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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.

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All submissions must be original, unpublished (including as full text in conference proceedings), and not under the review of any other publication synchronously.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

We follow the COPE Ethics Flowcharts for dealing with cases of possible scientific misconduct and breach of publication ethics (http://publicationethics.org/resources/flowcharts)

Human and Animal Rights, Informed Consent, Conflict of Interest

Bagcilar Medical Bulletin adopts highest ethical and scientific standards and ensures that it is free of influences regarding commercial interests. It is authors' responsibility that the articles are in accordance with ethical codes of conduct. Bagcilar Medical Bulletin takes as principle to comply with the ethical standards of 1975 Helsinki Declaration-Ethical Principles for Medical Research Involving Human Subjects- revised in 2004-http://www.wma.net/en/30publications/10policies/b3/index.html and WMA Statement on Animal Use in

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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.

Identifying information such as names, initials, hospital numbers, dates, photographs, and family pedigree must be avoided, unless disclosure is allowed by written consent of patient or the legal custodian of the patient. Informed consent for this purpose requires that an identifiable patient be shown in the manuscript to be published. Patient consent should be written and archived either with the journal, the authors, or both, as dictated by local regulations or laws. It must be mentioned in the text that informed consent was obtained from the participants. Especially for case report, identifying information should be avoided as much as possible. Eye masking on photos is not sufficient to conceal the identity of the patient. Authors have to stipulate lack of impact on scientific significance in case of changing the identifying information. Written informed consent should be taken from the patients presented in case studies; and it should be indicated in the manuscript.

Authors have to confirm in the section "Materials and Methods" that study has been conducted in compliance to above mentioned principles, approvals have been obtained from related institutional ethical committees and informed consents were collected.

When reporting experiments on animals, authors should indicate whether the institutional and national guides for the care and use of laboratory animals were followed as in "Guide for the Care and Use of Laboratory Animals" (www.nap.edu/catalog/5140.html) and approval from ethical committee should be taken. The editor and the publisher do not guarantee or accept responsibility for the published features or definitions of commercial products. If there is direct or indirect grant support, it should be acknowledged in the section titled "declaration of interest" and should include the full name of the sponsor and grant number. Existence or lack of sponsorship of any kind as well as the type of sponsorship (consulting etc) has to be acknowledged, as well.

Adopts WAME's definition http://www.wame.org/about/wame-editorial-on-coi which states that conflict of interest exists when author, peer reviewer or editor has a competing interest that could unduly influence (or be reasonably seen to do so) his or her responsibilities in the publication process. The types of competing interests that should be declared include financial ties, academic commitments, personal relationships, political or religious beliefs, institutional affiliations. The conflict of interest is to be acknowledged in the manuscript.

Language

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.

Title Page

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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databases, author should be sure that abstract represents the content of the article accurately. Abstract should inform about the basis of the study and include the purpose, basic procedures (selection of cases and laboratory animals, observatory and analytical methods), key findings and conclusions. New and significant apects of the study or observations should be stated. 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).

Manuscript Types

Original Research

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.

The selection and description of the participants

The election, source of population, inclusion and exclusion criteria of the people who participate to experimental or clinical study must be clearly defined in this section. The particular study sample must be explained by the authors (i.e., why the study is performed in a definite age, race or sex population, etc.)

Technical information

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.

Statistics

The statistical methods must be described with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. If possible, findings should be quantified and presented with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Relying solely on statistical hypothesis testing, such as P values, which fail to convey important information about effect size must be avoided. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. The computer software used must be specified.

Results

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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be discussed, results should be compared and contrasted with findings of other studies in the literature and the different findings from other studies should be explained. The new and important aspects of the study and the conclusions that follow from them should be emphasized. The data or other information given in the Introduction or the Results section should not be repeated in detail.

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.

Tables, Graphics and Illustrations

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.

Brief Research

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.

Case Report

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.

Review

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.

Letter to the Editor

Letter to the Editor is short and decisive manuscript. They should be preferably related to articles previously published in the Journal or views expressed in the Journal. The letter should not include preliminary observations that need a later study for validation.

Tables

Tables capture information concisely and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text. Each table should be typed or printed with double spacing on a separate sheet of paper. The tables should be numbered consecutively in the order of their first citation in the text and a brief title for each table should be supplied. Any internal horizontal or vertical lines should not be used and a short or an abbreviated heading should be given to each column. Authors should place explanatory matter in footnotes, not in the heading. All nonstandard abbreviations should be explained in footnotes, and the following symbols should be used in sequence: *,†,‡,§,ǁ,¶,**,††,‡‡. The statistical measures of variations, such as standard deviation and standard error of the mean should be identified. Be sure that each table is cited in the text. If you use data from another published or unpublished source, obtain permission and acknowledge that source fully. Additional tables containing backup data too extensive to publish in print may be appropriate for publication in the electronic version of the journal, deposited with an archival service, or made available to readers directly by the authors. An appropriate statement should be added to the text. Such tables should be submitted for consideration with the paper so that they will be available to the peer reviewers.

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Illustrations (Figures)

Figures should be either professionally drawn and photographed, or submitted as digital prints in photographic-quality. In addition to requiring a version of the figures suitable for printing, authors are asked for electronic files of figures in a format (for example, JPEG or GIF) that will produce high-quality images in the Web version of the journal; authors should review the images of such files on a computer screen before submitting them to be sure they meet their own quality standards. For X-ray films, scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, sharp, glossy, black-and-white or color photographic prints should be sent, usually 127x173 mm. Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication. Figures should be made as self-explanatory as possible, since many will be used directly in slide presentations. Titles and detailed explanations belong in the legends-not on the illustrations themselves. Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background. Photographs of potentially identifiable people must be accompanied by written permission to use the photograph. Figures should be numbered consecutively according to the order in which they have been cited in the text. If a figure has been published previously, the original source should be acknowledged and written permission from the copyright holder should be submitted to reproduce the figure. Permission is required irrespective of authorship or publisher except for documents in the public domain. Accompanying drawings marked to indicate the region to be reproduced might be useful to the editor. We publish illustrations in color only if the author pays the additional cost.

Legends for Illustrations (Figures)

The legends for illustrations should be typed or printed out using one spacing, starting on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, each one clearly should be identified and explained in the legend. The internal scale should be explained and the method of staining in photomicrographs should be identified. Units of Measurement.

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples. Temperatures should be in degrees Celsius, blood pressures should be in millimeters of mercury. Authors must consult the Information for Authors of the particular journal and should report laboratory information in both local and International System of Units (SI). Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

Abbreviations and Symbols

Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

Acknowledgement(s)

All forms of support, including individual technical support or material support must be acknowledged in the author's footnote before references.

Case Reports and Word Limitation

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 /),

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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.

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

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

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

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

For the citation from a translated book:

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

5. For the citation from thesis:

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

6. For the citation from posters:

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

7. Online Article:

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

SUBMISSION TO JOURNAL

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

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

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

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

SUBMISSION CHECKLIST

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

Ensure that the following items are present:

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

YAZARLARA BİLGİ

Derginin Tanımı

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

Editoryal Politikalar ve Hakem Süreci

Yayın Politikası

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

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

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

Genel İlkeler

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

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

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

Yazarların Sorumluluğu

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

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

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

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

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

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

Editör ve Hakem Sorumlulukları ve Değerlendirme Süreci

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

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

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

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

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

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

Açık Erişim İlkesi

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

Yayın Etiği

İlke ve Standartlar

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

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

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İnsan ve Hayvan Hakları, Bilgilendirilmiş Olur, Çıkar Çatışması

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

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

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

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

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

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

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

Dil

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

Yazıların Hazırlanması

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

Başlık

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

Öz ve Anahtar Sözcükler

Makalenin İngilizce başlığı İngilizce özde, Türkçe başlığı da

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

Makale Türleri

Orijinal Araştırma

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

Öz

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

Anahtar Kelimeler

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

Giriş

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

Yöntem ve Gereçler

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

Olguların Seçimi ve Tanımlanması

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

Teknik Bilgi

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

İstatistik

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

Bulgular

Ana bulgular istatistiksel verilerle desteklenmiş olarak eksiksiz

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

Tartışma

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

Sonuçlar

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

Tablo, Grafik ve Şekiller

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

Kısa Araştırma

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

Olgu Sunumu

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

Derleme

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

Editöre Mektup

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

Tablolar

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

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

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

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

Şekiller

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

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

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

Şekillerin Dipnotları

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

Ölçüm Birimleri

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

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

Teşekkür(ler)

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

Kelime Sayısı Sınırlandırması

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

Makale Hazırlığı :

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

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

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

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

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

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

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

Kaynaklar

Kaynaklarla İlgili Genel Konular

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

Özler kaynak olarak gösterilmemelidir. Kabul edilmiş ancak yayınlanmamış makalelere atıflar "basımda" ya da "çıkacak" şeklinde verilmelidir; yazarlar bu makaleleri kaynak gösterebilmek için yazılı izin almalıdır ve makalelerin basımda olduğunu ispat edebilmelidir. Gönderilmiş ancak yayına kabul edilmemiş makaleler, "yayınlanmamış gözlemler" olarak gösterilmeli ve kaynak yazılı izinle kullanılmalıdır. Genel bir kaynaktan elde edilemeyecek temel bir konu olmadıkça "kişisel iletişimlere" atıfta bulunulmamalıdır. Eğer atıfta bulunulursa parantez içinde iletişim kurulan kişinin adı ve iletişimin tarihi belirtilmelidir. Bilimsel makaleler için yazarlar bu kaynaktan yazılı izin ve iletişimin doğruluğunu gösterir belge almalıdır.

Referans Stili ve Formatı

Tek tip kurallar esas olarak National Library of Medicine, tarafından uyarlanmış olan bir ANSI standart stilini kabul etmiştir. Kaynak atıfta bulunma örnekleri için yazarlar www.nlm.nih.gov/bsd/uniform_requirements.html sitesine başvurabilirler. Dergi isimleri National Library of Medicine kaynağında yer alan şekilleriyle kısaltılmalıdır.

Kaynaklar yazının sonunda (Kaynaklar) başlığı altında metindeki geçiş sırasına göre numaralandırılıp dizilmelidir. Metin içinde ise () şeklinde parantez içinde referans numarası belirtilmelidir. Kaynakların listesiyle metin içinde yer alış sırası arasında bir uyumsuzluk bulunmamalıdır.

Kaynakların doğruluğundan yazar(lar) sorumludur. Tüm kaynaklar metinde belirtilmelidir. Kaynaklar aşağıdaki örneklerdeki gibi gösterilmelidir. Altı yazardan fazla yazarı olan çalışmalarda ilk altı yazar belirtilmeli, sonrasında "ve ark." ya da "et al." ibaresi kullanılmalıdır. Kaynak dergi adlarının kısaltılması National Library of Medicine'de belirtilen kısaltmalara (https://www.ncbi.nlm.nih.gov/nlmcatalog/journals) uygun olmalıdır. National Library of Medicine'da indekslenmeyen bir dergi kısaltılmadan yazılmalıdır.

Kaynaklar için örnekler aşağıda belirtilmiştir:

1. Dergilerdeki makaleler için örnekler:

MEDLINE'da yer alan ve kısaltması MEDLINE'a göre yapılan dergi makalesi için: 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.

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

2. Ek sayı için:

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

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.

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

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

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Çeviri Kitaptan Alıntı için:

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

5. Tezden alıntı için:

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

6. Kongre bildirileri için:

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

7. Online Makale:

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

Makalenin Dergiye Gönderilmesi

Çevrimiçi gönderim (online submission) ile birlikte Bağcılar Tıp Bülteni web sitesinin (www.ijfed.org) ilgili kısımlarındaki talimatlara uyarak makale gönderilebilmekte, hakem süreçleri de bu yolla yapılabilmektedir.

Makalelere eşlik eden ve aşağıdaki bilgileri içeren bir kapak mektubu olmalıdır.

• Aynı ya da çok benzer çalışmadan elde edilen raporların daha önce yayına gönderilip gönderilmediği mutlaka belirtilmelidir. Böyle bir çalışmaya özgül olarak atıfta bulunulmalı ve ayrıca yeni makalede de eskisine atıfta bulunulmalıdır. Gönderilen makaleye bu tip materyalin kopyaları da eklenerek editöre karar vermesinde yardımcı olunmalıdır.

• Eğer makalenin kendisinde ya da yazar formunda belirtilmemişse çıkar çatışmasına neden olabilecek mâli ya da diğer ilişkileri belirten bir ifade olmalıdır.

• Makalenin tüm yazarlar tarafından okunup kabul edildiğini, önceden belirtilen şekilde yazarlık ölçütlerinin karşılandığını, her yazarın makalenin dürüst bir çalışmayı yansıttığına inandığını belirten bir ifade olmalıdır. Mektup editöre yardımcı olabilecek tüm diğer bilgileri içermelidir. Eğer makale önceden başka bir dergiye gönderilmişse önceki editörün ve hakemlerin yorumları ve yazarların bunlara verdiği cevapların gönderilmesi faydalıdır. Editör, önceki yazışmaların gönderilmesini hakem sürecini dolayısıyla yazının yayınlanma sürecini hızlandırabileceğinden istemektedir.

Yazarların makalelerini göndermeden önce bir eksiklik olmadığından emin olmalarını sağlamak için bir kontrol listesi bulunmaktadır. Yazarlar derginin kontrol listesini kullanıp gönderilerini kontrol etmeli ve makaleleri ile birlikte bu formu göndermelidirler.

SON KONTROL LİSTESİ

• Editöre sunum sayfası
- Makalenin kategorisi
- Başka bir dergiye gönderilmemiş olduğu bilgisi
- Sponsor veya ticari bir firma ile ilişkisi (varsa belirtiniz)
- İstatistik kontrolünün yapıldığı (araştırma makaleleri için)
- İngilizce yönünden kontrolünün yapıldığı
• Telif Hakkı Devir Formu
• Yazar Katkı Formu
• ICMJE Potansiyel Çıkar Çatışması Beyan Formu
• Daha önce basılmış materyal (yazı-resim-tablo) kullanılmış ise izin belgesi
• İnsan öğesi bulunan çalışmalarda "gereç ve yöntemler" bölümünde Helsinki Deklarasyonu prensiplerine uygunluk, kendi kurumlarından alınan etik kurul onayının ve hastalardan "bilgilendirilmiş olur (rıza)" alındığının belirtilmesi
• Hayvan öğesi kullanılmış ise "gereç ve yöntemler" bölümünde "Guide for the Care and Use of Laboratory Animals" prensiplerine uygunluğunun belirtilmesi
• Kapak sayfası
- Makalenin Türkçe ve İngilizce başlığı (tercihen birer satır)
- Yazarlar ve kurumları
- Tüm yazarların yazışma adresi, iş telefonu, faks numarası, GSM, e-posta adresleri
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• Anahtar Kelimeler: 3-10 arası (Türkçe ve İngilizce)
• Tam metin makale
• Teşekkür
• Kaynaklar
• Tablolar-Resimler, Şekiller

BAGCILAR MEDICAL BULLETIN
Bağcılar Tıp Bülteni

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ORIGINAL RESEARCH

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The Correlation of Pain Catastrophizing Scale and Sedation in Patients Undergoing Gastroscopy

Gastroskopi Yapılan Hastalarda Ağrı Katastrofizasyonu ile Sedasyon İlişkisi

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Abstract

Objective: Catastrafization is defined as considering the worst possible consequence of events and danger and increasing the likelihood of this. In this study, the Catastropization scale applied to patients to compare pain catastrophization before the esophagogastroduedonoscopy procedure and the pain at the vascular access of patients and the amount of sedation applied were compared.

Method: Patients planned for esophagogastroduodenoscopy were informed about the pain catastrophizing scale before the procedure and asked to answer the form. The pain of the patient during vascular access was recorded according to the numerical pain rating scale. Sedation was applied to all patients during the esophagogastroduedonoscopy procedure. Sedation relationship applied to the patient was evaluated by both pain assessment methods.

Results: A positive correlation was observed between the intensity of pain during vascular access (DyNRS) and the amount of sedation applied during endoscopy, and between Pain Catastrophizing scale and DyNRS.

Conclusion: In this study, it was concluded that there was a relationship between the intensity of vascular pain and sedation consumption, and the amount of sedation consumption will increase as the level of pain increases.

Keywords: Endoscopy, numeric rating scale, pain catastraphizing scale, sedation

Öz

Amaç: Katastrafizasyon, olaylar ve tehlikeyle ilgili olabilecek en kötü sonucu düşünüp bunun olabilirliğini artırmak olarak tanımlanmaktadır. Bu çalışmada özefagogastroduedonoskopi işlemi öncesi ağrı katastrofizasyonunu belirlemek için hastalara uygulanan katastrafizasyon skalası ile hastalara damar yolu açılışındaki ağrısı ve uygulanan sedasyon miktarı karşılaştırıldı.

Yöntem: Özefagogastroduodenoskopi planlanan hastalar işlem öncesinde acı felaket ölçeği hakkında bilgilendirildi ve formu cevaplamaları istendi. Hastanın damar yolu açma esnasındaki ağrısı Numerik Ağrı Değerlendirme skalasına göre kaydedildi. Tüm hastalara özefagogastroduedonoskopi işlemi esnasında sedasyon uygulandı. Her iki ağrı değerlendirme yöntemi ile hastaya uygulanan sedasyon ilişkisi değerlendirildi.

Bulgular: Hem vasküler erişim sırasında ağrının yoğunluğu (DyNRS) ile endoskopi esnasında uygulanan sedasyon miktarı arasında hem de Acı Felaket ölçeği ile DyNRS arasında pozitif yönde korelasyon görüldü.

Sonuç: Bu çalışmada, damar yolu ağrı şiddeti ile sedasyon tüketimi arasında bir ilişki olduğu ve ağrı düzeyi arttıkça sedasyon tüketim miktarında da artış olacağı sonucuna varılmıştır.

Anahtar kelimeler: Ağrı katastrafizasyon skalası, endoskopi, numerik değerlendirme skalası, sedasyon

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Introduction

The presence of alarm symptoms such as dysphagia, vomiting, gastrointestinal bleeding, anemia, anorexia and loss of weight could indicate malignancy in patients over the fifty years of age. The primary method of diagnosis is upper endoscopy (1,2). Endoscopic procedures are used for monitoring, screening and treatment of benign or malignant lesions (3). Today, it is very important to ensure the comfort of the patient during endoscopy. Sedation facilitates the work for both the physician and the patient, particularly due to the prolongation of the procedure in cases where biopsy is performed for diagnostic purposes or during endoscopy performed for treatment. Sedation is preferred by the endoscopist and the patient since it reduces anxiety, causes short-term retrograde amnesia and enables the patient to feel less pain during the procedure. Administration of sedation may vary according to the experience of the anesthetist, nature of the procedure applied to the patient, experience of the endoscopist regarding the procedure, and the socio-cultural state of the patient.

Previous studies have shown that the cognitive state of the individual plays an important role in sensing the pain and evaluating the intensity. Catastrophizing has been defined as "thinking about the worst possible consequence regarding the cases and threat and increasing likelihood of experiencing". "The pain catastrophizing scale" (PCS) was developed by Sullivan et al. (4) in order to evaluate the severity of catastrophizing.

In the present study, we aimed to investigate the correlation between the amount of sedation consumed during endoscopic procedures with the intensity of pain during vascular access (DyNRS) and PCS.

Materials and Methods

This retrospective observational cross-sectional study was carried out in the University of Health Sciences Turkey, Trabzon Kanuni Training and Research Hospital Clinic of Endoscopy after obtaining the approval from the Clinical Research Ethics Committee (13/03/2020-KAEK-2020/15) of the same hospital.

Patients over the 18 years of age, who were admitted to the general surgery, internal medicine and gastroenterology clinics with epigastric complaints and planned for elective esophagogastroduodenoscopy (EGD), were included in the study after obtaining written and verbal informed consent. An evaluation was performed prior to endoscopy, and the emergency patients, patients with coagulopathy and infection, patients who were not administered sedation, patients who received long-term opioid treatment due to psychiatric diseases, and patients who did not desire to participate in the study were excluded.

At the preparation room before the endoscopic procedure, gender, age, body mass index (BMI), educational background, chronic pain information, smoking habits, comorbidities of the patients were recorded along with the drugs they used regularly. Patients were informed about the numeric rating scale (NRS). Next, the patients were informed about the PCS and asked to complete the PCS-TR form. Prior to the procedure, the non-dominant hand skin was cleansed with alcohol and venous vascular access was opened with an 18 Gauge needle. The pain experienced by the patient during the opening of the vascular access was recorded according to NRS (vascular access NRS= DyNRS). All perioperative procedures and follow-ups were carried out by a single anesthetist. During EGD, sedation was administered to all patients with intravenous 1 mg/kg propofol. In cases where patients experienced pain during the procedure or moved in a way to prevent the procedure, 0.3-0.5 mg/kg intravenous propofol was applied as additional dose and it was recorded.

Pain intensity: The presence and severity of pain experienced during the opening of the venous access was evaluated by NRS of 10 cm (0= no pain, 10= maximum pain). NRS is a reliable method, which evaluates the subjective pain intensity, does not require verbal or literacy skills, is easy to use and is accepted by in the global literature (5).

PCS: PCS was developed in order to determine the pain catastrophizing in 1995. The Turkish version was tested for reliability and validity by Suren et al. (6) and the Cronbach alpha coefficient was found to be 0.90. It consists 13 questions in 3 different question types, which are rumination, magnification and helplessness. Each question is scored between 0 and 5. The total score to be obtained from the scale ranges from 0 to 52. The high scores indicate negative results (4).

Statistical Analysis

Descriptive analyses were performed in order to provide information regarding the general characteristics of the study groups. Data related to the continuous variables were given in the form of mean ± standard deviation and categorical variables were given as n (%). Comparisons between the groups were made using the Mann-Whitney U test and associations were expressed as the Spearman's rank correlation coefficients (r_s). The p-values were

accepted to be statistically significant when they were calculated as below 0.05. A package statistics software was used for calculations (IBM SPSS Statistics 19, SPSS inc., an IBM Co., Somers, NY).

Results

The number of patients included in the study was 64 (18 male and 46 female), the mean age was 39.8±11.9 years and the BMI was 26.7±5 kg/m^2. When the vascular access was opened during premedication prior to the endoscopy, the median pain intensity value of the patients was measured as (DyNRS) 2 (1-4), the median PCS was 17.50 (10-31.50) (Table 1), the duration of the endoscopy procedure was 5.53±2.15 minutes and the amount of propofol used for sedation was observed to be 80.3±16.2 mg (Table 2).

When we analyzed analgesic needs, we showed that patients having normal PCS scores needed significantly lower doses of analgesic premedication than patients having higher PCS scores (median rank scores 21.61 mg vs 40.97 mg, p<0.001) (Table 3). Similarly, patients having low DyNRS values (<4) needed significantly lower doses of analgesic premedication than patients having higher DyNRS values (≥4) (median rank values 30.99 mg vs. 36.60 mg, p=0.044) (Table 3).

No significant relationship was observed in statistical evaluations performed for educational background, BMI and smoking habits (p>0.05) (Table 3).

A significant positive correlation was observed between DyNRS and endoscopy and the amount of sedation administered during endoscopy (r_s=0.407, p=0.040). A positive correlation was observed between PCS and DyNRS (r_s=0.390, p=0.033). Moreover, there was a significant positive correlation between PCS and the amount of propofol used during endoscopy for sedation (r_s=0.545, p=0.000) (Table 4).

Table 1. Demographic features of pain scores

	Lower quartile (Q1)	Median	Upper quartile (Q3)	Min-max
PCS	10	17.50	31.50	2-51
DyNRS	1	2	4	0-8

PCS: The pain catastrophizing scale, DyNRS: The intensity of pain during vascular access

Table 2. Demographic features of patients

	Mean±SD	Min-max
Age (year)	39.8±11.9	20-63
BMI (kg/m^2)	26.7±5.1	20.7-34.1
Total sedation amount (mg)	80.3±16.2	55-130
Endoscopy time (min)	5.53±2.15	3.17-8.25

BMI: Body mass index, SD: Standard deviation

Discussion

In the present study, it was aimed to determine the PCS level during the preoperative period and to estimate the sufficiency of sedation during the procedure as well as providing the patients with a comfortable experience. In addition, the correlation between PCS and DyNRS was also discussed.

When used in appropriate doses, sedation and analgesia improves the comfort of both the patient and the clinician in day surgeries. It also increases the achievement level of the procedure. Therefore, planning is important for providing an effective and reliable analgesia (7). Hence, the pain that is experienced at all degrees of severity, regardless of localization in the perioperative process of day surgeries, may cause functional disorders in all organs and lead to complications such as the increase in morbidity and mortality.

Table 3. Comparison by total sedation amount of demographic and clinical features of patients

		n	Mean ranks	p
PCS	<17	28	21.61	**0.000***
	≥17	36	40.97	
Gender	Female	46	31.50	0.485*
	Male	18	35.06	
Smoking	Yes	17	31.71	0.835*
	No	47	32.79	
BMI (kg/m^2)	≥20-<25 (normal)	19	28.95	0.860*
	≥25 (overweight)	39	29.77	
DyNRS	<4	43	30.99	0.044*
	≥4	21	35.60	

*: Mann-Whitney U test, PCS: The pain catastrophizing scale, DyNRS: The intensity of pain during vascular access, BMI: Body mass index, The significant p-values were marked as bold characters.

Table 4. Correlation between pain scores and the amount sedation

Correlation	n	Spearman's rho (r_s)	p
Sedation amount-PCS	64	0.545	**0.000**
Sedation amount-DyNRS	64	0.407	0.040
PCS- DyNRS	64	0.390	0.033

PCS: The Pain Catastrophizing scale, DyNRS: The intensity of pain during vascular access, r_s: Spearman's rank correlation coefficients, The significant p-values were marked as bold characters.

Pain perception is a complex experience that includes emotional and behavioral components in addition to physiologic components. It becomes more difficult to reduce the pain in individuals with previous experience of pain or who believe that they have excessive pain. This relationship between the catastrophizing and severity of pain has not been fully clarified yet (4).

Vascular access is a compulsory intervention in order to administer and continue anesthesia in patients undergoing surgery. Vascular access is a painful and stressful intervention for patients. They usually state that they experience this pain quite intensively. It is reported that the cognitive perception of the individuals regarding pain and their psychological conditions are important when perceiving the intensity of the needle pain (5,8). In the same study, a relationship was found between DyNRS level and pain catastrophizing. Based on this relationship, certain advantages such as early mobilization and reduced complications and hospitalization could be achieved through appropriate analgesia (9,10). In our study, the amount of sedation administered to the patients with high levels of DyNRS during vascular access was found to be high. The level of PCS was also found to be high in patients with high DyNRS levels.

It was demonstrated that the patients with high PCS levels had more analgesic needs (11). In their study on patients undergoing total knee arthroplasty, Wright et al. (12) concluded that patients catastrophizing pain experienced more intensive pain during the postoperative period, and their needs for analgesic increased. In our study, we believed that sedation and the amount administered would be sufficient for determining how patients reflected their previous experiences of pain during vascular access and short-term procedures; therefore, there was no monitoring for the level of analgesia. The amount of sedation was found to be correlatively low in patients with low levels of PCS.

The results of our study regarding the PCS and DyNRS indicated that there could be positive correlation between PCS value and the vascular access pain intensity, similar to the results of the study by Suren et al. (6). Various studies have concluded that PCS value could predict the intensity of postoperative pain and the amount of analgesic consumption (8,13). In addition, the PCS value could predict both vascular access and postoperative pain intensities as well as analgesic consumption; therefore, the intensity of postoperative pain could be predicted by evaluating the vascular access pain (6).

The insufficient level of postoperative analgesia could extend the inpatient period (14,15). In our study, we did not monitor postoperative pain due to the short period of procedure; however, we could predict the pain intensity of the patient by monitoring the sedation level of the patient during the procedure. In addition, our monitoring methods did not include the hospitalization period; however, Tharakan and Faber (16) demonstrated a directly proportional relationship between hospitalization period and the consumption of analgesics. In the light of these data, we can conclude that when a sufficient level of sedation is administered to the patient during the procedure, we believe that the intensity of pain would also be low and the patient could be discharged from the health facility in a short time after the procedure. However, this was not the direct conclusion of our study, it was rather a secondary outcome.

In previous studies, different values have been observed for PCS. In their study, Pavlin et al. (17) found it to be 13, and Lautenbacher et al. (18) calculated it on patients of malignancy surgery as 19.38. In their study on 134 healthy individuals, Ruscheweyh et al. (19) calculated it as 10.7 in terms of headache, 11.0 in terms of backache and 16.7 in terms of toothache in young adults (20-40 years of age). They also determined it to be 13.3 in terms of headache, 13.5 in terms of backache and 13.5 in terms of toothache in the elderly (50-70 years of age) (19). We identified the PCS cut-off value as 17, as identified by Suren et al. (6) in their study where they performed the reliability and validity tests for PCS level in the Turkish community (PCS ≥17: high, PCS <17: normal).

PCS has also been reported to be associated with the level of anxiety and depression. In this respect, it has been stated that it was more likely for perioperative pain to become chronic in cases of insufficient postoperative analgesia treatment in patients with high levels of anxiety and depression (20,21). In our study, we assumed that the complications could be reduced by determining the sedation level through identifying the pain catastrophizing based on the anxiety level of the patient, which could be predicted by the PCS level.

Study Limitations

Despite its clear conclusions, our study also had certain limitations. These were the small number of cases and the fact that the levels and amounts of analgesia were not monitored during the identification of pain and catastrophizing scales of the patients due to the short period

of procedure. In addition, a perioperative anxiety scale was not used apart from the scales we administered. Despite the fact that PCS involved three different types of questions, which were rumination, magnification and helplessness, the sub-dimensions of PCS were not analyzed in our study since the administration and compilation periods of our procedure was quite short.

Conclusion

In the present study, it was concluded that there was a correlation between the vascular access pain intensity and the consumption of sedation, and that the amount of sedation consumption increased based on the increase in the vascular access pain intensity. Certain perioperative complications can be prevented by administering sufficient sedation during the intervention and by determining the level of PCS during the preoperative period. Despite the limitations of the present study, it was concluded that the levels of DyNRS and PCS levels could affect the amount of sedation directly; however, we believe that more comprehensive studies would be beneficial.

Ethics

Ethics Committee Approval: This retrospective observational cross-sectional study was carried out in the University of Health Sciences Turkey, Trabzon Kanuni Training and Research Hospital Clinic of Endoscopy after obtaining the approval from the Clinical Research Ethics Committee (13/03/2020-KAEK-2020/15) of the same hospital.

Informed Consent: Were included in the study after obtaining written and verbal informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.A., A.Ş., P.D.A., Design: A.A., P.D.A., A.Ş., Data Collection or Processing: P.D.A, A.A., A.Ş., Literature Search: A.A., A.Ş., Analysis or Interpretation: A.Ş., Writing: P.D.A., A.Ş.

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

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ORIGINAL RESEARCH

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Is Peer Assessment Reliable in Objectively Structured Clinical Examination?

Objektif Yapılandırılmış Klinik Sınavda Akran Değerlendirmesi Güvenilir midir?

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Abstract

Objective: The study was designed to evaluate the reliability of the peer assessment in the objectively structured clinical examination (OSCE) for the summative assessment of 4th grade students at the end of general surgery clerkship.

Method: The study was planned prospectively with the permission of the Dean of Medicine Faculty and approval of the ethics committee. The 6th grade students who were in the surgery rotation participated in the study as peer assessors (PA). Both peers and department of general surgery assessed the students. Pass/fail point was accepted as 60. The scores of OSCE and performance evaluation given by peers and faculty were compared statistically.

Results: Twenty-three students completed general surgery clerkship. Ten students (43.5%) were female. According to performance scores given by the faculty, 15 (65.2%) of the 23 students were successful, while all students were considered successful (having a grade of 60 or more) based on the scores of peer evaluation. There was a significant difference between the faculty members and PA with regard to the performance evaluation (p=0.008). The faculty members found five students (27.8%) successful in the OSCE (having a grade of 60 or more). However, ten students (43.5%) received a score of at least six from peer evaluation. Although there was a difference, it was not significant (p=0.063). Gender did not affect scoring in performance evaluation and OSCE application.

Conclusion: Although there was a difference between faculty members and peer evaluators in the performance evaluation, no difference was

Öz

Amaç: Genel cerrahi kliniğinde 4. sınıf öğrencilerine "objektif yapılandırılmış klinik sınav" (OYKS) uygulanmasında akran değerlendirmesinin güvenilir olup olmadığını değerlendirmek ve öğrencinin servis içindeki performansının akran değerlendirmesi üzerine etkilerini araştırmak amacıyla bu çalışmayı tasarladık.

Yöntem: Çalışma, Tıp Fakültesi Dekanlığından ve etik kuruldan izin alınarak prospektif olarak planlandı. OYKS uygulamasına katılan 4. sınıf stajyer öğrenciler çalışma grubu olarak belirlendi. Altıncı sınıf öğrencileri ise akran değerlendirici olarak çalışmada yer aldı. Bu çalışma için akran değerlendiricilerin ve öğretim üyelerinin performans puanı vermeleri ve OYKS uygulamasına katılarak değerlendirmeleri istendi. Sonuçlar istatiksel yöntemlerle değerlendirildi.

Bulgular: OYKS uygulamasına katılan 23 öğrenciden 10'u (%43,5) kız öğrenciydi. Genel cerrahi stajından sorumlu öğretim üyeleri tarafından verilen ortalama performans puanlarına göre, 23 öğrenciden 15'i (%65,2) başarılı oldu. Akran değerlendiricilerinin performans puanı ortalamalarına göre ise tüm öğrencilerin başarılı olduğu görüldü. Öğretim üyeleri ile akran değerlendiricilerin verdikleri performans puanları arasında istatistiksel olarak anlamlı fark bulunmuştur (p=0,008). Öğretim üyeleri ve akran değerlendiriciler tarafından stajyerlere verilen OYKS puanları karşılaştırıldı. Öğretim üyelerinin verdikleri puana göre, beş (%27,8) öğrenci altı veya daha yüksek puan alarak başarılı oldu. Akran değerlendiricilerin puanlamasına göre ise on (%43,5) öğrenci altı veya daha yüksek puan alarak başarılı oldu. Buna göre akran değerlendiricilerin OYKS'de daha fazla öğrenciyi başarılı bulduğu görüldü. Ancak iki grubun verdiği puanlarda

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Abstract

observed in OSCE. In conclusion, OSCE assessment by peer evaluators is reliable.

Keywords: Education, objective structured clinical examination, peer assessment, reliability, surgery

Öz

istatistiksel olarak anlamlı fark yoktu (p=0,063). Cinsiyetin performans değerlendirmesinde ve OYKS uygulamasında puanlamayı etkilemediği tespit edildi.

Sonuç: Çalışmamızda performans değerlendirmesinde öğretim üyeleri ile akran değerlendiriciler arasında fark olduğunu, OYKS uygulaması değerlendirmesinde ise farklılık olmadığını bulduk. Sonuç olarak akran değerlendirmesinin güvenilir olduğunu düşünüyoruz.

Anahtar kelimeler: Akran değerlendirmesi, cerrahi, eğitim, güvenilirlik, objektif yapılandırılmış klinik sınav

Introduction

Physicians are expected to be active, lifelong learners nowadays. Medical education is constantly changing to enable physicians to develop such an understanding (1). The education of medical students should prepare them to cope with future problems and ensure that they have the necessary skills to become active and self-directed learners rather than passive recipients of the information. Therefore, a transition from time-based to competency-based education occurred in medical education and the medical curriculum was revised accordingly. This also led to the revision of student assessment tools (2). Planning an outcome-based education is as important for student motivation as ensuring quality in educational programs because it defines learning outcomes and forms a basis for curriculum decisions in contemporary education. Lecturers should establish the most appropriate assessment and evaluation system to evaluate the expected learning outcomes of the students. The selected assessment tools should be valid, reliable, and practical, and have an appropriate impact on student learning. An assessment profile should be produced for each student, aiming at the learning outcomes the student is expected to achieve (3).

Objectively structured clinical examination (OSCE) was defined by Harden et al. (4) in 1975 to evaluate the learning outcomes required from students effectively and objectively, to ensure the standardization of examinations, and to regulate the examination process. The OSCE is designed as a new assessment tool that allows candidates' clinical skills, attitudes, problem-solving skills, and knowledge practices to be assessed in an exam. It is a performance-based exam consisting of multiple stations. At each station, the examiners evaluate high-level thinking skills according to preformed blueprint. OSCE is widely used in the assessment of practical skills in medicine. It has several advantages: it is an objective tool in assessing the student, it has a pre-structured question and answer format, and it can assess knowledge, skills, and attitudes in the clinic. It is a complex and time-consuming task to prepare and perform OSCE smoothly. It aims to provide the standardization and to reduce the number of variables that may affect performance evaluation. Therefore, in a well-designed OSCE, students' grades should only be influenced by their performances (5).

Peer assessment (PA) is considered an important tool in medical education. In this process, students of similar levels evaluate the learning outcomes of their peers, which also contributes to their training. PA, defined as peers' evaluations of their friends' achievements, learning outcomes or performances, is increasingly used in modern medical education (6). It can be used to encourage students to participate in educational activities and clarify the assessment criteria, improve team performances, or identify individual efforts (7). Students who perform their internship in the same clinical setting during their medical education have the advantage of observing their peers while performing their duties. Therefore, it was stated that peers had a higher chance of observing each other's performances than faculty members (8).

PA in OSCE stations that can be used in the evaluation of almost all professional competency areas can be an effective model in the OSCE. This study aimed to evaluate the reliability of the PA in the OSCE that was performed by our clinic without interruption and to investigate the effects of student performances in the service on the PA.

Materials and Methods

Members of the General Surgery Department, Faculty of Medicine, Gaziosmanpaşa University decided to conduct an OSCE in the evaluation of fourth-year interns studying at the faculty of medicine. For this purpose, the faculty members made the necessary preparations (training,

observation, and literature survey) and initiated the OSCE in our clinic in the 2017-2018 academic year.

Ethical Committee Approval

Permission no: 17713155-100 was obtained from the Deanship of the Faculty of Medicine to conduct studies on the OSCE for the fourth-year students and to ensure the participation of the sixth-year students (peer assessors) for the PA. The study was designed prospectively after obtaining the permission of Non-interventional Clinical Research from the Ethical Committee of Gaziosmanpaşa University, Faculty of Medicine (registration number: 19-KAEK-149 date: 28/05/2019).

The study was conducted with fourth-year students who had been receiving their undergraduate education in the academic year 2018-2019. The working group involved 23 fourth-year students who participated in the OSCE.

General Surgery Clerkship

In the fourth-year of medical education, the students receive eight-week training in the general surgery clinic as divided into four groups. The training involves three main objectives of learning: knowledge, skills, and attitude. The students receive not only theoretical and practical courses in the field of surgery, but also skills such as vascular access, nasogastric catheter application, Foley catheter placement, and suturing, and attitudes such as communication and professionalism.

General Surgery Clerkship Assessment

At the end of the clerkship, the students' success is assessed by a multiple-choice exam, the OSCE, the evaluation of the portfolio (a list of interventional procedures requested during the clerkship), and the evaluation score of the instructor to the students' attitude during the eight-week clerkship period. The students who score at least 60 out of 100 are considered successful at Gaziosmanpaşa University, Medical Faculty. Four student groups are trained in our clinic every year. Each group consists of an average of 25 students. The success assessment is as follows: the multiple-choice theoretical exam accounts for 30 points, the portfolio evaluation for 10 points, the assessment of professionalism (faculty member's opinion about each student's attitudes during the clerkship period) for 10 points, and the OSCE for 50 points. The portfolio evaluating the students' practical and communication skills and volunteer participation was conducted by all faculty members three days before the end of the clerkship. The grade indicated the student's performance evaluation by the professors. The grade was given out of 10 points for each student. Students who scored at least six were found successful for the clerkship. We also asked the peer assessors (in this case 6th grade students or interns) to give an opinion grade to the fourth-year clerks as they had participated in many procedures during their educations. For this purpose, fourth-year clerks were evaluated one by one together with the faculty members and the opinion grade was given. The multiple-choice exam was held in the following day.

Performance Evaluation

During the clerkship, faculty members in charge of the general surgery education observed the students in various settings such as the wards, the operating room, and during the lectures. They evaluated the students' performances according to their behaviors in various domains such as knowledge, attitude, communication, professionalism, and volunteering. In the same way, peer assessors (interns/six-grade students) also observed the students during their rotations of general surgery internship and formed opinions about them.

Before the OSCE

All students who were going to take the OSCE were informed by the faculty members about it at the beginning of the clerkship. We established five stations for the OSCE in the general surgery clinic. Students were informed about the application of the OSCE as well as the exam area. The rules to be followed during the OSCE were explained.

The OSCE Stations

Five stations were created in the OSCE application (Figure 1). During the creation of these stations, the exam topics were classified and the students drew lots for the OSCE questions in the last week of education period. The questions consisted of following topics for each station; the first station included basic topics such as fluid electrolyte, hemostasis, shock, surgical infections, and trauma. The second station included topics from the field of oncologic surgery such as the esophagus, stomach, and breast cancer. The questions at the third station were related to gastrointestinal diseases such as diverticulitis, acute appendicitis, and hemorrhoids. The questions at the fourth station were prepared from the field of endocrine surgery such as thyroid, parathyroid, and adrenal. The questions at the last station addressed the skills that needed to be acquired during a surgical clerkship, such as suturing, obtaining patient consent, and abdominal examination. Ten questions were prepared for each group, five questions out of 50 were drawn by lot and asked in the exam.

The OSCE Application

We asked the students to manage the patient through prepared scenarios at the four stations of the OSCE. Management of hyperparathyroidism, perianal abscess, soft tissue infection, and soft tissue sarcomas were the questions determined by lot. We also asked the students to perform an abdominal examination on a model at the practical station. Each station was rated out of ten points. Eight points were given for information and management, two points were given for the smoothness of the presentation order and the self-confidence of the student.

Before the OSCE, we conducted an evaluation with the responsible faculty members. There was one member of the department of general surgery and one of the peer assessors at each station. The faculty members at each station briefed the peer assessors on the question and assessment sheet and informed them about the procedure.

The OSCE application started with a ringtone after the preparations were completed. Students were given five minutes at each station. When the bell rang by surgery resident, the students changed the station. All 23 students completed the OSCE. The faculty members and the peer assessors evaluated the students at each station. Only the grades of the faculty members for students were taken into account as pass/fail point.

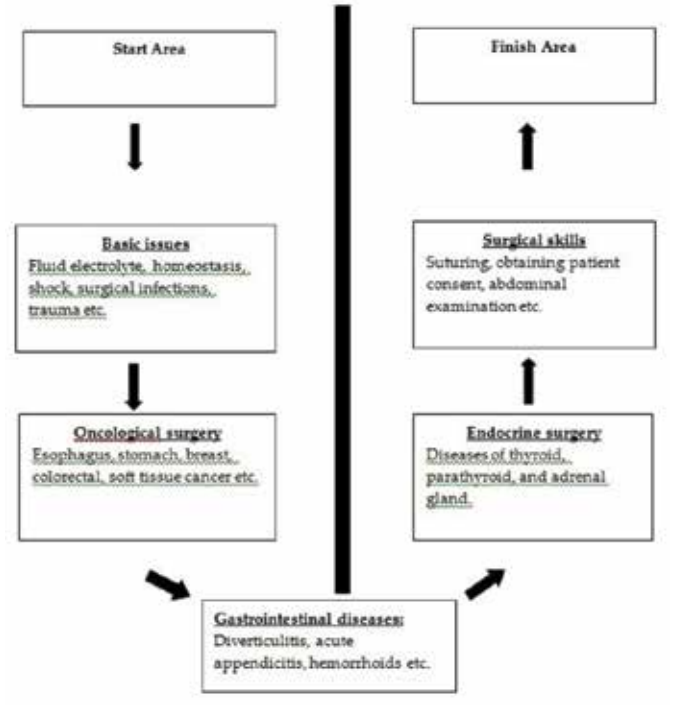

Figure 1. Schematic view of the OSCE stations
OSCE: Objectively structured clinical examination

After the OSCE

At the end of the OSCE, we evaluated the exam with all the faculty members and the peer assessors. We compared the performance and the OSCE scores of the peer assessors with those of the faculty members for the same student to examine whether the performance assessment of the peer assessors affected the outcome. The average of the scores obtained at the five stations was taken and students with a mean score of six or above were considered successful. We also investigated whether the gender of the students was important in the performance and OSCE assessments of faculty members and peer assessors.

Statistical Analysis

Data were expressed in frequency and percentage. The McNemar test was used to compare the categorical data between the groups. Pearson correlation coefficient was used for correlation between variables. A p-value <0.05 was considered significant. Analyses were performed using SPSS 19 (IBM SPSS Statistics 19, SPSS inc. an IBM Co., Somers, NY).

Results

Twenty-three students participated in the OSCE, ten (43.5%) were female students. Based on the average performance evaluation scores given by the faculty members responsible for the general surgery clerkship, 15 of the 23 students (65.2%) were successful. All students were successful according to the peer assessors' performance evaluation score averages. There was a significant difference between the faculty members and peer assessors regarding the performance evaluation scores (p=0.008) (Table 1).

We evaluated the scores given to the students by the faculty members and the peers in the OSCE (Table 2). The faculty members found five students (27.8%) successful in the OSCE by getting a score of six or above. As for the peer assessors, ten students (43.5%) received a score of at least six from them. Therefore, the peer assessors found

Table 1. Comparison of performance scores between faculty members and peer assessors

	Performance scores given by the faculty members (n=23)	Performance scores given by the peer assessors (n=23)	p
<6	8 (34.8%)	0 (0%)	0.008
≥6	15 (65.2%)	23 (100%)	
Total	23 (100%)	23 (100%)	-

more students successful in the OSCE. However, there was no statistically significant difference (p=0.063) (Table 2). We analyzed the performance evaluation scores given by the faculty members concerning gender and found no statistically significant correlation (Table 3) (p=0.379). The peer assessors gave a performance score indicating that all the students were successful.

There was no significant correlation between the scores given by the faculty members and the gender of the students (p=0.618) (Table 4). Again, the gender of the students did not play a role in the OSCE scoring by the peer assessors (p=0.222) (Table 5).

Table 2. Comparison of OSCE scores between faculty members and peer assessors

	OSCE scores given by the faculty members (n=23)	OSCE scores given by the peer assessors (n=23)	p
<6	18 (78.3%)	13 (56.5%)	0.063
≥6	5 (21.7%)	10 (43.5%)	
Total	23 (100%)	23 (100%)	-

OSCE: Objectively structured clinical examination

Table 3. Distribution of performance scores given by the faculty members by gender

Performance scores given by the faculty members	Female	Male	p
<6	2	6	0.379
≥6	8	7	
Total	10	13	-

Table 4. Distribution of OSCE scores given by the faculty members by gender

OSCE scores given by the faculty members	Female	Male	p
<6	7	11	0.618
≥6	3	2	
Total	10	13	-

OSCE: Objectively structured clinical examination

Table 5. Distribution of OSCE scores given by the peer assessors by gender

OSCE scores given by the peer assessors	Female	Male	p
<6	4	9	0.222
≥6	6	4	
Total	10	13	-

OSCE: Objectively structured clinical examination

Discussion

Assessment and feedback by peers are becoming a valuable and increasingly recognized method used to enhance the student experience in medical schools around the world. In addition, PA has the potential to help prepare students for their professional lives (9). An advantage of PA is that although teachers have only limited time to observe each student, students have more opportunities to observe each other (10,11). PA can both be reliable and valid and can provide an effective learning experience for students (12). In our study, we used PA to determine the development and success of each student during the eight-week training. For this purpose, we asked the faculty members and peer assessors to give a performance evaluation score to the students. We found that the peer assessors who monitored the interns during clinical clerkship period gave higher performance evaluation scores to all compared to those of faculty members. Although it has the potential for an accurate and valid assessment, factors such as reliability, interpersonal relationships, interests, inter-group interaction, and equivalence may influence the assessment (13). Our study included sixth-year students as peer assessors to minimize the effects such as intra-group interaction, personal interest, and friendship. However, we found that they gave high scores for the performance assessment. This may have been the result of their empathy with the interns as they were also students.

In addition, we found that peer assessors gave students higher scores in the OSCE performances. More people were successful in the OSCE; however, there was no statistical difference between the scores given by the peer assessors and those by the faculty members. A neutral and objective assessment is an important foundation of the OSCE. For this purpose, standardizing the scoring system and having the same questions for each candidate make the assessment easier and more reliable. Some evidence suggests that the training of assessors reduces the difference in scoring (5). Some studies show that peer assessors give high scores in the OSCE. On the other hand, there are also some studies indicating lower-scoring by peer assessors than that of faculty members, although not statistically significant (14-17). Despite the high scores given by the peer assessors in our study, the results were similar to those of the faculty members due to the standardized scoring system and the training they received about the implementation of the exam. In the performance assessment, the scores given by peer assessors were statistically significant. This may be due to the fact that the OSCE evaluates knowledge and skills

rather than attitude and behaviors such as communication, professionalism, and volunteering evaluated with performance assessment.

Some studies found that male assessors give higher scores to female students, albeit not significantly (18). This raises the question of whether male supervisors are softer to female students. However, it was stated that female students had better communication skills which might also have affected this result (19). Gender bias was not detected in most of the studies (20,21). We found no difference in opinion grades and the OSCE in relation to gender.

Study Limitations

Our study has some limitations worth mentioning: it was on a small scale. Assessing more students and having more assessors would increase the reliability. In addition, a higher number of stations can increase the effective evaluation in the OSCE. In our study, the number of stations was low. However, the educational institutions with limited resources still can apply the OSCE to the target evaluation.

We found that the peer assessors in our study gave higher scores in both performance assessment and the OSCE, and the difference was significant between the peer assessors and the faculty members in performance evaluation. This could either be due to the more time and place shared with students allowing the peer assessors to evaluate them promptly or to the biased attitude the peers have about them. A standardized performance assessment would increase reliability eliminating this interaction. Although peer assessors gave higher scores to the interns in the OSCE, there was no statistical difference.

Conclusion

As a conclusion, we think that PA can be performed safely in the OSCE with adequate training and a standardized scoring system.

Statement of Licensing Committee and Institution

Permission no: 17713155-100 was obtained from the Deanship of the Faculty of Medicine to conduct this study. Ethical committee approval for this study was obtained from the Local Research Ethics Committee registered under the number 19-KAEK-149 date: 28/05/2019. All methods were performed in accordance with the relevant guidelines and regulations of the institution.

Ethics

Ethics Committee Approval: Ethical committee approval for this study was obtained from the Local Research Ethics Committee registered under the number 19-KAEK-149 date: 28/05/2019.

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: İ.O., E.D., E.B., Design: H.D., E.D., H.B., Data Collection or Processing: E.D., M.F.D., O.D., Z.Ö., H.B., Analysis or Interpretation: E.D., O.D., İ.O., E.B., Literature Search: H.D., H.B., M.F.D., Z.Ö., O.D., Writing: İ.O., E.D., E.B., H.D., Z.Ö., M.F.D.

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ORIGINAL RESEARCH

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Comparison of Anastomosis Safety in Colonic Dissections Using Scalpel, Scissors and Cautery in Rats: Experimental Study

Sıçanlarda Bistüri, Makas ve Koter Kullanılarak Kolon Diseksiyonlarında Anastomoz Güvenliğinin Karşılaştırılması: Deneysel Çalışma

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Abstract

Objective: Postoperative anastomotic leakage is still an issue in modern surgery. Re-hospitalization due to postoperative anastomosis leakage prolongs hospital stay and re-operations increase the cost. There is still no consent on how to dissect the intestines. The objective of the present study is to analyze the safety of colonic anastomoses after dissections using scalpel, scissors and cautery in rats.

Method: There were 4 groups of 32 Wistar Hannover adult rodents. Each group consisted of 8 animals: group 1: sham, group 2: scalpel, group 3: scissors, group 4: cautery. Anastomosis was done over a single layer. Bursting pressure (BP) was measured at day 7. Tissue and blood samples were taken for the evaluation of biochemical and histopathological parameters.

Results: Statistically significant disparity was seen among the sham, scalpel, scissors and cautery groups regarding the mean BP average, mean hydroxyproline levels and fibrosis distributions.

Conclusion: Cautery is the best choice for hemostasis; however, when considering tissue healing, scalpel and the scissors were found to be safest alternatives.

Keywords: Anastomotic leak, colonic dissection, hydroxyproline, rats, tissue healing

Öz

Amaç: Postoperatif anastomoz kaçağı modern cerrahide hala bir sorundur. Postoperatif anastomoz kaçağı nedeniyle yeniden hastaneye yatış hastanede kalış süresini uzatır ve yeni ameliyatlar maliyeti artırır. Bağırsakların nasıl diseke edileceğine dair hala bir fikir birliği yoktur. Bu çalışmanın amacı, sıçanlarda bistüri, makas ve koter kullanarak diseksiyon sonrası kolon anastomozlarının güvenliğini karşılaştırmaktır.

Yöntem: Otuz iki yetişkin Wistar Hannover sıçanı rastgele olarak her biri 8 hayvan içeren 4 gruba ayrıldı: grup 1: sham grubu, grup 2: bistüri grubu, grup 3: makas grubu, grup 4: koter grubu. Anastomoz tek tek sütürler ile tek kat üzerinden yapıldı. Patlama basıncı 7. günde ölçüldü. Biyokimyasal ve histopatolojik parametrelerin değerlendirilmesi için doku ve kan örnekleri alındı.

Bulgular: Sham, bistüri, makas ve koter grupları arasında patlama basıncı ortalaması, ortalama hidroksiprolin seviyeleri ve fibroz dağılımları açısından istatistiksel olarak anlamlı bir fark tespit edildi.

Sonuç: Hemostaz için koter en iyi seçimdir, ancak doku iyileşmesi düşünüldüğünde, neşter ve makas en güvenli alternatifler olarak bulunmuştur.

Anahtar kelimeler: Anastomoz kaçağı, doku iyileşmesi, hidroksiprolin, kolon diseksiyonu, sıçan

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Introduction

Postoperative anastomotic leakage is seen in the intestinal and colonic operations at the rates of 1% and 0.5%-30%, respectively (1). 1% of the patients who were previously known to have an intestinal anastomosis are re-hospitalized due to postoperative anastomosis leakage and in addition, their hospital stay is prolonged. Secondary interventions to such patients are the leading problems of gastrointestinal surgery due to their difficulties. In a study involving 6,174 patients, Hammond et al. (2) reported that hospital stay after colonic anastomosis increased by 7.3 days and the average cost was $24,129.

The objective of the present study is to analyze the safety of colonic anastomoses after dissections using scalpel, scissors and cautery in rats.

Materials and Methods

Experimental Design

In this study, 32 adult Wistar Hannover rats (İstanbul Bağcılar Experimental Research and Skills Development Center, BADABEM) with an average weight of 300-500 grams were used. All animals were kept at room temperature of 22 °C for 12 hours in a dark/light cycle. Animals in all groups were fed freely with rat feed containing 21% protein. Fresh drinking water was given daily. All subjects were kept in separate cages in groups. The study was approved by the Local Ethics Committee of University of Health Sciences Turkey, Bağcılar Training and Research Hospital (project no: 2013-28). Patient consent form was not required due to the nature of the study.

Study Groups

Rats were randomly divided into 4 groups, each containing 8 animals:

Group 1, sham group,

Group 2, scalpel group, large intestine transection with scalpel,

Group 3, scissors group, large intestine transection group with scissors,

Group 4, cautery group, large intestine transection group with cautery.

Operative Procedure

The rats were anesthetized with ketamine hydrochloride (50 mg/kg, Ketalar; Farke-Davis, Istanbul, Turkey) and xylazine (10 mg/kg, Rompun: Bayer, Istanbul, Turkey) anesthesia, asepsis with 10% povidone iodine solution, and following the provision of antisepsis, a 3 cm incision was made in the abdominal median line under sterile conditions.

In Group 1, the descending colon was manipulated. The abdomen was closed without anastomosis.

In Group 2, the descending colon was cut with a scalpel 2 cm proximal to the peritoneal reflection in the scalpel group and anastomosed end-to-end over a single layer with 5.0 poli (glicolid-co-lactid) (Pegelak, Doğusan, Istanbul Turkey) suture.

In Group 3, the scissors group, the descending colon was cut with scissors 2 cm proximal to the peritoneal reflection and end-to-end anastomosis with 5.0 poli (glicolid-co-lactid) suture over a single layer was performed.

In Group 4, the cautery group, the descending colon was cut with cautery 2 cm proximal to the peritoneal reflection and end-to-end anastomosis with 5.0 poli (glicolid-co-lactid) suture over a single layer was done.

All procedures were performed by the same surgeon. 10 mg/1 mL paracetamol was administered intraperitoneally for analgesia before the incision was closed. Abdominal incisions were closed in two layers with 3.0 interrupted silk sutures (Doğusan, Istanbul, Turkey). Feeding was started immediately after the operation. On day seven, all animals were sacrificed. None of the rats experienced significant weight loss between the initial surgery and sacrification.

Bursting Pressure Measurement

The anastomosis line was resected as an anterior block, and the 2 cm distal and 2 cm proximal of the line were clamped. 0.9% NaCl stained with methylene blue was infused into the intestine at a rate of 2 mL/min. Intra-segment pressure was monitored. The pressure value at which the leak was seen in the anastomosis line was recorded as BP.

Hydroxyproline Analysis

The samples for hydroxyproline (H) levels were weighed, cut into small pieces, and homogenized in a phosphate buffer to yield a 20% homogenate. Aliquots of the homogenate were added to an equal volume of 6 N hydrochloric acid, and hydrolyzed in Teflon-capped vials at 102 °C for 16 hours. The H content of the tissue hydroxylates was determined spectrophotometrically by using the standard addition method developed by Kivirikko et al. (3) (Hypopronosticon, Kit lot/ch. B:E 92401, Organon Teknika., Boxtel, Holland). Results were expressed in milligrams, such as in H/100 mg (wet weight).

Histological Analysis

The degree of fibrosis of hematoxylin-eosin-stained preparations was evaluated under a light microscope using a scale adjusted for the severity of fibrosis. (0: minimal, 1: slight, 2: moderate, 3: severe).

Sacrifice and Necropsy

No deaths related to peritonitis or any complications of anastomosis leakage developed. At autopsy, none of the rats had any ileus or evidence of anastomosis insufficiency (feces within the abdominal cavity or abscess).

All groups were sacrificed with high dose ketamine anesthesia on postoperative 7th day and blood samples of all animals were taken by intracardiac puncture. Colonic anastomosis lines of all animals were removed, BP values of anastomosis line were measured.

Anastomosis lines were resected unblock 1 cm distal and proximal. The anastomosis line was divided by mesenteric borders. One segment was frozen in liquid nitrogen and stored at -80 °C for H analysis, the other segment was placed in formaldehyde solution for histopathological examination.

Statistical Analysis

Statistical analysis was performed by NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA). Descriptive statistical methods (mean, standard deviation, median, interquartile range) were used in the evaluation of the data, as well as Dunn's multiple comparison test in the Kruskal-Wallis test subgroup comparisons, Mann-Whitney U test in the comparison of the paired groups, and chi-square test in the comparison of the qualitative data. Results were evaluated at $p<0.05$ level of significance.

Results

There was a statistically significant difference among the mean sham, scalpel, scissors and cautery groups (p=0.0001) in BP average. The mean of the sham group was significantly higher than the mean of the scalpel, scissors and cautery groups (p=0.001) (Table 1). No statistically significant difference was found between scalpel cautery groups (p=0.748) (Table 2).

There was a statistically significant difference among the mean H levels of Sham, Scalpel, Scissors and Cautery groups (p=0.041). The mean H of the sham group was found to be significantly higher than the mean of scalpel, scissors and cautery groups (p=0.049, p=0.021). No significant difference was observed between scalpel and scissors groups and also between scalpel and cautery groups (p>0.05) (Table 2).

There was a statistically significant difference among fibrosis distributions of groups (p=0.0001). The presence of minimal fibrosis was significantly higher in the Sham group than in the Scalpel, Scissors and Cautery groups.

When the scalpel, scissors and cautery groups were compared, no significant difference was found in the distribution of fibrosis (Table 3).

Table 1. Bursting pressure and tissue hydroxyproline levels

		Pressure (mm/Hg)	Hydroxyproline (../100 mg)
Sham group	**Median (IQR)**	290 (286.25-300)	7657.97 (1715.49-11764.28)
Scalpel group	**Median (IQR)**	10 (0-148.5)	725.2 (114.545-2385.8)
Scissors group	**Median (IQR)**	120 (66.25-166.25)	1304.32 (1141.3-2478.66)
Cautery group	**Median (IQR)**	50 (2.5-68.75)	656.68 (368.51-774.09)
	p	**0.0001**	**0.041**

IQR: Interquartile range, p<0.05 level of significance

Table 2. Dunn's multiple comparison test of groups

Dunn's Multiple Comparison test	Pressure (p)	Hydroxyproline (p)
Sham group/Scalpel group	**0.001**	**0.021**
Sham group/Scissors group	**0.001**	**0.049**
Sham group/Cautery group	**0.001**	**0044**
Scalpel group/Scissors group	**0.040**	0.600
Scalpel group/Cautery group	0.748	0.916
Scissors group/Cautery group	**0.035**	**0.012**

p<0.05 level of significance

Table 3. Histopathological evaluation of each group

Fibrosis	Sham		Scalpel		Scissors		Cautery		p
Minimal	8	100.00%	0	0.00%	0	0.00%	0	0.00%	
Mild	0	0.00%	1	12.50%	0	0.00%	2	25.00%	**0.0001**
Intermediate	0	0.00%	5	62.50%	3	37.50%	4	50.00%	
Severe	0	0.00%	2	25.00%	5	62.50%	2	25.00%	

Discussion

To our knowledge, there is elevated mortality and morbidity rates in case of anastomotic leak or dissociation occur (4). Aforementioned complications occur more frequently in large bowel anastomosis operations. (13%-69%) (5). Risk factors for anastomotic leakage are smoking, chronic heart disease, diabetes and obesity (6-8).

Different techniques, materials and agents have been developed throughout years whereas no solution has been overcome yet (9). Some authors covered the anastomosis with different type of meshes but problem is still existing (10,11). Golden standard method for dissecting tissue is scalpel. This way of dissection is simple and low cost; however, it prolonged surgery time due to lack of hemostasis. It has some disadvantages like the lack of hemostasis which prolongs surgery time and risk of unintended injuries (12).

In the past decade, the invention of electrocautery has solved several defects of scalpel (13). Heat energy is used to denature proteins to ensure hemostasis (14), but electrocautery damages the tissue by heat energy (15).

Scalpel cuts are preferred over electrocauter in some studies in which they have fewer infection in wounds with an increase in wound durability (16,17). However, in some studies, no difference for infection rate in wounds is shown for electrocautery and scalpel (18).

Collagen filaments and filament improvement with the submucosal layer are related to the strength of the anastomosis (19). Recovery pursues the sequential states of tissue renovation mostly constructed by growth factors and cytokines (20). Fibrin and fibronectin template pro forma secures and attaches two ends of bowel at the hemostatic phase. Since day 3, temporary matrix evolves with fibroblasts, macrophages and new blood vessels making new granulation tissue (21). Fibroblasts mainly produce collagen (22). On the day 6 and 7, maximum peak of collagen production emerges, and this is correlated with breaking strength (23). Anastomotic repair and inhibition of submucosal fibers of collagen degradation promote angiogenesis and granulation texture deposition, including non-overlapping, and the acceleration of epithelization improved through different mechanisms (24).

Tissue H levels and BP are indirect indicators of anastomotic healing. To determine the level of H is a decent way for assessing the quantify of collagen texture (25,26).

Beginning at about 5 days, it approaches the normal level while the H condensation reduces by 40% and rises from normal level on the 10-14th day (27).

BP is an indication for the healing process of an anastomosis (28). Because of larger numbers of microorganisms, minimal arteriole nurture, and greater feces quantity, leak in left sided colon anastomosis risk is greater than the other parts (29).

Quality and quantity of newly synthesized collagen target to bring tissue strength to pre-anastomotic levels (30,31). The measurement of H is a decent parameter of anastomotic healing (32). BP measurement is robustness test of the anastomosis (33).

Conclusion

Leakage in left-sided colon anastomosis is still a serious complication. The etiology of colonic anastomotic leakage remains unclear. Minimal damage to colonic tissue when dissecting will cause the most acceptable outcomes. Cautery is best for hemostasis but scalpel and scissors dissection have the better results of tissue healing. More research is needed to introduce which way is the best for intestinal healing and to prevent complications.

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Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of University of Health Sciences Turkey, Bağcılar Training and Research Hospital (project no: 2013-28).

Informed Consent: Patient consent form was not required due to the nature of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.Y., O.B.G., C.E., K.Ö., A.B., Design: H.Y., O.B.G., A.Ç., F.Ç., H.U., E.Y., Data Collection or Processing: C.E., E.Y., K.Ö., A.K.A., H.U., A.B., H.Y., Analysis or İnterpretation: C.E., F.Ç., A.B., O.B.G, A.Ç., H.U., A.K.A., K.Ö., Writing: H.Y., A.Ç., F.Ç., A.K.A., E.Y.

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ORIGINAL RESEARCH

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Outcomes of Percutaneous Balloon Mitral Valvuloplasty in Significant Mitral Stenosis with Moderate Mitral Regurgitation - Single Center Study

Orta Derecede Mitral Yetersizliği Olan Anlamlı Mitral Darlığında Perkütan Balon Mitral Valvüloplastinin Sonuçları - Tek Merkez Çalışması

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Abstract

Objective: Rheumatic heart disease is the deposition of immune complexes which cause malfunction of the heart valves. Percutaneous mitral balloon valvuloplasty (PMBV) is an established treatment option in patients with symptomatic moderate or severe rheumatic mitral valve disease, but PMBV is not a preferred option in mitral stenosis (MS) patients with moderate mitral regurgitation (MR) due to the risk of severe MR. The aim of this study was to evaluate the safety and feasibility of PMBV in symptomatic MS patients with moderate MR by comparing the post-procedural parameters with those of MS patients with mild or no MR.

Method: Among 104 patients with symptomatic MS, 10 patients with moderate MR were classified as group 2 while 94 patients who had mild or none MR were classified as group 1 in the present work. All patients underwent PMBV and pre- and post-procedural mitral valve area, MRs were recorded and cardiovascular events and complications were assessed in 30 days.

Results: The only difference in both groups before and after the procedure was the severity of the MR. Cardiovascular death was not observed for both groups in 30 days. In group 1, there were 3 patients and in group 2, there was 1 patient who developed severe MR after PMBV. All patients who had post-procedural severe MR required mitral valve replacement in 30 days due to severe MR in group 1. The composite complication rate was similar between the groups.

Conclusion: PMBV might be an alternative treatment option for selected patients having significant MS with moderate MR.

Keywords: Mitral valve regurgitation, mitral valve stenosis, mitral valve valvuloplasty

Öz

Amaç: Romatizmal kalp hastalığı, kalp kapakçıklarında fonksiyon bozukluğuna neden olan bağışıklık komplekslerinin birikmesidir. Perkütan mitral balon valvüloplasti (PMBV), semptomatik orta veya şiddetli romatizmal mitral kapak hastalığı olan hastalarda belirlenmiş tedavi seçeneğidir. Ancak şiddetli mitral yetersizliği (MY) oluşma riski nedeniyle orta derecede MY olan mitral darlığı hastalarında PMBV tercih edilmez. Bu çalışmanın amacı, orta derecede MY olan semptomatik MS hastalarında PMBV'nin güvenilirliğini ve uygulanabilirliğini, işlem sonrası parametrelerini hafif MY olan veya olmayan mitral darlık hastalarınınkilerle karşılaştırarak değerlendirmektir.

Yöntem: Semptomatik mitral darlığı olan 104 hastadan orta derecede MY olan 10 hasta grup 2, hafif MY olan veya hiç olmayan 94 hasta grup 1 olarak sınıflandırıldı. Tüm hastalara PMBV uygulandı ve işlem öncesi ve sonrası mitral kapak alanı, MY'leri kaydedildi ve 30 gün içinde kardiyovasküler olaylar ve komplikasyonlar değerlendirildi.

Bulgular: İşlem öncesi ve sonrası her iki gruptaki tek fark MY'nin ciddiyetiydi. Otuz gün içinde her iki grupta da kardiyovasküler ölüm görülmedi. PMBV sonrası şiddetli MY gelişen hasta sayısı birinci grupta 3 ve ikinci grupta 1 hasta idi. Grup 1'deki tüm ileri MY hastalarda şiddetli MY gelişmesi nedeniyle 30 günde mitral kapak replasmanı gerekti. Kompozit komplikasyon oranı gruplar arasında benzerdi.

Sonuç: PMBV, orta derecede MY ile belirgin mitral darlığı olan seçilmiş hastalar için alternatif bir tedavi seçeneği olabilir.

Anahtar kelimeler: Mitral kapak darlığı, mitral kapak yetersizliği, mitral kapak valvüloplasti

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Introduction

Rheumatic valvular disease (RVD) is the result of superficial deposition of immune complexes and complements on heart valves. The deposition occurs progressively after rheumatic fever and causes the malfunction and dysfunction of the heart valves (1). These depositions might result in fibrotic alterations in the valves, particularly in the mitral valve, which might result in stenosis of mitral valve. This stenosis might present as the impairment of diastolic filling, increase in systolic pulmonary artery pressure (SPAP), increase in pressure of left atrium, reduced preload with the symptoms of progressive dyspnea, and decreased functional capacity (2). PMBV is an established treatment option for patients who have RVD. PMBV might be used in patients with moderate to severe MS. To date, several studies have explored the potential benefit of PMBV in symptomatic significant MS and favorable valve morphology, which have yielded promising results (3-6). Despite the fact that it is a robust method, PMBV might not be a treatment option for some patients. PMBV is not the preferred option in patients who have MS with moderate mitral regurgitation (MR) due to the risk of the exacerbation of MR after PMBV (7). Surgical mitral valve replacement (MVR) is the established treatment choice for patients who have MS with moderate MR, as an alternative to PMBV. Nevertheless, MVR has several disadvantages compared to PMBV, including higher risk of infective endocarditis, life-long anticoagulation, and the negation of the metallic valve.

The evidence concerning the efficacy and feasibility of PMBV in patients with MS accompanying moderate MR is scarce since most of MS patients with moderate MR are referred to MVR in daily practice. On the other hand, some patients with MS who have moderate MR might be a candidate for PMBV as a bridging procedure, which will postpone the surgical intervention, improve acute cardiac functions, and relieve the heart failure symptoms in selected patients.

In this study, we aimed to investigate safety and feasibility of PMBV in symptomatic MS patients with moderate MR by comparing the post-procedural parameters with those of MS patients with mild or no MR.

Materials and Methods

This study was a retrospective cohort study evaluating the safety and outcome of PMBV in patients who had significant MS with moderate MR. The investigation conforms to the principles outlined in the Declaration of Helsinki. The study was approved by the local ethics committee. All participants gave a written informed consent before being included in the study. Patients were selected among cases admitted to the cardiology clinic of a community tertiary hospital between January 2016 and February 2019. First, we investigated 158 consecutive patients who had symptomatic and significant rheumatic MS (MVA<1.5 cm^2). A total of 46 patients who had unfavorable morphology of mitral valve such as left atrial thrombus, required cardiac surgery for any other indication, severe MR, moderate or severe valve dysfunction in other valves were excluded from the study.

All patients underwent a baseline physical examination. The presence of atrial fibrillation was evaluated and recorded with electrocardiography. Transthoracic and transesophageal echocardiography (TEE) were performed to all patients, and two-dimensional MVA, mitral valve gradients, SPAP and severity of MR were evaluated. MR severity was calculated and evaluated with effective regurgitant orifice area (EROA) and regurgitant volume (RV) (8). The favorable characteristic of the mitral disease for PMBV was assessed with the score of Wilkins and was calculated for every patient before the procedure (9). After echocardiographic evaluations, the patients with moderate MR (n=18), who did not have any other contraindication for PMBV, were informed about the MVR and possible outcomes and complications of prosthetic valves. Among these patients, eight of them accepted surgical intervention for MVR, two of them rejected to have metallic prosthesis due to future possible pregnancies, five of them refused to be operated because of the risk of future metallic prosthesis complications and three patients had urgent PMBV due to acute pulmonary edema condition during their admission in the intensive coronary unit. Ten patients who refused to be operated or were unsuitable for the surgical intervention were informed about the risk of possible post-procedural MR after PMBV, which might be needed to treat with urgent surgery and informed consents were collected before the procedure. These 10 patients constituted group 2 while 94 patients who had mild or no MR were classified as group 1 in the present work.

All patients underwent PMBV in the catheter laboratory with the guidance of TEE during the procedure. PBMV was performed with a single balloon technique using Inoue Balloon. Initial balloon size was selected according to body surface area. Maximum balloon size was determined by the following formula: -patient height (cm)/10+10- (10). The proper placement and dilation of Inoue Balloon were evaluated with TEE guidance and assessed by the operator

with the synchronized views of both TEE and scopic view. After the dilation of the balloon, immediate calculations for mitral gradient and pulmonary artery systolic pressures were recorded.

After the procedure, all patients underwent post-procedural echocardiographic evaluation and two-dimensional (2D) MVA, mitral diastolic gradients, EROA, RV, SPAP were re-evaluated for the patients. The changes in EROA, 2D-MVA, SPAP and mitral diastolic gradients before and after the procedures were calculated.

Statistical Analysis

All statistical tests were performed with a commercially available software program (Statistical Package for the Social Science (SPSS) 20.0 for Windows, Chicago, IL, USA). All continuous variables were checked for normal distribution by the Kolmogorov-Smirnov test and presented as mean ± standard deviation while categorical variables were expressed as numbers or percentages. Chi-square test or McNemar test was used to compare categorical variables. Student t-test or paired sample test were used to compare continuous variables with normal distribution while Mann-Whitney U test or Wilcoxon test was used to compare the continuous parameters without normal distribution. P<0.05 was considered statistically significant.

Results

A total of 104 consecutive patients, including 18 male (17.3%) and 86 female (82.7%), with the mean age of 41.91±10.49 years were included in the final study cohort. A total of 94 patients with MR EROA value <0.20 cm^2 were categorized in group 1 (none/mild MR) while 10 patients with MR EROA≥0.20 cm^2 were classified under group 2 (moderate MR). Detailed demographics and echocardiographic parameters of each group and univariate comparison of these parameters are listed in Table 1. There was no statistical significance between the groups in terms of gender, age, pre-procedural and post-procedural SPAP, mean mitral gradients, 2D MVA, Wilkins score and presence of atrial fibrillation. Only difference for both groups before and after the procedure was the severity of the MR. The severity of MR, which was calculated by EROA, was found to be higher in group 2 before and after the procedure. When we compared the pre- and post-procedural echocardiographic findings, the mean 2-D MVA change in group 2 was 0.71±0.21 while it was 0.78±0.29 in group 1 (p=0.38). In the study, successful valvulotomy, which was defined as the increase of 2-D MVA >50%, was seen in 73 patients (77.7%) after the procedure in group 1, while it was in 6 patients (60%) in group 2 after the procedure (p=0.21).

Primary outcomes for both groups after the procedure are listed in Table 2. Cardiovascular death was not observed for both groups in 30 days. In group 1, there were 3 patients who required MVR in 30 days due to severe MR after the procedure. On the contrary, in group 2, there was one patient who had severe MR following the procedure; however, there was no requirement of MVR for this patient in 30 days. We

Table 1. Demographics, pre- and post-procedural echocardiographic findings of group 1 and group 2

Variables	Group 1 (n=94)	Group 2 (n=10)	p
Gender M/F	16 (17.1%)/78 (83%)	2 (20%)/8 (80%)	0.75
Age (years)	41.41±10.62	46.60±8.12	0.087
Pre-procedural PASP (mmHg)	51.39±16.80	60.07±19.98	0.10
Post-procedural PASP (mmHg)	34.21±6.02	37±4.80	0.16
Mean mitral gradients (pre-procedural)	16.44±5.51	16.2±5.55	0.89
Mean mitral gradients (post-procedural)	5.11±1.33	5.6±1.57	0.28
Pre-procedural 2-D MVA (cm^2)	0.98±0.23	1.09±0.23	0.15
Post-procedural 2-D MVA (cm^2)	1.76±0.19	1.79±0.73	0.46
Pre-procedural MR EROA (cm^2)	0.08±0.05	0.24±0.02	**<0.0001**
Post-procedural MR EROA (cm^2)	0.15±0.13	0.27±0.038	**0.005**
Wilkins score	7.23±1.12	7.10±1.128	0.34
Δ 2-D MVA (cm^2) (mean ± SD)	0.78±0.29	0.71±0.21	0.38
Presence of pre-procedural AF (y/n)	10 (10.6%)	1 (10%)	0.52
Presence of post-procedural AF (y/n)	17 (18.1%)	3 (30%)	0.80

PASP: Pulmonary artery systolic pressure (mmHg), All variables are expressed as mean ± standard deviations unless otherwise specified. SD: Standard deviation, EROA: Effective regurgitant orifice area, MR: Mitral regurgitation, MVA: Mitral valve area

Table 2. Primary outcomes of both groups after the procedure

	Group 1	Group 2
Cardiovascular death within 30 days	0 (0%)	0 (0%)
MVR for severe MR within 30 days (n-%)	3 (3.2%)	0 (%)
Peri-procedural Complications (n-%)	1 (1.8%)	1 (10%)
Composite (n-%)	4 (4.3%)	1 (10%)

MVR: Mitral valve replacement, MR: Mitral regurgitation

encountered only two major peri-procedural complications (1.92%) in the present work. There was one patient each in both groups, who had peri-procedural complications. One of these patients had pericardial effusion, and the other patient had a pericardial hematoma following PMBV. Both of these patients needed to undergo surgical intervention given to pericardial effusion and hematoma.

Pre-procedural and post-procedural comparisons of echocardiographic parameters for each group are shown in Table 3 and Table 4. For the groups, SPAP and the mean mitral gradients significantly decreased, and 2-D MVA and MR EROA significantly increased. The rate for the presence of atrial fibrillation was found to be higher for both groups after the procedure; however, only in group 1, this increase was found as statistically significant.

Discussion

In this present study, we evaluated the outcome of PMBV as an alternative procedure to MVR in delicately selected MS patients accompanied by moderate MR. Our study demonstrated that cardiovascular death and post-procedural complication rates were similar when compared to patients who had MS with moderate and none or mild MR. Only one of ten MS patients accompanied by moderate MR manifested with severe MR after PMBV, and only 3 of 96 patients (3.1%) with no or mild MR presented with severe MR after PMBV. As it is expected, the mean 2D-MVA of both groups was significantly increased after PMBV when compared to 2D-MVA before the procedure. Together with that, there was no significant difference between the groups in terms of mean increase in valve area after the procedure. Our study demonstrated that after PMBV, patients who had moderate MR with significant MS might had similar complication rates together with similar success rates when compared to the patients who had no or mild MR with significant MS.

Several studies have showed that the occurrence rate of severe MR in MS patients with mild or no MR after the procedure ranges between 1.4% and 9.4%. And in these cases, 1.3%-3.2% required MVR urgently due to the occurrence of severe MR (11-13). However, there are inadequate data on the occurrence of severe regurgitation after PMBV in patients with MS having moderate regurgitation for mitral valve. In a study, they performed PMBV to 21 patients who had moderate MR and they compared the procedural outcomes with 83 patients who had no or mild MR (13). Even though the regurgitation progressed in both groups, no patient presented with severe MR after the procedure and together with the improvement in symptoms due to mitral valve disease. Similarly, both groups in the present work had an increase in the rate of MR. While no MS patient with moderate MR showed severe MR in the study conducted by Lau et al. (14), one patient with moderate MR (10%) presented with severe MR after PMBV in our work. These results in previous studies are consistent with our findings for the occurrence of severe MR after the procedure.

On the other hand, we should discuss about the success rate of the procedure for patients who have moderate MR together with significant MS. In a study, Zhang et al. (15) performed PMBV in 25 patients who had MS with moderate

Table 3. Univariate comparison of pre- and post-procedural echocardiographic findings of group 1

Variables	Pre-procedural	Post-procedural	p
Pulmonary artery systolic pressure (mmHg)	51.39±16.80	34.21±6.02	**<0.0001**
Mean mitral gradients (mmHg)	16.44±5.51	5.11±1.33	**<0.0001**
2-D MVA (cm^2)	0.98±0.23	1.76±0.19	**<0.0001**
MR EROA (cm^2)	0.08±0.05	0.15±0.13	**<0.0001**
Presence of atrial fibrillation (y/n)	10/84 (10.6%)	17/77 (18.1%)	**0.019**

MVA: Mitral valve area, MR: Mitral regurgitation, EROA: Effective regurgitant orifice area, all variables are expressed as mean ± standard deviations unless otherwise specified

Table 4. Univariate comparison of pre- and post-procedural echocardiographic findings of group 2

Variables	Pre-procedural	Post-procedural	p
Pulmonary artery systolic pressure (mmHg)	60.07±19.98	37±4.80	**<0.0001**
Mean mitral gradients (mmHg)	16.2±5.55	5.6±1.57	**<0.0001**
2-D MVA (cm^2)	1.09±0.23	1.79±0.73	**<0.0001**
MR EROA (cm^2)	0.24±0.02	0.27±0.038	**0.02**
Presence of atrial fibrillation (y/n)	1/9 (10%)	3/7 (30%)	0.15

MVA: Mitral valve area, MR: Mitral regurgitation, EROA: Effective regurgitant orifice area, all variables are expressed as mean ± standard deviations unless otherwise specified

MR and compared their post-procedural findings with 25 patients who had MS with no or mild MR. Procedural successful rate for both groups was 92% in their study. Their findings showed that improvement in hemodynamics and MVA could be achieved with PMBV in patients who had MS either with moderate or no or mild MR. In our study, the success rate for procedures was 77.7% in group 1 and 60% in group 2; however, there was no significant difference between the groups. And improvement in MVA was accomplished in both groups.

One of the high volume studies is the study of Desabandhu et al. (16). They compared patients undergoing PMBV either with no or mild MR and moderate MR. In their study, 17 patients had moderate MR with significant MS and 208 patients had no or mild MR with significant MS. They found that there was no statistically significant difference in the primary outcome of the procedure in both groups. In their study, 2 patients (11.76%) had post-procedural severe MR in patients with moderate MR and 4 patients (1.92%) had post-procedural severe MR in patients with no or mild MR. Even though severe MR was higher in moderate MR group, the requirement for MVR was higher (1.44%) in the group with no or mild MR. Their comment for their study was that PMBV might be a safe option for selected patients who had significant MS with moderate MR and provide symptomatic benefits in these patients. In our study, our findings were similar to their findings. Cardiovascular death was not seen for both groups in 30 days and 3 patients required MVR after the procedure due to severe MR in group 1 and one patient had severe MR which did not require MVR in group 2 in 30 days. The patient in group 2, who did not require MVR, was followed up with medical therapy. The possible explanation for the requirement of MVR might be that the patients with moderate MR have higher volume load than the patients with no or mild MR. Because of higher volume load in these patients, patients with moderate MR might better tolerate severe MR after PMBV when compared to the patients with no or mild MR. Together with that, there was no significant difference in peri-procedural complication in both groups. Composite complication of cardiovascular death and severe MR at 30 days was not different between the groups.

Study Limitations

Several limitations for the present study should be acknowledged. First, and foremost, we had a small number of MS patients with moderate MR, who underwent PMBV as similar to the previous works. Nevertheless, the indications for PMBV in MS patients with moderate MR are rather limited and strict; hence, it was not possible to form a balanced study group. Second, this was a retrospective study with single-center data, which might limit the generalizability and reliability of our results. Another limitation was the limited follow-up period for the patients and we did not have the results of longer period for both groups.

Conclusion

Outcomes for PMBV in patients who had MS with moderate MR are similar to those in the patients who had MS with no/mild MR. PMBV might be an alternative treatment option for selected patients who had significant MS with moderate MR. However, prospective further studies with larger patient cohort are needed to validate our results.

Ethics

Ethics Committee Approval: All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.Ç., A.A.Ş., M.K., Design: Ö.Ç., A.A.Ş., M.K., Data Collection or Processing: Ö.Ç., A.A.Ş., M.K., Analysis or Interpretation: Ö.Ç., A.A.Ş., M.K., Writing: Ö.Ç., A.A.Ş., M.K.

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ORIGINAL RESEARCH

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The Brain Ischemic Volume Correlation with the Ischemic Modified Albumin Level

İskemik Beyin Hacminin İskemik Modifiye Albümin Seviyesi ile Korelasyonu

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Abstract

Objective: Cerebrovascular disease is a frequent cause of emergency department visits, and early diagnosis can reduce mortality and morbidity. It was aimed to evaluate the relationship between diffusion-weighted-magnetic resonance imaging (DW-MRI) and blood ischemic modified albumin (IMA) levels of cerebrovascular diseases in terms of demographic characteristics, mortality, and morbidity.

Method: This prospective cohort study included 44 patients diagnosed with ischemic stroke in the emergency room between January and July 2014 and 44 people in the control group. Age, gender, vital signs, co-morbid disease states, neurological deficit levels, IMA levels, DW-MRI involvement volumes, and mortality rates were analyzed in patients who were diagnosed with stroke and who had DW-MRI restrictions. Also, a control group of 44 volunteers who applied to our emergency department was added to compare the IMA level.

Results: The median age of the patients was 71 years (24 males, 20 females, range 47 to 83 years) and the median age of the control group was 68 (25 males, 19 females, range 52 to 79) years. The median age of the control group was close to that of the patient group, the two groups were also similar in terms of gender distribution. The most common co-morbid disease was hypertension 28 (63.6%), atrial fibrillation (AF) 14 (31.8%), diabetes mellitus (DM) 10 (22.8%) and coronary artery disease 10 (22.8%). The median value of the IMA level was 13.84 in the patient group and 8.66 in the control group. While the patients' NIHSS stroke score was high, the area of involvement in MRI and also IMA levels increased.

Öz

Amaç: Serebrovasküler hastalık, acil servis başvurularının sık bir nedenidir, erken tanı mortalite ve morbiditeyi azaltabilir. Çalışmamızda serebrovasküler hastalıkların difüzyon ağırlıklı-manyetik rezonans görüntülemeleri (DA-MRG) ile kan iskemik modifiye albümin (İMA) düzeyleri arasındaki ilişkinin demografik özellikler, mortalite ve morbidite açısından değerlendirilmesi amaçlandı.

Yöntem: Bu prospektif kohort çalışmasına Ocak-Temmuz 2014 tarihleri arasında acil serviste iskemik inme tanısı almış 44 hasta ile 44 kontrol grubu dahil edildi. İnme tanısı konulan ve DA-MRG kısıtlaması olan hastalarda yaş, cinsiyet, yaşamsal belirtiler, yandaş hastalık durumları, nörolojik defisit düzeyleri, İMA düzeyleri, DA-MRG tutulum hacimleri ve mortalite oranları analiz edildi. Ayrıca, İMA düzeyini karşılaştırmak için acil servisimize başvuran 44 gönüllüden oluşan bir kontrol grubu eklenmiştir.

Bulgular: Hastaların ortalama yaşı 66,98±16,36 ve %54,5'i (n=24) erkekti. Kontrol grubu ile hasta grubunun yaşları benzerdi. En sık görülen komorbid hastalık hipertansiyon 28 (%63,6); atriyal fibrilasyon 14 (%31,8), diabetes mellitus 10 (%22,8) ve koroner arter hastalığı 10 (%22,8) idi. İMA düzeyinin ortanca değeri hasta grubunda 13,84, kontrol grubunda 8,66 idi. Hastaların NIHSS inme skoru yüksek iken, MRG'deki tutulum alanı ve ayrıca İMA seviyelerinin arttığı görüldü. Ayrıca difüzyon kısıtlama alanı ve İMA düzeyleri pozitif ve orta düzeyde ilişkiliydi.

Sonuç: İMA düzeyi, akut iskemik inmede kullanılabilen bir parametre ve DA-MRG'de kısıtlılık alanının bir göstergesi olarak değerlendirilebilir.

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Abstract

Besides, diffusion involvement area and IMA levels were positively and moderately correlated.

Conclusion: IMA level can be considered as a parameter that can be used in acute ischemic stroke and as an indicator of the diffusion restriction area in MRI.

Keywords: Acute ischemic stroke, biomarkers, diffusion-weighted magnetic resonance imagining, ischemic modified albumin

Öz

Anahtar kelimeler: Akut iskemik inme, biyobelirteçler, difüzyon ağırlıklı-manyetik rezonans görüntüleme, iskemik modifiye albümin

Introduction

In acute cerebrovascular events, definitive diagnosis and treatment processes should be started immediately as soon as the patient's clinic begins. The primary aim of the diagnostic procedure is to clarify whether the clinical condition is a result of ischemic disease or another neurologic or metabolic condition. The sensitivity of a good physical examination is 99% and the specificity is 85%, which cannot differentiate the ischemic and hemorrhagic causes of the stroke (1). Computed tomography (CT) is used as the first choice for the differentiation of ischemic and hemorrhagic stroke (2). The sensitivity and specificity of the CT for the ischemic cerebrovascular diseases (CVD) are 39.8% and 91.7%, respectively, in the first six hours; with repetition of CT between 6 and 24 hours, the sensitivity and specificity increases slightly but still not enough for exact diagnosis (3). In the first six hours, we use DW-MRI, which has a sensitivity of 58.3 to 97.3% and specificity of 100% (3).

The delay in the diagnosis and treatment of CVD is generally observed in transportation to the hospital and the evaluation of the diagnostic tests in the hospital (4). Despite the usage of all diagnostic methods, the etiologic reason cannot be specified in 20% of the CVD (5). Therefore, some new biomarkers that can be useful for an early diagnosis such as ischemic modified albumin (IMA) are investigated (6) in CVD patients. IMA is a sensitive biomarker that has shown the increase in some ischemic conditions such as myocardial ischemia, muscle ischemia, pulmonary embolism, mesentery ischemia, and cerebral ischemia (6).

The study aimed to investigate the relationship of IMA levels with DW-MRI findings and demographic characteristics in terms of morbidity and mortality in patients admitted to the emergency department due to cerebrovascular stroke.

Materials and Methods

Study Design and Population

After local ethics committee approval was received for this prospective study, 88 patients, (44 patients, and 44 controls) who were admitted to the emergency department between January and July 2014, were included. After informing the patients and controls voluntarily, the ''information consent form'' was signed and included in the study.

In addition to patients who did not have DW-MRI and whose IMA levels were not considered, patients with endocrine pathology, psychiatric drug use, chronic liver disease, need for dialysis, central nervous system infection, chronic inflammatory disease, malignancy, severe anemia, hematological disease, severe dietary history, radiotherapy in the head and neck region, and pregnancy were not included in the study.

The National Institutes of Health Stroke scale (NIHSS) score was used in the definition of cerebrovascular stroke in the patient group. NIHSS score was classified as no symptoms if 0, minor stroke if 1-4, moderate stroke if 5-15, moderate-heavy stroke if 16-20, and heavy stroke if 21-42 (7). Forty four healthy volunteers who did not have any ischemic disease were included in the study.

Laboratory Design

The venous samples of the patients taken to a plastic gel vacuum tube were kept for 20 minutes at room temperature to complete the coagulation. The samples were centrifuged at 4.000 cycles for 10 minutes, hemolyzed or icteric samples were excluded and repeated from the same patient. The IMA level was detected by Tweak original commercial kits by enzyme-linked immunosorbent assay (ELISA) method. The IMA level measurement was performed by putting the ELISA kit (Eastbiopharm, Hangzhou Eastbiopharm Co. Ltd. China, ref: CK-E90172, lot: 201402) on the BioTEK Plate reader. The blood serum samples were incubated in microplate wells that were covered by antibodies

identifying IMA antigen for 30 minutes at 37 ºC. After the washing process, entrapped IMA antigens were incubated by adding the anti-human IMA antibodies that were conjugated with horseradish peroxidase for 30 minutes at 37 ºC. Following this step, the chromogen A and B solutions were added and incubated for 15 minutes at 37 ºC. The reaction was aborted by a stop solution. The absorbance of the yellow-colored product was measured by the spectrophotometric method at 450 nm wavelength. The absorbance was proportioned with IMA concentration. We obtained a standard calibration curve by marking the IMA standard concentration points. The unknown blood serum concentrations were determined by this obtained standard curve. The measurable concentration range of the ELISA kit was 1-60 U/mL, the lower limit of quantification was 1 U/mL.

Radiological Design

DW-MRI procedures were performed by 1.5T General Electric (GE®) MRI Machine. Hyperintense signal variances in apparent diffusion coefficient images were accepted as a diffusion restriction or a new infarct area. The infarct volume was calculated by ABC/2 formula, which is a fast method for estimating the affected volume of intracerebral area. This simple method provides a 3D analysis of the intracerebral area.

A; is the greatest hemorrhage diameter.

B; is affected area's diameter 90 degrees to A in the axial plane.

C; is the approximate number of CT slices with hemorrhage multiplied by the slice thickness.

The multiplication of A, B, and C were divided by 2 and the final result was accepted as the volume of the infarct region (8). Besides, measurements were made in centimeters (cm), then the formula gave the results as cubic centimeters (cm^3).

Statistical Analysis

All statistical analyses were calculated with SPSS 18.0 for Windows (New York, USA). Continuous variables were expressed as mean ± standard deviaton, and categorical variables as n (%). Median and minimum-maximum limits were given for age. Normal distribution was determined by the Kolmogorov-Smirnov test advertising histogram. Differences of continuous variables between the groups were calculated by the Mann-Whitney U test and Kruskal-Wallis test for non-normally distributed variables; student's t-test was used for normally distributed data; chi-square test was used for categorical variables. Correlations of continuous variables were calculated with the Pearson's correlation. P<0.05 was considered significant at 95% confidence interval.

Results

The median age of the patients was 71 years (24 males, 20 females, range 47 to 83 years) and the median age of the control group was 68 (25 males, 19 females, range 52 to 79) years. The median age of the control group was close to that of the patient group; The gender distributions of the two groups were similar (p=0.830, Table 1).

The most frequently observed co-morbidity in the patient group was hypertension with a rate of 63.6% (n=28); followed by AF, 31.8% (n=14), DM, 22.8% (n=10), and coronary artery disease, 22.8% (n=10) (Table 2).

When the vital signs of the patients we included in the study were examined, the mean systolic blood pressure value of the patients was 177.14±18.28 mmHg, the mean diastolic blood pressure value was 97.68±14.46 mmHg and the heart rate was 89.02±9.1 beats/minute as seen (Table 3).

The median IMA level was 13.84 U/mL (range 6.25-209.72 U/mL) in the patient group and 8.66 U/mL (range 1.79-49.58 U/mL) in the control group (Table 4).

IMA level was significantly higher in the patient group (p<0.001). While the NIHSS score was increasing the ischemic volume in DW-MRI, IMA level showed the increase

Table 1. Age and gender characteristics of patient and control groups

	Patient Median (min-max)/n (%)	Control Median (min-max)/n (%)	p
Age	71 (47-83)	68 (52-79)	-
Gender			0.830*
Male	24 (54.5)	25 (56.8)	
Female	20 (45.5)	19 (43.2)	

*: Chi-square, n: Number of patients, p<0.05

Table 2. Comorbid properties of the patient group

	n (%)
Hypertension	28 (63.6)
Atrial fibrillation	14 (31.8)
Diabetes mellitus	10 (22.8)
Coronary artery disease	10 (22.8)
Cerebrovascular disease	4 (9)
Other diseases	4 (9)

n: Patients number, p<0.05

(Table 5); also, there was a moderate positive correlation with ischemic volume in DW-MRI and IMA level (p<0.001, r=0.641).

The mortality rate was 6.8% (n=3). The IMA level and the ischemic volume in DW-MRI were similar in the dead and alive patients (p=0.172 and p=0.239, respectively).

Discussion

The early diagnosis of CVD is important for reducing mortality and morbidity. According to previous study reports, there is not a significant gender difference in CVD but most of the cases are reported over the age of 65 years (9,10). In our study, the median age of the patients was 71 years, males constituted 54.5% of all cases and it was found to be compatible with similar studies.

Hypertension can be observed before or after the CVD diagnosis (11-13). Only by regulating the blood pressure and controlling hypertension, we can decrease the CVD risk by up to 40% (14). Previous studies reported the mean systolic pressure on admission as around 155 mmHg (9,15). We know that CVD frequency increases with AF and DM (16) as we observed their frequency as 31.8% and 22.8%, respectively, in our study. Blood pressure values were found to be slightly higher than the values indicated in similar studies. The mean systolic blood pressure value was determined as 177.14±18.28 mmHg. Also, the most common co-morbid disease was hypertension, followed by AF and DM. We think that the average systolic pressure values are slightly higher, depending on the socioeconomic level and eating habits.

Table 3. Patient's blood pressure status and pulse numbers

	Mean ± SD	Min-max
Systolic arterial pressure (mmHg)	177.14±18.28	130-210
Diastolic arterial pressure (mmHg)	97.68±14.46	70-130
Heart rate (beats/min)	89.02±9.1	62-104

SD: Standard deviation, p<0.05

Table 4. Comparison of IMA levels of patient and control groups

	Patient level (min-max)	Control level (min-max)	p
IMA	13.84 (6.25-209.72)	8.66 (1.79-49.58)	**0.001**

p<0.05, IMA: Ischemic modified albumin

Table 5. The ischemic volume in DW-MRI and median IMA level according to NIHSS score

The ischemic volume			
	n	**DWMRI median (min-max)**	**IMA level median (min-max)**
Minor stroke (NIHSS 1-4)	16	3.91 (1-78.14)	14.42 (6.25-209.72)
Moderate stroke (NIHSS 5-15)	15	9.7 (1.92-24.35)	8.93 (6.25-25.63)
Moderate-severe stroke (NIHSS 16-20)	9	54.88 (4.3-88.2)	28.75 (8.93-196.30)
Severe stroke (NIHSS 21-42)	4	49.82 (5.65-131.83)	16.07 (10.72-159.89)
p	**-**	**0.002**	**0.017**

DWMRI: Diffusion weighted magnetic resonance imagining, IMA: Ischemic modified albumin, p<0.05

Free oxygen radicals produced in the process of ischemia, reperfusion, acidosis, and hypoxia lead to a structural change of transition metals like cobalt, copper, and nickel on N-terminal end, which causes a decrease in binding of albumin to these points (17-19). The IMA level is in the normal range in healthy people but smoking, age, race or gender do not also influence the level of IMA (20). The IMA level increases in CVD, acute mesentery ischemia, acute pulmonary embolism, and acute coronary syndromes (21-23). Abboud et al. (19) reported that the IMA level increased in ischemic stroke but did not increase in hemorrhagic stroke. Gunduz et al. (21) reported that the IMA level was higher in ischemic stroke than in hemorrhagic ones and suggested to use it in differential diagnosis. IMA level was found to be high as in similar studies. We think that the reason for this is that due to increased free radicals, the protein cannot be attached to the cell, it remains free in the blood and the IMA level increases accordingly.

DW-MRI is generally used for the diagnosis of ischemic stroke in the case of CT but suspicion of ischemic CVD is still present. In ischemic CVD, while the ischemic volume increases, the clinical condition gets worse (24,25). In SVO cases; as diffusion involvement became more common in DW-MRI, it was found that the NIHSS score and IMA levels increased and the patient's clinic worsened as a result. In similar studies, Can et al. (26) reported that the IMA level increased while the ischemic volume in DW-MRI increased. Additionally, Ahn et al. (27) reported that the IMA index [serum albumin concentration (g/dL) x23+IMA (U/mL)-100] was more sensitive than the IMA level in ischemic CVD. Also, some studies reported that the clinical condition of the patients with ischemic stroke was positively correlated with the IMA level (17,19). Consuegra-Sanchez et al. (23) reported that the IMA level

was higher in one-month and one-year mortality. In our study, there were not enough mortal cases and also the study population was low. Further studies with large patient sizes can give better results, especially about mortality.

Study Limitations

Our most important restrictive reason was that the study was single-centered. Also, late admissions were not included in the study. Moreover, the patients who came with the SVO clinic, patients who did not give consent to be included in the study, and other patients with comorbid diseases were excluded from the study.

Conclusion

The IMA level can be used in the differential diagnosis of CVD and also positively correlated with ischemic volume. The IMA level may be useful as a new biomarker for the patients who have normal CT results but show clinical symptoms of ischemic CVD.

Ethics

Ethics Committee Approval: All subjects gave their in formed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Project identification code: 2013-703-04/12/2013.

Informed Consent: It is a prospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.D., M.E.K., Ç.Ç., S.A.U., S.İ., Design: B.D., M.E.K., Ç.Ç., İ.B., S.A.U., S.İ., Data Collection or Processing: B.D., M.E.K., İ.B., C.Y., S.A.U., S.İ., Analysis or Interpretation: B.D., M.E.K., C.Y., K.Ü., İ.B., Literature Search: B.D., A.C., Ç.Ç., K.Ü., C.Y., Writing: B.D., A.C., Ç.Ç., K.Ü., C.Y., S.İ.

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ORIGINAL RESEARCH

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The Relationship Between Interatrial Block and PASI Score in Patients with Psoriasis

Psoriazisli Hastalarda İnteratriyal Blok ve PACİ Skoru Arasındaki İlişki

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Abstract

Objective: The relationship between the interatrial block (IAB) and atrial fibrillation (AF) has been demonstrated in previous studies. The aim of this study is to investigate the relationship of the IAB with the psoriasis area severity index (PASI) score in psoriasis.

Method: Patients with psoriasis who were examined at the cardiology outpatient clinic between January 2017 and May 2019 were retrospectively screened. Two hundred and thirty-eight patients whose electrocardiogram (ECG) and PASI scores were available were included in the study. IAB was defined as if P wave duration was equal to or longer than 120 msec with (advanced IAB) or without (partial IAB) biphasic P morphology in the inferior electrocardiographic leads. The prevalence of IAB in patients with psoriasis and its relationship with the severity of psoriasis were evaluated in the present study.

Results: The mean age was 35 (18-62) years, 53% of the study population were male. The median PASI score was 6. IAB was observed in 9.9% of patients. Partial IAB was observed in 6% of patients whereas the prevalence of advanced IAB was 3.0%. No statistically significant difference was observed between the PASI score in patients with and without IAB [6.0 (3.0-13.5) vs. 7.0 (2.5-22.5), respectively, p=0.35]. The mean P wave duration (PWD) was 101 (90-111) ms. No statistically significant correlation was observed between PWD and the PASI score (p=0.35, r=0.06).

Conclusion: No significant correlation was identified between IAB and the PASI score, which is used for assessing the severity of psoriasis.

Keywords: Atrial fibrillation, electrocardiography, interatrial block, psoriasis, psoriasis area severity index, stroke

Öz

Amaç: İnteratriyal blok ve atriyal fibrillasyon arasındaki ilişki daha önceki yayınlarda gösterilmiştir. Bu çalışmanın amacı interatriyal blok (IAB) ve psoriazis alan ciddiyeti indeksi (PACİ) arasındaki ilişkinin araştırılmasıdır.

Yöntem: Ocak 2017-Mayıs 2019 arasında kardiyoloji polikliniğinde muayene olan psoriasis hastaları retrospektif olarak taranmıştır. Elektrokardiyografilerine ve PACİ skorlarına ulaşılan 238 hasta çalışmaya alındı. IAB P dalga süresi 120 msn üzerinde ve bifazik morfoloji eşlik ediyorsa ileri (aIAB), etmiyorsa parsiyal IAB (pIAB) olarak tanımlandı. IAB'nin psoriasis hastalarında yaygınlığı ve psoriazisin şiddetiyle ilişkisi değerlendirildi.

Bulgular: Hastaların ortalama yaşı 35 (18-62) yıldı, %53'ü erkekti. Ortalama PACİ değeri 3,29±3,81 idi. IAB hastaların %9,9'unda görüldü. Bu hastaların %6'sında pIAB, %3'ünde aIAB izlendi. Total IAB izlenen hastaların PACİ değerleri ile IAB olmayan hastaların PACİ değerleri arasında anlamlı istatistiksel fark saptanmadı [6,0 (3,0-13,5) vs. 7,0 (2,5-22,5), p=0,35]. Ortalama P dalga süresi (PDS) 101 (90-111) msn idi. PDS ile PACİ skoru arasında istatiksel açıdan anlamlı olmayan korelasyon izlendi (p=0,35, r=0,06).

Sonuç: Psoriazisin şiddetini gösteren PACİ skoru ile IAB blok arasında anlamlı ilişki bulunmadı.

Anahtar kelimeler: Atriyal fibrillasyon, elektrokardiyografi, inme, interatriyal blok, psoriazis, psoriazis alan ciddiyet indeksi

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Introduction

Psoriasis is a chronic, immune-mediated systemic disease of unknown etiology. It is estimated that 1-5% of the world population is affected by this disease (1,2). Although it is mostly known for involving the skin and joints, recent studies have shown that the incidence of cardiovascular diseases has increased in patients with psoriasis (3). While cardiovascular risk factors are frequently observed in patients with psoriasis, it has also been recently demonstrated that there is a close relationship between psoriasis and myocardial infarction (4). These comorbid conditions additionally increase morbidity and mortality in patients with psoriasis.

AF is the most common cardiac arrhythmia with a demonstrated association with both morbidity and mortality in clinical practice. AF increases mortality, sudden cardiac death, heart failure, and stroke. Current studies show that AF is responsible for 20-30% of ischemic stroke (5). With appropriate anticoagulation, a reduction can be provided in thromboembolic complications. Due to its episodic nature, the diagnosis of paroxysmal AF is the challenge that delays to start an appropriate anticoagulation treatment (6).

The IAB is caused by the conduction delay on the Bachmann's bundle, which is responsible for connection of the right atrium to the left electrically (7). In one Finnish study, the prevalence of partial and advanced IAB in general population aged over 30 years was 9.7% and 1.0%, respectively (8). Several studies have shown that IAB is an independent predictor of AF (9,10). The increased frequency of IAB has also been demonstrated in patients with silent brain infarction (11). A recently published article demonstrated an increased prevalence of partial and advanced IAB in patients with embolic stroke with undetermined source (12). In the same study, advanced IAB independently predicted AF (12).

This study aimed to demonstrate the relationship between the PASI score and IAB.

Materials and Methods

Patients with psoriasis who were examined at the cardiology outpatient clinic between January 2017 and May 2019 were retrospectively screened. Patients with available PASI scores and ECG recordings were included in the study. Patients with other than sinus rhythm, previous history of atrial arrythmias, structural heart diseases, hypo- and hyperthyroidism were excluded from the study. Baseline medical history and laboratory values of the patients were recorded. Standard 12-derivation ECG recordings were reevaluated. ECGs were scanned at 300 DPI, then transferred to electrophysiology (EP) calipers software (EP Studios, Inc, Version 3.1) and all measurements were performed in this software. The start of the P wave is the point with the first upward or downward deflection of the isoelectric line, whereas the end of the P wave was considered as the point where the wave returned to the isoelectric line (Figure 1). ECGs were evaluated by two different cardiologists in terms of IAB and were evaluated by a third cardiologist when there was a conflict in the diagnosis.

IAB was defined as if P wave duration (PWD) was equal to or longer than 120 msec with (advanced IAB) or without [partial IAB (pIAB)] biphasic P morphology (terminal negative deflection) in the inferior electrocardiographic leads (Leads II, III and aVF).

To calculate PASI score, the body was divided into several regions: head, upper and lower extremities and trunk. Each involved area was scored on a 0 to 6 scale. Each area was assessed in terms of erythema, infiltration and desquamation, which were scored separately on a 0 to 4 scale. Then all scores were summed up to achieve the final PASI score which was ranging from 0 to 72. PASI<5 was classified as mild, PASI 5-10 as intermediate, and PASI>10 as severe psoriasis.

PASI scores were obtained from the previous medical records. The highest value was taken if there were multiple PASI score values.

The study was approved by Bezmialem Vakıf University Ethics Committee (no:16/297). Informed consents were

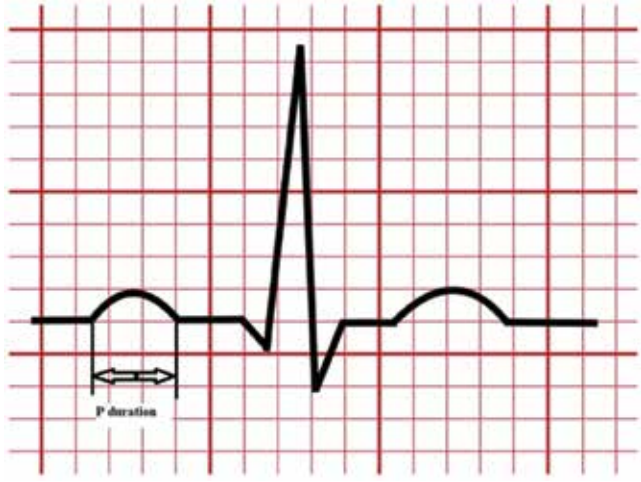

Figure 1. P wave duration measurement

provided and the study was conducted according to the guidelines on clinical investigations of Declaration of Helsinki.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation, while skewed variables were showed as median ± interquartile range. The normality was tested by visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov or Shapiro-Wilk tests as appropriate). The Mann-Whitney U test was used to compare PASI scores in patients with and without IAB. For checking correlation, the Spearman's test was used. All reported p-values were 2-sided and $p<0.05$ was considered as statistically significant. SPSS version 20 was used to perform statistical analyses.

Results

The study evaluated 238 patients whose ECG and PASI scores and clinical information were fully available. The mean age was 35 (18-62) years, 53% of study population were male (Table 1). The median PASI score was 6. pIAB was observed in 6.9% of the patients and the prevalence of advanced IAB was 3.0%. No statistically significant difference existed between the PASI score in patients with and without IAB [6.0 (3.0-13.5) vs. 7.0 (2.5-22.5)], respectively, p=0.35). The mean PWD was 101 (90-111) ms. No statistically significant correlation was observed between PWD and the PASI score (p=0.35, r=0.06) (Table 2).

Discussion

The study revealed that there was no significant relationship between the PASI score and IAB. Although the PASI score is relevant to the severity of psoriasis, it varies widely with treatment. In our study, we considered the highest PASI values of the patients. This study showed that the PASI value could not predict IAB. Although the frequency of AF increased in psoriasis and the relationship of IAB with AF was shown, we found in this study that the risk of AF could not be estimated with the PASI score.

AF is responsible for 25% of strokes (13). Therefore, revealing the factors predicting AF will be effective in preventing stroke (13). The relationship between psoriasis and AF has been demonstrated in the Danish cohort. 36,765 patients with mild psoriasis were compared with 4,478 patients with severe psoriasis and 4,478,926 controls without psoriasis. Both AF and the risk of stroke were found to be high in patients with psoriasis (3). Similar results were demonstrated in the meta-analysis conducted by Upala et al. (14). A cohort study published by Egeberg et al. (15) showed an increased risk of AF and stroke in psoriasis. The risk of AF and stroke was more common in patients with psoriasis accompanied by depression.

Many studies have shown that IAB is an independent predictor of AF (9). The IAB is known for the delay of conduction on the Bachmann's pathway or the delay of the transition from right to left due to its complete block, and the PWD being longer than 120 msec in ECG (7). Its prevalence increases with age. In a study, in which 1,353 healthy males under the age of 35 years were screened, IAB was observed in 5.4% of those under the age of 20 years and 9.1% of those under the age of 35 years (16). In this study, IAB was considered if the PWD was 110 msec and above. In our study, the mean age of the patients was 35 years,

Table 1. Baseline characteristics of study population

	Values
Age, men (years)	35 (18-62)
Gender male, n (%)	137 (53.1)
Hypertension, n (%)	23 (8.9)
DM, n (%)	7 (2.7)
CAD, n (%)	6 (2.3)
CVA, n (%)	0 (0)
Hyperlipidemia, n (%)	10 (3.9)
Depression, n (%)	18 (7)
Laboratories	
Hemoglobin, mean (g/dL)	14.1 (13.2-15.4)
WBC, mean ($x10^9$)	7.61 (6.45-9.53)
Neutrophils, mean ($x10^9$)	4.31 (3.53-5.31)
Lymphocytes, mean ($x10^9$)	2.27 (1.89-2.76)
CRP	2 (1-6)
PASI score, median, (IQR)	6.0 (2.9-14.3)
Advanced IAB, n (%)	12 (4.7)
Partial IAB, n (%)	20 (7.8)
Total IAB, n (%)	32 (12.4)
P wave duration, msn, median (IQR)	101 (90-111)

CAD: Coronary artery disease, CRP: C-reactive peptide, CVA: Cerebrovascular accident, DM: Diabetes mellitus, IAB: Interatrial block, PASI: Psoriasis area severity index, WBC: White blood cell, IQR: Interquartile range

Table 2. Correlation between PASI and IAB

	IAB (-)	IAB (+)	p
P wave duration, msn, median (IQR)	99 (90-106.25)	128.5 (123-132.75)	<0.001
PASI, median (IQR)	6.0 (3.0-13.5)	7.0 (2.5-22.5)	0.35

IAB: Interatrial block, PASI: Psoriasis area severity index, IQR: Interquartile range

while IAB was seen in 12.4% of the population. In another study, the prevalence in patients with 70-80 years of age was 37.4% (29.7% pIAB, 7.7% aIAB), and 39.4% (19.7% pIAB, 19.7% aIAB) in the population over 100 years of age (17). IAB prevalence varies in different patient populations. Its prevalence in the patient population with heart failure was identified to be 10% (18). Increased frequency of IAB has also been shown in patients with silent brain infarction (11). To the best of our knowledge, no study on the prevalence of IAB has been performed in the patient population with psoriasis so far.

Although it has been shown in different studies that the incidence of AF increased in psoriasis, the mechanism of this relationship could not be elucidated in detail yet. Active inflammation is thought to be involved in pathophysiology (19). Chronic inflammation is known to be effective in left atrial remodeling (20), which creates a substrate for AF. Histopathological studies performed in patients with AF have revealed inflammatory cell infiltration (21) and oxidative damage in atrial tissue (22). Inflammation causes prolonged PWD (23) and atrial electromechanical delay (24). While PWD is an electrocardiographic indicator (25) showing non-homogeneous spread of sinus stimulation, it also shows that inter- and intra-atrial conduction time is prolonged.

PASI was developed to evaluate the effectiveness of retinoid therapy in chronic plaque psoriasis (26). The prevalence (based on body surface area) and severity of psoriatic plaques are calculated by the physician separately for all four anatomical regions. The severity of erythema, desquamation and induration is scored in a 5-point system (0- no involvement, 1- mild, 2- moderate, 3- serious, 4- very serious). Values between 0 and 6 are assigned according to the percentage of involvement of the four anatomical regions. Zero- no involvement, 1=1-9%, 2=10-29%, 3=30-49%, 4=50-69%, 5=70-89%, 6=90-100%. The PASI score ranges from 0 to 72. High scores indicate more serious disease (27). PASI is one of the most validated scales in demonstrating the severity of psoriasis. Easy of application and good correlation with other objective scales are some of the advantages of the test. However, it is among the disadvantages of the score that it cannot always accurately predict the severity of the disease in terms of the patient and does not show a linear correlation with the severity of the disease (27). However, the score is frequently used in clinical evaluations of psoriasis. It is also used in the investigation of cardiovascular morbidity and mortality in psoriasis. In a study conducted by Al- Mutairi et al. (28), in which the data of 1,661 patients were examined, they showed that the risk of CAD was higher in patients with a PASI score of more than 10 compared to patients with a score of less than 10.

Study Limitations

The study has all the limitations of retrograde and observational studies. Another limitation is the low number of patients. By increasing the number of samples, the probability of type II error can be reduced. Another limitation of the study is that the study is single-centered. Increasing the number of centers and samples requires the study results to be approved in a larger study.

Conclusion

No significant relationship was identified between IAB and the PASI score, which was used for assessing the severity of psoriasis in this study. It was thought that the lack of relationship might be due to the constant variability of the PASI score. Our result needs to be confirmed with larger studies.

Ethics

Ethics Committee Approval: The study was approved by Bezmialem Vakıf University Ethics Committee (no:16/297).

Informed Consent: Informed consents were provided and the study was conducted according to the guidelines on clinical investigations of Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.B. A.E., R.Ö., Design: N.B., E.K., A.E., Data Collection or Processing: N.B., A.E., Analysis or Interpretation: N.B., E.K., R.Ö., Writing: N.B., E.K., R.Ö.

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

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ORIGINAL RESEARCH

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The Comparison of Two Versus More Than Two Tracts Percutaneous Nephrolithotomy for the Management of Staghorn Calculi

Staghorn Böbrek Taşlarının Yönetiminde İki ve İkiden Fazla Giriş Perkütan Nefrolitotominin Karşılaştırılması

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Abstract

Objective: In this study, we evaluated the outcomes of two tracts and more than two tracts for percutaneous nephrolithotomy (PCNL) performed in patients with staghorn calculus.

Method: We performed multi-tract PCNL on 132 patients with staghorn calculi, whose stone burdens varied between 7 and 28.2 cm^2 in our clinics between March 2015 and August 2019. We compared the outcomes and complications of multi-tract PCNL in two groups of patients. Group 1 included patients with two percutaneous tracts, while the patients in group 2 had more than two percutaneous tracts. Stone surface areas and locations were preoperatively recorded. Intraoperative data included number of tracts, blood transfusion rates and operative times. Postoperative stone-free rates (SFR) were also investigated.

Results: Group 1 included 93 patients, while group 2 included 39. The mean stone burden (MBS) was 10.4 cm^2 in group 1 and 11.3 cm^2 in group 2, with no statistical difference. Blood transfusion rates were 22.5% (21/93) in group 1 and 46.1% (18/39) in group 2 ($p<0.05$). The mean operative times were 135 min in group 1 and 168 min in group 2. SFR were 74.1% (69/93) and 74.3% (29/39), respectively, and there was no significant difference ($p=0.93$). Major complications were recorded in 4 patients (3.4%). In group 2, two patients had undergone angioembolization due to A-V fistula, and intubated thoracostomy was performed on 1 patient due to the development of hydropneumothorax.

Conclusion: Our study has demonstrated that performing more than 2 tracts for complete clearance of stones does not significantly increase SFR. In addition, increasing number of tracts is associated with higher blood transfusion rates, prolonged operative times and enhanced complication rates.

Keywords: Multiple tracts, PCNL, staghorn stones

Öz

Amaç: Bu çalışmadaki amacımız staghorn taşı olan hastalarda iki ve ikinin üzerinde giriş yapılan perkütan nefrolitotomi (PKNL) sonuçlarının ve komplikasyonlarının değerlendirilmesidir.

Yöntem: Kliniğimizde Mart 2015 ve Ağustos 2019 arası taş yükü 7 ve 28,2 cm^2 arasında değişen staghorn kalkül nedeniyle multipl giriş yapılan 132 hasta çalışmaya dahil edildi. Hastalar iki gruba ayrılarak multipl giriş PKNL sonuçları ve komplikasyonları incelendi. Grup 1'de iki giriş yapılan hastalar incelenirken, grup 2'de ikiden fazla giriş yapılan hastalar incelendi. Taş yüzey alanları ve lokasyonları operasyon öncesi kayıt altına alındı. Giriş sayıları, kan transfüzyon oranları ve operasyon zamanları intraoperatif veriler olarak kaydedildi. Postoperatif taşsızlık oranı kayıt altına alındı.

Bulgular: Grup 1 93 hastayı içerirken grup 2 39 hastayı içermekteydi. Ortalama taş yükü grup 1'de 10,4 cm^2 iken grup 2'de 11,2 cm^2 idi, istatistiksel olarak anlamlı fark saptanmadı. Kan transfüzyon oranı grup 1'de %22,5 (21/93) iken grup 2'de %46,1 (18/39) olarak saptandı ($p<0,05$). Grup 1 için ortalama operasyon süresi 135 dakika iken grup 2 için 168 dakika olarak saptandı ($p<0,05$). Taşsızlık oranı sırasıyla %74,1 (69/93) ve 4,3 (29/39) idi, iki grup arasında istatistiksel olarak anlamlı fark saptanmadı ($p=0,93$). Sadece dört hastada majör komplikasyon gelişti (%3,4). Grup 2'de iki hasta A-V fistül nedeniyle anjioembolizasyona gönderildi, bir hastaya da hidropnömotoraks nedeniyle torakostomi uygulandı.

Sonuç: Çalışmamız 2'den fazla girişin taşsızlık oranını anlamlı olarak yükseltmediğini ortaya koymuştur. Aynı zamanda giriş sayısı arttıkça kan transfüzyon oranı, operasyon süresinde uzama ve komplikasyon oranlarında artış gözlenmiştir.

Anahtar kelimeler: Multipl giriş, PKNL, staghorn böbrek taşı

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Introduction

Kidney stone is one of the most common diseases in daily urology practice. Thanks to the technological developments, PCNL, a minimally invasive method, is now preferred over open surgery for the management of kidney stones with its increased success and decreased complication rates. Nowadays, PCNL has taken its place as the first-line option for the management of large and multiple kidney stones, staghorn stones and lower calyceal calculi (1,2).

Although several studies compared the outcomes of single- and multi-tract PCNL previously (3,4), Chen et al. (5) reported that multi-tract PCNL assisted by EMS LithoClast master was safe and effective in achieving great stone clearance rate in one session, with acceptable morbidity for the treatment of staghorn calculi. In our study, we evaluated the outcomes of multi-tract PCNL of the management of staghorn calculi. The difference of our study from the others is the comparison of patients with two and more access tracts.

Materials and Methods

Patients

This retrospective study was carried out with the University of Health Sciences Turkey, Okmeydanı Training and Research Hospital Ethics Committee's approval dated 16.04.2019 and numbered 1,234. Informed consent form was obtained from all patients.

We compared the stone-free rates (SFR), morbidities and complications of 132 patients who underwent standard PCNL procedures for staghorn kidney stones in our clinics between March 2015 and June 2019 and who required multiple tracts at the same session. The comorbidities (hypertension, diabetes mellitus) of the patients were recorded. The patients were divided into 2 groups according to the number of tracts created to completely eliminate the stones (group 1 with 2 and group 2 with >2 access tracts). Two tracts were performed for 93 (70.4%) cases, while more than two tracts were performed for 39 (29.6%). The patients who underwent PCNL with more than two tracts were selected according to stone burden and stone location. Staghorn stones filling renal pelvis and extending to at least one calyx were defined as partial, and those filling renal pelvis and all calyces as complete staghorn stones. We included patients who underwent surgery due to kidney stones for the first time. Patients with solitary kidney and congenital kidney anomalies were excluded from the sample.

Intervention methods

Each patient was evaluated preoperatively with urine cultures, serum creatinine tests, urinary ultrasound, kidney-urinary bladder (KUB), intravenous pyelogram (IVP) and/or non-contrast upper abdominal computed tomography (CT). Patients with preoperative urinary infection detected in antibiotic susceptibility tests were treated accordingly to avoid any perioperative emergence of potential bacteremia.

During the procedure, all patients underwent prophylactic antibiotherapy. An open-end ureteral catheter was inserted endoscopically in the lithotomy position to deliver contrast material into the kidney subject to PCNL procedure, and to prevent the inadvertent escape of small stone fragments into the ureter during lithotripsy. After the patient was placed in the prone position and the kidney was fully outlined with the contrast material under fluoroscopic guidance, an 18-gauge needle was inserted through skin using the bull's eye technique. A co-axial dilator and a carrier sheath were placed over a guide wire previously inserted. The tract was dilated with a balloon catheter, inflated to 14 AP and threaded over a carrier catheter. Intracorporeal lithotripsy was achieved using an ultrasonographic (Storz) and/or pneumatic lithotripter (El-Med). The procedure was performed for the other calyx or calices in the same manner and terminated after the placement of a 14F Malecot nephrostomy tube. If an additional nephrostomy tube was suspected to be insufficient for complete drainage or bleeding in other tracts, these tracts were also intubated. After obtaining a nephrostogram, tubes were withdrawn during the postoperative period (Figure 1).

Measured Outcomes

Stone burden was calculated with preoperative KUB and non-contrast CT for non-opaque stones. In calculating

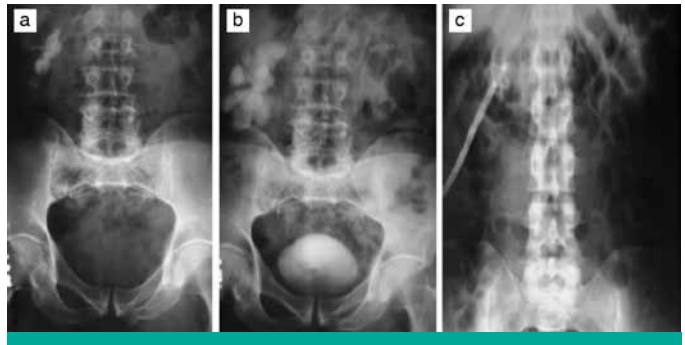

Figure 1. a) Kidney-urinary bladder X-ray b) Preoperative intravenous pyelogram c) Postoperative KUB X-ray of the staghorn stone

KUB: Kidney-urinary bladder

the stone burden, the largest length and largest width of the stone were used. Postoperative hemoglobin (Hb) loss, blood transfusion rates, complication rates, duration of operation and SFR were recorded in both groups. The patients were monitored at the 1st and 3rd months with KUB and non-contrast CT for non-opaque stones, hemogram, measurements of BUN, creatinine, and urinalysis. Stone free rate was measured by KUB or non-contrast CT at the postoperative 3rd month.

Statistical Analysis

Statistical analyses were performed using the Fisher's Exact test, chi-squared test and independent t-test for independent factors. $p<0.05$ was considered as statistically significant.

Results

One hundred thirty two renal units in 132 patients aged between 21 and 66 years (median age: 34.5 years) underwent standard PCNL in our clinics due to the presence of staghorn calculi (Table 1). There were 33 females and 99 males, with 36 complete and 96 partial staghorn stones removed. In total, 318 tracts were created to eliminate the stones from 132 renal units. Two-4 tracts were constructed for each renal unit. Two (n=93 pts), 3 (n=24 pts) and 4 (n=15 pts) access tracts were constructed. The mean preoperative Hb value was 14.18 g/dL (10.6-17.2 g/dL) (Table 1). The mean preoperative serum creatinine value was 0.96 mg/dL (0.51-3.36 mg/dL) (Table 1). The mean postoperative drop in Hb levels was 2.4 g/dL (1-7.2 g/dL). Blood transfusion was required for 26 (29.5%) patients. Rates of blood transfusion were 22.5% (14/62) and 46.1% (18/39) in groups with 2 and more than 2 tracts, respectively. When evaluated for the rate of blood transfusions, the incidence of bleeding was statistically significantly higher in group 2 ($p<0.05$).

Table 1. Patients' demographic data

Age, (years)	34.5 (21-66)
Female/male ratio	1:3
Hypertension	32 (24%)
Diabetes mellitus	30 (22.7%)
Preoperative mean Hb (g/dL)	14.18 g/dL (10.6-17.2 g/dL)
Preoperative mean creatinine value	0.96 mg/dL (0.51-3.36 mg/dL)
Drop in Hb	2.4 g/dL (1.4-7.2)
Duration of nephrostomy	2.42 (2-6) days
Time to discharge	5.2 (4-14) days

Hb: Hemoglobin

Our mean SFR was 64.7. SFR achieved at one session was 74.1% (69/93) in group 1 and 74.3% in group 2 (29/39). No statistically significant difference was seen between the two groups ($p=0.93$).

The MBS was 10.4 cm^2 (7-25 cm^2) in group 1 and 11.3 cm^2 (7.5-28.2 cm^2) in group 2. Stone burdens were similar between the groups ($p=0.88$). The mean operation times were 135 min in group 1 and 168 min in group 2, and these results were statistically significant ($p<0.05$).

In all patients, major complications were seen only in 4 (3.4%) (Table 2). In group 2, 3 patients had undergone angioembolization due to A-V fistula, and intubated thoracostomy was performed on 1 patient due to the development of hydropneumothorax. A 26 cm- long 4.8 F double J (DJ) ureteral catheter was placed in patients with residual stones of >0.7 cm detected on KUBs obtained on the postoperative 1st month, and they were then transferred to an Extracorporeal Shock Wave Lithotripsy (ESWL) unit. Ureterorenoscopy was performed and a DJ catheter was inserted in 3 patients due to the presence of ureteral stones. Nephrostomy tube was withdrawn in an average of 2.42 days after obtaining an antegrade renogram. The mean hospital stay was 5.2 days (4-14 days) (Table 1).

Discussion

Currently, PCNL is an increasingly prevalent treatment method with convenient long-term effectiveness and complication rates in the management of staghorn kidney stones. In a prospective, randomized study on 79 patients with staghorn calculi, where PCNL and open surgery were compared, PCNL blood loss, infection rates and hospital stay were found to be decreased, while SFR was similar (6). In two separate studies performed with the same aim, blood loss was stated to be less in PCNL compared to open surgery (7). In a retrospective study on

Table 2. Stone characteristics and postoperative outcomes

	2 tracts (93 patients)	>2 tracts (39 patients)	p
Mean stone burden	10.4 cm^2 (7-25 cm^2)	11.3 cm^2 (7.5-28.2 cm^2)	p=0.88
Stone free rate	74.1% (69/93)	74.3% (29/39)	p=0.93
Blood transfusion rate	21/93 (22.5%)	18/39 (46.1%)	p<0.05
Duration of operation (mins)	135 mins	168 mins	p<0.05
Major complication	None	3 A-V fistula 1 Hydropneumothorax	p<0.05

119 patients with staghorn calculi managed with PCNL, postoperative SFR was reported to be 80%, 87.5% and 84.8% based on the location and type of the staghorn stone. Multiple tracts were created on 33 patients (27.7%), and a seriously higher requirement for transfusion was noticeable (8,9). Winfield et al. (10) intended to send their patients home with minimal number of residual stone particles using multi-tract PCNL (up to 4 tracts) and other assisted management modalities in multiple sessions (up to 5). They reported an 86 % SFR within the first 6 months.

In a study where factors affecting blood loss after PCNL were investigated on 301 patients, 7.9% of the patients received blood transfusions, and diabetes, multiple tracts and prolonged operation time were indicated as factors increasing blood loss (11). In a study where factors effecting renal bleeding were investigated, the presence of staghorn calculi and multiple tracts were found to be among the most important etiologic factors (12). In a study investigating safety and the efficacy of multiple tracts in the presence of the staghorn stones in 149 patients, SFR and blood transfusion rates in one PCNL session were found to be 70.7% and 30.8%, respectively (13).

Thanks to its lesser morbidity along with SFR similar to those of open surgery, PCNL has become a valuable technique for the management of staghorn stones. It must not be forgotten that many authors have recommended the application of minimally invasive surgical principles (14). In studies performed, dimercaptosuccinic acid scanning (15) or IVP (16) demonstrated that endourological interventions did not affect postoperative renal function. PCNL is a prominently valuable intervention in the management of staghorn kidney stones. In staghorn calculi, the success of PCNL depends on the achievement of an optimal renal access. PCNL is highly effective when performed through a single tract, and it should not be forgotten that multiple tracts might result in increased blood loss, as shown in our study.

In our study, SFR was not different between the groups with 2 or more than 2 tracts, having nearly equal MBS. Inability to detect any statistically significant difference in SFR in the 2 groups with similar stone burdens led us to think that different calyceal locations of stones, rather than the stone burden, are a relatively more important factor in achieving improved SFR.

Besides, with increased number of tracts, increased blood transfusion rates, operation times and complications were noted. As in other studies, the number of tracts was determined as the most important factor influencing blood transfusion rates (8,9,11).

In a study where more than 1,000 cases were investigated for complications of PCNL, the incidence of major complications was found to be between 0.9 and 4.7 percent (17). In our study, major complication rate (3.4%) was similar to that of the mentioned study in the literature.

Our SFR rates achieved in one session were 74.1% in group 1 and 74.3% in group 2, which were lower than those found in other studies. In the recently updated American Urological Association Nephrolithiasis Guidelines panel on the Management of Staghorn Calculi, a mean SFR of 78% was established after PCNL monotherapy (1). Latest advances in instrumentation and technology have improved SFR, enhanced therapeutic effectiveness and decreased morbidity. Widespread use of flexible nephroscopy, and laser lithotripsy has lessened the number of tracts required for the management of staghorn calculi. Wong and Leveille used a rigid nephroscope for percutaneous access together with a flexible nephroscope and holmium: YAG laser lithotriptor through a single percutaneous access site for the management of 45 patients with partial or complex staghorn stones (18). They achieved a 95% SFR using an average of 1.6 procedures for each patient. Still, in our study, blood transfusion rates were found to be 22.5% in group 1 and 46.1% in group 2, which were higher than those reported in other trials. In the American Urological Association Nephrolithiasis Guidelines panel on the Management of Staghorn Calculi, a 14-24% blood transfusion rate was given for PCNL monotherapy (1).

The unavailability of flexible nephropscope and holmium YAG laser lithotripter in our clinics was in our opinion the most important reason for our lower SFR and higher blood transfusion rates compared to those mentioned in the literature. However, when we comparatively evaluated our patients with each other, we could not observe any superiority in regards to creating more than two tracts over 2 tracts in terms of SFR.

We believe that there is a need for further studies comparing the results of previous PCNLs and those performed using a flexible nephroscope and holmium YAG laser lithotripter in order to obtain more satisfactory outcomes.

Study Limitations

There were various limitations of our study, as it was a retrospective study with the limited number of patients. In addition, floroscopy time and postoperative pain score were not recorded in many patients, so these parameters

were not included in the study. If these parameters had been added, the article would have been better.

Conclusion

Although PCNL is the first-line alternative in the management of staghorn calculi aiming complete clearance of calculi, using more than 2 racts in PCNL does not achieve a significant increase in SFR. Besides, increasing the number of tracts is associated with higher blood transfusion rates, longer operation times and numerous other complications. In our opinion, it is crucial to achieve desirable stone-free rates using a minimal number of properly-placed tracts under the guidance of suitable and sophisticated technical equipment. This is an important factor preventing the patient from the burden of unnecessary morbidity.

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Ethics

Ethics Committee Approval: This study was carried out with the University of Health Sciences Turkey, Okmeydanı Training and Research Hospital Ethics Committee's approval dated 16.04.2019 and numbered 1,234.

Informed Consent: Informed consent form was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.E., Y.T.Ö., Design: M.E., Y.T.Ö., Data Collection or Processing: M.E., Y.T.Ö., Analysis or Interpretation: M.E., Literature Search: M.E., Writing: M.E.

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High Flow Nasal Oxygen Therapy in Pediatric Intensive Care Unit

Çocuk Yoğun Bakım Ünitesinde Yüksek Akışlı Nazal Oksijen Tedavisi

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Abstract

Objective: Acute respiratory failure is the most common reason for hospitalization to pediatric intensive care units. Invasive and non-invasive respiratory support methods are used for the treatment of patients with acute respiratory failure findings. The aim of this study is to evaluate the effectiveness of high flow nasal cannula (HFNC) oxygen therapy in pediatric intensive care.

Method: This retrospective observational study was conducted between February 2017 and January 2018 in pediatric intensive care unit of Bahçeşehir Liv Hospital, İstinye University Faculty of Medicine. Patients aged between 1 month and 18 years, who received HFNC oxygen therapy for respiratory support in the pediatric intensive care unit, were included in the study.

Results: HFNC therapy was received by 67 patients during one year of the study. 58.2% of the patients were male. The mean age of the patients was 37.2 months (R, 1-192), and their average body weight was 11.8 kg (R, 2.8-50). 65.7% of patients had an underlying disease. The most underlying disease was neurological disease with the rate of 35.8%. 94% of our patients received HFNC therapy due to acute respiratory failure, 3% due to acute heart failure and 3% due to shock. 40.3% of our patients received HFNC therapy due to pneumonia, 16.4% due to bronchopneumonia, 14.9% due to bronchiolitis, and 11.9% due to postextubation. 71.6% of patients receiving HFNC therapy improved their clinical findings without intubation. After HFNC therapy, there was a statistically considerable decrease in the respiratory rate, heart rate and retraction of the patients. HFNC therapy failure rates were statistically significantly higher in patients with underlying disease and especially in those with cardiac disease.

Conclusion: As a result, it is known that HFNC therapy has been used effectively in children in recent years, and it provides improvement in vital findings and blood gas parameters. In our study, 71.6% of our patients benefited from HFNC therapy.

Keywords: High flow nasal cannula oxygen therapy, pediatric intensive care, respiratory failure

Öz

Amaç: Çocuk yoğun bakım ünitelerine yatışın en sık nedeni akut solunum yetmezliğidir. Akut solunum yetmezliği bulguları olan hastalara tedavi amaçlı invazif ve non-invazif solunum destek yöntemleri kullanılmaktadır. Bu çalışmanın amacı çocuk yoğun bakımda yüksek akışlı nazal kanül oksijen (YANKO) tedavisinin etkinliğini değerlendirmektir.

Yöntem: Bu retrospektif gözlemsel çalışma, Şubat 2017 ile Ocak 2018 tarihleri arasında İstinye Üniversitesi Tıp Fakültesi, Bahçeşehir Liv Hastanesi, Çocuk Yoğun Bakım Ünitesi'nde gerçekleştirilmiştir. Bir ay ile 18 yaş arasında çocuk yoğun bakım ünitesinde solunum desteği amacıyla yüksek akışlı nazal kanül oksijen tedavisi alan hastalar çalışmaya alındı.

Bulgular: Bir yıllık çalışma süresi içerisinde 67 hastamız YANKO tedavisi aldı. Hastaların %58,2'si erkekti. Hastaların ortalama yaşları 37,2 ay (R, 1-192), ortalama vücut ağırlıkları 11,8 kg (R, 2,8-50) idi. Hastaların %65,7'sinde altta yatan bir hastalık vardı. En sık altta yatan hastalık %35,8 ile nörolojik hastalık grubu oluşturuyordu. Hastalarımızın %94'ü akut solunum yetmezliği, %3'ü akut kalp yetmezliği ve %3'ü şok nedeniyle YANKO tedavisi aldı. Hastalarımızın %40,3'ü pnömoni, %16,4'ü bronkopnömoni, %14,9'u bronşiolit, %11,9'u ekstübasyon sonrası akut solunum yetmezliği nedeniyle YANKO tedavisi aldı. YANKO tedavisi alan hastaların %71,6'sı entübe olmadan klinik bulguları düzeldi. YANKO sonrası hastaların solunum sayısı, kalp hızı, retraksiyon düzeylerinde istatistiksel olarak anlamlı düşüş saptandı. Altta yatan hastalığı olan ve özellikle kardiyak hastalığı olanlarda YANKO tedavisi başarısızlık oranları istatistiksel olarak anlamlı yüksek bulundu.

Sonuç: Sonuç olarak, son yıllarda YANKO tedavisinin çocuklarda etkin bir şekilde kullanıldığı, vital bulgular ve kan gazı parametrelerinde düzelme sağladığı bilinmektedir. Çalışmamızda hastalarımızın %71,6'sı YANKO tedavisinden fayda gördü.

Anahtar kelimeler: Çocuk yoğun bakım, solunum yetmezliği, yüksek akışlı nazal kanül oksijen tedavisi

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Introduction

Acute respiratory failure is one of the most important causes of mortality and morbidity in children, and it is defined as the inability of the respiratory system to provide adequate oxygen distribution or carbon dioxide excretion (1). The most common reason for hospitalization to pediatric intensive care units is acute respiratory failure. Invasive and non-invasive respiratory support methods are used for the treatment of patients with acute respiratory failure symptoms (2). Non-invasive respiratory support methods have become more preferable due to the disadvantages and high risk of complications associated with invasive mechanical ventilation (MV) (3). In the literature, most of the data on non-invasive MV are based on adult studies. Data on non-invasive MV treatment in children are limited (4,5). HFNC oxygenation therapy for non-invasive MV application in children is a treatment method that has found an increasing usage area both in the world and in our country. It is observed that this treatment, which was initially applied in preterm newborns, was started to be applied frequently in intensive care units, child and adult emergency services and other services over time (6-8). The aim of this study is to evaluate the effectiveness of HFNC oxygen therapy in pediatric intensive care.

Materials and Methods

This retrospective observational study was conducted between February 2017 and January 2018 in pediatric intensive care unit of Bahçeşehir Liv Hospital, İstinye University Faculty of Medicine. The efficacy of HFNC oxygen therapy was investigated in patients in need of respiratory support in a 19-bed pediatric intensive care unit where hospitalized critical pediatric patients aged between 1 month and 18 years. Treatment consent was obtained from the relatives of all patients in the intensive care hospitalization. Age, gender, body weights, underlying disease, reason for admission to intensive care, respiratory failure type, vital signs, blood gas values, reason for admission to HFNC therapy, HFNC application parameters, used prongs, vital signs before and after HFNC and blood gas values were examined. Whether patients received sedation during HFNC support, their nutritional status, and duration of stay at HFNC were evaluated. Success status of patients under HFNC therapy was recorded. Patients between the ages of 1 month and 18 years who had acute respiratory failure, shock, and who needed respiratory support after extubation were included in the study.

Patients with severe respiratory failure who needed intubation and patients with decompensated shock were excluded from the study. Fisher & Paykel Airvo 2 system (Fisher & Paykel Healthcare Ltd, New Zealand) device was used for HFNC treatment. Fisher & Paykel nasal cannulas suitable for age and weight were used. Ethics committee approval for this study was obtained from İstinye University.

Statistical Analysis

SPSS 15.0 windows program was used for statistical analysis. As descriptive statistics, numbers and percentages for categorical variables, and mean, standard deviation, minimum, maximum and median for numerical variables were given. Student's t-test was performed for two independent groups of numerical variables when normal distribution criterion was satisfied, and Mann-Whitney U test was performed when the two groups did not satisfy the normal distribution criterion. Paired t-test was performed for dependent group analysis of numerical variables when their difference satisfied the normal distribution criterion, and Wilcoxon analysis was performed when the criterion was not satisfied. Alpha significance level was regarded as $p<0.05$.

Results

HFNC therapy was received by 67 patients during one year of the study. The demographic characteristics of the patients are given in Table 1. 58.2% of the patients were male. The mean age of the patients was 37.2 months (R, 1-192), and their average body weight was 11.8 kg (R, 2.8-50). There was

Table 1. Demographic characteristics		n (%)
Gender	Male	39 (58.2)
	Female	28 (41.8)
Age (month)	-	37.2±48.2 (1-192)
Weight (kg)	-	11.8±11.0 (2.8-50)
Underlying disease	No	23 (34.3)
	Neurological disease	24 (35.8)
	Liver disease	1 (1.5)
	Cardiac disease	13 (19.4)
	Immune deficiency	1 (1.5)
	Malnutrition	3 (4.5)
	Other	2 (3.0)
The reason for hospitalization in intensive care	Respiratory failure	63 (94.0)
	Heart failure	2 (3.0)
	Shock	2 (3.0)
Respiratory failure type	Type 1	40 (61.5)
	Type 2	25 (38.5)

of patients n (%)

an underlying disease in 65.7% of the patients. The most underlying disease was neurological disease with the rate of 35.8%. 94% of our patients received HFNC therapy due to acute respiratory failure, 3% due to acute heart failure and 3% due to shock. 61.5% of patients with respiratory failure were in type 1 (hypoxic) respiratory failure.

40.3% of our patients received HFNC therapy due to pneumonia, 16.4% due to bronchopneumonia, 14.9% due to bronchiolitis, and 11.9% due to postextubation. The mean duration of HFNC treatment was 5.6 hours (R, 1-25), and the mean flow was 25.4 (R, 10-60) Lt/min. 76.1% of the patients did not receive sedation during HFNC therapy. Ketamine and midazolam were used in patients receiving sedation. 70.1% of the patients were fed under HFNC treatment. 71.6% of patients receiving HFNC therapy improved their clinical findings without intubation. HFNC therapy failed in 28.4% of our patients and they were intubated (Table 2).

Table 2. Features of HFNC therapy applied to children

		n (%)
HFNC indication	Pneumonia	27 (40.3)
	Bronchiolitis	10 (14.9)
	Bronchopneumonia	11 (16.4)
	Pulmonary edema	5 (7.5)
	Postextubation	8 (11.9)
	Aspiration	1 (1.5)
	Atelectasis	1 (1.5)
	Shock	2 (3.0)
	Hypoventilation	2 (3.0)
Duration of stay in HFNC	-	5.6±8.7 (1-25)
HFNC flow	-	25.4±12.1 (10-60)
FiO_2	-	80.7±8.8 (58-95)
Sedation	No	51 (76.1)
	Ketamine	11 (16.4)
	Midazolam	5 (7.5)
Nutrition	Yes	47 (70.1)
	No	20 (29.9)
Intubation	No	48 (71.6)
	Yes	19 (28.4)

HFNC: High flow nasal cannula, FiO_2: Fraction of Inspired Oxygen

Vital findings and blood gases of patients before and after HFNC treatment are shown in Table 3. After high flow nasal oxygen therapy, a decrease was found in the respiratory and heart rates of the patients. In addition, retractions decreased and there was an increase in saturation values. Considerable improvements in pH, PO_2 and saturation values were observed in blood gas parameters. Gender, age and weight were not statistically different in patients for whom the treatment was successful and failed. Table 4 shows that HFNC treatment failure rates were found to be statistically significantly higher in patients with underlying disease and especially in those with cardiac disease.

After HFNC, there was a statistically significant decrease in the respiratory rate, heart rate and retraction levels of the patients. Table 5 shows that systolic blood pressure, oxygen saturation, blood gas levels, pH, and oxygen saturation levels were statistically significantly increased (p=0.001, p<0.001, p=0.002 p<0.001, p=0.001, p=0.011, p=0.016, respectively).

Vital signs and blood gas parameters of the successful and unsuccessful patients after HFNC are given in Table

Table 3. Vital findings and blood gas levels before and after HFNC treatment

	Before HFNC		After HFNC	
	Mean ± SD	**Min-max (median)**	**Mean ± SD**	**Min-max (median)**
Respiration rate	43.2±16.2	20-90 (43)	34.5±13.3	16-100 (32)
Heart rate	149.2±25.5	77-199 (150)	127.1±23.0	70-180 (126)
Systolic blood pressure	102.9±18.0	44-142 (101)	108.4±14.8	83-143 (107)
Retraction	1.76±0.52	1-3 (2)	0.96±0.56	0-2 (1)
Oxygen saturation	95.6±5.0	79-100 (98)	98.0±3.6	82-100 (99)
Blood gases pH	7.36±0.14	6.81-7.63 (7.38)	7.40±0.07	7.25-7.62 (7.39)
PCO_2	46.4±19.5	20-132 (43)	43.4±10.2	26-74 (43)
PO_2	84.5±54.2	26-288 (65)	96.2±64.9	22-354 (86)
HCO_3	24.6±7.0	10-48 (24)	26.1±4.8	18-38 (25)
Lactate	2.23±1.57	0.6-6.9 (1.5)	2.09±2.10	0.7-13.8 (1.77)
Saturation	85.2±15.8	38-99 (91)	92.2±10.1	50-100 (97)

HFNC: High flow nasal cannula, SD: Standard deviation, pH: Power of hydrog

Table 4. Comparison of successful and unsuccessful groups in HFNC therapy

		Results		
		Successful	**Unsuccessful**	**p**
Gender	Male	25 (52.1)	14 (73.7)	0.106
	Female	23 (47.9)	5 (26.3)	
Age (month)		39.2±46.8 (21)	32.2±52.7 (5)	0.159
Weight (kg)		12.8±11.2 (7.75)	9.1±10.2 (6)	0.109
Underlying disease		27 (56.3)	17 (89.5)	0.010
	Neurological disease	16 (33.3)	8 (42.1)	0.500
	Liver disease	1 (2.1)	0 (0.0)	1.000
	Cardiac disease	6 (12.5)	7 (36.8)	0.038
	Immune deficiency	1 (2.1)	0 (0.0)	1.000
	Malnutrition	1 (2.1)	2 (10.5)	0.192
	Other	2 (4.2)	0 (0.0)	1.000
The reason for hospitalization in intensive care	Respiratory failure	44 (91.7)	19 (100)	1.000
	Heart failure	2 (4.2)	0 (0.0)	-
	Shock	2 (4.2)	0 (0.0)	-
Respiratory failure type	Type 1	28 (60.9)	12 (63.2)	0.863
	Type 2	18 (39.1)	7 (36.8)	-

HFNC: High flow nasal cannula

Table 5. Mean-standard deviation- 95% minimum-maximum levels of vital signs and blood gas changes before and after HFNC

		95% CI		
Difference before and after HFNC	**Mean ± SD**	**Min**	**Max**	**p**
Respiration rate	7.30±14.74	2.97-	11.62	0.001
Heart rate	19.03±26.32	9.38-	28.69	<0.001
Systolic blood pressure	-9.00±13.79	-13.19-	-4.81	<0.001
Retraction	0.77±0.44	0.50-	1.03	0.002
Oxygen saturation	-2.68±4.41	-4.09-	-1.26	0.001
Blood gases	-0.06±0.14	-0.10-	-0.01	0.011
pH				
PCO_2	5.69±19.89	-0.36-	11.73	0.086
PO_2	-15.71±71.92	-38.71-	7.29	0.175
HCO_3	-1.18±4.27	-2.48-	0.12	0.073
Lactate	0.56±1.54	0.03-	1.09	0.080
Saturation	-7.83±17.59	-13.38-	-2.28	0.016

HFNC: High flow nasal cannula, SD: Standard deviation, CI: Confidence interval

Table 6. Vital signs and blood gas values of the successful and unsuccessful patients after HFNC

	Successful	**Unsuccessful**	**p**
Respiration rate	42.1±15.3 (42)	46.6±18.6 (47)	0.333
Heart rate	150.1±24.2 (151)	146.5±29.6 (146)	0.633
Systolic blood pressure	104.0±15.7 (103)	99.3±24.6 (99)	0.396
Retraction	1.68±0.58 (2)	2.00±0.00 (2)	0.160
Oxygen saturation	95.2±5.2 (97)	97.0±4.4 (100)	0.170
Blood gases			
pH	7.37±0.11 (7.38)	7.33±0.20 (7.39)	0.957
PCO_2	42.8±15.8 (41)	55.3±24.8 (49.5)	0.039
PO_2	87.3±58.8 (66)	76.7±38.9 (64)	0.898
HCO_3	23.4±5.7 (24)	27.6±9.1 (27)	0.075
Lactate	2.37±1.62 (1.6)	1.86±1.40 (1.4)	0.203
Saturation	86.3±15.6 (93.5)	82.6±16.5 (87)	0.362

HFNC: High flow nasal cannula

6. Respiratory rate, heart rate, systolic blood pressure, retraction and saturation values between the two groups were not statistically different. There was no statistical difference performed between two groups in blood gas parameters of pH, PO_2, HCO_3, lactate and saturation values. In the unsuccessful group, the mean PCO_2 in blood gas before HFNC was found to be statistically significantly higher than the patients who succeeded (p=0.039).

Discussion

HFNC therapy has been widely used in adults in recent years. In adults, HFNC therapy is used due to acute hypoxemic

respiratory failure, post-extubation respiratory support, oxygenation before intubation or before bronchoscopy, postoperative respiratory failure and acute pulmonary edema. Many studies of HFNC therapy in bronchiolitis in children have been reported. In addition, there have been studies reporting usage of HFNC therapy for asthma, sleep apnea, pneumonia, critical child patient transport, and postextubation respiratory support (9). The number of studies in the literature on HFNC therapy in the pediatric intensive care unit is very low.

In our study, 67 patients received HFNC treatment within 1 year. In our study, 71.6% of our patients benefited from HFNC therapy. In the study conducted by McKiernan et al. (10) it was showed that intubation rates of patients decreased from 23% to 9% with HFNC therapy. In the retrospective study of Schibler et al. (11), which was performed on intensive care patients with viral bronchiolitis, it was observed that the intubation rates of patients decreased from 37% to 7% with HFNC therapy.

We conducted our study in a heterogeneous group of patients (underlying disease, reason for hospitalization in intensive care, respiratory failure type, etc.). 65.7% of patients had an underlying disease. The most underlying disease was neurological disease with the rate of 35.8%. Cardiac disease was the second most frequent with the rate of 19.4%. 94% of our patients received HFNC therapy due to acute respiratory failure, 3% due to acute heart failure and 3% due to shock. 61.5% of patients with respiratory failure were in type 1 (hypoxic) respiratory failure. HFNC treatment failure rate was higher in patients with underlying disease. In similar studies conducted earlier, failure rates were reported to be high in patients with underlying disease (2,12,13).

Many studies have been reported in the literature showing improvement in patients vital signs and blood gas values after HFNC therapy (14-17). In our study, a statistically significant decrease was found in the respiratory rate, heart rate and retraction levels of patients after HFNC therapy. Similarly, there was a statistically significant increase in pH and saturation levels from blood pressure, oxygen saturation, blood gas evaluations.

There are scarce data on non-invasive respiratory support for pediatric patients who develop respiratory failure after extubation (2,12). In our study, the success rate of patients who received HFNC therapy postextubation was 75%.

Study Limitations

I would like to inform you that it is a retrospective, non-randomized study. It has not been done in a single patient group. Most of our patients had an underlying disease. Bilevel positive airway pressure and continuous positive airway pressure could be tried in the group that failed HFNC. Multi-center prospective and randomized controlled studies are needed on the use of HFNC in the pediatric intensive care units.

Conclusion

It is known that HFNC therapy has been used effectively in children in recent years, and it provides improvement in vital findings and blood gas parameters. In our study, 71.6% of our patients benefited from HFNC therapy. We think that HFNC therapy should be used more frequently in pediatric intensive care units to prevent intubation in cases such as acute respiratory failure, heart failure and shock.

Ethics

Ethics Committee Approval: Ethics committee approval for this study was obtained from İstinye University (no:2/2020.K-036, date: 21.05.2020).

Informed Consent: Treatment consent was obtained from the relatives of all patients in the intensive care hospitalization.

Peer-review: Externally peer-reviewed.

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

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ORIGINAL RESEARCH

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Should I Perform an Electroencephalography in Patients with Syncope?

Senkoplu Hastalarda Elektroensefalografi Yapmalı Mıyım?

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Abstract

Objective: Temporary loss of consciousness that occurs with temporary global cerebral hypoperfusion is defined as syncope. Infrequent changes can be seen in electroencephalography (EEG) during syncope. These EEG changes and findings are in the form of symmetric slowed-waves, spikes, or spike-wave complexes. In this study, the results and necessity of EEG in patients who applied to the neurology outpatient clinic with the complaint of syncope were evaluated.

Method: In this study, the EEG results of 261 patients aged 17-86 years, who were evaluated in the general neurology outpatient clinic with the diagnosis of syncope between September 2018 and March 2019, were retrospectively analyzed. Patients with epilepsy were excluded. Data were obtained considering the demographic characteristics of the patients, comorbidities, the absence of epilepsy diagnosis, and the drugs they used.

Results: Of the 261 syncope patients, 77% (n=201) had normal EEG findings, while 16.5% (n=43) had symmetric slowed-waves and sharply-contoured waves, 1.5% (n=4) had sharp and sharply-contoured waves, 1.5% (n=4) had focal slowed-waves, and 3.4% (n=9) had spike, and spike-wave complexes.

Conclusion: In the diagnosis of patients presenting with syncope, taking a detailed history and questioning the background, first cardiovascular examination are more instructive than EEG. EEG should be performed in patients who cannot be decided with their clinic. Despite this, if it is still not sure, the diagnosis of epilepsy should be postponed and patients should be called for frequent control.

Keywords: Electroencephalography, epilepsy, seizure, syncope

Öz

Amaç: Geçici global serebral hipoperfüzyon ile ortaya çıkan geçici bilinç kaybı senkop olarak tanımlanmaktadır. Senkop esnasında elektroensefalografide (EEG) sık olmayan değişiklikler görülebilir. Bu EEG değişiklikleri ve bulguları simetrik yavaşlama, diken ya da diken-dalga kompleksleri şeklindedir. Bu çalışmada, senkop şikayetiyle nöroloji polikliniğine başvuran hastalarda yapılan EEG sonuçları ve gerekliliği değerlendirildi.

Yöntem: Bu çalışmada, Eylül 2018-Mart 2019 arasında senkop tanısı ile genel nöroloji polikliniğinde değerlendirilen 17-86 yaş aralığında 261 hastanın, EEG sonuçları retrospektif olarak incelendi. Hastaların demografik özellikleri, ek hastalıkları, epilepsi tanısının olmaması ve kullandıkları ilaçlar dikkate alınarak veriler elde edildi.

Bulgular: Hastaların %77'sinin (n=201) EEG'si normaldi. Hastaların %16,5'inde (n=43) simetrik yavaşlama ve keskin karakterli dalgalar, %1,5'inde (n=4) keskin ve keskin karakterli dalgalar, %1,5'inde (4) fokal yavaşlık ve %3,4'ünde (9) diken, diken-dalga kompleksleri izlendi.

Sonuç: Senkop ile başvuran hastalarda teşhiste, ayrıntılı öykü alınması ve özgeçmiş sorgulanması, öncelikle kardiyovasküler inceleme yapılması, EEG'den daha yol göstericidir. Kliniği ile karar verilemeyen, arada kalınan hastalarda EEG yapılmalıdır. Buna rağmen yine de emin olunmazsa epilepsi tanısı ertelenmeli, hastalar sık kontrole çağrılmalıdır.

Anahtar kelimeler: Elektroensefalografi, epilepsi, nöbet, senkop

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Introduction

The loss of consciousness is a frequent cause of emergency room visits in the general neurology practice. It is important to determine whether it is associated with an underlying neurological disorder.

Syncope is a temporary loss of consciousness because of general cerebral hypoperfusion that is characterized by rapid onset, short course, and spontaneous full recovery (1,2). Syncope can be categorized into three main groups as reflex (neurally mediated), orthostatic, and cardiovascular syncope. Reflex syncope is generally subdivided into two types (i.e. sympathetic and parasympathetic) based on the efferent pathways involved; vasovagal syncope is also a type of reflex syncope (3).

Vasovagal syncope is associated with reduced cardiac output resulting from bradycardia and reduced vasoconstriction due to the activation of the autonomous nervous system (4). Signs and symptoms of syncope may present in two distinct categories. The first category involves those that are related to the cause of syncope, such as palpitations as in arrhythmia and paleness in reflex symptom. On the other hand, the second category is related with the results of cerebral and retinal hypoperfusion, and involves visual disturbance, blurred consciousness, and motor effects such as the loss of voluntary motor control, myoclonic jerks, as well as stiffness (4,5).

Of all syncope events, 12% are accompanied by seizure-like symptoms due to the global cerebral hypoperfusion (6). Again, inter-ictal changes of electroencephalography (EEG) have been reported in up to 30% of these patients (7).

In this study, patients diagnosed with syncope by virtue of anamnesis, physical examination, and electrophysiological and cardiological investigations were evaluated.

Materials and Methods

Results of neurological examination, EEG, cranial magnetic resonance imaging (MRI), cardiologic examination, and systemic diseases were retrospectively evaluated among patients aged between 17 and 85 years, presenting to our neurology outpatient unit between September 2018 and March 2019. In hospital, patients who are at the age of 17 years and older are examined in adult neurology department. Patients who are children under the age of 16 years are evaluated by pediatric neurology department.

Inclusion criteria were for patients who had not previously been diagnosed and treated for syncope. Patients with diabetes mellitus characterized by recurrent episodes of hypoglycemia/hyperglycemia, known cardiac conduction disorders, epilepsy, history of cerebrovascular disorder, and intracranial mass lesion disorders were excluded.

Demographic characteristics of patients were recorded. Also, medication history, particularly drugs that could affect the orthostatic tolerance, was recorded.

Statistical Analyses

Statistical analysis was carried out using a SPSS® (Statistical Package for Social Sciences) 22.0 for Windows and Mac os x. Categorical variables were expressed as frequency distribution, and continuous variables as descriptive statistics [mean ± standard deviation (SD)]. The difference between the two independent groups for variables with normal distribution was tested using the Independent Sample t-test, while the Mann-Whitney U test was used for variables without normal distribution. The association between two independent categorical variables was evaluated with the chi-square test. Categorical variables were expressed as N (%), while variables with normal distribution were expressed as mean (± SD) and variables without normal distribution were expressed as median (minimum-maximum). A p-value less than 0.05 was considered statistically significant.

Results

Two hundred sixty one syncope patients (median age: 38 years, range 17-86 years) were assessed between September 2018 and March 2019. Of the participants, 47.5% (n=124) were female and 52.5% (n=137) were male. The male and female patients were comparable in terms of median age [39 (18-86), 37.7 (17-84)] (p=0.482). There was no gender difference between those with EEG pathology (p=0.884) (Table 1).

There were no drugs affecting orthostatic tolerance such as tricyclic antidepressant, monoamine oxidase inhibitor, antipsychotic, diuretic, α-adrenergic receptor blocker.

Table 1. Demographic characteristics of syncope patients

	Gender (261, %)		p
	Female 124 (47.5%)	Male 137 (52.5%)	
Age 38 (17-86)	37.5 (17-84)	39 (18-86)	0.482
EEG abnormality	29 (48.3%)	31 (51.7%)	0.884

EEG: Electroencephalography

Only, drugs containing α-adrenergic receptor blocker or diuretic were used for a long time in 14 patients. EEG results of patients using these drugs were normal.

One of our female patients had maternal history of seizures/pseudo-seizures. Her EEG result was normal.

Of all the patients, an EEG normality was detected in 77% (n=201). Among these 261 patients, sleep-deprived EEG was performed in 19.1% (50) patients with suspected EEG abnormality and clinically undetermined status, and the results of 18% (n=47) were normal and only 1.1% (n=3) were pathological findings.

In EEG, 16.5% (n=43) of the patients had symmetric slowed-waves and sharply-contoured waves, 1.5% (n=4) had sharp and sharply-contoured waves, 1.5% (n=4) had focal slowed-waves, and 3.4% (n=9) had spike, and spike-wave complexes (Table 2).

Doppler ultrasonography was performed in 13.4% (n=27) of the patients with normal EEG, and that showed occlusion (left internal carotid artery) in 1 patient, stenosis in 2 patients (1 of them, started treatment because of significant ischemic risk associated with >50% contraction), plaque in 7 patients (1 of them was started treatment because of ulcerated soft plaque) (Table 3).

A cranial MRI was performed to rule out possible cerebrovascular disorders, intracranial mass lesions, and other disorders. Cranial MRI in patients with EEG abnormalities showed no intracranial pathology that could be associated with syncope. But interesting point is that EEG abnormality was found in patients with significant MRI pathology. However, besides that, MRI of 68.3% (n=41) of syncope patients with EEG abnormality was normal (Table 4).

At the same time, patients with normal EEG were referred to cardiology unit considering cardiogenic syncope. Blood pressure Holter and echocardiography was performed in 24.4% (n=49) of the patients. Cardiac pathology was found in 11 (5.5%) patients.

In summary, among all patients, EEG normality was found in 77% (n=201), and results were pathological in 23% (n=60) of patients.

When EEG results were classified as (1) normal, (2) slow waves, and (3) epileptiform discharges (spike/sharp waves), among all the EEG reports, 77% (n=201) were normal, 16.5% (n=43) of them were slow waves, and 6.5% (n=17) of them were found epileptiform discharges (spike/sharp waves).

Table 2. EEG results in patients with syncope

	EEG				
Syncope	**Normal**	**Symmetric slowed-waves and sharply-contoured waves**	**Sharp and sharply-contoured waves**	**Focal slowed-waves**	**Spike, spike-wave complex**
n=261 (100%)	201 (77%)	43 (16.5%)	4 (1.5%)	4 (1.5%)	9 (3.4%)

EEG: Electroencephalography

Table 3. Carotid artery/vertebral artery Doppler US results in 36 syncope patients

	Normal	**Plaque**	**Stenosis**	**Occlusion**
n=36 (23.8%)	23 (8.8%)	9 (3.4%)	3 (1.1%)	1 (0.4%)

US: Ultrasound

Table 4. Cranial MRI results with EEG in syncope patients

	EEG	
Cranial MRI	**Normal**	**Abnormal**
Normal	160 (79.6%)	41 (20.4%)
Non-specific ischemic-gliotic foci	26 (78.8%)	7 (21.2%)
Ischemic encephalomalastic area	12 (60%)	8 (40%)
Arachnoid cyst	2 (66.7%)	1 (33.3%)
Megasisterna magna	1 (50%)	1 (50%)
Meningioma	0 (0%)	1 (100%)
Hippocampal atrophy/mesial temporal sclerosis	0 (0%)	1 (100%)

EEG: Electroencephalography, MRI: Magnetic resonance imaging

Discussion

Syncope is a temporary loss of consciousness because of general cerebral hypoperfusion and is characterized by its short course, complete spontaneous recovery and postural loss of tone (1,2,8). It represents the main symptom in 3% of all emergency room visits (8).

In vasovagal syncope, the reduced venous return to the heart triggers the reflex by decreasing the end-diastolic left ventricular volume. Powerful contractions in the face of low ventricular volume stimulates the cardiac mechano-receptors. C-fibers emerging from these receptors are conveyed to the brainstem, leading to parasympathetic stimuli (9).

Generally, EEG examination in syncope patients is normal. In this study, 77% of EEG results of syncope patients are normal. Approximately 12% of all syncope cases, seizure like symptoms may occur due to global cranial hypoperfusion (6). If the acute phase is prolonged, syncope may be associated with the convulsive phenomena and may be confused with epilepsy (10). This is probably one of the reasons for the increase in EEG examinations performed in syncope patients.

Several convulsion-related findings such as myoclonic contractions, tonic spasms, or urinary incontinence may occur even in cardiovascular syncope; however, these are generally less severe and short-lived. In addition of these, these patients do not experience the confusion following an episode, and autonomic signs are more marked (11,12). Thus, EEG is commonly requested particularly in patients with recurrent syncope or in those with convulsive phenomena after prolongation of the acute phase on the basis of the suspicion of epileptic seizures (10). There was no recurrent syncope history among the patients included in the study.

In this study, there was no statistically significant female/male difference among the patients. Although previous studies suggested a female predominance among patients presenting with syncope (13), there was a higher number of male patients in our study; however, the difference was not significant (p=0.421). In addition, it has been reported that syncope risk increases equally in children of mothers with syncope and fathers increase risk only in boys (13). Also, there was no gender difference between those with EEG pathological (p=0.884) (Table 1).

In epilepsy patients, EEG is important in supporting the diagnosis and monitoring of the patients with epilepsy diagnosis, but in epilepsy, the diagnosis is made clinically and EEG abnormalities do not suffice for a diagnosis. Interictal changes in EEG have been reported up to 30% in patients with syncope. These changes are generally diffuse or focal slowed-waves in the anterior regions of the head, and rarely spike or spike wave complexes (7). In our study, 60 (23%) patients with abnormalities in interictal EEG were found. Of abnormalities in interictal EEG; 16.5% (n=43) of them were slow waves, and 6.5% (n=17) of them were found to be epileptiform discharges (spike/sharp waves).

During syncope, EEG is more often seen as ‘‘slow-flat-slow’’ or ‘‘slow’’ pattern. In particular, the slow-flat-slow pattern is related to deeper circulation, loss of longer consciousness, lower minimum blood pressure, RR-interval longer than the maximum and more associated with asystole, thus more severe hypoperfusion (5). In our study, in syncope patients, the EEG result was pathological in 23% (n=60) of patients, and 16.5% (n=43) of them were slow waves, and 6.5% (n=17) of them were found to be epileptiform discharges (spike/sharp waves).

Excluding epilepsy requires attention in syncope patients. In addition to epilepsy, EEG can also be helpful in assessing the consciousness of patients with asystole. If the duration of asystole is more than six seconds, syncope occurs frequently and is strongly associated with ictal syncope. Ictal syncope is more common in the left temporal seizures than in the right one (14). EEG slowed-waves were observed in patients with asystole, and syncope developed a few seconds after this slowed-waves. It was also found that the first EEG slowed-waves developed before the period of unconsciousness with syncope (15). In some patients, ictal syncope may be the earliest sign of epilepsy (16). This is also confusing.

In some cases, even pseudosyncope is encountered. The EEG in psychogenic pseudosyncope is typically normal or increased myogenic artifact with no suppression of background waveforms. But in the course of neural mediated syncope, it firstly shows a slowing of background rhythms and thereafter high-amplitude delta activity may progress to flattening appropriate with cerebral hypoperfusion (16).

In all these cases, EEG is used. The use of EEG increases the complexity of diagnosis, treatment, and cost, while neglecting the clinic.

Most of our patients were diagnosed as cardiogenic and vasovagal syncope after our examination. We found that environmental factors were more effective in patients with vasovagal syncope. Among these factors, stress, hunger, long-standing, and warm environment were the most. As

a very remarkable result, only 6.1% (n=16) of our patients were diagnosed with seizure and treated for epilepsy.

Study Limitations

Our study has a limitation. Firstly, since this was a retrospective study, thus, the syncope was mostly reported by the patient, and no additional information could be obtained from patients' families. This situation precluded clinical assessment of the patients in point of epileptic seizures.

Conclusion

Since EEG recordings and/or video-EEG monitorization and even Holter as well as Tilt-table tests during syncope will be more informative clinically and so prospective studies are needed.

In the diagnosis of syncope patients, detailed anamnesis, medical history, and cardiovascular examination will provide more valuable information than EEG. In undetermined cases, an EEG should be performed. If the diagnosis is still obscure, the diagnosis of epilepsy should be delayed and the patient should be closely monitored.

Ethics

Ethics Committee Approval: The study was carried out according to the Helsinki Declaration and was approved by the Institutional Local Ethics Committee, University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital (2019-71/01).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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ORIGINAL RESEARCH

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CYP2C19*1 and CYP2C19*2 Polymorphism in Turkish Patients Being Diagnosed with Stable Coronary Artery Disease and Using Clopidogrel

Clopidogrel Kullanan, Koroner Arter Hastalığı Tanısı Mevcut Olan Türk Popülasyonunda CYP2C19*1 ve CYP2C19*2 Gen Polimorfizmi

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Abstract

Objective: The CYP2C19*1 has an entirely normal activity allele whose clopidogrel metabolism is normal. CYP2C19*2 called as non-functional alleles. In this study, we aimed to establish the CYP2C19*1 and CYP2C19*2 genotype frequencies both in Turkish patients with coronary artery disease (CAD), who used clopidogrel, and in healthy Turkish population as well as to present the differences in genotypes and alleles between both groups.

Method: One hundred healthy individuals and 200 patients diagnosed with CAD were included in the study. DNA was isolated and *CYP2C19* gene was amplified through the polymerase chain reaction method in the genomic DNAs obtained, and the polymorphic foci in these regions were specified.

Results: CYP2C19*1/1 genotype was identified in 132 patients (66%), CYP2C19*1/2 genotype in 62 patients (31%) and CYP2C19*2/2 genotype in 6 patients (3%) in the CAD group. In the control group, by contrast, 72 patients (72%) were identified with CYP2C19*1/1 genotype, 20 patients with CYP2C19*1/2 genotype and 8 patients with CYP2C19*2/2 genotype. There was a significant difference between the groups in terms of genotypes (p=0.034).

Conclusion: We found CYP2C19*1/2 and CYP2C19*2/2 genotype to be higher in the CAD patients than in the control group, highlighting the importance of checking *CYP2C19* gene polymorphism prior to the initiation of antiplatelet therapy in CAD patients.

Keywords: Clopidogrel metabolism, coronary artery disease, CYP2C19 polymorphism, Turkish population

Öz

Amaç: CYP2C19*1, klopidogrel metabolizması normal olan tamamen normal bir aktiviteye sahiptir. CYP2C19*2, işlevsel olmayan aleller olarak adlandırılır. Bu çalışmada, hem klopidogrel kullanan ve koroner arter hastalığı (KAH) olan Türk hastalarda hem de sağlıklı Türk popülasyonunda CYP2C19*1 ve CYP2C19*2 genotip frekanslarını belirlemeyi ve her iki grup arasındaki genotip ve alel farklılıklarını sunmayı amaçladık.

Yöntem: Çalışmaya 100 sağlıklı birey ve KAH tanısı almış 200 hasta dahil edildi. DNA izole edilerek ve *CYP2C19* geni polimeraz zincirleme reaksiyonu yöntemi ile amplifiye edilerek bu bölgelerdeki polimorfik odaklar belirlendi.

Bulgular: KAH grubunda 132 hastada (%66) CYP2C19*1/1 genotipi, 62 hastada (%31) CYP2C19*1/2 genotipi ve 6 hastada (%3) CYP2C19*2/2 genotipi tespit edildi. Kontrol grubunda ise 72 hasta (%72) CYP2C19*1/1 genotipi, 20 hasta CYP2C19*1/2 genotipi ve 8 hasta CYP2C19*2/2 genotipi ile tanımlanmıştır. Genotipler açısından gruplar arasında anlamlı fark vardı (p=0,034).

Sonuç: KAH hastalarında CYP2C19*1/2 ve CYP2C19*2/2 genotipinin kontrol grubuna göre daha yüksek olduğunu belirledik. Bu da koroner arter hastalarında antiplatelet tedaviye başlamadan önce *CYP2C19* gen polimorfizminin bakılmasının önemli olduğunu vurgulamaktadır.

Anahtar kelimeler: CYP2C19 polimorfizmi, klopidogrel metabolizması, koroner arter hastalığı, Türk popülasyonu

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Introduction

Irreversibly inhibiting the platelet P2Y12 receptor, thienopyridines are used as antithrombotic agents in the treatment of CAD, peripheral vascular and cerebrovascular diseases (1,2). Besides, clopidogrel is known as the most frequently used agent among thienopyridine drugs. Clopidogrel, which acts as a prodrug, proves an effective inhibitor of platelet aggregation due to the selective and irreversible blocking of the P2Y12 receptor in the platelet cell membrane. Moreover, its intestinal absorption is limited by a bowel effusion P-glycoprotein pump encoded by the *ABCB1* gene (1,2). Approximately 85% of this drug is hydrolyzed to an inactive metabolite by the esterases, while the remaining 15% is oxidized by the cytochrome P450 enzyme system and converted into active metabolite (thiol derivative-R-130964). As is well-known, the biotransformation of clopidogrel is made out of two steps. In addition, cytochrome P450 enzymes involved in clopidogrel biotransformation can be listed as CYP2C19, CYP2C9, CYP2B6, CYP3A4 and CYP1A2 (1,2).

Situated in the 10th chromosome (10q24.1-10q24.3), the genetic localization, where the CYP2C19 enzyme is coded, is 1.473 base pairs in length. This gene contains 9 exons and encodes a protein composed of 490 amino acids (1).

The Food and Drug Administration (FDA) describes the different alleles of CYP2C19 and their effects as follows: although the CYP2C19*1 allele is an ancestral type, it is a completely normal activity allele of clopidogrel, and also its clopidogrel metabolism is normal. Known as non-functional alleles of clopidogrel, CYP2C19*2 and CYP2C19*3 are termed as alleles deprived of a metabolism (clopidogrel resistance). The CYP2C19*4, CYP2C19*5, CYP2C19*6, CYP2C19*7 and CYP2C19*8 alleles may be deprived of clopidogrel metabolism or have low clopidogrel metabolism. With this warning, the FDA emphasizes that patients should be treated with clopidogrel by considering the genetic differences in CYP2C19 function (3).

The allele with normal activity is CYP2C19*1. On the other hand, the CYP2C19*2 polymorphism is the splicing damage mutation (rs4244285) resulting from the change of guanine adenine (G→A) at nucleotide position 681 of the cDNA sequence in exon 5. Altering the reading frame of the mRNA that starts with the amino acid 215, this change forms a non-functional protein by creating a stop code in the downstream region with 20 amino acids (1,2). The conversion of the prodrug clopidogrel into the active metabolite is inhibited, resulting in clopidogrel resistance.

To date, a considerable literature has grown up around the theme of the ethnic differences in the CYP2C19 genotype and its prevalence (4-15). It is now well established from a variety of studies that *CYP2C19* gene polymorphism is associated with clopidogrel resistance in patients using clopidogrel due to CAD. In addition, the existing body of research suggests that there are differences in CYP2C19 genotype in the group with CAD.

To this respect, the specific objective of this study is to establish the CYP2C19*1 and CYP2C19*2 allele frequencies both in Turkish patients with CAD, who thus use clopidogrel, and in healthy Turkish population as well as to present the differences in genotypes and alleles between both groups.

Materials and Methods

Having been approved by the Pamukkale University Ethics Committee, the study included 100 healthy volunteers and 200 patients diagnosed with CAD and using clopidogrel, all of whom lived in Denizli. A total of 300 individuals (100 controls and 200 patients) were informed about the informed consent of the Helsinki Declaration. All the individuals and patients consented, in writing, for the study after full explanation of what was involved. Written consent form was signed by all the participants (patients and control groups). This study is a prospective case-control study.

Data Collection

The data of the patients' age, gender and number of angiographic interventions were recorded in the data set.

Blood collection and DNA isolation

Initially, genomic DNA was isolated with standard phenol-chloroform method by taking blood into the anticoagulated (K3EDTA) vacuum tubes. Subsequently, the region specific to the *CYP2C19* gene was amplified through the polimerase chain reaction method in the genomic DNAs obtained, and the polymorphic foci in these regions were specified (4).

Statistical Analysis

SPSS statistical software version 23.0 was used for data analysis. Goodness of fit test was used for analyzing the distribution of the alleles and genotypes. Fisher's Exact and chi-square tests were used to compare the allele and genotype frequencies. Descriptive analysis was used to compare allele frequencies between the Turkish population and published data of other ethnic groups. A value of $p<0.05$ was considered as statistically significant.

Results

Table 1 presents the breakdown of data for the CAD group and the control group as well as the data for the Goodness of fit test according to the Hardy Weinber distribution. When the CAD patients and control group were evaluated together, CYP2C19*1/1 genotype was detected in 204 subjects (68%), followed by CYP2C19*1/2 genotype in 82 subjects (27.3%) and CYP2C19*2/2 genotype in 14 subjects (4.6%).

The CYP2C19*1 allele frequency was 490 (81.6%), whereas that of CYP2C19*2 was 110 (18.3%). As far as the genotype frequencies of the groups were concerned, CYP2C19*1/1 genotype was found in 132 patients (66%), CYP2C19*1/2 genotype in 62 patients (31%) and CYP2C19*2/2 genotype in 6 patients (3%) in the CAD group. On the other hand, there were 72 subjects (72%) with CYP2C19*1/1 genotype, 20 subjects with CYP2C19*1/2 genotype and 8 subjects with CYP2C19*2/2 genotype in the control group. A significant difference was found between the groups in terms of genotypes (p=0.034). The CYP2C19*1/1 genotype was found at higher percentages in the control group, whereas its CYP2C19*2/2 counterpart had a higher proportion in the CAD group (Table 2).

When it comes to the allele frequencies of the groups, the CYP2C19*1 allele frequency was 326 (81.5%) and that of CYP2C19*2 was 74 (19.5%) in the CAD group, while CYP2C19*1 allele frequency was 164 (82%) and that of CYP2C19*2 was 36 (18%) in the control group. No significant difference was found between the groups in terms of allele frequencies, which were similar in both groups (p=0.881) (Table 2).

Table 3-5 presents an overview of the data in other studies in which CYP2C19*1 and CYP2C19*2 genotype and alleles frequencies were investigated. The differences in these genotypes and alleles frequencies between our study and these studies can also be seen in these tables (4-23).

With respect to the relationship between the number of angiographic interventions and genotypes of the patients, 120 (90.9%) of the patients with CYP2C19*1/1 genotype underwent angiography only once, whereas 12 (9.9%) were exposed to angiography twice or more and to medical

Table 1. Non-parametric chi-square "goodness of fit" test

		CAD group n=200 subjects, n=400 alleles				
		Observed	**Expected**	**Expected proportion**	**Percentage deviation**	**Standardized residuals**
CYP2C19*2	*1/*1	132	132.85	0.66425	-0.64%	-0.07
	*1/*2	62	60.31	0.30155	+2.8%	+0.22
	*2/*2	6	6.85	0.03425	-12.41%	-0.32
		X^2=0.16, df=2, p=0.9231				
		Control group n=100 subjects, n=200 alleles				
		Observed	**Expected**	**Expected proportion**	**Percentage deviation**	**Standardized residuals**
CYP2C19*2	*1/*1	72	67.24	0.6724	+7.08%	+0.58
	*1/*2	20	29.52	0.2952	-32.25%	-1.75
	*2/*2	8	3.24	0.0324	+146.91%	+2.64
		X^2=10.4, df=2, **p=0.0055**				

CAD: Coronary artery disease

Table 2. Allele frequencies of CYP2C19*1 and *2 in CAD and control groups

CAD group n=200 subjects, n=400 alleles					**Control group n=100 n=200 alleles**				
Genotype	**n (%)**	**Allele frequency**		**p**	**Genotype**	**n (%)**	**Allele frequency**		**p**
*1/1	132 (66)	*1	81.5%	0.032	*1/1	72 (72)	* 1	82%	0.881
*1/2	62 (31)	*2	19.5%		*1/2	20 (20)	*2	18%	
*2/2	6 (3)				*2/2	8 (8)			

p-values are derived from Fisher's Exact test, CAD: Coronary artery disease

interventions during angiography. While 53 (77%) of the patients (CYP2C19*1/2 and CYP2C19*2/2) carrying the CYP2C19*2 allele underwent one angiography, 15 (23%) patients were subjected to 2 or more angiomas. Bearing the CYP2C19*2 allele heightened the risk of multiple angiographic interventions in the patient group by 2.83 times [p=0.16 and 95% confidence interval (CI) (1.24-6.45)] (Table 6).

Discussion

In 2017, the United States FDA issued some warnings on clopidogrel metabolism and the impact of the *CYP2C19* gene on this metabolism. In accordance with these warnings, it was reported that some patients might metabolize clopidogrel more poorly, and that clopidogrel activity would decrease in these patients (24).

In addition, FDA also warned that the CYP2C19*1 allele provides normal functional metabolism of clopidogrel, while CYP2C19*2 and CYP2C19*3 alleles cause dysfunction in the metabolism of clopidogrel. It was noted that if patients carry both of these non-functional alleles, they can be designated as poor metabolizers, whereas intermediate metabolizers are those who carry one copy of CYP2C19 encoding a non-functional allele, which might be either *1 or *2 (25).

There is a large body of literature that recognizes the variability of *CYP2C19* gene polymorphism in different ethnicities in healthy volunteers. As noted before, CYP2C19*1 allele frequency turns out to be 82%, while CYP2C19*2 allele frequency is 18% for healthy volunteers (control group) in our study. In contrast, CYP2C19*1 allele frequency is reported as 56%-74% and CYP2C19*2 allele frequency as 24% and 37% in the studies aimed at Chinese and Thai population (8-11,13). Our study is different from the Chinese and Thai populations in terms of *1 and *2 allele frequencies and healthy group population. For

Table 3. *CYP2C19* gene genotypes and allele frequencies of healthy group in different populations

Population	Subjects N	Alleles N	*1/1	*1/2	*2/2	*1	*2	Reference
Ethiopian	114	228	0.746	0.193	0.026	0.842	0.122	4
Zimbabwean	84	168	0.773	0.190	0.035	0.869	0.130	5
Chinese-Dai	193	286	0.419	0.440	0.046	0.663	0.303	6
Chinese-Han	101	202	0.316	0.465	N/E	0.56	0.37	7
Chinese-Li	100	200	0.48	0.49	0	0.740	0.245	8
Thai	1051	2102	0.407	0.351	0.073	0.63	0.27	9
Italian	360	720	0.794	0.189	0.017	0.889	0.111	10
Chinese-Hakka	6.686	13,372	0.417	0.396	0.097	0.64	0.31	11
Belgium	121	242	0.835	0.149	0.016	0.909	0.091	12
Beninese	111	222	0.739	0.261	0	0.87	0.13	12
Palestinian	100	200	0.81	0.19	0	0.905	0.095	13
Turkish	100	200	0.73	0.27	0	0.865	0.135	13
German	328	656	0.723	0.232	0.042	0.84	0.159	14
Turkish	404	804	0.76	0.223	0.099	0.875	0.121	14
Turkish	160	320	0.655	0.234	0.110	0.88	0.12	15
Turkish (present study)	**100**	**200**	**0.72**	**0.20**	**0.08**	**0.82**	**0.18**	**-**

Table 4. *CYP2C19* gene genotypes and allele frequencies in coronary artery disease population

Population	Subjects N	Alleles N	*1/1	*1/2	*2/2	*1	*2	Reference
Egyptian	230	460	75.2	23.1	1.7	86.7	13.3	16
Russian	81	162	84	16	0	92	8.0	17
Yakutsk (Russia)	268	536	65.67	33.58	0.075	82.46	17.54	18
Russian	143	286	83.92	15.38	0.070	91.60	8.40	18
Chinese	168	336	44.05	41.67	14.28	64.89	35.11	19
Chinese-Hakka	934	1868	40.36	40.26	9.42	63.17	31.64	11
Turkish	347	694	72.9	23.6	3.5	84.7	15.3	20
Turkish (present study)	**200**	**400**	**66.0**	**31.0**	**3.0**	**81.5**	**19.5**	**-**

instance, *1 allele frequency is higher than Chinese and Thai population, although that of *2 is lower in our study group. As far as the studies on African black race (Ethiopian, Zimbabwean, Beninese) are concerned, *1 allele frequency proves to be lower, whereas that of *2 is higher than our study (4,5,12). Previous research on European-Caucasian population (Italian, Belgium, German) establishes*1 allele frequency to be in the range of 84% -90.9%, while that of *2 is in the range of 9.1% -23% (10,12,14). *1 allele frequency reported in the existing study is lower than the percentages in Italian, Belgium and German population, but that of *2 is higher (10,12,14). Even though the allele frequencies in the healthy group are similar to those of the previous studies on the European, Turkish and Caucasian population, *2 allele frequencies turn out to be higher in our study (10,12-15).

With respect to the genotype frequencies in the studies on ethnic diversity, *1/1 genotype frequency is reported to be in the 31.6% -41.9% range, whereas *2/2 genotype frequency is in the range of 0% -9.7% in the Chinese population (6-8,11). In contrast to *1/1 genotype frequency in the current study which is noticeably different from the Chinese population,*2/2 genotype frequency seems to be in similar percentages both in our study's participants and in Chinese population (6-8). The last but not the least, *1/1 genotype frequency is considerably higher in our healthy volunteer group than in the Chinese population, while that of *1/2 is lower (6-8).

Research on the Caucasian population (Italian, Belgium, German) specifies *1/1 genotype frequencies to be between 70.6% and 83.5%.*1/1 genotype frequencies in our healthy volunteers are akin to the Caucasian population data unlike those of *2/2 which are higher in our healthy volunteers within our study than the aforementioned studies on the Caucasian population (10,12,14).

The earlier studies on the Turkish population have identified*1/1 genotype frequency as 65.5% -76%. On

Table 5. CAD and control groups in comparison studies

Population	Group (N)	Genotypes N (%)			Alleles (%)		p	Ref. no
		*1/1	*1/2	*2/2	*1	*2		
Russian	**CAD (561)**	448 (79.9)	106 (18.9)	7 (1.2)	89.3	10.7	0.086	21
	Control (694)	543 (78.2)	130 (18.7)	21 (3.0)	87.6	12.4		
Russian	**CAD (84)**	69 (82.1)	14 (16.7)	1 (1.2)	90.5	9.5	0.42	22
	Control (30)	23 (76.7)	6 (20.0)	1 (3.3)	86.7	13.3		
Kazakh Slav	**CAD (72)**	50 (69.4)	22 (30.6)	0.0	82.5	17.5	N/A	23
	Control (255)	179 (70.0)	71 (28.0)	5 (2.0)	84.7	15.3		
Turkish (present study)	**CAD (200)**	**132 (66.0)**	**62 (31.0)**	**6 (3.0)**	**81.5**	**19.5**	***0.034**	-
	Control (100)	**72 (72.0)**	**20 (20.0)**	**8 (8.0)**	**82.0**	**18.0**		

CAD: Coronary artery disease

Table 6. Genotypes and number of angiographic interventions

Number of intervention	Genotypes		p	95% CI
	CYP2C19*1/1 n (%)	CYP2C19*1/2 & CYP2C19 * 2/2 n (%)		
1	120 (90.9%)	53 (77%)	0.016	2.83 (1.24-6.4)
>1	12 (9.1%)	15 (23%)		

p-value is derived from chi-square test, CI: Confidence interval

the contrary, a study comparing Palestinian and Turkish populations reports no presence of genotype of *2/2 (13), though some findings in earlier studies establish*2/2 genotype frequency in healthy Turkish population to be around 10%. The results of healthy volunteers in our study seem to be consistent with the data of previous research with regard to both *1/1 and *2/2 genome frequencies (13-15).

When it comes to the CAD group within our study, *1 allele frequency is 81.5%, while that of *2 is 19.5%. Considering the allele frequencies concerning ethnicity, *2 allele frequency is lower in our study group than that reported by the previous studies on Chinese (11,19). In addition, *2 allele frequency in the Russian and Egyptian populations is reported as 8% and 13.3%, respectively (16,17). As can be noticed from the above-mentioned research, the percentages of *2 allele observed in this investigation are far above those observed by in these studies. However, earlier research on the Turkish CAD population has reported *2 allele frequency as 15.9%, consistent with the present data in our study (20).

With respect to genotype frequencies in CAD patients, *1/1 genotype frequency in the Chinese populations is lower than the patients in our study, whereas *2/2 genotype frequency is higher (11,19). In Russian and Russian-Yakutsk population, *2/2 genotype frequency is lower than our patient group (17,18). Moreover, genotype frequencies in our study are of similar nature to the previous study conducted on the Turkish population with CAD (20).

Studies comparing genotype and allele frequencies in individuals with CAD and healthy population report no difference in allele or genotype between control and CAD groups. However, a closer look into the pertaining studies will reveal the noticeable impact of the number of patients included in studies, and it is observed that as the number of patients increase, p value gets closer to the significance level (21-23). In our study, although no difference exists between the groups in terms of alleles in CAD group, there is a difference in genotypes in CAD group, which is mainly caused by the intermediate group. This case highlights the importance of checking *CYP2C19* gene polymorphism prior to the initiation of antiplatelet therapy in CAD patients.

As a review of current literature suggests, CYP2C19*2 allele is one of the overriding factors contributing to clopidogrel resistance (3). Having followed-up 1050 patients for cardiovascular diseases for 8 years, Rothenbacher et al. (26) concluded that the CYP2C19*2/2 genotype poses a risk for the development of cardiovascular diseases. Likewise, a meta-analysis by Singh et al. (27) revealed that CYP2C19*2 polymorphism might heighten the risk of stent thrombosis by 2.4 times (RR: 2.41, CI: 1.69-3.41, p<0.001). On the other hand, Nozari et al. (28) found that the risk of restenosis did not increase in individuals with CYP2C19*1/CYP2C19*2 genotype within one year.

Our study reveals that carrying CYP2C19*2 polymorphism (heterozygous or homozygous) may heighten the risk of secondary angiographic intervention. Although the number of our patients bearing homozygous polymorphism is highly low, our study may be considered as an important step towards unraveling the relationship between CYP2C19*2 polymorphism and increased risk of restenosis.

Study Limitations

Some limitations are inherent in our study. For example, we did not analyze alleles and genotype differences except CYP2C19*1 and *2 in our study. Further, we did not carry out the clinical follow-up of the patients in our study as well as not measuring clopidogrel metabolite.

Conclusion

As a conclusion, in our research, we studied *CYP2C19* gene polymorphism and CYP2C19*1 and CYP2C19*2 allele frequencies in the control group with 100 healthy volunteers and 200 CAD patients. In addition, the high frequency of percutaneous coronary intervention in individuals with CYP2C19*2 allele suggests that clopidogrel resistance is likely to pose an important challenge. CYP2C19*1/2 and *2/2 genotypes were found to be higher in CAD patients than the one in the control group, underlining how critical checking *CYP2C19* gene polymorphism is before setting out antiplatelet therapy in CAD patients.

Ethics

Ethics Committee Approval: Having been approved by the Pamukkale University Ethics Committee, the study included 100 healthy volunteers and 200 patients diagnosed with CAD and using clopidogrel, all of whom lived in Denizli.

Informed Consent: Written consent form was signed by all the participants

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.K., R.S., Design: A.K., İ.D.K., A.Y., Data Collection or Processing: A.Y., İ.D.K., A.K., Analysis or Interpretation: R.S., A.Y., İ.D.K., Literature Search: A.K., A.Y., Writing: R.S.

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ORIGINAL RESEARCH

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Contribution of Endorectal Ultrasound, Magnetic Resonance Imaging and Positron Emission Tomography to Operation Strategy in Rectal Cancer

Endorektal Ultrasonografi, Manyetik Rezonans Görüntüleme ve Pozitron Emisyon Tomografisinin Rektum Kanserinde Ameliyat Stratejisine Katkıları

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Abstract

Objective: Colorectal cancer is the most common type of cancer in the gastrointestinal tract. Preoperative staging is important for applying appropriate treatment modalities. The role of endorectal ultrasonography (ERUS), magnetic resonance imaging (MRI) and positron emission-computed tomography (PET-CT) in rectal cancer patients was evaluated.

Method: In this study, between October 2010-April 2012, 30 patients who were diagnosed as rectal cancer clinically and histopathologically were evaluated with ERUS, MRI and PET-CT preoperatively and results were compared with histopathologic findings.

Results: Between October 2010-April 2012, 30 patients who were diagnosed as rectal cancer with biopsy in Bezmialem University Medical Faculty Hospital General Surgery Department were included in this study [20 male (66.6%), 10 female (33.3%) and their ages are 38-75 years old, 21 of them received neoadjuvant treatment and 9 of them did not received]. All patients were evaluated with MRI, ERUS and PET-CT preoperatively. Rectal cancer patients who are primarily operated from rectal adenocarcinoma were included in this study. For T staging, preoperative MRI, ERUS and PET-CT staged 9 (31%), 12 (41%) and 12 (40%) of 30 patients accurately, respectively. For N staging, preoperative MRI, ERUS and PET-CT staged 15 (51%), 16 (55.1%) and 17 (56.6%) of 30 patients accurately, respectively. In comparison to other modalities, PET-

Öz

Amaç: Gastrointestinal sistemin en sık görülen kanserleri kolorektal kanserlerdir. Özellikle rektum kanserli hastalarda operasyon öncesi evreleme büyük önem taşımaktadır. Bunun sebebi ise evrelemeye göre tedavi yönetimindeki değişik olanakların hasta için tercih edilebilmesidir. Evreleme hasta için uygun tedavi yönetimini planlamaya yardımcı olmaktadır. Rektum kanserli hastaların endorektal ultrasonografi (ERUS), manyetik rezonans görüntüleme (MRG) ve pozitron emisyonu-bilgisayarlı tomografi (PET-BT) ile yapılan değerlendirilmelerinin ameliyat stratejisine etkileri araştırıldı.

Yöntem: Bu çalışmada; klinik ve histopatolojik olarak Ekim 2010-Nisan 2012 arasında rektum kanseri tanısı almış 30 olgu preoperatif olarak ERUS, MRG ve PET-BT ile değerlendirilmiş, sonuçlar histopatolojik bulgularla karşılaştırılmıştır.

Bulgular: Ekim 2010-Nisan 2012 tarihleri arasında Bezmialem Üniversitesi Tıp Fakültesi Hastanesi Genel Cerrahi Anabilim Dalında biyopsi ile rektum kanseri tanısı alan 30 hasta çalışmaya alınmıştır. Yirmi hasta erkek (%66,6), 10 hasta kadın (%33,3) idi. Hastaların yaşları 38 ile 78 arasındaydı, 21 hasta neoadjuvan tedavi gördü. Dokuz hasta neoadjuvan tedavi görmedi. Hastaların tümüne preoperatif MRG, PET-BT ve ERUS yapılmıştır. Çalışmaya opere edilen primer rektum adenokanserli hastalar dahil edildi. T evresini değerlendirmede MRG, ERUS ve PET-BT 30

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Abstract

CT did not yield a significant difference in staging and did not change operation strategy. PET-CT detected distant metastasis in 3 patients. One of them was liver and two of them were lung metastasis. Biopsies from mass predicted as lung metastasis did not result as metastasis. PET-CT has high rates of false positivity to detect distant metastasis. In statistical analysis, significant p-values for evaluation could not be obtained.

Conclusion: Efficacy of routine use of PET-CT on staging, evaluation of T, N and extramesorectal spread could not be shown.

Keywords: Imaging methods, PET-CT, rectum cancer

Öz

hastadan sırasıyla 9 (%31), 12 (%41) ve 12 (%40) hastada doğru evreledi. N evresini değerlendirmede MRG, ERUS ve PET-BT 30 hastadan sırasıyla 15 (%51), 16 (%55,1) ve 17 (%56,6) hastada doğru evreledi. PET-BT'nin diğer görüntüleme yöntemleri ile karşılaştırıldığında evrelemede anlamlı bir farklılık oluşturmadığı ve ameliyat stratejisini değiştirmediği görülmüştür. PET-BT ile üç hastada uzak metastaz saptandı. Bunlardan biri karaciğer, ikisi akciğer metastazı idi. Akciğer metastazı düşünülen kitlelerden alınan biyopsilerde metastaz saptanmadı. PET-BT'nin uzak metastazı saptamada yüksek yanlış pozitiflik oranı olduğu görülmüştür. İstatiksel analizde değerlendirme sonucu için anlamlı p-değerleri saptanmamıştır.

Sonuç: PET-BT'nin rektum kanseri evrelemesinde T, N ve ekstramezorektal yayılım değerlendirilmesinde rutin olarak kullanılmasının faydası gösterilememiştir.

Anahtar kelimeler: Görüntüleme yöntemleri, PET-BT, rektum kanseri

Introduction

The most common cancer of the gastrointestinal tract is colorectal cancer. Colorectal cancer is the fourth most common type of cancer (1). Preoperative staging is important in patients with rectal cancer since treatment is planned according to the management of the patient's initial application stage. The main purpose of treatment management is to prolong survival, to prevent distant metastasis, and to reduce local recurrence. Physical examination, endoscopic examination, double contrast colon radiography and histopathological methods are used in the diagnosis of rectal cancer. With these methods, rectal cancers can be diagnosed, but distant metastasis, bowel wall involvement, depth and lymph node spread cannot be determined for staging of the disease (2,3). A variety of imaging methods are used to investigate tumor localization and distant organ involvement in patients with histopathological diagnosis of rectal cancer.

In this study, 30 patients with clinically and histopathologically proved diagnosis of rectal cancer were staged by ERUS, MRI and PET-CT. These methods were compared with postoperative histopathological staging and their role in the diagnosis and staging of rectal cancer and the determination of surgical strategy were evaluated.

Materials and Methods

A prospective randomized clinical trial was planned and local ethics committee approval was obtained. All patients included in the study were informed succinctly and informed consent forms were signed. Between October 2010 and April 2012, a total of 42 patients with a diagnosis of rectal cancer by endoscopic biopsy were assigned to the Department of General Surgery, Bezmialem Vakıf University Medical Faculty, and 30 patients were randomly included in the study (20 males, 10 females, age range: 38-78 years, mean age: 60 years). Patients who had recurrence, an additional pathology that would prevent surgery or who did not accept the operation were excluded from the study. After diagnosis, all patients were staged with pelvic MRI, PET-CT and ERUS imaging. Twenty-one (70%) patients underwent surgery after neoadjuvant therapy and 9 (30%) were treated with primary surgery. In patients receiving neoadjuvant therapy, after 4-6 weeks of treatment, regression levels were evaluated by MRI and ERUS weekly according to Dworak regression staging (4).

Statistical Analysis

Statistical analysis of this study was done using GraphPad Prisma V.3 program. In-group and inter-group evaluations other than descriptive methods (mean, standard deviation, median) were performed through the Fisher Exact test, Friedman chi-square test, and Wilcoxon test with Bonferoni correction.

Results

Examination by PET-CT: One patient had T1, 13 had T2, 12 had T3, 3 had T4, 22 had N0 and 8 had N1. PET-CT showed rectal cancers in all patients except one patient. For T staging: it gave the accurate staging in 12 patients (40%), down stage in 10 patients (33.3%) and up stage in 8 (26.6%) patients. For N staging: it gave the accurate staging in 17 patients (56.6%), up staging (36.6%) in 11 patients, and down staging in 6 patients (20%). PET-CT showed distant metastasis in 3 patients. Two of these were in the lungs and one in the liver. Lung biopsies of patients with

lung metastasis were benign in PET-CT imaging. Liver metastasectomy was evaluated correctly. The PET-CT imaging technique correctly staged 1 (33%) patient with distant metastasis.

Examination by ERUS: Five patients were classified as T0, 3 as T1, 7 as T2, 13 as T3 and 1 as T4. ERUS imaging was not performed for one post-neoadjuvant patient, so this patient was excluded from the evaluation. The ERUS imaging technique gave 12 (41%) accurate staging, 6 (20%) over staging and 11 (38%) down staging for the T parameter. In N staging with ERUS: Twenty-nine patients (55%) were N0 and 13 (44%) were N1. The ERUS imaging technique gave 16 (55%) accurate staging, 6 (20%) over staging and 7 (24%) down staging for the N parameter. Three patients had lateral pelvic lymph nodes. One of these patients underwent lateral pelvic lymph node dissection and all four resected lymph nodes were negative.

Examination by MRI: 3 (10%) patients were T1, 17 (58.6%) patients were T2, 9 (31%) patients were T3 and 0 patient was T4. One post-neoadjuvant patient was excluded because MRI was not performed. MRI technique gave 9 (31%) accurate staging, 16 (55%) down staging and 4 (13%) over staging for the T parameter. Twelve (41%) patients had N0, 14 (48%) had N1 and 3 (10%) had N2. With MRI, 15 (51.7%) patients were staged correctly, 4 (13.7%) were down staged and 10 (34.4%) patients were over staged. On MRI imaging, 4 patients had lateral pelvic lymph nodes. Two patients underwent lateral pelvic lymph node excision. From both of these patients, 15 lymph nodes were removed and all were negative. In our study, abdominal MRI imaging detected that only one of 30 patients had metastasis in the liver. The biopsy from this metastatic mass was malignant. The accurate staging numbers obtained for all three imaging techniques are presented in Table 1.

Histopathological examination: 1 (0.3%) pT1, 11 (36%) pT2, 16 (53.3%) pT3 and 2 (0.6%) pT4.18 (60%) pN0, 10 (33.3%) pN1, 1 (3.3%) pN2 and 1 (3.3%) pN3.

In statistical analysis, it was seen that all three imaging techniques did not show any significant difference for T, N and M parameters (Table 2). For 21 patients who received neoadjuvant therapy, changes were observed in 13 patients in the T phase before and after neoadjuvant therapy with MRI and ERUS imaging techniques. The results obtained for both imaging techniques were statistically significant (p=0.001 for MRI and p=0.001 for ERUS).

When neoadjuvant therapy and MRI/ERUS imaging tests were compared in patients with differences in T stage, significant differences were observed in both imaging techniques and this suggests that both imaging techniques did not provide predictions for T stage change.

Table 1. Accurate staging distribution of imaging modalities according to TNM parameters

	MRI	PET-CT	ERUS
T	9 (31%)	12 (40%)	12 (41%)
N	15 (51.7%)	17 (56.6%)	16 (55%)
M	1 (3.4%)	1 (3.3%)	-

PET-CT: Positron emission computed tomography, ERUS: Endorectal ultrasonography, MR: Magnetic resonance

Table 2. p-values and statistical analysis of the accuracy of diagnostic tests (p<0.05 was considered statistically significant. Chi-square test for T and N stages, Fisher Exact test for stage M)

	T	N	M
MRI vs PET	0.47	0.70	1.00
MRI vs ERUS	0.41	0.79	-
ERUS vs PET-CT	0.91	0.91	-

PET-CT: Positron emission computed tomography, ERUS: Endorectal ultrasonography, MRI: Magnetic resonance imaging

Discussion

Approximately 10% of patients have local recurrence of rectal cancer in modern surgery with adjuvant and neoadjuvant treatments (5). Nevertheless, today the most important findings that predict the possibility of recurrence of the tumor are the stage of the tumor, the penetration of the bowel wall and lymph node involvement during diagnosis (6). It is controversial that local recurrence has no effect on survival, but it decreases the quality of life significantly. Preoperative staging of the rectal tumor and planning of the treatment are therefore essential. Although there are different approaches, the accepted methods for staging are ERUS, pelvic MRI and CT.

In many studies, the success of T staging with ERUS has been reported as 81-94%, with an over staging rate of 10% and a down staging rate of 5% (7-9). The most important clinical condition that negatively affects the accuracy of ERUS in rectal lesions is stenotic tumors (10,11). With ERUS imaging, it may be difficult to differentiate very early stage cancer, such as adenoma, which only affects the mucosa. Staging of adenoma and T1 tumors that have previously undergone ERUS may also lead to mistakes. The most common cause of upper staging is the formation of inflammatory cell accumulations around the tumor, desmoplastic changes and hypervascularity

by inducing a tumor, causing the appearance of tumor invasion in ERUS. In particular, pT2 tumors are staged as uT3 (12). In our study, pT2 was detected in 2 (10%) of 10 patients who were determined as uT3 after neoadjuvant treatment. In this study, 12 of 30 patients (41%) received accurate staging in T invasion, 6 patients (20%) resulted in over staging and down staging in 11 patients (38%) was observed. Accuracy rates in our study were lower than in the literature series.

The biggest problem with ERUS is the presence of false positive metastatic lymph nodes. The appearance of a large reactive lymph node can easily be considered malignant and may be omitted in imaging for a small metastatic lymph node (13-15). In our study, with ERUS, pathological lymph node was detected in 13 patients (44%). ERUS yielded accurate lymph node staging for 16 (55%) patients. These results show that there are deficiencies in the visualization of lymph nodes and the correlation of the displayed lymph nodes with pathology is needed.

The accuracy rates reported in MRI and T staging varied between 67% and 88% (16,17). The superiority of MRI to ERUS is the capability of viewing wider localizations. The advantage of MRI is that it can display mesorectum, mesorectal fascia and lymph nodes in perirectal fatty tissue (18-20). In our study, T staging was accurate in 31% of cases. This suggests that results of some of the patients are associated with neoadjuvant therapy. The efficacy of MRI in the evaluation of mesorectal fascia is high and the accuracy of MRI in mesorectal fascia involvement is between 91% and 100% in various studies (21,22). False positivity is the biggest problem in MRI lymph node evaluation. The reason is that large, malignant lymph nodes may cause reactive hyperplasia, or microscopic tumor invasion is detected in a small, benign lymph node. In the literature, accuracy rates in lymph node involvement with MRI vary between 43% and 85% (21-23). MRI technique performed 15 (51.7%) accurate staging, 4 (13.7%) down staging and 10 (34.4%) over staging for the N parameter.

Colorectal cancers are the leading tumors in which distant metastasis staging is important. The imaging of metastasis and the primary tumor both can be made with PET, but navigation of the tumor can be achieved by simultaneous tomography (23-25). PET-CT could not provide information about the degree of infiltration of the rectal wall because of the limited statical resolution. For this reason, PET-CT is not recommended for T staging. We could not find an appropriate study for the evaluation of T and N staging. PET-CT showed distant metastasis in three patients. Two of the suspected metastatic lesions in PET-CT were detected in the lungs. Biopsies were performed from the lesions and found to be benign nodules. Metastatic lesion was detected in the liver and metastasectomy was performed in one patient. PET-CT gave false positivity in 2 out of 3 patients (66.6%) for distant organ metastasis. The only isolated liver metastasis in one patient did not change our treatment strategy. In the literature, PET-CT analysis changed the staging of 17% of patients and differentiated the treatment management (26-28).

Another 37 patients in the lower rectum tumor study group changed the treatment scheme in 27% of patients (29). In our study, although the treatment scheme was not changed, biopsy was performed for 2 patients and it was a waste of time for the patient's treatment.

Conclusion

In this study, the efficacy of ERUS, MRI and PET-CT imaging techniques in the evaluation of locoregional dissemination was investigated in determining the surgical strategy of rectum cancer. PET-CT has a high rate of false positivity in detecting the presence of distant metastases. MRI and ERUS were found to be reliable in the evaluation of T stage in patients undergoing neoadjuvant therapy. In respect to this, our study has a limited patient number and should be supported by further clinical studies.

Ethics

Ethics Committee Approval: A prospective randomized clinical trial was planned and Local Ethics Committee approval was obtained (no: B.30.2.BAV.0.05.05/231, date: 01.02.2012).

Informed Consent: All patients included in the study were informed succinctly and informed consent forms were signed.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Development of Study Idea: M.M., Y.D.F., G.Ç., Design of the Study: M.M., Y.D.F., C.Ç., Data Acquisation and Proccess: M.M., Y.D.F., G.Ç., Data Analysis and Interpretation: G.Ç., C.Ç., H.K.B., Literature Review: C.Ç., H.K.B., S.A., Manuscript Writing: H.K.B., S.A., Manuscript Review and revisation: S.A., Y.D.F.

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ORIGINAL RESEARCH

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Is There Any Correlation Between De Ritis Ratio and Prostate Cancer in Males Who Underwent Transrectal Prostate Biopsy?

Transrektal Prostat Biyopsisi Yapılan Erkeklerde De Ritis Oranı ile Prostat Kanseri Arasında Herhangi Bir İlişki Var Mı?

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Abstract

Objective: This study aims to evaluate the diagnostic value of the De Ritis ratio (DRR) in predicting prostate cancer (PCa) and clinically significant prostate cancer (csPCa) in biopsy-naive patients with suspected PCa.

Method: We retrospectively reviewed medical records of 282 male patients who underwent transrectal ultrasound-guided prostate needle biopsy (PNB) between January 2015 and July 2019. Demographic and clinical characteristics of the patients including digital rectal examination findings, preoperative prostate-specific antigene (PSA), aspartate aminotransferase levels, alanine aminotransferase levels, prostate volume, comorbidities and pathological findings of the PNB specimens were noted in detail for each patient. The study cohort was divided into two groups according to the histopathological results of PNB specimens (group 1: patients with benign histopathology, group 2: patients with PCa). The receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic performance of PSA, PSA density and DRR in predicting PCa.

Results: The median age of the participants was 64 (59-69) years. While 71.6% (n=202) of the participants were in group 1, 28.4% (n=80) of them were in group 2. The median DRR value of group 1 was 1.08 (range: 0.89-1.32), and the median DRR value of group 2 was determined as 1.19 (range: 0.95-1.56), and the median DRR value of group 2 was found to be statistically significantly higher than that of group 1 (p=0.013). Statistically significant but a weak positive correlation was observed between PCa in PNB specimens and DRR (r=0.149, p=0.012), while there was no statistically significant correlation between csPCa in PNB specimens and DRR (r=0.002, p=0.983). The ROC curve analysis showed that the cut-off value of DRR for the presence of PCa in PNB specimens was 1.125 and

Öz

Amaç: Bu çalışma, prostat kanseri şüphesi olan biyopsi olmamış hastalarda prostat kanseri ve klinik anlamlı prostat kanserini öngörmede De Ritis oranının (DRR) tanısal değerini değerlendirmeyi amaçlamaktadır.

Yöntem: Ocak 2015 ile Temmuz 2019 arasında transrektal ultrason eşliğinde prostat iğne biyopsisi (TRUS-Bx) yapılan 282 erkek hastanın tıbbi kayıtlarını retrospektif olarak inceledik. Hastaların parmakla rektal muayene bulguları, biyopsi öncesi prostat spesifik antijen (PSA), aspartat aminotransferaz ve alanin aminotransferaz düzeyleri, prostat hacmi, komorbiditeleri ve TRUS-Bx örneklerine ait patolojik bulgularını içeren demografik ve klinik özellikler her hasta için ayrıntılı olarak not edildi. Çalışma grubu, TRUS-Bx örneklerinin histopatolojik sonuçlarına göre iki gruba ayrıldı (grup 1: benign patolojili hastalar, grup 2: prostat kanseri hastaları). Prostat kanserini öngörmede PSA, PSA dansitesi ve De Ritis oranının tanısal performansını değerlendirmek için ROC eğrisi analizi yapıldı.

Bulgular: Hastaların ortanca yaşı 64 (59-69) yıl idi. Hastaların %71,6'sı (n=202) grup 1'de, %28,4'ü (n=80) grup 2'de yer aldı. Grup 1'deki DRR'nin ortanca değeri 1,08 (aralık: 0,89-1,32) ve grup 2'nin ortanca DRR değeri 1,19 (aralık: 0,95-1,56) olarak belirlendi. Grup 2 DRR medyan değeri grup 1'den istatistiksel olarak anlamlı olarak daha yüksek bulundu (p=0,013). TRUS-Bx örneklerinde prostat kanseri ile DRR arasında istatistiksel olarak anlamlı ancak zayıf bir pozitif korelasyon gözlendi (r=0,149, p=0,012). Buna karşın TRUS-Bx örneklerindeki klinik anlamlı prostat kanseri ile DRR arasında istatistiksel olarak anlamlı bir korelasyon yoktu (r=0,002, p=0,983). ROC eğrisi analizi, TRUS-Bx örneklerinde prostat kanseri varlığı için DRR'nin eşik değerinin 1,125 olduğunu gösterdi ve eğri altındaki alan 0,595 (%95 güven aralığı=0,518-0,672, p=0,013) idi.

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Abstract

the area under curve was 0.595 (95% confidence interval=0.518-0.672, p=0.013) for the presence of PCa in PNB specimens.

Conclusion: This study suggests that DRR had restricted diagnostic importance in predicting PCa in biopsy-naive patients who underwent transrectal PNB.

Keywords: Alanine aminotransferase, aspartate aminotransferase, De Ritis ratio, prostate cancer

Öz

Sonuç: Bu çalışma, De Ritis oranının, transrektal prostat biyopsisi uygulanan biyopsi-naive hastalarda prostat kanserini öngörmede kısıtlı bir tanısal değeri olduğunu göstermektedir.

Anahtar kelimeler: Alanin aminotransferaz, aspartat aminotransferaz, De Ritis oranı, prostat kanseri

Introduction

Prostate cancer (PCa) is the 2nd most common form of cancer in men worldwide with an estimated 1,276,106 new cases and 358,989 deaths per year (1). Age-standardized incidence and mortality rates are 29.3 and 7.6, respectively (per 100,000) (1). Although prostate-specific antigen (PSA) is organ specific, not PCa specific, it is still the most important biomarker in the diagnosis and follow-up process of PCa. Different serum and urine biomarkers and ratios based on PSA such as PSA density (PSAD), PSA velocity, PSA doubling time, PCa antigen 3, (-2) pro-PSA isoform, and kallikrein-like peptidase 2 were investigated for diagnostic value in PCa diagnosis and follow-up (2). In recent years, multiparametric magnetic resonance imaging-guided fusion prostate biopsy has been recommended for the evaluation of any patient who has a suspicion of PCa with or without a history of negative prior prostate needle biopsy (PNB) (2-4). However, nearly 12% of clinically significant (cs) PCa would also be missed by fusion PNB techniques (5). Therefore, new biomarkers and imaging techniques are still needed in the PCa diagnosis process.

Attention to the various serum markers like aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] has recently increased in the urooncologic field in terms of their predictive and prognostic value in several malignancies. De Ritis ratio (DRR), which is calculated by dividing AST to ALT, was firstly described as a diagnostic marker for viral hepatitis and then its prognostic value in several malignancies including urologic malignancies was investigated (6-8). Recently, Ha et al. (9) reported that DRR had a predictive value in detection of csPCa in patients who had a negative PNB history. Moreover, higher DRR values could accompany worsened pathological outcomes and higher biochemical recurrence ratios in patients with localized PCa (10).

The current study aims to evaluate the diagnostic value of DRR in predicting PCa and csPCa in biopsy-naive patients with suspected PCa [elevated and/or rising PSA and/or abnormal findings at digital rectal examination (DRE)] as primary outcomes. In addition, the present study aimed to compare the predictive value of DRR in addition to well-known parameters which are associated with PCa such as PSA, PSAD and suspicious DRE findings as secondary outcomes.

Materials and Methods

Study Population

We retrospectively reviewed the medical records of 1,497 male patients who underwent transrectal ultrasound (TRUS)-guided PNB in the University of Health Sciences Turkey, Bağcılar Training and Research Hospital, Department of Urology between January 2015 and July 2019. The study was approved by the local Institutional Ethics Committee (IRB no: 2020.06.2.02.086). All steps of the study were planned and conducted following the principles of the Declaration of Helsinki. A written informed consent on admittance to hospital was obtained from all individuals, which permitted the use of respective medical information in clinical studies.

Demographic and clinical characteristics of the patients including DRE findings, preoperative PSA, AST, and ALT levels, prostate volume and PSAD, comorbidities, smoking and alcohol consumption status, and pathological findings of the PNB specimens were noted in detail for each patient. Serum AST and ALT levels, which were evaluated 1 to 4 weeks before the PNB, were obtained from the medical records of the patients. The DRR was calculated using the following formula, as previously described: the ratio of AST-to-ALT (6).

Patients who had high-grade prostatic intraepithelial neoplasia and/or atypical small acinar proliferation, who had a medical history of prostate operation, who had any other malignancy history, those using any drug potentially influence serum AST or ALT levels, and those with missing

clinical data were excluded. Patients with chronic liver diseases (hepatitis, liver cirrhosis, hepatitis B virus or hepatitis C virus carriers, etc.) were also excluded. Finally, a total of 282 patients who met the inclusion criteria were included in this study. The study cohort was divided into two groups according to the histopathological results of PNB specimens (group 1: patients with benign histopathology, group 2: patients with PCa).

Prostate Needle Biopsy Procedure and Pathological Evaluation

All PNB procedures were performed transrectally in a lateral decubitus position. A single dose of oral quinolone prophylaxis and rectal enema was administered to all patients in the morning of the PNB procedure. The perianal area was prepped with 10% of povidone-iodine. Periprostatic local anesthesia (2% lidocaine, 10 mL) was applied to all patients. 12-core systematic PNB samples were taken in accordance with the European Association of Urology guidelines on PCa recommendations (2). Additional biopsies were taken if necessary (e.g. for the hypo/hyper-echoic lesions on ultrasonography).

An experienced uropathologist from our institute evaluated the PNB specimens in accordance with the 2014 International Society of Urologic Pathology criteria (11). CsPCa in PNB specimens was defined according to the Epstein criteria (12). Patients in group 2 were further subclassified as csPCa and clinically non-significant PCa (nsPCa) and compared statistically in terms of DRR levels and other parameters associated with PCa.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25.0 software (IBM Corp., Armonk, NY, USA). The normal distribution of the quantitative data was analyzed by the Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous variables were expressed in median and interquartile range, while categorical variables were expressed in number and frequency. The Pearson chi-square and Fisher's Exact tests were used to compare qualitative data. Correlation coefficient and statistical significance for the relationships between DRE, PSA, PSAD, DRR, and PCa and csPCa were calculated with the Spearman's correlation analysis. A two-tailed $p<0.05$ was considered as statistically significant.

The receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic performance of PSA, PSAD and DRR in predicting PCa. The optimal cut-off value of DRR was determined to evaluate its diagnostic scanning performance [sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)] for predicting PCa.

Results

The median age of the participants was 64 (59-69) years. Suspicious DRE findings were observed in 64 (22.7%) patients. The median PSA and PSAD levels were 6.44 (4.47-10.60) ng/mL and 0.13 (0.09-0.22) ng/mL^2, respectively (Table 1). The median DRR level was 1.12 (0.90-1.36). PCa was detected in 80 (28.4%) patients and 69 (24.5%) of them were csPCa (Table 1). The demographic and clinical characteristics of the participants are summarized in Table 1.

Table 1. Demographic and clinical characteristics of the participants

		median (IQR)	n, %
Age (year)		64 (59-69)	-
DRE	Benign	-	218 (77.3%)
	Suspicious	-	64 (22.7%)
PSA (ng/mL)		6.44 (4.47-10.60)	-
Prostate volume (mL)		48 (35-70)	-
PSA density (ng/mL^2)		0.13 (0.09-0.22)	-
AST (U/L)		21.25 (17.60-26.00)	-
ALT (U/L)		18.70 (14.00-26.00)	-
De Ritis ratio		1.12 (0.90-1.36)	-
DM (yes)		-	57 (20.2%)
HT (yes)		-	108 (38.3%)
CAD (yes)		-	41 (14.5%)
COPD (yes)		-	15 (5.3%)
CVD (yes)		-	10 (3.5%)
Smoking (yes)		-	155 (55.0%)
Alcohol (yes)		-	45 (16.0%)
PI-RADS	PI-RADS 1	-	29 (34.9%)
	PI-RADS 2	-	18 (21.7%)
	PI-RADS 3	-	15 (18.1%)
	PI-RADS 4	-	14 (16.9%)
	PI-RADS 5	-	7 (8.4%)
Pathology	Benign	-	202 (71.6%)
	Prostate cancer	-	80 (28.4%)
csPCa (yes)		-	69 (24.5%)

IQR: Interquartile range, DRE: Digital rectal examination, PSA: Prostate-specific antigen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CVD: Cerebrovascular disease, PI-RADS: Prostate imaging-reporting and data system, csPCa: Clinically significant prostate cancer

The patients in group 2 were statistically significantly older than the patients in group 1 (p<0.001). The frequency of abnormal DRE findings was higher in group 2 when compared to group 1 (p<0.001). PSA levels, PSAD and DRR were statistically significantly higher in group 2 when compared to group 1 (p<0.001, for PSA and PSAD, p=0.013 for DRR) (Table 2). There was no statistically significant difference between the patients with csPCa and nsPCa when they were compared according to DRR levels (p=0.983). There were no statistically significant differences between the groups in terms of comorbidities except hypertension frequency (p>0.05, for each, p=0.045 for hypertension) (Table 2).

In correlation analysis, it was observed that there were statistically significant correlations in varying degrees between DRE findings, PSA levels and PSA density and PCa and csPCa in PNB specimens (Table 3). Statistically significant but a weak positive correlation was observed between PCa in PNB specimens and DRR (r=0.149, p=0.012), while there was no statistically significant correlation between csPCa in PNB specimens and DRR (r=0.002, p=0.983) (Table 3).

The ROC curve analysis showed that the cut-off value of DRR for the presence of PCa and csPCa in PNB specimens was 1.125, for both. The area under curve (AUC) was 0.595 [95% confidence interval (CI)=0.518-0.672, p=0.013] for the presence of PCa in PNB specimens, and the AUC was 0.502 (95% CI=0.318-0.686, p=0.983) for the presence of csPCa in PNB specimens (Figure 1a, b). The DRR cut-off value (1.125) had a sensitivity of 60.0% and 60.9%, and a specificity of 54.5% and 45.5% for predicting the presence of PCa and csPCa in PNB specimens, respectively. The PPV was 34.3% and NPV was 77.5% for predicting the presence of PCa in PNB specimens. The PPV was 87.5% and NPV was 15.6% for predicting the presence of csPCa in PNB specimens.

Discussion

In this retrospective study, we assessed the diagnostic value of DRR in biopsy-naive patients with suspected PCa. In addition, we also investigated the diagnostic importance of DRR in discriminating PCa and csPCa and compared it with well-known parameters that were associated with PCa such as PSA, PSAD, and DRE findings. According to

Table 2. Comparisons of the groups in terms of demographic and clinical data

Variables median (IQR)		Group 1 (benign) (n=202, 71.6%)		Group 2 (prostate cancer) (n=80, 28.4%)		
		n, %	median (IQR)	n, %	p	
Age (year)		63 (58-68)	-	68 (63-73)	-	[a]<0.001*
DRE	Benign	-	174 (86.1%)	-	44 (55.0%)	[b]<0.001*
	Suspicious	-	28 (13.9%)	-	36 (45.0%)	
PSA (ng/mL)		5.71 (4.18-8.26)	-	10.30 (6.01-32.27)		[a]<0.001*
Prostate volume (mL)		50.00 (38.00-75.00)	-	45.00 (30.00-60.00)	-	[a]0.005*
PSA Density (ng/mL²)		0.11 (0.08-0.16)	-	0.23 (0.14-0.87)	-	[a]<0.001*
De Ritis ratio		1.08 (0.89-1.32)	-	1.19 (0.95-1.56)	-	[a]0.013*
DM (yes)		-	42 (20.8%)	-	15 (18.8%)	[b]0.700
HT (yes)		-	70 (34.7%)	-	38 (47.5%)	[b]0.045*
CAD (yes)		-	26 (12.9%)	-	15 (18.8%)	[b]0.207
COPD (yes)		-	8 (4.0%)	-	7 (8.8%)	[c]0.139
CVD (yes)		-	7 (3.5%)	-	3 (3.8%)	[c]1.000
Smoking (yes)		-	113 (55.9%)	-	42 (52.5%)	[b]0.601
Alcohol (yes)		-	32 (15.8%)	-	13 (16.3%)	[b]0.933

[a]Mann-Whitney U test, [b]Pearson chi-square test, [c]Fisher's Exact test, *p<0.05, IQR: Interquartile range, DRE: Digital rectal examination, PSA: Prostate-specific antigen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CVD: Cerebrovascular disease

Table 3. Correlation of suspicious DRE, PSA, PSA density and DRR with histopathology

	Suspicious DRE		PSA (ng/mL)		PSA density (ng/mL²)		De Ritis ratio	
	r	p	r	p	r	p	r	p
PCa in PNB specimens	0.335**	<0.001	0.352**	<0.001	0.439**	<0.001	0.149*	0.012
csPCa in PNB specimens¶	0.288**	0.010	0.318**	0.004	0.350**	0.001	0.002	0.983

DRE: Digital rectal examination, PSA: Prostate-specific antigen, DRR: De Ritis ratio, PNB: Prostate needle biopsy, csPCa: Clinically significant prostate cancer

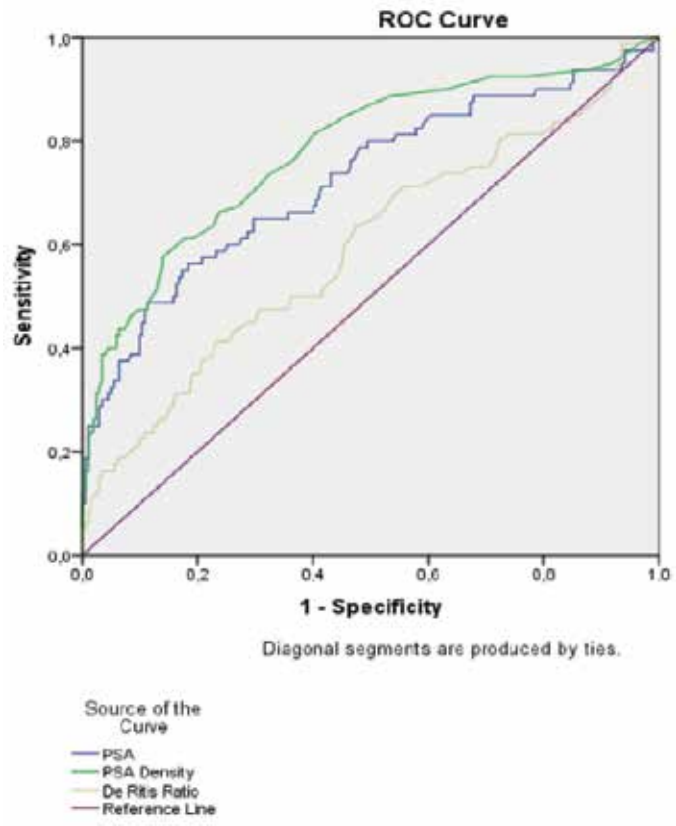

Figure 1a. ROC curve in predicting prostate cancer by De Ritis ratio

ROC: Receiver operating characteristic

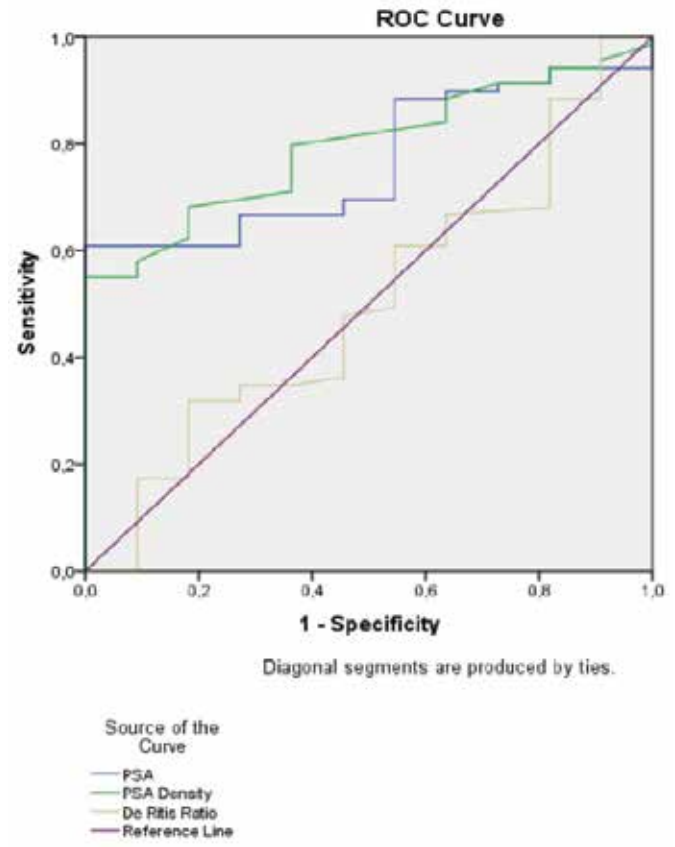

Figure 1b. ROC curve in predicting clinically significant prostate cancer by De Ritis ratio

ROC: Receiver operating characteristic

our study results, higher DRR levels were associated with PCa in PNB specimens. However, no significant difference was observed between the patients with csPCa and nsPCa in terms of DRR levels. Moreover, a weak correlation was observed between PCa in PNB specimens and DRR, while no correlation was observed between csPCa in PNB specimens and DRR. In light of these outcomes, our study suggests that DRR restricted diagnostic importance in predicting PCa in biopsy-naive patients who underwent transrectal PNB. Moreover, it is insufficient in discriminating csPCa and nsPCa.

It is well-known that tumor cells need adenosine triphosphate (ATP) as energy to grow rapidly (13). Glycolysis increases in cancer cells to produce sufficient ATP (13). It has been shown that the cytosolic nicotinamide adenine dinucleotide hydride/nicotinamide adenine dinucleotide (NADH/NAD) is required for the maintenance of glycolysis. AST is one of the important components of the malate-aspartate shuttle pathway that allows NADH/NAD conversion (14). Also, while AST is commonly produced in different tissue types such as the skeletal muscle, kidney, heart, and brain, ALT is considered as more liver-specific (15). Based on these two hypotheses, many studies investigating the relationship between DRR and urogenital cancers have been published (16-20). In a recently published meta-analysis, it was emphasized that DRR was a prognostic marker in solid tumors, and it was reported that it was inversely related to overall survival (OS), recurrence free survival, and cancer specific survival (CSS) in all tumors (21). Similarly, in the systematic review and meta-analysis examining the relationship between urogenital cancers and DRR, they reported that pretreatment DRR was a significant predictor for OS, CSS, and progression-free survival in urological cancers (22).

Although many studies have been conducted to evaluate the relationship between PCa and DRR, only few studies have focused on the relationship between pre-biopsy DRR values and PCa diagnosis (10,23-25). Zhou et al. (24) reported higher DRR values in PCa patients than in the benign prostate hyperplasia group in a recent retrospective study involving 404 patients who underwent PNB. They also reported that, according to the multivariate analysis results, the increase

in DRR values increased the risk of PCa incidence, but they did not find a relationship between the risk groups of PCa and DRR (24). In another study, Ha et al. (9) reported that the DRR levels were higher in patients with PCa in the second biopsy compared to benign pathologies but they did not find a statistically significant difference. However, they reported that DRR was effective in detecting csPCa.

Study Limitations

Nonetheless, there are some limitations to this study. First, retrospective design of the study may have precluded the elimination of unknown confounders. Second, many patients were excluded from the study due to missing data. Finally, our sample size is low for PCa, which is known to be seen at a high rate in the society. However, the main strengths of this study are that it is one of the rare studies of the clinical use of DRR value for detecting PCa following PNB in biopsy naive males. Owing to the strength of the ROC analysis used in our study, we believe that the results of this study are valuable and clinically relevant.

Conclusion

In light of these outcomes, our study suggests that DRR has restricted diagnostic importance in predicting PCa in biopsy-naive patients undergoing transrectal PNB. Moreover, it is insufficient in discriminating csPCa and nsPCa. Although it appears to be a limited diagnostic test in our study results, we think that its joint use with risk factors related to PCa may be valuable for clinicians.

Ethics

Ethics Committee Approval: The study was approved by the Local Institutional Ethics Committee (IRB no: 2020.06.2.02.086).

Informed Consent: A written informed consent on admittance to hospital was obtained from all individuals, which permitted the use of respective medical information in clinical studies.

Authorship Contributions

Concept: Y.Ş., M.Y., A.S., A.Y.M., İ.H., Design: Y.Ş., M.Y., A.S., A.Y.M., İ.H., Data Collection or Processing: Y.F., Y.Ş., Analysis or Interpretation: A.Ç., M.Y., Writing: A.Y.M., A.S., M.Y., Y.Ş., Y.F., A.Ç., İ.H.

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ORIGINAL RESEARCH

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The Quality of Life Measurements Following Oncoplastic Breast-conserving Surgery

Meme Koruyucu Onkoplastik Cerrahi Sonrası Yaşam Kalitesinin Ölçümü

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Abstract

Objective: Oncoplastic breast-conserving surgery (OBCS) is a widely accepted surgical option among breast cancer patients. We aimed to evaluate the histopathological findings of breast tumors and quality of life scores.

Method: The clinical and pathological data of 49 female patients who underwent OBSC in University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital between January 2015 and January 2019 for breast cancer were retrospectively evaluated. According to the location of the tumor, the racket method or J-mammoplasty techniques was selected. Quality of life and patient satisfaction assessment questionnaire was performed.

Results: The mean age was 48.1 (26-68) years. The most common incision pattern was the racket pattern (85%). The invasive ductal carcinoma (89.8%) was seen more than ductal carcinoma *in situ* (6.1%) and papillary carcinoma (4.1%). The distance to the surgical margin was approximately 7.1 mm (1-20). The estrogen receptor positivity was 74.2% (5-100%) and progesterone receptor positivity was 61.8% (5-98%). 61.2% received chemotherapy (100%, radiotherapy). Based on questionnaires, the score of quality of life and satisfaction was 34 (25-47). Especially, the body image function [22 (15-29)] and health functions [10 (7-13)], such as breast & arm symptoms, were better in the patients who had higher scores (p<0.001).

Conclusion: The histopathological patterns of the patients following OBSC potentially did not show any impact among the quality of life and satisfaction scores.

Keywords: Breast cancer, breast-conserving surgery, quality of life

Öz

Amaç: Meme koruyucu onkoplastik cerrahi (MKOC), onkolojik ve cerrahi alanda yaygın olduğu kadar meme kanseri hastaları arasında da oldukça fazla kabul görmektedir. Bu çalışmada, MKOC uygulanan hastaların meme tümörlerinin histopatolojik sonuçlarını ve yaşam kalitesi skorlarını değerlendirmeyi amaçladık.

Yöntem: Sağlık Bilimleri Üniversitesi, İstanbul Bağcılar Eğitim ve Araştırma Hastanesi'nde Ocak 2015 - Ocak 2019 tarihleri arasında meme kanseri nedeniyle MKOC uygulanan 49 kadın hastanın klinik ve patolojik verileri retrospektif olarak incelendi. Tümörün lokalizasyonuna göre, insizyon paternleri olarak raket yöntemi veya J-mamoplasti kullanılmıştır. Hastalara yaşam kalitesi ve hasta memnuniyeti değerlendirme anketi yapıldı.

Bulgular: Hastaların yaş ortalaması 48,1 (26-68) yıl idi. En yaygın insizyon paterni raket paterniydi (%85). En sık görülen histopatolojik bulgu invaziv duktal karsinom (%89,8), en az görülenler ise *in situ* duktal karsinom (%6,1) ve papiller karsinomdu (%4,1). Tümörlerin cerrahi sınıra uzaklığı yaklaşık 7,1 mm (1-20) idi. Östrojen reseptörü pozitifliği ortalama %74,2 (%5-%100) ve progesteron reseptörü pozitifliği ortalaması %61,8 (%5-%98) idi. Hastaların % 61,2'si kemoterapi, %100 radyoterapi aldı. Anket sonuçlarına göre, ortalama yaşam kalitesi ve memnuniyet skoru ortalaması 34 (25-47) idi. Hayat kalite skoru daha iyi olan hastalarda, özellikle vücut imajı fonksiyonu [22 (16-29)] ve meme ve kol semptomları gibi sağlık fonksiyonları [10 (7-13)] daha iyi idi (p<0,001).

Sonuç: MKOC yapılan hastaların histopatolojik paternlerinin, yaşam kalitesini ve memnuniyetini önemli ölçüde etkilemediğini göstermektedir.

Anahtar kelimeler: Meme kanseri, meme koruyucu cerrahi, yaşam kalitesi

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Introduction

Today, breast cancer is the most common malignant tumor among women. 18% of cancer-related deaths in women occur due to breast cancer, and an increase in the frequency of breast cancer is expected in the next 10 years (1). Depending on the importance of the female breast in today's society, the anatomical location of breast cancer is a highly emotional issue. Therefore, it is imperative for the surgeon performing breast surgery to have a basic understanding of which patients are candidates for breast reconstruction and what reconstructive options are. Whether autogenous tissue or breast implant will be used, the location of the scar, and how long the healing will take are the questions that need to be answered. Besides, the emotional, physical, and oncological needs of the patient must be met before and after a breast surgery (2,3).

Oncoplastic breast-conserving surgery (OBCS) is a widely accepted operation in the oncological and surgical field as well as among breast cancer patients (1,2). OBCS is an innovative therapeutic option for patients with an early stage of breast cancer; however, it is characterized by special approaches to tumor resection following a breast reconstruction (3,4). The main purpose of OBCS is to maintain or potentially improve a patient's quality of life, including long-term survival while providing a good breast appearance (1,5,6). Deformations and unsatisfactory cosmetic results following breast cancer surgeries have contributed to the increasing popularity of OBCS (7). Cosmetic and functional results of the surgery are highly related to the quality of life, while the poor aesthetic results are associated with psychosocial distress and a poor quality of life (8). To the best of our knowledge, the relationship between the histopathological findings of breast tumors and the quality of life of patients has not been studied before. In this retrospective study, we aimed to reveal the relationship between the histopathological results of breast tumors and the quality of life scores of the patients undergoing OBSC.

Materials and Methods

After obtaining the approval of our hospital's ethics committee for the study, clinical and pathological data of 49 female patients who underwent OBSC due to breast cancer between January 2015 and January 2019 at University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital were retrospectively analyzed. All patients underwent preoperative radiological imaging. Depending on the localization of the tumor, one of the techniques, namely the tennis racket method, or J-mammoplasty, was selected as an incision pattern of tumors. If the tumor to be excised was located on the upper quadrant of the breast, racket method was selected. Besides the histopathological data of the patients, the numbers of those who received chemotherapy or radiotherapy, and who imaged by positron emission tomography, magnetic resonance imaging, computed tomography, mammography, or ultrasonography were recorded. The Turkish version of quality of life and patient satisfaction assessment questionnaire (EORTC QLQ-BR23) was performed to the patients after the surgery, and the results were evaluated in three groups on a scale of 1-4, and then the scores were correlated with the histopathological findings reported. The quality of life score was dichotomized based on data review (less than 34.42 or greater than 34.42). QLQ-BR23 scores were measured as physical function [body image function, sexual function and health function (breast & arm symptoms)] (9,10).

Statistical Analysis

Descriptive statistics were reported as percentages for categorical variables and as mean with standard deviation for continuous variables. The analysis comparing clinical covariates and quality of life scores were performed using chi-square test for categorical variables and t-test for parametric continuous variables. The Mann-Whitney U test was used for the variables that did not execute the normal distribution assumption. Parametric variables were correlated with the Pearson correlation test, and non-parametric variables were correlated with the Spearman correlation test. Significance was accepted at the level of $p<0.05$. All analyses were completed by R software version 3.4.2.

Results

The mean age of the patients was 48.1 (26-68) (minimum-maximum) years (Table 1). The post-surgical follow-up period was 21.9 (8-35) months. While a segmental mastectomy was performed in all patients, an axillary dissection was performed in 22 patients (44.9%). The most common incision pattern was the tennis racket (93.8%). The most common histopathological cancer type was invasive ductal carcinoma (IDC) observed in 44 patients (91.8%), the least types were ductal carcinoma *in situ* in 3 patients (6.1%) and papillary carcinoma in 2 patients (4.1%). The most frequent location of the tumor was the upper outer quadrant detected in 65.3% of patients (n=32). 12.2% (n=6) of the other patients had a tumor localized in

Table 1. Demographic and pathological findings of patients

	(n=49)
Age (minimum-maximum)	48.1 (26-68)
Operation	n (%)
The tennis racket method	46 (93.8%)
J-mammoplasty	3 (6.2%)
Surgery type	
SM+SLNB	27 (55.1%)
SM+AD	22 (44.9%)
Histological type	
DCIS	3 (6.1%)
IDC	44 (89.8%)
Papillary CA	2 (4.1%)
Number of metastatic lymph nodes	
0	36 (73.5%)
1-10	12 (24.5%)
>10	1 (2%)
T stage	
T1	36 (73.5%)
T2	13 (26.5%)
N stage	
N0	34 (69.4%)
N1	11 (22.4%)
N2	3 (6.1%)
N3	1 (2.1%)
M stage	
M0	49 (100%)
Tumor localization	
Upper outer quadrant (superior lateral)	32 (65.2%)
Upper inner quadrant (superior medial)	4 (8.2%)
Lower outer quadrant (inferior lateral)	2 (4.1%)
Lower inner quadrant (inferior medial)	5 (10.2%)
Retro areolar quadrant	6 (12.3%)
Grade	
1	11 (22.5%)
2	28 (57.1%)
3	10 (20.4%)
ER positivity (n=37) (X ± SD)	74.2±25.6
PR positivity (n=33) (X ± SD)	61.8±28.0
CERBB-2 positivity	
0	17 (34.6%)
+1	7 (14.2%)
+2	9 (18.3%)
+3	16 (32.6%)
Distance to surgical margin (X ± SD), (mm)	7.1±4.9
Chemotherapy rate N (%)	30 (61.2%)
Radiotherapy rate N (%)	49 (100%)
Quality of life score (minimum-maximum)	34 (25-47)
Physical function	20 (15-29)
Sexual function	5 (3-9)
Health function	9 (7-13)

X ± SD: Mean ± Standard deviation, SM + AD: Segmental mastectomy + axillary dissection, SM+SLNB: Segmental mastectomy+sentinel lymph node biopsy, DCIS: Ductal carcinoma *in situ*, IDC: Invasive ductal carcinoma, CI: Confidence of interval, LN: Lymph node, ER: Estrogen receptor, PR: Progesterone receptor, Normally distributed data were recorded as mean ± standard deviation

the retro areolar quadrant, 10.2% (n=5) had a tumor in the lower inner quadrant, 8.2% (n=4) had in the upper inner quadrant, and 4.1% (n=2) had in the lower outer quadrant. No significant relationship was found between the histological types and tumor locations (p=0.125). However, the most common type, namely IDC, was detected in the upper outer quadrant.

The most common tumor grade was diagnosed in grade 2 (57.1%) and others were grade 1 (22.5%) and grade 3 (20.4%). Pathologically, the mean of CERBB-2 positivity was 2.3 (range: 1-3) among 32 patients (65.3%). The mean of estrogen receptor positivity was 74.2±25.6% among 37 patients, and progesterone receptor positivity was 61.8±28.0% among 33 patients. The mean distance of tumors to the surgical margin was 7.1±4.9 mm. 61.2% of the patients received chemotherapy and 100% received radiotherapy.

According to the results of the questionnaire, the mean quality of life and satisfaction score was 34 (25-47) among all patients, without any potential effect of the histological type of the tumor (p=0.513) (Table 1, 2). The physical functions [18.00 (16-27) vs. 22.00 (15-29), p<0.001] and health functions [8 (7-13) vs. 10 (7-13), p<0.001] were better in our patients with higher scores (Table 2). The findings of quality of life scores based on clinical and pathological parameters did not show any differences between the Tennis Racket and J-mammoplasty [35 (25-47) vs. 35 (26-42), p=0.716, and Segmental Mastectomy+Sentinel lymph node biopsy and Segmental Mastectomy+Axillary dissection [34 (25-47) vs. 36 (33-42), p=0.426], (Table 3). We did not report any significant correlation between the demographical and pathological variables with the quality of life scores of patients (p>0.05) (Table 4).

Table 2. Comparison of quality of life scores based on clinical parameters

	Quality of life score (n=25) (<34.42)	Quality of life score (n=24) (≥34.42)	p
Age (X ± SD)	49.00±8.63	47.21±10.05	0.506
Operation (J-mammoplasty) (%)	2 (8.0)	1 (4.2)	1
Surgery (SM+AD) (%)	11 (44.0)	11 (45.8)	1
Histopathology (%)	-	-	0.513
DCIS	2 (8.0)	1 (4.2)	-
IDC	22 (88.0)	23 (95.8)	-
Papillary carcinoma	1 (4.0)	0 (0.0)	-
Stage (%)			
1	14 (56.0)	15 (62.5)	0.475
2	11 (44.0)	8 (33.3)	-
3	0 (0.0)	1 (4.2)	-
Grade (%)	-	-	0.549
1	7 (28.0)	4 (16.7)	-
2	14 (56.0)	14 (58.3)	-
3	4 (16.0)	6 (25.0)	-
Quality of life score median (min-max)			
Physical function	18.00 (16-27)	22.04 (15-29)	<0.001*
Sexual function	4.96 (3-6)	5.17 (3-9)	0.623
Health function	8.64 (7-13)	10.17 (7-13)	<0.001*

X ± SD: Mean ± Standard deviation, *p<0.05 vs other groups. Normally distributed data were recorded as mean ± SD, SM+AD: Segmental mastectomy+axillary dissection, DCIS: Ductal carcinoma *in situ*, IDC: Invasive ductal carcinoma

Table 3. Results of quality of life scores based on clinical and pathological parameters

	Quality of life score median (min-max)	p
Surgery	-	0.716
The tennis racket method (n=27)	35 (25-47)	-
J-mammoplasty (n=22)	34 (26-42)	-
Operation	-	0.426
SM+SLNB (n=46)	34 (25-47)	-
SM+AD (n=3)	36 (33-42)	-
Grade	-	0.864
G 1 (n=11)	33 (27-36)	-
G 2 (n=28)	34 (25-47)	-
G 3 (n=10)	35 (33-42)	-
T stage		
T 1 (n=37)	34 (26-47)	0.270
T 2 (n=12)	33 (25-43)	-
Chemotherapy	-	0.639
Yes (30)	34 (26-47)	-
No (19)	35 (25-43)	-

SM+SLNB: Segmental mastectomy+sentinel lymph node biopsy, SM+AD: Segmental mastectomy+axillary dissection, *p<0.05 vs other groups

Discussion

Breast cancer is the most common malignant tumor among women in the world and accounts for about 30% of cancers in women. In our country, it is reported that 24.1% of all cancers are breast cancer (11). Breast cancer is one of the cancer types with the best lifespan since its 5-year survival rate is 75% after diagnosis. Despite early diagnosis and treatment, cancers are critical diseases that can significantly change the quality of life of women (12,13). In breast cancer cases, the life span is prolonged due to an early diagnosis and treatment, and therefore, the concept of quality of life gains prominence.

The vast majority of cancers can be treated by early diagnosis and application of several treatment methods, hence the patient's life span can be extended. Among treatment options which are chemotherapy, radiotherapy, surgery, and hormonotherapy, one or more of these methods are utilized in the treatment depending on the individual characteristics and disease status of patients diagnosed with cancer. Cancer treatment aims to treat the disease, prolong life, and reduce the symptoms and thus to improve the quality of life (11-13). That is our main goal in our clinic to enlighten the palliative care such as psychological support before and after the surgery to improve the quality of life even it was our weakness that we did not have the base measurements for each time of follow-up.

Due to cancer, the surgical removal of the breast, which is an extremely important organ for a woman since being one of the prominent symbols of femininity and sexuality in the female body, poses a threat to the feelings of sexuality, motherhood, attraction, and body image (14). For this reason, patients have to cope with the feelings of breast

Table 4. The correlation matrix of demographic and pathological variables with the quality of life scores of patients (n=49)

	Quality of life score		
	Pearson r	95% CI	p
Age	0.017	-0.266-0.297	0.910
Surgery type	-0.121	-0.389-0.166	0.406
Stage	-0.204	-0.461-0.086	0.165
T	-0.169	-0.432-0.121	0.252
N	-0.101	-0.375-0.188	0.493
Tumor localization	0.085	-0.202-0.358	0.561
Grade	0.070	-0.215-0.345	0.631
Distance to surgical margin	0.084	-0.215-0.368	0.584
Chemotherapy rate	0.011	-0.274-0.295	0.939

CI: Confidence interval, *p<0.05

loss as well as the diagnosis of life-threatening cancer (15). As we can understand that mastectomy has a negative impact on the psychology of patients comparing to breast conserving surgery which oncoplastic surgery is beneficial regarding the clinical and pathological results, consistent with our findings.

Breast loss following a mastectomy has significant effects on mental health and sexual life (16). In a study by Sertöz et al. (17), in 125 women living with breast cancer for an average of 1.5 years, a total mastectomy has been reported to impair the body perception resulting in the sexual problems. Moreover, Soygür et al. (18) reported that 72.9% of breast cancer patients had an adjustment disorder and 27.1% had a major depression. Based on those different findings in the literature, it was similarly seen in our study that the quality of life outcomes was greater in breast conserving surgery regarding the clinical and pathological characteristics (19). Also, it has been shown in many studies that the mastectomy surgery disrupts the body perception, resulting in a decrease in sexual satisfaction and spouse adjustment (20,21). Therefore, a decrease in the quality of life of patients undergoing a mastectomy is an inevitable result. In our study, we compared the histopathological results of breast tumors and the quality of life scores of patients undergoing OBSC. However, we reported that the quality of life and satisfaction assessment was not affected apparently following OBSC regardless of the stage of the disease and the histopathological type. Also, we did not observe any differences among the physical and health functions of the quality of life scores regarding the surgical or operational approaches which was consistent with the literature (22). Larger and multicenter prospective studies are needed to fully reveal the relationship between other histopathological findings of breast tumors and quality of life scores in patients undergoing an OBSC.

Opinions about which patients will receive breast reconstruction are as variable as the surgeons who perform the procedure. Principally, young patients with an early-stage disease without any comorbidity are the best candidates for the reconstruction, and therefore, unfortunately, older patients with severe breast cancer are the worse candidates. Due to a large number of different reconstructive options available today, all patients should first be offered at least these options (23). Especially, our patients' depression, anxiety and psychological unmet needs are seriously considered and followed in our daily clinical practice, which is consistent with the previous studies in our country (24).

Consistent with the literature regarding the breast cancer treatment, our measurements were similar to the findings of some base EORTC QLQ-BR23 results of the control group of the trial for a postsurgical lymphedema during follow-up period (25). The various post-operative studies regarding the OBCS are related to a better quality of life, better physical and psychological well-being, improved social- and emotional functioning, higher self-esteem and stable body image which were observed in our small population, even in the post-operative follow-up period, and the other sexual or psychological questionnaires were different (26). Consistently, as we reported that physical functions [18.00 (16-27) vs. 22.00 (15-29), $p<0.001$] and heath functions [8(7-13) vs. 10 (7-13), $p<0.001$] were better in our patients with higher clinical scores following surgery.

Study Limitations

The limitations in our study are that a small sample size of patients has been analyzed retrospectively from the data of a single center and single breast surgery group in a restricted region. Considering the preliminary results, it was observed that the patients who underwent oncoplastic surgery were not affected by the decrease in the quality of life depending on the histological type of cancer, suggesting the importance of providing more social and psychological support to these patients in the clinic before and after the oncoplastic surgeries.

Conclusion

Consequently, we reported that the histopathological patterns of the patients following OBSC potentially did not show any impact among the quality of life and satisfaction scores. Moreover, the possible complications of surgical trauma and prolonged recovery period obligate full evaluation of all patients, both physically and psychologically, following the reconstruction. For this reason, social and psychological support during the surgical interventions gains importance in the clinic. Thus, it is warranted to conduct prospective randomized national or international studies with a larger number of patients to investigate new clinical aspects to measure socio-demographic characteristics.

Ethics

Ethics Committee Approval: A non-interventional ethical approval was obtained from University of Health Sciences Turkey, İstanbul Bağcılar Training and Research

Hospital Ethical Committee (date: 27.12.2019 number: 2019.12.2.02.092).

Informed Consent: Patient consent could not be obtained because it was a retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Y.A., M.T., A.A., A.Ç., Design: Y.A., M.T., A.A., A.Ç., Data Collection or Processing: Y.A., N.A.H., T.V., G.E., A.A., Analysis or Interpretation: Y.A., N.A.H., M.T., H.Y., Writing: Y.A., A.A., M.T.

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ORIGINAL RESEARCH

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Bacterial Translocation Relationship with Enteral L-Glutamine and L-Alanine in Experimental Rat Burn Model

Deneysel Sıçan Yanık Modelinde, Enteral L-Glutamin ve L-Alanin ile Bakteriyel Translokasyon İlişkisi

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Abstract

Objective: The aim of this experimental study is to research the effects of L-alanine and L-glutamine, which are being widely used on intensive care patients, on the liver, structural changes in the small intestine, wound healing, and bacterial translocation.

Method: Twenty male Sprague Dawley rats which weighe 190-230 gr were used in this study. Rats were separated into two randomized groups. In accordance with experimental rat burn model, skin burn was created in every rat and both groups were fed equally for 21 days. The experimental group was administered L-glutamine + L-alanine containing product (Dipeptiven®, Fresenius Kabi BadHamborg, Germany) for 5 mL/kg/day orally. At the end of the 21st day, all rats were sacrificed. Biopsy materials were obtained from the liver, small intestine, and burn wound, and blood culture was taken under sterile conditions. In pathologic examination, structural changes in tissues and wound healing were evaluated. In microbiologic examination, the effects of L-glutamine and L-alanine on bacterial translocation were evaluated by comparing small intestine and blood cultures.

Results: No structural difference was seen among small intestine biopsies between two groups. No liver damage was seen in the experimental group while live biopsies showed grade 1 damage in the control group. Epithelization and granulation were detected as better in the pathologic examination of skin biopsies obtained from burn wound in the experimental group. Microbiologic examination showed bacterial replication in a total of 4 rats from the control group, two rats showed

Öz

Amaç: Bu deneysel çalışmanın amacı, yoğun bakım hastalarında sıklıkla kullanılan L-alanin + L-glutaminin, karaciğer, ince bağırsaktaki yapısal değişikliklere, yara iyileşmesine ve bakteriyel translokasyona etkilerinin araştırılmasıdır.

Yöntem: Bu çalışmada 190-230 gr olan 20 adet erkek Sprague Dawley rat kullanıldı. Deney, 2 grup üzerinde tasarlandı. Tüm ratlarda, deneysel rat yanık modeline uygun olarak yanık oluşturuldu ve her iki grup eşit şartlarda 21 gün beslendi. Deney grubuna, 5 mL/kg/gün L-glutamin + L-alanin içeren (Dipeptiven®, Fresenius Kabi BadHamborg, Almanya) preparat oral yolla verildi. Yirmi bir günün sonunda tüm ratlar sakrifiye edildi. Tüm ratlardan steril şartlarda, karaciğer, ince bağırsak, yanık yarasından biyopsiler ve kan kültürleri alındı. Patolojik incelemede karaciğer ve ince bağırsak dokularındaki yapısal değişiklikler ve yara iyileşmesi değerlendirildi. Mikrobiyolojik incelemede ince bağırsak ve kan kültürleri kıyaslanarak L- glutamin + L-alaninin bakteriyel translokasyona etkisi araştırıldı.

Bulgular: İki grup arasında ince bağırsak biyopsileri arasında hiçbir yapısal fark görülmedi. Karaciğer biyopsilerinde kontrol grubunda grade 1 hasarlanma mevcutken deney grubunda hasar tespit edilemedi. Yanık yarasından alınan deri biyopsilerinin patolojik incelemesinde deney grubunda epitelizasyon ve granulasyonun daha iyi olduğu tespit edildi. Mikrobiyolojik incelemede kontrol grubundaki iki ratın ince bağırsak ve kan kültürlerinde *S. aureus*, iki ratın ince bağırsak ve kan kültürlerinde de *S.epidermidis* olmak üzere toplamda dört ratta üreme tespit edildi.

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Abstract

replication of *S. aures* in the small intestine and blood culture and two rats showed replication of *S. epidermidis* in the small intestine and blood culture. No replication was determined in any rats from the experimental group.

Conclusion: In the light of findings acquired from this study done with experimental rat burn model, we think that the use of L-glutamine + L-alanine will have positive effects on wound healing and help preventing the bacterial translocation in burn patients as a supporting product.

Keywords: Bacterial translocation, burn, L-alanine, L-glutamine

Öz

Deney grubundaki hiçbir ratın ince bağırsak ve kan kültürlerinde üreme olmadı.

Sonuç: Deneysel rat yanık modelinde yapılan bu çalışmanın sonucunda elde ettiğimiz verilere göre, L-glutamin + L-alanin kullanımının, yanık hastalarının yara iyileşmesine olumlu etkisi olduğu, ek olarak da bakteriyel translokasyonu engellemeye yardımcı olduğu kanısına vardık.

Anahtar kelimeler: Bakteriyal translokasyon, L-alanin, L- glutamin, yanık

Introduction

Since severe burn cases with a large burn surface quickly enter the catabolic process, it is important to manage the process well starting from the early period. In addition to all the difficult stages such as fluid replacement, wound care, pain control, and replacement of electrolytes, enteral and parenteral nutritional supplement products are also needed (1).

Amino acids play an important role not only as protein building blocks but also as precursors in the biosynthesis of many important biological and physiological compounds. In severe stress situations such as sepsis, trauma, burns, malnutrition and prolonged oral nutrition and healing of surgical wounds, the need for glutamine exceeds its synthesis capacity and must be added to the diet. So, it becomes essential. The requirement of proteins, which are indispensable for life, is calculated according to the degree of the metabolic deficit, stress factor, and the degree of use and metabolization of the protein. Inflammation plays a vital role in the breakdown of the intestinal barrier, either directly or by inducing tumour necrosis factor-alpha. Studies in the literature reporting that glutamine increases intestinal barrier functions after both inflammation and immunosuppressive events are available (2).

Glutamine is vital as ammonia scavenger transport and as a precursor in nucleotide synthesis. It uses high amounts of glutamine in nucleotide synthesis to support the rapid conversion of the intestinal mucosa. In catabolic diseases supported by glutamine treatment, nitrogen balance and immune system function have been shown to improve and reduce mortality and morbidity (3). In addition to personal factors, it is important to protect the patient from infection during the burn healing process. In addition to systemic antibiotic treatment, the effect of food supplementation on the protection of bowel flora, mortality and morbidity reduction should not be ignored (4).

Many studies show that post-burn sepsis causes intestinal barrier disorder and damaged host defense. Bacterial translocation may increase the rate of infection in critically ill patients while leading to multiple organ failure. It was also found to be associated with enteral bacterial translocation in experimental studies that investigate morphological changes in rat intestinal villi after severe burns (5-7). Bacterial translocation (BT) occurs after thermal injury and may result from an ischemic intestine (8,9). Some medications have been tried enterally and parenterally to reduce bacterial translocation, even the effects of hyperbaric oxygen and ozone are controversial today (10-13).

In this study, we aimed to determine the effect of L-alanine + L-glutamine preparation on post-burn sepsis, structural changes in the liver and small intestine, wound healing and on bacterial translocation.

Materials and Methods

After getting approval from the local institutional review board (Dicle University Local Ethics Committee no: 2012/42), 20 adult rats with an average weight of 330 g were used in this study. Each rat was caged singly and was provided rat food and water. All rats were first anesthetized with 90 mg/kg intraperitoneal (Ketalar®, Pfizer). Then, the back of all rats was shaved. The shaved area was first wiped with povidone iodine, and then burned. According to the "rat burn model", a 170 °C stainless steel metal plate with equal elevation and equal pressure curve was burned for 30 seconds by touching the back skin of the rat. After burning, 20 rats were randomly divided into 2 groups and placed in separate cages. Throughout the entire experiment, all animals were housed in cages together so that 10 rats were in one cage under standard physical conditions. While both groups were fed in a standard way, additionally the preparation containing 5 mL/kg/day L-glutamine +

L- alanine (Dipeptiven®, Fresenius Kabi BadHamborg, Germany) was given by oral gavage for 21 days for the experimental group. After 21 days, intra-cardiac blood was collected from all rats and they were sacrificed by decapitation. The blood was taken into the ''Bactec pediatric®'' blood culture tubes. Biopsies were taken from the liver, small intestine and wound of all rats after the sacrifice. While blood culture samples and biopsy samples taken from the small intestine were sent for microbiological examination, they were also examined pathologically.

Histopathologic Analysis

The tissue specimens were kept in 10% paraformaldehyde solution for 48 hours, followed by immersion into routine paraffin. Samples of 5-micron sections were taken from tissues embedded in paraffin blocks and were stained with Hematoxylin-Eosin. The sections obtained were evaluated by a specialist pathologist and classified with a light microscope (Table 1).

Classification of liver damage:

Grade 0: Minimal damage or none.

Grade 1: Mild injury characterized by cytoplasmic vacuoles and nuclear local pycnosis.

Grade 2: Moderate injury; no necrosis, ballooning in hepatocytes, cytoplasmic vacuolization, sinusoidal dilation, congestion, blurring of borders between cells.

Grade 3: Moderate to severe injury; coagulation necrosis, cytoplasmic hypereosinophilia, large sinusoidal dilation, and congestion areas.

Grade 4: Serious injury; disruption of the architectural structure of cells with coagulation necrosis and distribution, bleeding into hepatic chords.

Classification of small bowel damage:

Grade 0: No damage.

Grade 1: Edema, congestion, mild inflammation.

Grade 2: Mild inflammation, mild hemorrhage.

Grade 3: Was scored as severe inflammation, intense bleeding areas and necrosis.

Table 1. Histopathologic scoring

Histopathologic score		
Grade 0	Inflammation	No
	Vascularization	No
	Epithelization	No
	Granulation tissue	No
Grade 1	Inflammation	Light
	Vascularization	Few capillaries
	Epithelization	Minimal epithelialization
	Granulation tissue	A thin layer
Grade 2	Inflammation	Middle
	Vascularization	Well differentiated capillary system
	Epithelization	Totally, thin layer
	Granulation tissue	A thick layer
Grade 3	Inflammation	Severe
	Vascularization	Extensive neovascularization
	Epithelization	Totally, thick layer
	Granulation tissue	A uniform thick layer

Microbiological Analysis

In our study, small intestine tissue samples from group 1 (control group) and group 2 (experimental group) subjects were taken for microbiological examination within 10 minutes in a sterile container. For this, tissue samples were planted on 2 sheep blood agar, 1 mac conkey agar, and 1 chocolate agar. Samples were incubated at 36.8 °C for 24 hours, and microorganisms that reproduced at the end of the incubation period were identified through conventional methods and automatization [Phoenix™ 100 (Becton Dickinson, MD, USA)].

The other sheep blood agar media was incubated at 36.8 °C for 48 hours in anaerobic medium (in the GASPAK jar). Conventional methods and VITEK 2 (bioMérieux, France) fully automated identification system were used for the typing of anaerobic microorganisms. On the other hand, blood samples taken from group 1 and group 2 subjects were inoculated into the BACTEC peds plus/F (BD, Sparks, MD)® blood culture bottles. Blood samples (1 mL) from reproductive blood culture bottles were planted in sheep blood agar, mac conkey agar, and chocolate agar media.

Samples were incubated for 24 hours at 36.8 °C and microorganisms grown at the end of the incubation period were identified by conventional methods and automated system [Phoenix™ 100 (Becton Dickinson, USA)].

The microorganism species growing in the intestinal tissue and blood culture bottles of subjects in group 1 and group 2 were recorded. If the microorganism breeding in the small intestine culture of the same rat also reproduced in the blood culture, it was interpreted that microorganism was the cause and that rat entered the sepsis. The reproduction of different microorganisms in the same rat was evaluated as contamination.

Statistical Analysis

As statistical tests; in evaluating continuous measurement variables, the Mann-Whitney U test, or the Student's t-test, was used according to their unequal or equal distribution. The categorical variables were evaluated with the chi-square test or the chi-square Fisher test. The results obtained were considered statistically significant when $p<0.05$.

Results

Pathological scoring was achieved as a result of the evaluation of tissue specimens; the histopathological results in the study are provided (Table 2, 3).

In histopathological examination, no difference was observed between the two groups in the small intestine structures (Figure 1, 2). In the examination of the liver tissues, eight of ten rats in the control group had grade 1 damage, whereas no rat in the experimental group was damaged (Figure 3, 4). When comparing the control group with the experimental group in the examination of the burn areas, epithelialization, granulation, and inflammation were less in the experimental group, and vascularization was similar in both groups.

Microbiological analysis results are given for group 1 (Table 4) and group 2 below (Table 5).

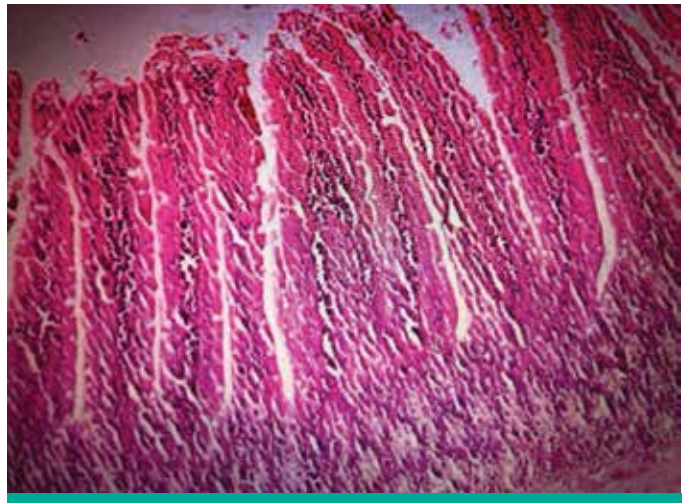

Figure 1. Ordinary-looking small intestine tissue in a normally fed rat

Table 2. Histopathological examination results in the control group

Group	Liver damage	Skin inflammation	Skin granulation	Skin vascularization	Skin epithelization
GRP.1.1	1	3	1	2	0
GRP.1.2	1	3	2	1	0
GRP.1.3	1	3	2	2	0
GRP.1.4	0	2	0	2	0
GRP.1.5	1	3	1	3	0
GRP.1.6	1	2	1	1	0
GRP.1.7	0	3	1	2	0
GRP.1.8	1	3	2	2	0
GRP.1.9	1	3	2	1	0
GRP.1.10	1	2	2	1	0

Table 3. Histopathological examination results in the experimental group

Group	Liver damage	Skin inflammation	Skin granulation	Skin vascularization	Skin epithelization
GRP.2.1	0	1	2	2	1
GRP.2.2	0	2	2	2	2
GRP.2.3	0	1	3	3	2
GRP.2.4	0	1	2	1	1
GRP.2.5	0	1	3	2	2
GRP.2.6	0	2	2	1	1
GRP.2.7	0	1	2	1	1
GRP.2.8	0	1	2	1	2
GRP.2.9	0	1	3	2	1
GRP.2.10	0	2	3	1	2

In microbiological examination, active microorganism was detected in 4 rats in the small intestine and blood cultures in the control group, whereas no active microorganism was observed in the experimental group. The probability of positivity in the small intestine culture between the two groups was significantly higher in the control group.

In statistical analysis, inflammation in liver tissue was significantly less in the experimental group (p=0.001). In the experimental group, epithelization and granulation in burn tissue were significantly higher and inflammation was significantly less than in the control group (p<0.05) (Figure 5). There was no significant difference in vascularization (p=0.88)

Discussion

Burn injuries are an important public health problem. Although it is seen in every age group, it is more common in children and the elderly compared to the community average. 90% of burn injuries are mild enough to be tracked from home. While wide and deep burns are treated in hospital, there may be other complications related to long-term hospitalization. Inpatient hospitalization increases the susceptibility to hospital infections in addition to socioeconomic and psychological problems. Gudaviciene,

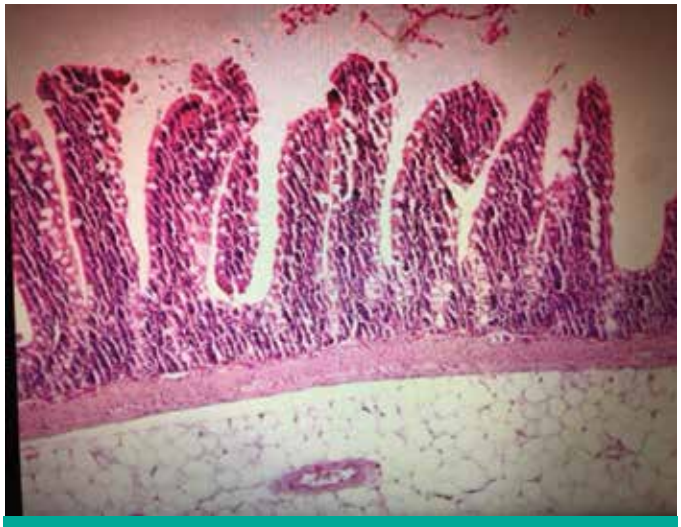

Figure 2. Ordinary looking small intestine tissue in a protein-fed rat

Table 4. Control group microbiological evaluation

Rat number	Positive culture in the small intestine	Positive culture in the blood	Evaluation
1	*S. aureus*	*S. aureus*	Active
2	*S. epidermidis*	*S. epidermidis*	Active
3	*E. coli*	Negative culture	Contamination
4	*S. aureus*	*S. aureus*	Active
5	*S. epidermidis*	*S. epidermidis*	Active
6	Negative culture	Negative culture	-
7	Negative culture	Negative culture	-
8	Negative culture	Negative culture	-
9	Negative culture	Negative culture	-
10	Negative culture	Negative culture	-

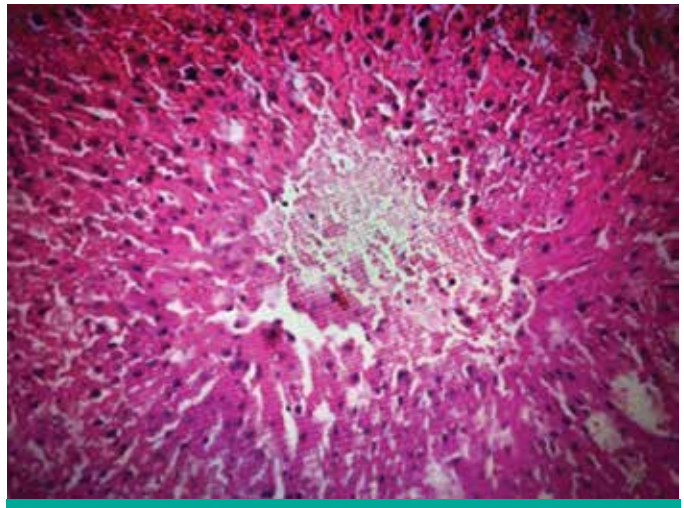

Figure 3. Grade 1 damage to the liver in a rat in the control group

Table 5. Microbiological evaluation of the experimental group

Rat number	Positive culture in the small intestine	Positive culture in the blood	Evaluation
1	Negative culture	Negative culture	-
2	*Peptostreptococcus* spp., *E. coli*, alpha hemolytic *streptococcus*	Negative culture	Contamination?
3	Negative culture	Negative culture	-
4	Negative culture	Negative culture	-
5	Negative culture	Negative culture	-
6	Negative culture	Negative culture	-
7	Negative culture	Negative culture	-
8	Negative culture	Negative culture	-
9	Negative culture	Negative culture	-
10	Negative culture	Negative culture	-

in his study, has reported that burn trauma accounts for 5-12% of all traumas, 10% of all burns are hospitalized, the rate of mortality increases rapidly as the burn rate exceeds 20%, and the most common causes of death are lung edema, pneumonia, sepsis and multiple organ failure. They reported that nutritional support contributed significantly to possible complications and survival and shortened the length of hospital stay (14). Severe burn damage causes serious metabolic disorders and increased metabolic rate. As a result, protein energy malnutrition occurs. This situation delays wound healing, increases muscle loss, causes growth and development retardation in children, and increases the tendency to infections over time. In the study of Grau Carmona et al. (15), it was reported that the hypermetabolic response resulting from thermal injuries is very severe and basal metabolism can increase up to 2 times. It was stated that these patients would need intensive nutritional support and that nutritional supplement should not be in the form of caloric supplement only. In particular, arginine + glutamine infusion, vitamin C, vitamin A and zinc administration have been reported to reduce morbidity and mortality in patients, as well as accelerating wound healing (15). Therefore, nutritional support is vital in preventing complications in the treatment process in large burn injuries. In the early 1970s, with the inclusion of nutritional support in burn treatment, the survival rates of people exposed to this trauma have been shown to increase significantly (16). Since then, research on the subject has continued increasingly in a wide variety of branches of nutrition. Nutritional products to be given to critical patients have been developed rapidly in recent years and new products have been released. What is given to which patient, which way to give and the full effect of the given substance are the main subjects of the research. In a study conducted on 30 patients in the burn intensive care unit, Guo et al. (2) concluded that cellular immune function increased in 14 patients in the group fed with an Arginine enriched enteral nutrition product. In the study of resuscitated severe burns by Yan et al. (3), early recovery was observed after resuscitation in the group fed with food supplemented with L-arginin. Peng and Weng (4) have reported in their studies that, in both patients and animal experiments, glutamine reduces intestinal damage, strengthens immunity and shortens hospital stay of burn patients. Previous studies have shown that post-burn injury is associated with impaired integrity of the intestinal barrier, increased intestinal permeability, more serious infections, and advanced septic complications (5,6).

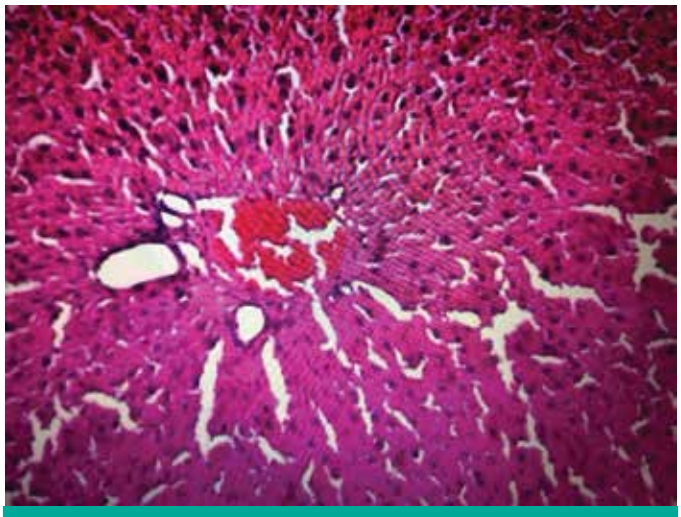

Figure 4. The usual-looking liver tissue in a rat in the experimental group

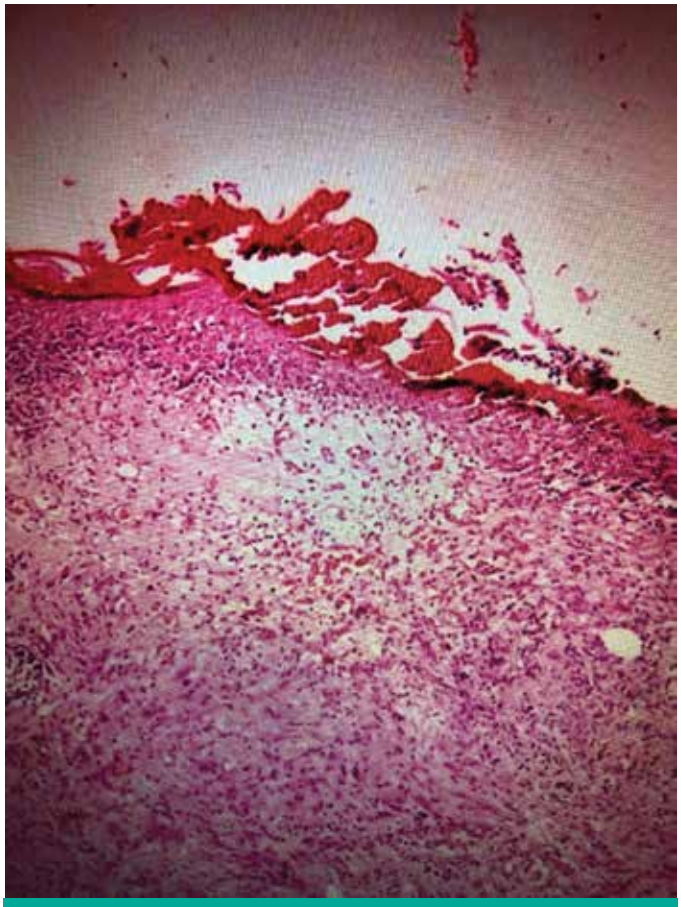

Figure 5. In a rat in the experimental group, surface epithelization is grade 2, inflammation is grade 1, and vascularization is grade 2 (H&E, 100X)

The metabolic rate varies between 118% and 210% in the estimation made according to the Harris-Benedict equation in adult patients who have experienced burn injury covering 25% of the body surface area (17). In burn

patients, whose more than 40% of the body surface area is affected, the metabolic rate at rest at 33 °C is 180% of the basal metabolic rate in acute application, 150% when the wounds are fully closed, 140% 6 months after the injury, 9 it reaches 120% after a month and 110% after 1 year. If such high calorie loss is not met, the patient develops weight loss and increases mortality and morbidity.

There are many studies on how to use supplements. In a study by De Luis et al. (18), parenteral nutrition was reported to be more beneficial than enteral nutrition, especially in a number of diseases such as burns, pancreatitis and septic inflammatory bowel disease (18). In the study of Soeters and Grecu (19), glutamine supplements were recommended to severe burn patients and the parenteral route was reported to be more beneficial than the enteral route. In the study conducted by Burns and Gill (20), it was reported that in an adult patient with short bowel syndrome, who had to be fed parenterally, parenteral nutrition caused complications such as liver lubrication, stenosis in the hepatic pathways, and existing complications in the liver, including omegaven, regressed (20). Although oral feeding is recommended in patients who can take orally in accordance with all these studies, there are studies reporting that parenteral delivery of additive proteins such as L-alanine and L-glutamine will be more beneficial. Both the enteral form and the parenteral form of L-alanine and L-glutamine have been developed commercially. Supplemental nutrients given in patients with deep burns can reduce mortality and morbidity. Although there are many studies on the content of supplementary nutrients, these studies are generally concentrated on fish oil (m-3), L-glutamine, and L-alanine. L-alanine turns into a non-essential amino acid arginine in the body. Arginine is a stimulant in growth hormone, prolactin, glucagon and insulin release, as well as a nitric oxide (NO) precursor. NO has been reported to regulate vasodilator and hepatic protein synthesis and reduce anti-inflammatory mediator release, creating an anti-inflammatory effect and suppressing the harmful inflammatory response. Arginine plays a major role in wound healing as it plays a key role in collagen synthesis. In recent studies, supplementation of post-traumatic arginine has been shown to reduce intestinal damage and accelerate wound healing. There is no consensus on its effect on bacterial translocation. There are studies reporting that it is effective in this regard, as well as studies that say it is not effective.

Glutamine is abundant in plasma and skeletal muscles and is classified as a non-essential amino acid. However, there are studies reporting that plasma levels decrease significantly after traumas, especially burns or severe surgical operations, so it may be essential in some cases. One of the most important tasks of glutamine is the fuel for fast-regenerating cells, especially erythrocytes. Many studies have been conducted on its effect on the gastrointestinal tract and its regulatory effect on intestinal functions has been demonstrated. Glutamine is recommended as an additional nutrient to prevent bacterial translocation in patients receiving radiotherapy or chemotherapy, fed parenterally for a long time, and in septic patients with small bowel damage expected. It has been demonstrated in clinical studies that multiple organ failure due to sepsis decreases in patients who are given glutamine as an additional nutrient (21). Glutamine is the leading molecule of glutathione, an antioxidant. Glutathione is used in visceral protein synthesis in the liver and ammonia synthesis in the kidney. Glutathione, which is abundant in muscle tissue, can also be obtained from the Krebs cycle in cases of increased stress. However, this situation causes muscle loss in the patient. In the study of Donmez et al. (22), in the sepsis model created in rats, the effect of glutamine and growth hormone on opening the anastomosis was evaluated after fistula repair in the intestines (22). In the same study, the combination of glutamine and growth hormone has been reported to have positive effects on wound healing in the intestinal wall and the use of glutamine in patients who have undergone intrabdominal surgery has been proposed.

In the study of Quirino et al. (23), the effect of arginine on bacterial translocation was investigated. In the intestinal obstruction model of the rats, the control group was fed in the standard way, while the experiment group was given food rich in arginine for 7 days. At the end of the 7th day, *E. coli* marked with Tc-99m was given from the small intestine lumen, and after 24 hours, all rats were sacrificed and the levels of marked bacteria in blood, mesentery, spleen, lung and liver were measured. In the control group, a statistically significant bacterial translocation was detected in the experimental group. In the same study, it was emphasized that arginine was effective in preventing bacterial translocation and it was suggested to be used in patients expected to have bacterial translocation.

Lack of specific modeling for bacterial translocation detection is among the limitation criteria. In addition, other limitations of the study included that the burn caused tissue defect susceptible to additional infections and the samples obtained were difficult to protect from

contamination. In order to prevent this, the defect areas of rats were covered with wound dressing spray for a day. And while tissue samples were taken, they were studied quickly and easily fixed.

Unlike other studies, in our study, no difference was found in the pathological examination of small intestine samples between the rats in the control group and the rats in the experimental group. On the other hand, in the small intestine and blood cultures taken in 2 rats in the control group, *S. aureus* was reproduced. However, in the other 2 rats, *S. epidermidis* was reproduced. These positive results were statistically significant and were interpreted as bacterial translocation. For this reason, although we did not find the positive effect of glutamine and alanine on the intestinal wall in our study, we think that it has positive effects in preventing bacterial translocation.

Conclusion

In this study, while no positive culture occurred in the experimental group in blood culture examination, positivity was detected in 4 rats in the control group. Accordingly, it suggests that giving L-alanine L-glutamine as oral nutritional supplement has protective effects against sepsis. In the histopathological examination of liver biopsies, no damage was detected in the experimental group, while grade 1 damage was observed in the control group, suggesting that oral L-alanine L-glutamine administration may have a protective effect in severe burns cases. While inflammation was moderate in skin biopsies taken from the control group, inflammation was less in skin biopsies taken from the experimental group. While the development of granulation tissue was low and irregular in the control group, it was found to be more regular and higher in the experimental group. While epithelialization was not observed in the control group, it was moderate in the experimental group. Our study has showed that oral L-alanine L-glutamine administration as a supplement has a positive effect on burn wound healing. We believe that this application will also contribute to preventing complications that may develop in severe burns and a secondary reduction in mortality and morbidity.

Ethics

Ethics Committee Approval: After getting approval from the local institutional review board (Dicle University Local Ethics Committee no: 2012/42).

Informed Consent: Consent was not obtained because it was an animal study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.B., M.D., S.G., P.K., Design: P.K., S.G., M.D., Data Collection or Processing: P.K., S.G., M.D., Analysis or Interpretation: S.G., P.K., M.D., M.B., Literature Search: P.K., S.G., Writing: P.K., S.G., M.B.

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

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CASE REPORT

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A Case of Severe Spontaneous Pneumomediastinum in Acquired Immunosuppressed Child with Respiratory Syncytial Virus and Human Bocavirus Co-infection

Solunum Sinsityal Virüs ve İnsan Bokavirüs Ko-enfeksiyonu Olan Edinilmiş İmmün Yetmezlikli Çocuk Olguda Ciddi Bir Spontan Pnömomediastinum Olgusu

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Abstract

Spontaneous pneumomediastinum is an uncommon, benign, and self-limiting disease based on the presence of free air in the mediastinal cavity. It can occur after a forced Valsalva's maneuver due to a cough, emesis or during an asthma exacerbation. We present a 4-month-old girl infant with an autoimmune hemolytic anemia and lymphopenia, who was admitted to the pediatric intensive care unit due to respiratory distress. A suspected pneumomediastinum image on chest X-ray was documented by the chest tomography. A polymerase chain reaction of the nasopharyngeal secretions was positive for a respiratory syncytial virus and human bocavirus. Additionally, she was examined for an immune deficiency due to her lymphopenia. The patient required mechanical ventilatory support for 26 days. She was treated with antibiotics, antiviral, and antifungal agents and corticosteroids. Intravenous immunoglobulin, trimethoprim sulfamethoxazole, and fluconazole prophylaxis were continued because of the ongoing lymphopenia. At the end of five weeks, the patient was discharged with a normal lymphocyte count and without any respiratory distress. In immunosuppressed patients, respiratory diseases may be severe and long. Therefore, complications including pneumomediastinum can be seen more frequently in this group of patients.

Keywords: Human bocavirus, immunodeficiency, respiratory syncytial virus, rituximab, spontaneous pneumomediastinum

Öz

Spontan pnömomediastinum, mediastinal kavitede serbest hava varlığına dayanan, nadir görülen, iyi huylu ve kendi kendini sınırlayan bir hastalıktır. Öksürük, kusma veya astım alevlenmesi nedeniyle yapılan zorunlu bir Valsalva manevrasından sonra ortaya çıkabilir. Bu olgu sunumunda, solunum sıkıntısı nedeniyle pediyatrik yoğun bakım ünitesine yatırılan, otoimmün hemolitik anemi ve lenfopenisi olan 4 aylık bir kız çocuğunu sunduk. Akciğer grafisindeki şüpheli pnömomediastinum görüntüsü akciğer tomografisi ile belgelendi. Nazofarengeal salgıların polimeraz zincir reaksiyonu, solunum sinsityal virüsü ve insan bokavirüsü için pozitifti. Hasta ek olarak lenfopeni nedeniyle bağışıklık yetersizliği açısından da tetkik edildi. Hasta 26 gün mekanik ventilatör desteğine ihtiyaç duydu. Bu sırada antibiyotik, antiviral ve antifungal ajanlarla ve kortikosteroidlerle tedavi edildi. Devam eden lenfopeni nedeniyle intravenöz immünoglobulin, trimetoprim sulfametoksazol ve flukonazol profilaksisi kullanıldı. Bağışıklık sistemi baskılanmış hastalarda, solunum yolu hastalıkları şiddetli ve uzun sürebilir. Ayrıca, pnömomediastinum gibi komplikasyonlar bu hasta grubunda daha sık görüldüğünden dikkatli olmakta fayda vardır.

Anahtar kelimeler: İmmün yetmezlik, insan bokavirüsü, rituximab, solunum sinsityal virüsü, spontan pnömomediastinum

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Introduction

Spontaneous pneumomediastinum (SPM) is defined by the presence of free air in the mediastinum. It was reported by Hammam for the first time. It is also rare at the pediatric age (1). The most common-known etiologic cause of pneumomediastinum (PM) is trauma, but in children, it occurs after a forceful Valsalva's maneuver due to cough, emesis or an asthma exacerbation (2).

In this article, we present a 4-month-old girl patient with an autoimmune hemolytic anemia and lymphopenia. She was admitted to our pediatric intensive care unit (PICU) due to an SPM which occurred secondary to the respiratory syncytial virus (RSV) and human bocavirus (HBoV) co-infection. Additionally, she was examined for an immune deficiency due to the lymphopenia.

Case Report

A 4-month-old girl infant was admitted to our emergency room with a 5-day history of respiratory distress. Her heart rate was 165 beats/min, respiratory rate was 64/min, and her blood pressure was 100/88 mmHg. Venous blood gas analysis showed pH 7.43, pCO_2 37.4 torr, HCO_3 24.3,white blood cell count revealed lymphopenia (lymphocyte count: 870 mL, normal: 3.190-10.626 mL) and direct coombs was negative. A suspected PM image on the chest X-ray was documented by a chest tomography (Figure 1, 2). The child was referred to our PICU because of her worsening clinical condition.

In the PICU, she was intubated due to a hypoxic respiratory failure. Her medical history revealed that she had been treated with three days of pulse methylprednisolone and once with rituximab (RTX) treatment, for autoimmune hemolytic anemia last month. When she was admitted to our hospital, she was on methylprednisolone therapy at a dose of 2 mg/kg/day. The patient was examined for lymphopenia with immunoglobulins, alpha 1 antitrypsin level, lymphocyte subgroups, autoimmune disorders, cystic fibrosis, and metabolic disease screening. The patient and her family were screened for tuberculosis because of its frequency in our country.

The following day, a diagnosis of RSV and HBoV co-infection was made by reverse transcriptase-polymerase chain reaction (PCR) on a nasopharyngeal swab. The patient required mechanical ventilatory support for respiratory failure for two weeks. With the continuation of PM sign on control chest tomography, she required mechanical ventilatory support for two more weeks. Congenital metabolic diseases and autoimmune disorders were ruled out with normal urine and blood aminoacids and negative autoimmune markers. The alpha 1 antitrypsin level was normal (143 mg dL, normal: 111-297 mg dL). Serum immunoglobulin levels were within a normal range (IgG: 717 mg dL, normal: 294-1.165 mg dL, IgA: 14.5 mg dL, normal: 13.5-72 mg dL, IgM: 58.5 mg dL, normal: 33-154 mg dL). Absolute lymphocyte counts were 590 cells µL and lymphocyte phenotyping demonstrated $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$ and $CD16^+56^+$ lymphopenia [$CD3^+$ cells µL: 499 (1.933-7.362), $CD4^+$ cells µL: 295 (1.262-5.269), $CD8^+$ cells µL: 204 (498-252), $CD19^+$ cells µL: 0, $CD16^+56^+$ cells µL: 49 (95-1.740)]. Due to T^- B^- NK^- (natural killer) severe combined immunodeficiency phenotypic presentation, adenosine deaminase (ADA) deficiency was considered

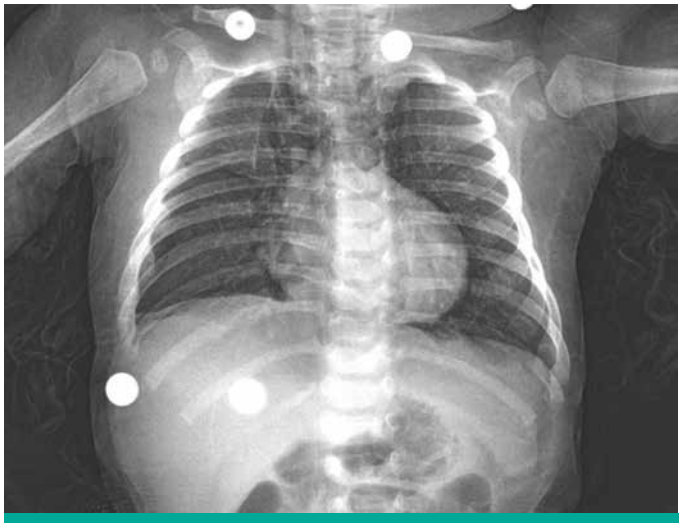

Figure 1. Chest X-ray of the patient

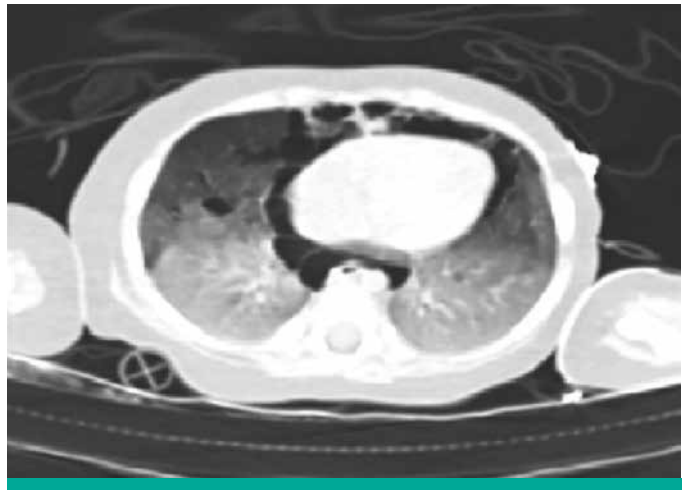

Figure 2. Chest CT scan of the patient
CT: Computed tomography

and excluded by the normal ADA enzyme levels. Because of severe viral infections and autoimmunity, signal transducers and activators of transcription (STAT1) mutation and lipopolysaccharide-responsive and beige-like anchor protein (LRBA) mutations were considered; *STAT1* gen sequencing was normal and LRBA protein expression by flow cytometry was detected as comparable to healthy controls. Whole exome sequencing was considered for screening monogenic diseases (e.g. MALT1 def., CARD11 def., BCL-10 def. etc.) that could be in a differential diagnosis, followed by a primary autoimmune hemolytic anemia and immunodeficiency. Intravenous immunoglobulin, trimethoprim sulfamethoxazole, and fluconazole prophylaxis were continued because of the ongoing lymphopenia. Tuberculosis PCR was negative.

After 26 days of intubation, she continued on a non-invasive mechanical ventilation with bilevel positive airway pressure) (epap: 6 cm H_2O, ipap: 11 cm H_2O) and then a non-rebreather mask with oxygen. At the time of discharge (48th day), her lymphocyte count was 2.240 mL (1.880-5.390 mL), but the lymphocyte phenotyping still demonstrated $CD19^+$ lymphopenia [$CD3^+$ %: 54.6 (51-85.3), $CD4^+$ %: 29.2 (29.7-63.6), $CD8^+$ %: 21.7 (11.5-33.7), $CD19^+$ %: 0.04 (7.9-53.6), $CD16^+56^+$%: 40 (2.3-17.2)], low recent thymic emigrant cells [RTE: %: 33 (63-90)], naif $CD4^+$ T cells [42.2% (60.4-95.5) and high memory $CD4^+$ T cells [50.3% (8.9-37.7)]. No mutation was detected in the *ADA* gene analysis which was performed before discharge.

Discussion

SPM might be triggered by respiratory tract infections, asthma, esophageal rupture, foreign body aspiration, and several circumstances involving a Valsalva maneuver (3). The incidence of SPM in childhood is between 1/8.000 and 1/15.000 in the emergency department admissions, and more frequent in male gender (4). Our patient was a girl and had no history of trauma, foreign body ingestion, or aspiration. According to the literature, emphysema is the most common finding in physical examination, but our patient had only respiratory distress (5). Therefore, although SPM can generally be diagnosed by chest graphy, chest tomography was needed twice for diagnosis in our case (6).

Lower respiratory tract infections such as bronchiolitis and viral pneumonia are the leading causes of hospitalization for infants. Prematurity, chronic pulmonary disease, and immune deficiency are the risk factors for these diseases. It is known that RSV is the most common acute pathogen which causes up to 75% of cases (7). However, RSV infection's potentiality for SPM is low, and there is little evidence in the literature (8). HBoV is another pathogen that is frequently found in hospitalized children under two years of age. The most challenging aspect for the patient was the ongoing lymphopenia during the treatment. This situation led to a prolonged hospitalization in contrast to the literature. The mean hospitalization period of SPM cases is between 4 and 6 days in the literature, but our case stayed for 48 days in PICU (9). Serum immunoglobulin levels were normal, but lymphocyte subsets revealed lymphopenia of T, B, NK cells. Although pulmonary diseases such as pneumonitis and pulmonary alveolar proteinosis are more common in patients with ADA deficiency (10), we excluded it by normal ADA enzyme levels and then normal gen analysis. STAT1 mutation and LRBA mutations were considered, *STAT1* gene analysis and LRBA expressions were normal. Due to a primary autoimmune hemolytic anemia and immunodeficiency, whole exome sequencing was attempted for monogenic diseases that could be in differential diagnosis. Since the patient had an absolutely normal lymphocyte count with normal lymphocyte subsets during the neonatal period and at the time of discharge, a history of infection, using immunosuppressive treatments such as RTX and CS for autoimmune hemolytic anemia and persistent lymphopenia, along with these medications, may suggest a secondary immunodeficiency rather than a primary one. In a meta-analysis of 21 studies, RTX was found to be a safe and effective therapy for autoimmune hemolytic anemia (11). Hypotension, fever and chills are the most common infusion-related side effects. D'Amico et al. (12) also investigated the effects of RTX on demyelinating diseases and found lymphopenia in one patient. Baris et al. (13) observed a lymphocyte subset changing in children diagnosed with nephrotic syndrome treated with corticosteroids (CSs), and it showed that T-cells were suppressed very early in the CS treatment and more susceptible to CSs more than B-cells. The change of B-cell subtypes shows a prolonged effect of CSs on B-cells, which may alter antibody production even after three months of CSs cessation (13).

At the follow-up of patient, clinical improvement with the decreasing infection and progress in lymphopenia confirmed the development of reversible secondary immunodeficiency.

Conclusion

In immunosuppressed patients with PM, respiratory diseases may be severe and long. When investigating the cause of immunodeficiency, the patient's previous diagnosis and treatment should be reviewed.

Consent was obtained from the family to use information about the patient.

Ethic

Informed Consent: Consent was obtained from the family to use information about the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Follow-up of the case: Ü.K.B., N.A., M.T.P., E.Ş., Literature review: N.K., N.A., M.T.P., Ö.D., E.Ş., Writing: Ü.K.B., N.K., M.T.P., Ö.D., E.Ş.

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LETTER TO THE EDITOR

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Ethics Committees in Pandemic Period: Dawn of a New Era

Pandemi Döneminde Etik Kurullar: Yeni Bir Çağın Şafağı

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Dear Editor,

Novel coronavirus caused a severe outbreak worldwide and the first case in Turkey was reported in March 2020. Rapid preventive actions were taken by the government in all areas of life. Clinical investigations became a topic of interest in this period. In the core of this research environment, ethics committees were asked for guidance and ethical considerations. The pandemic period has affected the clinical research environment in many ways. This may be the first report of experience during Coronavirus diseases-2019 pandemic from an ethics committee in Turkey.

The World Health Organization released guidelines for managing infectious disease outbreaks in 2016 after the Ebola outbreak in West Africa in 2015 (1). The aforementioned World Health Organization guideline (1) addresses some questions in ethics review in terms of time limitations, problems about expertise and the probable pressures from authorities which may limit the independence of researchers. Time limitations and the search for mechanisms of disease and the probable treatment modalities enable researchers work in the related outbreak. The urge for treatment and need for understanding the disease dictate rapid evaluation processes. However, even for the sake of this need, ethical issues cannot be overlooked. The authorities should enable the ethics committees with tools to overcome difficulties with the increased research needs.

Many authorities in many different countries have released regulations in order to control the immediate problems as the disease outbreak was evident (2). The European Network of Research Committees has also released a position statement for this pandemic period, addressing many issues including digital communication systems and their use in committee procedures (3). The Ministry of Health released the guidelines for the researchers and ethics committees very rapidly (4,5). First one (5) was released on March 19th and the revision on July 24th. According to these regulations, direct meetings were canceled and web-based meetings were recommended using a recommended programme (6). Whenever possible, signatures of the members of the ethics committee were required for the decision papers.

Similar experiences have been reported from India (7-9). I would like to summarize some problems and solutions which were imminent and were successfully solved during the outbreak. There are still some problems that need to be addressed and the probable solutions will require financial support.

After the cases were announced in March 2020, our institutional ethics committee declared the transient suspension of ethics committee meetings. The primary reasons for this suspension were as follows:

(i) The secretary of the committee contracted the disease and the face-to-face file application process was found to be severely dangerous.

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(ii) Our committee consists of 11 members, 5 of whom are outside the hospital. The external members of the committee were reluctant to join the meetings which were routinely made in the ethics committee room in the hospital and our hospital was one of the busiest pandemic hospitals of the region.

(iii) Need for a guideline from the authority.

After the guideline was released in March 2020 (4), the preparations were made in order to form a continuous application and evaluation processes and the system for meetings were prepared. Since there was no financial support for ethics committee, all available free-of-charge systems were utilized.

In University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital Ethics Committee, the following protocol has been utilized since May 2020: All applications are accepted by e-mail to the official mail address. All application papers were required to be complete with all signatures of all researchers. The signed papers were required to be scanned and the digital forms were sent to the committee's e-mail. After the review process by the reporters, applications were evaluated in the regular meetings which were made in every 2 weeks. The decision papers were prepared according to the circular letter sent by the Ministry. The decision papers were prepared in Word program and transformed to pdf format. In pdf format with a cover letter, the paper was digitally signed by the ethics committee chairman. The members were asked to send their decisions on each application as a list in word program and those lists were asked to be sent to the committee's e-mail.

For a rapid comparison, following figures will be descriptive. Before the first case was announced and preventive measures were taken, 4 ethics committee meetings were made from the beginning of 2020. In these 4 meetings, total number of decisions was 32. Of these 32 decisions, 29 were approved and 3 were rejected (90.6% approval rate). After the meetings were restarted in May 2020, within the first 3 meetings, 52 decisions were made. Of these 52 decisions, the number of approvals was 47 (90.4%). In spite of a rough figure, the following two conclusions could be withdrawn: (i) Researchers have adapted to the on-line application processes rapidly and the files could be prepared accordingly. (ii) As for the mid of October, the total number of decisions in 2020 is 161. For a quick comparison; the total numbers of decisions in 2018 and 2019 (whole year) were 127 and 100, respectively. It is evident that pandemic period caused a rapid increase in the number of researches made in our institution.

The following issues, however, should be addressed for improved evaluation processes. First, on-line applications should be made through a more professional website, similar to medical journals with necessary adjustments. Our temporary solution, although proved to be effective, is highly demanding both for the applicants and committee members. Second, the quality of academic (or investigator initiated) studies needs evaluation. Our committee receives applications mainly from the researchers of our institution (in 2018 and 2019, 94.5% and 95.0%, respectively) with a small percentage of researches made in other institutions. There are almost no applications of researches supported by the medical or pharma industry. The investigator initiated research applications are made with difficulties for the applicants, which need to be addressed and solved by our committee secretary, which is a highly demanding task. An effective research education and certification process should be considered similar to the animal studies.

Another issue specific to our ethics committee is the high number of applications in traditional and complementary medicine (TCM). We have been receiving TCM applications from the beginning of our committee studies. During this outbreak, there was a severe surge in the number of TCM study applications. The problems in TCM researchers seem to be more serious compared to other clinical studies. One of the possible reasons is the recent introduction of TCM regulations in 2019 (10) and the lack of knowledge by the researchers. Another and more important issue is the lack of understanding by the researchers. Researchers share some problematic opinion about research. They commonly think that TCM interventions are harmless and researches can be made with less caution compared to classic clinical studies. The concepts of "equipoise" and "volunteer safety" is commonly ignored or overlooked. The common understanding of "natural substances or traditional interventions are harmless" poses important risks for the years to come.

One of the important problematic understanding can be summarized under the heading of equipoise. Most of the investigator initiated clinical studies have serious drawbacks for any equipoise in the studies. This is a serious problem in the thesis of residents in medicine, but other academic studies have similar problems as well. Researches are commonly performed for academic promotions and one can easily see that applicants made researches in the areas outside the areas of their interest or daily practice.

Consequently, researchers have great difficulties in asking clinically relevant questions of debate.

The on-line meeting programme recommended by the authority (6) enabled committees to make on-line programmes despite a free charge software. As usual, we paid dearly since we bought cheaply. The programme has many problems that need to be solved and a continuous back-up was not available. Ethics committee procedures should be refined and be converted to digital area with necessary investment in order to achieve flawless ethics committee studies.

One of the biggest advantages of on-line applications for the applicants and committees is the ease in communication. Normally, applicants physically bring the files and the communication during applications is made either face-to-face or through telephone. During the outbreak period, the communications were made thorough e-mails which enabled the committee to document any communication. Although applicants insist on rapid immediate responses, the ease of communication seems to be working more efficiently as experience accumulates.

In conclusion, outbreaks have great opportunities for research environment along with the problems of their own. The ethics committees should focus on evaluation process without ignoring any necessary points even during the outbreak period. Application processes need refining and financial support for becoming more effective.

Keywords: Ethics, ethic committees, digital, pandemic

Anahtar kelimeler: Etik, etik kurul, dijital, pandemi

Ethics

Peer-review: Externally peer-reviewed.

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