14 years. 72% of the cases (n=121) were male. While the presence of melena was observed in 88.7% of the cases, it was seen that 61.9% of the cases had peptic ulcer and 12.5% of the general surgery consultation was performed.

Öz

Amaç: Üst gastrointestinal (GİS) kanamalar günümüzde mortalite ve morbiditenin önemli bir nedenidir ve halen hastaların takip ve tedavi maliyetleri yüksektir. Bu çalışmada üst GİS kanamalı hastaların risk skorlarının mortalite ve morbidite öngörüsündeki değerliliği araştırıldı.

Yöntem: Çalışmada Ocak 2015-Ocak 2016 tarihlerinde, Sağlık Bilimleri Üniversitesi, İstanbul Bağcılar Eğitim ve Araştırma Hastanesi İç Hastalıkları Kliniği'nin acil servisine üst GİS kanama tanısı ile gelen hastaların dosyaları retrospektif olarak incelendi. Endoskopik incelemelerde varis (özofageal ve gastrik) ile gelişen üst GİS kanaması varlığı görülen hastalar çalışmaya alınmadı. Endoskopik bulgulara göre Forrest sınıflaması yapıldı. Forrest sınıflamasında kanayan ülserler görünümlerine göre şu şekilde sınıflandırılmaktadırlar: "Forrest 1a; fışkırır tarzda aktif kanama", Forrest 1b; "sızıntı tarzında aktif kanama", Forrest 2a; "kanamayan görünür damar", Forrest 2b; "yapışık pıhtı", Forrest 2c; "düz pigmente lezyon", Forrest 3; "kanama bulgusu yok". Rockall skorlaması sınıflandırması yaş, nabız, sistolik kan basıncı, komorbid hastalık gibi klinik kriterlerin yanında, endoskopik tanı ve hemoraji gibi endoskopi bulgularına göre hesaplandı. Buna göre üçten düşük skor iyi prognozu gösterdi. Glasgow-Blatchford risk skorlama sınıflandırması üre azotu, hemoglobin, sistolik kan basıncı, nabız, melena varlığı, senkop, karaciğer hastalığının varlığı, kalp yetmezliği bulunması durumlarına göre hesaplandı. Bu skorlamada hastalar 0-23 puan aralığında olabilir ve skor artışına göre endoskopik müdahale gereksinimi de artmaktadır.

Bulgular: Çalışmaya katılanların yaş ortalaması 57,39±19,14 yıl idi. Olguların %72'si (n=121) erkekti. Olguların başvuruda %88,7'sinde melena varlığı görülürken, %61,9'unda peptik ülser, %12,5'inde genel cerrahi konsültasyon yapıldığı görüldü. Olguların Forrest sınıfları arasında yatış süreleri, kan transfüzyonu skor ortalamaları açısından anlamlı bir farklılık bulunmadı (p>0,05). Rockall ve Glasgow-Blatchford skorunun yatış

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Abstract

It was determined that there was no statistically significant difference in the Forrest classifications of the cases in terms of hospitalization duration and blood transfusion (p>0.05). Rockall and Glasgow-Blatchford scores were statistically remarkably higher in patients with hospitalization duration, need for blood transfusion, rebleeding, intensive care follow-up, surgical intervention, and mortality (p<0.05).

Conclusion: The association of Rockall and Glasgow-Blatchford risk scores with morbidity and mortality rates showed that patients should not be interpreted solely according to their endoscopic images. These scorings can be used in approach toward patients with Upper GI bleeding in comprehensive prospective studies.

Keywords: Risk assesment, risk scores, upper GI bleeding

Öz

süresi, kan transfüzyonu ihtiyacı, tekrar kanama, yoğun bakım takibi, cerrahi girişim ve mortalite görülen olgularda daha yüksek değerlere sahip olduğu bulundu (p<0,05).

Sonuç: Rockall ve Glasgow-Blatchford risk skorlarının morbidite ve mortalite oranları ile ilişkili olması hastaların sadece endoskopik görüntülerine göre değerlendirilmemeleri gerektiğini göstermiştir. Geniş çaplı prospektif çalışmalarda, üst GİS kanamalı hastalara yaklaşımda bu skorlamalar kullanılabilir.

Anahtar kelimeler: Risk belirlenmesi, risk skorları, üst GİS kanama

Introduction

Upper gastrointestinal (GI) bleedings occur in the lumen between the upper esophagus and ligament of Treitz (1). 85% of all GI bleedings usually arise from the upper GI (2-4). Peptic ulcers constitute of nearly 50% of these bleedings. 20% of peptic ulcer bleedings are severe and recurrent (5).

Upper GI bleedings constitute an important part of patients applying to surgical emergency unit. In the United States, approximately 150,000 hospitalizations occur for the assessment and treatment of ulcer bleedings every year (6). In the United Kingdom, 172 out of every 100,000 adults apply to the hospital every year due to upper GI bleeding (7). Mortality rate is around 10% despite the developing medical approaches (6). In a study, it has been revealed that hospitalization duration, endoscopic procedures and blood transfusion are among the most important reasons increasing the cost (8). Thus, there has been a tendency to putting patients into risk groups for mortality and rebleeding, based on various parameters like clinic, laboratory and endoscopic findings for years. For that purpose, various risk scoring systems that determine low and high risk patients for mortality and rebleeding and can be easily applied by clinicians in surgical emergency unit to direct the treatment of patients have been developed (9,10). In the Forrest classification, bleeding ulcers are classified according to their appearances (5). The Rockall scoring is based on age, presentation with shock, comorbidities, endoscopic diagnosis and endoscopic new bleeding symptom (11). Unlike the Rockall classification, the Glasgow-Blatchford scoring (GBS) does not involve endoscopic symptoms. The Rockall system has been seen to be an accurate indicator of re-bleeding and mortality. Rockall scoring is based on age, presentation with shock, comorbidity, endoscopic diagnosis, and endoscopic evidence of new bleeding. Accordingly, patients with a score of two or less are grouped as low risk (12). Various studies have found that these scoring systems are useful for the clinician to decide on follow-up and treatment rapidly, to predict mortality and morbidity of the disease and to determine risk factors for mortality and rebleeding (13,14).

The purpose of this study was to demonstrate the correlation of Rockall and GBS risk scoring, Forrest classification values and factors affecting mortality and morbidity rates in patients with upper GI bleeding.

Materials and Methods

The study was conducted with a total of 169 cases including 121 males (72%) and 47 females (28%), who were hospitalized in the internal medicine of emergency service of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital due to the diagnosis of upper GI bleeding. The patients were evaluated retrospectively between January 2015 and January 2016. The most common signs of upper GIS bleeding are haematemesis and/or melena (1). Patients who presented to the emergency department with the complaints of black slime stool, fresh blood coming from the anus, or vomiting blood were endoscopied with a pre-diagnosis of upper GI bleeding and the findings were recorded. The patients, whose endoscopy showed upper GI bleeding due to esophageal and gastric varicose veins, were excluded from the study.

The data about the patients' age, sex, comorbidities, medications, alcohol and smoking status, hospitalization duration, need for blood transfusion, general surgical consultation, referral to intensive care, need for a surgical intervention, rebleeding and mortality were recorded.

Urea, hemoglobin, platelet, prothrombin time, international normalized ratio, HbsAg, anti-Hbs and anti-HCV laboratory values of the patients during the application were checked. In the Forrest classification, bleeding ulcers were classified according to their appearances: Forrest 1a; squirting active bleeding, Forrest 1b; oozing active bleeding, Forrest 2a; non-bleeding visible vein, Forrest 2b; adherent clot, Forrest 2c; flat pigmented lesion, Forrest 3; ulcer with clean base, no sign of bleeding (5).

The Rockall scoring was calculated according to age, systolic blood pressure, comorbidities, endoscopic diagnosis and endoscopic new bleeding symptom. Accordingly, the patients with two or less scores were grouped as low risk (11).

The GBS is a pre-endoscopic score and includes the indicators: hemoglobin levels, urea, blood pressure, pulse, syncope, melena, and liver or cardiac problems. The GBS ranges from 0 to 23, with higher scores corresponding to increasing mortality. The GBS was showed to predict lower risk bleedings, and a GBS value of 1 or lower indicates very low risk group (12).

The connection between risk scores and hospitalization and the need for blood transfusion, in addition to assessment of rebleeding, surgical consultation, intensive care follow-up, surgical intervention and mortality rates with the Rockall and GBS, was evaluated.

Statistical Analysis

The results acquired from the study were assessed using the IBM SPSS Statistics 22. While assessing the study data, the convenience of parameters for normal distribution was assessed via the Shapiro-Wilks test. The Kruskal-Wallis test was used for intergroup comparisons of non-normally distributed parameters. The Student t-test was performed for two-group comparisons of normally distributed parameters and the Mann-Whitney U test was used for two-group comparisons of non-normally distributed parameters. The chi-square test was employed for the comparison of qualitative data. Correlations between the parameters were examined using the Pearson's and Spearman's Rho correlation analysis. The significance was assessed at the level of $p<0.05$.

Ethical Committee Approval

Approval for the study was taken from the Local Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital Training and Research Hospital (number: 2016/454). It was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from each participant.

Results

The cases included in the study were aged between 17 and 89 years (mean 57±19 years), male participants were aged 17-87 years (mean 54±18 years) and female participants were aged 19-89 years (mean 66±20 years). During the admission, 88.7% of the cases showed melena and 10.7% syncope. Table 1 shows the physical examination results of the cases during the application and the assessment of their laboratory parameters. In the upper GI endoscopy, 61.9% of the cases had peptic ulcer, 27.4% had erosive gastritis, 6.5% had cancer, 4.8% had esophagitis, and 17.9% had other lesions. The cases' hospitalization duration was 1-47 day(s) (mean 5.61±4.26) and blood transfusion was 0-14 unit(s) (mean 2.55±2.51). Surgical treatment was applied in cases where medical and endoscopic treatment methods were insufficient in upper GI bleeding and when the bleeding was accompanied by perforation, obstruction and malignancy. General surgery consultation was requested in patients whose hemoglobin level was below 8 g/dL, hemodynamic stability could not be achieved and bleeding developed for the second time despite 4-6 units of blood transfusion within 24 hours. General surgical consultation was observed in 12.5% of the cases, rebleeding in 9.5%, referral to intensive care in 3%, mortality in 3% and surgical intervention in 1.8% (Table 1).

It was determined that there was no statistically significant difference between the Forrest classifications of the cases in terms of hospitalization duration and blood transfusion, ($p>0.05$) (Table 2).

The cut-off values were found <6 for Rockall and <11 for GBS in this study. Score comparisons were made on the average point.

The Rockall score and GBS mean values were statistically significantly higher in the cases who had rebleeding than in the cases who did not ($p=0.008$, $p=0.015$, respectively). The Rockall score and GBS mean values were statistically significantly higher in the cases who were referred to intensive care than in the cases who were not (respectively $p=0.006$, $p=0.002$) (Table 3). The Rockall score and GBS mean values were statistically significantly higher in the cases who required general surgical consultation than in the cases who did not (respectively $p=0.001$, $p=0.001$) (Table 3). The Rockall score and GBS mean values were statistically significantly higher in the cases who had

Table 1. Characteristics of the cases

		Min-max	Mean ± SD
Age			
All patients		17-89	57±19
Male		17-87	54±18
Female		19-89	66±20
Hospitalization duration (day)		1-47	5.61±4.26
Blood transfusion (unit)		0-14	2.55±2.51
Thrombocyte		43,400-511,400	216,402±79,271
INR		0.92-10.2	1.57±1.33
Hemoglobin (gr/dL)		3.6-15	8.99±2.58
Urea		16-427	82.17±51.78
Systolic pressure (mmHg)		60-160	108.97±16.26
Diastolic pressure (mmHg)		40-90	67.74±9.88
Pulse (mn)		70-120	88±11
		n	**%**
Sex	**Male**	121	72
	Female	47	28
Alcohol		3	1.8
Smoking		60	35.7
General surgical consultation		21	12.5
Rebleeding		16	9.5
Referral to intensive care		5	3
Mortality		5	3
Surgical intervention		3	1.8
Comorbidities			
Total		100	59.5
HT		43	25.6
CHF		41	24.4
CAD		36	21.4
DM		28	16.7
CRF		18	10.7
Cancer		11	6.5
CVD		11	6.5
Other		44	26.1
Medication			
Total		121	72
ASA		40	23.8
NSAII		39	23.2
Coumadin		26	15.5
Clopidogrel		13	7.7
Other		42	25

Table 1. Continued

	Min-max	Mean ± SD
	n	**%**
Endoscopic pre-diagnoses lesions		
Peptic ulcer	104	61.9
Erosive disease	46	27.4
Cancer	11	6.5
Esophagitis	8	4.8
No lesions	30	17.9
Melena	149	88.7
Syncope	18	10.7

SD: Standard deviation, INR: International normalized ratio, CHF: Congestive heart failure, CAD: Coronary artery disease, CRF: Chronic renal failure, CVD: Cardiovascular disease, NSAII: Non-steroidal anti-inflammatory drug

surgical intervention than in the cases who did not (respectively p=0.019, p=0.001) (Table 3).The Rockall score and GBS mean values were statistically significantly higher in the cases who had mortality than in the cases who did not (respectively p=0.010, p=0.008). The table shows the correlation of the Rockall and GBS with rebleeding, surgical consultation, intensive care follow-up, surgical intervention, and mortality (Table 3).

There was a statistically significantly positive correlation between the Rockall score and hospitalization duration at the level of 46.9% (p=0.001). There was a statistically significant positive correlation between the Rockall score and blood transfusion levels at the level of 38.7% (p=0.001) (Table 4).

There was a statistically significant positive correlation between the GBS and levels of hospitalization duration at the level of 36.3% (p=0.001) (Table 4).

A positive correlation existed between the GBS and levels of blood transfusion at the level of 50.9% (p=0.001). The table shows the correlation of the Rockall and GBS with hospitalization duration and the need for blood transfusion (Table 4).

Discussion

A great part of the patients applying to the emergency surgical units suffer from upper GI bleeding. The rate of incidence of this picture, mortality and re-bleeding rates vary. It is required that the important clinical decisions should be made quickly for a severe and life-threatening disease like acute upper GI bleeding. Risk assessment is important for upper GI bleeding; however, no score accurately predicts all important clinical outcomes (15).

Table 2. Assessment of hospitalization duration, need for blood transfusion, in terms of Forrest classification

	F1b	F2a	F2b	F2c	F3	p
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Hospitalization duration (day) (median)	5.56±3.09 (5)	6.64±2.84 (6)	5.62±2.29 (5)	7±9.85 (5)	5.24±2.93 (4)	[1]**0.368**
Blood transfusion (unit) (median)	3.44±2.41(3)	2.64±2.66 (2)	2.62±1.71 (3)	2.11±3.21 (2)	2.38±2.45 (2)	[1]**0.077**

[1]Kruskal-Wallis test, p<0.05, F1b: Forrest 1b, F2a: Forrest 2a, F2b: Forrest 2b, F2c: Forrest 2c, F3: Forrest 3, SD: Standard deviation

Table 3. Assessment of hospitalization duration, need for blood transfusion, rebleeding, surgical consultation, intensive care follow-up, surgical intervention and mortality rates with the Rockall and Glasgow-Blatchford scores

	Rockall score	Glasgow-Blatchford score
	Mean ± SD (median)	Mean ± SD
Rebleeding		
No	3.86±2.35 (4)	11.6±3.63
Yes	5.56±2.63 (6)	13.88±2.36
p	[1]**0.008***	[2]**0.015***
Referral to intensive care		
No	3.93±2.38 (4)	11.67±3.49
Yes	7.2±1.92 (7)	16.6±3.58
p	[1]**0.006***	[2]**0.002***
General surgical consultation		
No	3.75±2.25 (4)	11.42±3.41
Yes	5.95±2.75 (5)	14.57±3.63
p	[1]**0.001***	[2]**0.001***
Surgical intervention		
No	3.95±2.35 (4)	11.69±3.49
Yes	8.33±2.89 (10)	18.67±2.08
p	[1]**0.019***	[2]**0.001***
Mortality		
No	3.91±2.33 (4)	11.69±3.5
Yes	7.6±2.88 (8)	16±4.36
p	[1]**0.010***	[2]**0.008***

[1]Mann-Whitney U test, [2]Student t-test, *p<0.05, SD: Standard deviation

Table 4. Investigation of the relationship between Rockall score, Glasgow-Blatchford score and hospitalization and need for blood transfusion

		Rockall score	Glasgow-Blatchford score
Hospitalization duration (day)	r	**0.469**	**0.363**
	p	**0.001*[1]**	**0.001*[2]**
Blood transfusion (unit)	r	**0.387**	**0.509**
	p	**0.001*[1]**	**0.001*[2]**

Sperman's Rho correlation analysis[1], Pearson's correlation analysis[2], *p<0.05

The present study revealed that the Forrest endoscopic risk classification was correlated only with general surgical consultation. It was found that the Rockall and Glasgow-Blatchford score mean values were significantly correlated with hospitalization duration, need for blood transfusion, rebleeding, surgical consultation, intensive care follow-up, surgical intervention and mortality rates.

In their study, Güngör et al. (16), reported that the Forrest 1a and 1b were encountered very often (33.3% and 44.4%, respectively). In the study by Önder et al. (17), it was detected that bleeding was the Forrest 1a at the rate of 51.5% and the Forrest 1b at the rate of 24.2%. They stated that it would be difficult to apply endoscopic hemostasis to these patients and even if it was applied, they would most likely need to have a surgical intervention due to higher risk of rebleeding. Thus, surgical intervention should not be delayed (17). The study by Klebl et al. (18) revealed no significant correlation between mortality, rebleeding and hospitalization for more than three days in patients with high Forrest classification (1a, 1b, 2a, 2b), either. In the present study, there were patients in the groups Forrest 1b (15.9%), Forrest 2a (6.5%), Forrest 2b (7.6%), Forrest 2c (11.2%) and Forrest 3 (57.9%) whereas there was no patient in the Forrest 1a. In the present study, no statistically significant difference was found between the Forrest groups of the cases in terms of rebleeding, referral to intensive care, surgical intervention and mortality rates. Rate of general surgical consultation was statistically significantly higher in the Forrest 1b than in the other groups.

In their study, Martinez-Cara et al. (19) calculated the average hospitalization duration as 7.7 days and found a significant correlation between hospitalization duration and high Rockall and GBS. In their study, Sengupta et al. (20) indicated that hospitalization duration of >7 days was high risk for GBS and found that there was no statistically significant difference between patients with high risk scores and prolongation of hospitalization. In their study, Aldemir et al. (21) reported that hospitalization duration was higher in patients with high Rockall risk scores. In their study, Önder et al. (17) found no correlation between

the Rockall risk score and hospitalization duration. In the present study, the average hospitalization duration of the cases was found to be 5.6 days. A statistically significant correlation was determined between the Rockall and GBS and hospitalization duration.

In their study, Martinez-Cara et al. (19) made blood transfusion at the rate of 62% and reported that the Rockall and Glasgow-Blatchford scorings were useful for determining the need for blood transfusion. Sengupta et al. (20) found a statistically significant correlation between high GBS and blood transfusion in their study. In the present study, the average blood transfusion was calculated to be 2.5. There was a statistically significant correlation between the Rockall score, GBS and blood transfusion levels.

Treatment strategies in upper GI bleedings have distinctly changed over the past twenty years. Even though acid suppression treatments and endoscopic hemostasis have led to the need for a surgical intervention, mortality has still remained at the level of 6-13% (22,23). In the study by Johnston et al. (24) surgical intervention was applied to 2.1% of the patients (23). In the study by Kalkan et al. (25) 1.1% of the patients needed surgical intervention (24). In the present study, surgical intervention was applied to 1.8% of the patients.

In other studies, mortality was reported between 8% to 20.3% (13,17,19,20,23,25). In the present study, the rate of mortality was 3%.

Budimir et al. (22) concluded that Rockall score was the good indicator of mortality and GBS was the good indicator of a need for blood transfusion. In the study conducted by Wang et al. (13) with 341 patients with nonvariceal upper GI bleeding, they found that a positive correlation existed between the Rockall score and rebleeding, surgical intervention and mortality. Klebl et al. (18) reported that mortality development was correlated with the Rockall score. Bryant et al. (26) determined in their study that the need for a surgical intervention and mortality risk were significantly correlated with patients whose GBS was greater than seven. They recommended early endoscopy especially for this group of patients (26). Yaka et al. (27) reported that GBS had superior sensitivity and specificity for predicting endoscopic treatment despite low positive predictive value.

In their study, Sengupta et al. (20) found a statistically significant correlation between high GBS and blood transfusion, but no significant correlation in terms of mortality. Custovic et al. (28) found that Rockall score was superior to GBS in indicating an essential for intervention as well as death rates. In the present study, it was determined that the Rockall and GBS were statistically significantly correlated with rebleeding, general surgical consultation, surgical intervention, referral to intensive care and mortality rates.

Conclusion

In the present study, the correlation of the Rockall and GBS with morbidity and mortality rates indicated that patients should not be assessed only according to their endoscopic images. It is necessary to make important clinical decisions rapidly for a serious and life-threatening disease like acute upper GI bleeding. There is a need for large-scale and comparative prospective studies to reveal the reliability of endoscopic and clinic risk scoring systems. By this way, risk scorings may come into clinical use in a more reliable way and clinicians may be able to access diagnostic and therapeutic decisions faster. In addition, risk scoring may enable to discharge low risk patients earlier and prevent a large portion of service beds from being occupied.

Ethics

Ethics Committee Approval: Approval for the study was taken from the Local Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (number: 2016/454). It was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from each participant.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.Ö., E.Y., Design: F.Ö., E.Y., Data Collection or Processing: F.Ö. C.D., A.G., Literature Search: H.Y., C.D., A.G., Analysis or Interpretation: C.D., A.G., H.Y., Writing: F.Ö., E.Y., H.Y.

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ORIGINAL RESEARCH

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Erythrocyte Sedimentation Rate May Predict Diagnosis of Lymphoma Without Fine-needle Aspiration Biopsy: A Retrospective Study

Eritrosit Sedimantasyon Hızı İnce İğne Aspirasyon Biyopsisi Olmadan Lenfoma Tanısını Öngörebilir: Retrospektif Bir Çalışma

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Abstract

Objective: To assess the relationship between routine blood values recorded before fine-needle aspiration biopsy (FNAB) and final diagnosis in patients whose diagnoses could not be confirmed with FNAB, necessitating surgical excisional biopsy (SEB) as a second invasive procedure.

Method: The data of patients who could not be diagnosed via FNAB and who underwent SEB of the cervical lymph node between March 2014 and March 2019 in the otolaryngology department of a research hospital were evaluated retrospectively. According to the definitive diagnosis determined by SEB, the cases were divided into 3 groups as follows: 1) benign, 2) other malignancies, 3) lymphoma.

Results: The frequency of males in the other malignancies group was significantly higher compared to the other two groups (p=0.007). Compared to the other two groups, C-reactive protein levels were statistically significantly lower in the benign group (p=0.001). Erythrocyte sedimentation rate (ESR) in the lymphoma group was significantly higher than in the other groups (p<0.001) and ESR was found to have 70.21% sensitivity, 75.76% specificity and 73.97% accuracy to discriminate lymphoma from other tumors with a cut-off point of >35.5 mm/hr (area under the curve= 0.784, 95% confidence interval: 0.708-0.861, p<0.001).

Conclusion: Although ESR is non-specific for the diagnosis of lymphoma in asymptomatic patients, it may be a supportive marker to reduce repetitive invasive procedures in symptomatic patients who may require cervical lymph node biopsy for diagnosis.

Keywords: C-reactive protein, erythrocyte sedimentation rate, fine-needle aspiration biopsy, lymphoma

Öz

Amaç: İnce iğne aspirasyon biyopsisi (İİAB) ile tanısı doğrulanamayan ve ikinci bir invaziv işlem olarak cerrahi eksizyonel biyopsi (CEB) gerektiren hastalarda İİAB öncesi kaydedilen rutin kan değerleri ile kesin tanı arasındaki ilişkiyi değerlendirmektir.

Yöntem: Bir araştırma hastanesinin kulak burun boğaz kliniğinde Mart 2014-Mart 2019 tarihleri arasında İİAB ile tanı konamayan ve servikal lenf nodu CEB yapılan hastaların verileri retrospektif olarak değerlendirildi. CEB'ye göre belirlenen kesin tanıya göre olgular şu şekilde 3 gruba ayrıldı: 1) benign, 2) diğer maligniteler, 3) lenfoma.

Bulgular: Diğer maligniteler grubundaki erkeklerin sıklığı diğer iki gruba göre anlamlı olarak daha yüksekti (p=0,007). Diğer iki grupla karşılaştırıldığında, C-reaktif protein seviyeleri benign grupta istatistiksel olarak anlamlı düzeyde daha düşüktü (p=0,001). Lenfoma grubunda eritrosit sedimantasyon hızı (ESR) diğer gruplara göre anlamlı düzeyde daha yüksekti (p<0,001) ve lenfomayı diğer tümörlerden ayırmada ESR'nin >35,5 mm/saat kesim noktasında %70,21 duyarlılık, %75,76 özgüllük ve %73,97 doğruluğa sahip olduğu saptandı (eğri altındaki alan =0,784, %95 güven aralığı: 0,708-0,861, p<0,001).

Sonuç: ESR, asemptomatik hastalarda lenfoma tanısı için spesifik olmasa da, tanı için servikal lenf nodu biyopsisine ihtiyaç duyan semptomatik hastalarda tekrarlayan invazif prosedürleri azaltmak için destekleyici bir belirteç olabilir.

Anahtar kelimeler: C-reaktif protein, eritrosit sedimantasyon hızı, ince iğne aspirasyon biyopsisi, lenfoma

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Introduction

Lymphomas are neoplasms of lymphoid cells and often begin in lymph nodes and spread to lymphoid tissues in the spleen, gastrointestinal system, liver and bone marrow (1,2). These clonal neoplasms arise from different differentiation steps of immature or mature B-cells, T-cells or natural killer cells (1). There are two main subtypes; non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). Global cancer data estimates show that 2.8% of cancers are NHL and 0.4% are HL (3).

Inflammation is the basis of various processes in cancer pathogenesis, including the formation and spread of cancer cells (4). The role of inflammation in the formation and spread of cancer has been studied for a long time and various types of cancer have been shown to develop on the basis of chronic inflammation (5,6). In other words, conditions suitable for cancer development may be provided by the presence of chronic inflammation (4). Similar to other types of cancer, the pathogenesis of lymphoma has also been associated with inflammation (7,8). Many markers have been identified in attempts to determine or assess inflammatory activity in the context of cancer, including lymphoma. Some studies have come upon the conclusion that these parameters may be utilized in the prediction or assessment of diagnosis, prognosis or response to treatment in lymphoma (9-13).

Surgical excisional biopsy (SEB) of the lymph node is recommended for the definitive diagnosis of lymphoma in current guidelines (14-17). Although fine needle aspiration biopsy (FNAB) performed for lymphoma diagnosis may provide conclusive results, its results may be insufficient for a definitive diagnosis, necessitating SEB. (18). Additionally, performing FNAB before SEB may be a cause of delay in diagnosis and could lead to the exposure to invasive interventions twice. If laboratory tests, which are routinely checked in all patients prior to FNAB, can direct clinicians to SEB without FNAB, an extra invasive procedure may not be needed. For this reason, in this study, we aimed to assess the relationship between routine blood values recorded before FNAB of the cervical lymph nodes and final diagnosis in patients who had required SEB of cervical lymph nodes due to inconclusive results with FNAB.

Materials and Methods

Patient Group

In this study, the data of patients who could not be diagnosed via FNAB and who underwent SEB of the cervical lymph node between March 2014 and March 2019 in Istanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital Otolaryngology Clinic were evaluated retrospectively. All patients examined were 18 years old or older. Data were collected between March 2019 and September 2020. Permission was obtained from the Clinical Research Ethics Committee of Kartal Dr. Lütfi Kırdar Training and Research Hospital to conduct the study (2019/514/148/6).

According to the sample size results calculated using laboratory values in the study of Okumura et al. (19), it was determined that there should be 44 individuals in each group to provide a power of 80% with 5% alpha error.

Exclusion Criteria

1- Patients with a previous diagnosis of lymphoma and having undergone SEB for recurrence verification without the use of FNAB.

2- Patients who were previously diagnosed with solid organ tumor and had undergone a biopsy for the assessment of metastasis.

Determination of Groups

According to the definitive diagnosis determined by SEB, the cases were divided into 3 groups as follows: 1) benign, 2) other malignancies, 3) lymphoma.

Variables of Interest

The age, gender and laboratory measurements of the patients recorded before FNAB were examined. The laboratory measurements examined were C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and hemoglobin levels and white blood cell, neutrophil, lymphocyte and platelet counts.

Patients who apply to our clinic with lymphadenopathy in the neck are first evaluated by ultrasonography and the size, number and characteristics of the lymph node are analyzed. If there is a finding in favor of infection in the patient, the patient is re-evaluated after 2 weeks of antibiotic treatment. In addition, if there are some infections (brucellosis, tuberculosis, etc.) in the history, they are referred to the infection department. If no response is obtained about lymphadenopathy after the antibiotic treatment given to the patient, planning is made for more detailed evaluations. If malignancy is suspected, detailed blood tests are requested (hemogram, sediment, CRP, serology) and peripheral smear, PPD skin test and

chest radiography are added to the tests. If the suspicion of malignancy persists as a result of all these examinations, FNAB is requested first. In cases where there is a strong possibility of lymphoma in the patient, lymph node excision is applied to the patient by taking the opinion of the hematology clinic.

In our hospital, excisional biopsies are performed in the operating room under sterile conditions and most of the patients are kept under observation in our service overnight. Meanwhile, intravenous antibiotic therapy is administered. Our patients discharged on the evening of the operation are sent home with oral antibiotics and are called for control the next day. There was no patient complicated with infection among the patients who underwent excisional biopsy. Before the procedure, patients with active infection (acute lymphadenitis) were not operated without antibiotic treatment. Sometimes, patients with tuberculosis may have lymph nodes fistulized to the skin, but no such patient was found in our study.

Statistical Analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). For the normality check, the Shapiro-Wilk test was used. Data were given as mean ± standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. Normally distributed variables were analyzed with One-Way analysis of variances (ANOVA). Non-normally distributed variables were analyzed with the Kruskal-Wallis test. Pairwise comparisons of these variables were performed with the Bonferroni correction method. Categorical variables were analyzed with chi-square tests. Diagnostic performances of the variables were evaluated with the receiver operating characteristic (ROC) curve analysis. The best cut-off value was determined based on the highest value obtained in ROC curve analysis according to Youden's index. $p<0.05$ values were accepted as statistically significant results.

Results

The benign, other malignancies and lymphoma groups were comprised of 62 (27 males), 37 (28 males) and 47 (24 males) patients, respectively. When the presentation symptoms were examined among the groups, the three most common symptoms encountered in lymphoma patients were weight loss (25.5%), fever (21.3%) and night sweats (8.5%). In the group of patients with other malignancies, the three most common presenting symptoms were weight loss (32.4%), oral intake-swallowing difficulty (21.6%) and hoarseness (18.9%) (Table 1).

Among other malignancies, the three most common malignancies were squamous cell carcinoma (29.7%), carcinoma metastasis (16.2%) and malignant mesenchymal tumor (10.8%).

Although age was similar in all three groups (p=0.053), gender distribution demonstrated a significant difference in 3-group comparison (p=0.007). Post-hoc corrections showed that only the other malignancies group had a significant difference from the other two groups, with a higher percentage of males.

The frequency of males in the other malignancies group was significantly higher compared to the other two groups (male percentages were 43.55%, 75.68% and 51.06%, respectively, p=0.007).

Compared to the benign group, hemoglobin level was significantly lower in the lymphoma group (mean hemoglobin levels were 13.33, 12.80 and 11.93, respectively, p=0.003) (Graphic 1), while neutrophil level was significantly higher in the other malignancies group (median neutrophil levels were 4.35, 5.9 and 4.9, respectively, p=0.017).

Compared to the other two groups, CRP level was significantly lower in the benign group (median CRP levels were 5, 17 and 15, respectively, p=0.001) (Graphic 2).

The ESR level of the lymphoma group was significantly higher than that of the other groups. In addition, the ESR level of the other malignancies group was higher than that of the benign group (Graphic 3). The only parameter with significant pairwise differences among all three groups was ESR (median ESR levels were 12, 24 and 52, respectively, p<0.001) (Table 2).

Table 1. Distribution of symptoms at presentation in groups

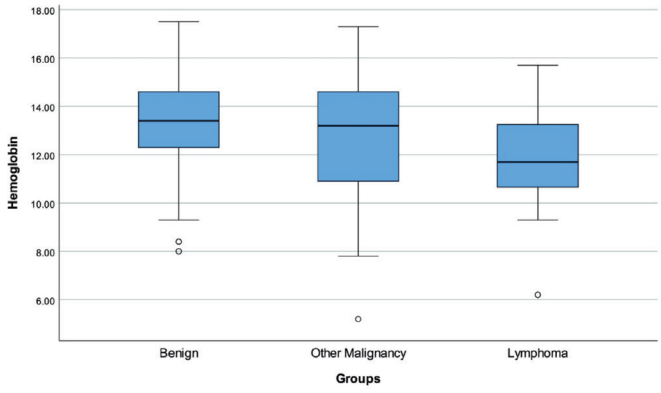
	Other malignancies n (%)	Lymphoma n (%)
Weight loss	12 (32.4)	12 (25.5)
Fever	1 (2.7)	10 (21.3)
Night sweats	-	4 (8.5)
Oral intake-swallowing difficulties	8 (21.6)	-
Hoarseness	7 (18.9)	-
Mass in the neck	1 (2.7)	-
Stuffy nose	1 (2.7)	-
Nasal and postnasal drip	1 (2.7)	-
Respiratory distress	1 (2.7)	1 (2.1)

The ROC analysis revealed that ESR had 70.21% sensitivity, 75.76% specificity and 73.97% accuracy for the discrimination of lymphoma from other malignancies and benign lesions with a cut-off value of >35.5 mm/hr (higher values in favor of lymphoma) (area under the curve =0.784, 95% confidence interval: 0.708-0.861, p<0.001) (Graphic 4).

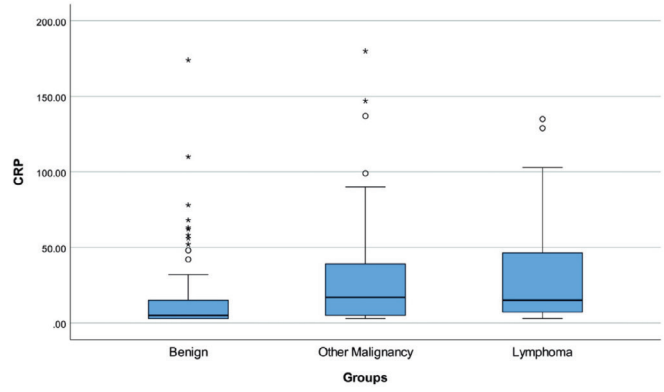
White blood cell (p=0.783), neutrophil (p=0.700), lymphocyte (p=0.431), hemoglobin (p=0.144), LDH (p=0.144), AST (p=0.711), ALT (p=0.116), and CRP (p=0.382) levels were found to be similar between the subtypes of lymphoma. Platelet (median levels were 342, 237.5, 207, and 203.5, respectively, p=0.007) and ESR (median levels were 78, 52.5, 28, and 36, respectively, p=0.019) values of patients diagnosed with HL were statistically significantly higher than in those with indolent lymphoma (Table 3).

Discussion

Diagnosis of lymphoma may be difficult for both patients and clinicians, especially considering the procedures required for diagnosis. In this study, which examined the possibility of limiting invasive procedures during the lymphoma diagnosis process by taking laboratory measurements into consideration, we found that hemoglobin levels were lower and CRP and ESR levels



Graphic 1. Box-plot of the hemoglobin values



Graphic 2. Box-plot of the CRP values
CRP: C-reactive protein

Table 2. Summary of patient characteristics and laboratory measurements

	Groups			
	Benign	**Other malignancies**	**Lymphoma**	**p**
N	62	37	47	N/A
Age	49.26±18.04	53.35±15.57	57.17±15.93	0.053
Gender, male	27 (43.55%)[a]	28 (75.68%)[b]	24 (51.06%)[a]	**0.007**
Hemoglobin	13.33±1.86[a]	12.80±2.64[ab]	11.93±1.87[b]	**0.003**
WBC (x1.000)	7.35 (6.1-8.6)	8.3 (6.4-10.3)	8.1 (6.4-12)	0.095
Neutrophil (x1.000)	4.35 (3.2-5.6)[a]	5.9 (3.9-7.2)[b]	4.9 (3.6-7)[ab]	**0.017**
Lymphocyte	2.1 (1.7-2.5)	1.9 (1.4-2.2)	1.85 (1.4-2.4)	0.099
Platelet	259.5 (216-304)	220 (189-297)	269 (197-348)	0.139
LDH	195.5 (181-232)	195 (175-248)	220 (187-312)	0.051
AST	20 (18-25)	20 (17-25)	22 (16-28)	0.781
ALT	18.5 (12-25)	16 (13-23)	22 (15-31)	0.053
CRP	5 (3-15)[a]	17 (5-39)[b]	15 (6-47.8)[b]	**0.001**
ESR	12 (6-30)[a]	24 (11-51)[b]	52 (25-78)[c]	**<0.001**

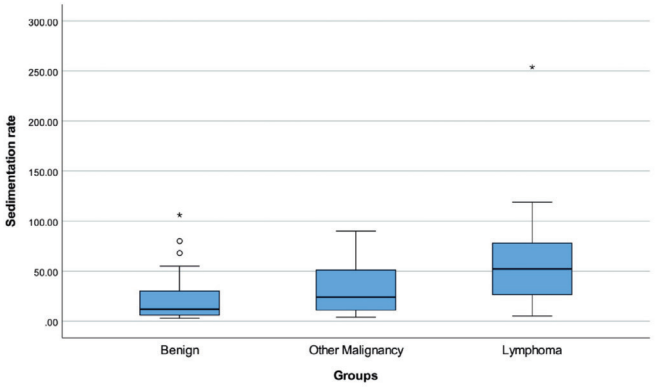
ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, WBC: White blood cell

Data are given as mean ± standard deviation or median (1st quartile-3rd quartile) for continuous variables according to the normality of distribution and as frequency (percentage) for categorical variables.

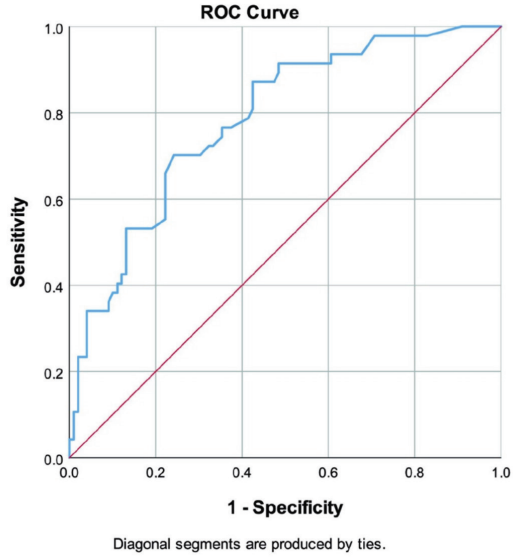
Same letters denote the lack of statistically significant difference between the groups

were higher in the lymphoma group compared to benign cases. Furthermore, although CRP levels showed lower inflammatory activity in the benign group, our results revealed that ESR was the only parameter that could differentiate lymphoma cases from both the benign group and the other malignancies group. ESR level was significantly higher in lymphoma cases.

ESR can be simply defined as the rate at which erythrocytes settle towards the bottom of the tube in anticoagulated blood. Despite its simplicity, ESR is a widely used inflammation marker in addition to its role in other purposes, such as determining acute phase response, tissue damage and response to treatment (20). Based on these features, ESR has been investigated to predict the diagnosis and prognosis of various cancer types, including lymphoma. In a study examining the predictability of various cancer diagnoses by assessing elevated inflammatory markers (adjusted for age and sex), Watson et al. (21) showed that CRP had 46.1% sensitivity and 75.4% specificity and ESR had 43.6% sensitivity and 75.6% specificity. Liu et al. (22) investigated the use of ESR and CRP in the differential diagnosis of intestinal lymphoma and active Crohn's disease. They reported 60.0% sensitivity and 80.0% specificity for an ESR threshold of >24.2 mm/hr and 62.1% sensitivity and 96.0% specificity for a CRP threshold of >19.7 mg/dL in the diagnosis of lymphoma (22). In our study, a >35.5 mm/hr cut-off for ESR was found to have a sensitivity and specificity of over 70% in distinguishing lymphoma from other malignancies and benign lesions. In previous studies, the levels of inflammation markers in the other malignancies, benign pathologies and lymphoma



Graphic 3. Box-plot of the sedimentation rates



Graphic 4. ROC curve of the sedimentation rate to discriminate lymphoma from other tumors

Table 3. Distribution of laboratory measurements according to lymphoma subtypes

	Hodgkin lymphoma	Diffuse large B-cell lymphoma (DLBCL)	Indolent lymphoma	T-cell lymphoma	p
WBC	8.250 (6.325-12.425)	8.100 (6.350-9.125)	9.100 (6.400-15.600)	7.550 (5.270-12.275)	0.783
Neutrophil	5.450 (3.647-7.725)	4910 (3.200-7.050)	5.150 (3.200-6.000)	4.150 (2.595-7.100)	0.700
Lymphocyte	1.925 (1.445-2.370)	1..570 (1250-2.625)	2.400 (1.130-7.600)	1.850 (1627.5-2072.5)	0.431
Hemoglobin	11.2 (10.6-12.9)	11.7 (10.3-13.1)	12.7 (9.9-14.1)	13.4 (13.2-14.1)	0.144
Platelet	342,000 (265,000-449,000)[a]	237,500 (157,250-296,000)[ab]	207,000 (125,000-344,000)[b]	203,500 (176,750-233,250)[ab]	**0.007**
LDH	220.5 (171-259.7)	229 (188.2-318)	190 (184-289)	382 (253.7-517)	0.218
AST	19.5 (16.3-27)	22.5 (15.7-37.5)	24 (19-34)	16 (15.2-29.5)	0.711
ALT	21 (12.8-28.5)	28.5 (15-37)	25 (17-39)	14.5 (10.7-19)	0.116
ESR	78 (40.5-88.3)[a]	52.5 (28-71.7)[ab]	28 (11.4-56)[b]	36 (17-59.5)[ab]	**0.019**
CRP	22.6 (9.6-66.2)	16.6 (8.5-27.5)	9.6 (3.3-27)	11.9 (5.1-69.9)	0.382

WBC: White blood cell, LDH: Lactate dehydrogenase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

Data are given as median (1st quartile - 3rd quartile) for variables

groups were not examined; whereas, we found that these groups were similar in terms of other parameters. In addition, various studies have shown that ESR value is characteristically higher in women and increases with age, regardless of other variables (23). Therefore, the higher frequency of female gender in the lymphoma group in our study may be one of the reasons causing higher ESR in this group; however, it was noted that the benign and lymphoma groups were similar with regard to gender distribution.

Another parameter considered as an indicator of inflammation is CRP (24). Allin et al. (25) showed that the probability of detecting any type of cancer increased 1.3 times in cases with increased CRP. In a review study, although the cause and effect relationship was not clarified, it was suggested that the increase in CRP was associated with cancer diagnosis and prognosis in different types of cancer (26). In a systematic review examining the relationship between CRP level and cancer, Heikkilä et al. (27) reported that increased CRP in cancer cases was shown in previous studies, but as a result of prospective studies, the causal relationship between CRP and cancer could not be clearly revealed. In different studies, it has been shown that CRP elevation is an important biomarker in the diagnosis and follow-up of various cancer types (28,29). The CRP-lymphoma relationship has been examined in other previous studies. Wieland et al. (30) reported that 64% of the patients diagnosed with HL had elevated CRP level at the time of diagnosis (with regard to reference range) and that CRP levels changed in relation with the severity of disease. Consistent with previous studies, the CRP level, which is among the parameters examined in our study, was found to be significantly lower in the benign group than in the other groups. Although a causal relationship could not be demonstrated in this study, it was thought that high CRP was caused by the increase in inflammatory activity due to the course of disease.

Another area of use of inflammatory markers is to evaluate the prognosis of disease and the response to treatment. Hamed Anber et al. (12) have reported that inflammatory markers above the reference values negatively affect prognosis and response to treatment in patients with lymphoma. Wu et al. (13) have suggested that the ESR value is associated with the prognosis of the disease in diffuse large B-cell lymphoma cases and that it can be used to predict the likelihood of successful treatment and recurrence. Kawaguchi et al. (31) reported that progression-free survival was shorter in follicular lymphoma cases with a CRP level above 5 mg/dL. In addition, many different studies have shown that increasing CRP level can predict diagnosis and progression in different types of lymphoma (32-34). Considering the studies conducted on this subject, it is thought that CRP and ESR levels may be important in predicting the severity of the disease, as well as directing clinicians in their approach to the diagnosis of other malignancies or lymphoma.

The diagnosis process of lymphoma patients generally depends on the approach of surgical branches. For this reason, it is important that the clinicians performing SEB are able to accurately assess patients from the beginning in terms of differentiating lymphoma, solid tumors and other diagnoses. Although the change in the laboratory values of lymphoma patients may be easily recognized by hematologists, the same familiarity may not be observed among surgeons. Although expensive imaging methods such as positron emission tomography and computed tomography may provide important clues in terms of staging and spread of lymphoma and solid organ tumors, biopsy is still essential for diagnosis (14-17). Additionally, the accessibility of these imaging methods is limited, their widespread use is unnecessary, and such approaches will increase diagnostic and treatment costs. However, biochemical parameters and hemogram results are laboratory measurements that are routinely evaluated in almost every patient.

The grouping of different malignancies or cases with different lymphoma types under the same category is an important limitation of our study because the levels of inflammatory markers may vary in different types of cancer. Analyses specific to the type of cancer may be useful in future studies. Lifestyle and behaviors (smoking, alcohol consumption, physical activity) and the presence of other chronic diseases may alter the levels of inflammatory markers (23); however, these were not questioned, representing another limitation. Additionally, the possible influence of disease stage on the outcomes was not studied. Studies to be carried out taking these parameters into consideration will reinforce the accuracy of our results. Due to the design of our study, it could not be determined whether the increase in inflammation markers was the cause or result of the pathology. Prospective studies can be useful in this respect. The higher prevalence of males in the other malignancies group may have affected the results; however, the benign and lymphoma groups were similar with regard to sex distribution.

Conclusion

It was determined that ESR, which is one of the laboratory measurements evaluated before FNAB, was an important biomarker that could have a role in directing clinicians to the diagnosis of lymphoma. Although ESR is non-specific, which limits its use in asymptomatic patients, it may be valuable in reducing repetitive invasive procedures among symptomatic patients (weight loss, fever, night sweats, etc.) who require cervical lymph node biopsy for diagnosis. When ESR is detected above a certain level, it may be feasible to prefer SEB directly (without FNAB analysis). Conducting prospective studies specific to the type and stage of lymphomas will be beneficial for the use of such parameters in early diagnosis and could reduce the number of invasive procedures. Additionally, it may be beneficial to further ascertain the role of inflammatory markers in the prediction of lymphoma prognosis and/or response to treatment.

Ethics

Ethics Committee Approval: The local ethical committee of our university approved the study protocol and all participants signed the written informed consent form.

Informed Consent: Written consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.T.E., O.F.B., Design: E.T.E., M.D.E., Data Collection or Processing: O.F.B., M.D.E., Analysis or Interpretation: E.T.E., M.D.E., Literature Search: E.T.E., O.F.B., Writing: E.T.E., O.F.B., M.D.E.

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

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ORIGINAL RESEARCH

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Sarcopenia and Balance in Community-dwelling Women with Postmenopausal Osteoporosis

Toplumda Yaşayan Postmenopozal Osteoporotik Kadınlarda Sarkopeni ve Denge

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Abstract

Objective: Sarcopenia and osteoporosis share common risk factors and biological pathways. In the present study, patients with postmenopausal osteoporosis were screened for sarcopenia using the algorithm proposed by the European Working Group on Sarcopenia in Older People (EWGSOP) and balance impairment was investigated in sarcopenic patients.

Method: Fifty three postmenopausal osteoporotic patients were evaluated for sarcopenia as per the algorithm proposed by the EWGSOP. Among the parameters included in the algorithm, gait speed was assessed using the timed up&go test (TUG), Jamar hand dynamometer was used to measure grip strength and calf circumference (an anthropometric method) was used for the measurement of muscle mass. Balance was assessed using the Berg balance scale and functional abilities using the TUG.

Results: Fifty three postmenopausal patients with osteoporosis with a mean age of 65.48±9.12 years (range 47-84) were enrolled in the study. Sixteen patients (30.2%) reported a fall within the previous year, 22 patients (41.5%) had a history of fracture and 17 patients (32.1%) had maternal history of hip fracture. Sarcopenia was present in 8 (15.1%) patients. There was no significant difference between balance measurements of sarcopenic and non-sarcopenic patients ($p>0.05$). Only muscle mass showed a positive weak correlation and a significant association with balance ($r=0.28$, $p<0.05$).

Conclusion: Despite low rate of balance impairment, most of our patients had a history of fracture. Balance is not the only risk factor for falls in postmenopausal patients. The use of anthropometry as a screening tool and usage of more objective methods for definitive diagnosis provide more accurate data for the measurement of muscle mass.

Keywords: Balance, osteoporosis, postmenopausal, sarcopenia

Öz

Amaç: Sarkopeni ve osteoporoz, ortak risk faktörlerini ve biyolojik yolları paylaşır. Bu çalışmada postmenopozal osteoporozlu hastalar, Avrupa Yaşlılarda Sarkopeni Çalışma Grubu (EWGSOP) tarafından önerilen algoritma kullanılarak sarkopeni açısından tarandı ve sarkopenik hastalarda denge bozukluğu araştırıldı.

Yöntem: Elli üç postmenopozal osteoporotik hasta, EWGSOP tarafından önerilen algoritmaya göre sarkopeni açısından değerlendirildi. Algoritmada yer alan parametrelerden yürüme hızının değerlendirilmesinde zamanlı kalk&yürü testi (ZKY), kavrama gücü ölçümünde Jamar el dinamometresi ve kas kütlesi ölçümünde baldır çevresi (cm) kullanıldı. Denge, Berg denge ölçeği ve fonksiyonel yeterlilik ZKY kullanılarak değerlendirildi.

Bulgular: Ortalama yaşı 65,48±9,12 (47-84) yıl olan 53 postmenopozal osteoporoz hastası çalışmaya alındı. On altı hasta (%30,2) bir önceki yıl içinde düşme bildirdi, 22 hastada (%41,5) kırık öyküsü ve 17 hastada (%32,1) annede kalça kırığı öyküsü vardı. Sekiz (%15,1) hastada sarkopeni saptandı. Sarkopenik ve sarkopenik olmayan hastaların denge ölçümleri arasında anlamlı bir fark bulunmadı ($p>0,05$). Sadece kas kütlesi denge ile pozitif zayıf bir korelasyon ve anlamlı bir ilişki gösterdi ($r=0,28$, $p<0,05$).

Sonuç: Sarkopenik hastaların oranı çok düşük saptandı ve sarkopenik hastalarda denge bozukluğu anlamlı değildi. Sarkopeni taramasında kas kütlesinin ölçümü için antropometrik ölçümler yerine daha objektif yöntemlerin kullanılması, daha doğru veri sağlayacaktır.

Anahtar kelimeler: Denge, osteoporoz, postmenopozal, sarkopeni

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Introduction

Osteoporosis is an important public health problem concern due to aging of the global population (1). In the recent FRACTURK study, the prevalence of osteoporosis at the femoral neck in women over the age of 50 years was reported to be 33.3% in Turkey (2).

Postural control is the natural ability to maintain the center of gravity of an individual within the base of support (3). Postural imbalance is common in older women with osteoporosis, who also have an increased tendency to fall (4,5).

Sarcopenia is characterized by progressive reduction in muscle strength and fat-free mass with advancing age (6). Although the negative effects of reduced muscle mass and strength on function and autonomy in geriatric population have been recognized, there have been no clear criteria for the classification of sarcopenia until recently. Thus, the European Working Group on Sarcopenia in Older People (EWGSOP) was established to formulate a common definition of sarcopenia (6). A recent systematic review and meta-analysis showed that the EWGSOP classification was associated with reduced physical function and high mortality (7). The prevalence of sarcopenia in people living in nursing home aged over 65 years in Turkey was reported to be 29% (8).

Sarcopenia and osteoporosis share common risk factors and biological pathways and are associated with physical disability resulting in the loss of independence in advanced age (9).

There is evidence to suggest that both muscle strength and muscle mass are related to the risk of falls. However, a limited number of studies are available on the association between sarcopenia defined by the EWGSOP and osteoporosis and balance impairment (10).

In the present study, patients with postmenopausal osteoporosis were screened for sarcopenia using the algorithm proposed by the EWGSOP. The timed up&go (TUG) and calf circumference, which are easy to use and uncostly parameters for clinic practice, were chosen as parameters and tested for suitability, and balance impairment was investigated in sarcopenic patients.

Materials and Methods

The study was conducted in 53 community-dwelling older women with postmenopausal osteoporosis, who presented to a tertiary care hospital's physical medicine and rehabilitation, osteoporosis outpatient clinic between January and April 2019. Patients diagnosed with secondary osteoporosis, patients with malignancy, inflammatory joint disease, diabetes mellitus, neuromuscular disorder, generalized cardiovascular disease, and thyroid/parathyroid dysfunction, and those using antiepileptics, steroids, anticoagulants and antiandrogenic medications were excluded. Out of 70 patients, 10 were excluded from the study because of inflammatory joint diseases, 5 because of inability to walk, and 5 because of multiple comorbidities (diabetes mellitus, thyroid disease, cardiovascular disease). And, the study was conducted with 53 patients. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of our university (decision no: 2018/0235) and the study is registered in clinicaltrials.gov (NCT03832088). Patients were evaluated for sarcopenia as per the algorithm proposed by the EWGSOP after they gave written informed consent (Figure 1).

Among the parameters included in the algorithm, gait speed was assessed using the TUG, Jamar hand dynamometer was used to measure grip strength, and calf circumference (an anthropometric method) was used for the measurement of muscle mass. These parameters were chosen because they were easy to use, cheap and practical.

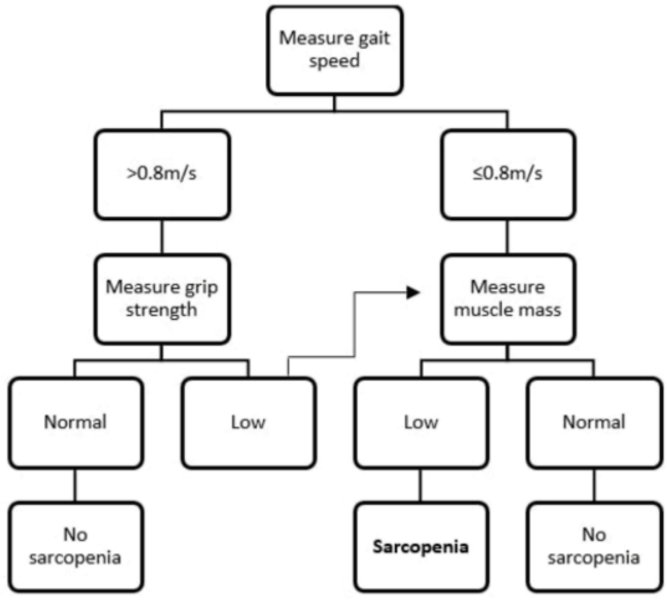

Figure 1. EWGSOP-suggested algorithm for findings of sarcopenia case (6)

EWGSOP: European Working Group on Sarcopenia in Older People

TUG is commonly used in geriatrics clinics for assessing functional mobility. TUG has been shown as a sensitive and specific measurement assessing the risk of falling (11). Grip strength is shown to be used as diagnostic component in frailty (12) and sarcopenia (13).

Decreased calf circumference can reflect a decrease in muscle mass with limited physical activity. Recently, calf circumference measurement has been validated and result of more than 33 cm for females and 34 cm for males is considered as normal (14). Calf circumference was measured with inelastic tape in standing position, at the maximum circumference in the plane perpendicular to the longitudinal line of the calf. Three measurements were performed to obtain the average of three measurements.

Balance was assessed using the Berg balance scale (BBS), a 14-item scale designed to measure balance of an older adult in a clinical setting. Total score was 56. score of 41-56 indicated low fall risk, 21-40 indicated medium fall risk, and 0-20 indicated high fall risk. A cut-off score of 45/56 was supported for independent safe ambulation (15).

Other clinical parameters, including age, body mass index (BMI), 25-hydroxy-vitamin D level, menopausal age, history of falls within the previous year, history of fracture and maternal history of hip fracture, were also evaluated.

Statistical Analysis

All statistical analyses were performed using the SPSS Statistics Version 25.0 software package (IBM, Chicago, IL). Descriptive statistics were presented as mean ± standard deviation and minimum-maximum values for continuous variables. Frequencies (number of cases) were provided with their percentages for categorical variables. Pearson r correlation analysis was used to test the level of correlation between two continuous variables if normality assumptions were met and Spearman rho correlation analysis if not. The size of the effect was interpreted based on the Cohen's classification (1988), where a correlation coefficient between 0.10 and 0.29 indicated a weak association, a correlation coefficient between 0.30 and 0.49 represented a moderate association and a correlation coefficient between 0.50 and 1.0 represented a strong association. Since normality assumptions were not met due to the number of patients with or without sarcopenia, the Mann-Whitney U test was used for continuous variables and chi-square test for categorical variables when comparing the two groups. For all analyses, the statistical significance was set at 0.05.

Results

A total of 53 postmenopausal patients with osteoporosis with a mean age of 65.48±9.12 years (range 47-84) were enrolled in the study. The mean menopausal age of the patients was 49.09±5.57 years (range 32-57). Sixteen patients (30.2%) reported a fall within the previous year. Among 53 patients, 22 (41.5%) had a history of fracture and 17 (32.1%) had maternal history of hip fracture.

Patients had a mean BMI (n=50) of 26.97±5.06 kg/m^2 (16.60-43.60). Based on BMI values, 1 (2%) patient was lean, 18 (36%) patients had normal weight, 18 (36%) were overweight, 11 (22%) had class I obesity and 2 (4%) had class II obesity. Vitamin D status was determined and the average vitamin D concentration was found to be 23.84±12.43 ng/mL (6.60-56.80). According to their vitamin D status, 20 (41.7%) patients had vitamin D deficiency, 17 (35.4%) had vitamin D insufficiency, and 11 (22.9%) had normal vitamin D levels.

Sarcopenia screening was conducted using the algorithm suggested by EWGSOP and patient assessment included the measurements of 3 parameters. Gait speed was evaluated with the TUG test, muscle strength with Jamar hand dynamometer and muscle mass with the calf circumference measurement. Thus, sarcopenia was present in 8 (15.1%) patients and absent in 45 (84.9%) patients. The relationship between sarcopenia and balance was investigated and no significant difference was found between balance measurements of sarcopenic and non-sarcopenic patients (Table 1).

Additionally, correlations of balance with diagnostic variables of sarcopenia (balance and gait speed, muscle strength and muscle mass) were examined (Table 2). Statistically, only muscle mass showed a positive weak correlation and a significant association with balance.

Table 1. Summary of descriptive statistics for balance measurements and results of Mann-Whitney U test

Sarcopenia	Balance					
	n	Mean ± SD	Minimum	Maximum	U	p
Yes	8	51.50±4.20	44.00	55.00	172.00	0.84
No	45	51.31±4.70	39.00	56.00		

SD: Standard deviation

In order to examine whether sarcopenia was associated with other clinical parameters, the difference in clinical data between sarcopenic and non-sarcopenic patients was analyzed using the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. Among all continuous variables, a between-group difference was observed only for BMI values. Non-sarcopenic patients had significantly greater BMI values (27.75±4.98 kg/m^2) versus sarcopenic patients (22.89±3.71 kg/m^2) (U=71.5, p<0.05). No statistically significant differences were found for other variables.

Correlations among the measures of diagnostic variables of sarcopenia (balance and gait speed, muscle strength and muscle mass) and other variables were also analyzed. Table 3 presents the continuous variables and correlation levels.

Whether there was any difference between sarcopenic and non-sarcopenic patients in terms of diagnostic variables of sarcopenia (balance and gait speed, muscle strength and muscle mass) was analyzed by evaluating the difference among respective values of the variables. The results revealed that gait speed and muscle strength values were not significantly different between sarcopenic and non-sarcopenic patients but muscle mass values were significantly greater in non-sarcopenic patients than in sarcopenic patients (Table 4).

The correlation between the BBS scores and 10-year risk of a major fracture or hip fracture was investigated using the Spearman rho coefficients of correlation. The findings showed that BBS scores were not correlated with 10-year risk of a major fracture or 10-year risk of a hip fracture. In addition, the relationship of balance with other clinical data of patients was examined and a moderate negative correlation was found between age and balance (n=52, rho=-0.39, p<0.01).

Discussion

Sarcopenia is a syndrome characterized by generalized progressive loss of muscle mass and muscle strength that is associated with consequences like physical disability, poor quality of life, and death (13). Sarcopenia occurs with the interaction of many factors. In addition to aging, female gender, muscle development in younger ages and basal muscle mass, nutritional disorders, physical inactivity,

Table 2. Spearman rho correlations among balance, gait speed, muscle strength and muscle mass

Variables	Balance	Gait speed	Muscle strength	Muscle mass
Balance	1.00	-0.19	-0.04	0.28*
Gait speed	-	1.00	0.06	-0.24
Muscle strength	-	-	1.00	0.09
Muscle mass	-	-	-	1.00

*p<0.05

Table 3. Spearman rho correlations among diagnostic variables of sarcopenia and other variables

	Age (n=52)	Menopausal age (n=46)	BMI (n=50)	L1-4 (n=52)	L2-4 (n=52)
Gait speed	0.35*	-0.29*	0.02	-0.22	-0.19
Muscle	0.07	0.07	0.74**	0.36**	0.31*
Mass muscle strength	-0.40**	0.275	-0.01	-0.15	-0.20

*p<0.05, **p<0.0, BMI: Body mass index

Table 4. Results of Mann-Whitney U test based on sarcopenia

Variables	Sarcopenia	n	Mean ± SD	Minimum	Maximum	p
Gait speed	Yes	8	9.59±2.21	6.26	12.83	0.98
	No	45	9.72±2.20	4.75	16.65	
Muscle mass	Yes	8	30.13±1.46	27.00	31.00	<0.001
	No	45	36.63±3.05	32.00	46.00	
Muscle strength	Yes	8	30.63±11.48	45.00	30.63	0.74
	No	45	33.29±13.55	5.00	80.00	

SD: Standard deviation

vitamin D deficiency, and comorbid chronic diseases play a role in the development of sarcopenia. In 2017, the prevalence of sarcopenia in the age group of 60-69 years in Turkey was found to be 15.4% (16). The rate of sarcopenia in our study was consistent with these data.

A vicious circle begins in elderly individuals, contributing to sarcopenia and osteoporosis. This vicious cycle begins with a decrease in physical performance and loss of balance, continues with the fear of falling and consequently avoiding physical activity, resulting in a further increase in osteoporosis and sarcopenia (17). A recent study has reported that the incidence of sarcopenia and osteoporosis is very high, and osteoporosis treatment is shown to gain favor not only for osteoporosis itself but also for the sarcopenia clinic (18).

The musculoskeletal system has an important contribution to the maintenance of balance. Muscle weakness is one of the major factors for the loss of balance, so the maintenance of balance becomes challenging in sarcopenia. Although it is not known whether it is a cause or effect in osteoporosis, the relationship between decreased muscle strength and bone mineral density has been shown (19). Although no significant relationship between muscle strength and BMD was detected in our study, a correlation between lumbar BMD and muscle mass was found.

Several studies have reported impaired postural balance in osteoporotic and sarcopenic patients (19-22). However, there are other studies demonstrating otherwise (23,24). Balance impairment was found at a rate of 1.9% in our study sample. However, although BBS scores yielded this rate of balance impairment, 30.2% of our patients had a history of fall within the previous year and 41.5% had a history of fracture. Many intrinsic and extrinsic factors contribute to the increased risk of falls. Risk factors accumulate with age and also, aging is an independent risk factor for falls. The increased risk of falls among our patients may be explained by other risk factors.

Balance was investigated using the BBS in our study and the BBS was not found to effectively predict the risk of falls or fracture. It can be considered that the threshold BBS scores may not be applicable for Turkish population.

A recent study has showed that task items in BBS are not challenging to discriminate less severe balance disorders and are less useful for detecting balance and falling risk in community dwelling older adults (25). Schaubert and Bohannon (25) also examined the BBS and showed that most of the items were considered as easy to perform by geriatric population since they obtained high scores. Only a few items, such as putting one foot in front of the other and standing on one foot, caused some difficulties for older subjects and this is consistent with our findings.

Participants' 25-hydroxy-vitamin D levels were measured during winter. Participants were selected from the patients who came to the outpatient clinic for annual postmenopausal osteoporosis follow-up. Last controls of the patients were 1 year ago and therefore, most of them did not take vitamin D supplements for a long time. This may be one of the reasons for the high rate of vitamin D insufficiency and deficiency (58.3% in total).

Grip strength was reduced in 94.1% of our patients but despite this high rate of diminished muscle strength, sarcopenia was present at a relatively low rate (15.1%).

Anthropometric measurements offer convenience and cost-effectiveness, and provide fast results but their reproducibility is low. While calf circumference was reported to be correlated with muscle mass in the literature (26,27), fat deposits and loss of skin elasticity in the elderly due to aging make it difficult to obtain accurate measurements. Since the average BMI value was high in our sample, the mean calf circumference values were also high. The reason for the low number of patients with sarcopenia detected by the sarcopenia screening algorithm in our study was resulted from high muscle mass values of the patients. This might have affected our findings.

Study Limitations

The sample size of our study was relatively small. Studies with a higher number of patients may yield significant results. The study was carried out in a single center and the results cannot be generalized. Although the diagnosis of sarcopenia by anthropometric measurement is not recommended, it may serve as a screening tool. Calf circumference was used as an anthropometric measurement in our study. However, it should be considered that the calf circumference is high in obese patients and may cause false results. It is also recommended to include non-osteoporotic sarcopenic patients as a group in future studies.

Conclusion

The rate of sarcopenia in our sample was very low and balance disorder was not significant in sarcopenic patients. We believe that for the purpose of sarcopenia assessment, calf circumference may be useful in measuring muscle mass as a screening criterion. Bioelectric impedance analysis or dual energy X-ray absorptiometry should be used for

definitive diagnosis as they provide more accurate data for the measurement of muscle mass.

Ethics

Ethics Committee Approval: This study was approved by the university Ethics Committee on June 27, 2018 (decision no: 2018/0235).

Informed Consent: All participants signed an informed consent form prior to the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.D.K., Ş.Y., A.İ., Design: B.D.K., A.İ., F.B., Y.Y., Data Collection or Processing: B.D.K., F.B., Ş.Y., Y.Y., Analysis or Interpretation: B.D.K., A.İ., Y.Y., Literature Search: B.D.K., F.B., Ş.Y., Writing: B.D.K., A.İ.

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

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CASE REPORT

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Prenatal Diagnosis of Twin Reversed Arterial Perfusion (Trap) Sequence: A Case Report

Twin Reversed Arterial Perfusion (Trap) Sekansının Prenatal Tanısı: Olgu Sunumu

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Abstract

Twin reversed arterial perfusion (TRAP) sequence is a rare condition of monochorionic twin pregnancy. It has an incidence of 1:35.000 pregnancies and constitutes 1% all monochorionic pregnancies. The etiopathogenetic mechanisms are not well defined. There is co-existence of a normal pump twin and an acardiac recipient twin. A 22-year-old nulliparous woman was referred with TRAP sequence. The prognosis in TRAP sequence is lethal for acardiac twin and the fetal mortality of the pump twin is very high due to the cardiac failure. The obstetrician should be aware of TRAP-sequence in twin/multiple pregnancies.

Keywords: Monochorionic twin pregnancy, prenatal diagnosis, sequence, twin reversed arterial perfusion (trap)

Öz

Twin reversed arterial perfusion (TRAP) sekansı monokoryonik ikiz gebeliklerde nadir görülen bir durumdur. Görülme insidansı 1:35,000 olup, tüm monokoryonik gebeliklerin yaklaşık %1'inde görülebilir. Etiyopatogenetik mekanizması tam olarak bilinmemektedir. Normal bir donör ikiz ve bir akardiyak alıcı ikiz birlikte bulunmaktadır. Olgu sunumumuzda 22 yaşında, nullipar 23. gestasyonel haftada ultrasonografik olarak tanı konulan TRAP sekansını rapor ettik. TRAP sekansı prognozu akardiyak ikiz için ölümcül olup, donör ikizde de konjestif kalp yetmezliği gelişmesi durumunda mortalite oldukça yüksektir. Kadın hastalıkları ve doğum uzmanları ikiz/çoğul gebeliklerde TRAP sekansına karşı dikkatli olmalıdır.

Anahtar kelimeler: Gebelik, monokoryonik ikiz, prenatal tanı, sequence, twin reversed arterial perfusion (trap)

Introduction

Twin reversed arterial perfusion (TRAP) sequence is a rare condition of monochorionic twin pregnancy. It has an incidence of 1:35.000 pregnancies and constitutes 1% all monochorionic pregnancies (1-3). There is co-existence of a normal pump twin and an acardiac recipient twin. The blood flows via an arterioarterial anastomosis from an umbilical artery of a pump twin into the umbilical artery of an acardiac twin and returns through a venovenous anastomosis to the pump twin. The poorly oxygenated blood from the healthy twin enters the other twin abdominally and principally perfuses the lower extremities and the body, subsequently lower concentrations of oxygen reaching the superior body parts. The upper half of the body of an acardiac twin is extremely poorly developed and sometimes not developed at all. The pump twin suffers from high output cardiac failure; therefore, it may present with cardiomegaly, ascites, pleural effusion, polyhydramnios, and skin edema (4).

The prognosis in TRAP syndromes is lethal for acardiac twin and the mortality rate for the pump twin is very high (50-75%) due to congestive heart failure (5,6).

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Case Report

A 22-year-old nulliparous woman was referred to our perinatology unit at the 23rd week of gestation with TRAP sequence. Amniotic fluid sampling was performed at the 21st week of gestation, revealing a normal 46, XX karyotype. Ultrasonographic examination showed a monochorionic monoamniotic twin pregnancy. The recipient twin demonstrated well- developed lower limbs, partially developed lumbar and thoracic spine, absent cervical spine, under-developed abdominal and chest organs (Figure 1). The heart, head and upper limbs were absent. The recipient twin was retrogradely perfused by a normal pump twin without the signs of cardiac compromise. She had a dyspnea due to the polyhydramnios, the measurement of four quadrants was calculated as 30 cm. Pelvic examination revealed a cervix 40% effaced and 0.5 cm dilated and she had uterine contractions. Tocolytic treatment was begun immediately and therapeutic amniocentesis was performed to reduce the amniotic volume and to avoid premature labor. The patient underwent corticosteroid therapy for fetal lung maturation. Fetal MR imaging and subsequent minimal invasive operative interventions were offered as alternative options, but the patient refused. However, at the 26th week of gestation, cardiomegaly, ascites and pleural effusion were demonstrated in pump twin. Therefore, a cesarean section was performed. The acardiac twin weighed 940 g and its gender was not clear (Figure 2). The pump twin weighed 850 g, was of female gender and was admitted to the neonatal intensive care unit with Apgar scores 4 and 7 at 1st and 5th min, respectively.

The histopathologic examination of the acardiac twin revealed total absence of cranial structures, cervical spines, heart, lungs, liver, gall bladder, stomach, and upper limbs. The fetus had bilateral kidneys and surrenal glands, edema of the skin, the intestine segments in omphalocele sac and lower extremities with four fingers each. The umbilical cord had two vessels. The acardiac twin was classified as holocardius (if the heart is totally absent) and acephalus (if the head is totally absent) with respect to the abnormalities (4,6). The pump twin is still alive at neonatal intensive care unit.

Discussion

The prenatal diagnosis of a complicated monochorionic multiple pregnancy and in such a case as we presented, a so-called TRAP-sequence during ultrasonographic examination is feasible and can be easily established during the first or second- trimester-screening (7,8). The etiopathogenetic mechanisms are not well defined. Although one twin is completely normal in terms of fetal anatomy, cardiomegaly and hydrops may develop secondary to cardiac overload in advanced stages. The acardiac twin most often has an underdeveloped head and upper part of body, and impressive edema involving mostly the upper body (9). An acardiac twin may be detected ultrasonographically by noticing fetal movement without

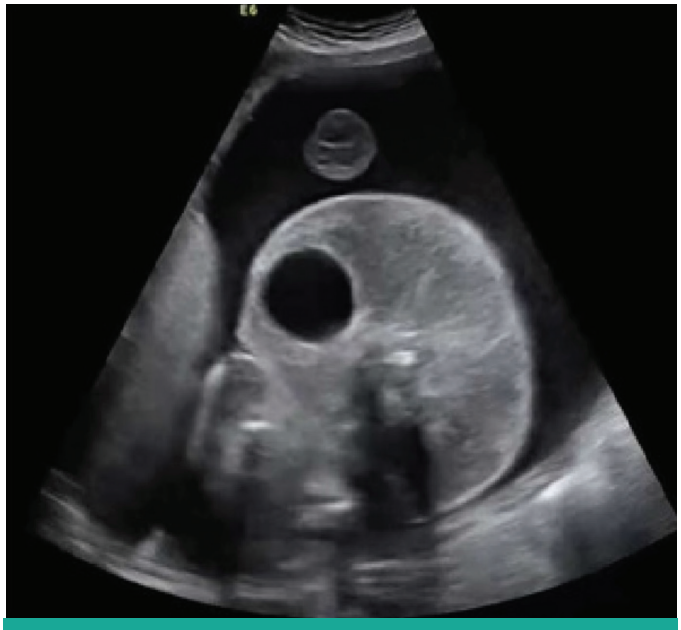

Figure 1. Ultrasonographically abdominal plane of acardiac fetus

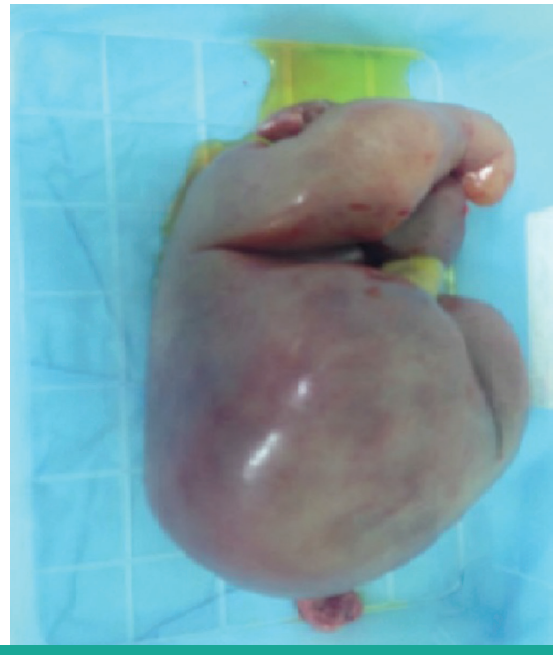

Figure 2. Macroscopic view of the acardiac fetus

a heartbeat. Doppler examination shows pathognomonic flow-pattern in terms of reversed arterial perfusion from the pumping twin towards the recipient twin. Generally, reversed arterial blood supply enters the acardiac twin via a single umbilical artery. The umbilical vessels drain usually in hypogastric or superior mesenteric artery (7,10).

In our case, there was no chromosomal and congenital anomaly. However, about one-third of the cases were reported to have an abnormal karyotype in literature (7). In addition, congenital anomalies are present in about 9% of pump twins. Potential risk of the pumping fetus is congestive cardiac failure developing due to the increased cardiac output. This high cardiac output also increases perfusion of the fetal kidneys, resulting in the overproduction of fetal urine and subsequent polyhydramnios. Preterm labor or premature rupture of membranes in TRAP-sequences may occur due to polyhydramnios. Treatment modalities include a broad spectrum of possible strategies, depending on the situation of the pumping twin. Therapeutic amniocentesis may reduce the amniotic volume to avoid premature labor. Conservative management includes different tocolytic approaches and digitalis- treatment to support the cardiac performance of the pump twin. The aim of the operative interventions is to separate the two blood-circuits of twins (7,10-15).

Ethic

Informed Consent: Written and verbal consent of the patient was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Follow up of the Case: Y.C., İ.Y., S.A., Literature Review: B.A., S.A., Y.C., Writing: Y.C., İ.Y., B.A., Manuscript Review and Revisation: B.A., S.A., İ.Y.

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CASE REPORT

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Prenatal Diagnosis of a Rare Type of Conjoined Twin, Cephalothoracoomphalopagus: A Case Report

Yapışık İkizin Nadir Bir Türü Olan Sefalotorakoomfaloselin Prenatal Tanısı: Olgu Sunumu

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Abstract

Conjoined twins are a rare outcome of a monoamniotic and monochorionic gestation. We present a case of cephalothoracoomphalopagus conjoined twin diagnosed by prenatal ultrasonographic examination. A 26-year-old gravida 2, para 1 woman was referred to our perinatology unit for evaluation because of suspected conjoined twins at 24 weeks of gestation. Her medical history was unremarkable. There was no family history of genetic abnormalities. The diagnosis of conjoined twins was confirmed by prenatal ultrasonographic examination. Conjoined twins occur when two identical individuals are joined by part of their anatomy and share their vital one or more organs. The incidence of conjoined twins ranges from 1:50,000 to 1:250,000 live births. We present a case of male cephalothoracoomphalopagus conjoined twin, which is extremely rare type of conjoined twins. A prenatal diagnosis of shared organs dictates pregnacy termination or possible surgical separation strategies.

Keywords: Conjoined, prenatal, prenatal diagnosis, twins, ultrasonography

Öz

Nadir görülen yapışık ikizler monoamniyotik ve monokoryonik gebelik sonucu oluşur. Biz prenetal ultrasonografik muayene ile tanı konulan sefalotorakoomfoloselli yapışık ikiz olgusunu sunuyoruz. Yirmi altı yaşında, gravida 2, parite 1 kadın hasta, 24 haftalık şüpheli yapışık ikiz tanısıyla bizim perinatoloji ünitesine sevk edilmişti. Genetik anamoli açısından aile öyküsü yoktu. Yapışık ikiz tanısı prenatal ultrasonografik muayene ile onaylandı. Yapışık ikizler aynı iki bireyin anatomik bölümlerinin birleşmesi ile ve bir veya daha çok vital organlarının paylaşılması ile oluşur. Yapışık ikiz insidansı her canlı doğumda 1:50.000'den 1:250.000'e kadar değişir. Biz yapışık ikizlerin nadir bir türü olan erkek sefalotorakoomfoloselli yapışık ikiz olgusunu sunduk. Paylaşılan organların prenatal tanısı gebelik terminasyonunun kabul ettirilmesi veya cerrahi seperasyon yöntemleri ile konulur.

Anahtar kelimeler: Bitişik, ikizler, prenatal, prenatal tanı, ultrasonografi

Introduction

Conjoined twin is a very rare condition and its incidence varies from 1/50,000 to 1/250,000 per live birth. It is also possible to be seen in 1% of monozygotic twins (1). Although antenatal diagnosis is very difficult, it is very important. In this case report, we presented a case of conjoined twins with a rare diagnosis of cephalothoracoomphalopagus.

Case Report

A 26-year-old female patient with gravida 2 and parity 1 was referred to the perinatology unit of our clinic with

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the suspicion of twin anomaly at 24 weeks. There was no feature in the patient's history. There was no family history for genetic anomaly. In prenatal ultrasonographic examination, monochorionic monoamniotic twin pregnancy with 4 upper extremities, 4 lower extremities, 2 hearts, 2 kidneys, 2 lungs, single cerebrum, single head and single umblical cord was observed. Conjoined twins were diagnosed ultrasonographically. Termination was offered to the patient, but she refused. When the patient was 25 weeks old, she applied to our clinic with the complaint of water leakage. Active water discharge was observed in her vaginal examination. Spontaneous vaginal delivery occurred when the patient was 25 weeks and 1 day old. Conjoined twin ex fetuses were observed in male genders with attached head and thorax regions. His macroscopic examination supported the prenatal ultrasonographic data (Figure 1). Pathological examination result was reported as conjoined twins in male gender with anal atresia with single cerebrum, mouth, pituitary, umbilical cord, esophagus, larynx, stomach, intestine and pancreas, 3 adrenal glands, 2 kidneys, 2 hearts, 2 lungs, adhered to each other from the head and thorax parts.

Figure 1. Macroscopic image of cephalothoracoomphalopagus twin

Discussion

Conjoined twin is a very rare form of monozygotic twins. This is seen in monochorionic monoamniotic pregnancies. It occurs as a result of incomplete separation of a single fertilized ovum between the 15th and 17th gestational days (1,2). It is generally seen in female fetuses. Births of conjoined twins are very traumatic; these fetuses are usually premature. However, 60% of them are born alive and die in a very short time after birth (2). It is named according to the conjoined body areas. Cephalothoracoomphalopagus is the rarest type (3). Although prenatal diagnosis is very difficult, the possibility of conjoined twins should be considered in twin fetuses that cannot be well visualized in a single gestational sac in ultrasonographic examination (4). In such a situation, the diagnosis should be supported by fetal magnetic resonance imaging (MRI) (Figure 2). Diagnosis by ultrasonography and MRI in the early gestational week is important in making early termination decision with the approval of the family.

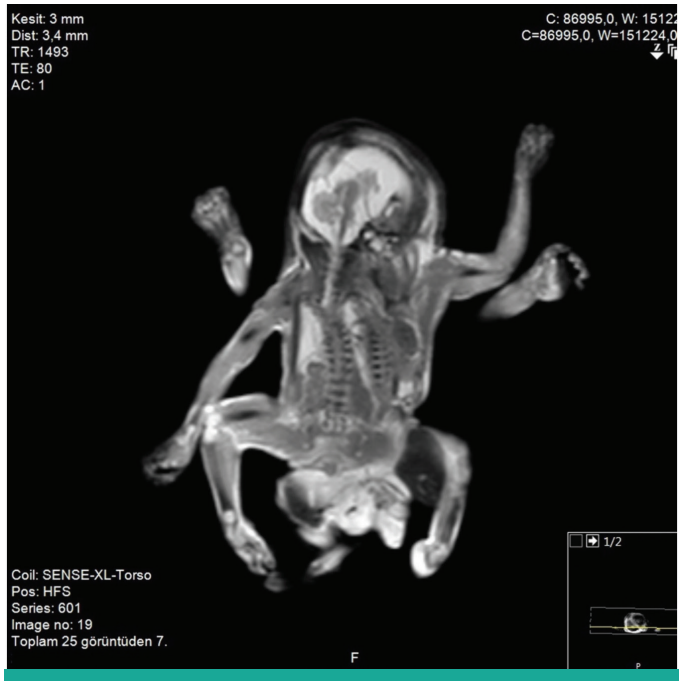

Figure 2. MR image of cephalothoracoomphalopagus twin

MR: Magnetic resonance

Ethic

Informed Consent: Consent of patient was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Follow-up of the Case: Y.C., İ.Y., S.A., Literature Review: B.A., S.A., Y.C., Writing: Y.C., İ.Y., B.A., Manuscript Review and Revisation: B.A., S.A., İ.Y.

Conflict of Interest: The authors declare that there is no conflict of interest with regard to this manuscript.

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CASE REPORT

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Reconstruction of Huge Cutaneous Defects of Thoracic Large Meningomyelocele: A Technical Note

Torasik Geniş Meningomyeloselin Dev Kutanöz Defektlerinin Rekonstrüksiyonu: Teknik Not

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Abstract

In meningomyelocele (MMC) cases, postnatal sac repair and repairment of overlying tissue defect in early period is a challenging surgical process. Infection control, hemodynamic follow-up and selection of the appropriate reconstruction technique are important. Repairment of thoracolumbar huge defects is extremely difficult due to the anomalies of adjacent bony and soft tissues. The aim of the study is to report the method of repairment of the thoracolumbar huge defect in a patient with a large MMC and also to review the options of repairment of such defects and to provide a common surgical discipline. A term newborn with a mainly thoracic large MMC, 10x15 cm in size, was operated on the 5th postpartum day. After the excision of MMC and repairment of neural tube, operation was performed for the closure of skin defect. Tissue defect was reconstructed with a Z advancement-rotation flap. There were no early or late complications after the operation. We concluded that the repairment of the defects with flaps after giant MMC excisions in a single-session reduces the morbidity.

Keywords: Flap, meningomyelocele, reconstruction

Öz

Meningomyelosel (MMC) olgularında postnatal kese onarımı ve üstteki doku defektinin erken dönemde tamiri zorlu bir cerrahi işlemdir. Enfeksiyon kontrolü, hemodinamik takip ve uygun rekonstrüksiyon tekniğinin seçimi önemlidir. Torakolomber büyük defektlerin onarımı, bitişik kemik ve yumuşak doku anomalileri nedeniyle son derece zordur. Çalışmanın amacı, MMC'si büyük olan bir hastada torakolomber dev defektin onarım yöntemini bildirmek, bu tür defektlerin onarım seçeneklerini gözden geçirmek ve ortak bir cerrahi disiplin sağlamaktır. Postpartum 5. günde ağırlıklı olarak torasik, 10x15 cm boyutlarında geniş MMC'li term yenidoğan, önce MMC'nin eksizyonu ve nöral tüp onarımı ardından deri defekti kapatılması için ameliyat edildi. Doku defekti flep ile onarıldı. Operasyon sonrası erken veya geç komplikasyon olmadı. Tek seansta dev MMC eksizyonları sonrası defektlerin fleplerle onarılmasının morbiditeyi azalttığı sonucuna vardık.

Anahtar kelimeler: Flap, meningomyelosel, rekonstrüksiyon

Introduction

Meningomyelocele (MMC) has the priority, among the most severe and complex congenital anomalies compatible with life among the congenital defects involving the spine observed in neurosurgery practice. MMC is herniated from a bone and skin defect, including the spinal cord, nerve roots and meningeal structures. It is a neural tube defect characterized by a completely open (myelochisis) or sac-like lesion. Patients often have motor and sensory defects in the lower extremities, urinary bladder and anal sphincter (1,2). Generally, the relevant segment and nerve roots below it are non-functional.

Prognosis is related to the level of the lesion. Functional prognosis worsens as it rises to higher levels, sphincter

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dysfunction associated with different levels of motor loss (L1-S1-roots) may be observed (S2-S4 roots). Mostly paraplegia is present in lesions between T10 and L4 levels, and ambulation of the patient is generally not possible (3).

Healthy repair of the meninges and the tissue defect on it prevents serious complications, especially meningitis, reduces the risk of developing an epidermoid/dermoid tumor, which is a kind of embryological residual tumor, and ensures maximum preservation of current sensory and motor functions.

Reconstruction of the defect after the excision of large MMCs is challenging and the viability of flaps is difficult due to the lying position of the children. In patients who are mostly newborns, repair of the meningeal membranes that are resistant to infections and trauma is valuable for the healthy growth of the patient as possible. Also, the fact that most of the cases are in the neonatal period brings some surgical risks along with itself. Closing the defect as soon as possible and in a single session, keeping the bleeding as minimal as possible by tightly control, and completing the surgery with the principle of maximum respect to the tissue reduce the morbidity and mortality.

In this study, we aimed to present the method of repairment of the thoracolumbar huge defect in a patient with large MMC whose primary closure was not possible and also to review the options of appropriate flap selection for repairment of such defects and to provide a common surgical discipline.

Case Report

On the 5th postpartum day after pregnancy without follow-up, the baby girl was in a prone position due to the giant mass localized in the mainly thoracic region (Figure 1). There was no family history. The mass was covered with a thin epithelium layer and followed by wet dressing. There was excessive cerebrospinal fluid (CSF) leak. Care was taken to keep the dressing moist with sterile saline for several hours during preoperative follow-up. In the neurological examination of the patient, both lower extremities were plegic. Head circumference was 37 cm, at the 97th percentile.

Magnetic resonance imaging revealed that the vertebral canal was open, the sac was connected to the subarachnoid distance, and there were nerve fibers in it. Hydrocephalus and Chiari type 2 malformation were detected as additional anomalies. The patient, who was diagnosed with MMC, was operated for the excision of the sac and repair of the defect to be formed. Informed consent was obtained from the family of the patient. The patient, whose intubation was performed in the lateral position by anesthesia, was placed in the prone position and surgery was started to be performed. During the entire surgery, care was taken to ensure that the patient was normothermic, and the fluid-electrolyte balance was preserved.

The existing sac was opened in a controlled manner and contents of it were revealed. The area around the sac was freed starting from the superior side of the sac with an incision at the border of the healthy skin around the sac, which was made in a way to preserve the healthy skin tissue where the sac met the lumbar skin, but also not to leave the primitive MMC sac in the area. The excised tissues with primitive epithelium residue were sent to pathology. Then, anatomical tissue definition was made in the skin-subcutaneous distance. It was observed that the cord was in a sheet shaped in the placode. It was tracked that there were neural elements attached to the skin in the sac. The sac was excised, preserving the nerve fibers located on the wall and adjacent to the inner surface. Neural placode was turned into a tube by pia-pial sutures.

The dural tissues were dissected from the base of the sac and primarily sutured by making a tube around the neural tissue. After that, it was ensured that there was no CSF leak by applying positive pressure.

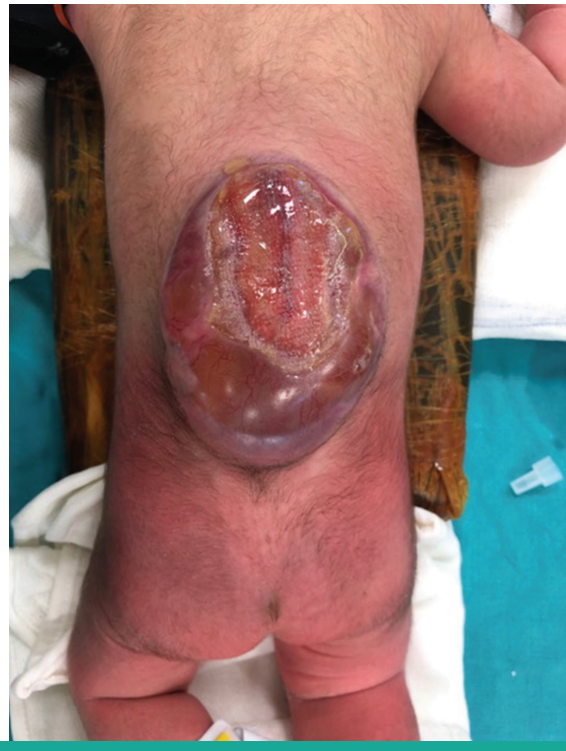

Figure 1. Preoperative view of a giant thoracic mass

The repairment of huge soft tissue defect was planned by staining and covering. Flaps were elevated by drawing Z plasty with round angles that centered 90 degrees, one of the midlines of the defect rotated superiorly and the other one inferiorly, by measuring the defect diameter (Figure 2). The lower part of latissimus dorsi muscle was turned as a strip and brought closer to the midline. Donor areas were closed primarily in the lateral areas without stretching (Figure 3). There was no need for drains (4).

In the postoperative period, no dehiscence, necrosis or seroma developed at the wound side. On the postoperative 10th day, sutures were extruded (Figure 4).

Discussion

Spinal dysraphism is the most important cause of major disabilities in childhood and adulthood (3). MMC is a very serious type of spinal dysraphism and it is well known in neurosurgical and neonatology practice. Its incidence is 1-2 per 1.000 births (5).

Although the anomaly can be located along with the vertebral canal (3), thoracolumbar and lumbosacral localization are the most common regions.

In MMC, the vertebral canal remains open, the meninges protrude out of the skin, and there is a cystic mass associated with the subarachnoid space that is lined with epithelium and filled with CSF. In these masses located in the midline, vertebral canal opening and overlying skin defects are observed.

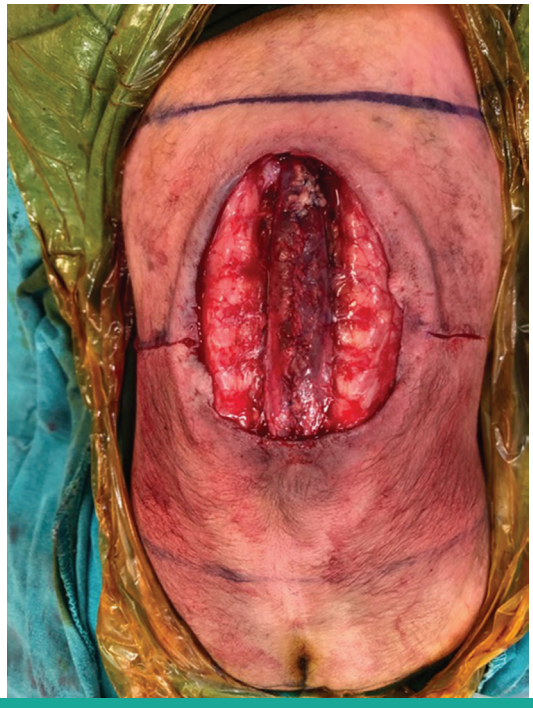

Figure 2. The sac was closed and flap drawings were made

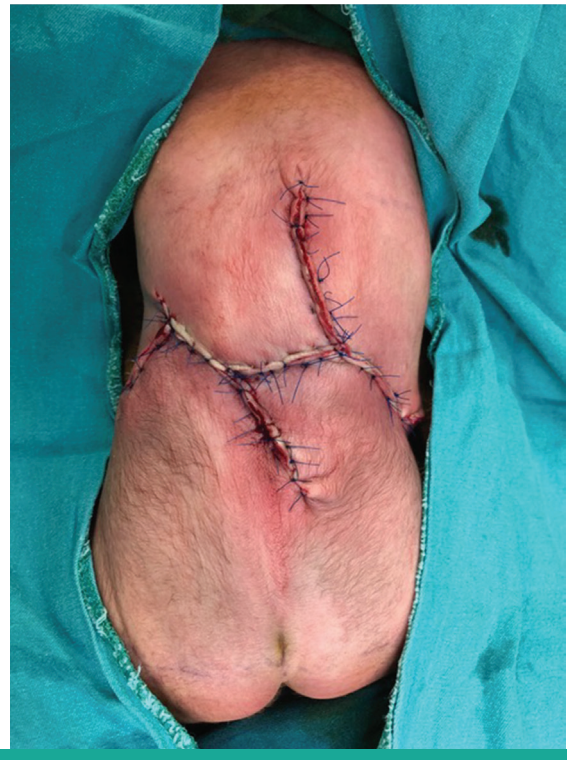

Figure 3. Early postoperative view

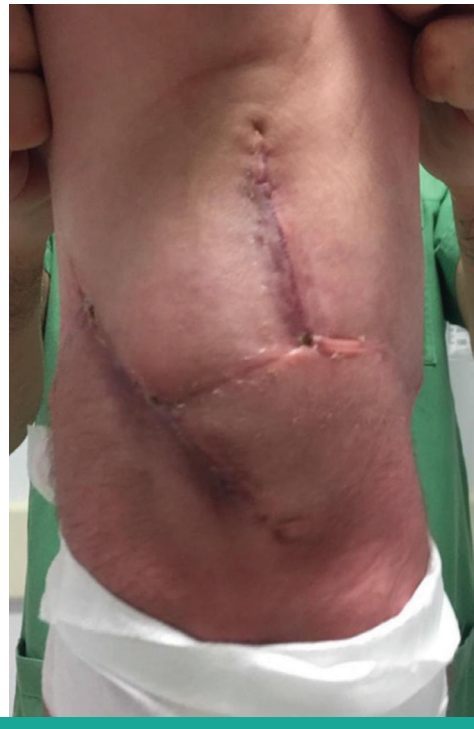

Figure 4. The defect area healed smoothly in the late postoperative period

Hydrocephalus is present in most (85%) of MMC cases. A rapid increase in existing hydrocephalus can be observed, especially with the closure of the defect. The newborn should be followed closely with daily fontanel and head circumference monitoring. It should be monitored at the appropriate time for planning shunt surgery.

Prone lying position is recommended for healthy children, especially for the prevention of reflux during infancy process. Newborns with MMC have to lie in this position anyway.

They should be placed in the prone position and neural tissues should be protected from trauma and external factors. Surgery should be planned as soon as the newborn is vitally stable -within the first few days if possible- especially since they tend to become infected rapidly. The ideal surgical approach is to close the defect within the first 24 hours. Motor examination of the newborn should be evaluated in detail and sphincter functions should be checked. Since orthopedic, urological and cardiac problems may accompany frequently, a multidisciplinary approach should be kept in mind and consultation should be planned if necessary.

The surgical procedure routinely used in MMC practice is primarily to create the neural tube that has not formed yet (6). The surgical procedure performed for this purpose has some key points. The first of them is the completion of removal of the zona epitheliosa layer. It is very important to remove the zona epitheliosa completely in order to prevent future epidermoid cysts. The liberated neural tube should not be closed too tightly in order to prevent the tense spinal cord problem in the future. The second important point is to close the dura, which is the next step after the neural tube is created (6-8). The dura must both coils the neural tube and allows CSF circulation within it. The dura must be dissected from its adhesions in the fascia and must be closed in a watertight fashion.

After closing the dura, the fascia should be closed in accordance with the subcutaneous and skin anatomy. Fascia is very weak, especially in cases with large defects, and may not be fully closed. At this stage, blunt and careful dissections should be preferred over sharp dissections and finger dissection. Bilateral ventral skin dissection towards the abdomen should always be kept in mind to cover small defects, but if there is a need for flap, the surrounding tissue should never be touched for the purpose of forwarding. During the reconstruction phase, the overly tight covering of the layers and their being forced to combine causes necrosis, necessitating a possible secondary surgery, and additional problems come into play by extending the hospitalization period. Therefore, in surgical procedures where the size of the defect is calculated in a way that cannot be easily covered with the surrounding soft tissue, the flap must be designed and drawn before the sac repair and the flap drawing should not be exceeded and the surrounding tissue should be protected.

Healthy repair of meninges and overlying tissue defects in patients prevents serious complications, especially meningitis, and provides maximum protection of sensory and motor functions (3). For reconstruction purposes, primary suturing, skin grafts, Z plasty, tissue expander applications, rotation and advancement flaps, composite muscle-skin flaps, perforator flaps and free flaps can be used. While some of these are in one session, some cannot be completed in one session.

Primary repair can be preferred only in cases where the defect diameter is less than 5 cm, without creating tension in the suture lines (1). In cases where the defect is larger, it is not possible to repair the defect with primary suturing. At that stage, Z plasty incisions can be made to extend the tissue edges. Skin grafting may give us a temporary solution during the child's growth phase. Closing a full-thickness defect with only skin causes defects in the compression areas and CSF leakage again according to the position of the decupit. The early or late ulcer opening, even if the graft is adhered, infection development and susceptibility to traumas of skin grafting applications primarily suggest that these types of defects should be repaired with flap. Local skin flaps can provide repairment opportunities close to the desired purposes, as the defect will remain small in small sacs. Single or bilateral skin advancement flaps, bipediculated skin flaps, Limberg flaps and rotation flaps can be selected for the repair of the defect that occurs after large sac excisions. Prolonged operation time, excessive blood loss, and the risk of loss, even if partial, can be considered as disadvantages (1,2). However, flap instead of direct repair, at least, reduces the chance of dehiscence after stretching due to the lying position (9,10). Limberg flap, which is the first choice among local skin flaps, is often advantageous in the use of such defects. The biggest advantage of this type of flaps, which are made with the principle of 120 degrees and 60 degrees, is that there is no need for muscle use, and that the operation time and the amount of bleeding are less. However, when there is a partial or full thickness necrosis, a muscle skin flap should be planned (8,9). Muscle flap removal should be among

the last options, as there are patients who cannot use their lower extremities in adulthood and need trunk muscles for trunk posture (11,12). Since this situation is directly related to the defect diameter, flap design should be made with appropriate drawings. At the stage of muscle inclusion into the flap, M. latissimus dorsi or M. gluteus maximus can be selected according to the location of the defect (13). Whether one or both muscles will be included in the flap in a split shape depends on the location of the defect. Specifically, different flap options have been introduced. In thoracodorsal flaps, the inclusion of M. latissimus dorsi in the flap ensures safe closure of the defect and offers the option of additional skin graft to the muscle flap in the closure of large defects.

Although graft and flap options are used, dermal tissue equivalents are another alternative and combined with simultaneous skin graft in children who do not have sufficient tissue support or develop fistula (12).

Flap selection in MMC defects also varies according to the location of the defect. While fasciocutaneous flaps are a good choice for defects at all levels, several flaps can be designed at the same time depending on the size of the defect. After giant MMC excisions, if the defect exceeds approximately 60% of the thoracic region, as in this case, treatment options are limited (14). The latissimus dorsi muscle in the upper-level settlers and the gluteus maximus muscle in the lumbar local ones can be included in flaps (15). Bottom located defects are more suitable for perforator flaps. In our case, the bilateral latissimus dorsi muscle flap was chosen to support the midline while the drawings were made according to the ZAR flap drawings and the flaps were elevated (4). Limberg flaps were not preferred due to the fact that 60/120 degree drawings might result in necrosis even in partial in such large defects. Since the patient was going to undergo shunt operation in the urgent period, a single-session operation was directed. Tissue expanding application was not the appropriate choice for this patient, as it had two sessions, required a long period of inflation, and could be exposed at times (16). With ZAR flaps, it was observed that the full layer of subcutaneous and skin tissue covering the midline muscle provided a complete compression-resistant tissue integrity. The second advantage of this technique was that there was no need for skin grafts for donor sites, so donor site morbidity was low.

Making perforator flaps requires experience linked to the learning curve. In young children, the chances of success are reduced due to the narrow calibration of the perforator vessels (17). The perforator flap options recommended for lumbar MMC defects are wider. Whittemore et al. (17) described a superior gluteal artery-based perforator flap. It may be preferred in smaller defects and defects close to the sacrum.

Conclusion

The diameter and location of the defect are important in the reconstruction of thoracic MMC defects. In the closure of very large defects, one session should be planned as early as possible, in a way to keep the operation time short, and in lying position in childhood and the trunk posture in adulthood. In addition, the fact that the selected flap contains muscle tissue reduces the chance of fistula by covering the dural repair area more properly.

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Ethic

Informed Consent: Written informed consent was obtained from the parents/legal guardians for the publication of this case report and any accompanying images.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: P.K., N.S.B., Design: P.K., N.S.B., E.S., Data Collection or Processing: P.K., N.S.B., E.S., Analysis or Interpretation: P.K., N.S.B., E.S., Drafting Manuscript: P.K., N.S.B., M.B., E.S., Critical Revision of Manuscript: P.K., N.S.B., M.B., Writing: P.K., N.S.B., M.B., E.S.

Conflict of Interest: The authors declare that there is no conflict of interest with regard to this manuscript.

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CASE REPORT

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Arthrotomy and Washing Procedure for Neonatal Bacterial Arthritis in a Series of Cases

Bir Olgu Serisinde Yenidoğan Bakteriyel Artriti için Artrotomi ve Yıkama Prosedürü

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Abstract

Septic arthritis is a rare health issue during neonatal period. It should be remembered that the treatment of this disease can lead to serious problems in the long term when it is late. In this series of cases, we presented arthrotomy and washing procedures in three neonatal patients with septic arthritis. We evaluated the pros and cons of the procedure and we compared it to non-surgical treatment methods. We have concluded that the washing procedure can be more effective than non-surgical methods.

Keywords: Arthritis, arthrotomy, neonate

Öz

Septik artrit, yenidoğan döneminde nadir görülen bir hastalıktır. Bu hastalığın tedavide geç kalındığında uzun vadede ciddi problemlere yol açabileceği unutulmamalıdır. Bu olgu serisinde septik artrit tanılı üç yenidoğan hastamıza artrotomi ve yıkama prosedürünün uygulamasını sunduk. Prosedürü kar zarar açısından değerlendirdik. Cerrahi olmayan yöntemlerle karşılaştırdık. Eklem yıkama prosedürünün cerrahi olmayan yöntemlerden daha etkili olabileceğini düşünmekteyiz.

Anahtar kelimeler: Artrit, artrotomi, yenidoğan

Introduction

Septic arthritis (SA) is an important condition for the neonates, which may cause permanent disability if left untreated. It is more important for neonates because early treatment may leave no complications but being late in treatment may cause permanent effect by damaging articular cartilage and causing osteonecrosis. Especially when the joints are weight-bearing, the consequences can be more catastrophic. It is also challenging to diagnose SA in neonates because the symptoms appear silently. If parents recognize most common symptoms such as grimace, crying and restlessness during diaper changing, they should apply to a hospital early. Open surgical drainage is recommended for bacterial arthritis of the hip in infants. Factors to be considered before the procedure include the site and extent of the joint involvement, duration of symptoms, and the suspected organism (1). Based on clinical reports, arthrotomy is the preferred procedure for bacterial arthritis of the shoulder in infants (2). We presented a case series of three neonates that had arthrotomy and surgical washout therapy for the treatment of SA and we obtained consent from the families of the cases.

Case Reports

Case 1

A 3.390-g male neonate was born by cesarean delivery, at 39 weeks of gestation to a 28-year-old gravida 3 mother. The neonate was seen in the delivery room, and given to the

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mother after a full physical examination was performed. On follow-up, respiratory distress was detected by the attending physician, and the patient was admitted to neonatal intensive care unit (NICU). On the 2nd day of the admission, C-reactive protein (CRP) level was significantly increased to 84 mg/dL. On the sixth day, a limited range of motion and 2x2 centimeters sized swelling on the front medial side of the right elbow was detected. In the control laboratory analysis, CRP and erythrocyte sedimentation rate (ESR) were 42 mg/dL and 32 mm/h, respectively. Diagnostic arthrotomy was performed and it showed no collection of fluid in the joint space. Two days later, arthrocentesis was performed and joint aspiration fluid showed no sign of infection. After the patient completed his 14-day antibiotic regimen for sepsis, follow-up X-ray images were taken and they revealed callus formation (Figure 1, 2). Eventually, the neonate was diagnosed with distal humeral epiphysis separation fracture.

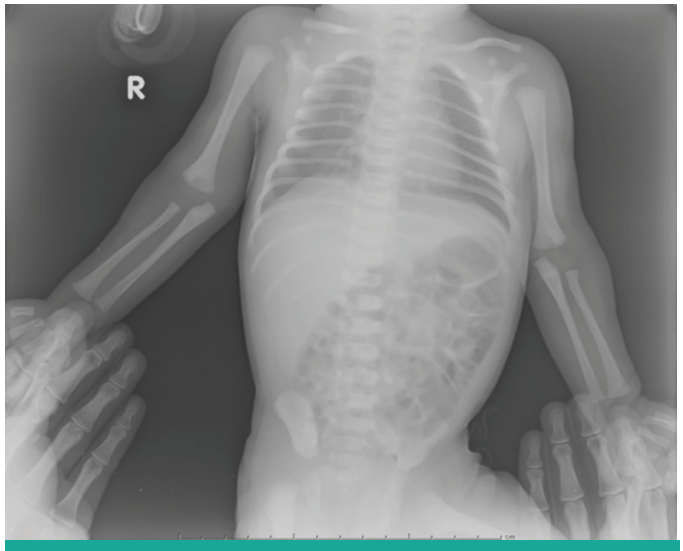

Figure 1. Radiographs of the right elbow

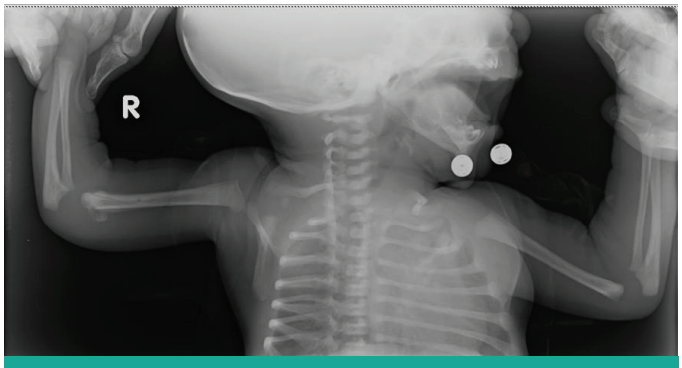

Figure 2. Radiograph at 3 weeks showing sufficient callus formation

Case 2

A 3.450-g female neonate was born by vaginal delivery at 40 weeks of gestation to a 32-year-old gravida 4 mother. On the postnatal 10th day, she was admitted to the hospital for crying during diaper changing and her mother realized a decrease in right leg movements. Physical examination revealed that the newborn was grimacing during the right hip joint movements. There was no swelling or the redness of the joint. Laboratory analysis revealed CRP and ESR values as 58 mg/dL and 28 mm/h, respectively. Diagnostic arthrotomy showed a collection of fluid in the joint space and the joint was irrigated. Arthrocentesis was performed and aspiration fluid showed signs of infection. *S. aureus* was obtained from the synovial culture specimen.

Case 3

A 3.350-g female neonate was born by vaginal delivery at 38 weeks of gestation to a 26-year-old gravida 2 mother. On the postnatal 20th day, she was admitted to the hospital for crying and restlessness. Physical examination revealed crying and increased restlessness when she moved the left hip joint. There was no swelling or redness by inspection. Laboratory analysis revealed CRP and ESR values as 52 mg/dL and 45 mm/h, respectively. Diagnostic arthrotomy showed a collection of fluid in the joint space and the joint was irrigated. Arthrocentesis was performed and aspiration fluid showed signs of infection. *S. agalactia* was obtained from the the synovial culture and hemoculture specimen.

Discussion

SA is difficult to diagnose in patients younger than 3 months; even more difficult to diagnose in neonates because of the paucity of signs and symptoms. There is a lack of research guiding physicians as to which variables about irrigation and debridement in the management of pediatric SA (3).

Neonatal infections are unique to several forms as they are transmitted from mother to the fetus or newborn infant by diverse modes and neonates are less capable of responding to infection because of one or more immune deficiencies. In the descriptive study of Sreenivas et al. (4), 29 neonates presenting to the department of orthopaedics with acute SA were investigated. It was seen that the mean age of presentation were 23.8 days in their study, and there was female predominance. In the same study, it was also shown prematurity and anemia still appeared to be important risk factors for neonatal SA (4). Hip and knee joints are commonly affected in other studies (5,6).

Female gender was predominant in our cases. The median application time of the cases was determined as 8.6 days. The joint regions identified in our cases were the elbow and hip joints, respectively. However, none of our cases were preterm newborns.

The goals of treatment include sterilization and decompression of the joint space and removal of inflammatory debris to relieve pain and prevent deformity or functional sequel (7). Joint arthrotomy and washing procedures were performed in our cases, and then the treatment was continued with antibiotics. All cases were followed closely in the NICU.

Medical treatment was administered for 21 days with the recommended dose and dose range suitable for SA. The results of the blood culture were asked daily to ensure proper antibiotic selection. Due to the increase in CRP and ESR levels in a case, osteomyelitis was suspected and a magnetic resonance imaging (MRI) examination was performed. According to MRI results, the patient was diagnosed with osteomyelitis and the treatment was planned to be extended to 9 weeks. All patients were monitored closely during the treatment for ESR and acute phase reactants.

Arthrotomy and the open washout therefore remain the treatment of a choice to clear the microbial load from the joint (8). Although drainage and antimicrobial therapy are well-established cornerstones of therapy for bacterial arthritis, there are little evidence for controlled trials to guide decisions on the optimal procedure for drainage or the choice, route, or duration of antimicrobial therapy (8,9). All aspirated materials should be sent to the laboratory and bacteriological examination. The presence of bacteria confirms the diagnosis of osteoarthritis. However, bacterial culture negative finding does not exclude infection (10,11). *S. aureus* was obtained in synovial culture in only one of the cases and *S. agalactiae* was obtained in both of hemoculture and synovial cultures in one of them.

For possible complications in the postoperative period, 8-week follow-ups were scheduled. Patients continued the antibiotic treatment because of *S. agalactia* growth of both cultures. The initial total treatment time was 6 weeks for both babies. In the third case, total therapy was extended up to 9 weeks because the patient was additionally diagnosed with osteomyelitis. Hip dislocation as a procedure-related complication was observed in one of the cases. Routine use of open arthrotomy and washout therapy for SA in the newborn period should be evaluated for short and long term complications with comprehensive studies. However, this morality may be a suitable method of this period for the treatment of SA.

Conclusion

We have evaluated that arthrotomy and washing treatment can be applied in neonatal SA cases and complication rate of the procedure is similar to that of non-surgical methods.

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Ethic

Informed Consent: We obtained consent from the families of the cases.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: Ç.C.G., T.K., Design: Ç.C.G., T.K., Data Collection or Processing: T.K., Ş.H., Analysis or Interpretation: T.K., Ş.H., Literature Search: Ç.C.G., T.K., E.C., Ş.H., Writing: Ç.C.G., T.K., E.C., Ş.H.

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

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