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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, Türk Medline, Türkiye Atıf Dizini, 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.

Bağcılar Tıp Bülteni/Bagcilar Medical Bulletin, yazıların İngilizce dilinde, yazıların özetlerinin Türkçe ve İngilizce dillerinde online olarak yayınlandığı bir dergidir.

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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Derginin Sahibi

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.

General Principles

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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Publication Ethics and Publication Malpractice Statement

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Bagcilar Medical Bulletin is committed to upholding the highest standards of publication ethics and observes the following principles of Publication Ethics and Malpractice Statement which is based on the recommendations and guidelines for journal editors developed by the Committee on Publication Ethics (COPE), Council of Science Editors (CSE), World Association of Medical Editors (WAME) and the International Committee of Medical Journal Editors (ICMJE).

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/

For this reason, regarding the subjects of clinical experiments, it should be indicated in the submitted manuscripts definitely that the above mentioned codes of conduct were applied. Besides approvals, from national or local ethical committees should be sent together with the papers as well. Manuscripts that report the results of experimental investigation with human subjects must include a statement that informed consent was obtained after the procedure(s) had been fully explained. In the case of children and those under wardship or with confirmed insanity, authors are asked to include information about whether the legal custodian's assent was obtained. And a letter of affirmation signed by all authors, confirming the collection of informed consents has to be sent to the journal.

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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).

Manuscript Organization And Format

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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On the title page, include full names of authors, academic or professional affiliations, and complete address with phone, fax number(s) and e-mail address (es) of the corresponding author. Acknowledgments for personal and technical assistance should be indicated on the title page.

Abstract and Key Words

Title of the manuscript in English should be written in English abstract, and a Turkish title must be for Turkish abstract.. All articles should include abstract and keywords. For abstracts are most distinct parts of an article and take place on the electronic

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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.

Material and Methods

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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The methods, apparatus (the manufacturer's name and address in parentheses), and procedures in sufficient detail must be defined to allow others to reproduce the results. References to established methods, including statistical methods (see below) must be given and brief descriptions for methods that have been published but are not well-known must be provided; new or substantially modified methods must be described, the reasons for using them must be given, and their limitations of the methods must be evaluated. The all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration must be identified. Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarized in the abstract.

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The results should be presented in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. The all the data in the tables or illustrations should not be repeated in the text; only the most important observations must be emphasized or summarized. Extra or supplementary materials and technical detail can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

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

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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Case reports consider new, interesting and intriguing case studies in detail. They should be unique and present methods to overcome any health challenge by use of novel tools and techniques and provide a learning source for the readers. Case reports comprise of: Abstract (unstructured summary), Key-words, Introduction, Case Report, Discussion, Reference, Tables and Figures. Written informed consent of the patient should be obtained and indicated in the manuscript.

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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.

The manuscript should have an unstructured abstract representing an accurate summary of the article, key words, introduction, conclusion. Authors submitting review article should include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarized in the abstract.

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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.

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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 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

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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.

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

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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 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

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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 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.

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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. 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

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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 /),

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.

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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.

MEDLINE'da yer almayan ve kısaltması olmayan dergi makalesi için: Maner F. Yeme bozukluklarının tedavisi. Anadolu Psikiyatri Dergisi 2009;10(Ek 1):55-56.

3. Baskıdaki makale için:

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. 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.

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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:

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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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- Yazarlar ve kurumları
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• Teşekkür

• Kaynaklar

• Tablolar-Resimler, Şekiller

BAGCILAR MEDICAL BULLETIN
Bağcılar Tıp Bülteni

CONTENTS / İÇİNDEKİLER

ORIGINAL RESEARCH

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The Importance of De Ritis Ratio in Patients with Bladder Cancer

Mesane Kanseri Hastalarında De Ritis Oranının Önemi

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Abstract

Objective: Numerous studies prove the relationship between serum aspartate transaminase/alanine transaminase (AST/ALT) ratio (De Ritis Ratio) and cancer cases. However, the results obtained by the researchers are controversial, and most scientific articles have different results. There are studies revealing the De Ritis Ratio relationship in urothelial carcinoma patients. Therefore, in this study, we aimed to reveal the relationship between De Ritis Ratio and bladder cancer.

Method: This study was carried out after getting the approval of our hospital's ethics committee dated 26/07/2018 and numbered 2018/12. One hundred seventy two patients who had bladder cancer and 68 healthy individuals in the control group were included in the study. It was evaluated whether there was a relationship between AST/ALT values and tumor stages and pathologies of these patients, and it was retrospectively investigated whether the De Ritis ratio differed between healthy and bladder cancer individuals.

Results: In this study, in which 240 individuals (including 172 patients and 68 controls) were evaluated, no statistical significance was observed between AST/ALT ratio and tumor stage, tumor pathology, ultrasound findings, and tumor size. However, a statistical difference was observed between the control group and the patient group in values of AST/ALT ratio. The De Ritis ratio (AST/ALT) in bladder cancer patients was higher than in the control group (mean: 1.18/0.91).

Conclusion: According to the findings of this study, AST/ALT ratio in bladder tumor patients differs compared to the control group. Therefore, it can be thought that the rate of De Ritis is a parameter that helps diagnosis and prognosis of these patients.

Keywords: Aspartate transaminase to alanine transaminase ratio, bladder cancer, De Ritis

Öz

Amaç: Çok sayıda çalışmada belirtildiği üzere, serum aspartat transaminaz/alanin transaminaz (AST/ALT) oranı (De Ritis Oranı) ile kanser olguları arasında ilişki bulunmaktadır. Ancak araştırmacıların elde ettikleri sonuçlar tartışmalıdır ve çoğu bilimsel makalede farklı sonuçlar bulunmaktadır. Ürotelyal karsinoma hastalarında De Ritis oranının arttığını gösteren araştırmalar mevcuttur. Bu çalışmada diğer araştırmalarla benzer bir biçimde De Ritis oranı ile mesane kanseri arasındaki ilişki araştırılmıştır.

Yöntem: Bu çalışma hastanemizin 20/07/2018 tarihli ve 2018/12 belge no'lu etik kurulu onayı müsaadesince gerçekleştirilmiştir. Çalışmaya mesane kanserinden ameliyat edilen 172 hasta ve 68 sağlıklı bireyden oluşan kontrol grubu dahil edilmiştir. Bu hastaların AST/ALT değerleri ile tümör evreleri, patolojileri arasında bir ilişki olup olmadığı değerlendirilmiş, ayrıca De Ritis oranının sağlıklı ve hasta bireyler arasında farklılık gösterip göstermediği retrospektif olarak araştırılmıştır.

Bulgular: Yüz yetmiş iki hasta ve 68 kontrol grubu olmak üzere toplamda 240 kişinin değerlendirildiği bu çalışmada, AST/ALT oranı ile tümör evresi, tümör patolojisi, ultrason bulguları, tümör boyutu arasında herhangi bir istatistiksel anlamlılık gözlenmemiş, buna karşın kontrol grubu ile mesane kanseri hastaları arasında AST/ALT oranı bakımından istatistiksel olarak farklılık gözlenmiştir. Mesane kanseri hastalarında De Ritis oranı (AST/ALT) kontrol grubuna göre yüksek bulunmuştur (ortalama: 1,18/0,91).

Sonuç: Bu çalışmanın bulgularına göre, mesane tümörü hastalarında AST/ALT oranı kontrol grubu ile karşılaştırıldığında farklılık göstermektedir. Bu nedenle, De Ritis oranının bu hastaların değerlendirilmesinde teşhise ve hastalığın seyrine yardımcı bir parametre olduğunu düşünülebilir.

Anahtar kelimeler: Aspartat transaminaz/alanin transaminaz oranı, De Ritis, mesane kanseri

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Introduction

Urothelial carcinomas typically occur in the human urinary system. Malignancies included in the group of urothelial carcinomas involve the kidneys, bladder and auxiliary organs. These cancers are most frequently in the bladder cancer (BC), ureters, and urethra, respectively. BC is the second most common type of cancer in the genitourinary system.

Generally more than 90% of bladder tumors are urothelial carcinomas, which differs from normal urothelium in that it presents more epithelial layers, changes in cellular maturation, prominent nucleoli and more mitosis. The macroscopic presentation of urothelial carcinoma can be papillary (more frequent), sessile, infiltrative (malignant characteristic), nodular, or mixed carcinoma *in situ* (CIS). In the examination of cystoscopy, CIS may appear as an area of hyperemia and flat, or often go unnoticed. It consists of a tumor of poorly differentiated urothelial cells and is confined to the epithelium, which can cause symptoms of polyuria, dysuria and urinary urgency. Ultrasonography and other imaging methods are unable to identify CIS because of its flat appearance.

Bladder cancer is usually operated with transurethral tumor resection, a modern method and a minimally invasive surgical procedure, if no other medical condition is involved. However, pelvic lymph node dissection (PLND) and radical cystectomy (RC) have been used as traditional surgery methods for local muscle invasive BC (MIBC). RC with PLND is sometimes used to treat non-muscular invasive BC (NMIBC), including Bacille Calmette-Guerin resistant cases and high grade tumors. In this cancer, the prognosis of NMIBC patients is generally good, if the malignant cells increase and the disease does not occur in MIBC. However, in most NMIBC patients, approximately 30% of them have MIBC unfortunately. As a result, half of the operated patients have cancer again within 2 years. The 3-year survival rate in the operated patients is less than 50% (1). However, even if RC is performed, the prognosis of the disease is poor. Cancer recurrence occurs in more than 30% of patients after RC (2) and BC, and this cancer is the 13th most common cause of cancer-related deaths (3).

Transurethral resection of bladder tumor represents the first step in the diagnostic and treatment process of BC (4). As much as 75% of newly diagnosed BCs are diagnosed at the stage of NMIBC disease, i.e. limited to mucosa (Ta and CIS) or to the lamina propria (T1) (5). However, eligible patients are difficult to identify due to the poor prognostic value of the current clinical staging system, resulting in inadequate use (6). Therefore, a preoperative prognostic factor that can be stratified sufficiently is required for optimal preoperative treatment of patients.

Various biomarkers for early diagnosis and prognosis prediction of BC, such as Engrailed-2 protein, bladder tumor antigen, methylation biomarkers, cytokeratin 20, Nuclear matrix protein 22, soluble FAS [the FAS belongs to the tumor necrosis factor receptor superfamily], and fibroblast growth factor receptor have been discussed. There are also many mRNA-based biomarker tests, such as the Cx bladder monitor, XPERT BC, and BC test (7,8).

In 1957, the serum activity rate of aspartate transaminase (AST) and alanine transaminase (ALT) was first discovered by Fernande De Ritis and was then referred to as the De Ritis ratio (AST/ALT) (9). ALT and AST enzymes are found in the red blood cells, brain, kidney, heart, skeletal muscle, but are found in the liver mostly. Because they are found in most vital organs, they are also used as an indicator of many diseases (10,11). Cancer and non-cancerous tissues have been shown to be important prognostics because they produce these enzymes in many malignant tumors. These include multiple myeloma, colon, pancreatic, renal cell carcinoma (RCC) and upper system urothelial cancer (12,13). It is also assumed that the De Ritis ratio is associated with increased anaerobic glycolysis, a process known as the Warburg effect. In this study, we suggest that for all these reasons, the De Ritis ratio may play a diagnostic role in BC, because BC has been reported to be associated with glucose metabolism (14,15).

Materials and Methods

In this retrospective analysis, medical records of 172 patients who applied with BC and who underwent transurethral resection-bladder tumor in our clinic between 2016 and 2019 and 78 healthy controls were examined. This study was carried out after getting the approval of our hospital's ethics committee dated 26/07/2018 and numbered 2018/12. The study was approved by the local ethics committee and Informed consent was obtained from appropriate patients. The mean age of the patients (mean ± standard deviation) was 62.18±14.04 years and the mean age of the control group was 61.79±11.73 years. The ages of the patients varied between 18 and 92 years, the ages of the control group were between 30 and 85 years. 13% of patients were female and 87% were male (Table 1). Plasma AST and ALT levels were analyzed by standard clinical methodology within 7 days

before surgery. Pathological features included tumor size, tumor stage, and deep tissue invasion.

Statistical Analysis

Data were analyzed by using Statistical Package for the Social Sciences software package version 20 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine whether the data showed normal distribution. In the study, power analysis was performed with G-Power 3.1.9.2 software to calculate the number of samples. Considering the Kolmogorov-Smirnov and Shapiro-Wilk analyses, the Mann-Whitney U tests were applied to determine whether the parameters that did not show normal distribution differed between the groups. The average and standard deviations of these test parameters are given in results section. The Kruskal-Wallis test, one of the non-parametric tests, was used to determine whether the AST/ALT values of BC patients changed according to the tumor stages, pathologies, and ultrasound (USG) findings. In the study, discriminant analysis was performed to determine whether BC patients differed in terms of their tumor stages and AST/ALT values. Another purpose of this analysis is to detect the group that belongs to any of the groups, but which group is not known, with the least error. It is possible to sum up the purposes of discriminant analysis in two groups: To determine the discriminant functions and to determine the discriminant variables that affect the inter-group discrimination through these functions.

Results

Of the 172 patients included in the study, 151 were male and 21 were female. Forty four of the individuals in the control group were male and 24 were female. The pathological stages (tumor grade) of these patients were distributed as follows, 66.6% (n=115) of the patients were at the low grade stage, 33.4% (n=57) at the high grade stage. When BC patients were classified according to their T stage, it was found that 42% (n=73) of these patients were at the T0 stage, 36% (n=36) were at the T1 stage, 22% (n=37) were at the T2 stage, and there were no patients in the T3 and T4 stages. Patients' serum AST mean and standard deviation values were 20.91±9.02 IU/L, respectively. The minimum AST value measured in the serum of patients was 7 IU/L, the maximum AST value was 65 IU/L. The mean and standard deviation value of patients' ALT value was 19.67±10.23 IU/L, respectively. The mean and standard deviation value of AST was 15.87±4.27 IU/L in the serum of the control group. The mean and standard deviation value for ALT was 14.83±7.90 IU/L in patients.

Table 1. Demographic properties of patient and control groups

	Average value	Standard deviation	Min-max age	% Male	% Female
Patients' age	62.18	14.04	18-92	87	13
Control group's age	61.79	11.73	30-85	84	16

Min: Minimum, Max: Maximum

The results of the Shapiro-Wilk test and Kolmogorov-Smirnov tests were applied to determine the normal distribution ($p<0.005$). Accordingly, no parameters of BC patients used in the study showed normal distribution.

The AST, ALT and ''De Ritis'' values were obtained from AST/ALT ratio and a statistically significant difference could not be detected compared to tumor stage, pathological stage, multifocal classification values with the Kruskal-Wallis test. This means that there was no difference in terms of ALT, AST and De Ritis ratio among the T0, T1 and T2 classes of the Tumor Stage parameter, and no difference between tumor grade classes of low grade and high grade according to AST, ALT and De Ritis ratios.

The relationship between USG and length values and ALT value was significant (Table 2).

According to the discriminant function analysis results, the test parameter separating the patient and control groups was AST ($p=0.000$). ALT and De Ritis ratio were not effective in separating these two groups (Table 3).

Table 2. Kruskal-Wallis test results

		AST	ALT	De Ritis
Tumor grade	Chi-square	2.119	2.606	4.025
	Df	2	2	2
	Asymp. sig.	0.347	0.272	0.134
T stage	Chi-square	3.741	4.342	4.064
	Df	2	2	2
	Asymp. sig.	0.154	0.114	0.131
Multifocal	Chi-square	0.281	1.98	1.879
	Df	2	2	2
	Asymp. sig.	0.869	0.372	0.391
Length	Chi-square	1.959	13.361	7.43
	Df	3	3	3
	Asymp. sig.	0.581	0.004	0.059
USG	Chi-square	11.894	13.301	3.277
	Df	3	3	3
	Asymp. sig.	0.008	0.004	0.351

AST: Aspartate transaminase, ALT: Alanine transaminase, USG: Ultrasound

When the De Ritis ratios of the patient and control groups were compared with the Mann-Whitney U test, there was a significant difference between the patient and the control groups (Table 4).

The mean and standard deviation values of De Ritis ratios of the patient and control groups were clearly different from each other. De Ritis rates were higher in the patient group than in the control group (Table 5).

Discussion

Aspartate transaminase is an enzyme found in the body cells, heart and liver, and to a lesser extent in the kidneys and muscles. ALT, on the other hand, is an enzyme mostly found in the liver and in smaller amounts in the kidneys, heart and muscles. In healthy individuals, AST and ALT are low in blood. Italian, Internal Medicine specialist medical doctor and also a great philanthropist, Fernande De Ritis showed in 1957 that amino transaminases could be used to distinguish between viral hepatitis and alcohol-induced hepatitis. This index, which Fernande De Ritis defined as the AST/ALT ratio, has now passed into the medical literature as the "De Ritis Ratio" (7). These transaminase enzymes, which are strongly involved in cellular metabolism and cancer cell cycle, are indicators that can be easily measured in the blood (16). Scientific studies have stated that AST/ALT ratio is a prognostic factor, as listed as follows; Stocken et al. (15) in pancreatic cancer, Bezan et al. (14) in non-metastatic RCC, Nishikawa et al. (16) De Ritis ratio as a significant predictor of recurrence-free survival in patients with upper urinary tract urothelial carcinoma following nephroureterectomy, Rawson and Peto (17) in lung cancer, Tan et al. (18) in distal cholangiocarcinoma (19,20). According to the hypothesis suggested by Nobel laureate famous biochemist and medical doctor Otto Heinrich Warburg, which was referred to as "Warburg effect", it is assumed that cancer, malignant growth, and tumor growth are due to the fact that tumor cells produce energy as a result of the breakdown of glucose without oxygen (glycolysis). This is in contrast to healthy cells that produce energy mainly from the oxidative breakdown of pyruvate. Pyruvate is a final product of glycolysis and oxidized in mitochondria. Therefore, according to Warburg, carcinogenesis is due to a decrease in mitochondrial oxidative phosphorylation. Warburg assumed that the main difference between normal and cancerous cells was the ratio of glycolysis to oxidative phosphorylation (19). Ha et al. (20) found the relationship between De Ritis ratio and clinicopathological findings in their studies. In their study, they retrospectively investigated the clinicopathological data of 118 patients with metastatic urothelial BC after RC. and found that the high rate of De Ritis in urothelial BC patients, which were receiving RC therapy, was significantly associated with the rate of De Ritis with poor prognosis. They stated that this rate might further increase the predictive accuracy for prognosis in BC (20). In the findings obtained in this study,

Table 3. Discriminant function analyses results of the patient and control groups.

Step	Entered	Wilks' Lambda				Exact F			
		Statistic	df1	df2	df3	Statistic	df1	df2	Sig.
1	AST	0.939	1	1	219.000	14.336	1	219.000	0.000

(At each step, the variable that minimizes the overall Wilks' Lambda is entered, Maximum number of steps is 6. Minimum partial F to enter is 3.84. Maximum partial F to remove is 2.71. F level, tolerance, or VIN insufficient for further computation). AST: Aspartate transaminase

Table 4. Mann-Whitney U test results of De Ritis ratio in the patient and control groups

	De Ritis
Mann-Whitney U	2275.5
Wilcoxon W	3095.5
Z	-3.333
Asymp. Sig. (2-tailed)	0.001

Table 5. Descriptive statistical results of De Ritis ratio in the patient and control groups

De Ritis ratio	**Patients**	Mean	1.181773	**Control**	Mean	0.914028
		Standard deviation	0.407367		Standard deviation	0.342533
		Minimum	0.466667		Minimum	0.416667
		Maximum	2.25		Maximum	1.5

De Ritis ratio differs positively in BC patients, especially in patients with advanced tumor stage, compared to the control group.

Conclusion

According to our study results, De Ritis ratio was higher in BC patients than in the control group. In addition, as a result of the statistical analysis, the patient and control groups were separated from each other in terms of De Ritis ratio. According to this result, De Ritis ratio can provide information about the diagnosis of BC patients and the course of the disease. De Ritis ratio did not cause a significant difference between tumor stages, tumor sizes and pathological stages. This is because the tumor stages of patients included in this study were close to each other. The tumor stages of patients included in this study were T0, T1, and T2. Among these patients, there were no patients in the T3 and T4. The situation was the same in pathological stages. According to the patients' pathologies, bladder tumors were superficial and did not cross the basement membrane and retain the muscle layer. Tumor diameters measured before surgery and preoperative USG measurements were compatible with each other. The results of this study and the studies of Ha et al. (20), Nishikawa et al. (16) and Bezan et al. (14) are parallel to each other. In future studies to be carried out for the same purpose, more reliable results can be obtained if the following are considered, firstly, liver functions of the patient and control groups should be equivalent, viral hepatitis, alcohol use, human herpes viruses (HSV, VZV, EBV, CMV), Coxsacki B, Adenovirus, Measles, Rubella, Mumps, non A-E Hepatitis Viruses (TTV and SEN-V), Hepatitis A, B, C, D, E, G, metabolic diseases, Alpha-1 Antitrypsin Deficiency, Hemochromatosis and Systemic diseases can cause AST/ALT increase.

Ethics

Ethics Committee Approval: This study was carried out after getting the approval of our hospital's ethics committee dated 26/07/2018 and numbered 2018/12.

Informed Consent: Informed consent was obtained from appropriate patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: K.E., Design: R.A., Data Collection or Processing: M.D., Analysis or Interpretation: R.E., Literature Search: K.T., Writing: K.E.

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ORIGINAL RESEARCH

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Predictive Role of Monocyte to High-density Lipoprotein Ratio for Plaque Morphology in Asymptomatic Intermediate Carotid Stenosis

Asemptomatik Orta Düzey Karotis Darlığında Plak Morfolojisi için Monosit/Yüksek Yoğunluklu Lipoprotein Kolesterol Oranının Öngörücü Rolü

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Abstract

Objective: Carotid plaques are divided into calcified, mixed and fatty types according to the morphological ultrastructure. Increased risk of rupture, thromboembolism and stroke are more pronounced in mixed and fatty carotid plaques due to composition and instability.

The present study aimed to assess the role of monocyte to high-density lipoprotein cholesterol (HDL-C) ratio (MHR) to predict mixed and fatty plaques in patients with intermediate carotid artery stenosis.

Method: A total of 223 asymptomatic patients who had 50-70% stenosis in the carotid artery were included in this retrospective cohort study. Patients were assigned into three groups based on plaque morphology: 94 with calcified, 71 with mixed and 58 with fatty plaques. Groups were compared in terms of MHR. Predictive role of MHR for mixed and fatty plaque was investigated.

Results: MHR was significantly higher in the mixed and fatty plaque groups (16.951±5.935 vs 20.181±9.405 vs 11.200±4.126, p<0.001). It, with a cut off of 13.61, had 71.8% sensitivity and 56.6% specificity for the prediction of mixed plaque [area under the curve (AUC): 0.645, 95% confidence interval (CI): 0.571-0.718, p=0.001]. Moreover, MHR, with a cut off of 14.40, had 77.6% sensitivity and 62.4% specificity for the prediction of fatty plaque (AUC: 0.746, 95% CI: 0.675-0.818, p<0.001). Multivariate regression analysis showed MHR was a significant independent predictor of mixed [odds ratio (OR): 1.230, p<0.001] and fatty (OR: 1.364, p<0.001) plaques in intermediate carotid artery stenosis, after adjusting for other risk factors.

Conclusion: MHR plays a favorable role for the prediction of mixed and fatty plaques in asymptomatic intermediate carotid artery stenosis.

Keywords: Carotid artery, monocyte to high-density lipoprotein ratio, plaque morphology

Öz

Amaç: Karotis plakları morfolojik alt yapıya göre kalsifik, mikst ve yağlı tiplere ayrılır. Mikst ve yağlı karotis plaklarının bileşimi ve kararsızlığı nedeniyle artmış rüptür, tromboembolizm ve inme riski daha belirgindir. Bu çalışma, orta düzey karotis arter darlığı olan hastalarda monosit/yüksek yoğunluklu lipoprotein kolesterol (HDL-C) oranının (MHR) mikst ve yağlı plakları öngörmedeki rolünü değerlendirmeyi amaçlamıştır.

Yöntem: Bu retrospektif kohort çalışmaya karotis arterde %50-70 stenozu olan toplam 223 asemptomatik hasta alındı. Hastalar plak morfolojisine göre üç gruba ayrıldı: 94 kalsifik, 71 mikst ve 58 yağlı plak olanlar. Gruplar MHR açısından karşılaştırıldı. MHR'nin mikst ve yağlı plak için öngörücü rolü araştırıldı.

Bulgular: Mikst ve yağlı plak grubunda MHR anlamlı olarak daha yüksekti (16,951±5,935'e karşı 20,181±9,405'e karşı 11,200±4,126, p<0,001). Mikst plak tahmini için 13,61 cut-off değerinin üzerinde, %71,8 duyarlılığa ve %56,6 özgüllüğe sahipti [Eğrinin altındaki alan (EAA): 0,645, %95 güven aralığı (GA): 0,571-0,718, p=0,001]. Ayrıca MHR, yağlı plak tahmini için 14,40 cut-off değerinin üzerinde, %77,6 duyarlılığa ve %62,4 özgüllüğe sahipti (EAA: 0,746, %95 GA: 0,675-0,818, p<0,001). Çok değişkenli regresyon analizinde; diğer risk faktörleri ayarlandıktan sonra, orta düzey karotis arter darlığında, MHR'nin hem mikst [olasılık oranı (OO): 1,230, p<0,001) hem de yağlı (OO: 1,364, p<0,001) plakların anlamlı bağımsız prediktörü olduğu bulunmuştur.

Sonuç: MHR, asemptomatik orta düzey karotis arter stenozunda mikst ve yağlı plakların öngörülmesinde olumlu bir rol oynamaktadır.

Anahtar kelimeler: Karotis arter, monosit/yüksek yoğunluklu lipoprotein oranı, plak morfolojisi

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Introduction

Atherosclerosis is identified as a major cause up to 20-30% of all ischemic strokes in the world (1). The pathogenesis is multifactorial involving inflammation and immune mechanisms (2). Rupture of atherosclerotic plaque causes the activation of coagulation, aggregation of platelets and thrombus formation. Composition should be taken into consideration rather than stenosis severity while interpreting vulnerable plaque (3). Plaques that constitute high triglyceride and low density lipoprotein (LDL) have higher tendency to rupture.

Monocytes are key players of innate immunity. They release proinflammatory cytokines in all stages of inflammation (4,5). Atherosclerotic process from the onset to rupture is mediated by these cytokines (6,7). Monocytes ingest lipoprotein and convert to foam cells. Subsequently, they become main cellular component of atherosclerotic plaque.

Monocyte has a proinflammatory effect, while high-density lipoprotein (HDL) acts as an anti-inflammatory molecule that antagonizes this effect. HDL alleviates the deleterious effect of monocytes by reversing cholesterol transport in the plaque (8,9). Therefore, monocyte/HDL-cholesterol ratio (MHR) is a novel parameter used to evaluate the inflammatory condition. MHR is strikingly high among patients with cardiovascular diseases (10) and stroke (11). Additionally, it plays a strong predictive role for the prognosis after stroke (11).

Carotid plaques are divided into calcified, mixed and fatty types based on morphology detected by computed tomography angiography (CTA) (12). Mixed and fatty plaques have thin fibrous cap and high lipid content. They are unstable and easily ruptured causing transient ischemic attack and stroke (13).

Severity of stenosis and symptoms are two main factors that determine the risk of stroke in carotid artery (14). According to current guidelines (15), two situations requiring intervention are as follows: 1) Symptomatic patients with at least 50% carotid artery stenosis, 2) Asymptomatic patients with at least 70% carotid artery stenosis. There is a gray zone including asymptomatic patients with intermediate (50-70%) carotid artery stenosis. Identification of high risk individuals with intermediate carotid artery stenosis for developing symptoms is crucial. It may be beneficial to construct algorithms by adding MHR and plaque morphology to predict absolute risk. The relationship between these parameters remains to be elucidated. Hence, we hypothesize that MHR plays a strong role for the prediction of mixed and fatty plaques in asymptomatic intermediate carotid stenosis. The present study compares fatty, mixed and calcified plaques that cause asymptomatic intermediate carotid artery stenosis with respect to MHR.

Materials and Methods

Study Population

We retrospectively reviewed the medical records of 305 patients, who were admitted to the cardiology outpatient clinic with a 50-70% stenosis in the carotid artery between 2013 and 2015. Patients with any of the followings were excluded: ischemic or non-ischemic stroke, Acute Coronary syndrome, previous cardiac surgery, known coronary artery disease, atrial fibrillation, concomitant severe valvular disease, heart failure, cardiomyopathy, congenital heart defects, renal or hepatic disease, hematological disorders, malignancy and acute or chronic inflammatory disorders. Finally, 223 consecutive patients with asymptomatic intermediate carotid stenosis were enrolled in the study. Patients were divided into three groups as follows: 1) Ninety-four patients with calcified plaque, 2) Seventy-one patients with mixed plaque, 3) Fifty-eight patients with fatty plaque. Carotid stenosis and morphology were evaluated through CTA in each patient. Evaluation of each patient was performed by a multidisciplinary team including radiologist, neurologist, cardiologist and cardiothoracic surgeon. Local ethics comitte approved the study with the number 3.841 on 06.03.2020. Declaration of Helsinki were taking into consideration while conducting the study.

Statistical Analysis

Mean ± standard deviation were used to assess continuous variables and number and percentages were used to assess categorical variables. Test of normality was performed either Shapiro-Wilk test or Kolmogorov-Smirnov test. Student t-test was the test of choice to investigate differences between continuous variables with normal distribution. If the distribution was not normal for continuous variables, Mann-Whitney U test were performed. Chi-square test was used to assess difference between categorical variables. Sensitivity and specificity analysis were conducted with the receiver-operating characteristics (ROC) curve. Additionally, variables that had predictive value for mixed and fatty plaques in univariate analysis were integrated into multivariate logistic regression to determine statistical significance. A two sided p-value which was smaller than 0.05, was considered statistically significant.

Results

Baseline demographical characteristics and clinical, laboratory data of 223 patients (94 calcified, 71 mixed, 58 fatty) were summarized in Table 1. Fatty plaque group were younger (64.98±7.812 vs 71.31±10.683 vs 72.63±8.257, p<0.001) and smoking (41.4 vs 23.9 vs 20.2%, p=0.013) was more cammon among this group. Additionally white blood cell count (8.899±2.567 vs 8.362±1.959 vs 7.314±1.667×10^3/L, p<0.001), neutrophil count (5.861±2.164 vs 5.139±1.857 vs 3.938±1.241×10^3/L, p<0.001) and monocyte count (0.725±0.230 vs 0.685±0.168 vs 0.552±0.177×10^3/L, p<0.001) were higher in fatty plaque group.

Total cholesterol (188.36±42.791 vs 198.06±43.089 vs 211.71±40.230 mg/dL, p=0.003) and LDL (116.97±34.816 vs 120.89±33.450 vs 130.05±31.044 mg/dL, p=0.041) were lower in fatty plaque group due to more statin usage (25.9%). HDL (38.52±8.923 vs 42.77±10.469 vs 49.94±7.377 mg/dL, p<0.001) was significantly lower in fatty plaque group, respectively.

There was no difference in terms of antiaggregant and statin usage between three groups (Table 2). Few patients were taking acetylsalicylic acid (36.2 vs 28.2 vs 24.5%, p=0.300) and clopidogrel (5.2 vs 7 vs 7.4%, p=0.857) in each group.

Table 1. Patient characteristics by carotid plaque morphology

	Calcified plaque	Mixed plaque	Fatty plaque	p
n	94	71	58	-
Age (years)	72.63±8.257	71.31±10.683	64.98±7.812	**<0.001**
Gender (male) (%)	49 (52.1%)	41 (57.7%)	39 (67.2%)	0.188
Hypertension (%)	54 (57.4%)	48 (67.6%)	35 (60.3%)	0.410
DM (%)	18 (19.1%)	24 (33.8%)	18 (31%)	0.079
Smoking (%)	19 (20.2%)	17 (23.9%)	24 (41.4%)	**0.013**
Hemoglobin (gr/dL)	13.300±1.587	13.338±1.539	13.924±1.607	**0.043**
MPV	8.483±1.296	8.248±1.720	8.199±1.505	0.443
RDW	14.286±1.457	14.270±1.798	14.279±2.176	0.998
WBC (x10^3/L)	7.314±1.667	8.362±1.959	8.899±2.567	**<0.001**
Lymphocyte count (x10^3/L)	2.511±0.638	2.175±0.863	2.304±0.800	**0.017**
Neutrophile count (x10^3/L)	3.938±1.241	5.139±1.857	5.861±2.164	**<0.001**
Monocyte count (x10^3/L)	0.552±0.177	0.685±0.168	0.725±0.230	**<0.001**
Platelet count (x10^3/L)	243.45±60.477	242.30±63.528	254.45±56.130	0.457
Glucose (mg/dL)	104.28±31.119	117.46±58.641	121.38±48.560	0.052
Creatinine (mg/dL)	0.891±0.185	0.881±0.216	0.954±0.234	0.105
Total cholesterol (mg/dL)	211.71±40.230	198.06±43.089	188.36±42.791	0.003
LDL cholesterol (mg/dL)	130.05±31.044	120.89±33.450	116.97±34.816	0.041
HDL cholesterol (mg/dL)	49.94±7.377	42.77±10.469	38.52±8.923	**<0.001**
Triglyceride (mg/dL)	167.07±79.581	149.85±73.564	153.76±71.977	0.311
NLR	1.628±0.523	3.142±0.403	2.922±1.952	**<0.001**
MHR	11.200±4.126	16.951±5.935	20.181±9.405	**<0.001**

Data is presented as means ± SD or n (%), SD: Standard deviation, DM: Diabetes Mellitus, HDL: High density lipoprotein, LDL: Low density lipoprotein, MHR: Monocyte count/HDL cholesterol ratio, MPV: Mean platelet volume, NLR: Neutrophil count/lymphocyte ratio, PDW: Platelet distribution width, RDW: Red cell distribution width, WBC: White blood cell

Table 2. Medications taken by patients

	Calcified plaque	Mixed plaque	Fatty plaque	p
n	94	71	58	-
ASA (%)	23 (24.5%)	20 (28.2%)	21 (36.2%)	0.300
Clopidogrel (%)	7 (7.4%)	5 (7%)	3 (5.2%)	0.857
ASA + Clopidogrel (%)	2 (2.1%)	3 (4.2%)	1 (1.7%)	0.622
Statin (%)	18 (19.8%)	19 (26.8%)	15 (25.9%)	0.454

Data is presented as n (%), ASA: Acetylsalicylic acid

Monocyte to high-density lipoprotein cholesterol ratio was found to be higher in fatty and mixed groups (20.181±9.405 vs 16.951±5.935 vs 11.200±4.126, p<0.001). Sensitivity and specificity analysis were conducted with the ROC curve and the respective areas under the curve (AUCs) were used to investigate the predictive value of MHR for prediction of mixed and fatty plaques (Figures 1,2). MHR had 71.8% sensitivity and 56.6% specificity for prediction of mixed plaque [AUC: 0.645, 95% confidence interval (CI): 0.571-0.718, p=0.001]. Moreover MHR had 77.6% sensitivity and 62.4% specificity for prediction of fatty plaque (AUC: 0.746, 95% CI: 0.675-0.818, p<0.001).

Multivariate regression analysis showed MHR was a significant independent predictor of both mixed [odds ratio (OR): 1.230, p<0.001] and fatty (OR: 1.364, p<0.001) plaques in asymptomatic patients with intermediate carotid artery stenosis, after adjusting for other risk factors (Table 3,4).

Table 3. Univariate and multivariate regression analyses of the predictors of mixed carotid plaque morphology

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Age (years)	0.983 (0.948-1.018)	0.336	-	-
Gender (male)	1.255 (0.675-2.335)	0.473	-	-
Hypertension (%)	1.546 (0.812-2.942)	0.185	-	-
DM (%)	2.156 (1.059-4.390)	0.034	1.117 (0.358-3.487)	0.848
Smoking (%)	1.243 (0.592-2.610)	0.566	-	-
Hemoglobin (gr/dL)	1.016 (0.836-1.234)	0.876	-	-
WBC (x10^3/L)	1.324 (1.120-1.564)	0.001	1.736 (0.776-3.881)	0.179
Lymphocyte count (x10^3/L)	0.552 (0.361-0.845)	0.006	1.534 (0.238-9.890)	0.653
Neutrophile count (x10^3/L)	1.716 (1.358-2.170)	<0.001	0.295 (0.093-0.937)	**0.038**
Platelet count (x10^3/L)	1.000 (0.994-1.005)	0.902	-	-
Glucose (mg/dL)	1.008 (1.000-1.016)	0.053	1.005 (0.994-1.017)	0.350
Creatinine (mg/dL)	0.793 (0.167-3.759)	0.770	-	-
Total cholesterol (mg/dL)	0.992 (0.985-1.000)	0.044	1.000 (0.990-1.009)	0.925
NLR	4.158 (2.527-6.839)	<0.001	11.883 (1.656-85.249)	**0.014**
MHR	1.267 (1.171-1.370)	<0.001	1.230 (1.124-1.346)	**<0.001**

DM: Diabetes Mellitus, MHR: Monocyte count/HDL cholesterol ratio, NLR: Neutrophil count/lymphocyte ratio, WBC: White blood cell, CI: Confidence interval

Table 4. Univariate and multivariate regression analyses of the predictors of fatty carotid plaque morphology

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Age (years)	0.913 (0.878-0.949)	<0.001	0.838 (0.782-0.898)	**<0.001**
Gender (male)	1.885 (0.954-3.726)	0.068	-	-
Hypertension (%)	1.127 (0.579-2.195)	0.725	-	-
DM (%)	1.900 (0.891-4.052)	0.097	-	-
Smoking (%)	2.786 (1.349-5.756)	0.006	1.084 (0.344-3.419)	0.890
Hemoglobin (gr/dL)	1.294 (1.042-1.607)	0.020	1.423 (0.992-2.041)	0.055
WBC (x10^3/L)	1.485 (1.243-1.773)	<0.001	0.817 (0.437-1.527)	0.526
Lymphocyte count (x10^3/L)	0.699 (0.451-1.081)	0.108	-	-
Neutrophile count (x10^3/L)	2.060 (1.607-2.640)	<0.001	1.088 (0.409-2.893)	0.866
Platelet count (x10^3/L)	1.003 (0.998-1.008)	0.277	-	-
Glucose (mg/dL)	1.009 (1.001-1.018)	0.026	1.000 (0.989-1.010)	0.982
Creatinine (mg/dL)	3.948 (0.854-18.252)	0.079	-	-
Total cholesterol (mg/dL)	0.986 (0.978-0.995)	0.001	0.990 (0.978-1.002)	0.118
NLR	4.067 (2.470-6.698)	<0.001	7.785 (2.643-22.929)	**<0.001**
MHR	1.341 (1.234-1.457)	<0.001	1.364 (1.219-1.525)	**<0.001**

DM: Diabetes Mellitus, MHR: Monocyte count/HDL cholesterol ratio, NLR: Neutrophil count/lymphocyte ratio, WBC: White blood cell, CI: Confidence interval

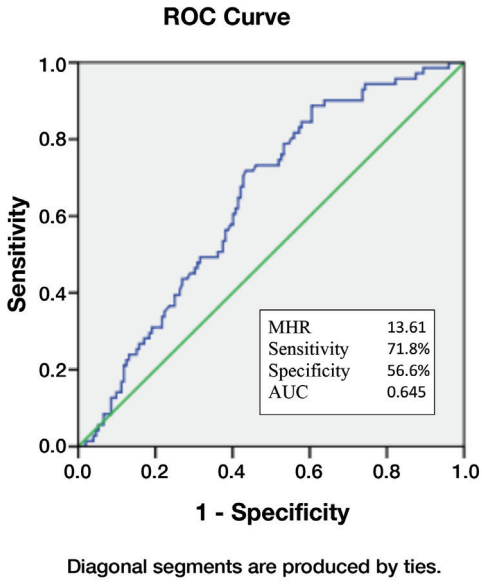

Figure 1. A monocyte/high density lipoprotein ratio (MHR) cut off of 13.61 predicts mixed carotid plaque morphology in patients with 50-70% stenosis of the carotid artery, with a sensitivity of 71.8% and a specificity of 56.6%

ROC: Receiver operating characteristic, AUC: Area under the curve

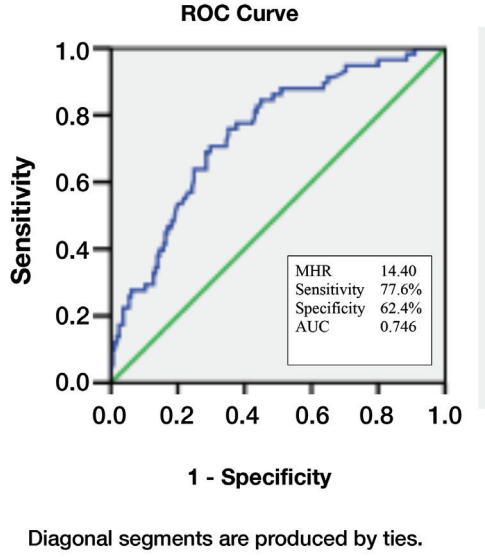

Figure 2. A monocyte/high density lipoprotein ratio (MHR) cutoff of 14.40 predicts fatty carotid plaque morphology in patients with 50-70% stenosis of the carotid artery, with a sensitivity of 77.6% and a specificity of 62.4%

ROC: Receiver operating characteristic, AUC: Area under the curve

Discussion

The main findings of the study were as follows: 1) A raised MHR was found to be significantly higher in asymptomatic 50-70% carotid artery stenosis with mixed and fatty plaques, 2) MHR had moderate sensitivity and specificity to predict mixed and fatty plaques and 3) MHR was found to be a significant independent predictor for mixed and fatty plaques in patients with intermediate carotid artery disease, after adjusting for other risk factors in multivariate analysis.

Atherosclerosis is the main pathological finding in patients with ischemic heart disease and cerebrovascular disease (16). Fibrous cap and necrotic center are two layers of atherosclerotic plaque. Foam cells derived from macrophages are the main cellular component and cholesterol crystals are the main acellular component of the plaque. Monocytes and macrophages provoke atherosclerotic process via cytokine secretion and foam cell formation. Cytokines activate all stages of atherosclerosis, including onset, progression, rupture and thrombus formation (17). Total amount of inflammatory markers were found to have a predictive role for subsequent cardiovascular disease (18,19). Moreover, monocyte count as a progenitor of foam cells was shown to be a predictor of new plaque formation (20).

High density lipoprotein, as an antiatherosclerotic molecule, reverses cholesterol transport from the plaque and inhibits activation, adhesion and infiltration of monocytes (8). Murphy et al. (7) postulated in their study that HDL exerted its effect through CD11b molecule on the surface of monocytes. CD11b is responsible for binding to endothelial cells and migrating from vascular wall.

Monocyte/high density lipoprotein ratio emerges as a combination of these two parameters and reflects the underlying inflammatory process. Previous studies demonstrated that MHR was useful for the diagnosis of subclinical carotid atherosclerosis in diabetics (21) and had a prognostic role for patients with coronary artery disease undergoing percutaneous coronary intervention (22).

Stenosis severity and plaque morphology were detected by CTA in this study. Calcified, mixed and fatty plaque morphology in asymptomatic patients with intermediate carotid stenosis were compared in terms of MHR. Previous studies reported calcified plaque constituted higher smooth muscle and lower intraplaque hemorrhages and fatty content. Hence, this plaque was very stable and was more frequently found in asymptomatic patients compared to patients who had ischemic cerebrovascular event (23). Increased risk of rupture and thromboembolism were demonstrated with fatty plaques in the same study (23).

Another study by Ahmadi et al. (24) found an additional prognostic role of mixed and fatty plaques in symptomatic with nonobstructive coronary artery disease.

Identification of high risk individuals with intermediate carotid artery stenosis for developing symptoms is crucial. Morphological ultrastructure could give substantial information. Although there are studies comparing the morphological status of plaques causing asymptomatic intermediate carotid artery stenosis in terms of inflammatory parameters (22), no clinical study in the literature has evaluated the predictive value of MHR for this purpose. The relation between mixed and fatty plaques and novel inflammatory markers should be definitely set. Our study showed that MHR had a strong predictive role for mixed and fatty carotid plaques in the carotid artery. Taken together with close relationship of these plaques with other inflammatory markers reported in previous studies (25), mixed and fatty plaques are very unstable and put the patient at high risk category. Few patients were taking antiaggregant and statin in our study. Aggressive medical treatment including high dose statins and antiaggregants may be initiated earlier in asymptomatic intermediate carotid stenosis with mixed and fatty plaque morphology. Additionally, early invasive strategy could be taken into consideration for fatty plaques.

Study Limitations

Some limitations of our study are as follows. It was a single center study and performed in the small population. Serial MHR changes were not evaluated because we only measured MHR at baseline. Due to the lack of registration, no comparison was made between inflammatory marker levels such as C-reactive protein with MHR. Moreover, not all comorbidities and environmental factors that might affect inflammatory markers were taken into account.

Conclusion

Monocyte/high density lipoprotein ratio is a marker of inflammation and atherosclerosis. Increased MHR may be one of the factors associated with the presence of fatty and mixed carotid artery plaques that cause asymptomatic intermediate stenosis.

Ethics

Ethics Committee Approval: The study was approved by the local ethics committee with the number 3841 on 06.03.2020 and the study was conducted in accordance with ethical principles described by the Declaration of Helsinki.

Informed Consent: It is a retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.E., Design: A.E., Data Collection or Processing: E.K., Analysis or Interpretation: E.K., Writing: A.E.

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

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ORIGINAL RESEARCH

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Short-term Results of Patients Presented to the Pediatric Emergency Department with Fever

Çocuk Acil Servisine Ateş Şikayeti ile Başvuran Hastaların Kısa Dönem Sonuçları

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Abstract

Objective: The aims of this study were to investigate the general characteristics of the patients who presented to the pediatric emergency department with fever, to determine the relationship between the socio-demographic characteristics of the families and the admission to the emergency department, to investigate the relationship between the treatments administered and the duration of fever reduction, and to evaluate the impacts of fever on the life of the child and the family during the period after admitting to emergency department.

Method: The study group consisted of patients who presented to the pediatric emergency department with the complaint of fever between 5th of March and 31st of May 2009 and whose measured axillary temperature was 38 °C and above. The physical examination of the patients was performed, treatment was arranged in accordance with their diagnoses and the information was obtained from the parents about the socio-demographic characteristics of the families. Parents who were reached after 7-10 days were asked questions about the duration of fever reduction, whether there was a need to apply to another health institution, the methods used to reduce the fever and whether the child attended school.

Results: Two hundred forty five patients were included in the study: however, as 17 parents could not be reached at the controls after 7-10 days, the study was completed using the data of 228 patients. 73.1% of the patients were admitted to our emergency department within the first 24 hours after the onset of fever. A total of 57 patients (23.3%) were prescribed only antipyretic treatment, 181 (73.9%) were prescribed antipyretic and antibiotic treatment, and seven (2.9%) were treated as hospitalized. It was learned that 189 patients (82.8%) had reduced fever while 39 patients (17.2%) were admitted to a health institution again. The school absenteeism rate in children aged 7 years and over was 72.9%.

Conclusion: We think that there should be time for the anxiety reduction and education of patients, who are admitted with fever, and their relatives even in busy emergency departments and we suggest that antibiotic treatment should be reduced, and symptomatic treatment should be given at the first admission.

Keywords: Antibiotic, children, emergency, fever

Öz

Amaç: Çocuk acil servisine ateş şikayeti ile başvuran hastaların genel özelliklerinin incelenmesi, ailelerin sosyo-demografik özelliklerinin acil servise başvuru ile arasındaki ilişkinin saptanması, düzenlenen tedaviler ile ateşin düşme süresi arasındaki ilişkinin araştırılması ve ateşin acil servis başvurusu sonrasındaki dönemde çocuk ve ailenin yaşamına etkilerinin değerlendirilmesi amaçlanmıştır.

Yöntem: Çalışma grubu 5 Mart- 31 Mayıs 2009 tarihleri arasında çocuk acil servisine ateş şikayeti ile başvuran ve ölçülen aksiller ateş düzeyi 38 °C ve üzeri olan hastalardan oluşmaktadır. Hastaların fizik muayeneleri yapılarak, tanılarına uygun tedavileri düzenlenmiş ve ebeveynlerden ailelerin sosyo-demografik özellikleri hakkında bilgiler alınmıştır. Yedi-10 gün sonra ulaşılan ebeveynlere ateşin düşme süresi, bu süreçte başka bir sağlık kuruluşuna başvurup başvurma gereksinimi olup olmadığı, ateşi düşürmek için kullanılan yöntemler ve çocuğun okula devamsızlık yapıp yapmadığı ile ilgili sorular sorulmuştur.

Bulgular: Çalışmaya 245 hasta dahil edilmiş, 7-10 gün sonraki kontrollerde 17 ebeveyne ulaşılamadığı için çalışma 228 hastanın verileri üzerinden tamamlanmıştır. Olguların %73,1'lik kısmı ateş başladıktan sonraki ilk 24 saat içerisinde acil servisimize başvurmuştur. Toplam 57 hastaya (%23,3) sadece antipiretik tedavi reçete edilirken, 181 hastaya (%73,9) antipiretik ve antibiyotik tedavisi reçetelenmiş, yedi hasta (%2,9) ise hastaneye yatırılarak tedavi edilmiştir. Verilen tedavi ile 189 hastanın (%82,8) ateşinin düştüğü, 39 hastanın ise (%17,2) tekrar bir sağlık kuruluşu başvurusu olduğu öğrenilmiştir. Yedi yaş ve üzeri çocuklarda okul devamsızlık durumu ise %72,9 olarak saptanmıştır.

Sonuç: Biz, acil servisi yoğun sağlık kuruluşlarında dahi ateşle başvuran hasta ve hasta yakınlarının kaygılarını giderme ve eğitimi için vakit ayrılması gerektiğini düşünmekte, antibiyotik tedavisinin azaltılıp ilk başvuruda semptomatik tedavi verilmesini önermekteyiz.

Anahtar kelimeler: Acil, antibiyotik, ateş, çocuk

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Introduction

Fever is one of the most frequent complaints that is encountered in children's emergency services. The two major reasons for this are that infectious diseases are seen more frequently in children due to the still-developing immune system in them and that fever in children still remains an important source of fear for their families (1).

Fever is most often caused by simple viral diseases that heal spontaneously. Other causes of fever include serious life-threatening bacterial infections, collagen vascular diseases, neoplastic diseases, acute metabolic disorders or drugs used (2). Parallel to the high frequency of fever, antipyretics and antibiotics constitute the most frequently prescribed medication groups in pediatric age group. Improper use of antibiotics leads to the development of bacterial resistance while imposing an additional burden on the national economy (3,4). In fact, in the United States of America (USA), approximately half of the antibiotics given to children have been reported to be given unnecessarily (5).

The aims of this study were to examine the general characteristics of patients admitted to the children's emergency services in a training and research hospital where the number of daily patient admissions is very high, to determine whether there was a relationship between the socio-demographic characteristics of families and the admission to the emergency room, as well as between the medication and time required to reduce fever and to evaluate the effects of fever on the lives of children and families during the period after admission to emergency service.

Materials and Methods

This study was conducted on 245 patients who aged between 31 days and 18 years and were admitted to Okmeydanı Training and Research Hospital children's emergency services with a complaint of fever and whose axillary fever was 38 °C or above between March 5th and May 31st 2009. Ethics committee approval was obtained from ethics committee of the same hospital before the study. Due to the fact that 17 parents could not be reached for the evaluation between 7 and 10 days after the admission, 228 cases were included in the study. The physical examinations of the patients were performed, and the treatment schedules were arranged according to their diagnoses. Identification information (name-surname, gender, age) of the patients, history of admission to another health institution due to the current fever complaint, information regarding accompanying symptoms and complaints, time period between the onset of fever and the admission to the emergency room, the diagnoses and treatment schedules (antipyretic, oral antibiotics, intramuscular antibiotics, hospitalization), socio-demographic characteristics of families (mother's age, education and employment status, total number of individuals and children living in the family, number of rooms in the house, number of people sharing the room of the patient, smoking status of the family members), whether other family members had fever or any other complaints within past two weeks and whether the patient had a travel history within past two weeks were recorded. Parents were given standard education on the measurement methods of body temperature, methods to reduce fever, and arranged treatments, and they were contacted by phone between 7 and 10 days after the treatment. The time period for the fever to reduce during the existing disease (0-24 hours, 24-48 hours, 48-72 hours, >72 hours), whether they were readmitted to a health institution during the same disease condition, methods applied to reduce the fever and school absenteeism due to this particular disease were questioned.

Statistical Analysis

Number Cruncher Statistical System (NCSS) 2007 & Power Analysis Sample Size (PASS) 2008 Statistical Software (Utah, USA) was used for the statistical analysis for the evaluation of the results. Besides descriptive statistical methods for the data (mean, standard deviation, frequency), the Kruskal-Wallis test was employed to analyze quantitative data. Qualitative data were analyzed by the chi-square test. 95% confidence intervals were calculated and a p-value lower than 0.05 was considered as statistically significant.

Results

One hundred thirty one (53.5%) of our patients were male and 114 (46.5%) were female. The mean age of the cases was found to be 59±46.78 months. During the admission, the body temperature of the cases ranged between 38 and 40.5 °C and the mean body temperature was 38.85±0.53 °C. The number of daily patient admissions to the hospital with fever complaints ranged between 1 and 5 (mean =1.13±0.46, median =1). The time between the onset of fever and admission to the emergency service was between 0 and 12 hours in 98 patients (40%), between 12 and 24 hours in 81 patients (33.1%), between 24 and 48 hours in 34 patients (13.9%), between 48 and 72 hours in 22 patients (9%), and 72 hours and above in 10 patients (4%).

While there were no additional complaints accompanying fever in 43 cases (18%), 98 patients (40%) reported one accompanying complaint, 67 patients (27.3%) had two accompanying complaints, 36 patients (14.7%) had three or more accompanying complaints. Additional complaints accompanying fever are listed in Table 1 and the diagnoses made in our patients are listed in Table 2.

The mean age of the mothers participated in the study was 31.05±6.36 years (minimum-maximum =18-50). Of the mothers, 13 (5.3%) were illiterate, 150 (61.2%) were primary school, 27 (11%) were secondary school, 43 (17.6%) were high school and 12 (4.9%) were university graduates. While 194 (79.2%) of the mothers were housewives, 51 (20.8%) were working. The average number of adults living at home was 2.40±0.98 (minimum-maximum =1-8 and median =2). The average number of children living at home was 2.02±0.98 (minimum-maximum =1-7 and median =2). The total number of people living at home varied between three and 12, with an average of 4.43±1.45 and a median of four infants. The number of rooms in the house ranged between one and six, with an average of 3.14±0.71 and a median of three rooms. The number of individuals with whom the child shared his/her room ranged between zero and six, with an average of 1.44±0.96 and a median of one. Seventy-four of the mothers (30.2%) stated that there was an individual who had fever in the past two weeks in the family, and 76 mothers (31%) stated they had an individual with a complaint other than fever in the last two weeks. Travel history was stated in twenty-three (9.4%) families in the last two weeks. There were smokers in one hundred and forty-two families (58%), while there were no smokers in 103 families (42%).

Table 1. Distribution of additional symptoms that accompany fever

	n	%
Cough	67	27.3
Vomiting	48	19.6
Abdominal pain	36	14.7
Sore throat	36	14.7
Weakness	31	12.6
Headache	26	10.6
Anorexia	23	9.4
Diarrhea	22	8.9
Nasal flow	20	8.2
Nausea	16	6.5
Leg pain	7	2.8
Nasal congestion	4	1.6
Earache	4	1.6
Wheezing	2	0.8
Unrest	2	0.8
Dyspnea	2	0.8
Oral aphthae	1	0.4
Constipation	1	0.4
Eruption	1	0.4

Table 2. Diagnoses

	n	%
AVURI	56	22.9
Acute tonsillitis	147	60
Acute sinusitis + AOM	10	4.1
Pneumonia	13	5.3
Meningitis	3	1.2
Acute bronchitis	1	0.4
UTI	6	2.4
AGE	7	2.9
Bacteremia	2	0.8

AVURI: Acute viral upper respiratory infection, AOM: Acute otitis media, UTI: Urinary tract infection, AGE: Acute gastroenteritis

We provided 57 patients (23.3%) with only antipyretic treatment, 92 patients (37.6%) with antipyretic and oral antibiotic treatment, and 89 patients (36.3%) with antipyretic and intramuscular antibiotic treatment, and seven patients (2.9%) were hospitalized and treated. Seven to 10 days later, 189 of the parents (82.8%) that were reached by phone stated that their children's fever decreased with the treatment given, and 39 parents (17.2%) indicated that they required to apply to a health institution again. Among these, treatment schedule was not changed in 19 patients (48.7%) (12 of the patients were in another institutions while seven of the patients were in the same institution). Ten patients (25.6%) were given antipyretic treatment in addition to the ongoing antibiotic treatment (seven of them were in another institutions while three of them were in same institution), while in 10 patients (25.6%), antibiotic treatment schedule was altered (in seven patients the antibiotic that was given was changed into another antibiotic and in three patients, antibiotic administration route was changed to intramuscular administration). Considering the duration of fever to reduce, fever was reduced within the first 24 hours in 82 children (35.9%), within 24-48 hours in 85 children (37.2%), within 48-72 hours in 49 children (21.4%), and over 72 hours in 12 children (5.2%). The data regarding the follow-up controls that were performed after seven to 10 days later are indicated in Table 3 and alterations in treatment are given in Table 4.

In this study, no statistically significant relationship was found between the educational status of the mother and the time between the onset of fever and admission to the emergency service, as well as no significant relationship between the educational status of the mother and time required for fever to reduce (p>0.05). There were no statistically significant relationships between the treatment given and the time to fever to reduce or the duration of additional complaints to alleviate (p>0.05). On the other hand, a statistically significant relationship was found between the treatment given and the presence of additional treatment, that is, the requirement of the admission to another health institution (p<0.01). It was observed that children who were treated only with antipyretics were admitted to another health institution more often. There was no statistically significant difference between the duration of fever to reduce and the number of people living at home (p>0.05). There was no statistically significant relationship between pre-diagnosis and duration of fever to reduce (p>0.05).

Table 3. Findings detected in controls after 7-10 days

		n	%
Time to reduce fever	0-24 hours	82	36
n=228	24-48 hours	85	37.3
	48-72 hours	49	21.5
	>72 hours	12	5.3
Time to reduce accompanying symptoms	0-24 hours	39	20.7
	24-48 hours	60	31.9
n=188	48-72 hours	34	18.1
	>72 hours	55	29.3
	Not	19	27.1
	1 day	13	18.6
School absenteeism period	2 days	14	20
n=70	3 days	11	15.7
	≥4 days	13	18.6
Peripheral cooling	+	84	36.8
n=228	-	144	63.2

Discussion

In the list of "distribution of the diseases in children within the last six months", which included the infants aged between zero and six years and was released in 2012 by Turkey Statistics Institute, revealed that the three most common diseases that could be seen along with fever were diarrhea, upper respiratory tract infections such as tonsillitis, pharyngitis and otitis media, and infectious diseases such as chickenpox (6). In the study conducted by Halıcıoğlu et al. (7), the most common etiological causes in children admitted to the emergency service due to fever were found to be respiratory infections and gastroenteritis. In our study, we found acute viral upper respiratory tract infections and upper respiratory tract infection diseases such as tonsillitis, sinusitis and otitis media as the highest disorders with a rate of 87% among the patients who were admitted to our emergency service. It is noteworthy that the majority of our patients were male in accordance with other studies (8).

In our study, we observed that 73% of the patients were admitted to the emergency room within the first 24 hours after the onset of fever. This might have resulted from that patients did not know the role of fever in the follow-up of the disease and the methods to reduce the fever, as well as the fact that they still saw the fever as an anxious condition (9,10). In a study by Poirier et al. (11), people caring for children responded to a question about why they were afraid of fever as "due to risk of convulsion (32%), risk of death (18%) and risk of brain damage (15%)". It can be

Table 4. Treatment schedule

		Treatment			
		Antipyretic	**Antipyretic + oral antibiotics**	**Antipyretic + i.m. antibiotics**	**Hospitalized**
7-10 days after controls	Not	36	75	70	7
	Application to different health institutions, no treatment changes	3	4	5	0
	Application to different health institutions, antibiotics were given	10	0	0	0
	Application to different health institutions, different antibiotics were given	0	1	7	0
	Application to our hospital, no treatment changes	3	1	3	0
	Application to our hospital, i.m. transition to antibiotic administration	3	0	0	0

thought that this situation can be reduced by increasing the education levels of the people who care for the child, in the conditions of our country, the educational levels of mothers. However, in our study, we could not find a statistically significant relationship between the educational status of the mother and the time period between the onset of fever and admission to the emergency service ($p>0.05$). In the study conducted by Şen Celasin et al. (8), it was found that there was no statistically significant relationship between the education status of the mother and the period during which the child stayed with fever. Bertille et al. (12), in their studies, found that as the education level of the parents increased, the rates of admission to the emergency services increased. All these results can suggest that regardless of the educational background, the anxiety experienced by mothers for their children is similar. Moreover, in our study, no statistically significant relationship was found between the educational status of the mother and the time required for fever to reduce ($p>0.05$).

According to the 2008 data of the Child Emergency and Intensive Care Association, 30% of all emergency admissions in our country was constituted by admissions to the child emergency services (13). The child emergency service in our hospital is a tertiary child emergency unit that serves families with different sociocultural characteristics in a wide region. According to the data of the Ministry of Health in 2017, it served approximately 180,000 patients within the first nine months of the year (14). It is pleasing for us that the fever of 82% of the patients who were admitted to our emergency service with a fever complaint reduced with the treatment given by us and they did not need to apply to another health institution. Moreover, it was observed that the treatment schedule of approximately 50% of the patients who applied to the health institution for the second time was not altered. However, the fact that the rate of antibiotic prescription was as high as 74% was also very thought-provoking. Although upper respiratory tract infections that do not require antibiotics are common in children, studies still show that children have been prescribed antibiotics at high rates for these diseases (15,16). Among the drugs prescribed to outpatients in our country, antibiotics maintain their first place (17,18). We think that one of the reasons for the high rate of antibiotic prescription in our study was that rapid diagnostic tests for streptococcal infections and diagnostic tests that detected specific viral pathogens such as influenza were not initiated to be used during the study period. We did not find a statistically significant relationship between the treatment given in our study and either the time required for fever to reduce or the period of reduction of additional complaints ($p>0.05$). However, there was a significant relationship between the treatment given and receiving additional treatment, that is, re-applying to a healthcare institution ($p<0.01$), and this was particularly high in the antipyretic treatment group. Despite this, we think that the first treatment option should be tried as antipyretic because there was no association between the type of treatment and time required for fever to reduce as observed for the antipyretic group and the antipyretic and antibiotic combinatorial treatment group.

For their children with fever, it is known that mothers perform a number of traditional practices including removing the children's clothes, making lukewarm shower or making lukewarm application and wiping the body with substances such as water with vinegar. Removing clothes of children is not effective in reducing fever by itself. Making lukewarm application is effective in reducing fever; however, it cannot maintain its fever reducing effect for as long as antipyretics (19). Nevertheless, such methods are also performed by medical staff on the patients who are admitted to emergency services. In our study, we found that 36% of the mothers performed the peripheral cooling (making lukewarm shower and making lukewarm application) to reduce the fever of their children.

An effect of fever on the lives of the family and the child was on education. In our study, among the children aged seven years and over, we found that 19 children (27.1%) did not have school absenteeism, while 51 children (72.9%) was absent from school at least for one day. In the questionnaire named "Assessment of the reasons of absenteeism of students according to student opinions", which was conducted by Şanlı et al. (20), for the question of "Could you provide your reasons for absenteeism?", 42.86% of the students answered as an acute or a chronic disease. This reminds us again how much precautions are necessary before the disease occurs.

Study Limitations

First of all, our study was a prospective study with a limited number of patients but was conducted in a restricted time period. Moreover, although the body temperature measurements performed at the first admission of the patients to the emergency service were reliable, mothers were trusted in the home measurements, numerical data were not requested, and the time for fever to reduce and the time for the alleviation of additional complaints were evaluated subjectively according to the mother's responses. In addition, although the date that the study

was conducted was years ago, the data was re-evaluated over the new sources in the discussion. As of the study period, the limitations of microbiological diagnostic tools led to inability to prove the patient's diagnosis in terms of laboratory results. Today, when considering that emergency services are more advanced than they were on the date of the study, updating data with new studies will contribute more to the literature.

Conclusion

Fever is still one of the most common complaints among patients admitted to pediatric emergency services. Regardless of their educational status, it also has an ominous feature for all parents. In order to overcome this situation, it is necessary to teach parents about the methods to measure body temperature, to reduce fever and the follow-up fever management with better education programs. It is clear that managing situations regarding fever well will have a positive impact on the child's educational life. Our duty as physicians should be to decrease the frequency of antibiotic prescription. This may be possible by trying antipyretic treatment option before antibiotics in the cases of fever.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from ethics committee of the same hospital before the study.

Informed Consent: The informed consents of patients were approved by their parents.

Peer-review: Externally and internally peer-reviewed.

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ORIGINAL RESEARCH

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Retrospective Evaluation of the Clinical Findings and Bone Mineral Densitometry Results of Children with Celiac Disease

Çölyak Hastalığı Olan Çocukların Klinik Bulguları ve Kemik Mineral Dansitometri Sonuçlarının Retrospektif Olarak Değerlendirilmesi

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Abstract

Objective: Children diagnosed with Celiac disease should be closely followed-up for osteoporosis that may develop. We aimed to evaluate the osteoporosis conditions through bone densitometry in patients with the diagnosis of celiac disease, who were given a strict gluten-free diet.

Method: The complaints at the time of admission, anthropometric data, laboratory findings at the time of admission, laboratory findings after gluten-free diet and bone densitometer results of 80 patients, who were followed-up at the pediatric gastroenterology outpatient clinic of our hospital and diagnosed with Celiac disease, were retrospectively investigated.

Results: The study was conducted between December 2015 and February 2016 with patients diagnosed with Celiac disease. The study was conducted with a total of 80 cases, 31 (38.8%) boys and 49 (61.3%) girls. The mean age of the cases was 10.01±4.75 years. While the most common symptoms of the cases with gastrointestinal system findings were abdominal pain and diarrhea, the most common findings apart from the gastrointestinal system were growth and developmental delay and anemia. In our study, the frequency of osteoporosis was 14%.

Conclusion: In our study, it is shown that the majority of children diagnosed with Celiac disease apply to the hospital with findings apart from the gastrointestinal system or asymptomatically. It is important to carefully question the non-gastrointestinal system findings of the disease. Requesting Bone Mineral Densitometry in the follow-up of Celiac disease is an important marker for diagnosis and increase in length of patients with osteoporosis.

Keywords: Celiac disease, child, osteoporosis

Öz

Amaç: Çölyak hastalığı tanısı almış çocuklar, gelişebilecek osteoporoz açısından yakın takipte olmalıdır. Çölyak tanısı almış ve sıkı glutensiz diyet başlanan çocukların kemik dansitometre ile osteoporoz durumları değerlendirilmesi amaçlanmıştır.

Yöntem: Hastanemiz çocuk gastroenteroloji polikliniğinden takipli Çölyak hastalığı tanısı olan 80 çocuğun başvuru yakınmaları, antropometrik verileri, başvuru sırasındaki laboratuvar bulguları ile glutensiz diyet sonrası bakılan laboratuvar bulguları ve kemik dansitometre sonuçları retrospektif olarak araştırıldı.

Bulgular: Çalışma Aralık 2015 ve Şubat 2016 tarihleri arasında hastanemizde Çölyak hastalığı tanılı hastalar ile yapılmıştır. Çalışma 31'i (%38,7) erkek, 49'u (%61,3) kız toplam 80 olgu ile yapılmıştır. Olguların yaş ortalaması 10,01±4,75 yıldı. Gastrointestinal sistem bulguları olan olguların en sık semptomu karın ağrısı ve ishalken, gastrointestinal sistem dışı en sık görülen bulgular büyüme gelişme geriliği ve anemi olmuştur. Çalışmamızda, osteoporoz sıklığı %14 olarak saptanmıştır.

Sonuç: Çalışmamızda Çölyak hastalığı tanısı almış çocukların çoğunluğunun gastrointestinal sistem dışı bulgularla hastaneye başvurdukları veya asemptomatik oldukları gösterilmektedir. Hastalığın gastrointestinal sistem dışı bulgularının dikkatle sorgulanması önemlidir. Çölyak hastalığı takibinde Kemik Mineral Dansitometre istenmesi osteoporoz olan hastaların tanı alması ve boy uzaması açısından önemli bir belirteçtir.

Anahtar kelimeler: Çocuk, Çölyak hastalığı, osteoporozis

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Introduction

Celiac disease (CD, gluten enteropathy) is a proximal small bowel disease developing as permanent intolerance against gluten in wheat, and gluten-like and other grain proteins in grains such as barley, rye, oats in genetically susceptible people. Gluten sensitive enteropathy is also called celiac ''sprue'' (non-tropical sprue) (1). Although the disease is known as an enteropathy, it has become a disease of every system with the findings of the extra-gastrointestinal system that were revealed in recent years.

Gluten is a protein found in wheat and other grains, and it causes the disease with its prolamin part that can be dissolved in alcohol. Peptide sequences rich in glutamine and proline in the gliadin are responsible for gluten toxicity (2,3). It is known that mucosal damage occurs due to the overstimulation of cellular and humoral immunity and interferon gamma produced by gluten-specific T cells is activated in gluten enteropathy (4).

Most patients have an atypical or silent clinical course (1-5). The disease is diagnosed with biopsy findings of intraepithelial lymphocyte increase, crypt hyperplasia and villus atrophy in the small intestine mucosa (5). It is important to detect antigliadin antibody, anti-tissue transglutaminase antibody, and/or anti-endomysium antibody (IgA-EmA) in the first step of diagnosis. After the diagnosis, the antibody levels are expected to decrease or disappear completely with a strict gluten-free diet. This is important for follow-up.

The clinical course of CD can be quite different and variable. The gastrointestinal (GIS) tract and non-GIS symptoms of CD are mostly due to absorption disorder developed in the proximal small intestine. Fatty, dull-looking, more frequent and abundant stool is the most important finding of this pathology. However, typical symptoms such as diarrhea and abdominal distention in infants are becoming less common. In addition, even patients with very mild findings can be diagnosed with serological tests. According to current data, it should be noted that there are 5-7 undiagnosed celiac patients for every patient diagnosed (6). The detection of large number of asymptomatic cases from symptomatic cases through community screening has caused the disease to be compared to the "iceberg" model (7).

In this study, the admission complaints, laboratory data at the time of diagnosis and serological test results of the patients, who were followed up in pediatric gastroenterology outpatient clinic, were evaluated. Additionally, laboratory results of the patients in the period after the diet and bone densitometry results in terms of osteoporosis were evaluated.

Materials and Methods

This retrospective study was conducted at University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, in the Pediatric Gastroenterology Outpatient Clinic, with Celiac patients. The study was approved by the Ethics Committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital on 23.02.15 with decision no: 2015/04/02. In the study, patients' complaints upon admission to the Pediatric Gastroenterology Outpatient Clinic, clinical findings, laboratory data and bone densitometer values were scanned from the patients' files. The study was conducted between December 2015 and February 2016 and the files of 80 patients were examined retrospectively. Patients who were not examined in our hospital and had no results in their files were excluded from the study. The waiver of consent was not required due to the retrospective design of the study.

Anthropometric measurements of patients were examined with the Endo C program. Standard deviation score (SDS) calculations of patients' height, weight and body mass index values were obtained. Tests of all patient were performed in the same laboratory and at similar times. Bone densitometry measurements of patients (n=55) were performed on the same device.

Patients' bone densitometry (BMD) measurements were obtained considering age. The results of the patients were adjusted according to patients' age and ethnicity. Since the z-score cannot be obtained in patients who are 4 years old and under, patients in this age group were not included in the bone densitometer measurement. Twenty five patients were under the age of 4 years so we had 55 patients' BMD results.

Statistical Analysis

Statistical analysis was conducted using NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. In addition to descriptive statistical methods (mean ± standard deviation) used to evaluate the data, the study utilized in dependent t-test to compare binary groups and the chi-square test to compare qualitative data. The results were evaluated according to significance level of $p<0.05$.

Results

Eighty patients aged between 1 and 18 years were included in the study; 31 (38.7%) were boys and 49 (61.3%) were girls. The mean age of patients was 10.01±4.75 years. Complaints of patients began between 20 months and 16 years with an average of 6.33±4.63 years.

The patients were divided into three groups according to their symptoms. While 45% of the cases had non-GIS symptoms, 13.75% of the cases were asymptomatic. The most common non-GIS findings in patients were growth and developmental retardation and anemia. In the cases with GIS findings (%41.25), 11.25% had abdominal pain and 7.5% had diarrhea. Other admission complaints and findings were 6.25% constipation, 6.25% abdominal swelling, 6.25% vomiting, and 3.75% reflux (Table 1).

In the follow-up of CD, the height SDS value in patients who had become anti-endomysium antibody negative after gluten-free diet was found to be significantly higher than patients who had not yet become celiac antibodies negative (Table 2).When the results of bone densitometry according to the IgA-EmA negativity of the patients were examined, 6 patients with osteoporosis were IgA-EmA negative and 2 patients were IgA-EmA positive (Table 2).

Table 1. Distributions of the complaints

	n	%
▪ GIS symptoms		
Constipation	5	6.25
Vomiting	5	6.25
Abdominal pain	9	11.25
Abdominal swelling	5	6.25
Diarrhea	6	7.5
Reflux complaints	3	3.75
Total	33	41.25
▪ Non-GIS symptoms		
Growth and developmental retardation	21	26.25
Iron deficiency anemia	11	13.75
Hypertransaminasemia	3	3.75
Cholelithiasis	1	1.25
Total	36	45
▪ Asymptomatic patients		
Celiac in sister/brother	3	3.75
Type 1 DM	6	7.5
Chronic disease	2	2.5
Total	11	13.75

GIS: Gastrointestinal, DM: Diabetes Mellitus

Calcium, phosphorus, alkaline phosphate bone isoenzyme and Parathormone (PTH) measurements of the cases (included only 55 patients who have BMD results) were not statistically significant according to the bone densitometry status (Table 3).

The frequency of osteoporosis was 14% (n=8) of the study (55 patients had BMD results). 87% of patients with osteoporosis had vitamin D deficiency. While there was no correlation between Alkaline Phosphate Bone Isoenzyme increase and vitamin D deficiency, there was a significant relationship between Alkaline Phosphate Bone Isoenzyme and PTH. The weight SDS and height SDS values of patients with normal bone densitometry were significantly higher than those whose bone densitometry revealed osteopenia and osteoporosis (Table 4).

Discussion

Celiak Disease is an enteropathy triggered by the consumption of gluten-containing wheat, barley, rye and oat foods and formed by an immune mechanism. The disease is more common in women than in men. In our study, including 38.7% boys and 61.3% girls, the disease was found to be more common in girls. According to our study, the average age of the onset of thebcomplaints in patients was 6.33±4.63 years, which was attributed to the widespread screening and diagnosis of atypical patients.

Celiac patients can have GIS findings or non-GIS findings or they can be completely asymptomatic. Celiac patients are referred to hospitals with GIS related findings such as diarrhea, fatty stool, abdominal pain, abdominal distention and constipation due to malabsorption. However, almost half of the patients are referred to hospitals with extraintestinal and atypical findings such as anemia, osteoporosis, short stature, growth and developmental retardation, hypertransaminasemia, and neurological problems (8). In a study conducted by Akay Hacı et al. (9) in 2015, 58.3% of the cases had non-GIS findings. Similarly, in our study, 41.25% of the cases presented with gastrointestinal findings and 45% with non-gastrointestinal findings, while 13.75% of the cases were found to be asymptomatic. Ertekin et al. (10) and other studies found that the most common complaint was the developmental reterdation. The most frequent complaint in our study was growth retardation (26.25%) and respectively iron deficiency anemia (13.75%) and abdominal pain (11.25%).

In asymptomatic patients presenting with atypical symptoms, iron deficiency anemia, high liver enzyme

Table 2. Evaluation of bone densitometry results about IgA-EmA negative status

After diet		IgA-EmA status		p
		Currently (+) (n=43)	Currently (-) (n=37)	
Weight SDS	M ± SD	-1.03±1.24	-0.74±1.39	[c]0.324
	Min-max (Median)	-4-1.10 (-1)	-3.9-1.8 (-0.60)	
Height SDS	M ± SD	-1.33±1.21	-0.72±1.25	[c]0.031*
	Min-max (Median)	-3.6-1 (-1.3)	-3.5-2 (-0.9)	
BMI SDS	M ± SD	-0.20±1.01	-0.37±1.55	[c]0.569
	Min-max (Median)	-1.8-1.9 (-0.20)	-5.-2.3 (-0.20)	
		n (%)	n (%)	
Bone densitometry	Normal	13 (46.4)	15 (55.6)	[f]0.114
	Osteopenia	13 (46.3)	6 (22.2)	
	Osteoporosis	2 (7.1)	6 (22.2)	

[c]:Student's t-test, [f]:Fisher Freeman Halton test, *: p<0.05, IgA-EmA: Anti-tissue transglutaminase antibody-anti-endomysium antibody, M: Mean, SD: Standard deviation, Min: Minimum, Max: Maximum, SDS: Standard deviation score, BMI: Body mass index

Table 3. Evaluation of laboratory results according to bone densitometer results

		Bone densitometry results			p
		Normal (n=28)	Osteopenia (n=19)	Osteoporosis (n=8)	
Calcium (mg/dL)	M ± SD	10.21±1.86	9.68±0.60	10.06±0.81	[g]0.547
	Min-max (Median)	8.1-19 (9.8)	8-10.4 (9.85)	9.1-11.2 (10.1)	
Phosphorus (mg/dL)	M ± SD	4.53±0.49	4.41±0.74	4.31±0.79	[g]0.276
	Min-max (Median)	3.4-5.1 (4.65)	3.2-6.5 (4.2)	3.4-5.8 (4.2)	
Alkaline phosphate (bone isoenzyme) (U/L)	M ± SD	131.68±52.49	98.58±49.69	126.88±45.19	[g]0.205
	Min-max (Median)	39-258 (116.5)	16-182 (105)	60-179 (135.5)	
PTH (pg/mL)	M ± SD	37.08±12.44	39.39±15.44	53.90±30.30	[g]0.326
	Min-max (Median)	17-68 (33)	16-81 (35.5)	23-116 (46.5)	
Vitamin D (ng/mL)	M ± SD	25.58±23.34	27.26±21.25	19.99±10.22	[g]0.755
	Min-max (Median)	3-128 (21)	3.7-98 (22.7)	7-39 (19.7)	

[g]:Kruskal-Wallis test, M: Mean, SD: Standard deviaton, Min: Minimum, Max: Maximum, PTH: Parathormone

Table 4. Evaluation of weight SDS, height SDS, BMD SDS results according to bone densitometer results

		Bone densitometry results			p
		Normal (n=28)	Osteopenia (n=19)	Osteoporosis (n=8)	
Weight SDS	M ± SD	-0.39±0.89	-1.23±0.86	-1.53±1.40	[g]0.009**
	Min-max (Median)	-2.1-1.1 (-0.45)	-2.6-0.5 (-1.25)	-3.9- -0.3 (-1)	
Height SDS	M ± SD	-0.40±1.09	-1.51±1.04	-1.56±0.95	[g]0.003**
	Min-max (Median)	-2.1-2 (-0.35)	-3.6-0.6 (-1.3)	-3.1- -0.6 (-1.25)	
BMD SDS	M ± SD	-0.23±1.34	-0.52±0.83	-0.83±1.38	[g]0.265
	Min-max (Median)	-5-1.5 (-0.10)	-1.6-1 (-0.6)	-3.5-0.5 (-0.5)	

M: Mean, SD: Standard deviation, SDS: Standard deviation score, BMD: Bone densitometry, Min: Minimum, Max: Maximum

levels, cholelithiasis cases, and CD should be kept in mind in the differential diagnosis and necessary serological tests should be requested (11).

Development retardation and short stature in CD are thought to originate from nutritional deficiencies, low serum somatomedin activity, and defects in growth hormone release (12). Patients catch up to their peers by gaining height and weight in a short time with a strict gluten-free diet. For this reason, CD should definitely be considered in differential diagnosis when approaching a short child. It is important to suspect CD and make an

early diagnosis for the growth and development of patients. According to our study, a strict gluten-free diet created a significant difference in the height of the patients with CD and IgA-EmA negativity was found to be a significant parameter in terms of height growth in Celiac patients.

Although it was said that there was an improvement in the bone mineral densitometer in the first year after a gluten-free diet, Margoni et al. (13) found lower bone densitometry even in the second year of the gluten-free diet. Although Kuloğlu et al. (14) and other pediatric studies found that there was a slight increase in the first year after gluten-free diet, it was revealed that Celiac patients might have lower bone densitometry than normal individuals despite normal diet and negative antibodies.

In untreated patients, the BMD was found to be lower than in normal individuals and rapidly returned to normal with a strict gluten-free diet therapy. In the study conducted by Kondolot et al. (15) in 2009, 22% of 41 celiac patients who had BMD measurements had osteopenia, 12.2% had osteoporosis, and rickets were found in two patients (14.3%). In the study of Tau et al. (16) on 24 celiac patients aged 1 to 11 years, BMD measurement of the patients diagnosed with z-score values was found to be quite low. In this study, 17% had osteoporosis (Z score was below -2 standard deviation). Zanchi et al. (17) stated that osteopenia was detected at the rate of %18 in dual energy X-ray absoptiometry screening in 54 celiac children without treatment. Similarly, in our study, osteopenia was found in 34% of cases and osteoporosis was found in 14%.

The most important point here is that it is known that patients diagnosed with CD are more at risk in terms of vitamin D deficiency compared to the normal population and vitamin D level and BMD measurement of these patients should be followed closely.

Scotta et al. (18) showed that patients with prepubertal diagnosis might have a significant improvement in bone mineral densitometry. However, the diagnosis in the postpubertal period has been proven by studies to have no significant effect on bone mineral densitometry. Turner et al. (19) did not find a significant difference in BMD in asymptomatic and symptomatic patients.

In CD, the only effective treatment of which is a life-long gluten-free diet, no negative effects of the gluten-free diet were encountered in the long term (20). Morbidity and mortality increase significantly in patients that are not on diet, GIS symptoms improve with gluten-free diet, height and weight reach the expected level, hematological and biochemical parameters come to normal limits. In asymptomatic Celiac patients, feeling of physical and psychological well-being has been reported with gluten-free diet therapy. In addition, according to the studies conducted, an improvement in bone mineralization was detected in patients with prepubertal diagnosis. Patients who follow a strict gluten-free diet or have limited gluten intake may have osteoporosis in the years to come, as well as osteopenic or normal.

Obviously, our study has strengths and weaknesses. The limitations of our study arise mainly from the small number of patients and the variation in final follow-up determination time-points. In spite of these limitations, the results of this study strongly suggest that diagnosis and treatment are made before puberty, thereby preventing osteopenia in adult life. In addition, daily calcium and protein intake are not the same in every child with CD.

Studies have not yet been sufficient to determine the minimal amount of gluten that will cause osteoporosis. The mechanism of vitamin D deficiency causing osteoporosis, increased PTH levels, decreased intestinal calcium absorption and other parameters on bone mechanism have not been fully clarified.

Conclusion

In summary, our findings and other studies suggest that it is important to carefully question the non-GIS findings of the disease, such as growth retardation, anemia, shortness, and osteoporosis. In cases where CD is suspected, complaints at admission must be taken into consideration. Early diagnosis in CD prevents serious complications such as osteoporosis. If timely recognized and treated, the disease prognosis is good.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital on 23.02.15 with decision no: 2015/04/02.

Informed Consent: The waiver of consent was not required due to the retrospective design of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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ORIGINAL RESEARCH

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Association of Cervical Screening Results with Colposcopic Findings

Servikal Tarama Sonuçlarının Kolposkopik Bulgular ile İlişkisi

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Abstract

Objective: Cervical cancer is the fourth most common female cancer. In addition to early cancer diagnosis, the screening strategy of cervical cancer is based on early diagnosis of precancerous lesions [high-grade cervical lesions (HSIL)] to prevent cancer progression. The evaluation of clinical findings is very important for the monitoring and further modifications of the present cancer screening programs. This study aimed to review the relationship between the admission characteristics, human papilloma virus (HPV) types, Papanicolaou smear results and the colposcopic diagnoses of the patients who were referred for colposcopy.

Method: The characteristics and colposcopic diagnoses of 420 patients who were referred to a University Hospital between the years of 2016 and 2018 upon the detection of high-risk-HPV DNA positivity were evaluated retrospectively. The clinical properties, colposcopic findings, and sociodemographic features of the patients with HSIL and cancer were obtained through the file records.

Results: During the study period, 21 patients with carcinoma *in situ* and/or cancer and 131 patients with HSIL had been diagnosed. When the patients with HSIL were analyzed, it was found that 76.3% (n=100) of the patients had HPV type 16 and/or 18 positivity, and 23.7% (n=31) of the patients had other types of high risk HPV positivity. Besides, it was observed that smear results were negative in approximately half of the cases (n=57, 50.9%). When different triage options to detect HSIL and above lesions were compared between each other, the highest sensitivity value (92.11%) and the highest negative predictive value (84.21%) were obtained by the triage of the patients with HPV 16 and/or 18 positivity and/or ASC-US and above. It was also observed that cytology alone was the triage method with the lowest sensitivity (30.92%).

Conclusion: The results of the present study were compatible with the data of the current national cervical cancer screening program. Referring patients with HPV 16/18 and/or abnormal cytology to detect HSIL is a highly sensitive triage method. However, it should be considered that, even in this triage method, approximately 8% of the cases can be missed.

Keywords: Cervical cancer, human papilloma virus, screening, triage

Öz

Amaç: Serviks kanseri en sık görülen dördüncü kadın kanseridir. Serviks kanserinin tarama stratejisi, erken kanser tanısına ek olarak kansere progresyonun önlenmesi amacıyla prekanseröz lezyonların [yüksek dereceli servikal lezyonlar (HSIL)] erken tanısı temelinde oluşturulmuştur. Klinik bulguların değerlendirilmesi, kanser tarama programının monitorizasyonu ve gelecekteki modifikasyonlar için oldukça önemlidir. Bu çalışmada kolposkopi için refere edilen hastaların başvuru özellikleri, insan papilloma virüsü (HPV) tipleri ve Papanicolaou smear sonuçları ile kolposkopik değerlendirme bulguları arasındaki ilişkinin değerlendirilmesi amaçlanmıştır.

Yöntem: 2016-2018 yılları arasında yüksek riskli HPV DNA pozitifliği saptanması üzerine bir üniversite hastanesine refere edilen toplamda 420 hastanın başvuru özellikleri ve kolposkopik tanıları retrospektif olarak değerlendirildi. HSIL ve kanser saptanan olguların sosyodemografik ve klinik özellikleri ile kolposkopi bulgularına dosya kayıtları üzerinden ulaşıldı.

Bulgular: Çalışma süresince hastaların 21 tanesinde kanser ya da karsinoma *in situ*, 131 tanesinde HSIL saptandı. HSIL saptanan olgular incelendiğinde, hastaların %76,3'ünde (n=100) HPV tip 16 ve/veya 18 pozitif olduğu ve hastaların %23,7'sinde (n=31) ise diğer yüksek riskli HPV pozitifliği olduğu izlendi. Yine bu olguların Pap smear sonuçları incelendiğinde olguların yaklaşık yarısında (n=57, %50,9) smear sonucunun negatif olduğu izlendi. Kolposkopi için yönlendirilen tüm hastalarda, HSIL ve üzeri lezyonları yakalamak amacıyla uygulanabilecek diğer triyaj yöntemleri birbirleri ile karşılaştırıldığında; en yüksek sensitivite değeri (%92,11) ve en yüksek negatif prediktif değer (%84,21) HPV 16 ve/veya 18 pozitifliği ve Pap smear sonucu ASCUS ve üzeri olguların triyajı ile elde edildi. Tek başına sitolojinin ise en düşük sensitiviteye (%30,92) sahip triyaj yöntemi olduğu izlendi.

Sonuç: Çalışmamız güncel ulusal servikal kanser tarama programının verileri ile uyumludur. HSIL olgularının saptanabilmesi için HPV 16/18 ve/veya anormal sitoloji saptanan hastaların refere edilmesi oldukça sensitif bir triyaj yöntemidir. Ancak bu triyaj yönteminde bile olguların yaklaşık %8'inin atlanabileceği göz önünde bulundurulmalıdır.

Anahtar kelimeler: İnsan papilloma virüsü, servikal kanser, tarama, triyaj

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Introduction

Cervical cancer ranks fourth among all the female cancers in terms of both frequency and mortality (1). It is also a cancer type that can be prevented by vaccination and appropriate screening strategies. In addition to early cancer diagnosis, the screening strategy of cervical cancer is based on early diagnosis of precancerous lesions to prevent cancer progression. Approximately 99% of cervical cancers are associated with persistent high-risk Human papilloma virus (HPV) infections (2). And HPV infection test has been recommended by many professional associations, including the World Health Organization, European Union and US Preventive Services Task Force in the primary screening programs (3-5).

Turkey, as one of the leading countries in the world in this manner, adopted the HPV-based screening program in 2014 (5). According to the new early cancer diagnosis program, all cases with HPV 16 and HPV 18 infections or all cases with cytological abnormalities with other high-risk HPV (hrHPV) infections are referred for colposcopy. However, the data evaluating the relationship between the admission characteristics of high-grade intraepithelial lesion (HSIL) and cancer cases diagnosed after colposcopic evaluation following the primary screening still remain insufficient. The evaluation of this relationship is very important for the monitoring and further modifications of the cancer screening programs.

The present study aimed to review the relationship between admission characteristics and colposcopic evaluation results of the patients referred from cervical cancer screening program. The study also planned to evaluate the HPV types and Papanicolaou (Pap) smear results of the patients with cancer.

Materials and Methods

As a result of the early diagnosis of cancer program, the referral characteristics and colposcopic diagnoses of patients, who were referred to a university hospital between 2016 and 2018 upon the hrHPV DNA positivity, were evaluated retrospectively. Approval for the study was obtained from the Institutional Scientific Research Ethics Committee.

At the time of admission, the current hrHPV subtypes of patients were divided into three categories as HPV 16, HPV 18, and hrHPV-other. The Pap smear test results were classified as benign findings, atypical squamous cells with undetermined importance (ASCUS), atypical glandular cells, low grade intraepithelial lesion (LSIL), and HSIL at the time of admission. Colposcopic findings and final histopathological results were analyzed in three categories: benign findings, low grade squamous intraepithelial lesion/LSIL (CIN I) and high-grade intraepithelial lesion/HSIL (CIN 2/3). The clinical properties, colposcopic findings, and sociodemographic features of the patients with HSIL and cancer were obtained through the file records.

In our clinic, all colposcopic examinations were performed through a binocular colposcope with 40-fold magnification and a green filter feature connected to a digital screen. In accordance with our colposcopy application protocol, after washing the cervix with saline, it was scanned with a green filter for atypical vascularization, and then 3% acetic acid was applied to the cervix. After a one-minute-long application, the cervix was scanned for aceto-white appearance and stained with Lugol solution, and areas without Lugol involvement were noted. Biopsy was taken from suspicious areas, and the highest-grade lesion from biopsy results was evaluated as the pathology result of the patient.

Statistical Analysis

Descriptive values of quantitative continuous variables (such as age) were examined using the standard descriptive statistical methods (arithmetic mean, standard deviation, and median). Categorical variables (asset frequency) were presented with their frequencies and percentages. The evaluation of the quantitative measurements was carried out using the Student's t-test or the Wilcoxon signed rank test according to the distribution characteristics of the data. Comparisons of categorical variables were carried out using the chi-square or the Fischer's exact test, depending on the status of the case distributions. Cases with a p value of <0.05 were considered statistically significant.

Results

A total of 420 patients were referred to our unit for colposcopy during the study period. Among these patients, 21 cancer or carcinoma *in situ* and 131 HSIL were diagnosed histopathologically. The demographic data of these cases are presented in Table 1.

Only 3 (14.3%) of the carcinoma *in situ* and cancer cases had abnormal LSIL as a result of the Pap smear test, and in 18 (85.7%) cases, the Pap smear was reported either negative or inadequate. HPV 16 was detected in 18 (85.7%) of 21 cases, while HPV 18 was detected in 4 (19%) cases. In one case, HPV types 16 and 18 were observed together.

The admission characteristics and histopathological and clinical diagnoses of *in situ* cancer or carcinoma cases are summarized in Table 2.

Examining the patients with HSIL, it was found that 100 (76.3%) women had HPV type 16 and/or 18 positivity, and 31 (23.7%) women had other hrHPV positivity. Examining the Pap smear results of these cases, it was observed that smear results were negative in approximately half of the cases (n=57, 50.9%). The admission characteristics of the cases with HSIL are presented in Table 3.

Table 1. Demographic characteristics of patients with high grade cervical lesion, carcinoma *in situ* and cancer

	HSIL	Ca *in situ* + Ca	p
Age (mean ± SD)	43.08±8.48	47.95±7.95	0.019
Parity (mean ± SD)	2.38±1.10	2.33±1.11	0.853
Abortus (mean ± SD)	0.82±1.02	1.40±1.14	0.021
Number of partners (mean ± SD)	1.21±0.50	1.05±0.21	0.161
Menopausal status			
Premenopause [n (%)]	97 (74%)	12 (57.1%)	0.182
Postmenopause [n (%)]	34 (26%)	9 (42.9%)	

HSIL: High grade cervical lesion, Ca: Cancer; n: number, SD: Standard deviation

Table 2. Screening features and presentation of the cases with invasive or *in situ* cancer

Patients' number	Age	HPV type	Pap smear	Diagnoses
1	33	18	Negative	Adeno Ca
2	38	16	Negative	Invaziv SCC
3	38	16	Negative	Microinvasive SCC
4	40	16	Inadequate	Invasive SCC
5	42	16	Inadequate	Microinvasive SCC
6	43	16	Inadequate	Microinvasive SCC
7	45	16	LSIL	Microinvasive SCC
8	46	16	LSIL	Adenoca Insitu
9	46	16	Negative	Adenoca Insitu
10	47	16	Negative	Invasive SCC
11	48	18	Negative	Invasive SCC
12	50	16	Negative	Microinvasive SCC
13	50	16	Negative	Microinvasive SCC
14	52	16	Negative	Invasive SCC
15	53	18	Inadequate	Microinvasive SCC
16	54	16	LSIL	Microinvasive SCC
17	59	16	Negative	Invasive SCC
18	60	16	Inadequate	Adeno Ca
19	60	16	Negative	Invasive SCC
20	61	16	Inadequate	Adenoca Insitu
21	42	16,18	Negative	Invasive SCC

SCC: squamous cell carcinoma; Ca: cancer; LSIL: low grade cervical intraepithelial lesion, HPV: Human papilloma virus, Pap: Papanicolaou

Examining the HPV type 16/18 status of the patients, it was seen that in HPV type 16 positive patients were determined in 84 (64.12%) while HPV type 18 patients were detected only in 12 (0.9%) of the total patients. In 4 of the patients, both HPV type 16 and HPV type 18 were found to be positive.

Comparing all triage methods that could be applied to all patients referred for colposcopy to detect HSIL-and-above lesions between each other, the highest sensitivity value (92.11%) and the highest negative predictive value (84.21%) were obtained with the triage of HPV 16 and/or 18 positivity and hrHPV positivity with ASCUS-and-above Pap smear test results. It was observed that cytology was the sole triage method with lowest sensitivity (30.92%). The sensitivity and specificity values of the different triage protocols are given in Table 4.

Discussion

In this study, 420 patients who were referred for colposcopy as a result of screening were evaluated, and a total of 8 invasive cancer, 8 microinvasive cancer, 2 adenocarcinoma and 3 adenocarcinoma *in situ* cases were detected. In only three of these cases, the Pap smear results were reported as LSIL, and remarkably, in all other cases, the Pap smear result was found to be negative or inadequate. The HPV type 16 was detected in all of these cases. These results confirm the superiority of HPV screening to Pap smear screening in cervical cancer screening. Also, these results indicate that even if the smear screening is negative, a colposcopic evaluation of patients with HPV 16 is required.

In the monitorization of the cervical cancer screening program, the examination of detected high-grade lesions and cancers is an important parameter. Interestingly, HPV screening histopathologically revealed HSIL in 23.7% of the cases with high-risk types other than 16-18. As a result of

Table 3. Human papilloma virus and papanicolaou smear results of the patients who had high grade cervical lesions

		n	%
HPV	Type 16 and/or 18	100	67.2
	Other hrHPV types	31	23.7
Smear	Inadequate	33	25.2
	Negative	17	13
	ASCUS	8	6.1
	LSIL	31	23.7
	HSIL	2	1.5

HPV: Human papilloma virus, ASCUS: Atypical squamous cells with undetermined importance, LSIL: Low grade cervical lesions, HSIL: High grade cervical lesions, hrHPV: High risk human papilloma virus

Table 4. Diagnostic evaluation of different triage protocols

	HPV 16/18		ASCUS+ cytology		HPV16/18 or ASCUS+		HPV16/18 or LSIL+	
	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI
Sensitivity	79.61%	72.32-85.70%	30.92%	23.68-38.92%	92.11%	86.62-95.85%	88.16%	81.93-92.83%
Specificity	47.39%	41.28-53.55%	67.54%	61.57-73.11%	23.88%	18.90-29.45%	26.87%	21.65-32.60%
PPV	46.18%	42.75-49.66%	35.07%	28.71-42.02%	40.70%	38.74-42.68%	40.61%	38.38-42.87%
NPV	80.38%	74.49-85.18%	63.29%	60.10-66.36%	84.21%	74.85-90.53%	80.00%	71.29-86.56%
Accuracy	59.05%	54.18-63.79%	54.29%	49.39-59.12%	48.57%	43.70-53.47%	49.05%	44.17-53.94%

HPV: Human papilloma virus, ASCUS: Atypical squamous cells of undetermined significance, LSIL: Low grade squamous epithelial lesions, PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval

the evaluation following the collection of the prospective follow-up results of these cases, the risks of HPV types in terms of pre-invasive and invasive cancer can be evaluated more precisely and modifications may be evaluated for the screening program.

Cervical cancer ranks fourth among all the cancer cases seen in women (1). However, almost all cervical cancers can be prevented with early diagnosis and vaccination programs (6). To adopt a more effective screening program, Turkey launched the National Cancer HPV-based screening program in 2014. In the fourth year of the new screening program, Gultekin et al. (4) published the patient data of one million cases reported in Turkey. In these data, it was reported that HPV positivity was found in 3.5% of all women who participated in the screening program and 1.6% of these patients were referred to colposcopy (5).

The examination of the data from Turkey showed that if the screening was carried out only with the Pap smear test, HSIL and/or cancer would have been missed in 45.9% of the cases. Then, Gultekin et al. (7), in a very recent study, have shared the data of four million patients in Turkey. According to this study, for the HPV-positive women, cytology has been reported as normal in 69.2% and as inadequate in 16.6%. The positive predictive value of triage was found to be 26.4% with sole Pap smear test. It has been also stated that, besides HPV types 16 and 18, some other types of hrHPV infections may also be important in HSIL cases. This result also brings the extended genotype triage system into question. Similarly, in the present study, the rate of HSIL associated with other HPV types was found to be 23.7%.

Using the Pap smear method for scanning has scientific and organizational problems (8). The main problem is low sensitivity and high false negativity in capturing cases with HSIL and above. Also, Pap smear tests are not accurate in detecting adenocarcinoma. Similarly, in the present study, of the adenocarcinomas in situ and adenocarcinoma cases, only one had abnormal smear results during screening. Also, the maintenance and installation of cytology-based screening programs are very difficult. HPV DNA testing, on the other hand, is more advantageous as the screening test with its lack of complex quality standards, allowing long scanning intervals, the ease of application, and objectivity (9).

In a recent systematic review comparing cytology and HPV-based screening in the cervical cancer screening program, covering the research carried out between 1992 and 2015, approximately 40 studies examining more than 140,000 women were evaluated (10). In the review, HPV tests and cytological evaluation were compared with different thresholds. The authors reported that the rate of false negativity of cytology in detecting CIN 2 and above lesions was quite high compared to the HPV test. In the present study, in accordance with this result, the sensitivity value of cytology was found to be very low (30.92%) only in detecting CIN 2 and above lesions. However, with the addition of HPV tests to cytology, this rate increased to 92.11%. In the present study, when LSIL was accepted as the cytological threshold value instead of ASCUS, it was seen that the sensitivity decreased (88.16%) although there was no significant increase in the specificity values.

With the Addressing the Need for Advanced HPV Diagnostics study (11,12), cervical precancerous lesions were found to be more common in patients with high-prevalence HPV 16 and/or HPV 18 cases compared to other high-risk HPVs. Although the importance of detecting other HPV genotypes is not clearly demonstrated, current guidelines recommend performing colposcopy for patients with positive HPV DNA if their cytology is abnormal in women over 30 years of age (3). Evaluating the recent studies, it was seen that the cancer rate varied between 0.6% and 9.3% in HPV type 16 or 18 positive cases (12,13). In the present study, HPV 16 and/or HPV 18 were detected in all 21 cancer cases. However, only

three of the cases had abnormal smear results. Examining the CIN 3 cases, almost one fourth of the HSIL cases had another hrHPV positivity. In 12 of these 31 cases, cytology result was reported as normal or inadequate.

Examining the data containing four million women in Turkey, in addition to HPV 16/18 cases, HPV types 33, 31, 35 and 45 were also regarded as important HPV types (7). For all these subtypes, in this study, The HPV DNA analysis was reported to show a positive predictive value exceeding 10% for HSIL. There are similar studies that are in line with this result (14,15). Extensive studies are required to determine the relationship of HPV infection other than HPV type 16/18 with wide genotyping and HSIL and above lesions. On the other hand, in line with the results of the present study, the positive predictive value of the Pap smear test did not change according to the choice of the threshold as LSIL or ASCUS. This was associated with knowing the initial HPV values during cytology screening and performing the cytology screening in high quality central laboratories.

Other than the basic sociodemographic data of the patients, the inability to include detailed clinical data in the analysis and its retrospective design were the limitations of the present study. The fact that the study was a single-center study and the number of patients were the strengths of our study.

Conclusion

The results of the present study were compatible with the data of the current cervical cancer screening program. The results also indicated that HPV screening was more sensitive in cervical cancer screening compared to Pap smear screening. Referencing patients with HPV 16/18 and/or abnormal cytology to detect HSIL cases in patients is a highly sensitive triage method. However, it should be considered that, even in this triage method, approximately 8% of the cases can be missed.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Institutional Scientific Research Ethics Committee (date 16/04/020, number: 60116787-020/26602).

Informed Consent: Verbal consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.K., T.G., Design: D.K., T.G., Data Collection or Processing: D.K., T.G., Analysis or Interpretation: D.K., T.G., Writing: D.K.

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ORIGINAL RESEARCH

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Correlation of Early Subarachnoid Hemorrhage on Serum Endothelin and von Willebrand Factor with Clinical and Radiological Parameters

Erken Dönem Subaraknoid Kanamanın Serum Endotelin ve von Willebrand Faktörü Üzerindeki Etkisinin Klinik ve Radyolojik Parametrelerle Korelasyonu

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Abstract

Objective: This study aimed to determine the changes in endothelin and von Willebrand factor (vWF) serum levels during early period aneurysmal subarachnoid hemorrhage (SAH) compared to healthy individuals and to analyze them according to clinical and radiological findings.

Method: This is a prospective study consisting of 36 cases that were referred to our hospital's emergency department between January 2018 and January 2019 for aneurysmal SAH. The control group had the same demographic features as our patients. The diagnosis of aneurysmal SAH was confirmed by computed tomography (CT), CT angiography, and digital angiography within the first 6 hours after admission. The patients' blood samples were collected within 6 hours after the occurrence of severe headache. Endothelin and vWF levels in the blood of the patient and control groups were measured by photometric methods. The results were correlated with the endothelin and vWF levels of healthy individuals and compared with the patients' Glasgow Coma scale (GCS) and Fisher scale (FS) scores.

Results: Of the 36 patients included in this study, 24 (66.7%) were female and 12 were male (33.3%). The average age was 52.13±14.40 (range: 19 to 80) years. At the time of admission, GCS, and FS scores were 11.3 and 3.1 on average, respectively. A total of 36 healthy individuals (24 females and 12 males) with an average age of 49.6±11.7 (range: 22 to 76) years were included in the control group. A significant negative correlation was found between the FS score and the GCS score of the patients (r=-0.501, p=0.002). There was a significant correlation between the GCS score of the patients and the endothelin and vWF values. It was observed that

Öz

Amaç: Biz bu çalışmada, anevrizmal subaraknoid kanamanın (SAK) erken döneminde hastaların serum endotelin ve von Willebrand faktörü (vWF) düzeylerinin sağlıklı kişilere göre artışını belirlemeyi ve klinik ve radyolojik bulgulara göre analiz etmeyi amaçladık.

Yöntem: Çalışmamız, Ocak 2018 ile Ocak 2019 arasında anevrizmal SAK nedeniyle hastanemiz acil servisimize başvuran 36 olgunun oluşturduğu prospektif bir çalışmadır. Kontrol grubunu, hastalarımızla aynı demografik özellikleri taşıyan sağlıklı bireyler oluşturdu. Anevrizmal SAK tanısı, başvurudan sonraki ilk 6 saat içinde bilgisayarlı tomografi (BT), BT anjiyografi ve dijital anjiyografi ile doğrulandı. Hastaların kan numuneleri şiddetli baş ağrısının ortaya çıkmasından sonraki 6 saatlik sürede toplandı. Hastaların ve kontrol grubunun kanlarında endotelin ve vWF düzeyleri fotometrik yöntemlerle ölçüldü. Sonuçlar, sağlıklı kişilerin endotelin ve vWF düzeyleri ile ve hastaların Glasgow Koma skalası (GKS), Fisher skalası (FS) sonuçları ile karşılaştırılarak korele edildi.

Bulgular: Çalışmamıza dahil edilen 36 hastanın 24'ü (%66,7) kadın ve 12'si erkek (%33,3) idi. Ortalama yaş 52,13±14,40 (dağılım: 19-80) yıldı. Hastaların başvuruları sırasında GKS ve FS sırasıyla ortalama 11,3 ve 3,1 idi. Kontrol grubuna yaş ortalaması 49,6±11,7 (dağılım: 22-76) olan 36 (24 kadın ve 12 erkek) sağlıklı birey dahil edildi. Hastaların FS skorları ve GKS skorları arasında anlamlı negatif korelasyon bulundu (r=-0,501, p=0,002). Hastaların GKS skorları ile endotelin ve vWF değerleri arasında anlamlı bir korelasyon saptandı. GKS skoru düştükçe artan oranda bir endotelin ve vWF değerleri olduğu görüldü (r=-0,465 p=0,004, r=-0,465 p=0,004). Hastaların FS skorları ile endotelin ve vWf değerleri arasında da anlamlı

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Abstract

there was an increasing rate of endothelin and vWF values as the GCS score decreased (r=-0.465 p=0.004, r=-0.465 p=0.004). There was also a significant relationship between FS score and endothelin and vWF values. It was observed that as FS score increased, endothelin, and vWF values also increased (r=0.571, p<0.001, r=0.538, p=0.001).

Conclusion: Evidence suggests that inflammation plays an important role in the acute phases of aneurysmal SAH-related neural damage. Our study showed that serum endothelin and vWF levels increased in the first day of bleeding in aneurysmal SAH patients and that they were associated with the GCS and FS scores.

Keywords: Endothelin, Fisher scale, subarachnoid hemorrhage, von Willebrand factor

Öz

bir ilişki kaydedildi. FS skoru arttıkça artan bir endotelin ve vWF değerleri olduğu görüldü (r=0,571, p<0,001, r=0,538, p=0,001).

Sonuç: Ortaya çıkan kanıtlar, anevrizmal SAK ile ilişkili nöral hasarın akut fazlarında enflamasyonun önemli bir rol oynadığını göstermektedir. Çalışmamız anevrizmal SAK hastalarında kanamanın ilk gününde serum endotelin ve vWF düzeylerinin arttığını ve bunların GKS ve FS skorlarıyla ilişkili olduğunu göstermiştir.

Anahtar kelimeler: Endotelin, Fisher skalası, subaraknoid kanama, von Willebrand faktör

Introduction

Subarachnoid hemorrhage (SAH), which means bleeding in the subarachnoid space, is a critical situation associated with high morbidity and mortality. Typically, the first and only symptom of SAH is sudden and serious headache, which is defined as the most severe headache in life. Although the most common cause of SAH in the literature is trauma, the most common cause of non-traumatic SAH is aneurysm ruptures (80-85%). With regard to the remaining causes, it is seen that approximately 10% of them are non-aneurysmal perimesencephalic SAH and among the rest, the leading ones are due to vascular malformation or vasculitis (1-3).

Factors significantly associated with unfavorable outcomes after SAH include the neurological status on the day of admission and the amount of blood in computed tomography (CT) on admission. The Glasgow Coma scale (GCS) is frequently used for evaluating patients with neurological conditions. In the radiological grading of SAH, the Fisher scale (FS) which is based on CT, is used as a Reliable scale to determine SAH severity (4).

When blood is present in the subarachnoid space, the components in the blood content act as powerful activators of neuroinflammation. This neuroinflammation plays an important role in the initial injury that occurs at the first moment of the SAH and in subsequent secondary injuries. Many factors contribute to the activation of neuroinflammation after SAH (5,6). In addition, some studies have found that vasoactive and spasmogenic compounds can be described in high concentrations in the cerebrospinal fluid (CSF) and plasma of patients with SAH (7,8).

Endothelin is a potent vasoconstrictor peptide from the endothelium, which is released after endothelial cell injury. According to the literature, it has been related to the mechanism of cerebral vasospasm (CVS) that develops after aneurysmal hemorrhage (9-12). Similarly, experimental and clinical studies have pointed von Willebrand factor (vWF), which increases in circulation, as a marker of vascular damage. Plasma vWF is synthesized and secreted mainly from vascular endothelial cells. When endothelial cells are activated or injured, their expression increases and may indicate endothelial dysfunction and/or susceptibility to thrombosis (13).

We aimed to determine the change in endothelin and vWF serum levels in early period aneurysmal SAH compared to healthy individuals and to analyze them according to clinical and radiological findings.

Materials and Methods

Patient Population, Data Collection, and Control Participants

Our prospective study consisted of cases that were referred to our hospital's emergency department for non-traumatic SAH between January 2018 and January 2019. Our institution's ethics committee approved this prospective study (decision number: 2018.20/264). The data used in this study were collected prospectively without any risk for patients. A total of 36 patients who were referred to our emergency unit due to non-traumatic SAH were included in this study.

The control participants, consisting of healthy individuals who presented to our outpatient clinic with headache in the same period but did not have any cranial pathology based on brain magnetic resonance imaging findings, were included in this study. The control group had the same demographic features as the patient group. The

control group patients were informed about the study and informed consent was obtained.

Clinical and neurological status evaluation of the patients was made according to the GCS score. The GCS score was evaluated as 3-8 for severe, 9-13 for moderate, and 14-15 for mild neurological damage. In the radiological grading of SAH, FS was performed to determine the SAH severity (Table 1).

Inclusion Criteria

Thirty-six patients referred to the emergency department due to severe headache, altered consciousness, and the development of neurology deficit were included. All of these patients were radiologically and clinically diagnosed within the first 6 hours of admission. Patients who had SAH due to trauma (even if there was an underlying aneurysmatic/vascular pathology) were not included in this study. Patients with negative aneurysms in digital angiography (DSA) were excluded from the study.

Patients who were admitted after trauma or were known to have coagulation abnormalities, active/chronic infection, malignancy, kidney or liver dysfunction, severe myocardial dysfunction and/or any other immune deficiency syndrome (such as AIDS, lymphoma, leukemia) were excluded from the study.

The diagnosis of aneurysmal SAH was confirmed by CT, CT angiography, and DSA within the first 6 hours after admission. All the patients with aneurysm were included in either surgical or endovascular treatment within the first 24 hours.

Blood Sample Collection

Since the patients' serum endothelin and vWF levels changed over time, the patients' blood samples were collected within 6 hours after the occurrence of the severe headache. Blood samples collected from the cubital vein in the volunteer patients and healthy individuals were put into the gel biochemistry tubes and centrifuged at 3.500 g for 10 minutes at room temperature after coagulation. The separated serums were stored at -80 °C until the study was completed.

Table 1. Fisher scale

CT finding	
1	No SAH
2	Diffuse thin (<1 mm) SAH
3	Localized clots and/or layers of blood >1 mm in thickness
4	Diffuse or no SAH, intraventricular or parenchymal blood present

SAH: Subarachnoid hemorrhage, CT: Computed tomography

Measurement of Endothelin and vWF Levels

Serum endothelin (Bioassay technology laboratory, Shangai-China - E1238Hu) and vWF (Bioassay technology laboratory, Shangai-China - E1774Hu) levels were measured at 450 nm with photometric methods using commercially purchased kits. Results were reported as ng/L for endothelin and ng/mL for vWF.

Statistical Analysis

Data analysis was done using Statistical Package for the Social Sciences (SPSS) 21.0 statistics program. In addition to descriptive statistics, frequency, percent value, mean and standard deviation were used to identify the demographic characteristics of the cases. Data with normal distribution were evaluated by the independent sample t-test. The p-value <0.05 was considered significant. The normality of the distribution was evaluated by the Kolmogorov-Smirnov test. For correlation analysis, the Spearman correlation test was used. Statistical significance was accepted when p-values were <0.05.

Results

Of the 36 patients included in our study, 24 (66.7%) were female and 12 (33.3%) were male. The average age was 52.13±14.40 (range: 19 to 80) years. At the time of admission, GCS and FS were 11.3 and 3.1 on average, respectively. A total of 36 healthy individuals (24 females and 12 males) with an average age of 49.6±11.7 (range: 22 to 76) years were also included in the control group. The difference was statistically insignificant (p>0.05). The age, gender, location of ruptured aneurysm, FS, and GCS scores of each patient were recorded (Table 2).

There was a significant difference in endothelin and vWB values between patients and control participants (p<0.001). A statistically significant difference was observed in the increasing trend after bleeding (Table 3).

A significant negative correlation was found between the FS and GCS scores of the patients (r=-0.501, p=0.002). There was a significant correlation between the GCS score of the patients and the endothelin and vWF values. It was observed that there was an increasing rate of endothelin and vWF values as the GCS score decreased (r=-0.465 p=0.004; r=-0.465 p=0.004). There was also a significant relationship between FS and endothelin and vWF values. It was observed that as FS increased, endothelin and vWF values also increased (r=0.571, p<0.001; r=0.538, p=0.001) (Table 4).

Table 2. Baseline demographic and clinical characteristics of patients

	n=36
Gender	
Female	24 (66.7%)
Male	12 (33.3%)
Age	52.13
Location of aneurysm	
Anterior circulation	32 (88.9%)
Posterior circulation	4 (11.1%)
Treatment	
Surgical treatment	18 (50%)
Endovascular treatment	18 (50%)
Glasgow Coma scale	Mean 11.3
(3-8)	10
(9-13)	7
(14-15)	19
Fisher scale	Mean 3.1
1	0
2	8
3	15
4	13

N: Total number of patients

Discussion

This study shows that circulating endothelin and vWF increased significantly in patients with SAH. It also shows that serum endothelin and vWF levels increase as the patients' initial admission GCS score worsens and they tend to increase in parallel with an increase in the amount of blood on tomography.

Subarachnoid hemorrhage causes early brain damage due to temporary cerebral ischemia and the toxic effects of subarachnoid blood. It also causes secondary brain damage due to increased intracranial pressure, destruction with intracerebral hemorrhage, formed shifting, and herniation (14,15). Also, there is a delayed brain injury stage due to cerebral ischemia caused by CVS between the 3rd and 14th days of hemorrhage (16). SAH also generates a systemic response that can cause a Systemic Inflammatory Response syndrome. Increased plasma inflammatory cytokines contribute to this systemic response (17-22).

When endothelial cells are stimulated by cytokines or vascular damage, the barrier function of the endothelium is impaired. Vasomotion is impaired due to an increase or decrease in the production of vasoactive substances,

Table 3. Comparison of endothelin and von Willebrand factor values with the control group in early subarachnoid hemorrhage

	Mean	n	SD	t	p
Endothelin-SAH	66.4583	36	46.80790	6.690	<0.001
Endothelin-control	14.8589	36	5.22645	-	-
vWF-SAH	40.7885	36	18.08301	10.812	<0.001
vWF-control	8.9959	36	3.30477	-	-

SAH: Subarachnoid hemorrhage, vWF: von Willebrand factor, SD: Standard deviation, N: Total number of patients, t: Statistical t parameter

Table 4. The Spearman's correlation coefficients

		GCS	FS	Endothelin	vWF
GCS	Correlation coefficient	1.000	-0.50**	-0.465**	-0.465**
	Sig. (2-tailed)	0	0.002	0.004	0.004
	n	36	36	36	36
FS	Correlation coefficient	-0.501**	1.000	0.571**	0.538**
	Sig. (2-tailed)	0.002	0	0.000	0.001
	n	36	36	36	36
Endothelin	Correlation coefficient	-0.465**	0.571**	1.000	0.693**
	Sig. (2-tailed)	0.004	0.000	0	0.000
	n	36	36	36	36
vWF	Correlation coefficient	-0.465**	0.538**	0.693**	1.000
	Sig. (2-tailed)	0.004	0.001	0.000	0
	n	36	36	36	36

vWF: von Willebrand factor, FS: Fisher scale, GCS: Glasgow Coma scale, **: It is a statistical sign showing that it is statistically very strongly related, N: Total number of patients

and prothrombotic/procoagulant activity increases. Vasoconstriction, leukocyte adhesion, platelet activation, affinity to thrombosis, coagulation disorders, pro-oxidative changes, and vascular inflammation occur (23,24).

While the NO, prostacyclin, and endothelium-induced hyperpolarizing factor released from the endothelium have vasodilation activities in the arrangement of the endothelial vascular tonicity, endothelin has a vasoconstrictor activity. Structurally, endothelin has three forms. Endothelin-1 (ET-1) is synthesized in endothelial cells, ET-2 in intestinal cells, and ET-3 in neurons. There are two types of endothelin receptors (ET-A and ET-B) in the vessel wall. ET-1, which is mainly responsible for vasoconstriction, is not stored in endothelial cells, but de novo synthesized with stimuli such as thrombin, angiotensin II, shear stress, and hypoxia (25-28). In the SAH model performed by Lei et al. (29) on rabbits, they showed that ET-1 affected cerebral microcirculation after SAH by perfusion CT scan. They found that ET-1 increased in CSF and peripheral blood after SAH, and showed that blood circulation perfusion decreased when ET-1 increased (29). The clinical study conducted by Zimmermann and Seifert (30) supports the hypothesis that ET-1 is the main cause of CVS after SAH.

Another plasma protein that occurs in endothelial injured is vWF, which is a plasma glycoprotein that is a mediator of platelet adhesion. vWF is constantly secreted into the plasma by the endothelium and is also stored in the Weibel-Palade bodies in endothelial cells. When endothelial cells are stimulated, membrane fusion of the bodies causes large amounts of vWF to pass into the blood and mechanisms that result in platelet aggregation/thrombus formation begin (31-34). In the study of McGirt et al. (32) based on the previous studies about morphological changes caused by endothelial cell damage in peripheral vasculature, they showed increases in serum vWF, MMP-9, and VEGF levels before the development of CVS and predicted the onset of CVS correctly. Tang et al. (33) have assumed that the vWF/ADAMTS13 balance plays an important role in thrombosis; they have shown that a decrease in ADAMTS13 activity causes less disruption of vWF and thus an increase in vWF activity. They have assumed that endothelial dysfunction and unbalanced vWF/ADAMTS13 are correlated with delayed cerebral ischemia formation and poor clinical outcome (33). Similarly, Wan et al. (31) showed that vWF/ADAMTS13 was associated with pathogenesis in early brain injury, and that ultra-early treatment with rADAMTS-13 reduced early brain damage after experimental SAH.

In our study, we found a significant difference in the early serum endothelin and vWF values of patients who had SAH compared to the control group participants. In the early days of bleeding, we observed that both serum endothelin and vWF levels were higher in patients than in normal subjects.

Also, we compared the FS scores of the patients with their serum endothelin and vWF levels. FS used to evaluate neurological prognosis in SAH is the first and the best known classification system for SAH in CT scans. This scale is useful in predicting mortality, morbidity and/or CVS. FS evaluates the amount of blood seen on CT and predicts the prognosis of the clinical result. Clinical studies on the factors responsible for neuroinflammation have shown that SAH patients with high FS have significantly higher inflammatory factor levels in both plasma and CSF compared to SAH patients with low FS (35-37).

We found that in accordance with current literature, there is a significant correlation between serum endothelin and vWF levels and the FS. It was observed that as FS increased, endothelin and vWF values increased and they tended to increase in parallel with the increase in the amount of blood on tomography.

The limitation of our study is that we had a small sample size and only a single time point (early stage) was observed.

Conclusion

Evidence suggests that inflammation plays an important role in the acute phases of aneurysmal SAH-related neural damage. Our study showed that serum endothelin and vWF levels increased in the first day of bleeding in aneurysmal SAH patients and that they were associated with GCS and FS scores. The endothelium dysfunction and platelet activation were correlated with the occurrence of clinical outcomes. This is a preliminary clinical study that can be used as a basis in future studies.

Ethics

Ethics Committee Approval: The non-interventional ethics committee of Bezmialem Vakıf University has approved this prospective study (decision number: 2018.20/264).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed

Authorship Contributions

Concept: S.K., M.G.P., Design: S.K., M.G.P., Data Collection or Processing: S.K., M.G.P., E.M.G., Analysis or Interpretation:

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ORIGINAL RESEARCH

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Effect of Static and Dynamic Stretching on Knee Muscle Strength in Trained Players

Antrenmanlı Sporcularda Statik ve Dinamik Germe Egzersizlerinin Diz Kas Gücü Üzerine Etkisi

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Abstract

Objective: The study examined the effects of two different stretching exercises on knee muscle strength in basketball players in order to determine the most appropriate pre-competition protocols for basketball conditioning.

Method: Thirty-two basketball players (mean age 22.75±2.73 years, weight 87.47±10.99 kg, height 188.85±7.35 cm, body mass index 24.46±1.89) participated in this study. They performed two different stretching protocols according to basketball training experience in randomly assigned order: randomized in consecutive manner according to admission order, well-trained basketball players (training frequency = 5 days/week, groups I and II), less-trained basketball players (1 day/week, groups III and IV). Basketball players in groups I and III were exposed to isokinetic tests-one each after dynamic stretching and, 1 week later, after static stretching. In groups II and IV, similar evaluations were made after static stretching and, 1 week later, after dynamic stretching. Five days/week were included in the well-trained group. The less-trained group consisted of basketball players who trained 1 day/week.

Results: In less-trained basketball players, static stretching resulted in higher extensor muscular strength and endurance values, whereas dynamic stretching increased knee flexor strength and endurance.

Conclusion: Our results suggest that before competitions, stretching exercises should be chosen depending on the conditioning of the basketball player (well-trained, less-trained). Including both static and dynamic stretching into the "stretching" concept seems effective.

Keywords: Dynamic stretching, isokinetic test, static stretching

Öz

Amaç: Bu çalışmanın amacı, basketbol oyuncularında fiziksel dayanıklılığı artırmak için müsabaka öncesi en uygun protokolün belirlenmesinde iki farklı germe egzersizinin etkilerini incelemektir.

Yöntem: Bu çalışmada, 32 basketbol oyuncusu (ortalama yaş 22,75±2,73, kilo 87,47±10,99 kg, boy 188,85±7,35 cm, vücut kitle indeksi 24,46±1,89) yer almıştır. Basketbol oyuncuları antrenman deneyimlerine göre iki farklı germe egzersizi yapmak üzere randomize olarak gruplara ayrılmıştır: ardışık rastgele seçim yapılarak iyi antrenmanlı basketbol oyuncuları (antrenman sayısı =5 gün/hafta, grup I ve II), kötü antrenmanlı basketbol oyuncuları (1 gün/hafta, grup III ve IV). Grup I ve III için dinamik germe, ardından bir hafta sonra statik germe, grup II ve IV için statik germe, ardından bir hafta sonra dinamik germe egzersizleri sonrası izokinetik test uygulanmıştır.

Bulgular: Düşük-idmanlı basketbol oyuncularında, statik germe egzersizleri, daha yüksek ekstansör kas gücü ve dayanıklılık verileri gösterirken, dinamik germe, diz fleksör gücü ve dayanıklılığını artırmıştır.

Sonuç: Bulgularımız, basketbol oyuncularında antrenman durumuna göre (iyi antrenmanlı, kötü antrenmanlı) germe egzersizlerinin seçilmesini önermektedir. Hem statik hem de dinamik germe egzersizleri etkili bulunmuştur.

Anahtar kelimeler: Dinamik germe, izokinetik test, statik germe

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Introduction

Physical training is an important part of basketball performances (1). Stretching applied during the warm-up period increases the energy absorbent capacity of muscles, thus decreasing injury risk. In addition, it prepares the body for upcoming physical activity. Thus, stretching exercises are a part of athletes' pre-competition warm-up protocols (2,3).

Flexibility is a component of physical fitness that athletes desire to develop. Static and dynamic-stretching exercises are among the methods that bring flexibility. Static stretching (SS) is defined as stretching where the athletes stay in a stretching position for a certain period (4). Dynamic stretching (DS), on the other hand, consists of slow-paced dynamic movements that are similar to upcoming actual physical activity (5).

Muscle strength is one of very important sports components for preventing injury and enhancing performance. Isokinetic dynamometers are very useful to evaluate muscle strength. These dynamometers determine the muscle balance and forces between the dominant and non-dominant extremities as well as the agonist and antagonist muscles. Today, isokinetic devices are used for muscle rehabilitation and muscle training (6).

Isokinetic testing provides an objective quantitative measure for muscle functions. It also provides results on such parameters as muscle work, power, and endurance. With these objective parameters, it is possible to follow the progress of athletes or patients during rehabilitation periods and competitive performances (7).

Pre-competition warm-up, which has become a traditional practice, has limited scientific evidence to support its importance. Warm-up protocols usually reflect personal experiences of coaches, instructors and athletes. Previous studies have supported the positive effects of stretching exercises using static, dynamic or proprioceptive neuromuscular facilitation stretching techniques on increasing the joint mobility. Moreover, previous studies have also suggested that these positive effects include reduction in muscle injuries and improvement of sports performance (8). In this study, isokinetic tests were performed by basketball players after following SS and DS exercises, with a view of establishing their advantages and weaknesses. The aim of the study was to determine the most appropiate pre-competition exercise protocols for basketball players.

Materials and Methods

A quantitative, cross-sectional, and prospective study was conducted between 11.12.2013 and 11.06.2014 with the approval of the Ethics Committee of Trakya University Faculty of Medicine (protocol number: TÜTF-GOKAEK 2013/185) and the written informed consent was obtained from all participants.

Thirty-two male basketball players who met the eligibility criteria and committed to participate were included in this study. The eligibility criteria of the study were as following: having been involved in basketball for ≥5 years, male gender, age of 18-30 years, absence of inflammatory or infectious joint pathology, commitment to participate in the study, absence of previous knee surgery, and absence of neurological disease affecting knee joint innervation.

Exclusion criteria of the study were as following: a history of cardiovascular or pulmonary disease that might hamper exercise, an inflammatory or infectious pathology of the knee joint, uncontrolled endocrine pathology, significant system or organ failure, neurological disease affecting the knee joint innervation, and previous knee surgery. Basketball players who met the eligibility criteria and committed to participate in the study were examined according to their ages, height, weight, and dominant extremities.

Thirty-two basketball players included in the study were classified in two groups according to their training frequencies (Figure 1). Basketball players who trained 5 days/week were included in the well-trained group. The less-trained group consisted of basketball players who trained 1 day/week. Well-trained basketball players were randomized into groups I and II, and less-trained basketball players were randomized into groups III and IV. Basketball players in groups I and III were applied two isokinetic tests, one after DS and, 1 week later, the other after SS. Basketball players in group II and IV were subjected to the same evaluation following SS and, 1 week later, after DS, respectively.

All basketball players performed stretching exercises after cycling for 7 min, which was at a speed of 80-90 revolution per minute (rpm) in the bicycle ergometer.

Dynamic Exercise Group: First, basketball players performed DS exercises after warming up in the bicycle ergometer at 80-90 rpm for 7 min. In dynamic exercises, movements lasted for 15 s each, to be repeated after resting for 20-s (Table 1). DS exercises practiced by basketball players were as follows (Figure 2):

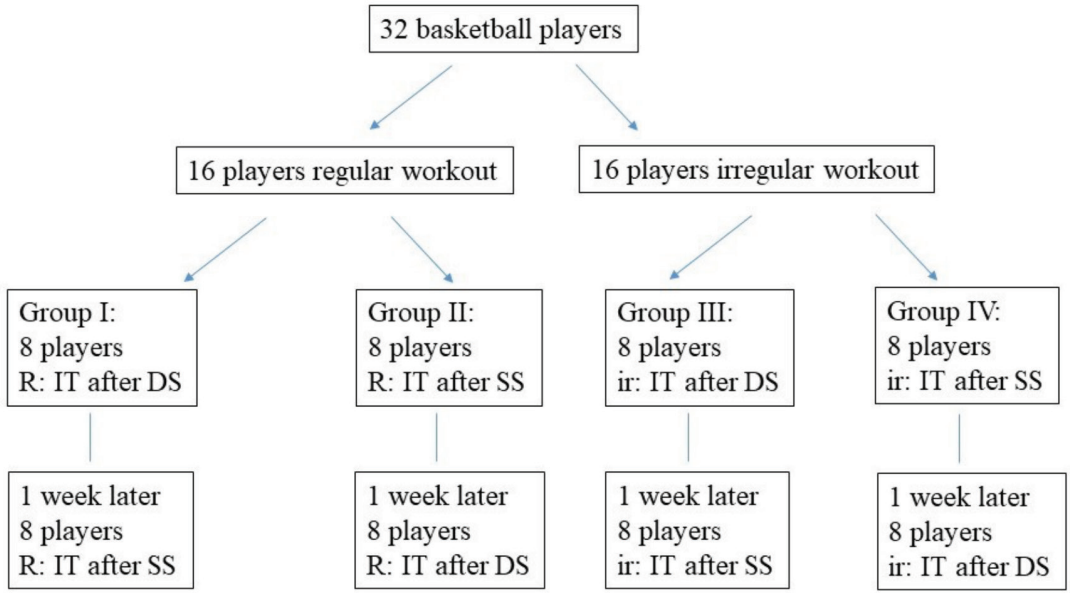

Figure 1. Experimental design

IT: Isokinetic test, SS: Static stretching, DS: Dynamic stretching, R: Regular, ir: Irregular

Table 1. Duration of stretching exercises applied to right and left extremity muscles

Muscles	Dynamic-stretching exercises	Static-stretching exercises
Hamstring	75 s	80 s
Quadriceps	45 s	40 s
Adductors	60 s	40 s
Hip extensors	45 s	20 s
Hip flexors	15 s	20 s
Gastrocnemius	75 s	80 s

s: Second

DS exercise 1- Basketball players assumed a supine position with their upper limbs by the side of the body and their forearms supinated. When they performed cycling exercises, they flexed their hips and knees such that the knees touched their hands in a rhythmical pattern. This exercise stretches the hip extensors and hamstring muscles (Figure 2-1).

DS exercise 2- Basketball players' lower limbs were semi-flexed, their shoulders were abducted to 70°, and their forearms were externally rotated with the palms facing up. Movements were repeated rhythmically along the line (right and left, then to the left). This exercise stretches adductor, quadriceps and gastrocnemius muscles (Figure 2-2).

DS exercise 3- From a standing position, basketball players raised one lower limb forward to flex the hip and knee to 90° flexion, and then brought the limb back to the floor by hyperextending the hips and knees. Then, they moved the same lower limb forward by stepping rhythmically and flex the other lower limb such that the knee touched the floor while the hip was in hyperextension. This exercise stretches hip flexors, quadriceps, hip extensors, hamstring and gastrocnemius muscles (Figure 2-3).

DS exercise 4- While standing, basketball players abducted their hips to at least 50° abduction. One lower limb was flexed to 90° flexion at the knee and hip; the BW was transferred to that side and the adductor muscles of that side were stretched; during this, the other lower limb was in full extension. The trunk was then rotated 180° while the same position was maintained. Then, the lower limb in full extension was flexed to at 90° hip and knee flexion. This exercise stretches adductor muscles, while the other lower limb is in full extension (Figure 2-4).

DS exercise 5- While the basketball players were standing, one upper limb was flexed at the shoulder to 180° flexion while the knee of the opposite side was flexed to 90° flexion (right upper limb and left lower limb; then the left upper limb and the right lower limb). These movements were repeated rhythmically. This exercise stretches hip extensors and hamstring muscles (Figure 2-5).

DS exercise 6- Basketball players attempted to rhythmically touch the toes with the contralateral hands while they were walking. During this movement, the elbow was extended and shoulder was abducted, whereas the lower limb was

in maximum flexion. This exercise stretches hamstring and gastrocnemius muscles (Figure 2-6).

DS exercise 7- Basketball players were standing with their shoulders at 90° flexion and the elbow and wrist in full extension; then, they placed their palms on the wall. Basketball players transferred their weights to one of their lower limbs and they put the other lower limb forward. This lower limb was placed in maximum adduction and maximum abduction positions for 15 s each. The same movements were repeated for the other lower limb. This exercise stretches adductor muscles (Figure 2-7).

DS exercise 8- Basketball players were standing with their knees at full extension while hips were at full flexion; then hip extension repeated rhythmically in 15 seconds. The same exercise was repeated for the other side. This exercise stretches hamstring and gastrocnemius muscles (Figure 2-8).

Static Exercise Group: Basketball players warmed up on the bicycle ergometer for 7 min at 80-90 rpm speed. Then, they performed static-stretching exercises consisting of six movements. Five of the static exercises were repeated for 20 s for one extremity, and the same movement was repeated for the other extremities. They rested for 15 s and moved to the other movement. One of the static exercises was directed to both limbs and the exercise lasted 20 s. The exercise was repeated after resting for 15 s (Table 1).

Static-stretching exercises (Figure 3) were as follows:

SS exercise 1- While the basketball players were standing, they positioned both their lower limbs at a minimum 50° abduction at the hip. On one side, they positioned the knee and the hip to 90° flexion. Then, the body weight (BW) was transferred to that side, and the abductor muscles were stretched while the other lower limb was in full extension. The same exercise was repeated for the other side (Figure 3-1).

SS exercise 2- Basketball players moved one of their lower limbs forward, with the knee and the hip at 90° flexion, and then, placed the other lower with the hip in hyperextension. The same exercise was repeated for the other side. This

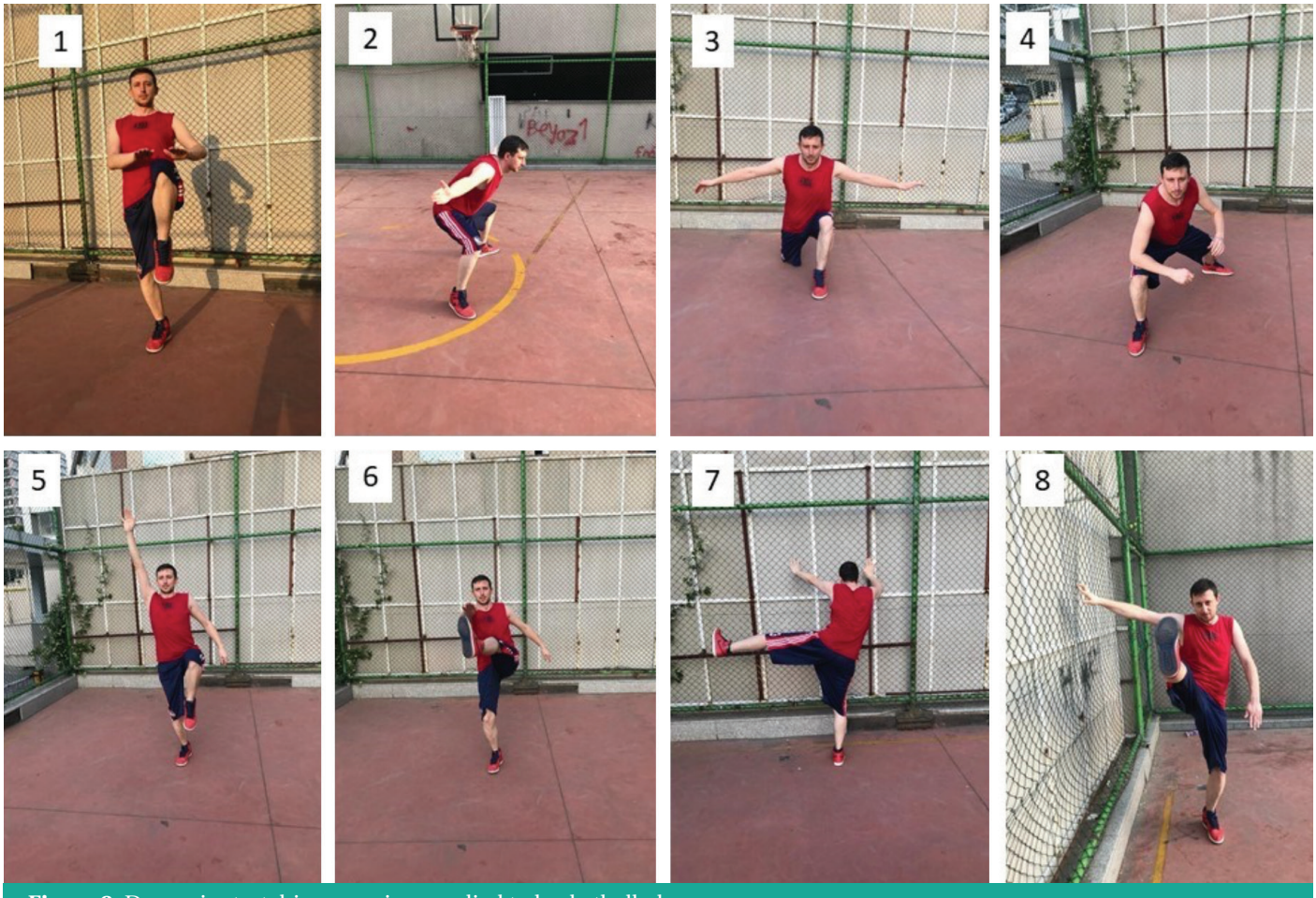

Figure 2. Dynamic stretching exercises applied to basketball players

exercise stretches hip flexors, quadriceps, hip extensors and hamstring muscles (Figure 3-2).

SS exercise 3- While basketball players were sitting with their backs straight, both lower limbs were stretched out with the hips at maximum abduction. While the lower-limb tension was maintained, the trunk was laterally flexed to make contact with one of the thighs, and the basketball players tried to touch their toes. The exercise was repeated on the other side. This exercise stretches adductor, hamstring and gastrocnemius muscles (Figure 3).

SS exercise 4- Both the lower limbs were stretched and positioned perpendicular to the other. The trunk was brought to touch the thighs while the tension of lower limbs was maintained. This exercise stretches hamstring and gastrocnemius muscles (Figure 3-4).

SS exercise 5- Basketball players stood standing while using support with one hand for balance. With the help of the other hand, the contralateral lower limb was flexed backward to the hip level. The same process was repeated for the other side. This exercise stretches the quadriceps muscle (Figure 3-5).

SS exercise 6- Basketball players stood two feet away from the wall. While one lower limb was stretched, the opposite lower limb was twisted one step forward and both hands were placed on wall for balance. During this stretching exercise, attention was on the heels' not being raised from the floor. The same process was repeated for the other side. The gastrocnemius muscles in both the extremities were stretched (Figure 3-6).

Isokinetic Evaluation

CSMI Cybex HUMAC NORM (model number 502.140 with isokinetic tests and exercise systems) was used for isokinetic evaluation. The device was calibrated before each test. The protocol for knee flexion and extension isokinetic muscle strength and endurance measurements were as following: Submaximal four trials at 60°/s angular velocity, and 6-s rest, four tests at maximum force and 20-s rest. Submaximal four trials at 240°/s angular velocity, and 6-s rest, 20 tests at maximum force and termination of test. Before the test, the basketball players were informed regarding the purpose of this study, devices and the application; they also received motivational instructions during the test. Values of peak torque (PT), % BW, total work (TW) and TW % BW were

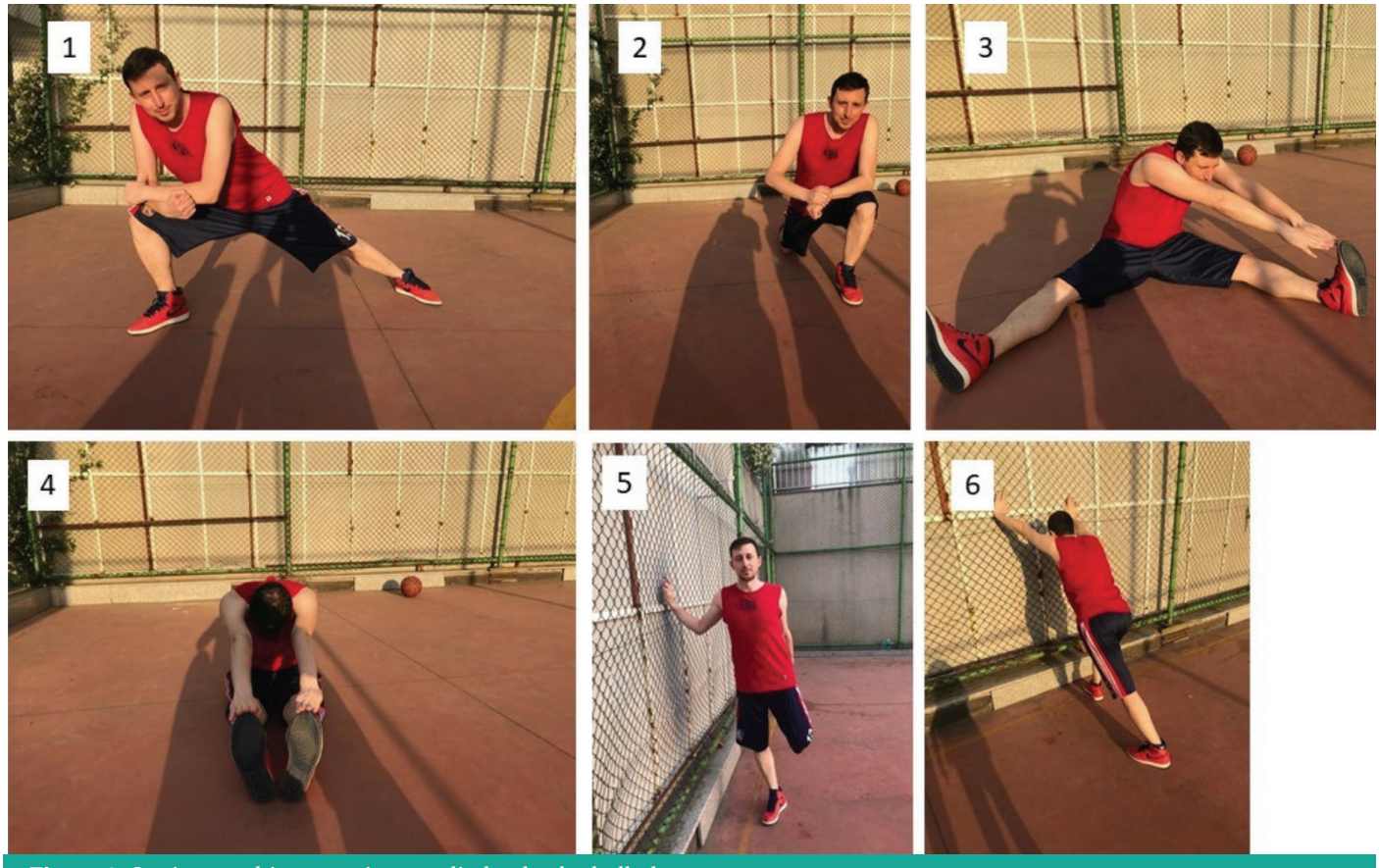

Figure 3. Static stretching exercises applied to basketball players

recorded (9). PT value: It is the highest torque value among all test parameters obtained in the full range of motion in each full-joint movement at angular velocity. Among all test parameters, it is accepted as the gold standard in terms of accuracy, precision and reliability. Its measure is Newton meter.

PT% BW: It is important to compare the test results among individuals and to evaluate the functional strength of the muscles that hold the weight. TW: It is the distance a force moves a certain resistance. Power: The amount of work done in time unit. Its unit is Watt. The endurance is the measurement of the fatigue developed in the muscle (10,11). The low PT % BW emphasizes the need for more strength training, a low TW value reflects lack of endurance and need of high repetition training. Moreover, low average power values highlight that power-based exercises should be applied (12).

Statistical Analysis

The data obtained from the study were saved in computer files. IBM Statistical Package for Social Sciences (SPSS) Statistics version 22 was used for statistical analyses (license number: 10240642). All parameters were normally distributed (Kolmogorov-Smirnov test). For group comparisons, One-Way ANOVA test and the paired sample t-test were used. The level of significance was set at p values of <0.05.

Results

Mean age, weight, and body mass index values of the groups are provided in Table 2. The mean age of all basketball players was 22.75±2.73 (18-28) years. The mean age was lower in group II than in group III (p=0.017). The mean height was higher in group I than in group IV (p=0.049). There were no other differences among the groups. The groups with no difference between the weight and body mass index averages were suitable for comparison (p>0.05) (Table 2).

Results of the First Evaluation

The mean values of right knee extensor PT (EPT), flexor peak torque (FPT), extensor TW (ETW), flexor total work (FTW); left knee FPT, ETW, ETW % BW and FTW % in group I (R: IT after DS) were significantly higher than those in group IV. The mean values of right knee EPT was higher in group 1 than in group III. The mean values for EPT % BW in group II (R: IT after SS) were higher than those in group iii and group IV (Ir: IT after SS). In the first measurements in the right knees, group III had lower mean FTW% BW than group I and group II. These differences were statistically significant (p≤0.05). There were no other statistically significant differences among the groups (Tables 3 and 4).

Results of the Evaluation Made 1 Week after

The mean values for right knee EPT and left knee ETW % BW in group IV were lower than those in groups I and II. The mean values for right knee EPT, FPT and ETW as well as left knee FPT, ETW and FTW were higher in group I than in group IV. The average values for both right and left knee ETW and FTW were higher than those in group III. The mean values of right and left knee flexor, PT % BW in group II were higher than those in group IV. These differences were statistically significant (p≤0.05). There were no other statistically significant differences among other groups (p>0.05, Tables 3 and 4).

Difference between the Two Evaluations

Within- Groups:

A significant difference was observed in the amount of change in the mean values for left and right knee FPT and left knee flexor PT % BW. The differences in the values were found to be higher in group II than in group I. In group II (R: IT after SS), the difference observed between the left knee FPT and flexor PT % BW was higher than that in group III (Ir: IT after DS). These differences were statistically significant (p≤0.05). No other statistically significant differences were found within the groups for other parameters (p>0.05, Tables 3 and 4).

Discussion

Most athletes are recommended to perform pre-activity DS and post-activity SS. SS may lead to performance degradation when it is performed before activity. To

Table 2. Evaluation of groups according to mean age, height, weight and body mass index

	Group I	Group II	Group III	Group IV	p
Age	22.25±1.49	20.63±2.50	24.5±2.93	23.63±2.50	0.018*
Height	194±6.95	191.38±8.31	186.25±5.18	183.75±8.94	0.042*
Weight	94.88±13.83	84.75±8.66	83.88±10.15	86.38±11.34	0.204
BMI	25.11±2.23	23.12±1.56	24.14±2.38	25.48±1.40	0.091

Data presented are mean values ± standard deviation, BMI: Body mass index, One-Way ANOVA test,*: p<0.05

decrease this risk, the following stretching exercises are recommended: resting period following SS, a general warm-up period or DS (13).

There are many studies showing that performance level can vary according to the type of stretching employed. DS improves physical performance, whereas SS improves flexibility. Therefore, when choosing stretching exercises, all the following are considered: i.e., improving flexibility, preventing injuries and improving strength (14).

However, there are also studies that suggest both types of stretching should be performed, in addition to aerobic running, for improving flexibility (15). Some studies have

Table 3. Evaluation of groups according to right and left knee (60°/sec) extensor and flexor peak torque (Newton meters) means

		Group I	Group II	Group III	Group IV	[1]p
R-EPT	Before	311±43.87	286±51.40	243.38±31.39	247±25.82	0.005**
	After	300.5±51.64	295.63±52.86	246.88±33.32	231±29.20	0.005**
	Difference	-10.5±21.47	9.63±19.63	3.5±21.27	-16±18.60	0.060
	[2]p	0.209	0.208	0.656	0.045*	-
R-FPT	Before	218.25±29.70	188.25±39.43	180.88±29.81	171.25±25.28	0.034*
	After	217.75±22.74	210.13±26.04	187.13±24.99	178.38±23.49	0.009**
	Difference	-0.5±15.11	21.88±19.22	6.25±11.08	7.13±13.21	0.039*
	[2]p	0.928	0.015*	0.155	0.171	-
L-EPT	Before	305.5±50.53	278.13±59.90	249.25±50.64	250.5±29.95	0.092
	After	282.25±42.13	285.75±60.27	249±52.09	245.13±33.27	0.213
	Difference	-23.25±31.43	7.63±26.72	-0.25±16.08	-5.38±7.76	0.064
	[2]p	0.075	0.446	0.966	0.091	-
L-FPT	Before	206.38±34.76	174.88±33.29	174.88±29.67	155.75±32.31	0.034*
	After	204±29.84	197±31.04	173.25±23.04	165.13±28.38	0.029*
	Difference	-2.38±11.81	22.13±11.95	-1.63±31.30	9.38±10.64	0.044*
	[2]p	0.587	0.001**	0.887	0.041*	-

Data presented are mean values ± standard deviation, R: Right knee, L: Left knee, EPT: Extensors peak torque, FPT: Flexors peak torque, [1]One-Way ANOVA test, [2]Paired sample t-test,*: p<0.05,**: p<0.01

Table 4. Evaluation of groups according to right and left knee (240°/s) extensor and flexor total work means

		Group I	Group II	Group III	Group IV	[1]p
R-ETW	Before	2.257±363.62	1822.38±367.40	1511.75±450.97	1628.5±278.33	0.002**
	After	2302.25±371.13	2008.5±455.45	1679.38±525.97	1658.88±267.61	0.013*
	Difference	45.25±184.87	186.13±214.96	167.63±168.35	30.38±117	0.188
	[2]p	0.511	0.044*	0.026*	0.487	-
R-FTW	Before	2041.25±327.67	1853.38±305	1472.5±307.72	1592.88±156.65	0.002**
	After	2140.25±340.32	1936.13±456.22	1620.63±295.7	1706.25±161.97	0.017*
	Difference	99±192.81	82.75±244.09	148.13±358.94	113.38±103.29	0.956
	[2]p	0.190	0.370	0.281	0.017*	-
L-ETW	Before	2245.5±329.22	1843.75±310.63	1670.5±322.37	1542.13±235.97	0.001**
	After	2238.5±339.87	2006±345.43	1743.13±256.8	1549.75±299.63	0.001**
	Difference	-7±149.59	162.25±250.17	72.63±154.60	7.63±198.11	0.299
	[2]p	0.898	0.109	0.226	0.916	-
L-FTW	Before	1987.88±305.23	1740.38±335.99	1428.88±233.59	1494.63±239.33	0.002**
	After	1966±417.11	1864.63±270.45	1548.38±282.44	1586.88±290.40	0.035*
	Difference	-21.88±234.67	124.25±338.32	119.5±290.91	92.25±155.75	0.660
	[2]p	0.800	0.333	0.283	0.138	-

Data presented are mean values ± standard deviation, R: Right knee, L: Left knee, ETW: Extensors total work, FTW: Flexors total work, [1]One-Way ANOVA test, [2]Paired sample t-test,*: p<0.05,**: p<0.01

reported that DS increases agility, speed and strength (8,15), whereas some other studies report that SS negatively affects the performance (2,8,14,16,17). Kurt and Fırtın (15) suggest that professional athletes may avoid SS before training or competitions to prevent a decrease in anaerobic performance.

Few studies have investigated performance variables, such as endurance (18) and power (19,20), which we examined in our study. The results of this study suggested that DS exercises in well-trained basketball players improved knee extensor and flexor strength and endurance; on the other hand, SS was found to increase extensor strength and knee muscle endurance in less-trained basketball players. These results are consistent with previous studies that did not find any decrease in performance caused by the DS (21). Yamaguchi and Ishii (20) examined 30-s static and DS effect on limb strength. As a result of this study, it was suggested that the 30-s SS did not affect muscular performance, whereas DS led an increase in lower-limb strength (20). Although the results of group II in our study are consistent with the values from the previous study, different results were obtained in group IV. In group IV (Ir: IT after SS) EPT values were found to be statistically significantly lower after SS than after DS. In the same group, PT and PT % BW values were measured after DS, and they were significantly higher than those measured after SS. Values of the left and right knee flexor strengths (PT and PT% BW) were measured after DS and they were significantly higher in group II (R: IT after SS) than those measured after SS (right PT, PT % BW and left PT, PT % BW).

In our study, differences in the TW (endurance, maintenance of maximal muscle power) were similar among the four groups. Measurements taken after the DS in group II showed a statistically significant increase. In group IV, measurements taken after DS in right flexor (TW and BW values) suggested a significant increase than those after SS. DS is recommended as the primary stretching method before high-speed and force-requiring activities (22). In this type of stretching, athletes perform similar movements that they perform in competitions; thus, they also focus on competitions at the same time (23).

The less-trained group III showed a statistically significant increase in measurements of the right extensor (TW and TW % BW values) after SS than after DS. Unlike results of the present study, knee flexion and extension maximal performance (1- RM =1- Max repetition) measured 10 min after SS decreased by 7.3% and 8.1%, respectively (24). This decrease in performance may be because of the type of activity following the stretching type and the stretching routine. In recent years, conventions regarding warm-up routines have been changed because some types of stretching have been reported to cause performance loss (25). Many athletic teams and individuals have also added DS to their warm-up routines. DS is expected to be superior to SS because DS includes movements similar to those in future competitions (26); however, this has not yet been fully substantiated using scientific research. Many research studies suggest that combining static and DS may have decreased the negative aspects of SS (25).

O'Sullivan et al. (27) examined the short-term effects of warming up with static and DS on hamstring flexibility. Their research included participants with hamstring injuries and a control group. This study suggested that SS increased hamstring flexibility whereas DS had no effect. Therefore, the lack of evaluation on hamstring flexibility is a limitation of our study. Similar research has been conducted with fewer participants, but the sample size (32 people) was another limitation (20,21,28). Further studies should investigate not only the optimal warm-up parameters according to time, intensity and resting intervals but also include dynamic and static-stretching combinations, sports-specificity, environmental conditions and psychological factors.

Thus, we found that SS increases knee extensor strength and endurance in less-trained basketball players; however, DS increases knee flexor strength and endurance.

Conclusion

Our study results suggest that before competitions, static and DS exercises might affect performance positively in less-trained basketball players. In addition, we found that DS exercises following a warm-up contribute to knee extensor and flexor strength and endurance in well-trained basketball players. Therefore, we suggest that SS should be included in stretching exercise protocols, although with less frequency compared to DS.

Ethics

Ethics Committee Approval: A quantitative, cross-sectional, and prospective study was conducted between 11.12.2013 and 11.06.2014 with the approval of the Ethics Committee of Trakya University Faculty of Medicine (protocol number: TÜTF-GOKAEK 2013/185).

Informed Consent: The written informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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ORIGINAL RESEARCH

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Evaluation of Childhood Posterior Fossa Malignant Tumors: A Single-center Study

Çocukluk Çağı Arka Çukur Habis Tümörlerinin Değerlendirilmesi: Tek Merkezli Çalışma

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Abstract

Objective: The aim of this study is to determine the clinical and radiological findings, early surgical results, and complication rates of children who were admitted to the neurosurgery clinic due to the posterior fossa malignant tumor.

Method: The records of patients under the age of 18 who were diagnosed as malignant posterior fossa tumors in our clinic between 2011-2020 were scanned. The demographic features, symptoms, signs, surgeries, pathological results, and complications of the patients were recorded. Pre and postoperative neuroimaging of patients are examined; The location of the tumor, the presence of a residual tumor and of hydrocephalus were examined.

Results: Thirty-three patients were identified, the median age of these children was 7. Among the symptoms of admission were headaches (57.6%) and gait disturbance (48.5%). Papilledema, ataxia, and nystagmus were also common. Six patients had preoperative cranial nerve palsy and 3 patients had hemiparesis. Preoperative hydrocephalus was present in 66.7%. The most common tumor type was medulloblastoma (39.4%). The rate of high-grade tumors among the operated tumors was 66.7%. Seven of the resected tumors had invasion into the brain stem. Tumor resection was performed in 24 patients, in 12 patients total resection was achieved. Tumor surgery was not performed in patients with diffuse pontine glioma. External ventricular drainage (EVD) was inserted in 30.3% of all patients. Only 4 of them needed ventriculoperitoneal (V-P) shunt. High-grade tumors had a higher risk of complications than low-grade tumors (p=0.038). The complication rate was high in totally removed tumors (p=0.034). The most common complication was CSF fistula (16.7%). Three patients with EVD had signs of infection. Three patients had a hematoma at the postoperative tumor site. Hydrocephalus developed in two patients without EVD and V-P shunts were inserted to these patients. Four of 6 patients with V-P shunt inserted had postoperative intraventricular blood. Postoperative hemiparesis was observed in two

Öz

Amaç: Arka çukur habis tümörleri nedeniyle nöroşirurji kliniğine yatırılan çocukların klinik ve radyolojik bulguları ile birlikte erken cerrahi sonuçları ve komplikasyon oranlarının belirlenmesi amaçlanmıştır.

Yöntem: 2011-2020 yılları arasında kliniğimizde malign posterior fossa tümörü tanısıyla tedavi olan 18 yaş altındaki hastaların verileri tarandı. Hastaların demografik özellikleri, şikayetleri, klinik bulguları, yapılan ameliyatlar, patoloji sonuçları ve komplikasyonlar not edildi. Ameliyat öncesi ve sonrası görüntüleme yöntemleri incelendi. Tümörün yerleşim yeri, rezidü tümör varlığı, hidrosefali olup olmamasına bakıldı.

Bulgular: Otuz üç hasta tespit edildi, bu çocukların ortanca yaşı 7 idi. Başvuru şikayetleri arasında en fazla baş ağrısı (%57,6) ve dengesizlik (%48,5) vardı. Papilödem, ataksi ve nistagmus ön planda idi. Ameliyattan önce 6 hastada kranial sinir paralizisi ve 3 hastada hemiparezi vardı. Ameliyat öncesi hidrosefali %66,7'sinde vardı. En fazla görülen tümör medulloblastomdu (%39,4). Opere edilen tümörler içinde yüksek dereceli tümör oranı %66,7 idi. Rezeksiyon yapılan tümörlerden 7 tanesinde beyin sapına invazyon görüldü. Yirmi dört hastaya tümör rezeksiyonu yapıldı, bunların 12'sinde total çıkarım sağlandı. Diffüz pontin gliom olan hastalara cerrahi yapılmadı. Tüm hastaların %30,3'üne eksternal ventriküler drenaj (EVD) takıldığı tespit edildi. Bunlardan sadece 4'ünün ventriküloperitoneal (V-P) şant ihtiyacı oldu. Yüksek dereceli tümörlerde herhangi bir cerrahi komplikasyon gelişme oranı düşük dereceli tümörlere göre daha fazlaydı (p=0,038). Total çıkarılan tümörlerde de komplikasyon oranı yüksekti (p=0,034). En fazla görülen komplikasyon BOS fistülüydü (%16,7). EVD'si olan 3 hastada enfeksiyon bulguları vardı. Üç hastada tümör lojunda hematom vardı. EVD'si olmayan iki hastada (%8,3) hidrosefali gelişti ve bu hastalara V-P şant takıldı. Şant takılan 6 hastadan 4'ünde ameliyat sonrası ventrikül içinde kan vardı. Daha önce güçsüzlüğü olmayan iki hastada ameliyattan sonra hemiparezi gelişti. Üç hastada (%12,5) mutizm ve bir hastada dizartri vardı. İki hastada yoğun bakım takibi sırasında pnömoni gelişti ve bu çocuklardan biri ameliyattan sonra ikinci ayda kaybedildi.

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Abstract

patients without previous weakness. Three patients (12.5%) had mutism and one patient had dysarthria. Two patients had pneumonia during intensive care follow-up and one of these children died two months later.

Conclusion: In children with posterior fossa malignant tumors; We found that a high degree of the tumor, brainstem invasion, complete removal of the tumor, and presence of postoperative blood in the ventricle increase the risk of complications.

Keywords: Chilhood malignant tumors, complication, pediatric brain tumors, posterior fossa tumors

Öz

Sonuç: Çocukluk çağı arka çukur habis tümörlerinde, yüksek dereceli tümör varlığı, beyin sapı invazyonu, tümörün total çıkarılması ve ameliyat sonrası ventrikül içinde kan olması komplikasyon riskini artırmaktadır.

Anahtar kelimeler: Çocukluk çağı malign tümörleri, komplikasyon, pediyatrik beyin tümörü, posterior fossa tümörü

Introduction

Malignant central nervous system tumors are the second most common malignancies in children after leukemia and they are the most common pediatric solid organ tumors (1). The proportion of tumors located in the posterior fossa in childhood is between 54% and 70% and higher than in adults (2). Symptoms and signs of posterior fossa tumors are primarily due to increased intracranial pressure and secondary to local compression of cerebellar nuclei and brain stem. In addition, it can cause hydrocephalus by causing obstruction in the circulation pathways of cerebrospinal fluid (CSF) (3). Most of these tumors need to be treated urgently and the risk of morbidity and mortality is high (4).

In this study, the clinical and radiological findings, early surgical results, and complication rates of children that were treated for a malignant tumor located in the posterior fossa were investigated in our clinic.

Materials and Methods

This retrospective study was made with the decision of the local ethics committee numbered 2020.06.2.01.085. For the study, written and verbal consent was obtained from the families.

Between 2011 and 2020, there were 76 consecutive children treated in our clinic due to brain tumors. Of these, 35 were diagnosed as malignant posterior fossa tumors. The data of these 35 patients were analyzed by scanning from the hospital archive system. Two patients were excluded from the study because their data were insufficient. Patients at the age of 18 years and older and children with supratentorial tumors and infratentorial benign tumors were excluded from the study. For all 33 children, age, gender, symptoms, clinical signs, whether they were operated, the timing of surgery, whether external ventricular drainage (EVD) and/or ventriculoperitoneal (VP) shunt was inserted, type of tumor, grade, Ki-67 index, neurological status, early surgical complications, and results when leaving the hospital were recorded. Preoperative and postoperative magnetic resonance imagings and computed tomography were scanned. Tumor localization, whether there was a cyst or bleeding, presence of hydrocephalus, tumor removal rate (total if 100% removed; subtotal if removed 90% and above; partial if removed below 90%), and the presence of blood in the postoperative ventricles were evaluated by the same specialist doctor.

Statistical Analysis

Nominal variables were compared using the Fisher's exact test or chi-square test, according to the number of subjects. The F test was used to evaluate the distribution characteristics of countable variables, which were compared with the Student's t-tests. A p-value of <0.05 was considered significant.

Results

Clinical Features

The median age of 33 children was 7 years (17 months-17 years; min-max). Girl to boy ratio was 18/15. The patients were divided into 4 different groups by age: those younger than 3 years old (21.4%), those at the age range of 3-6 years (24.2%), those at the age range of 6-10 years (27.3%), and those at the age over 10 years (27.3%). The most common symptoms of admission were headache (57.6%) and gait disturbance (48.5%). Four patients were brought to the emergency service due to epileptic seizures. Papilledema, ataxia, and nystagmus were frequently observed in the examination findings of the children. Six patients had preoperative cranial nerve paralysis. Of these, 3 patients had abducens nerve, 1 patient had the oculomotor nerve, 1 patient had the facial nerve, and 1 patient had hypoglossal

nerve paralysis. All three patients had extremity weakness (Table 1).

Pathology and Surgery

The most common tumor was medulloblastoma (39.4%). Then, diffuse pontine glioma, ependymoma, pilocytic astrocytoma were seen, respectively. One patient had hemangioblastoma and 1 patient had Ewing sarcoma/primitive neuro-ectodermal tumors (PNET) (Table 2). The rate of World Health Organization Grade III and IV tumors among the operated tumors was 66.7%. All of the patients were operated on prone position. Tumor resection was performed in 24 patients without diffuse pontine glioma (Table 3). Total removal was achieved in half of the patients who underwent tumor resection. Three of the subtotally removed tumors (patient no: 5, 15, 22) were operated again within 24 hours and removed totally. Endoscopic third ventriculostomy (ETV) was performed in one of the patients with pontine glioma. 52% of 25 patients who underwent surgery were operated under emergency conditions. EVD was inserted into 10 (30.3%) of all patients (one with diffuse pontine glioma). Only 4 of them needed VP shunts (one of them diffuse pontine glioma).

Table 1. The rates of 33 patients' symptoms and signs

	n	Percentage
Symptom		
Headache	19	57.6
Gait disturbance	16	48.5
Vomiting	13	39.4
Dizziness	5	15.2
Seizure	4	12.1
Diplopia	2	6.1
Weakness	2	6.1
Signs		
Papilledema	23	69.7
Ataxia	22	66.7
Nystagmus	17	51.5
Dysmetria	12	36.4
Cranial nerve palsy	6	18.2
Dysdiadochokinesia	6	18.2
Paresis	3	9.1
Dysarthria	2	6.1

Table 2. Distribution of tumors

	n	Percentage
Medulloblastoma	13	39.4
Diffuse pontine glioma	9	27.2
Ependymoma	5	15.2
Pilocytic astrocytoma	4	12.2
Hemangioblastoma	1	3
Ewing sarcoma/PNET	1	3

PNET: Primitive neuro-ectodermal tumors

Complications

The rate of development of any surgical complications in Grade III and Grade IV tumors was 13/18 and was significantly higher compared to low-grade tumors (p=0.038). The complication rate in totally removed tumors was also significantly higher than subtotally removed ones (p=0.034). There was no statistical relationship between age, gender, tumor size, timing of surgery and complication development (p=0.362, p=0.653, p=0.552, p=0.613, respectively). The most common complication was CSF fistula (16.7%). Only 1 patient with CSF fistula was operated due to dura repair. Three patients with EVD had signs of infection. *Staphylococcus epidermidis* and *Stenotrophomonas maltophilia* were grown in the CSF culture samples. All 3 patients healed with antibiotic therapy. Three patients had a postoperative hematoma at the tumor site (one of the epidural hematoma), these patients were re-operated due to hematoma evacuation. Hydrocephalus developed in two patients (8.3%) who did not receive EVD in the early postoperative period and VP shunts were inserted in these patients. Four of 6 patients with VP shunt inserted had postoperative intraventricular blood. Postoperative hemiparesis developed in two patients without previous weakness. Three patients (12.5%) had mutism and one patient had dysarthria. Two children had pneumonia during intensive care follow-up, one of whom died two months after surgery.

Discussion

Posterior cranial fossa has a very limited volume compared to the supratentorial area. It has a brain stem, cerebral aqueduct, 4th ventricle, outlet foramens and cerebellum. A growing posterior fossa tumor can lead to the dysfunction of the structures in this region in a short time, causing brain stem and cerebellar findings. In addition, they can cause herniation or hydrocephalus with the mass effect and edema (2). In our series, 22 patients had preoperative hydrocephalus. Thirteen of these patients were operated urgently. Three of these 13 patients were also in the herniation table. Partanen et al. (5) reported the EVD rate as 10/22 after the posterior fossa tumors they operated, and our EVD rate was similar.

Table 3. Early surgical results and complications of patients undergoing tumor resection

No	Age (years)	Gender	Pathology	Ki-67 (%)	Preoperative hydrocephalus	Tumor removal rate	EVD	Shunt	Complications	Result (GCS)
1	17 m	G	Anaplastic ependymoma	30	Y	Subtotal (95%)	Y	Y	7th nerve paralysis, hematoma	15
2	17 m	G	Medulloblastoma	15	Y	Subtotal (90%)	Y	N	Pneumonia	3 (ex)
3	18 m	B	Anaplastic ependymoma	30	N	Total	N	N	Pneumonia, hemiparesis, 9th nerve paralysis	15
4	20 m	B	Pilocytic astrocytoma	3	N	Total	N	N	None	15
5	21 m	B	Ependymoma	12	Y	Subtotal (90%)	N	Y	CSF fistula, hydrocephalus	15
6	29 m	G	Anaplastic ependymoma	20	Y	Partial (80%)	Y	N	Infection, 6th nerve paralysis	15
7	3	G	Ewing sarcoma/ PNET	20	Y	Partial (70%)	Y	N	Epidural hematoma	15
8	5	G	Anaplastic ependymoma	70	Y	Total	N	N	None	15
9	5	G	Pilocytic astrocytoma	4	Y	Subtotal (95%)	Y	N	None	15
10	6	G	Medulloblastoma	80	N	Total	N	N	None	15
11	6	G	Medulloblastoma	18	Y	Subtotal (95%)	N	N	CSF fistula	15
12	7	B	Pilocytic astrocytoma	3	Y	Partial (70%)	N	Y	Mutism, hydrocephalus	15
13	7	G	Medulloblastoma	40	Y	Subtotal (90%)	N	N	None	15
14	7	B	Medulloblastoma	30	Y	Total	N	N	Mutism, CSF fistula	15
15	8	B	Medulloblastoma	30	Y	Partial (80%)	Y	Y	CSF fistula, infection	15
16	8	B	Medulloblastoma	70	Y	Total	N	N	6th and 7th nerve paralysis	15
17	11	G	Medulloblastoma	80	Y	Total	N	N	None	15
18	11	G	Medulloblastoma	9	Y	Total	N	N	None	15
19	12	G	Medulloblastoma	60	Y	Total	N	N	6th and 7th nerve paralysis, hemiparesis	15
20	13	B	Pilocytic astrocytoma	2	N	Total	N	N	None	15
21	14	B	Medulloblastoma	70	Y	Total	Y	Y	Mutism, infection, 9th nevre paralysis	15
22	15	G	Medulloblastoma	20	Y	Partial (70%)	Y	N	Mutism, dysarthria	15
23	15	G	Hemangioblastoma	1	Y	Total	N	N	None	15
24	17	B	Medulloblastoma	80	Y	Partial (80%)	Y	N	Hematoma	15

M: Months, G: Girl, B: Boy, Y: Yes, N: No, EVD: External ventricular drainage, GCS: Glasgow Coma scale, CSF: Cerebrospinal fluid, PNET: Primitive neuro-ectodermal tumour

The classic symptoms of posterior fossa tumors are irritability, lethargy, nausea, vomiting, headache, and behavioral changes with increased intracranial pressure (6). Our patients had similar symptoms and in addition, four patients had epilepsy. In a study, clinical signs were most commonly reported as ataxia, papillary stasis, dysmetria, and dysdiadokinesia (7). In our series, 51% of patients had nystagmus and 18% had cranial nerve palsy.

Yağcı Küpeli et al. (8) reported that the median age was 8 years in childhood tumors similar to ours. In the same study, it was reported that tumors were more common in males in all age groups. Similarly, Erdinçler et al. (4) found

the proportion of boys as 66%. However, in our series, posterior fossa tumors were more common in girls.

The most common types of tumors found in the posterior fossa are cerebellar astrocytomas, medulloblastomas, and brainstem gliomas (1). The most common tumors in our patients were medulloblastoma and diffuse brainstem glioma. Medulloblastoma rate was most common, similar to the literature. Abraham et al. (9) 51.3% and Lee et al. (10) reported it as 35.9%. However, Yağcı Küpeli et al. (8) reported as 7.9% and Shanmugavadivel et al. (11) as 10.9% among the posterior fossa tumors, and these rates are lower than our study. In addition, one of our patients had Ewing sarcoma/PNET, which is rare in the posterior fossa, and was urgently operated due to left cerebellar hemisphere compression and hydrocephalus (Figure 1). It has been reported that ependymomas are more common in males in childhood and its rate in the posterior fossa is 5.2% (5,12). It was 15.6% in our study, but more in girls. Cerebellar astrocytomas are benign tumors of the central nervous system. It constitutes 30% of childhood posterior fossa tumors (13). In our patients, the rate of pilocytic astrocytoma was lower than in other series.

Diffuse pontine gliomas have a poor prognosis. Surgical treatment has been abandoned in the treatment of diffuse pontine gliomas. However, a stereotaxic biopsy can be performed for collecting samples from the tumor. In patients with brainstem lesions, the postoperative morbidity of stereotactic biopsy has been reported between 0 and 20% and mortality between 0 and 3% (14). Children with diffuse pontine glioma treated in our clinic did not undergo any surgery for the tumor. Patients were followed up by pediatric oncology. One of the patients underwent EVD and then VP shunt due to acute hydrocephalus. ETV was performed on another patient.

Depending on the type of tumor, tumor localization may vary. It has been reported that tumors in the posterior fossa are mostly located in vermis localization (5). In our series, although tumors were more common in vermis origin, the rate of tumors in the fourth ventricle was higher. This was because the tumor reached a large volume and filled the fourth ventricle in a high proportion of patients. Lee et al. (10) reported the rate of tumors with extensive cerebellum and brain stem as 43.6%. This was in a quarter of our patients. Two of our patients whose tumors were totally removed had postoperative hemiparesis and these children had brainstem invasion. In another aspect, invasion into the brainstem was the most important reason for total resection of the tumor. Three of our patients were re-operated due to residual tumors. In a study with 22 patients, it was reported that 2 patients were operated twice, and 1 patient was operated three times (5). In 3 of our patients, there was postoperative bleeding in the tumor site and they were re-operated. Ur-Rehman et al. (15) gave this rate as 3.8%.

Partanen et al. (5) reported that at least one complication developed in 19 out of 22 patients. In our patients, this rate was 15/24 and most of the complications occurred in high-grade tumors. Ur-Rehman et al. (15) reported that in 79 infratentorial tumors they operated, the most common surgical complications were hydrocephalus and CSF fistula. Similarly, we saw the most common complication was CSF fistula. However, only one patient had to repair the dura mater. Bilginer et al. (13) reported CSF fistula in 6.4% of patients after 31 pilocytic astrocytoma operations.

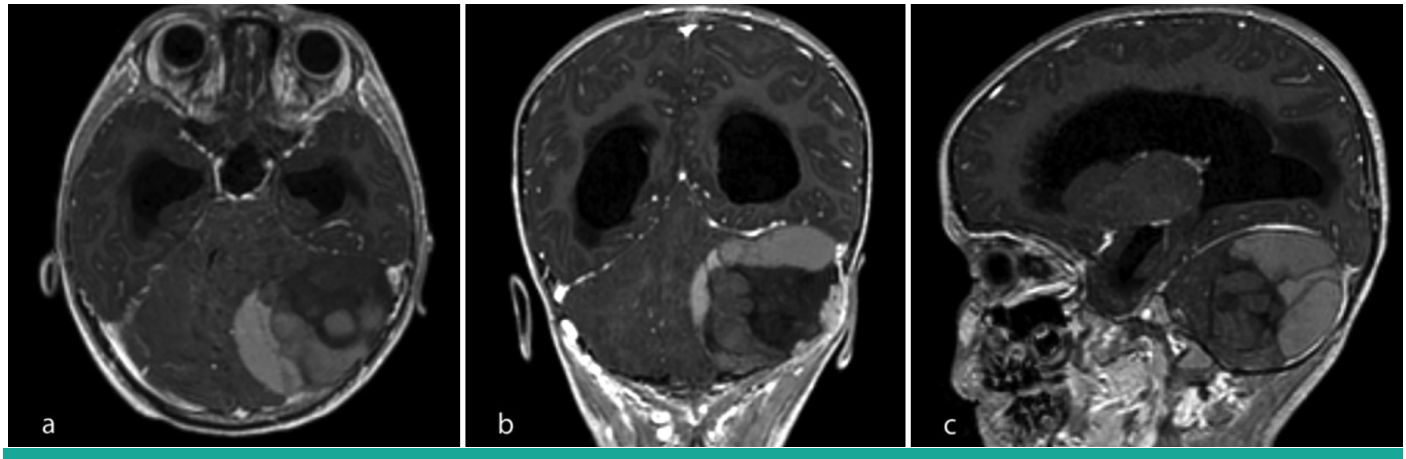

Figure 1. Contrasted MRIs of the patient with Ewing sarcoma/PNET tumor; a) axial, b) coronal, c) sagittal sections
MRI: Magnetic resonance imagings, PNET: Primitive neuro-ectodermal tumors

VP shunt or ETV application has been reported at different rates due to hydrocephalus in various series. Lee et al. (10) reported the rate of patients developing postoperative permanent hydrocephalus as 61.5%. In another study, they reported this rate as 9.4% (9). In the same study, being under the age of six years and the presence of intraventricular blood were shown as risk factors for hydrocephalus. One-quarter of our operated patients had VP shunts inserted and patients who needed shunt had a high rate of intraventricular blood.

The rate of wound infection in posterior fossa surgery has been reported around 6% (15). In our series, there were no children with wound infections. Abraham et al. (9) stated that 4 of 14 patients requiring shunts had meningitis and two patients developed staphylococcus in the CSF culture. In our series, there were 3 cases showing signs of meningitis. VP shunts were inserted into two of them due to hydrocephalus. In addition, 2 patients were diagnosed with pneumonia during intensive care follow-up and a child died due to this reason in the second postoperative month. Aslantürk et al. (3) reported death rate as 20% in the early postoperative period and reported that two of them were due to surgical air embolism in a sitting position. We operated all patients in the prone position and did not see air embolism.

One of the complications that occur after posterior fossa tumor surgery is mutism. Cámara et al. (16) reported cerebellar mutism at a rate of 19/36. Gora et al. (17) gave this rate as 18.2% in 33 children with midline posterior fossa tumors. In the same study, they identified medulloblastoma, maximum size >45 mm tumor, superior cerebellar peduncle, and middle vermian incision as risk factors for mutism. Three patients who developed mutism from our patients had midline tumors, all of them were operated with vermian incision, and two had cerebellar peduncle involvement. Studies have shown that there may be findings accompanying mutism such as ataxia, dysarthria, and facial nerve palsy (18). One of our patients who developed mutism had difficulty swallowing, and another had dysarthria after mutism. In addition, another patient with anaplastic ependymoma had difficulty swallowing. Lee et al. (10) have stated that this complication is seen more than known. Children who were operated for 183 posterior fossa tumors were examined with videofluoroscopic swallowing study in the early period, and 39 of them had postoperative swallowing difficulty. In the same study, the most important risk factor for difficulty swallowing was shown as brain stem invasion.

The limitations of this study are its retrospective design, low number of patient group, insufficient long-term surgical follow-up, and evaluation of chemotherapy and radiotherapy treatments. Having more information about tumor biology, advances in imaging methods and microsurgical techniques, and prospective clinical studies will reduce morbidity and mortality in the future for children with posterior fossa tumors.

Conclusion

In our study, high-grade tumor, brainstem invasion, total tumor removal, and intraventricular blood increased the risk of complications in children. Total resection should be aimed for posterior fossa tumors, but it should be noted that the rate of morbidity increases as the resection amount increases in patients with brainstem invasion. Our goal in the treatment of these children should be to improve long-term quality of life, to maintain cognitive function and growth, to minimize complications, and to reduce the risk of secondary malignancies in the course of the disease.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Turkey, Bağcılar Training and Research Hospital Ethical Committee (decision number: 2020.06.2.01.085).

Informed Consent: For the study, written and verbal consent was obtained from the families.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.E., Design: B.E., Data Collection or Processing: B.E., İ.G., Analysis or Interpretation: N.S.B., Writing: B.E., İ.G., N.S.B.

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ORIGINAL RESEARCH

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Facet Dislocation Fractures of Subaxial Cervical Spine: A Treatment Algorithm for Surgical Approach Decision

Subaksiyel Servikal Omurganın Faset Dislokasyon Fraktürleri: Cerrahi Yaklaşım Kararı için Tedavi Algoritması

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Abstract

Objective: To perform an analysis of the surgical approach choice in subaxial cervical spine (SCS) facet dislocations.

Method: The inclusion criteria were as follows: radiologically confirmed traumatic SCS facet dislocation, 18-70 years of age, stable medical condition, and isolated cervical trauma. The management scheme was based on the presence of traumatic disc herniation (TDH) and the grade of dislocation according to the Allen and Ferguson classification (AFC). In the absence of TDH, the reduction was attempted via traction under general anesthesia before surgery. In the presence of TDH, the reduction was attempted after anterior discectomy. Posterior open reduction was performed in case of an unsuccessful reduction attempt. Anterior stabilization was sufficient in AFC distractive flexion stage (DFS) 2 fractures while combined stabilization was performed in DFS 3 and 4 fractures.

Results: Thirty-two patients were included in the study. TDH was detected in 14 patients. The number of patients with DFS 2, 3, and 4 fractures was 6, 18, and 8, respectively. Posterior open reduction was needed in 9 patients. Anterior stabilization was performed in 6 patients (3 with TDH, 3 without TDH) and combined stabilization was performed in 26 patients (11 with TDH, 15 without TDH) via 6 anterior, 7 anterior-posterior, 15 posterior-anterior, and 4 anterior-posterior-anterior approaches. Satisfactory follow-up results were achieved in radiological and neurological evaluations, and neck pain scores.

Conclusion: The treatment algorithm for subaxial facet dislocations based on DFS and TDH presence provided satisfactory results.

Keywords: Allen and Ferguson classification, decision-making, facet dislocation fracture, subaxial cervical spine, subaxial injury classification and Severity scale, traumatic disc herniation

Öz

Amaç: Bu çalışmada subaksiyel servikal omurga (SSO) faset dislokasyon fraktürlerinde cerrahi yaklaşım seçimi algoritması geliştirilmesi amaçlanmıştır.

Yöntem: Çalışmaya dahil edilme kriterleri şu şekildeydi: Radyolojik olarak gösterilmiş travmatik SSO faset dislokasyon fraktürü, 18-70 yaş, medikal olarak stabil durum ve izole servikal travma varlığı. Tedavi algoritması temel olarak, travmatik disk herniasyonu (TDH) varlığına ve Allen ve Ferguson sınıflamasına (AFS) göre dislokasyon derecesine göre düzenlenmekteydi. Radyolojik incelemelerde TDH saptanmazsa, cerrahi girişim öncesinde genel anestezi altında traksiyon ile redüksiyon denenmesi yapılmaktaydı. TDH varlığında ise traksiyon denemesi öncesinde anterior diskektomi yapılmaktaydı. Eğer traksiyon ile redüksiyon girişimi başarısız olursa, posterior açık redüksiyon yapılmaktaydı. AFS'sine göre distraktive fleksiyon evre (DFE) 2 fraktürlerinde anterior stabilizasyon uygulanırken, DFE 3 ve 4 dislokasyonlarda kombine stabilizasyon yapılmaktaydı.

Bulgular: Çalışmaya 32 hasta dahil edildi. On dört hastada radyolojik incelemelerde TDH saptandı. Altı hastada DFE 2, 18 hastada DFE 3 ve 8 hastada DFE 4 faset dislokasyon fraktürü mevcut idi. Posterior açık redüksiyon 9 hastada gerekli oldu. Altı hastaya (3 TDH'si olan, 3 TDH'si olmayan) anterior stabilizasyon ve 26 hastaya (11 TDH'si olan, 15 TDH'si olmayan) kombine stabilizasyon uygulandı. Altı anterior, 7 anterior-posterior, 15 posterior-anterior ve 4 anterior-posterior-anterior yaklaşım uygulandı. Radyolojik, nörolojik değerlendirmelerde ve boyun ağrısı skorlarında tatmin edici sonuçlar elde edildi.

Sonuç: DFE ve TDH varlığına göre oluşturulan subaksiyel faset dislokasyonları için cerrahi tedavi algoritması ile başarılı sonuçlar elde edilmiştir.

Anahtar kelimeler: Allen ve Ferguson sınıflaması, faset dislokasyon fraktürü, karar verme, subaksiyel servikal omurga, subaksiyal yaralanma sınıflaması ve Şiddet ölçeği, travmatik disk hernisi

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Introduction

The section of the cervical spine from C3 to C7 is called the subaxial cervical spine (SCS) (1,2). The incidence of cervical spine fractures increased as a result of increased number of high energy traumas (3,4). A substantial part of these fractures is localized in the SCS (3,5,6). In particular, according to the literature, 44% to 62% of all cervical fractures are observed between the C5 and C7 segments (3,5,6). SCS fractures can be divided into many subgroups. Facet dislocation fractures occur in case the cervical spine is subjected to severe distraction and flexion forces due to the trauma (7).

The facet dislocations are considered unstable fracture which requires surgical intervention, and decompression, reduction, and fixation are performed during procedures (8-10). Several different modalities are considered for surgical approaches such as anterior alone, posterior alone, anterior-posterior, posterior-anterior, and anterior-posterior-anterior (APA) approaches (8-12). And the choice of surgical approach in such fractures is still a debate (11,12).

Reduction in facet dislocations can be performed via 3 different methods: closed, anterior, and posterior (13). Closed reduction is a commonly used method in initial management (14,15). However, 22% to 40% of the facet dislocations are associated with cervical traumatic disc herniation (TDH) (16,17). And, in the presence of TDH, a high risk of spinal cord compression and neurological deterioration is present in closed reduction attempts without an initial cervical discectomy (13). For this reason, the presence of disc herniation is crucial in the choice of treatment method.

The grade of facet dislocation fracture is correlated with the intensity of the trauma force that the cervical spine is subjected to (7). According to the Allen and Ferguson classification (AFC), which is based on the direction of trauma, facet dislocation fractures occur with severe distractive flexion and are divided into four stages commensurate with the severity of trauma (7). Distractive flexion stage (DFS) 1 refers to the injury of the posterior ligament complex with single facet subluxation, DFS 2 consists of unilateral facet dislocation with minimal corpus displacement, DFS 3 lesion is bilateral facet dislocation with approximately 50% corpus displacement anteriorly, and DFS 4 defines anterior displacement of the upper vertebrae over the lower vertebrae beyond the length of a corpus diameter with bilateral facet dislocation (7).

Different results are reported in the literature for anterior, posterior, and combined approaches (8,9,11,12). And, the choice of surgical approach in such fractures is still a debate (11,12). Therefore, in our retrospective study, we aimed to establish a management modality producing radiological and clinical optimal results in facet dislocation fractures. A treatment algorithm based on the stage of dislocation and the presence of TDH is formed.

Materials and Methods

This study was conducted following the World Medical Association Helsinki Declaration. Approval for this research was obtained from our local clinical research ethics committee. Patients who were operated between August 2014 and August 2018 were included in the study. The following were considered as the inclusion criteria in the study: radiologically confirmed traumatic SCS (C3-C7) facet dislocation fracture, 18-70 years of age, stable medical condition with Class I-III according to the American Anesthetic Association (ASA), and presence of isolated cervical trauma. And, the following were considered as the exclusion criteria in the study: unstable medical condition with ASA Class IV-V, presence of multiple trauma, and previous cervical spine operation.

Subaxial injury classification and Severity scale, based on the fracture morphology, the status of the discoligamentous complex, and neurological status, was used for treatment considerations and surgical decision (18). According to this scale, the surgical treatment decision was made in patients with a score of 5 or above, while the conservative treatment decision was made in patients with a score of 3 or below. In patients with 4 points, the decision was made according to the surgeon's choice. In all patients, cervical spinal magnetic resonance (MR) imaging and cervical spinal computed tomography (CT) were performed before surgery. Attention was paid to the osseous damage in three columns of vertebrae and the type of facet dislocation on CT images. Status of posterior ligament complex and cervical intervertebral disc and the presence of an extruded disc compressing the dural sac and nerve roots were investigated on MR images.

Operations were performed under general anesthesia. Fiberoptic intubation was performed to avoid from possible damage of hyperflexion during endotracheal intubation. Closed reduction attempt was performed under general anesthesia before the operation. Primarily, Gardner-Wells tongs (GWT) were used for closed reduction. Somatosensory evoked potentials and motor evoked potentials monitoring

was routinely used during reduction attempts, position changes and surgical approaches to reduce the potential neurologic deterioration risk. When the closed reduction failed, a posterior open reduction was performed.

The treatment scheme formed for the management of SCS facet dislocations is shown in Figure 1. The choice of surgical approach was made according to the staging of the AFC and the presence of the TDH. Anterior stabilization (Figure 2) was performed in patients with DFS 2 fracture, while combined anterior and posterior stabilization (Figure 3) was performed in patients with DFS 3 and 4 fractures. In the presence of TDH on MR images, an initial anterior cervical discectomy was performed to prevent additional neurological injury during reduction.

In patients with TDH, following the removal of the extruded disc material via an initial anterior discectomy, manual traction was performed by an assistant staff for reduction. In case of successful reduction attempt, a single session anterior approach was accomplished with stabilization in patients with DFS 2 fracture. Additional posterior stabilization was performed in patients with DFS 3 and 4 fractures. In case of unsuccessful reduction attempt, the patients were taken to the prone position and posterior open reduction and stabilization were performed. Subsequently, the patients were placed in the supine position again and anterior stabilization was performed, and the approach termed APA was completed.

In patients without TDH, closed reduction was attempted with traction under general anesthesia before surgery. In case of successful reduction, anterior fusion via a single approach was performed in patients with DFS 2 dislocation, and combined (anterior and posterior) stabilization was performed in patients with DFS 3 and 4 dislocations. In the event of unsuccessful closed reduction, an initial posterior open reduction and stabilization was

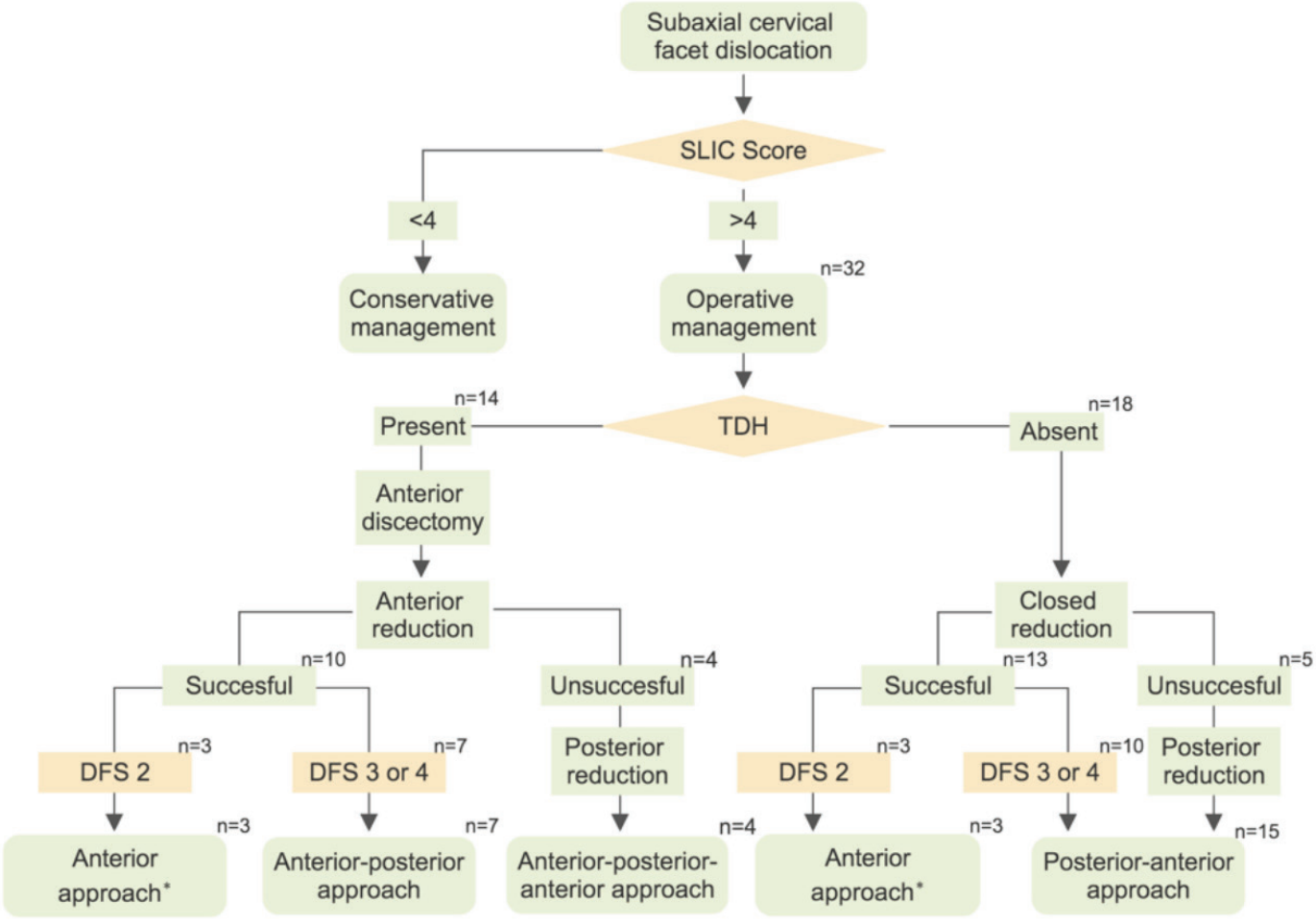

Figure 1. Treatment algorithm for the management of subaxial cervical facet dislocations

SLIC: Subaxial Cervical Spine Injury Classification, TDH: Traumatic disc herniations, DFS: Distractive flexion stage
**Anterior approach was performed in 6 patients in total*

performed. And, anterior stabilization was performed in the second stage.

A transverse incision from the midline to the medial border of the sternocleidomastoid muscle was used in the anterior approach. After vertical platysma incision, blunt dissection was performed to achieve a surgical corridor lateral to the trachea and esophagus, and medial to the carotid sheath. A self-retaining retractor placed underneath the musculus longus colli was used for surgical exposure. After anterior discectomy, reduction was attempted with traction in necessary cases. Anterior cervical plate systems (APSs) were used for anterior stabilization. A cervical interbody polyetheretherketone (peek) cages were placed after discectomy, and stabilization was consolidated with APSs. In patients who underwent corpectomy, tricortical osseous autograft from the iliac crest was placed in the corpectomy cavity, and stabilization was ensured with APSs.

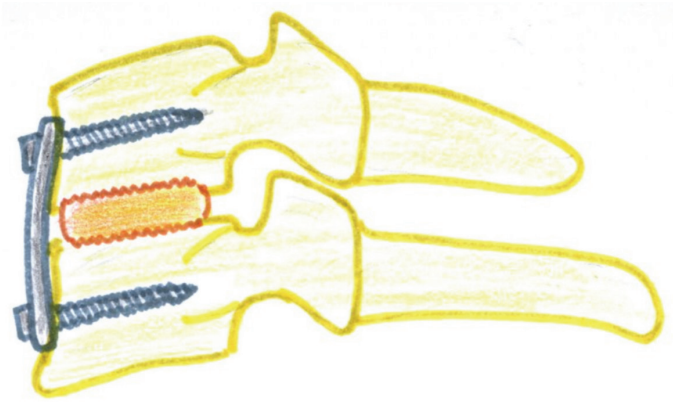

Figure 2. Illustration of anterior stabilization

A midline incision was planned for posterior stabilization. The paraspinal muscle dissection was performed for exposing spinous processes, laminae, and facets (lateral masses), and a self-retaining retractor was placed. In case of unsuccessful reduction via manual traction, the apex of the superior articular process of the inferior facet was resected using a high-speed drill to release the locked facets. Short

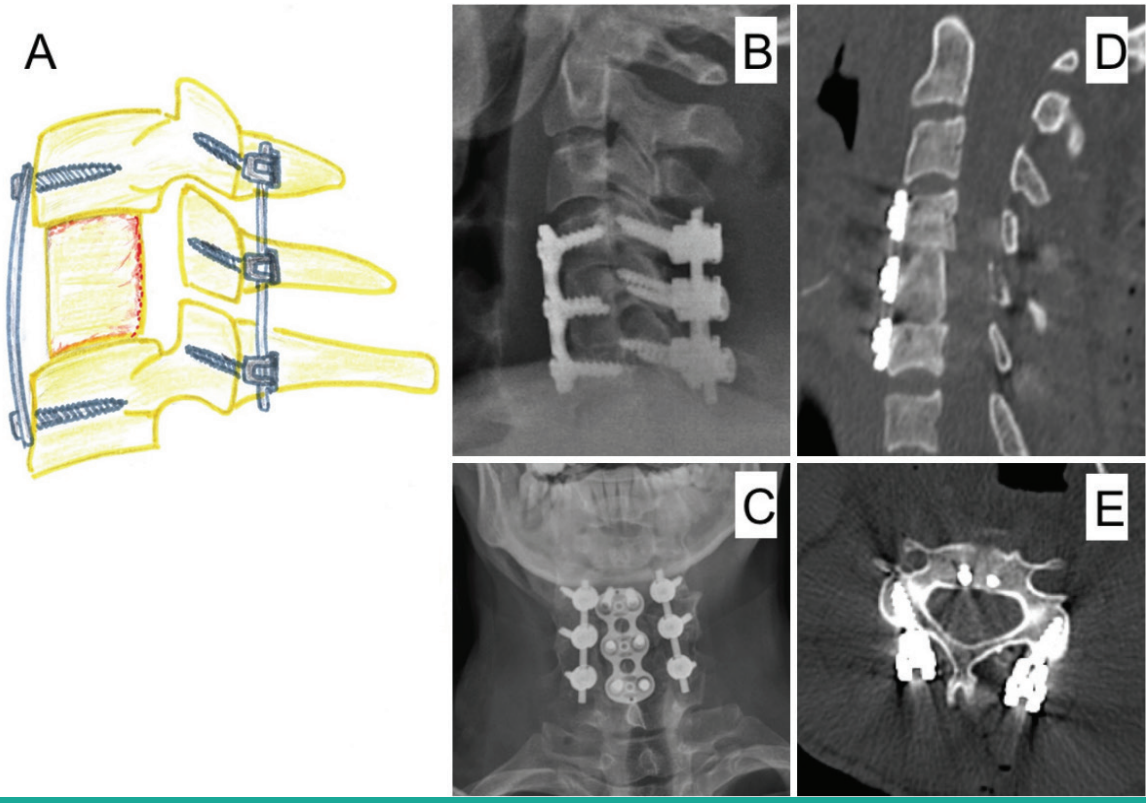

Figure 3. Illustration of combined stabilization
A. Illustration of combined anterior and posterior stabilization
B. Lateral view of X-ray showing sagittal alignment after combined stabilization
C. Mid-sagittal image of computed tomography (CT)
D. Anterior-posterior view of X-ray
E. Axial CT image showing anterior corpus and lateral mass screws

segmental fixation, using lateral mass screws at C3-C6, and pedicle screws at C7 and T1 vertebrae, was carried out in the reduced position.

Patients were called for a control examination in the first, third, and sixth months, first year, and subsequent years after discharge. Radiological and clinical records were analyzed to evaluate the results of the treatment. Evaluation of the neurological status of the patients was made using the American Spinal Injury Association (ASIA) Impairment scale. Changes in neck pain were evaluated using the Visual Analog scale (VAS).

Radiological evaluation was performed via lateral and anteroposterior cervical spine radiographs at each control examination, and via CT scan at 3 months, 6 months, 1 year, and subsequent years control visits. In the radiological follow-up, angulation of the upper endplate of the upper vertebra with the lower endplate of the lower vertebra, evaluated in sagittal imaging, was determined as traumatic kyphosis angle (Figure 4). The trabecular bone formation between the graft material and vertebral corpus and no sign of failure in implants were accepted as successful fusion during follow-up.

Statistical Analysis

Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS) Statistics for Windows, version 25.0 (IBM Corp., Armonk, New York, USA). Numerical variables were summarized as mean and standard deviation. Numerical variables were assessed using independent samples t-test. A p value of <0.05 was considered significant for all statistical analyses.

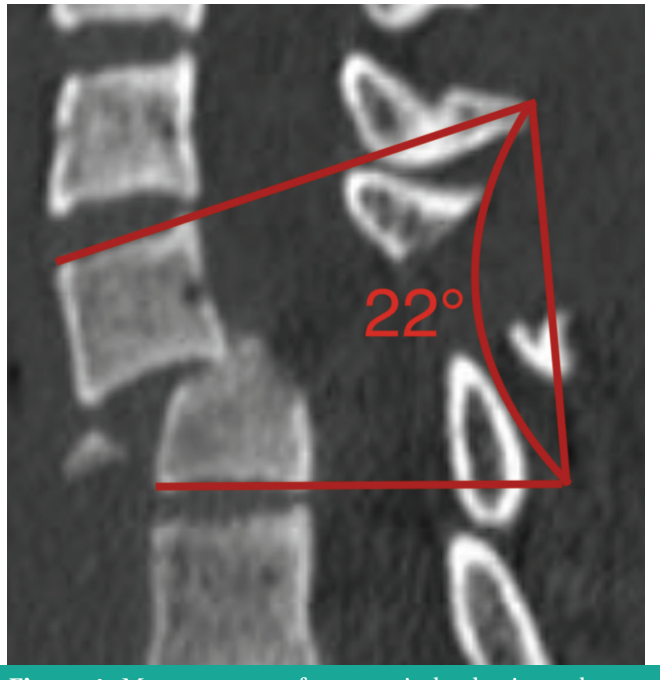

Figure 4. Measurement of traumatic kyphosis angle on sagittal cervical tomography image

Results

The characteristics of patients at admission were summarized in Table 1. A total of 32 (8 women and 24 men) patients were included in the study. The average age was 37.4±16.1 years, and the age distribution was 18-58 years. The most common cause of trauma was fall (n=20, 62.5%), followed by traffic accidents (n=10, 31.25%). Unilateral and bilateral facet dislocation was observed in 6 and 26 patients, respectively. In the staging according to AFC, most of the patients had DFS 3 dislocation (n=18, 56.2%), followed by DFS 4 fracture (n=8, 25%). Neurological status evaluated according to ASIA Impairment scale revealed that 8 (25%) patients had a complete neurological injury (ASIA grade A), 20 (62.5%) patients had an incomplete neurological injury (ASIA grade B-C-D) and 4 patients were neurologically intact (ASIA grade E). Fractures were most frequently observed at C6-C7 level (n=15, 46.9%) followed by C5-C6 level (n=10, 31.3%). On cervical vertebral MR images, TDH was detected in 14 (43.7%) patients.

Table 1. Characteristics of patients at admission

Total number		32
Age (Mean ± SD)		37.4±16.1
Gender	Female	8 (25%)
	Male	24 (75%)
Trauma mechanism	Fall from high	20 (62.5%)
	Traffic accidents	10 (31.25%)
	Jumping into shallow water	2 (6.25%)
Severity of dislocation (AFC)	DFS 2	6 (18.8%)
	DFS 3	18 (56.2%)
	DFS 4	8 (25%)
Neurological status (ASIA)	Grade A	8 (25%)
	Grade B	5 (15.6%)
	Grade C	6 (18.8%)
	Grade D	9 (28.1%)
	Grade E	4 (12.5%)
Fracture level	C3-C4	1 (3.1%)
	C4-C5	4 (12.5%)
	C5-C6	10 (31.25%)
	C6-C7	15 (46.9%)
	C7-T1	2 (6.25%)

SD: Standard deviation, AFC: Allen and Ferguson classification, DFS: Distractive flexion stage, ASIA: American Spinal Injury Association

The reduction was attempted with traction under general anesthesia before the operation in 18 patients without TDH. Closed reduction was successful in 13 of these patients. In 3 patients with DFS 2 dislocation, single session anterior stabilization was performed in the supine position. In the other 10 patients with DFS 3 or 4 dislocations, combined anterior and posterior stabilization was performed. In 5 patients for whom reduction was unsuccessful, posterior open reduction was performed via an initial posterior approach and was maintained by the combined posterior and anterior stabilization.

An initial anterior cervical discectomy was performed in 14 patients with TDH on MR images. Subsequently, the reduction was attempted by manual traction performed by an assistant staff during surgery. The reduction was achieved in 10 of these patients. Single session anterior stabilization was performed in 3 with DFS 2 fracture of these 10 patients. In the other 7 patients with DFS 3 or 4 fractures, combined anterior and posterior stabilization was performed. In 4 patients with unsuccessful reduction attempt after discectomy during the anterior approach, the patients were switched to the prone position, and posterior open reduction and stabilization were performed. Subsequently, the patients were placed in the supine position again for anterior stabilization and the combined anterior and posterior stabilization was accomplished.

The methods applied during the choice of approach for patients are summarized in Figure 1. Also, the number of approaches selected for patients is shown in Figure 1. In total, single anterior stabilization was performed in 6 patients, and combined anterior and posterior stabilization was performed in 26 patients. Out of the patients who underwent combined stabilization, 7 were performed initial anterior subsequent posterior (AP) approach, 15 were performed initial posterior subsequent anterior (PA) approach, and 4 were performed APA approach. Reduction attempt with manual traction was successful in 23 patients, while the posterior open reduction was necessary for 9 patients (5 with DFS 3 dislocation; 4 with DFS 4 dislocation). Preoperative and postoperative radiological images of a sample patient were presented in Figure 5.

Operative and postoperative data of patients were summarized in Table 2. The mean operation time was longer, and the mean amount of bleeding was more in the APA approach than others. The average length of hospital stay was 24.3±29.5 days. The hospital stay was significantly longer in patients with complete neurological injury. This period was 12.3±12.1 days in patients with incomplete medulla spinalis injury.

During hospitalization, pulmonary embolism (PE) was observed in 3 patients (2 with DFS 4 dislocation, and 1 with DFS 3 dislocation) and diabetes insipidus (DI) was

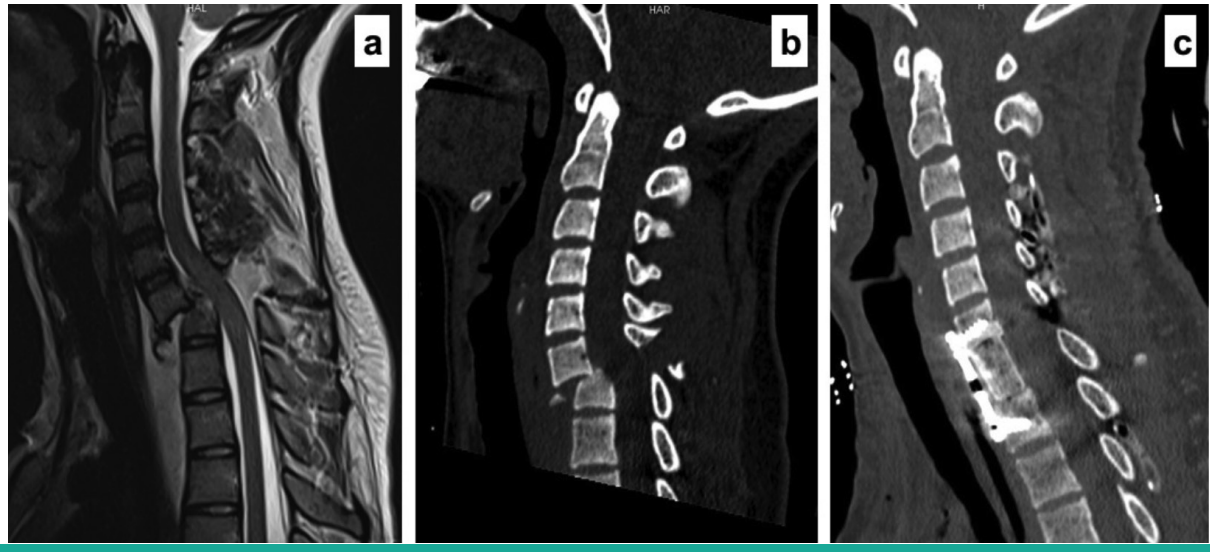

Figure 5. An illustrative case of distractive flexion stage 4 subaxial cervical facet dislocation
A. Preoperative sagittal T2-weighted magnetic resonance image
B. Preoperative sagittal cervical computed tomography (CT) image
C. Sagittal cervical CT image after reduction and combined anterior and posterior stabilization
CT: Computed tomography

observed in 1 patient. PE was successfully treated with anticoagulant medication in all three patients. DI was defined on the 25th day after operation in a patient with C6-C7 DFS 4 fracture who was treated with a PA approach and resolved with medical treatment. A patient with C5-C6 DFS 4 dislocation with ASIA grade A neurological status suffered from respiratory failure due to intercostal muscle paralysis and was lost due to the septic shock during intensive care unit treatment.

General follow-up data of patients were summarized in Table 3. The mean follow-up period was 38.4±11.5 (Distribution: 15-64) months. Neck pain was evaluated with VAS score, the averages were 7.4±1.9 before the operation and 1.7±0.6 at end of follow-up. Significant improvement was observed in all examinations after treatment compared to the preoperative period ($p<0.001$). Preoperative radiological examinations revealed kyphotic deformity in 20 patients. The mean angle of the deformity was 20.5±6.3° kyphosis in the preoperative period. This angle was observed as 3.3±2.5° lordosis at the end of follow-up. No neurological deterioration was observed after intervention in 24 patients with an incomplete injury. Various levels of neurological improvement were observed in patients with an incomplete injury, but no neurological improvement was observed in all 8 patients with complete medulla spinalis injury (ASIA grade A). The osseous fusion rate was 87% after 3 months, and 100% after one-year follow-up.

Table 2. Operative and postoperative data of patients

Operation time (min)	
Anterior approach	121±47
Anterior - posterior approach	197±51
Posterior - anterior approach	189±39
Anterior - posterior - anterior approach	257±53
Blood loss (mL)	
Anterior approach	123±49
Anterior - posterior approach	190±55
Posterior - anterior approach	203±56
Anterior - posterior - anterior approach	305±89
Hospitalization duration (days)	24.3±29.5
Complete injury (ASIA A)	56.3±40.9
Incomplete injury (ASIA B-C-D-E)	12.3±12.2
Complication	
Pulmonary embolism	3 (9.4%)
Diabetes insipidus	1 (3.1%)
Mortality	1 (3.1%)

ASIA: American Spinal Injury Association

Neurological status follow-up data of patients stratified according to the severity of dislocation (AFC) were shown in Table 4. The worst neurological condition was present in patients with DFS 4 fracture and all patients were classified as ASIA grade A. And the best neurological condition was observed in patients with DFS 2 fracture, besides 4 of 6 (66%) patients were presented without any neurological deficits. Worst neurological status outcome was observed in the subgroup of patients with DFS 4 fracture. No neurological improvement was observed in all patients of this subgroup during follow-up. However, a favorable neurological condition course was observed in patients with DFS 2 fracture, all of the patients ended up with ASIA grade E at the end of follow-up.

Data for TDH appearance, posterior open reduction requirement, and chosen surgical approach results of patients stratified AFC were summarized in Table 5. While TDH presence rate was 44% in the present cohort series, this rate was 50%, 56%, and 13% in DFS 2, 3, and 4 subgroups, respectively. The success rate of reduction attempt with traction was 100% in patients with DFS 2 fracture, while the

Table 3. Data of patients during follow-up

Follow-up variables		Examination timing					
		Preoperative	Postoperative	3 months	6 months	1 year	Last follow-up
Deformity angle		20.5±6.3° kyphosis	5.9±3.6° lordosis	4.8±3.3° lordosis	4.2±2.7° lordosis	3.4±2.3° lordosis	3.3±2.5° lordosis
Neck pain (VAS)		7.4±1.9	4.2±2.1*	2.8±0.9*	2.5±1.2*	1.9±0.8*	1.7±0.6*
Neurological status (ASIA)	Grade A	8	8	7	7	7	7
	Grade B	5	4	2	1	0	0
	Grade C	6	6	5	6	4	3
	Grade D	9	9	8	8	9	8
	Grade E	4	5	9	9	11	13
Osseous fusion		-	-	87%	90%	100%	100%

*: $p<0.001$ (compared with the preoperative period using Student's t-test Calculator), VAS: Visual Analog scale, ASIA: American Spinal Injury Association

posterior open reduction was required in 33% and 55% of patients in the DFS 3 and DFS 4 subgroups, respectively. Consequently, the anterior approach was performed in all patients with DFS 2 fracture; and the PA approach was the most common intervention in DFS 3 (44%) and DFS 4 (87%) subgroups.

Discussion

In the present study, satisfactory clinical and radiological results were obtained in the treatment of facet dislocation of the SCS with surgical approach selection according to the severity of the facet dislocation graded by AFC, and with reduction attempt with manual traction arranged according to TDH presence. Performing combined stabilization in DFS 3 and 4 fractures, relatively higher stages based on AFC, and anterior stabilization in stage 2 fractures, and carrying out an anterior discectomy in the presence of TDH before reduction attempt via traction provided appropriate outcomes. In case of unsuccessful closed reduction, proper alignment was achieved via posterior open reduction without any neurological deterioration occurrence.

The epidemiology of spine traumas shows that 44% to 62% of all cervical spine fractures are localized between C5 and C7 levels (3,5,6). In our series, the ratio of C5-C6 and C6-C7 fractures among the five segments was 78.1%. The male/female ratio in spinal fractures was observed between 1.6 and 3 in the literature (3-5). This rate was found 3 in our study. The most common cause of spinal fractures is defined as falling from height, followed by traffic accidents (3-5). Similar results were obtained in our series.

The choice of surgical method is determined according to the type of facet dislocation, the neurological status, and the presence of disc herniation (8,19). Patients with no or incomplete neurological injury are more likely to recover than patients with a complete injury (20). Our series supports these data. At a one-year follow-up, no neurological improvement was observed in patients with complete injury (ASIA A), while other patients (ASIA B to E) improved at different rates. Therefore, maintaining the existing neurological status is important in the choice of treatment method. However, one of the potentials accompanying subaxial facet dislocation is TDH. In the literature, the rate of TDH presence in subaxial facet dislocation patients was reported between 22% and 40% (16,17). Reduction of dislocation in the presence of TDH can provoke the existing injury and worsen the neurological status of the patient (8). Therefore, if present, the extruded disc material was removed via discectomy before the reduction attempt in our series. Another factor influencing the management

Table 4. Neurological status follow-up data of patients stratified according to the grade of dislocation (AFC)

Dislocation severity (AFC)	Neurological status (ASIA)	Examination timing					
		Preop	Postop	3 months	6 months	1 year	Last follow-up
DFS 2	Grade D	2	1	-	-	-	-
	Grade E	4	5	6	6	6	6
DFS 3	Grade B	5	4	2	1	-	-
	Grade C	6	6	5	6	4	3
	Grade D	7	8	8	8	9	8
	Grade E	-	-	3	3	5	7
DFS 4	Grade A	8	8	7*	7	7	7

AFC: Allen and Ferguson classification, ASIA: American Spinal Injury Association, DFS: Distractive flexion stage, *: One patient died during follow-up, Preop: Preoperative, Postop: Postoperative

Table 5. TDH appearance, open reduction requirement, and chosen surgical approach results of patients stratified according to the grade of dislocation (AFC)

Dislocation severity (AFC)	TDH		Reduction attempt with traction		Surgical approach			
	Present	Absent	Successful	Unsuccessful	Anterior	AP	APA	PA
DFS 2	3	3	6	-	6	-	-	-
DFS 3	10	8	13	5	-	6	4	8
DFS 4	1	7	4	4	-	1	-	7

AFC: Allen and Ferguson classification, TDH: Traumatic disc herniation, AP: Anterior-posterior, APA: Anterior-posterior-anterior, PA: Posterior-anterior, DFS: Distractive flexion stage

scheme in our series is the severity of the fracture. The severity of the facet dislocation affects the success of the procedure performed during the treatment. AFC is used for staging the fracture in our series (7). According to this classification, while anterior stabilization was sufficient in DFS 2 fractures with unilateral facet dislocation and listhesis below 50% of the corpus distance, combined anterior and posterior stabilization was performed in DFS 3 or 4 fractures with bilateral facet dislocation and listhesis above 50% of the corpus distance. The third factor affecting treatment management in our series was whether the reduction with traction was successful or not. In case of an unsuccessful attempt, an open reduction was performed with the posterior approach. In the scheme designed to obtain an effective surgical intervention using these factors, anterior, AP, PA, and APA approaches have been performed.

Management recommendations for facet dislocations of the SCS have been previously reported (8,21). Previous publications indicated closed reduction with manual traction in the first phase of treatment (8,21). The successfully closed reduction rate was reported as 80.5% (33/41 patients) by Reindl et al. (21) Also, open reduction was performed with an anterior approach in the other 8 patients. However, neurological deterioration was observed in 1 patient of this series (21). In another series by Jiang et al. (8), closed reduction was successful in 22 (42.3%) of 52 patients and no neurological deterioration occurred in any patient. In our series, the success rate of closed reduction was 68.7% (22/32 patients) and no new neurological deficits were observed due to reduction.

Posterior open reduction was performed in cases where the reduction with traction was unsuccessful in our series. Posterior open reduction was also implemented by Nakashima et al. (17). In 40 patients of facet dislocation accompanied with TDH, posterior open reduction and posterior arthrodesis were performed without any new neurological deficits (17). However, 25 (62.5%) of patients in this series had a complete neurological injury (ASIA A) (17). The complete injury rate was lower (25%) and the posterior open reduction was only performed in the absence of TDH in our series. To reduce the risk of a new neurological deficit, the extruded material was removed by discectomy before reduction attempt in the presence of TDH. In another study by Park et al. (22), in which open reduction and pedicle screw fixation were performed in a single session posterior approach, disc material was excised with a postero-lateral approach in the presence of TDH.

Anterior approaches are preferable for the removal of the disc material in the presence of TDH (10,23). Feng et al. (23) applied the combined approach consisting of anterior decompression and grafting before posterior stabilization in their series with 21 patients with lower cervical facet dislocation accompanied by TDH. In this series, improvement in kyphotic deformity and satisfactory results in neurological status were obtained, but a significant decrease in neck mobility developed due to the length of posterior segmental stabilization (23). In a study by Jiang et al. (8), an initial cervical discectomy was advised in the treatment method of lower cervical facet dislocations in the presence of TDH. Similar to our series, the reduction was attempted with manual traction after discectomy. In cases of successful reduction, the anterior approach was considered sufficient (10). However, the stage of fracture dislocation was not taken into account in this series (10). In our series, the anterior approach was sufficient in unilateral facet dislocation with listhesis shorter than 50% corpus distance (DFS 2 fracture), whereas the combined anterior and posterior stabilization was preferred in DFS 3 or 4 dislocations. In case of unsuccessful closed reduction, Jiang et al. (8) performed an APA approach similar to our series with posterior open reduction and subsequently anterior stabilization.

In the anterior approach suggested by Liu and Zhang (13), the success rate was 82% for the reduction attempt using traction with Caspar pins. In our study, the overall success rate of the reduction attempt with traction was 72%. While this rate was 71.4% in the manual traction performed after anterior discectomy in patients with TDH, this rate was 72.2% in the traction performed using GWT before the operation in patients without TDH. Liu and Zhang (13) suggested performing anterior facetectomy in case traction with Caspar pins did not provide successful reduction. And they reported a 100% reduction rate after facetectomy (13). In our study, if the reduction was not achieved with traction, a posterior partial facetectomy was performed. Similarly, a 100% reduction was achieved after facetectomy. However, to provide sufficient stabilization, Liu and Zhang (13) used anterior corpus screw plus anterior pedicle screw and plate fixation.

Conclusion

A management chart for facet dislocation fractures of the SCS is advised in the present study. As the result of the interventions applied according to this chart, radiological

and clinical satisfactory results were obtained. The proposed algorithm for facet dislocations can be effective when the management is planned according to the grade of the dislocation and the presence of TDH.

Ethical Statements

All procedures were performed following the ethical standards of the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval for this research was obtained from our local clinical research ethics committee.

Ethics

Ethics Committee Approval: Approval of this research eas obtained from Erzincan Binali Yıldırım University Clinical Research Ethics Committee (approval no: 05/28, date: 29/04/2020).

Informed Consent: Written informed consent was obtained from the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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ORIGINAL RESEARCH

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Assessment of the Quality and Reliability of the Information on Bone Tumor on Youtube

Kemik Tümörleri ile Alakalı Youtube Videolarının Kalite ve Güvenilirlik Analizi

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Abstract

Objective: Our aim is to assess the content quality and reliability of Youtube videos on bone tumors.

Method: We searched Youtube using the keyword "bone tumors," and included the first 50 videos listed in our study. Two orthopedic surgeons analyzed the videos, and then, we examined them in terms of length, number of views and likes, and source. To evaluate their content quality, the Global Quality score (GQS) (0-4), Journal of the American Medical Association (JAMA) (0-5), and DISCERN (15-75) scoring systems were used; based on these, the obtained data were statistically analyzed.

Results: Of the 50 videos analyzed, four (8%) included animation, while 46 (92%) did not; 12 (24%) were uploaded by doctors, 23 (46%) by health channels, 10 (20%) by universities, three (6%) by clinics, and one (2%) each by a hospital and a trainer. The average video length was 16 minutes and 18 seconds (38-6.088 seconds), average number of views was 14,856.24, and average number of likes was 130.50 (1-1448). The mean scores of GQS, JAMA, and DISCERN were 2.22 (1-4), 2.12 (1-3), and 33.48 (15-75), respectively. There was no statistical significance in the scores and video length, or the number of likes and views between the two researchers.

Conclusion: Youtube videos on bone tumors have low content quality. Improvement of the same will help dispense correct information to patients, so that they can continue their treatment. We believe that patient treatment compliance can be increased by accelerating the patient's preparation and adaptation process for treatment with accurate information.

Keywords: Bone tumors, video analysis, video quality, youtube

Öz

Amaç: Çalışmanın amacı Youtube'daki kemik tümörleri ile alakalı videoların kalitesini ve güvenilirliğini değerlendirmektir.

Yöntem: Youtube arama sekmesine anahtar kelime olan 'bone tumors' yazılarak ilk çıkan 50 video çalışmaya dahil edildi. Videolar iki ortopedik cerrah tarafından analiz edildiler. Tüm videolar uzunluk, izlenme sayısı, like sayısı ve videonun kaynağı bilgileri ile analiz edildiler. Videoların kalitesini değerlendirmek için Global Kalite skoru (GKS) (score range: 0-4), Journal of the American Medical Association (JAMA) (0-5) ve DISCERN (15-75) skorlama sistemleri kullanıldı. Elde edilen veriler bu skorlama sistemlerine göre istatistiksel olarak analiz edildiler.

Bulgular: Analiz edilen 50 videodan 4 (%8) video animasyon içeriyorken 46 (%92) video ise içermiyordu, 12 (%24) video hekimler, 23 (%46) video sağlık kanalı, 10 (%20) video üniversite, 3 (%6) video klinik, 1 (%2) video hastane, 1 (%2) video ise trainer tarafından eklenmişti. Ortalama video uzunluğu 16 dakika 18 saniye (38-6,088 saniye), ortalama izlenme sayısı 14856,24 (41-84,253), ortalama like sayısı 130,50 (1-1,448) idi. Ortalama GKS skoru 2,22 (1-4), ortalama JAMA 2,12 (1-3), ortalama Discern skoru ise 33,48 (17-66) idi. Her iki araştırmacı arasında skorlama sistemleri ve video uzunluğu, beğeni sayısı ve izlenme oranları açısından istatistiksel olarak fark yoktu.

Sonuç: Kemik tümörleri ile alakalı Youtube videolarının kalitesi düşüktür. Bu durum iyileştirilerek malignitesi olan hastalara daha doğru enformasyon sağlanabilir ve hastalar daha doğru bilgilerle tedavi süreçlerini devam ettirebilirler.

Anahtar kelimeler: Kemik tümörleri, video analizi, video kalitesi, youtube

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Introduction

In today's times, Internet is the easiest way to access information. A majority of people refer to sources online to obtain information prior to their medical applications, as well as in other areas. Video sharing sites such as YouTube have become very popular in this respect.

More than 1.9 billion people visit Youtube every month and can find a huge number of medical education videos (1). Patients frequently visit the platform and benefit from its rich video archive while trying to gather information about their diseases (2-5).

Those suffering from orthopedic disorders are among these patients. In particular, patients with suspected malignancy are more anxious and may need a more comprehensive search; they may increase their levels of anxiety by constantly thinking the worst and referring to the most unfavorable examples online. Our Google search for "bone tumors" on March 10, 2020 yielded 62 million results, which may be an indication for that this particular search is very popular. However, studies show that the content quality of health information videos online is low (6). In order for people to access more accurate information, videos with better quality content on health information are needed (7).

Bone tumors can be perceived in various ways, and because patients suspect of having them and worry, they conduct online searches.

Thus, the purpose of our study was to evaluate the content quality of Youtube videos on bone tumors for those who want accurate information.

Materials and Methods

We did a search on Youtube using the keyword "bone tumors" on March 10, 2020 and included the first 50 videos that were listed in our study. Videos in English that were repeated and those that comprised only product advertisements and not related to bone tumors were excluded.

The videos were analyzed by two independent orthopedic surgeons. We recorded information on the videos' length, number of views and likes, and the source (i.e., the uploader), and then scored them using the Global Quality score (GQS), Journal of the American Medical Association (JAMA) and DISCERN scoring systems to evaluate their content quality (8-10) (Figure 1,2) (Table 1).

Scoring was done by taking the means of the scores provided by both surgeons. The GQS is a system that scores between 0 and 4, from the lowest quality to the most quality. The JAMA scoring system comprises four criteria, each scored either 0 or 1, adding up to a maximum of 5 points and a minimum of 0 to measure the content quality of the videos. The DISCERN scoring system comprises 15 questions; its scores between 63 and 75 points are classified as "excellent," 51 and 62 as "good," 39 and 50

Section 1 – Is the publication reliable?
1. Are the aims clear?
2. Does it achieve its aims?
3. Is it relevant?
4. Is it clear what sources of information were used to compile the publication?
5. Is it clear when the information used in the publication was produced?
6. Is it balanced and unbiased?
7. Does it provide details of additional sources of support and information?
8. Does it refer to areas of uncertainty?
Section 2 – How good is the quality of information?
9. Does it describe how alcohol affects the fetus?
10. Does it describe any benefits for reducing alcohol use in pregnancy?
11. Does it describe the risks?
12. Does it describe the role of other lifestyle factors?
13. Does it provide alternatives to drinking alcohol?
14. Does it provide support for shared decision-making?
Section 3 – Overall rating of the publication
15. Based on the answers to all of the above questions, rate the overall quality of the publication as a source of information about treatment choices

Figure 1. Discern scoring system

as "average," 28 and 38 as "poor," and <28 as "very poor." Higher scores obtained from the scale indicate a higher quality of information. This study does not contain any human or animal resources, ethical approval was not needed for this study.

Statistical Analysis

The Shapiro-Wilk test was conducted to evaluate the fitness of the numerical variables to a normal distribution, and then, the Mann-Whitney U test to compare the non-normally distributed variables in two independent groups. Relationships between the variables that were not normally distributed were analyzed using the Spearman's rank correlation coefficient. The SPSS 22.0 Windows software package was used for the analyses. For all analyses, $p<0.05$ was considered as statistically significant.

Table 1. JAMA scoring system

JAMA scoring system rating section	No	Yes
Authorship authors and contributors, their affiliations, and relevant credentials should be provided	0	1
Attribution references and sources for all content should be listed clearly, and all relevant copyright information should be noted	0	1
Disclosure website "ownership" should be prominently and fully disclosed, as should any sponsorship	0	1
Advertising, underwriting, commercial funding arrangements or support, or potential conflicts of Interest		
Currency dates when content was posted and updated should be indicated	0	1

JAMA: Journal of the American Medical Association

Score	Global score description
1	Poor quality, poor flow of the site, most information missing, not at all useful for patients
2	Generally poor quality and poor flow, some information listed but many important topics missing of very limited use to patients
3	Moderate quality, suboptimal flow, some important information is adequately discussed but others poorly discussed, somewhat useful for patients
4	Good quality and generally good flow, most of the relevant information is listed, but some topics not covered, useful for patients
5	Excellent quality and excellent flow, very useful for patients

Figure 2. Global Quality score

Results

Of the 50 videos analyzed, four (8%) included animation, while 46 (92%) did not; 12 (24%) were uploaded by doctors, 23 (46%) by health channels, 10 (20%) by universities, four (8%) by clinics, and one (2%) each by a hospital and a trainer. The average video length was 16 minutes and 18 seconds (38-6.088 seconds), the average number of views was 14,856.24, and the average number of likes was 130.50 (1-1.448). The mean scores of GQS, JAMA, and DISCERN scoring systems were 2.22 (1-4), 2.12 (1-3), and 33.48 (17-66), respectively (Table 2).

The statistical analysis showed a positive, medium correlation between the video length and GQS score ($p=0.001$), and a positive, weak correlation between the video length and GQS and DISCERN scores ($p=0.000$/$p=0.006$). There were no statistically significant differences between the video length and JAMA score ($p=0.978$).

There was a significant correlation between the number of views and GQS and DISCERN scores, but not between the number of views and JAMA score ($p=0.049$/$p=0.079$/$p=0.038$).

There was no significant correlation between the number of likes and GQS, JAMA, and DISCERN scores ($p=0.058$/$p=0.067$/$p=0.071$). The statistical analyses are summarized in Table 3.

On the other hand, with respect to the videos uploaded by doctors, the length ($p=0.012$), number of views ($p=0.025$),

Table 2. Scores of videos according to scoring systems

Scoring systems	Global Quality scores	JAMA	DISCERN
Scores	2.22 (1-4)	2.12 (1-3)	33.48 (17-66)

JAMA: Journal of the American Medical Association

Table 3. Statistical analysis of data

		Correlations		
		Video length	Number of views	Likes
GQS	r	0.533	0.280	0.269
	p	**0.000**	**0.049**	**0.058**
	n	50	50	50
JAMA	r	0.004	0.079	-0.062
	p	**0.978**	**0.586**	**0.667**
	n	50	50	50
DISCERN	r	0.382	0.295	0.258
	p	**0.006**	**0.038**	**0.071**
	n	50	50	50

GQS: Global Quality scores, JAMA: Journal of the American Medical Association

number of likes (p=0.003), and JAMA scores (p=0.011) were significantly higher than those of videos uploaded by other sources. The JAMA scores of videos uploaded by health channels were significantly higher than those of videos uploaded by universities (p=0.001).

There were no significant differences about scoring system between two surgeons. (p=0.012).

Discussion

Our study shows that the content quality of Youtube videos on bone tumors, searched using the keyword "bone tumors," is low.

This study is the first to focus on orthopedic malignancies, and it provides information on the effects of video content quality on patients. Of the 50 videos reviewed, 12 were uploaded by doctors, 23 by health channels, 10 by universities, four by clinics, and one each by a hospital and a trainer. This indicates that the topic is addressed mostly by professionals. Although a literature review has shown that video uploading by patients is done at a level that cannot be underestimated, in our study, health professionals are prominent (11).

The mean video length in our study was 16.18 minutes. Previous studies have shown a range of 6.17-10.35 minutes (12,13), which means that our mean was higher.

Furthermore, in our study, the length, number of views and likes, and JAMA scores of videos uploaded by doctors were higher than those uploaded by other sources. This indicates that the doctors' videos are of a higher quality in terms of content. This may indicate that the videos uploaded by doctors are more scientific.

Several scoring systems have been used in the literature to determine the content quality of Youtube videos (14,15), we used three- GQS, JAMA, and DISCERN- and our data analysis revealed their scores as 2.22, 2.12, and 33.48, respectively. Thus, the mean scores according to these systems correlate with low content quality. Previous studies have compared this with the source of videos, showing that those uploaded by clinicians had high content quality (16). However, for most of the videos reviewed in our study, which were uploaded by health professionals, we did not find it relevant to make such a comparison.

There was no significant correlation between the number of likes and scores. This shows that the likes do not correlate with the content quality of the video, and there are other studies showing that videos of low content quality have more likes (17,18).

The selection of this topic is based on the consideration that cancer patients may want to do more research on their diseases. This is because malignancies are always a matter of curiosity for patients- they are stressed because of their illness and feel the need to gather more information. It is known that Youtube videos with low content quality negatively affect the patient-doctor relationship (19). Additionally, a literature search on Youtube videos related to other malignancies reveals that there is no study focusing on bone tumors (20). Orthopedic studies in the literature focusing on quality assessment of Youtube videos are limited in number. These are on scoliosis, femoroacetabular impingement, hip arthritis, anterior cruciate ligament injury, and reconstruction (21-24) among other topics. However, there is a lack of studies on orthopedic malignancies. Therefore, we contribute to the literature by studying the content quality of videos on bone tumors and reporting that patients who are curious about this topic receive information from videos with low content quality.

While our method of selecting and analyzing the first 50 videos in the search list can be considered a limitation, it should be noted that there are studies in the literature that have conducted similar types of evaluations (25,26). In addition, considering that patients watch those videos that show up first in search results, the number of our videos is acceptable. Doing the search on different days and performing the assessment at different times would have been another limitation; hence, to prevent that, both of us completed our analyses on the same day.

In this study, the all videos related to bone tumors were analyzed by two independent surgeons. All videos rated by surgeons got close scores in the scoring system. One of our main goals here was to demonstrate that videos got the same results by all surgeons watching.

The dissemination of accurate and reliable information regarding the "bone tumors" may also play a significant role in educating patients and optimizing outcomes. More accurate information about the bone tumors can have a positive impact on patient outcomes in a multifactorial manner. If patients are properly informed, they will be more likely to seek timely treatment, and better outcomes may ensue.

In sum, a majority of the Youtube videos on bone tumors have low content quality, which may become patients'

primary source of information due to easy access to videos. Thus, improving the content quality of videos would be beneficial for both patients and health professionals. Our study is the first to assess the content quality of Youtube videos on bone malignancies, and further research is needed on this topic.

Ethics

Ethics Committee Approval: This study does not contain any human or animal resources, ethical approval was not needed for this study.

Informed Consent: No patients data were used.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.B.T., Design: S.B.T., Data Collection or Processing: E.Ö., Analysis or Interpretation: S.B.T., Writing: S.B.T.

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

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ORIGINAL RESEARCH

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Interleukin-6 Levels in the Cervicovaginal Fluid of Pregnant Women and Its Predictive Value in Preterm Delivery

Hamile Kadınlarda Servikovajinal Sıvıda İnterlökin-6 Düzeyleri ve Preterm Eylem Prediktivitesi

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Abstract

Objective: The aim of this study was to determine interleukin (IL)-6 levels in the cervicovaginal fluid of pregnant women and its value in predicting preterm delivery.

Method: One hundred and eleven pregnant women were retrospectively included in the study. Cervicovaginal secretions for each pregnant woman were obtained with a sterile Dacron swab for IL-6 detection. IL-6 was determined using an enzyme-linked immunosorbent assay method.

Results: The mean IL-6 levels were found to be significantly higher in the preterm delivery group (5.84±2.09 pg/mL) than in the term delivery group (2.24±0.77 pg/mL) (p=0.001). Relationships were found between IL-6 levels and the frequency of intra-amniotic infection, preterm birth and the history of previous preterm birth.

Conclusion: A strong association was found between increased cervicovaginal fluid IL-6 levels and preterm delivery. Results suggest that measurement of IL-6 levels from cervicovaginal swab samples during pregnancy can be used to identify patients with risk as a predictive biomarker for preterm birth.

Keywords: Cytokines, IL-6, premature birth

Öz

Amaç: Bu çalışmanın amacı hamile kadınların servikovajinal sıvı örneklerinde interlökin (IL)-6 düzeylerini analiz etmek ve preterm doğum için prediktif rolünü belirlemektir.

Yöntem: Çalışmaya 111 gebe kadın retrospektif olarak dahil edildi. Her kadın için servikovajinal sekresyonlar, IL-6 saptaması için steril bir Dacron sürüntüsü ile elde edildi. IL-6, enzime bağlı immünosorbent test yöntemi kullanılarak belirlendi.

Bulgular: Ortalama servikovajinal sıvı IL-6 düzeyleri erken doğum grubunda (5,84±2,09 pg/mL) term dönem doğum grubuna göre (2,24±0,77 pg/mL) anlamlı olarak daha yüksek bulundu (p=0,001). IL-6 ile intra-amniyotik enfeksiyon, preterm doğum ve önceki preterm doğum öyküsü arasında pozitif ilişki saptandı.

Sonuç: Artmış servikovajinal sıvı IL-6 düzeyleri ile erken doğum arasında güçlü bir ilişki bulunmuştur. Hamilelik döneminde servikovajinal sıvı IL-6 seviyesinin ölçümü, yüksek riskli kadınların erken doğum eyleminin saptanması için bir öngörücü biyobelirteç olarak kullanılabilir.

Anahtar kelimeler: Erken doğum, IL-6, sitokinler

Introduction

Preterm birth is described as delivery before the 37th week of gestation and is associated with significantly elevated perinatal morbidity and mortality. It is a heterogeneous condition with multi-factorial etiology, including demographic factors, placental ischemia, decidual hemorrhage, placental abruption, trauma, stress, environmental factors, genital tract infections and chronic conditions such as blood clotting disorders, gestational diabetes, and hypertension (1). Preterm birth has a profound effect on health systems due to the short and long-term

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disabilities related to the condition. It creates high economic and social costs to families and health care systems, and is further associated with conditions including cerebral palsy, necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, and Respiratory Distress syndrome (2). Beck et al. (3) found that 28% of all neonatal deaths in the first week of life were seen after preterm birth. Considering that the estimated global frequency of preterm birth is 9.6%, 10 to 13 million babies are born with preterm delivery in one year and face the inherent risks of this condition (3). Early detection of preterm labor is important, but it is considered to be very difficult since its initial symptoms are usually mild and further symptoms often appear too late. Since the underlying etiology of preterm labor still remains uncertain, maternal biomarkers predicting preterm labor are still being widely investigated.

It has been previously suggested that the inflammatory pathway plays an important role in the etiopathogenesis of preterm delivery (4). IL-6 is a multifunctional cytokine and is widely expressed in the female reproductive tract and gestational tissues. It is involved in inflammation and has a central role in the host defense mechanism through the stimulation of immunoglobulin production, activation of T-cell proliferation, and differentiation of myeloid cells. The production of prostaglandins can be induced by IL-6, causing uterine contractions and cervical ripening. Several studies in the literature have found altered levels of IL-6 in relation to preterm delivery, but their results remain inconsistent (5). This study aimed to determine IL-6 levels in the cervicovaginal fluid of pregnant women and to identify its predictive value for preterm delivery.

Materials and Methods

Study Design

This retrospective study was carried out from November 2017 to June 2018 in Istanbul, Turkey. A total of 111 pregnant women with singleton gestation were recruited from a private gynecological practice. The study included 45 patients with term delivery and 66 patients who had preterm labor. Gestational age was assessed according to the last menstruation date and first trimester obstetric radiologic examination. Preterm delivery was defined as birth before the 37th week of gestation. Participants with hypertensive disorders in pregnancy, obstetrical hemorrhage, vaginal bleeding, cervical cerclage, fetal anomalies, multiple pregnancy, fetal growth restriction, premature rupture of the membrane, and malignancies were excluded from the study. A total of 22 patients were excluded according to the exclusion criteria. Obstetric data and clinical results of patients, including maternal age, maternal education status, the presence of intra-amniotic infection, marital status, the history of previous preterm birth and birth weeks of infants were obtained from patients' medical files. Intra-amniotic infection was diagnosed via the presence of 2 or more of the following criteria: temperature ≥38 °C, maternal or fetal tachycardia, uterine tenderness, elevated peripheral white blood cell count, and purulent amniotic fluid.

Ethical Issues

Ethics committee approval was obtained from the non-interventional Clinical Research Ethics Committee of İstanbul Medipol University (decision number: 519, decision date: 25/06/2020). All research procedures were conducted in agreement with the ethical standards specified in the Declaration of Helsinki. Written and verbal informed consent was obtained from participating women prior to sampling and their participation in this study.

Detection of Interleukin-6

Cervicovaginal secretion samples were obtained and collected from each pregnant woman included in the study for 3 to 8 weeks gestation at the time of initial admission for further analysis. Samples were frozen at -40 °C up to 12 months until IL-6 testing. After collecting all patients' cervicovaginal samples, they were analyzed together after delivery. To obtain cervicovaginal fluid, a sterile Dacron swab was placed into the posterior fornix following positioning of a sterile speculum, and gently rotated for 15 seconds to ensure complete absorption of cervicovaginal secretion. The swab was transferred into to a test tube containing phosphate-buffered saline and stored at -40 °C. Before biochemical analyses, the sample was thawed and centrifuged at 4 °C and 5.000 RPM for 10 minutes. The supernatant was used for the measurement of IL-6 levels via an ELISA kit (Elabscience Biotechnology, USA) as per the manufacturer's instructions. The color intensities were determined using an ELx 800 microplate absorbance plate reader (BioTek, USA) with a 450 nm filter. The results were expressed in picograms per milliliter (pg/mL).

Statistical Analysis

The SPSS version 22.0 soft¬ware (Chicago, IL, USA) was used to perform all statistical analyses. The Shapiro-Wilk test was used to assess the normality of distribution. Data were expressed as mean ± standard deviation or frequency (percentage). Comparison of the groups was performed using the Mann-Whitney U test. The Spearman's correlation

test was used to evaluate correlations. P<0.05 values were accepted as statistically significant results.

Results

A total of 111 pregnant women with singleton gestation were involved in the study. The mean age was 31.65±4.87 years for patients with preterm delivery and 31.24±4.67 years for women with term delivery (p=0.926). Nine patients with preterm delivery had intra-amniotic infection, while one patient presented intra-amniotic infection in the term group (p=0.039).

No significant differences were found between the groups in terms of age and history of previous preterm birth (all, p>0.05). Age, education status, history of previous preterm birth, and intra-amniotic infection status were shown in Table 1.

The mean IL-6 levels were 5.84±2.09 pg/mL in women with preterm delivery and 2.24±0.77 pg/mL in those with term delivery. The boxplot distribution graph of IL-6 levels was shown in Figure 1. IL-6 levels were found to be significantly higher in the preterm delivery group (p=0.001) (Figure 2).

Correlation analyses between patients' characteristics and IL-6 levels were shown in Table 2. Positive relationships were found between IL-6 levels and the absence of intra-amniotic infection, preterm birth and the history of previous preterm birth. We also showed a negative correlation between IL-6 and birth week. Furthermore, intra-amniotic infection was also found to be associated with preterm delivery (Table 2).

Discussion

The current study aimed to investigate cervicovaginal levels of IL-6 and to determine predictive value of cervicovaginal fluid IL-6 levels for preterm delivery. We demonstrated increased IL-6 levels in the cervicovaginal samples of women

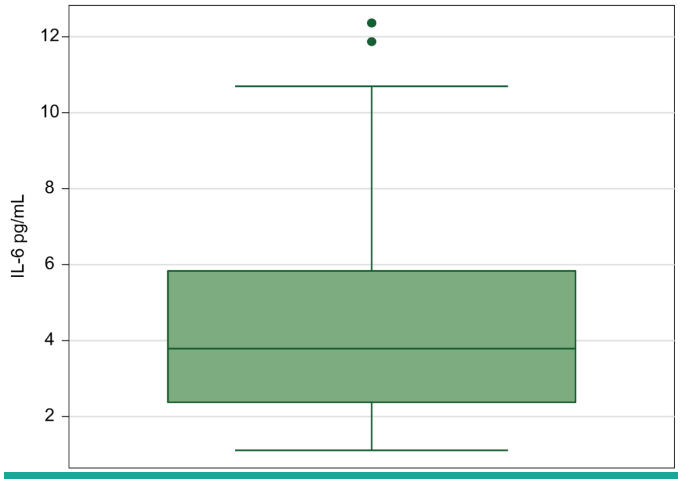

Figure 1. Box plot, distribution of IL-6
IL-6: Interleukin-6

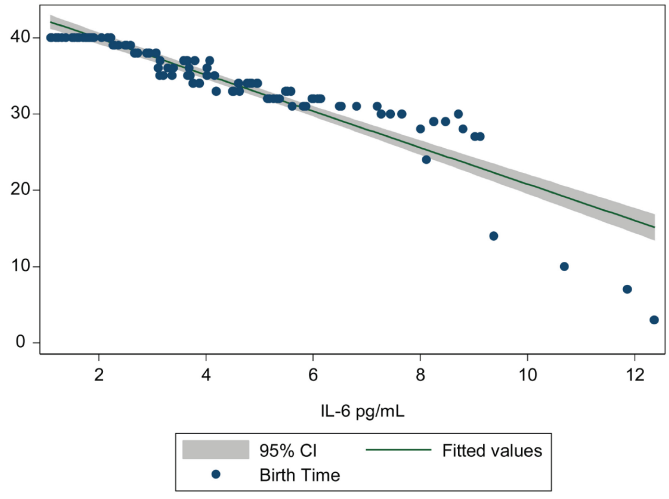

Figure 2. OLS scatterplot, relationship between IL-6 levels and birth time
IL-6: Interleukin-6, CI: Confidence interval

Table 1. Demographic data of participants

	Total (n=111)	Women with term delivery (n=45)	Women with preterm delivery (n=66)	p
Age	31.49±4.77	31.24 ±4.67	31.65±4.87	0.926
Education status				
University	60 (54.1%)	23 (51.1%)	37 (56.1%)	
High school	27 (24.3%)	12 (26.6%)	15 (22.7%)	0.158
Post-graduate	24 (21.6%)	10 (22.2%)	14 (21.2%)	
The presence of intra-amniotic infection	10 (9%)	1 (2.2%)	9 (13.6%)	**0.039**
The history of previous preterm birth	24 (21.6%)	8 (17.7%)	16 (24.2%)	0.417
IL-6	4.38±2.45	2.24±0.77	5.84±2.09	**0.001**

IL-6: Interleukin-6. n: Number
Data are presented as mean (standard deviation) or frequency (percentage)

Table 2. Relationship between patients' characteristics and IL-6 levels

		INF	EDU	Age	BW	PB	PPB	IL-6
Intra-amniotic infection	r	1	0.087	0.054	**-0.339**	**0.196***	-0.012	**0.316****
	p	-	0.361	0.574	**0.001**	**0.040**	0.897	**0.001**
Education status	r	0.087	1	0.088	0.035	-0.036	-0.060	-0.022
	p	0.361	-	0.357	0.712	0.706	0.531	0.821
Age	r	0.054	0.088	1	-0.136	0.042	0.186	0.079
	p	0.574	0.357	-	0.155	0.661	0.051	0.411
Birth week	r	**-0.339****	0.035	-0.136	1	**-0.637****	**-0.237***	**-0.919****
	p	**0.001**	0.712	0.155	-	**0.001**	**0.012**	**0.001**
The presence of PB	r	**0.196***	-0.036	0.042	**-0.637****	1	0.077	**0.726****
	p	**0.040**	0.706	0.661	**0.001**	-	0.421	**0.001**
Previous PB	r	-0.012	-0.060	0.186	**-0.237***	0.077	1	**0.311****
	p	0.897	0.531	0.051	**0.012**	0.421	-	**0.001**
IL-6	r	**0.316****	-0.022	0.079	**-0.919****	**0.726****	**0.311****	1
	p	**0.001**	0.821	0.411	**0.001**	**0.001**	**0.001**	-

INF: The absence of intra-amniotic infection, EDU: Education status, BW: Birth week, PB: Preterm birth, PPB: Previous preterm birth, IL-6: Interleukin-6

who experienced preterm birth. This result suggests that the evaluation of cervicovaginal IL-6 may have predictive value for preterm delivery and could be important in the management of women at risk for preterm delivery.

Preterm birth is described as the occurrence of birth before 37 weeks of gestation and is one of the major causes of perinatal mortality and morbidity worldwide. Antenatal prediction of preterm birth would be critical in determining women at high risk and in reducing the burden of morbidities related to this condition, yet assessment remains uncertain and difficult. Many maternal or fetal characteristics associated with the occurrence of preterm labor have been identified, such as maternal age, history of preterm birth, ethnicity, low socioeconomic status, low education, pregnancy weight, psychosocial stress, drug and alcohol abuse, environmental factors and intrauterine infection (2,4,5). In accordance with the literature, we demonstrated that ten mothers had intra-amniotic infection in our study group and 9 of them resulted in preterm labor. In addition, 24 of our patients had a previous history of preterm pregnancy and 7 of them resulted with preterm delivery. We also found positive association between intra-amniotic infection and preterm labor. Our results indicate that intra-uterine infection and previous preterm birth history are important characteristics for preterm labor. These patients should be considered as high-risk for preterm labor and should be monitored closely.

Researchers have reported biological pathways associated with preterm delivery, including inflammation, extracellular matrix degradation, fetal infection, fetal stress, fetal anomalies and abnormal estrogen metabolism (4). IL-6 is a pleiotropic pro-inflammatory cytokine and has been investigated in numerous gynecological diseases including unexplained infertility, recurrent miscarriage, preeclampsia, and preterm labor (6). The expression of IL-6 is altered with infection, inflammation and stress caused by stimuli with various factors, such as tumor necrosis factor-alpha, IL-1 and lipopolysaccharide (7). The expression of IL-6 has been found to be low in the early and mid-trimester, but increased in the presence of uterine infection (8). Intra-amniotic infection increases the production of cytokines and triggers the synthesis and release of prostaglandins that are responsible for cervical ripening and uterine contraction; thus, infections may result in preterm labor through this mechanism (7). Genetic studies have shown relationships between a single nucleotide polymorphism in the promoter region of the IL-6 gene and elevated risk of preterm delivery (9). Several studies in the literature have found altered levels of IL-6 in various biological fluids (serum, amniotic fluid and cervicovaginal fluid) in relation with preterm delivery. Romero et al. (8) showed higher IL-6 levels in the amniotic fluid of mothers who had preterm delivery with intra-amniotic infection compared to those without infection, suggesting that amniotic fluid IL-6 may have diagnostic and prognostic value for preterm labor. Jung et al. (10) revealed that higher levels of cervicovaginal IL-6 were related to delivery within 7 days among women with preterm labor. Lockwood et al. (11) demonstrated 4.2-fold increased cervical IL-6 concentrations among

patients with preterm labor compared to those that had term labor. In a study conducted by Reyna-Vallasmil and colleagues, cervicovaginal IL-6 levels were measured in the second trimester and preterm labor developed in women with higher IL-6 levels (12). LaShay et al. (13) showed increased cervicovaginal IL-6 in 135 women with the symptoms of suspected preterm delivery. Lange and coworkers revealed an elevation of cervical IL-6 levels in 31 patients with preterm delivery, who had intact membranes (14). Perales-Puchalt et al. (15) demonstrated in a study involving 100 mothers with a threat of preterm labor that five women who delivered within two days and six women who delivered within 7 days had high cervical IL-6. They also found a high negative predictive value of cervical IL-6 levels for the prediction of preterm birth. Woodworth et al. (16) showed in 660 cervicovaginal fluid samples that the positive and negative predictive values for cervicovaginal IL-6 were 16% and 97%. Furthermore, they reported that IL-6 levels were strongly associated with the occurrence of delivery within 14 days of collection (16). In agreement with these studies, we found higher cervicovaginal IL-6 levels in women who had preterm labor. We also found correlations between IL-6 and the absence of intra-amniotic infection and also duration of pregnancy. Our study supports current evidence that IL-6 is involved in parturition and is an effective predictor of preterm delivery. IL-6 may be involved in the etiology and pathogenesis of preterm delivery through its stimulation of prostaglandin synthesis. IL-6 may release into the cervicovaginal fluid during the breakdown of chorio-decidual adhesion or as a direct response to increased inflammation. Our study also demonstrates that circulating cytokines may have a role in the pathophysiology of preterm delivery. Our results indicate that cervical IL-6 levels can be utilized as a cheap, direct and practical method to predict preterm labor, and could be an alternative to amniotic fluid testing.

There were several limitations in this study. The most important was the fact that we performed only a single cervicovaginal IL-6 measurement. Besides, the sample size of study can be considered small; however, we excluded patients that could have confounding factors. Larger studies are necessary to confirm our findings.

Conclusion

This retrospective study demonstrates that cervicovaginal fluid IL-6 levels were altered in women with preterm birth. There is a strong association between increased cervicovaginal fluid IL-6 levels and prediction of preterm delivery. Measurement of cervicovaginal IL-6 levels during pregnancy may be used as a predictive biomarker for the detection of preterm birth and women at high-risk; thereby providing early interventions and intensive antenatal care opportunity to reduce perinatal morbidity and mortality.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the non-interventional Clinical Research Ethics Committee of İstanbul Medipol University (decision number: 519, decision date: 25/06/2020).

Informed Consent: Written and verbal informed consent was obtained from participating women prior to sampling and their participation in this study.

Peer-review: Externally peer-reviewed.

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CASE REPORT

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Anesthetic Management in Premature Newborn with Huge Sacrococcygeal Teratoma: A Case Report

Dev Sakrokoksigeal Teratomu Olan Prematür Yenidoğanın Anestezi Yönetimi: Olgu Sunumu

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Abstract

Sacrococcygeal teratomas are the most common congenital tumors in newborns. The primary treatment is early surgical resection. However, the risks of surgical procedures and tumor morphology, as well as the challenges of premature newborns, make the anesthetic management distinguished. In this case report, we present anesthesia management of 3.420 gr newborn on the postnatal 3rd day, who was born by caesarean delivery with 176x130x130 mm huge sacrococcygeal teratoma at 32 weeks of gestation.

Keywords: Anesthesia, premature newborn, sacrococcygeal teratoma

Öz

Sakrokoksigeal teratomlar yenidoğanlarda en sık görülen konjenital tümörlerdir. Birincil tedavisi erken cerrahi rezeksiyondur. Bununla birlikte, cerrahi prosedür, tümör morfolojisi ve prematür yenidoğan ile ilişkili zorluklar anestezi yönetimini karmaşık hale getirir. Bu olgu sunumunda 3,420 gr ağırlığında, 32. gestasyon haftasında sezaryen ile doğurtulmuş, 176x130x130 mm boyutlarında dev sakrokoksigeal teratomu olan 3 günlü yenidoğanın anestezi yönetimini sunduk.

Anahtar kelimeler: Anestezi, prematüre yenidoğan, sakrokoksigeal teratom

Introduction

Sacrococcygeal teratoma (SCT) is the most common congenital tumors in newborns (1). The primary treatment is the total excision of the tumor as early as possible after birth (2,3). During the excision of massive tumors with high vascularity, the intraoperative phase becomes complicated due to fast and massive hemorrhage, massive transfusion, hypovolemia, hyperpotassemia, coagulopathy, acidosis, and hypothermia (1,4,5).

In this case report, we presented the anesthetic management for the excision of a huge SCT of 176x130x130 mm on the postnatal 3rd day.

Case Report

A female newborn who was diagnosed with a mass in the gluteus as shown by the prenatal ultrasound and delivered as 3.420 gr at 32 weeks of gestation by emergency caesarean section was included in the study. The mass was thought

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to be a SCT (Figure 1), thus, it was decided to perform an operation.

The newborn was assessed in intensive care preoperatively. Physical examination results were normal but SCT of approximately 20x15 cm starting from the perineum, involving the rectum and extending behind the sacrum

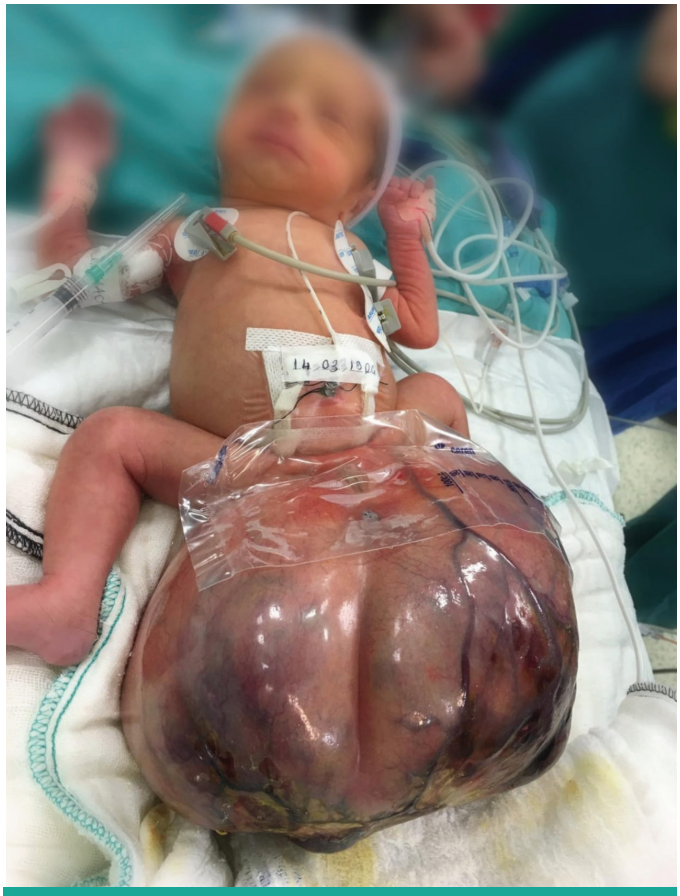

Figure 1. Huge sacrococcygeal teratoma of 3-day-old newborn (176x130x130 mm in size)

covered with highly vascular and regional erosions was observed. The magnetic resonance imaging showed that the mass was 135 mm on the cranio-caudal plane, 176x130 mm on the axial plane, smoothly contoured, lobulated in some regions, solid and multicystic, filling the presacral and precoccygeal region, with no extension into the abdomen. Cranial and echocardiographic images were considered to be normal, and hemoglobin was 15.7 gr/dL^{-1}, hematocrit (Hct) was 46.1%, platelet (Plt) was 158,000 µL^{-1}, ctivated partial thromboplastin time was 29.8 sec, prothrombin time was 15 sec, international normalized ratio was 1.3, fibrinogen was 121 mg/dL, and alpha-fetoprotein (AFP) was >54,000. Erythrocyte suspension (ES), fresh whole blood (WB), fresh frozen plasma (FFP) and Plt suspension were prepared preoperatively. On the postnatal 3rd day, the operating room was heated to 25 °C, infusion pumps and vasoactive drugs were prepared before anesthesia induction. Electrocardiogram, oxygen saturation and non-invasive BP were monitored. For venous access, preoperatively placed umbilical and right brachial central venous catheters were used. The induction was done with 1 µg kg^{-1} of fentanyl, 0.6 mg kg^{-1} of rocuronium, 8% sevoflurane and 50-50% O_2-medical air mixture, and the newborn was intubated with number 3 endotracheal tube. The anesthesia was maintained with 2-2.5% sevoflurane in 50-50% O_2-medica-air and ventilated manually throughout the operation. The fluid infusion was done using Ringer's lactate and at 0.9 NaCl 50 mL/hour. Invasive arterial pressure was monitored in the left radial artery after intubation, and nasopharyngeal temperature, urine flow and arterial blood gas (ABG) (Table 1) were monitored. The newborn was put into prone position. As the mass was huge and highly vascular, erythrocyte transfusion was started at

Table 1. Arterial blood gas analyses of the patient in preoperative, intraoperative and postoperative period

	Preoperative	Intraoperative	Postoperative	ICU period
pH	7.28	7.22	7.41	7.45
$PaCO_2$ (mmHg)	48	42	26	27
PaO_2 (mmHg)	188	100	260	100
Hct (%)	46.7	30	22.1	27
Hbg (gr/dL)	15.3	10	7.1	9
Ca^{2+} (mmol/L)	1	0.37	0.86	1.1
Na^+ (mmol/L)	134	137	141	146
K^+ (mmol/L)	3.5	3.7	4.2	3.5
Glucose (mg/dL)	78	377	275	152
Lactate (mmol/L)	2.2	2.7	7	9.9
BE (mmol/L)	-4,8	-9	-4	9

BE: Base excess, Ca^{2+}: Calcium, K^+: Potassium, Na^+: Sodium, Hbg: Hemoglobin, Hct: Hematocrit, ICU: Intensive care unit, $PaCO_2$: Partial pressure of carbon dioxide, PaO_2: Partial pressure of oxygen

the same time with the surgical excision. Whereas the heart rate (HR) was 135 bpm and the blood pressure (BP) was 85/60 mm/Hg at the beginning of the operation, sudden bradycardia (40 bpm), hypotension (20/15 mm/Hg) and circulatory collapse developed as soon as having started to excise the tumor in 30 minutes in the operation. Twenty µg of adrenalin (3 intermittent doses) and 20 µg/kg of atropine were administered, and 10 µg/kg/min of dopamine and 10 µg/kg/min of noradrenaline infusions were started, concurrently transfusion was continued with manual WB and FFP infusions. The patient had no hypothermia and her temperature was 36 °C during surgery. Hemodynamic stabilization was attained approximately 5 minutes after the circulatory collapse (HR: 120 bpm, BP: 80/50 mm/Hg). Acidosis, hypocalcemia and hyperglycemia were detected in the ABG analyses. The transfusion was maintained since Hct dropped from 46% to 30% due to the hemorrhage continuing on the surface of the mass. The operation was completed in 225 minutes with the newborn in the prone position and the mass excised weighed as 1.450 gr. Throughout the operation, total of 100 mL of ES, 235 mL of WB, 80 mL of FFP, and 600 mL of crystalloid fluid infusion were administered. At the end of the operation, the newborn was transferred to the neonatal intensive care unit (ICU) in an intubated state and without inotrope infusion. During ICU follow up, the patient also did not need inotropic agent. The mean urine output of the patient was about 5.05 cc/h in ICU. Lactate level of the patient was 2 mmol/L at the discharge from the ICU. Weighed as 1.410 gr in the early postoperative phase in the intensive care, the newborn was extubated on the postoperative 1st day. Weighed as 3.075 gr on day 65, her AFP was measured as 397 u/mL and she was discharged from the hospital.

Discussion

SCTs are surgically removed in total, the survival rate is 77%-94% (1). Timing of the surgery is recommended to be as soon as possible immediately after birth because any delay may result in the development of coagulopathy (1,4,5). In case of huge and highly vascular SCTs, it may result in massive hemorrhage complication. During the dissection of SCT, massive hemorrhage is the biggest cause of intraoperative mortality (1,4-6). The rate of hemorrhagic mortality was reported as 3.8% (6). Therefore, for patients with huge SCT, it is recommended to keep blood products available to allow for commencing transfusion as soon as the surgery begins. Also, large intravenous routes and invasive hemodynamic monitoring are recommended (1,4-7). In these operations, another problem is hypothermia, which may develop during the operation due to loss of heat from a large tumor site in spite of all the measures taken (1,4-6).

There are studies that report more stable SCT cases requiring less blood transfusion. Silay et al. (8) experienced short-term hemodynamic instability 5 minutes after the excision of a mass of 980 g from a 40-week-old baby. They ensured hemodynamic stabilization with 100 mL of blood transfusion and volume and inotrope infusion (8). During the excision of a mass of 850 gr from a 38-week-old baby weighting 4.460 gr, Akin et al. (9) completed the operation without blood transfusion. Unlike these cases, our case was a premature, weighting 3.420 gr and the mass excised weighed 1.450 gr; in other words, the mass was too big considering the weight of the baby and highly vascular. We think that the sudden hemodynamic compromise and the need for massive blood transfusion in our case are also attributable to these causes.

Conclusion

The risk of morbidity and mortality is high while operating on particularly large SCTs with high vascularity in premature newborns. The primary cause of mortality is the massive hemorrhages from the surgical and intratumoral site. Therefore, in such patients, blood products must be prepared preoperatively, large intravenous routes must be placed, and invasive hemodynamic monitoring must be done throughout the operation.

Ethics

Informed Consent: Consent form was taken from patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.G.Ö., M.E., H.C.G., S.D., M.B.Y., N.T., A.S., Design: F.G.Ö., M.E., H.C.G., S.D., M.B.Y., N.T., A.S., Data Collection or Processing: F.G.Ö., M.E., H.C.G., S.D., M.B.Y., N.T., A.S., Analysis or Interpretation: F.G.Ö., M.E., H.C.G., S.D., M.B.Y., N.T., A.S., Writing: F.G.Ö., M.E., H.C.G., S.D., M.B.Y., N.T., A.S.

Conflict of Interest: The authors declare that there is no conflict of interest with regard to this manuscript.

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