ISSN: 2619-9793 • E-ISSN: 2148-094X

istanbul MEDICAL JOURNAL

İSTANBUL TIP DERGİSİ

VOLUME 21 • ISSUE 4 • JULY 2020

istanbulmedicaljournal.org

galenos yayınevi

istanbul MEDICAL JOURNAL

İSTANBUL TIP DERGİSİ

Owned by on behalf of the University of Health Sciences Turkey, İstanbul Training and Research Hospital
Özgür YİĞİT

galenos yayınevi

Galenos Publishing House
Owner and Publisher
Derya Mor
Erkan Mor

Publication Coordinator
Burak Sever

Web Coordinators
Turgay Akpınar
Fuat Hocalar

Graphics Department
Ayda Alaca
Çiğdem Birinci
Gülşah Özgül

Finance Coordinator
Sevinç Çakmak

Project Coordinators
Pınar Akpınar
Gamze Aksoy
Saliha Tuğçe Evin
Melike Eren
Hatice Sever
Duygu Yıldırm

Project Assistants
Gülay Akın
Özlem Çelik
Rabia Palazoğlu

Research&Development
Mert Can Köse
Mevlüde Özlem Akgüney

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Turkey
Phone: +90 (212) 621 99 25 **Fax:** +90 (212) 621 99 27
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr
Publisher Certificate Number: 14521

Printing at: Üniform Basım San. ve Turizm Ltd. Şti.
Matbaacılar Sanayi Sitesi 1. Cad. No: 114 34204 Bağcılar, İstanbul, Turkey
Phone: +90 (212) 429 10 00
Certificate Number: 42419
Printing Date: July 2020
ISSN: 2619-9793 **E-ISSN:** 2148-094X
International periodical journal published three times in a year.

İSTANBUL MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

istanbul MEDICAL JOURNAL

İSTANBUL TIP DERGİSİ

istanbul
MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

AIMS AND SCOPE

İstanbul Medical Journal is the scientific, peer reviewed, open access publication of İstanbul Training and Research Hospital. The journal is printed six times in a year; on January, March, May, July, September, November and its publication language is Turkish and English.

The aim of the journal is to publish high level clinical and experimental studies conducted in all fields of medicine. Reviews comprising the latest research findings, reports on rare and educative cases and letters to the editor are also published.

The target population of the journal includes specialists in all fields of medicine, academicians and relevant health care professionals.

The İstanbul Medical Journal is indexed in Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, EBSCO, DOAJ, Hinari, ROOT INDEXING, Türk Atif Dizini, Türk Medline, J-GATE, Proquest, Ardi, Goali and Oare, CABI.

Processing and publication are free of charge with the journal. No fees are requested from the authors at any point throughout the evaluation and publication process. All manuscripts must be submitted via the online submission system, which is available at www.istanbulmedicaljournal.org. The journal guidelines, technical information, and the required forms are available on the journal's web page.

All expenses of the journal are covered by the İstanbul Training and Research Hospital. Potential advertisers should contact the Editorial Office. The journal does not publish advertisement.

Statements or opinions expressed in the manuscripts published in the journal reflect the views of the author(s) and not the opinions of the İstanbul Training and Research Hospital, editors, editorial board, and/or publisher; the editors, editorial board, and publisher disclaim any responsibility or liability for such materials.

All published content is available online, free of charge at www.istanbulmedicaljournal.org. Printed copies of the journal are distributed to the members of İstanbul Training and Research Hospital as well as the members of the editorial board and the journal's reviewers, free of charge.

Open Access Policy

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

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

Editor: Feray AKBAŞ

Address: Clinic of Internal Diseases, University of Health Sciences Turkey, İstanbul Training and Research Hospital, İstanbul, Turkey

E-mail: atlibatur@yahoo.com

Publisher : GALENOS PUBLISHING HOUSE

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

Phone: +90 (212) 621 99 25 Fax: +90 (212) 621 99 27 E-mail: info@galenos.com.tr/yayin@galenos.com.tr Web: www.galenos.com.tr

OPEN ACCESS

İSTANBUL MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

INSTRUCTIONS TO AUTHORS

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

Originality, high scientific quality, and citation potential are the most important criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts that have been submitted to another journal for evaluation and rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts that have been presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

Manuscripts submitted to İstanbul Medical Journal will go through a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in their fields in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or by the editorial board members of the journal. The Editor in Chief is the final authority in the decision-making process for all submissions.

An approval of research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net) is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement should be included that shows that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. In experimental animal studies, the authors should indicate that the procedures followed were in accordance with animal rights as per the Guide for the Care and Use of Laboratory Animals http://oacu.od.nih.gov/regs/guide/guide.pdf and they should obtain animal ethics committee approval. Information on patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Materials and Methods section of the manuscript. It is the authors' responsibility to carefully protect the patients' anonymity. For photographs that may reveal the identity of the patients, signed releases of the patient or of their legal representative should be enclosed.

All submissions are screened by a similarity detection software (iThenticate by CrossCheck).

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with COPE guidelines.

Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors

(ICMJE - www.icmje.org). The ICMJE recommends that authorship be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged in the title page of the manuscript.

İstanbul Medical Journal requires corresponding authors to submit a signed and scanned version of the authorship contribution form (available for download through www.istanbulmedicaljournal.org) during the initial submission process in order to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without further review. As part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all the responsibility for authorship during the submission and review stages of the manuscript.

İstanbul Medical Journal requires and encourages the authors and the individuals involved in the evaluation process of submitted manuscripts to disclose any existing or potential conflicts of interests, including financial, consultant, and institutional, that might lead to potential bias or a conflict of interest. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors. Cases of a potential conflict of interest of the editors, authors, or reviewers are resolved by the journal's Editorial Board within the scope of COPE and ICMJE guidelines.

istanbul MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

INSTRUCTIONS TO AUTHORS

The Editorial Board of the journal handles all appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office regarding their appeals and complaints. When needed, an ombudsperson may be assigned to resolve cases that cannot be resolved internally. The Editor in Chief is the final authority in the decision-making process for all appeals and complaints.

When submitting a manuscript to İstanbul Medical Journal, authors accept to assign the copyright of their manuscript to İstanbul Training and Research Hospital. If rejected for publication, the copyright of the manuscript will be assigned back to the authors. İstanbul Medical Journal requires each submission to be accompanied by a Copyright Transfer Form (available for download at www.istanbulmedicaljournal.org). When using previously published content, including figures, tables, or any other material in both print and electronic formats, authors must obtain permission from the copyright holder. Legal, financial and criminal liabilities in this regard belong to the author(s).

Statements or opinions expressed in the manuscripts published in İstanbul Medical Journal reflect the views of the author(s) and not the opinions of the editors, the editorial board, or the publisher; the editors, the editorial board, and the publisher disclaim any responsibility or liability for such materials. The final responsibility in regard to the published content rests with the authors.

MANUSCRIPT PREPARATION

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2016 - http://www.icmje.org/icmje-recommendations.pdf). Authors are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.istanbulmedicaljournal.org. Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Authors are required to submit the following:

- Copyright Transfer Form,
- Author Contributions Form, and
- ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors)

during the initial submission. These forms are available for download at www.istanbulmedicaljournal.org.

Preparation of the Manuscript

Title page: A separate title page should be submitted with all submissions and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, and highest academic degree(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: A Turkish and an English abstract should be submitted with all submissions except for Letters to the Editor. Submitting a Turkish abstract is not compulsory for international authors. The abstract of Original Articles should be structured with subheadings (Objective, Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Methods, Results, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Editorial Comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

istanbul
MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

INSTRUCTIONS TO AUTHORS

Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Report, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	30	6	7 or tatal of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Journal Article: Rankovic A, Rancic N, Jovanovic M, Ivanović M, Gajović O, Lazić Z, et al. Impact of imaging diagnostics on the budget – Are we spending too much? Vojnosanit Pregl 2013; 70: 709-11.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

istanbul MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

INSTRUCTIONS TO AUTHORS

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

REVISIONS

When submitting a revised version of a paper, the author must submit a detailed “Response to the reviewers” that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer’s comment, followed by the author’s reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal’s webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

Editor : Feray AKBAŞ

Address: Clinic of Internal Diseases, University of Health Sciences Turkey, İstanbul Training and Research Hospital, Samatya, Fatih, İstanbul, Türkiye

E-mail: atlibatur@yahoo.com

Publisher : GALENOS PUBLISHING HOUSE

Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 Fındıkzade 34093 İstanbul, Turkey
Phone: +90 (212) 621 99 25
Fax: +90 (212) 621 99 27
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr

İSTANBUL MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

CONTENTS

istanbul
MEDICAL JOURNAL
İSTANBUL TIP DERGİSİ

CONTENTS

Case Reports

İstanbul Med J 2020; 21(4): 234-41
DOI: 10.4274/imj.galenos.2020.89725

Current Approach to Hyperbaric Oxygen Therapy

Hiperbarik Oksijen Tedavisinde Güncel Yaklaşım

Füsun Kocaman Ürütük

Şişli Florence Nightingale Hospital, Hyperbaric Oxygen Therapy Center, İstanbul, Turkey

ABSTRACT

Hyperbaric oxygen (HBO) therapy is a therapy method based on inhalation of 100% pure oxygen through a mask or endotracheal tube or directly from the environment while subjected to a fully closed pressure chamber with >1 atmosphere. It has been successfully used to treat many diseases from different medical specialties. This review, apart from describing the general features of HBO therapy, emphasises on its therapeutic application in different medical specialties. This would promote its usage, alongside other methods, by physicians from different clinical fields.

Keywords: Hyperbaric oxygen, decompression illness, carbon monoxide, diabetic foot, vascular disease, osteomyelitis, post-operative wounds, crush, grafts flaps, filling injection complications, radionecrosis, sudden deafness, sudden blindness

ÖZ

Hiperbarik oksijen (HBO) tedavisi, tamamen kapalı bir basınç odası içerisinde, 1 atmosferden daha yüksek basınçlarda, ortamdan, maskeyle veya endotrekeal tüp vasıtasıyla fasılalı olarak %100 saf oksijen solutulmasına dayanan bir tedavi yöntemidir. Farklı tıp dallarından birçok hastalıkta başarı ile kullanılmaktadır. Bu derlemede, HBO tedavisinin genel özelliklerinin tanımlanması dışında, farklı olarak, branşlara göre kullanım alanlarının vurgulanması, böylece farklı kliniklerden hekimlerin bu tedavi yöntemini hastaları için kullanabilmelerine rehberlik edilmesi amaçlanmıştır.

Anahtar Kelimeler: Hiperbarik oksijen, dekompresyon hastalığı, karbonmonoksit, diyabetik ayak, periferik vasküler hastalık, osteomiyelit, postoperatif yara, ezilme yaralanması, riskli greft flepler, dolgu komplikasyonu, radyonekroz, ani işitme kaybı, ani görme kaybı

Short History

Oxygen was first found in 1772 by Swedish chemist Carl Wilhelm. However, he himself has not reported this scientifically. In 1774, the English chemist Joseph Priestly published and introduced it in the scientific framework (1). Hyperbaric oxygen (HBO) therapy first started in France in the late 19th and early 20th centuries. In 1834, Junod explained the positive effects of high pressure oxygen, and in 1876 mobile compartments were put into use. Production of hyperbaric chambers began from 1860. Paul Bert, considered the father of Hyperbaric Medicine, has described the effectiveness of HBO therapy. In the same years, Haldane reported that carbon monoxide intoxication was effectively treated with HBO therapy (1-4).

Definition

HBO therapy is a therapy based on the inhalation of 100% pure oxygen intermittently in a completely closed pressure chamber, at pressures higher than 1 atmosphere, from ambient air, by mask or by endotrekeal tube (Figure 1-3) (5).

Mechanism of Hyperbaric Oxygen Therapy

The two main rules of HBO therapy, pressure and 100% oxygen, also form the basis of the mechanism of effect.

1. Effects of pressure

2. Effects of oxygen

1. The effects of pressure: According to Boyle-Mariotte law, gases contract with the effect of pressure applied externally. During pressurization, also called the compression phase of HBO therapy, a contraction occurs in gas-containing cavities in the body. The air in the middle ear can be narrowed by manoeuvres such as Valsalva, Frenzel; the air in the lungs can be narrowed by breathing; and the air in the sinuses and intestines can be balanced spontaneously. With this effect, it is possible to downsizing air bubbles present in the tissue and intravascular area and reduce tissue blood pressure in diseases such as gas gangrene, air and gas embolism, and decompression sickness. The bubble, which has lost its spheric form, may disappear or be eliminated from the lungs (5-9).

Address for Correspondence/Yazışma Adresi: Füsun Kocaman Ürütük MD, Şişli Florence Nightingale Hospital, Hyperbaric Oxygen Therapy Center, İstanbul, Turkey
Phone: +90 555 721 66 69 **E-mail:** fkocaman@yahoo.com **ORCID ID:** orcid.org/0000-0002-2498-9330

Cite this article as/Atıf: Kocaman Ürütük F. Current Approach to Hyperbaric Oxygen Therapy. İstanbul Med J 2020; 21(4): 234-41.

Received/Geliş Tarihi: 22.05.2020
Accepted/Kabul Tarihi: 01.06.2020

2. The effects of oxygen: According to Henry's law, under pressure, the solubility of gases in liquids increases. In HBO therapy conducted in 2.8 atmospheres, the amount of oxygen dissolved in plasma is six times the amount in normobaric conditions. The dissolved oxygen carried by the plasma can provide the amount needed for the tissue to survive, even if there is no oxygen due to hemoglobin. By this mechanism, the antimicrobial effect of leukocytes is supported, adherence of leukocytes to the capillary wall is reduced, physiological vasoconstriction occurs in normal tissues, fibroblast growth and collagen construction increase, making of superoxide dismutase is triggered, adenosine triphosphate, the cell membrane present in tissue edema, is conserved; osteoclastic activity is regulated, capillary proliferation increases, ocular lens flexibility is reduced, surfactant construction is reduced in the lungs, separation of carbon monoxide (CO) gas from hemoglobin and suppressing alpha toxin production in gas gangrene. In the case of hyperoxia, it is also possible to withdraw the edema at intersellular distance to the intravascular area while vasoconstricting and reduce the distance that dissolved oxygen must exceed to reach the tissue (5-8).

Indications for Hyperbaric Oxygen Therapy

The United States-based Undersea and Hyperbaric Medical Society (UHMS) and the European Committee for Hyperbaric Medicine (ECHM) have been working extensively on the creation of indications lists for HBO therapy. Lists of indications that can be applied according to these commissions are given in Table 1 (10,11).

Figure 1. Multiplace pressure chamber

According to the HBO therapy application list in annex 2D-3 of the Health Implementation Comminique in our country, the indication list evaluated under the Social Security Instution of is summarized in Table 2 (12).

In addition, there are diseases that are being investigated and positive results are being reported, with extensive research expected.

Emergency Medicine and Hyperbaric Oxygen Therapy

Apart from CO poisoning and sudden vision loss, decompression sickness and air/gas embolism, which lead to the birth of undersea medicine, are diseases that emergency physicians may encounter in their emergency clinics.

Anamnesis of those suffering from decompression disease is most likely a recent history of diving or a history of exposure to high pressure and associated skin and neurological involvement. In this disease, which develops after diving accompanied by deep and missed safety stops, which are not done according to the rules, HBO therapy to be applied allows the bubbles to shrink, the edema around the bubble to

Figure 2. Control panel

Figure 3. Hyperbaric oxygen therapy unit

Table 1. Indications for hyperbaric oxygen therapy

UHMS indications	ECHM indications
• Air and gas embolism • Arteriel insufficiencies • Carbon monoxide (CO) poisoning • Clostridial myonecrosis • Compromised grafts and flaps • Acute traumatic ischemia • Decompression sickness • Radiation injury • Idiopathic sudden sensorineural hearing loss • Intracranial abscess • Necrotizing soft tissue infections • Refractory osteomyelitis • Severe anemia • Thermal burns	**1. Absolute Indications** • CO poisoning • Open fractures with crush injury • Prevention of osteoradionecrosis after dental extraction • Mandible osteoradionecrosis • Soft tissue radionecrosis (cystitis, proctitis) • Decompression illness • Gas embolism • Anaerobic and mixed bacterial infections • Sudden deafness **2. General Indications** • Diabetic foot lesions • Femoral head avascular necrosis • Compromised skin grafts and musculocutaneous flaps • Central retinal artery occlusion • Crush Injury without fracture • Osteoradionecrosis (bones other than mandible) • Soft tissue radionecrosis other than cystitis and proctitis • Application of preoperative or pre-implant protection to radiotherapy-treated tissue • Ischaemic ulsers • Refractory chronic osteomyelitis • 2nd degree more than 20% body surface area • Pneumatosis cystoides intestinalis • Neuroblastoma stage IV **3. Relative Indications** • Selected cases in acute and chronic brain trauma, chronic stroke, postanoxic encephalopathy • Radio-induced lesions of larynx • Radio-induced lesions of the central nervous system • Reperfusion syndrome • Limb replantation • Selected non-healing wounds secondary to systemic processes • Sickle cell disease • Interstitial cystitis

UHMS: Undersea and Hyperbaric Medical Society, ECHM: Europen Committee for Hyperbaric Medicine

Table 2. Social security institution hyperbaric oxygen therapy indication list

Decompresson sickness
Air embolism
CO poisoning and toxic effect of gases and cyanides
Gas gangrene
Soft tissue infections, fasciitis, necrotizing fasciitis
Crush, compression, post-traumatic Injuries
Diabetic foot wounds and infections
Peripheral vascular disease, vascular-induced ulcers such as Buerger's disease, infections, and wounds that develop after thromboembolism
Venous ulcers
Chronic ulcers
Decubitus ulcers
Postoperative wound, infection, vascular complications
Spondylodiscitis, intervertebral disc infection: acute, subacute, chronic osteomyelitis
Prosthetic infection and inflammation
Avascular necrosis
Late effects of cystitis, dermatitis, proctitis and other radiation due to RT
After graft and flap operations
Burns
Frostbite
Intracranial abscess
Anoxic encephalopathy
Malign otitis externa
Sudden sensorineural hearing loss
Retinal artery occlusions

RT: Radiotherapy, CO: Carbon monoxide

decrease and the inflammation to be reduced. The patient's skin and neurological signs are reduced, especially when the blisters shrink. It should be remembered that the only treatment for decompression disease is the HBO therapy, and that it should be seen by an undersea medicine physician even if there is a claim that safe diving is performed in the story (2,8,13-16).

Air gas embolism is the condition of gas bubbles in the vascular area. This condition may be iatrogenic after some surgical intervention or invasive procedures, or may develop after lung barotrauma in diving or other hyperbaric environments. This disease can result in Aacute respiratory distress syndrome, brain edema, lack of brain metabolism, and sudden death. In non-fatal cases, air bubbles block circulation; it can be seen that hemoconcentration develops when platelets, leukocytes, fibrinogen and thrombin adhere to the bubble, and the clinical picture is rapidly aggravated. In the following period, the thrombotic process comes to the fore and deterioration occurs in the vessel wall. This disease can be an unintended complication of diving, surgical practice and undersea medicine practice. As soon as the clinical picture is recognized, the bubbles in the vascular site of the patient receiving HBO therapy shrink, the nitrogen load in the bubble is reduced, the activation of the

adhesion cascade decreases, hypoxia of ischemic tissue regresses, and brain edema decreases. HBO therapy can be applied to the patient who needs intensive care support until the clinical picture declines (2,17-20).

Internal Medicine and Hyperbaric Oxygen Therapy

In our country, the incidence of CO poisoning caused by coal and wood stove is high, especially in winter. CO binds to hemoglobin due to its high affinity as a gas, creating hypoxia within the cell at the mitochondrial level. It has been proven that this causes ultrastructural changes in myocytes and swells in mitochondria in electron microscopic investigations of the myocardial, and this is due to deterioration of the energy use of the myocardial (21,22). HBO therapy speeds up the separation of CO gas from hemoglobin, shortening the time it takes to be excreted from the body and correcting intracellular hypoxia. In the studies, it was determined that damage due to CO intoxication in the myocardium was also improved with HBO therapy (23,24).

In patients diagnosed with CO intoxication in the emergency department,

- CO level over 25%,

- CO level over 20% and pregnant,

- Loss of consciousness and/or in the presence of pathological neurological signs,

- In the presence of end organ damage such as ischemic findings in electrocardiogram,

- In severe metabolic acidosis.

HBO therapy should be used to reduce mortality and increase cure rate (24-29). It should be kept in mind that intracellular hypoxia can persist even if the CO level in blood gas decreases, and that myocardial damage and clinical signs may be seen even in patients below the levels mentioned above (22).

General Surgery and Hyperbaric Oxygen Therapy

Surgical interventions, for whatever purpose, disrupt the integrity of the body and create a controlled and clean wound on the skin. In normal wound healing;

- 1st day hemostasis,

- 0-3 day inflammatory phase,

- 3-15th day remodelization phase

occurs and the process continues. The wound healing stops due to an intrinsic or extrinsic problem occurring in one or more of these processes and the clinical picture of the postoperative wound appears. Infection and ischemia are the most common causes of wound healing delay (2). The infection causes an exaggerated response in the inflammatory phase of wound healing, resulting in rapid depletion of oxygen in the tissue, resulting in insufficient blood flow due to the effect of tissue edema. However, ischemia occurs because the tissue reaches less oxygen than it needs. The wound location is hypoxic, hypoglycemic, acidotic, hyperkalemic, hyperlactic, and hypercarbic due to these reasons. Especially, fibroblast proliferation, lysine and proline hydroxylation in collagen synthesis, angiogenesis, and leukocytosis activity are oxygen-dependent functions. This whole healing process is interrupted by lack of oxygen (2,30-32).

Diabetic foof ulcer develops in 2.2% of diabetic patients every year and training for prevention of ulcer provides serious benefits to the national economy (33). Diabetic patients account for a significant proportion of non-traumatic amputations and morbidity all over the world. In diabetic foot treatment with multidisciplinary approach, good regulation of diabetes, proper dietary protocol, control of infection, correction of vascular pathologies, adequate and timely debritmans, daily optimal wound healing environment, reducing pressure on the foot area and HBO therapy should be added to the protocol. Educating the patient about diabetic foot and explaining the importance of following medical treatment and diet program will reduce recurrence in amputations of foot ulcers, and the addition of HBO therapy will decrease the amputation rate (34-38). Such publications can be seen as an indication that attention needs to be paid to patient selection and the time at which the patient is referred to an HBO therapy clinic.

The main reason behind all non-healing wounds, postoperative wounds, soft tissue infections and diabetic foot wounds are lack of oxygen and the problem in wound healing processes. HBO therapy attempts to restore healthy functioning of this process by providing the oxygen that tissue needs, reducing edema, controlling infections, regulating intracellular metabolism, and increasing the effectiveness of antibiotics. In recent years, the use of perioperative HBO therapy has also started to be suggested by publications (39,40). It is important to recognize the patient at risk during the preoperative period, to identify early complications in the wound healing process during the postoperative period and to take the necessary precautions.

In addition to surgical, nephrological and intensive care support, HBO therapy can also be applied in severe energy traumas, earthquake, traffic accident, industrial accident, crush injuries, compartment syndrome, risky flap/graft and organ replantation. The main pathology in all of these diseases is ischemia and tissue edema. While the increase of edema causes vicious circle by increasing hypoxia in the tissue, reduction of edema, supply of needed oxygen to the tissue, re-provision of microcirculation, elimination of hypoxia and breaking of the cycle can be achieved with HBO therapy. Unlike normobaric oxygen, HBO therapy can enhance tissue viability and reduce the need for amputation by increasing the amount of dissolved oxygen in the plasma, reducing the need for operations, shortening the duration of hospitalization and preventing the risk of hospital infection (41-44).

Plastic Surgery and Hyperbaric Oxygen Therapy

In addition to diabetic foot wounds, postoperative wounds, compromised grafts/flaps, organ replantation, HBO therapy can also be useful in the prevention and relief of complications of medical aesthetic applications (2,40,44-47).

In risky grafts and flaps, HBO therapy supports preoperative site preparation, control of infections, reduction of graft/flap edema during postoperative period, increase of collagen production and reduction of rejection (44-46).

Successful HBO therapy practices have been reported following replantations of tissue losses such as ear amputation and penile amputation. The replanted tissue continues to be fed with dissolved oxygen from microcirculation and merges with healthy tissue (47,48).

After filling applications to replace the tissue loss on the face caused by aging, sudden vision loss and tissue necrosis may develop and HBO therapy may be applied to these types of cases. HBO therapy reduces edema in the filling area, is useful in correcting hypoxia and reduces scar formation (48,49).

Orthopedics and Hyperbaric Oxygen Therapy

Indications of HBO therapy in orthopedics can be summarized as postoperative wound healing, osteomyelitis and avascular necrosis.

Osteomyelitis is a pyogenic infection of the bone that can be difficult to treat, progressive and recurrent. Hypoxia, ischemia and necrosis develop in the bone due to infection. Furthermore, the strong structure of the bone causes the infection to be controlled and the effectiveness of the antibiotic therapy to decrease in bone tissue (50). Surgery, antibiotics sensitive to bone culture and HBO therapy are applied in the treatment. From the point of view of Hyperbaric Medicine, whatever the cause, this is a kind of closed wound and local oxygen support is important in correcting hypoxia in the tissue, controlling the infection and in remission of the disease. HBO therapy removes hypoxia by correcting edema and microcirculation, increases bactericidal activity of neutrophils with increased oxygen in tissue, increases vascularization, allows antibiotics to be transported and penetrated to the problem area, and accelerates postoperative wound healing (50-52).

Etiopathogenesis of avascular necrosis includes corticosteroids, alcohol, infections, dysbaric conditions, infiltrating diseases of the bone marrow, coagulation defects, autoimmune diseases. Basically, it is a bone disease which is associated with tissue edema due to decreased local blood circulation, which leads to necrosis in the bone and creates the need for prosthetics in the later stages (53-55). In addition to bone drill operation, HBO therapy also has the effect of reducing existing hypoxia and edema, improving metabolism in bone tissue and regulating osteoclastic and blastic activity, enabling bone tissue regeneration (54,56-59).

In orthopedics, HBO therapy can also be used for perioperative and postoperative wound healing (39,40).

Vascular Surgery and Hyperbaric Oxygen Therapy

Wounds related to peripheral artery disease accompanied or not by diabetes, venous ulcers and sternum osteomyelitis following cardiac surgery are groups of patients that vascular surgeons and undersea physicians can follow together. In cases where oxygen transport is restricted due to mechanical reasons, such as peripheral artery disease and Buerger's disease, even if the gold standard treatment is surgical, HBO therapy carries oxygen needed for tissue regeneration, dissolved in plasma, and provides major factors for wound healing. In addition, reduction of carbon dioxide retention and residual substances will reduce claudication and decrease the limitation of the patient's ability to activity (37,60-63). Because of this effect, it is possible to stop the deterioration of the tissue and wound during the preoperative period and to recover faster both the existing wound and the operation wound during the postoperative period.

In ulcers that develop due to venous insufficiency, surgical intervention, restriction of patient standing time, elastic bandages, appropriate varicose veins, as well as the application of HBO therapy will accelerate wound healing. HBO therapy plays an active role in reducing local edema, in the development of granulation tissue in the wound, and in accelerating epithelization, and provides wound healing (2,31,63).

In addition to the treatment of sternal infections and osteomyelitis that develop after cardiothoracic surgery, HBO therapy can be used. HBO therapy with its effects such as reduction of hypoxia, reduction of edema, support of immune resistance of the patient, increase of antibiotic effectiveness, reduces the duration of antibiotic therapy in this disease and reduces relapses (64-67).

Radiation Oncology and Hyperbaric Oxygen Therapy

While in radiotherapy (RT) the target is cancerous tissue, neighboring normal tissue is also damaged and suffers loss of healthy cells and capillary vessels. In tissue that has lost its cells and blood supply, fibrosis develops accompanied by hypoxia. The tissue in this condition has problems in healing due to a surgical intervention, trauma or a spontaneous wound. Osteonecrosis of the jaw after RT applied in head and neck cancers, radiation cystitis after RT applied in genital region cancers, proctitis can be given as an example of these diseases. HBO therapy removes hypoxia in the tissue in these diseases, speeding up new cell construction, collagen production and angiogenesis/neovascularization (2,68-72). According to the Marx protocol, giving HBO therapy prior to surgery, such as tooth extraction, especially to the patient who has received RT due to head and neck cancer provides protection from osteoradionecrosis (69).

Eye Diseases and Hyperbaric Oxygen Therapy

Retinal artery occlusion is one of the emergency indications by both ophthalmologists and undersea physicians. It is characterized by sudden blindness that develops immediately following occlusion of the retinal artery and its branches due to reasons such as thrombus, embolism, vasculitis. The aim should be to reduce or dissolve the thrombus/embolism, to restore circulation and to provide tissue nutrition with the help of collaterals or diffusion until this is achieved. Retinal cells are very sensitive to hypoxia. Therefore HBO therapy should be administered very quickly in such cases (2,73,74).

Otolaryngology and Hyperbaric Oxygen Therapy

Sudden hearing loss, malignant otitis externa and postoperative wound healing are indications that otolaryngology will be supported by undersea physicians.

Sudden hearing loss is defined as greater than 30 decibels sensorineural hearing reduction, over at least three contiguous frequencies, occurring over 3 days or less (75). In etiology, vascular causes, viral cochleitis, autoimmune diseases and acoustic trauma can be considered. The common feature of all these causes is hypoxia in the inner ear (75,76). HBO therapy, which is added to steroid therapy, corrects hypoxia in

the inner ear, reduces edema, reactivates cells whose metabolism has stopped, and restores hearing (2,75-77).

Otitis externa is a life-threatening, progressive infection of the soft tissue of the external ear canal. Patients may have diseases such as diabetes, immunosuppressive use, or cancer. HBO therapy, when added to appropriate antibiotics, regresses edema in the outer ear tract, increases the effectiveness of antibiotics, strengthens body defense mechanisms, provides remission of osteomyelitis in bone tissue. HBO therapy should be considered as an adjuvant therapy pathway, especially in resistant cases (78,79).

Neurosurgery and Hyperbaric Oxygen Therapy

Spondylodiscitis and intracranial abscesses are in neurosurgical indications where HBO therapy is used.

Intracranial abscesses are formed by aerobic and anaerobic agents in the brain tissue. HBO therapy reduces edema around the abscess, acts bactericidal to anaerobic microorganisms inside the abscess, reduces hypoxia, increases antibiotic penetration, strengthens body defense mechanisms and helps control the infection in the abscess. HBO therapy may be useful, especially if any of these parameters are present (51,80,81):

- Multiple abscesses,

- Deep and large abscess,

- Early stage abscess that does not require surgery,

- High-risk patient profile,

- Non-surgical, risky abscess,

- Anaerobic or multiple bacterial isolation,

- Failure to respond to standard treatment.

As a result, HBO therapy is a treatment that has hyperoxic, edema-reducing, infection-fighting, immune system-supporting, neovascularization-enhancing, inflammation-reducing, wound healing-accelerating effects. In the light of scientific studies, a new effect is emerging every day and the list of diseases it can treat is expanding. With the new data to be added to the literature in the coming years, it can be seen that this branch of science is very open to development and progress, and in its current form it can take place in the treatment protocols of many diseases from different clinics.

Ethics

Peer-review: Internally peer-reviewed.

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

References

1. Clarke D. History of hyperbaric therapy. Neuman T, Thom S, editors. Physiology and Medicine of Hyperbaric Oxygen Therapy. Philadelphia: Saunders Elsevier; 2008.p.3-23.
2. Çimşit M. Hiperbarik Tıp. İstanbul-Türkiye: Efil Yayınevi; 2009.
3. Wattel F. A history of hyperbaric medicine. Mathieu D, editor. Handbook on Hyperbaric Medicine. Dordrecht: Springer; 2006.p.1-11.
4. Kindwall EP. Hyperbaric oxygenation - general considerations- A history of hyperbaric medicine. Kindwall EP, editor. Hyperbaric Medicine Practice. Arizona: Best Publishing Company; 1995.p.1-16.
5. Hardy K. The physics of hyperbaric oxygen therapy. Neuman TS, Thom SR, editors. Physiology and Medicine of Hyperbaric Oxygen Therapy. Philadelphia: Saunders Elsevier; 2008.p.57-64.
6. Welslau W. Physics of hyperbaric pressure. Mathieu D, editor. Handbook on Hyperbaric Medicine. Dordrecht: Springer; 2006.p.15-24.
7. Hammarlund C. Hyperbaric oxygenation - general considerations- The physiologic effects of hyperbaric oxygen. Kindwall EP, editor. Hyperbaric Medicine Practice. Arizona: Best Publishing Company; 1995.p.17-32.
8. Welslau W. Physiologic effects of increased barometric pressure. Mathieu D, editor. Handbook on Hyperbaric Medicine. Dordrecht: Springer International Publishing; 2006.p.31-48.
9. Ratzenhofer-Komenda B, Fovory R, Welslau W, Somlle-Jüttner FM, Mathieu D. Physiologic effects of hyperbaric oxygen transport and tissue oxygen pressure. Mathieu D, editor. Handbook on Hyperbaric Medicine. Dordrecht: Springer International Publishing; 2006.p.49-74.
10. UHMS. Moon RE, editor. Hyperbaric Oxygen Therapy Indications 14th Edition. Best Publishing Company; 2019.
11. Mathieu D, Marroni A, Kot J. Consensus Conference. Diving and Hyperbaric Medicine 2017; 47: 24-32.
12. Sağlık Uygulama Tebliği. 05.07.2018 tarih ve 30469 Mükerrer Sayılı Resmi Gazete. Ek 2-D-3, 2013. Available from URL: https://www.resmigazete.gov.tr/eskiler/2018/07/20180705M1-1.htm
13. Elliott DH. Disorders approved for treatment with hyperbaric oxygen, Decompression sickness. Kindwall EP, editor. Hyperbaric Medicine Practice. Arizona: Best Publishing Company; 1995.p.311-26.
14. Moon RE, Gorman DF. Decompression sickness. Neuman TS, Thom SR, editors. Physiology and Medicine of Hyperbaric Oxygen Therapy. Philadelphia: Saunders Elsevier; 2008.p.283-320.
15. Marroni A, Cronje FJ, Meintjes J, Cali-Corleo R. Dysbaric Illness. Mathieu D, editor. Handbook on Hyperbaric Medicine. Dordrecht: Springer International Publishing; 2006.p.173-216.
16. Vann RD, Butler FK, Mitchell SJ, Moon RE. Decompression illness. Lancet 2011; 377: 153-64.
17. Hoesen KV, Neuman TS. Gas embolism venous and arterial gas embolism. Neuman TS, Thom SR, editors. Physiology and Medicine of Hyperbaric Oxygen Therapy. Philadelphia: Saunders Elsevier; 2008.p.257-81.
18. Mathieu D, Tissier S, Boulo ML. Gas embolism. Mathieu D, editor. Handbook on Hyperbaric Medicine. Dordrecht: Springer International Publishing; 2006.p.217-38.
19. Kindwall EP. Disorders approved for treatment with hyperbaric oxygen- Gas embolism. Kindwall EP, editor. Hyperbaric Medicine Practice. Arizona: Best Publishing Company; 1995.p.327-42.
20. Malik N, Claus PL, Illman JE, Klingerman SJ, Moynagh MR, Levin DL, et al. Air embolism: diagnosis and management. Future Cardiol 2017; 13: 365-78.
21. Tritapepe L, Macchiarelli G, Rocco M, Scopinaro F, Schiallaci O, Mastuscelli E, et al. Functional and ultrastructural evidence of myocardial stunning after acute carbon monoxide poisoning. Crit Care Med 1998; 26: 797-801.
22. Song L, Bian G, Yang W, Li HF. Variant angina induced by carbon monoxide poisining. Medicine (Baltimore) 2019; 98: 16.
23. Satran D, Henry CR, Adkinson C, Nicholson CI, Bracha Y, Henry TD. Cardiovascular manifestations of moderate to severe carbon monoxide poisining. J Am Coll Cardiol 2005; 45: 1513-6.

24. Mathiue D, Mathieu-Nolf M, Linke JC, Favory R, Wattel F. Carbon monoxide poisining. Mathieu D, editor. Handbook on Hyperbaric Medicine. Dordrecht: Springer International Publishing; 2006.p.239-62.

25. Weaver LK. Carbon monoxide poisoning. Crit Care Clin 1999; 15: 297-317.

26. Kao LW, Nañagas KA. Carbon monoxide poisoning. Emerg Med Clin North Am 2004; 22: 985-1018.

27. Hampson NB, Dunford RG, Kramer CC, Norkool DM. Selection criteria utilized for hyperbaric oxygen treatment of carbon monoxide poisoning. J Emerg Med 1995; 13: 227-31.

28. Huang CC, Ho CH, Chen YC, Lin HJ, Hsu CC, Wang JJ, et al. Hyperbaric oxygen therapy is associated with lower short- and long-term mortality in patients with carbon monoxide poisoning. Chest 2017; 152: 943-53.

29. Eichcorn L, Thudium M, Jüttner B. The diagnosis and treatment of carbon monoxide poisining. Dtsch Arztebl Int 2018; 115: 863-70.

30. Knighton DR. Mechanisms of wound healing. Kindwall EP, editor. Hyperbaric Medicine Practice. Arizona: Best Publishing Company; 1995.p.119-40.

31. Jain KK. HBO therapy in wound healing, plastic surgery, and dermatology. Kain JJ, editor. Textboof of Hyperbaric Medicine Sixth Ed. Cham: Springer International Publishing 2017.p.183-206.

32. Tapias LF, Wright CD, Lanuti M, Muniappan A, Deschler D, Mathisen DJ. Hyperbaric oxygen in the prevention and management of tracheal and oesophageal anastomotic complications. Eur J Cardiothorac Surg 2020; 57: 1203-9.

33. Ramsey SD, Newton K, Blough D, McCulloch DK, Sandhu N, Reiber GE, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. Diabetes Care 1999; 22: 382-7.

34. Eleftheriadou I, Kokkinos A, Liatis S, Makrilakis K, Tentolouris N, Tentolouris A, et al. Atlas of the Diabetic Foot. Third ed. New Jersey: Wiley Blackwell, 2019.

35. Boulton AJ, Armstrong DG, Albert SF, Frykberg RG, Hellman R, Kirkman MS, et al. American Diabetes Association; America Association of Clinical Endocrinologists. Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologist. Diabetes Care 2008; 31: 1679-85.

36. Kaya A, Aydin F, Altay T, Karapinar Levent, Ozturk Hasan, Karakuzu Cengiz. Can major amputation rates be decreased in diabetic foot ulcers with hyperbaric oxygen therapy? Int Orthop 2009; 33: 441-6.

37. Goldman RJ. Hyperbaric oxygen therapy for wound healing and limb salvage: a systematic review. PM R 2009; 1: 471-89.

38. Liu R, Li L, Yang M, Boden G, Yang G. Systematic review of the effectiveness of hyperbaric oxygenation therapy in the management of chronic diabetic foot ulcers. Mayo Clin Proc 2013; 88: 166-75.

39. Boet S, Martin L, Cheng-Boivin O, Etherington N, Louge P, Pignel R, et al. Can preventive hyperbaric oxygen therapy optimise surgical outcome?: A systematic review of randomised controlled trials. Eur J Anaesthesiol 2020; 37: 1-13.

40. Friedman T, Menashe S, Landau G, Sherf M, Wiser I, Seligman Y, et al. Hyperbaric oxygen preconditioning can reduce postabdominoplasty complications: a retrospective cohort study. Plast Reconstr Surg Glob Open 2019; 7: e2417.

41. Torp KD, Murphy-Lavoie HM. Acute traumatic ischemia hyperbaric evaluation and treatment. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2020.

42. Garcia-Covarrubias L, McSwain NE Jr, Van Meter K, Bell RM. Adjuvant hyperbaric oxygen therapy in the management of crush injury and traumatic ischemia: an evidence-based approach. Am Surg 2005; 71: 144-51.

43. Jain KK. Hyperbaric oxygenation in traumatology and orthopedics. Kain JJ, editor. Textboof of Hyperbaric Medicine. 6th ed. Cham: Springer International Publishing 2017.p.429-42.

44. Mesimeris TA. Comprimised skin graft and falp. Mathieu D, editor. Handbook on Hyperbaric Medicine. Dordrecht: Springer International Publishing; 2006.p.329-62.

45. Nemiroff PM. Disorders approved for treatment with hyperbaric oxygen, Hyperbaric oxygen in skin grafts and flaps. Kindwall EP, editor. Hyperbaric Medicine Practice. Arizona: Best Publishing Company; 1995.p.565-80.

46. Zamboni WA, Baynosa RC. Comprimised grafts and flaps. Neuman TS, Thom SR, editors. Physiology and Medicine of Hyperbaric Oxygen Therapy. Philadelphia: Saunders Elsevier; 2008.p.373-96.

47. Shapell HW, Kislevitz M, Reddy G, Amirlak B, Morey A. Successful replantation of amputated penis with adjuvant hyperbaric oxygen therapy. Undersea Hyperb Med 2019; 46: 695-9.

48. Mass CS. Complications in the cosmetic Office setting. Complications in facial plastic surgery. Capone RB, Sykes JM, editors. New York: Thieme Medical Publishers Inc 2012.p.10-6.

49. Hwang K. Hyperbaric oxygen therapy to avoid blindless from filler injection. J Craniofac Surg 2016; 27: 2154-5.

50. Kemmer A, Stein T, Heirholzer C. Persistent osteomyelitis. Mathieu D, editor. Handbook on Hyperbaric Medicine. Dordrecht: Springer International Publishing; 2006.p.429-50.

51. Britt MW, Calhoun J, Mader JT, Mader JP. Disorders approved for treatment with hyperbaric oxygen- The use of hyperbaric oxygen in the treatment of osteomyelitis. Kindwall EP, editor. Hyperbaric Medicine Practice. Arizona: Best Publishing Company; 1995.p.419-28.

52. Kirby JP. Hyperbaric oxygen therapy as an elective treatment. Mo Med 2019; 116: 184-7.

53. Ditri L, Montanari Y, Melamed Y, Reis D. Femoral head necrosis. Mathieu D, editor. Handbook on Hyperbaric Medicine. Dordrecht: Springer International Publishing; 2006.p.547-52.

54. Assouline-Dayan Y, Chang C, Greenspan A, Shoenfeld Y, Gershwin ME. Pathogenesis and natural history of osteonecrosis. Semin Arthritis Rheum 2002; 32: 94-124.

55. Shier A, Abdelrazek M, Soliman A, De Sanctis V, Elsayed A, Abdulla M, et al. Short-term outcome and MRI changes in three adult patients with sickle cell disease and aseptic osteonecrosis after treatment with hyperbaric oxygen threrapy: a preliminary report. Case Rep Oncol 2020; 13: 365-72.

56. Bosco G, Vezzani G, Mrakic Sposta S, Rizzato A, Enten G, Abou-Samra A, et al. Hyperbaric oxygen therapy ameliorates osteonecrosis in patients by modulating inflammation and oxidative stress. J Enzyme Inhib Med Chem 2018; 33: 1501-5.

57. Ververidis AN, Paraskevopoulos K, Keskinis A, Ververidis NA, Molla Moustafa R, Tilkeridis K. Bone marrow edema syndrome/transient osteoporosis of the hip joint and management with the utilization of hyperbaric oxygen therapy. J Orthop 2020; 22: 29-32.

58. Baig SA, Baig MN. Osteonecrosis of the femoral head: etiology, investigations, and management. Cureus 2018; 10: e3171.

59. Li W, Ye Z, Wang W, Wang K, Li L, Zhao D. Clinical effect of hyperbaric oxygen therapy in the treatment of femoral head necrosis: a systematic review and meta-analysis. Orthopade 2017; 46: 440-6.

60. Nakamura H, Makiguchi T, Atomura D, Yamatsu Y, Shirabe K, Yokoo S. Changes in skin perfusion pressure after hyperbaric oxygen therapy following revascularization in patients with critical limb ischemia: a preliminary study. Int J low Extrem Wounds 2020; 19: 57-62.

61. Conte MS, Bradbury AW, Kohl P, White JV, Dick F, Fitridge R, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. Eur J Vasc Endovasc Surg 2019; 58: 1-109.

62. Heyboer M, Grant WD, Byrne J, Pons P, Morgan M, Igbal B, et al. Hyperbaric oxygen for the treatment of nonhealing arterial insufficiency ulcers. Wound Repair and Regen 2014; 22: 351-5.

63. Roeckl-Wiedmann I, Bennett M, Kranke P. Systematic review of hyperbaric oxygen in the management of chronic wounds. British Journal of Surgery 2005; 92: 24-32.

64. Yu WK, Chen YW, Shie HG, Lien TC, Kao HK, Wang JH. Hyperbaric oxygen therapy as an adjunctive treatment for sternal infection and osteomyelitis after sternotomy and cardiothoracic surgery. J Cardiothorac Surg 2011; 6: 141.

65. Shields RC, Nichols FC, Buchta WG, Claus PL. Hyperbaric oxygen therapy for chronic refractory osteomyelitis of the sternum. Ann Thorac Surg 2010; 89: 1661-3.

66. Barili F, Polvani G, Topkara VK, Dainese L, Cheema FH, Roberto M, et al. Role of hyperbaric oxygen therapy in the treatment of postoperative organ/space sternal surgical site infections. World J Surg 2007; 31: 1702-6.

67. Mills C, Bryson P. The role of hyperbaric oxygen in the treatment of sternal wound infection. Eur J Cardiothorac Surg 2006; 30: 153-9.

68. Pasquier D, Schmutz J, Lartigau E. Radio-induced lesion in normal tissues. Mathieu D, editor. Handbook on Hyperbaric Medicine. Dordrecht: Springer International Publishing; 2006.p.363-400.

69. Marx RE. Disorders approved for treatment with hyperbaric oxygen- Radiation injury to tissue. Kindwall EP, editor. Hyperbaric Medicine Practice. Arizona: Best Publishing Company; 1995.p.447-504.

70. Feldmeier JJ. Principles of wound management, Poblem wounds: the irradiated wound. Sheffield PL, Smith APS, Fife C, editors. Wound Care Practice. Arizona: Best Publishing Company; 2004.p.369-88.

71. Marx RE, Johnson RP, Kline SN. Prevention of osteoradionecrosis: a randomized prospective clinical trial of hyperbaric oxygen versus penicillin. JADA 1985; 111: 49-54.

72. Junior LHF, Limirio PHJO, Soares PBF, Dechichi P, De Souza Castro Filice L, Quagliatto PS, et al. The effect of hyperbaric oxygen therapy on bone macroscopy, composition and biomechanical properties after ionizing radiation injury. Radiat Oncol 2020; 15: 95.

73. Weinberger A, Siekmann U. Acute ischemic ophthalmological disorders. Mathieu D, editor. Handbook on Hyperbaric Medicine. Dordrecht: Springer International Publishing; 2006.p.527-36.

74. Beiran I, Goldberg I, Adir Y, Tamir A, Shupak A, Miller B. Early hyperbaric oxygen therapy for retinal artery occlusion. Eur J Ophtalmol 2001; 11: 345-50.

75. Bagli BS. Clinical efficiancy of hyperbaric oxygen therapy on idiopathic sudden sensorineural hearing loss. Undersea Hyperb Med 2020; 47: 51-6.

76. Bayoumy AB, De Ru JA. The use of hyperbaric oxygen in acute hearing loss: a narrative review. Eur Arch of Otorhinolaryngol 2019; 276: 1859-80.

77. Körpinar S, Alkan Z, Yiğit O, Gör AP, Toklu AS, Cakir B, et al. Factors influencing the outcome of idiopathic sudden sensorineural hearing loss treated with hyperbaric oxygen therapy. Eur Arch Otorhinolaryngol 2011; 268: 41-7.

78. Barthelemy A, Rocco M. Sudden deafness. Mathieu D, editor. Handbook on Hyperbaric Medicine. Dordrecht: Springer International Publishing; 2006.p.451-68.

79. Amaro CE, Espiney R, Radu L, Guerreiro F. Malignant (necrotizing) externa otitis: the experience of a single hyperbaric centre. Eur Arch Otorhinolaryngol 2019; 276: 1881-7.

80. Lampl L, Frey G. Intra-cranial abscess. Mathieu D, editor. Handbook on Hyperbaric Medicine. Dordrecht: Springer International Publishing; 2006.p.291-304.

81. Kutlay M, Colak A, Yıldız S, Demircan N, Akın ON. Stereotactic aspiration and antibiotic treatment combined with hyperbaric oxygen therapy in the management of bacterial brain abscesses. Neurosurgery 2008; 2: 540-6.

İstanbul Med J 2020; 21(4): 242-57
DOI: 10.4274/imj.galenos.2020.13463

Mysterious Side of COVID-19 Pandemic: Children

COVID-19 Pandemisinin Gizemli Yanı: Çocuklar

Hacer Efnan Melek Arsoy[1], Öner Özdemir[2]

[1]Sakarya University Training and Research Hospital, Clinic of Pediatrics, Sakarya, Turkey
[2]Sakarya University Faculty of Medicine, Department of Pediatrics, Division of Allergy and Immunology, Sakarya, Turkey

ABSTRACT

As of December 31, 2019, the Severe Acute Respiratory syndrome Coronavirus-2 (SARS-CoV-2) was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei province of China and has been responsible for over 40,000 deaths worldwide. Data on the epidemiologic characteristics and clinical features, diagnosis and management of infected children are limited. Despite the high mortality rate of Middle East Respiratory syndrome and SARS in adults, the morbidity and mortality rates in children are low. Understanding the role of paediatric population in the transmission dynamics of the outbreak is important and critical for effective disease containment with respect to the public health. The aetiology of the milder disease form caused by the CoVs, including SARS-CoV-2, remains unknown in children. İnfected children may be asymptomatic or have fever, dry cough, and fatigue and rarely have severe disease. Asymptomatic children may be driving the transmission of CoV more than we realise. Early diagnoses and treatment along with careful isolation can limit the outbreak. Children may help in future development of immunotherapy and vaccines for SARS-CoV-2. This review aimed to summarise current data available on SARS-CoV-2 pandemic to manage the diagnosis, treatment, and prevention of CoV disease 2019 in the paediatric population.

Keywords: Coronavirus, COVID-19, SARS-CoV-2, newborn, children

ÖZ

31 Aralık 2019'dan itibaren dünya çapında 40,000'den fazla ölümden sorumlu olan 2019'un yeni koronavirüsü [Şiddetli Akut Solunum sendromu - Koronavirüs-2 (SARS-CoV-2)], Çin'in Hubei eyaletindeki bir şehir olan Wuhan'da pnömoni olgularının nedeni olarak tanımlanmıştır. Enfekte çocukların epidemiyolojik özellikleri ve klinik özellikleri tanı, tedavisi ile ilgili veriler sınırlıdır. Orta Doğu Solunum sendromu ve SARS'da yetişkinlerde yüksek mortalite oranına rağmen, çocuklarda ölüm ve morbidite oranları azdır. Salgının bulaşma dinamiklerinde pediyatrik popülasyonun rolünün anlaşılması, halk sağlığı kontrolünün etkili olması için önemli ve kritiktir. Çocukların SARS-CoV-2 de dahil olmak üzere koronavirüslerin neden olduğu hastalıkları neden daha hafif atlattıkları bilinmemektedir. Enfekte çocukta semptom olmayabileceği gibi ateş, kuru öksürük ve yorgunluk olabilir ya da nadiren kritik seyredebilir. Asemptomatik çocuklar virüsün farkettiğimizden daha fazla yayılmasına neden olabilir. Erken teşhis ve tedavi ve dikkatli izolasyon salgını sınırlandırabilir. Çocuklar SARS-CoV-2 için immünoterapi ve aşıların gelecekteki gelişimine yardımcı olabilir. Bu derlemede pediyatrik popülasyonda COVID-19'un tanısı, tedavisi ve önlenmesine rehberlik etmek için SARS-CoV-2 pandemisi hakkındaki mevcut veriler özetlenmiştir.

Anahtar Kelimeler: Koronavirüs, COVID-19, SARS-CoV-2, yenidoğan, çocuk

Introduction

On 31 December 2019, unknown pneumonia cases were reported in people associated with the Huanan Seafood Wholesale Market in Wuhan, Hubei Province, China. On January 7, 2020, the Chinese health authorities confirmed that this case community was associated with a new type of coronavirus (1). Later, this clinical picture was named Coronavirus disease 2019 (COVID-19), and its factor was reported as "Severe Acute Respiratory syndrome Coronavirus 2 (SARS-CoV-2)" (2).

COVID-19, which has been declared a pandemic with current data, continues to spread by increasing the number of infected cases and mortality day by day. SARS-CoV, an epidemic with viruses from the same family, appeared in 2002-2003, while 8,000 cases and 800 deaths occurred; Middle East Respiratory syndrome (MERS)-CoV appeared in 2012, causing 2,500 cases and 800 deaths (3). On March 11, 2020, the World Health Organization (WHO) classified the COVID-19 infection as a pandemic. As of March 31, 2020, more than 825,000 confirmed cases and more than 40,000 deaths (an approximate fatality rate of 4.8%) have

Address for Correspondence/Yazışma Adresi: Hacer Efnan Melek Arsoy MD, Sakarya University Training and Research Hospital, Clinic of Pediatrics, Sakarya, Turkey
Phone: +90 506 845 68 52 **E-mail:** efnan198381@hotmail.com **ORCID ID:** orcid.org/0000-0002-9812-5447

Cite this article as/Atıf: Melek Arsoy HE, Özdemir Ö. Mysterious Side of COVID-19 Pandemic: Children. İstanbul Med J 2020; 21(4): 242-57.

Received/Geliş Tarihi: 16.04.2020
Accepted/Kabul Tarihi: 02.06.2020

been reported. Comparison of the characteristics of SARS, MERS and COVID-19 diseases are shown in Table 1 (3,4).

For now, the main source for the disease is patients infected with COVID-19. Contagion is known to be through droplets or contact from the respiratory tract, but there is no clear information about the fecal-oral or vertical transition. One of the key differences of the coronavirus 2019 pandemic is that most of the information is generated by adult patient data. MERS-CoV infection, which is from the same family as COVID-19 disease factor, also affects children less and has less mortality if the affected patient does not have any underlying comorbid disease (5). As discussed in detail below, information about infected children and infants is limited and scattered.

The first pediatric case was reported on January 20 in Shenzen. On February 10, 398 confirmed cases of children were reported in China outside the Hubei region. Hubei region was excluded because children were screened less in there (6,7). Numbers reported from Italy on 18 March were that 1.2% of 22,512 cases were children and it did not cause death in children (8). On March 16, the United States announced that 5% of 4,226 COVID-19 cases were children (9). In a report from China, only 2% of COVID-19 infections were in people under 20 (10). Similarly, only 6.3% of the nearly 8,000 infections in South Korea have been seen in those under the age of 20 (11). Like MERS-CoV, there may be different reasons why SARS-CoV-2 is rarely seen in children. As discussed below, children surviving with asymptomatic or mild symptoms may be due to low exposure to the virus, immature immune systems and a number of factors that are not yet identified. The more screening is done, the higher the rate may appear in children and adolescents.

This article is compiled in order to make earlier diagnosis of asymptomatic children which are considered as a hidden source rather than the patient in infectious and epidemic prevention studies and to review the innovations in treatment, with the differences in diagnosis, stimulant clinical findings and laboratory data.

Etiopathogenesis

Coronavirus was first isolated in the tissue culture of a patient with a cold in 1965. Culture durations are 4 days in human airway epithelial cells and 6 days in Vero E6/Huh - 7 cells. CoVs are single-chain, enveloped, ribonucleic acid (RNA) viruses that can be isolated from different animals in diameters of about 60 to 140 nm (12). SARS-CoV-2 has low resistance to external environment, it is easily deactivated at 56 °C in 30 minutes or with 60-80% ethanol and chlorinated disinfectants, chloroform (excluding chlorhexidine) and peracetic acid (13).

The Coronaviridae family is part of the Nidovirales team, consists of the Coronavirinae and Torovirinae subfamilies, causing various diseases in the respiratory, enteric, neurological and hepatic system by infecting mammals and birds (3). The virus family can be examined in 4 groups. Alpha and beta groups infect mostly mammals, gamma and delta mostly birds. The most known subgroup is the genus Alpha-coronavirus, which causes classic cold symptoms in human. SARS-CoV and MERS-CoVise are in genus Beta-coronavirus. It is known that both

Table 1. Comparison of the characteristics of SARS, MERS and COVID-19 diseases (3,4,9)

Properties	SARS	MERS	COVID-19
The first reported patient	Guangdong, China November 2002	Zarga, Jordan April 2012 Saudi Arabia June 2010	Wuhan, China December 2019
Virus	SARS-CoV	MERS-CoV	SARS-CoV-2
Subgroup of the virus	Beta-coronavirus	Beta-coronavirus	Beta-coronavirus
Host cell receptor	ACE-2	Dipeptidil peptidaz 4	ACE-2 (possibly)
Animal host	Bat (natural carrier) Musk cat and raccoon (intermediate host)	Bat (natural carrier) Single humped camel (intermediate host)	The bat (possible natural carrier) can be the intermediate host in the seafood market (pagolin?)
Incubation period	2-14 days	2-13 days	2-14 days
The period from the start of the disease until the hospital application	2-8 days	0-16 days	0-9.1-12.5 (data incomplete)
Contagion rate	2-3	>1	2.2
Number of patients	8098	2506	825,000 (31 March 2020)
Adult	93%	98%	90%?
Child	5-7%	2%	2.5-10%?
Age range	1-91 years	1-94 years	36 hours-89 years
Gender M/F	43-57%	64.5-35.5%	56-44%
Number of deaths	774	862	41000 (31 March 2020)
Mortality	9.6%	35-40%	4.8% (31 March 2020)
Effects in pregnancy	3/12 pregnancy death No vertical transition	No vertical transition	No vertical transition? (In 36 hour newborn SARS-CoV-2 PCR +)

SARS: Severe acute respiratory syndrome, MERS: Middle East respiratory syndrome, COVID-19: Coronavirus disease 2019, M/F: male/female, PCR: polymerase chain reaction, ACE-2: angiotensin converting enzyme-2

viruses tend to infect intrapulmonary epithelial cells instead of upper respiratory epithelial cells (14). SARS-CoV-2 virus, which has a cytopathic effect in cell culture and is in beta group, has been shown to have a 86.9% nucleotide sequence similarity with bat-derived SARS-like CoV (bat-SL-CoVZC45, MG772933.1) in phylogenetic analysis. The SARS-CoV-2 chain is 79% similar to SARS-CoV and 50% similar to MERS-CoV (15). Its phylogenetically similar features shed light on the treatments developed.

Differences in Sensitivity of Children and Adults to COVID-19

There are some studies investigating why the disease is transmitted in children with a milder clinic picture. Due to the immature immune system in children, there are some data supporting the rarely occurrence or slight affect of some infections. For example; It has been shown that immature mice do not have poliovirus-induced paralysis due to maturational changes of the axonal transport system (16). Another thesis is that children have a more active natural immune response. Unlike adults, less exposure to air pollution and cigarette smoke, and other factors such as underlying diseases are thought to be the reason for the healthier airways of children. In addition, acute respiratory distress syndrome (ARDS) was associated with a much stronger immune response reaction in adults. One of the most remarkable reasons among these is that the distribution, maturation and functional differences of viral receptors vary depending on age. SARS-CoV, SARS-CoV-2 and human coronavirus NL63 use the SARS-CoV receptor, namely angiotensin converting enzyme-2 (ACE-2) as a cell receptor to enter the host cells in humans. As a result, these and similar effects can be cited as the reason why children are more resistant to COVID-19 infections (17).

Expression of ACE-2 in the lungs of mice has been found to be significantly reduced with increasing age. Although this is not consistent with children's low sensitivity to SARS-CoV-2, it has also been noted that ACE-2 functions as the protective mechanism of the lungs. It has been demonstrated in experimental mouse studies and pediatric patients that ACE-2 plays a protective role from severe lung damage caused by virus infections involving the respiratory tract. ACE-2 also protects against acute severe lung damage triggered by sepsis, respiratory syncytial virus (RSV), acid aspiration, SARS, and terminal bird flu H5N1 virus infection. In addition, administration of the recombinant ACE-2 protein has been shown to reduce the severity of lung damage caused by RSV. Even decrease in ACE-2 protein levels in the lungs of mice was detected during RSV infection (18).

In a different study, it was reported that the main reason for children to be less affected is that ACE-2 protein actually acts as a receptor for virus entry, but is related to the development and function of ACE-2 protein, such as low sensitivity, low binding ability or differences of ACE-2 in children. Thus, the fact that ACE-2-induced intracellular response in alveolar epithelial cells in children lower than in adults is considered as the reason of that children are less affected by the disease (19).

ACE-2 is a surface molecule and is also expressed in the upper esophageal epithelial cells and in the absorptive parts of enterocytes in the ileum and colon, and mostly in AT-2 cells located in the lungs. This explains how COVID-19 affects the digestive system, like the lungs, as a potential pathway. The ACE-2 expression level in Asian populations is significantly higher than in European and American populations. ACE-2 expression in men's cells is higher than in women's. The high incidence of coronavirus in Asian men can explain the pneumonia rates (19).

In adults infected with the SARS-CoV-2 virus, there is a markable or progressive decrease in the number of peripheral absolute lymphocytes at an early stage. Both the CD4+ and CD8+ lymphocyte count decrease, and the neutrophil/lymphocyte ratio increases as SARS-CoV-2 consumes lymphocytes as an early and prominent sign (20). This proves that the virus used lymphocytes to reproduce and spread in the early stages. Adult cases become severe within 7-10 days from the onset of the disease. As a result of rapid virus replication, inflammatory cell infiltration, proinflammatory cytokines, and chemokine response increase, transition to ARDS, which is fatal lung injury occurs (20). The fact that the number of leukocytes and absolute lymphocytes is quite normal and there is no decrease in lymphocytes after the SARS-CoV-2 infection in children suggests that there is fewer immune dysfunction.

On the other hand, mild COVID-19 disease in children may be associated with trained immunity/active immunization. The creation of a trained immune system is a new immune model. Some designated vaccines, such as Bacillus Calmette Guerin (BCG), create immune memory by training natural immunity. In a study in mice, nonspecific protection against influenza virus has been demonstrated by stimulating trained immunity depending on BCG vaccine administration. Most of the children in China and Asia are regularly vaccinated according to the routine scheme, which also includes BCG. In the light of this information, it should be investigated in more detail in terms of educating the immune system with vaccination, which may be one of the reasons why children have less ARDS than adults (21).

Infectiousness

Although the incubation period of the virus is known as 5-6 days, it can be extended up to 14 days. Contagion begins 1-2 days before symptoms begin. The infection was initially seen among the adults, and then the elderly and children become infected by spreading around the family and creating a "cluster". SARS-CoV-2 is transmitted from human to human by droplet, contact and aerosol. Infection occurs when these droplets are inhaled or touched on the surfaces contaminated by the virus and then brought to the nose, mouth and eyes. Although it is known that it cannot travel more than 2 meters in the air and cannot remain suspended for a long time, it has been shown in an article that SARS-CoV-2 aerosols can remain active for at least 3 hours under experimental conditions (22). Therefore, attention should be paid to aerosol-forming conditions and processes to reduce spread in this way (Table 2) (23).

Vaginal birth is considered as a transmission route due to close mother-baby contact. Although it is thought that the possibility of transmission in vaginal birth is high, there is no evidence of this. SARS-CoV-2 was found to be negative in all babies born with cesarean from 9 symptomatic pregnant women with COVID-19. Amniotic fluid, cord blood samples from six patients, nasopharyngeal specimen from neonates and breast milk samples resulted negative for SARS-CoV-2 (24). In an article suggesting vertical transition and showing that newborns were affected, thrombocytopenia was observed along with 1/10 death

Table 2. Aerosol-forming states and processes (95)	
Cough/Sneezing	Endotracheal intubation
Drug administration with nebulization	Separation of ventilator circuits
Oxygen therapy with nasal cannula	Open system tracheal aspiration
Oxygen delivery rate is more than 6 min/liter	Tracheostomy
Oxygen therapy with high flow nasal cannula	Bronchoscopy
Non-invasive mechanical ventilation	Cardiopulmonary resuscitation
Positive pressure ventilation with balloon mask	

incidence, premature birth, fetal distress, respiratory failure, impaired liver function (25). In a letter-type article, it was claimed that a serum-specific IgM-type antibody specific to SARS-CoV-2 was detected in the serum of the newborn, suggesting a vertical transition (26).

The isolation of SARS-CoV-2 in stool and anal swab in mother and infant without gastrointestinal symptoms supports possible faecal-oral passage as a potential passageway. The subsequent positivity of fecal RNA from the positivity of pharyngeal RNA may suggest that the virus has been ingested and passed into the digestive system. Also, fecal RNA negativity occurs much later than pharyngeal RNA negativity. After pharyngeal samples become negative, sputum and stool tests can remain positive for up to 39 and 13 days, respectively. It may be related to the fact that the digestive system clears the virus much slower than the respiratory system (27-29). In the urine sample, RNA was detected in very few patients. Despite this, many studies have not shown virus spread in the urinary system (27,28,30).

Is There a Connection Between Transmission and Viral Load?

Seventy six COVID-19 patients verified with reverse transcription polymerase chain reaction (RT-PCR) were evaluated at Nanchang University. The average viral load of severe cases was found to be 60 times higher on average than mild cases, suggesting that higher viral loads may be associated with serious clinical consequences. In 90% of mild cases, the RT-PCR tests became negative on the 10th day after the onset of the disease, also demonstrating early viral clearance in mild cases. In all severe cases, RT-PCR test was positive on the 10th day or later. Patients with severe COVID-19 disease picture appear to have a high viral load and a long virus release time. This finding suggests that the viral load of SARS-CoV-2 may be a useful marker to assess disease severity and prognosis (31).

Clinical Findings

It is known that the incubation period of SARS-CoV-2 is between 1 and 14 days (an average of 5.2 days) and symptoms of 97.5% of those symptomatic occur within 10.5 days (32). The latest diagnosis was made on day 42 from the onset of the disease (average 2 days, range: 0 to 42 days) (33).

In the series prepared with data of 2,143 children (median age 7), including 731 (34.1%) laboratory-approved cases and 1,412 (65.9%) suspected cases with COVID-19 infection, without gender difference, more than 90% of all patients have asymptomatic, mild or moderate clinical picture. The most common clinical symptoms in 171 confirmed patients were cough (48.5%), pharyngeal erythema (46.2%), fever (41.5%), diarrhea (8.8%), fatigue (7.6%), nasal flow (7.6%) and vomiting (6.4%). 32.2% of the patients had a high fever of 38 °C. Tachycardia (42.1%) and tachypnea (28.7%) were common findings at admission (33). Another study on 6 children aged 1 to 7 years hospitalized with COVID-19 in Wuhan, all had fever >39 °C and cough, four of them had viral pneumonia on imaging, and one patient was taken into intensive care. All children were recovered and discharged (34). In the study conducted out of the neonatal group, most of the patients' (8/10) fever recovered within 24 hours (35). One of the diagnosed patients had only diarrhea (36). 5.2% of patients had dyspnea, central cyanosis, severe with less than 92% oxygen saturation level and 0.6% of them had respiratory failure, ARDS, shock, multiorgan failure (encephalopathy, heart failure, coagulation disorder and acute renal failure, etc). Only 4 children had oxygen saturation below 92% (33). In the first case series article on children with COVID-19, it was additionally shown that the fever period was shorter and resolved rapidly in mild cases (28). Some patients with or without cough symptoms may have patchy infiltration in their pulmonary X-rays. In a 10-year-old asymptomatic child, frosted glass opacity was observed in his radiological examination. Therefore, in case of doubt, only clinical findings may not be sufficient for diagnosis.

The clinical course of COVID-19 is generally milder in children than in adults. It can range from asymptomatic infection to severe respiratory distress in newborns and children. Critical and severe cases were higher in groups under 1 year and under 5 years. Patients with critical condition and rapidly developing respiratory failure who need invasive mechanical ventilation generally have an underlying disease history. It appeared in 7-months-old patient with intensive care need hydronephrosis, receiving chemotherapy treatment for leukemia, having intussusception (37), congenital heart disease and moderate malnutrition; and in a 13-month-old patient with hydronephrosis and left kidney stone (38). Following the intensive care follow-up and multiorgan dysfunction in a 55-day-old baby with an unknown underlying disease, on the 11th day, the clinical picture started to improve and patient discharged (39). Focal pneumonia finding in computerized tomography (CT) scan in children (4/10) also improved without requiring additional oxygen therapy (35). 1.6-2.5% of 123 children reported in the USA were hospitalized, and none of them needed intensive care (9).

Six child deaths, the diagnosis of which was clarified until March 29, 2020, were reported. Deaths of 10-months-old with intussusception and multiorgan failure (36), 14-years-old whose data are not clearly explained in the study (37), 3-years-old with leukemia in Iran, 6-years-old with asthma and 35-days-old with no information (40), and a child under 1 year in Chicago, 12-years-old girl in Belgium and a 13-year-old male in England has been reported (41,42).

The lowest APGAR scores of the newborns were 8/9 in the study, which was followed by 9 pregnant women who had a cesarean with symptomatic COVID-19 without severe COVID-19 pneumonia. In SARS infection, pregnant women infected with SARS-CoV-2 were monitored more closely because 50% of pregnant women needed intensive care, 33% received mechanical ventilation support, and the mortality rate in this group of patients was 25% higher than the population. However, none of the pregnant women needed intensive care.

Data on newborns are limited. While a 17 day newborn had symptoms of fever, cough and vomiting, the asymptomatic 30 hour newborn born from a mother infected with the SARS-CoV-2 was diagnosed with a viral nucleic acid test. In another newborn, whose mother was infected with SARS-CoV-2, fever occurred on its 5th day of birth, vital signs of these newborns remained stable, and no severe or emergency occured (43,44).

The classification of the clinical picture of the patients provides guidance for the course of the disease and treatment needs. Clinical condition classification (45):

1. Asymptomatic - silent - infection

Pediatric patients with positive SARS-CoV-2 RT-PCR test without clinical symptoms or abnormal pulmonary imaging

2. Acute upper respiratory tract symptom findings

Only in the presence of cough, fever, sore throat, nasal congestion, fatigue, headache, myalgia and weakness without the appearance of pneumonia or sepsis on pulmonary imaging.

3. Mild pneumonia

In the presence or absence of fever, respiratory system symptoms such as cough and symptoms indicating pneumonia from pulmonary imaging and in the period that have not met the criteria for severe pneumonia.

4. Severe pneumonia

In the presence of one of the following criteria:

- Increased respiratory rate: 70/min respiratory rate under 1-year-old, sedated over 1-year-old and over 50/min without fever,

- Oxygen saturation: <92%,

- In the presence of hypoxia symptoms: nasal wing breathing, difficult respiratory symptoms such as moaning, cyanosis, intermittent apnea, etc,

- Consciousness disorders; somnolence, coma, or convulsion,

- Symptoms of dehydration with difficulty feeding or food rejection.

5. Critical cases

In the presence of one of the following criteria and need of intensive care:

- Respiratory failure requiring mechanical ventilation support,

- Shock,

- Accompanied by other organ failures.

Laboratory Evaluation

The leukocyte count is normal (69.2%) or decreased in the early stage of the disease. 4.6% neutrophilia and 6% neutropenia were observed (46). The lymphocyte count is reduced and lymphopenia deepens as the severity of the disease increases. Lymphopenia may be rarely seen in very young children depending on the immune system response (47,48).

Increased liver enzymes and raise in inflammatory indicators such as C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), sometimes hyperglycemia have been detected in studies coducted on adults (48). Most children cases have high CRP and ESR levels and normal PCT levels. PCT and CRP increase was seen in 13.6% and 10% of the patients, respectively (46). It is recommended that attention should be paid to increase in PCT in children in terms of coinfection (8/20: 40%) -influenza A and B viruses, mycoplasma, RSV and cytomegalovirus- (49). Bacterial coinfections should also be noted. In severe cases, high D-dimer levels are remarkable. Liver, muscle enzymes, troponin I, LDH levels and myohemoglobin levels have increased in some patients (39,45). IL-6 level which also increases in viral diseases may be high during the course of disease in critically ill patients. It may be useful to follow up with the number of CRP and lymphocytes as a prognostic marker (46). Higher plasma cytokines IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1A and TNF-α (cytokine storm) in adult patients in intensive care than patients in non-intensive care units were measured (50).

SARS-CoV-2 nucleic acid test positivity in nasopharyngeal swab, sputum, lower respiratory tract secretions, stool and blood samples are diagnostic tests. Although nasopharyngeal swab is the most commonly used test, it provides less than 50% positivity. Repetitive tests are required (51).

Imaging Methods

In diagnosed patients, pulmonary X-ray sensitivity is 59%, CT sensitivity is 98% and RT-PCR sensitivity is 71% (52). In COVID-19 patients, findings in favor of the disease can be detected in lung imaging rate close to clinical and laboratory findings rate. Therefore, it is an important examination in the diagnostic approach. Viral pneumonia-like changes were detected in 70.4% of 134 children in lung imaging (38).

In suspicious and diagnosed cases, pulmonary X-ray should be performed as soon as possible. If necessary, pulmonary CT scan should be performed immediately. Multiple small plaques and interstitial changes in the lung periphery can be observed in the early stages of the disease, and bilateral multiple ground glass opacities and/or infiltrations in later stages. Bilateral pulmonary lesions (more than 50%) are more common than unilateral lesions. Small nodular appearance and pleural effusion are much rarer. The halo sign around the lesion is more specific to pediatric patients. Lung consolidation exists in more serious cases (49).

In 81 adult patients' radiological findings, COVID-19 pneumonia tends to occur as air bronchograms, peripheral infiltration and bilateral, subpleural, ground-glass opacities mostly in the right lower lobe in pulmonary CT scans. Abnormal pulmonary CT findings may be present even in asymptomatic patients. The lesions spread rapidly within 1-3 weeks after the onset of symptoms, and the frosted glass appearance

increases or can turn into a consolidation pattern and peak approximately 2 weeks after the onset. Follow-up age, involvement characteristics in CT, male gender, underlying comorbidities and progressive radiographic deterioration may be risk factors for poor prognosis in patients with COVID-19 pneumonia (53).

In the first newborn case with COVID-19 pneumonia, increased linear opacities were detected on pulmonary CT scan (43). The youngest patient, diagnosed with COVID-19, with viral pneumonia on CT scan without mild fever, is a 24 hour case (38).

Pneumomediastinum was detected in an adult COVID-19 patient's pulmonary CT scan following the development of respiratory distress during hospital follow-up. Spontaneous formation of pneumomediastinum in COVID-19 patients should be closely monitored as a potential indicator of ingravescent disease (54). The classification made by evaluating CTs of adult COVID-19 cases according to their periods (Table 3) will be useful for patient follow-up and staging (55).

Diagnosis

Clinic is often used for diagnosis. In the epidemiological study in China, laboratory values (normal or low white blood cell count, increased CRP) and abnormal chest X-ray were used for diagnosis in the presence of at least two symptoms (fever, respiratory symptoms, gastrointestinal symptoms or fatigue) (37).

Definitive diagnosis of COVID-19 is made using nasal or pharyngeal swabs or blood samples. RTS-PCR results should have been found positive by amplifying SARS-Cov-2 nucleic acid on the samples taken. Epidemiological data can be obtained by genetic sequencing. However, this test also has certain limitations; high false negative rates have also been reported. The use of rapid antibody test is also recommended to quickly identify a large number of infected patients and asymptomatic carriers in the fight against the virus. The measurement of IgM and IgG antibodies against SARS-CoV-2 virus in the blood of patients at different stages can be done by immunochromatographic card test within 15 minutes. The sensitivity of this test is 88.66% and its specificity is 90.6%. This test can be used for rapid screening of symptomatic or asymptomatic SARS-CoV-2 vectors (56).

Early Diagnosis of Critical Cases

In the light of experiences from community-acquired pneumonia cases, those who had contact with infected cases or had a concomitant disease (congenital heart disease, bronchopulmonary hypoplasia, respiratory anomaly, severe malnutrition) or immune deficiency or immune compromised (prolonged use of immunosuppressants, etc) can be diagnosed early. Cases with this features are likely to become serious cases in the presence of one of the following criteria (45).

- Dyspnea: In the absence of sedation and no fever, respiratory rates to be >50/min in 2-12 months old, > 40/min in 1-5 years old, >30/min in over 5 years old.

- Persistent high fever for 3-5 days,

- Low mental response, lethargy, mental fog and change,

- Increased enzyme levels (myocardial, liver enzymes and lactate dehydrogenase),

- Unexplained metabolic acidosis,

- Infiltration in bilateral or multiple lobes, lung imaging with pleural effusion, or rapid deterioration in general condition,

- Patients under 3 months,

- Extra pulmonary complications,

- Coinfection with other viruses and or bacteria.

Differential Diagnosis

Influenza, parainfluenza, adenovirus, RSV, rhinovirus, human metapneumovirus, SARS-CoV, other viral infections, mycoplasma pneumonia, chlamydia pneumonia and bacterial pneumonia are important in the differential diagnosis. The possibility of coinfection should also be considered during diagnosis (45).

Patient Management

Depending on their medical condition, suspicious patients should be isolated in a single room or at home. Cases with definitive diagnosis can be kept in the same area (in cohort) at home or hospital. Critical cases should be admitted to the intensive care unit as soon as possible. In case of a pandemic, national (Ministry of Health) algorithms must be followed (57-59).

Medical staff must protect themselves first. Hand hygiene should be provided with alcohol-based hand antiseptic. During the processes causing droplets or aerosolization, protective equipments are bone, goggles and face shield, FFP2 (N95) or FFP3 mask, apron and if possible at least 2 layers of gloves. It is recommended to use in accordance with the dressing and take off algorithm (Figure 1) (23). Especially during operations that produce aerosols, it is necessary to minimize its spread and take protective measures (Table 2) (23).

If medication is required via the inhalation route, an aerochamber or metered dose inhaler may be used. During treatment with the nasal cannula, wearing a surgical mask on the cannula, attaching the bacteria virus filter suitable for the ventilator circuits, using the double circuit in the ventilator in which the expiratory air is not given outside, performing the operations that create an aerosol in a negative pressure room can reduce the risk. Maneuvers should be carried out to use the balloon mask as little as possible. If it is still necessary to use a balloon mask, a virus filter and PEEP valve should be installed between the mask and the balloon. Balloon mask should also be made in accordance with the e-c technique. Low pressure should be used and a transparent pouch should be used to prevent virus spread. Use of laryngeal mask instead of balloon mask may be a good choice in suitable patients. Using a video laryngoscope, if available, during intubation may increase the distance between the patient and the doctor. After the intubation tube passed the vocal cords, the cuff must be inflated using the cuff manometry. Aspiration should be performed with a closed system (23). It is important to make sufficient neuromuscular blockade to reduce aerosol production during interventions such as tracheal intubation and to perform the procedures smooth and uncomplicated.

Isolation for diagnosed pediatric patients;

Inpatients need to be isolated in a single room, and those with high infectivity need to be isolated in a negative pressure ward. Attention should be paid to strict disinfection of children's stool and secretions. Outpatients should be isolated with the guidance of a doctor at home, under the supervision of the parents and treated under the supervision of the community and the doctor's remote guidance. In 14 days after the disease, isolation should be terminated by respecting SARS-CoV-2 nucleic acid in respiratory secretions at least 2 times with a negative result. In daily care, attention should be paid on regular ventilation of the room, 30 minutes each time, 2 times/day; the use of an appropriate size mask and hand cleaning are points to be considered. The patients should rest, drink plenty of water, and eat nutritious foods that are easy to digest and keep balanced diet. Wearing long-sleeved clothing can be good for hygiene. Latex gloves can be worn to hold secretions and contaminated paper towels. The waste is placed in a disposable bag, sealed, and a disinfectant is sprayed on the outer surface of the packaging bag before throwing it in the trash bin. The floor of other rooms in the house, various surfaces and toys should be wiped periodically with disinfectants containing chlorine (disinfectants must remain on the surface for 5 minutes). Children's used clothes, towels and sheets are thoroughly washed with hot soapy water.

General Treatment

General treatment mainly includes bed rest and supportive therapy. Ensuring adequate calorie and water intake; preservation of water-electrolyte balance and homeostasis; monitoring vital signs and oxygen saturation; other necessary biochemical evaluations, including keeping the airways open and supplying oxygen when needed, following routine blood and urine tests, CRP, liver and renal function, myocardial enzyme levels and coagulation parameters, blood gas should be planned according to the patient's condition. Pulmonary imaging may need to be renewed intermittently. CT scan is recommended (45). For patients in critical condition, prophylaxis should not be forgotten for the risk of gastointestinal bleeding. In addition, besides mechanical protection measures such as variable air pressure beds to protect the patient against venous thromboembolism, pharmacological prophylaxis (preferably low molecular weight heparin or heparin 5000 units can be applied under the skin 2 times a day) can be performed in adolescents if there are no contraindications (60).

Symptomatic Treatment

Patients with high fever are closely monitored. In cases exceeding 38.5 °C, physical cooling (warm water bath, antipyretic patch use etc) or antipyretic drug treatment should be performed. Orally administered ibuprofen 5-10 mg/kg/dose and acetaminophen 10-15 mg/kg/dose are used. Rapid treatment should be performed in case of convulsions or seizures (45).

There are thoughts about the use of ibuprofen, even if it has not been clarified, that it facilitates the formation of the infection. Some clinicians defend the use of acetaminophen as antipyretic because they think that the early use of non-steroidal anti-inflammatory drugs (NSAIDs) has negative effects on the course of the disease. With these concerns and results from the studies conducted with a small number of young patients suggested that NSAID drugs increased disease severity with the theory that they had negative effects on the patient's immune response. The European Medicines Agency and WHO do not block the use of NSAIDs within clinical indications (61-64).

Oxygen Treatment

When hypoxia occurs, effective oxygen therapy, including nasal cannula, oxygen mask should be performed immediately. Nasal high flow oxygen therapy and noninvasive or invasive mechanical ventilation should be performed when necessary. In non-invasive methods, caution should be exercised in terms of droplet and aerosolization and the risk of late invasive treatment. Information can be obtained from WHO's manual for respiratory support and ARDS management (23,60).

Pharmacotherapy

There is no proven specific treatment for the treatment of COVID-19 patients until results of ongoing clinical trials are revealed. However, since none of these treatments shows significant benefit in the treatment of other coronaviruses (MERS, SARS, etc), it is suspected to be tried in COVID-19 treatment. WHO and The Centers for Disease Control and Prevention (CDC) does not recommend any specific treatment in children or adolescents. However, in the case series mentioned earlier, 59% of 34 children diagnosed with COVID-19 were administered with Lopinavir (LPV)/Ritonavir (RTV) treatment. None of the children received glucocorticoid or immunoglobulin (65).

Antiviral Treatment

While interferons are used in viral respiratory diseases; LPV/RTV and arbidol are used in treatment of Human Immmunodeficiency Virus (HIV); oseltamavir is used in the treatment of influenza. Antiviral treatment should be administered only in critical cases. Reducing symptoms and maintaining immune balance is the main target (38).

Interferon (IFN)-α

Interferon (IFN)-α can reduce viral load in the early stage of infection; it can help alleviate symptoms and shorten the duration of the disease. Based on our clinical research and experience of using IFN-α in the treatment of bronchiolitis, viral pneumonia, acute upper respiratory tract infection, foot and mouth disease, SARS and other viral infections in children, the recommended use is as follows (66-71):

1. IFN-α nebulization: In 2 mL of sterile water, IFN-α 200,000-400,000 IU/kg or 2-4 μg/kg, nebulization twice daily for 5-7 days,

2. IFN-α2b spray: It is applied to the high-risk population in close contact with patients suspected of being infected with SARS-CoV-2, or patients who have been diagnosed only at an early stage with upper respiratory symptoms. 1-2 sprays should be used on both sides of the nasal cavity and 8-10 sprays on the oropharynx. The interferon-α2b dose per application is 8,000 IU, it is applied every 1-2 hours, 8-10 sprays per day, for 5-7 days. Since IFN-α2b nebulization is applied in MERS - CoV and SARS-CoV, it may be considered for COVID-19 infection (72).

In a study published by the Zhejiang University School of Medicine, nebulized IFN-α2b for children, LPV/RTV with corticosteroids for

complications (ARDS, encephalitis, hemophagocytic syndrome or septic shock), and intravenous immunoglobulin for severe cases are recommended (73).

Lopinavir/Ritonavir (Kaletra®)

It is a protease inhibitor used in the HIV treatment. LPV is usually combined with RTV to increase the half-life of LPV by inhibition of cytochrome P450. It has been tried to apply in the treatment of adult patients with COVID-19 pneumonia, but its effectiveness and safety are still unclear (74,75).

A successful case of MERS - CoV disease has been reported in South Korea who is treated with triple combination therapy LPV/RTV/ribavirin and IFN-α (74). The efficiency and safety of combined LPV/RTV/ribavirin therapy is still being evaluated in clinical studies and pediatric cases need to be treated more cautiously. In critical and appropriate cases, it can be considered if it is suitable for children. It can be dosed considering the anti-HIV treatment in children. HIV antigen/antibody should be checked before starting the medication.

LPV 250 mg / RTV 50 mg blister strip is used orally, twice daily for 5 days. Oral liquid form with LPV content of 16 mg/kg is recommended in children between 14 days-6 months (57). Between 6 months-18 years; 200 mg-50 mg in the range of 15-25 kilograms, 300 mg-75 mg in the range of 26-35 kilograms, 400 mg-1000 mg 2 times a day if more than 35 kilograms (57).

LPV/RTV is safe in pregnant women in category C, syrup and tablet forms are available (76,77).

Remdesivir

Remdesivir (GS5734) is an RNA polymerase inhibitor, adenosine nucleotide analogue with *in vitro* activity against multiple RNA viruses, including SARS, Ebola, MERS-CoV, SARS-CoV-2, both *in vitro* and animal studies (78). The pneumonia and general condition disorder developed in the first adult case in the USA improved after treatment with remdesivir. However, since this is limited to only one adult case, efficiency needs to be further verified (27). It is thought that it may be effective for both prophylaxis and treatment of human coronavirus infections (79).

Drugs considered to be effective against SARS-CoV-2, such as remdesivir or LPV-RTV, should be considered as rescuer therapy. It is suitable to be used after examining the profit-loss ratio, benefit and features as in adults. The pharmacology of intravenous remdesivir is unknown, phase 3 studies are ongoing and may not be possible as it is not licensed (80).

Adult use is recommended as 200 mg intravenously in a lump, and then 100 mg intravenously daily for 5-10 days (81). For children weighing less than 40 kilograms, following 5 mg/kg intravenous loading, 2.5 mg/kg once a day; and for children weighing more than 40 kilograms, 100 mg intravenously is once a day following 200 mg intravenous loading.

Arbidol, Oseltamivir and Other Anti-influenza Drugs

Arbidol is administered for adults infected with SARS-CoV-2; however, its effectiveness and safety remain uncertain. It has been discovered that Arbidol can block viral fusion of influenza A and B viruses, as well as hepatitis C virus (82). Oseltamivir and other anti-influenza agents can be administered in the presence of coinfection with the influenza virus. In case of clinical necessity, the dose of oseltamavir can be administered for 5 days, in accordance with the dosage schedule in influenza disease (57,83).

Ribavirin

Ribavirin; is a guanosine analogue. It is used in hepatitis C treatment. It has been shown to be ineffective and even harmful and hemolyzed against SARS-CoV and MERS-CoV (67,84-86).

It has been reported that ribavirin and IFN synergistically inhibit SARS-CoV replication in animal and human cell lines. Given the adverse reactions and lack of *in vitro* efficacy, the use of ribavirin for COVID-19 treatment should be seriously considered, even in combination with other antiviral drugs (87).

The use of Ribavirin 200 mg capsules in the presence of clinical indications: for children 2 g (30 mg/kg) loading dose and then 4x1 g (17 mg/kg/every 6 hours/4 days) or 4x0.5 g (8 mg/kg/every 8 hours/6 days), for a total of 10-14 days (57).

Table 3. Progressive stages of computerized tomography imaging in COVID-19 infection (87)

	Phase 1	Phase 2	Phase 3	Phase 4
Stage	Early stage	Progressive stage	Peak stage	Recovery stage
The day the symptom started	0-4 day	(5-8. day)	(9-13 day)	(after 14th day)
Localization	Peripheral mostly in the lower lobes	Bilateral multilobular	Common	Common Sequelae in places
Properties	Focal ground glass density or consolidation (42%)	New or progressive consolidation	Concentration in consolidation, Widespread ground glass appearance, Parenchymal bands	Resolving consolidation Regression in CT images but full resorption after 26th day
	Multifocal opacities (42%)	Flagstone view		
	No CT findings (17%)	Diffuse ground glass appearance		

COVID-19: Coronavirus disease 2019, CT: computerized tomography

Other Drug Treatments

Nafamostat

In addition to being a short-acting anticoagulant that prevents clotting, it is a synthetic serine protease enzyme inhibitor with anti-cancer and anti-viral effects. It is used in pancreatitis treatment and renal disease. It is a potential inhibitor that prevents membrane fusion in MERS-CoV infection. Its use for SARS-CoV-2 is under trial (88,89).

Antibiotics

In terms of bacterial or fungal coinfection, unnecessary use of antibiotics should be prevented by monitoring the patients closely. Antibiotics or antifungals should be used correctly and when necessary, with timely collection of samples for clinical status changes and pathogen analysis.

Azithromycin

Preliminary data evaluating the combination of hydroxychloroquine and azithromycin for the treatment of COVID-19 have been published recently. Combination therapy with azithromycin compared to the use of hydroxychloroquine only has more significant reduction in viral load. However, basal viral loads were higher in patients who received hydroxychloroquine monotherapy in the study. Despite this, the negation rate of tests on the sixth day of both groups was similar. It is recommended to avoid routine use due to insufficient data (90,91).

For 1-5 months old children 10 mg/kg/dose (maximum: 500 mg/dose); for children over 6 months, 10 mg/kg in first day, single dose per day (maximum: 500 mg / dose), followed by a single dose of 5 mg/kg per day for 2-5 days (maximum: 250 mg/dose), it is recommended to administer a total of 5 days.

Anakinra and Tocilizumab

In adults, COVID-19 produces secondary hemophagocytic lymphohistiocytosis (HLH; fulminant with multiorgan failure and hypercytokinemia with a mortality), except ARDS. Viral infections in adults are the most common cause of secondary HLH and occur in 3-7.3% of sepsis cases. In studies conducted in China, it is thought that mortality may caused by virally induced hyperinflammation (92).

Anakinra which blocks IL-1 is beneficial in patients with hyperinflammation (93). In addition, the trial of tocilizumab used for IL-6 receptor blockade has been approved in adults (91,93). There are studies regarding the curative effects of combined use of tocilizumab with chloroquine, especially on its cytokine storm. The dose is 12 mg/kg for children weighing less than 30 kilograms, and 8 mg/kg (maximum: 800 mg/dose) for children weighing more than 30 kilograms (91).

Glucocorticoids

The use of glucocorticoids should be tailored to the severity of the systemic inflammatory response, the degree of dyspnea, the presence of ARDS, and progression in pulmonary imaging. Glucocorticoids are recommended as methylprednisolone at a dose not exceeding 2 mg/kg daily for a short period of time (3-5 days) (45,60).

WHO and CDC do not recommend the use of glucocorticoids in patients with COVID-19 pneumonia unless there is a different indication in adult patients (eg. exacerbation of chronic obstructive pulmonary disease) (94). Glucocorticoids have been associated with an increased risk of mortality in influenza patients and delayed viral clearance in patients with MERS-CoV infection. Although it is widely used in the treatment of SARS, there is no evidence of its usefulness, as well as convincing evidence for its short- and long-term adverse effects (95).

There are differences between the results obtained in influenza, SARS and different viral pneumonia conditions. Due to the methodological limitations in the current evidence, the use of corticosteroids is controversial. It is known that there are potential risks associated with high-dose corticosteroids, such as secondary infections, long-term complications, and long-term viral scattering, in the treatment of COVID-19 pneumonia. However, in critical patients, excessive inflammation and cytokine-related lung damage can cause rapidly progressing pneumonia. The Chinese Thoracic Society has made recommendations on the use of corticosteroids in COVID-19 pneumonia. According to the expert consensus statement, the following basic principles should be followed when using corticosteroids (96):

- Before using corticosteroids, the benefits and harm should be reviewed;
- Corticosteroids should be used with caution in critical patients with COVID-19 pneumonia;
- For patients with hypoxemia due to underlying diseases or patients who take corticosteroids regularly for their chronic diseases, should be careful in case of more use of corticosteroids;
- Drug dose should be low-medium dose (≤0.5-1 mg/kg methylprednisolone or equivalent, daily) and should be used for a minimum period of time (≤7 days).

Intravenous Immunoglobulin

Immunoglobulin can be used for indication in severe cases, but more research is needed for its effectiveness (97).

Convalescent (Obtained from Recovered Patients) Plasma Support

It may be beneficial to administer serum from patients who recovered and developed antibodies against COVID-19 infection to the patients infected with COVID-19. In a wide metaanalysis, it was observed that the same method was applied in SARS and mortality decreased (98).

Chloroquine

It is widely used in autoimmune diseases and especially against malaria. It inhibits virus-cell fusion by increasing endosomal pH. Therefore, it shows a potential antiviral drug feature. It also affects the glycolysis of cellular receptors of SARS-CoV-2 (99). In *in vitro* studies, chloroquine

Figure 1. The order of wearing and take off personal protective equipment (95)

inhibits the entry and following steps of SARS-CoV-2 into the cell. Chloroquine, being as *in vitro*, stabilizes the immunomodulatory activity by increasing the antiviral effect (100). Chloroquine is also an effective inhibitor of SARS infection by affecting the binding areas on cell surface for S protein of ACE-2 and SARS CoV (99). Suggested usage criteria are as follows: SARS-CoV-2 positivity and increased alanine aminotrans-ferase (ALT) or asportate aminotrans-ferase (AST) values 5 times higher than the upper limit or creatinine clearance <50 mL/min or non-pregnant patient receiving mechanical ventilation support.

The recommended dosage for moderate disease in adults; hydroxychloroquine tablets are recommended orally, 200 mg twice a day, then 200 mg once a day for 4 days, or 250 mg twice a day for 5 days (81). The dose in children is 10 mg/kg, twice a day (maximum: 600 mg/dose) after loading 3 mg/kg (maximum: 200 mg/dose) 3 times a day for 4 days, totally 5 days (57).

The time can be extended in case of prolonged ventilation or deep immunosuppression (91). It should be noted that hydroxychloroquine prolongs QTc in electrocardiography (ECG). Basal ECG should be taken. Dose adjustment is not required in renal or liver disorders.

Mefloquine

It is an antimalarial agent, whose effectiveness has not been proven yet, especially in Russia.

Nitric Oxide

It is a selective vasodilator. It can be effective in the case of ARDS, which can be a complication of SARS-CoV-2. The use of inhaled nitric oxide in the SARS-CoV epidemic reduced pulmonary hypertension, cured severe hypoxia, and reduced the duration of ventilation support. Studies on its use in COVID-19 are ongoing. It is applied as 30 ppm on the first day, 20 ppm on the 2nd day and 10 ppm on the 3rd day and decreases with oxygenation control with 10 ppm on the 4th day (101,102).

Drugs in Different Combinations

In addition, three different potential drug combinations (sirolimus and dactinomycin, mercaptopurine and melatonin, toremifene and emodin) are candidates for use (103).

Certain drugs whose effectiveness has been investigated by clinical trials in COVID-19 treatment are shown in Table 4 (13,57,91,104).

Treatment of Severe and Critical Cases

In accordance with the symptomatic treatment bases, preventive therapy, complication therapy, treatment of underlying conditions, treatment of secondary infections and, in case of indication organ functions oriented support should be provided.

Respiratory and Circulatory Support

Children with no change in their condition despite receiving noninvasive ventilation support for 2 hours, or children who are unable to tolerate noninvasive ventilation, have increased secretions, and have severe cough or hemodynamically unstable should be immediately taken to invasive mechanical ventilation support. In invasive mechanical ventilation, a low tidal volume "lung protective ventilation strategy" should be adopted to reduce lung damage associated with the ventilator. If necessary, ventilation in the prone position, lung recruitment maneuvers or extracorporeal membrane oxygenation (ECMO) can be performed. It is recommended to regulate microcirculation with full fluid support, use of vasoactive drugs, and when necessary, monitor hemodynamic data (60).

ECMO therapy is used as a life-saving approach in resistant ARDS cases. In a study of 6 adult patients who received ECMO treatment, 5 of the patients (83%) died. Even if this number is small, it emphasized certain points to be considered on the application of ECMO therapy. During ECMO therapy, lymphopenia deepened and lymphocyte function impaired. The progressive increase in IL-6 level was thought to be secondary to parenchymal damage during ECMO. This increase is correlated with mortality. Therefore, monitoring the close lymphocyte count and IL-6 level is recommended. IL-6 levels of survivors after ECMO have reached their normal levels in a short time (47). In COVID-19 disease, while keeping in mind that the immune system is significantly affected, the immunological status of the patients should be taken into consideration when selecting candidates for ECMO (105).

Traditional Chinese Medicine

This disease is in the category of epidemic in traditional Chinese medicine. Some traditional treatments have been made in China, depending on the patient's condition, local climatic characteristics and children's physical characteristics.

Recommendations for the Care/Treatment of Neonates Exposed to COVID-19 Disease

Neonatologists should wear their protective equipment (hats, glasses, protective clothing, gloves, N95 masks, etc) to revive newborns born from the confirmed and/or suspected COVID-19 mother. If the mother's SARS-CoV-2 test is positive, the newborn should be isolated and tested for SARS-CoV-2.

Routine corticosteroids are not recommended for all women with confirmed COVID-19 infection between 34th and 37th weeks of pregnancy. Considering the additional risk factors, it is recommended to follow the international recommendations regarding fetal lung maturation while discussing the benefit of this treatment between 34th and 37th weeks of gestation (106).

Although it is recommended in some studies to examine every critical patient in neonatal intensive care for COVID -19 and to monitor all of them in intensive care, there are different opinions on this issue (107). Testing not every intensive care newborn, but newborns from families infected with SARS-CoV-2 or exposed to other infected persons regardless of their symptoms prevents misuse of resources. Early diagnosis and early isolation are mandatory for SARS-CoV-2 control. If the newborn does not have a clinical need for isolation, it does not need to be monitored in intensive care (79).

As in MERS management, newborns infected with SARS-CoV-2 should be placed in negative pressure rooms or in rooms with highly efficient

particulate air filters in outlet ventilation. Treatment mainly depends on the clinical experience of adult patients, as there are few pediatric cases. There is no specific drug treatment for newborns (108). Symptomatic and supportive therapy, oxygen support, pulmonary edema and oxygenation status should be followed closely and appropriate hydration should be performed. In addition, maintaining electrolyte and acid-base balance is the mainstay of treatment. In cases with severe ARDS, due to the lack of adequate evidence-based data, high dose pulmonary surfactant, inhaled nitric oxide, high frequency oscillatory ventilation and ECMO can be used, depending on the diagnosis and classification criteria.

WHO stated that late clamping of the umbilical cord does not increase the risk of transmission of pathogens from the mother to the fetus, even in any identified infection in the mother. Since vernix caseosa contains antimicrobial peptides, washing is not recommended in 24 hours after birth. After birth, it is recommended to minimize transmission from mother with COVID-19 to newborn. In order to prevent contact with respiratory secretions, the mother should pay attention to the use of masks and hand hygiene if there is no other feature in her clinical condition (109). It is not recommended to keep the mother and baby in isolation separately, except in situations that require intensive care. It is emphasized that being separated may cause negative effects on nutrition and attachment. Close monitoring of the newborn is recommended (59,110). It is recommended that mother and baby be separated only by consulting a multidisciplinary board when necessary. Looking at the previous data for separation, although it is a standard practice in pulmonary tuberculosis, it is discussed in maternal influenza infection cases. Patients should be informed about potential risks and benefits (109).

Cases have been reported in 10 newborns born from an infected mother with the COVID-19 virus (25). Although all 9 infants tested once had negative results for COVID-19 infection, neonatal complications following fetal distress were probably secondary to maternal disease. The condition of 2 babies out of 10 has become critical: while 34-week and 6-day-old newborn, whose first complaint was moaning, continued to live with immunoglobulin, platelet, plasma support; 34-week and 5-day-old newborn, whose first complaint was tachycardia, died after going rapidly into disseminated intravascular coagulation and multiple organ failure, not responding to blood transfusions and symptomatic support therapy. For these reasons, maternal-infant couples affected by SARS-CoV-2 should be closely followed up and monitored. In case of symptom development, newborns should be admitted to the neonatal unit immediately and isolated by initiating supportive treatments if necessary.

Criteria for Discharge

Patients with definitive diagnosis can be discharged from isolation or transferred to the relevant departments for the treatment of other diseases if all the following criteria are met:

1. Body temperature in the normal range for more than 3 days,

2. Significant improvement of respiratory symptoms,

3. Negative respiratory SARS-CoV-2 nucleic acid test result 2 times in succession (sampling interval is at least 1 day).

In suspected patients, when the test of the respiratory tract pathogen nucleic acid is negative 2 times in succession, they can be discharged from the isolation (sampling interval is at least 1 day) (45).

Table 4. Certain drugs whose effectiveness is investigated by clinical trials in the treatment of COVID-19 (13,57,91,104)

Antiviral agents			
Baloxavir	Antiviral	It is effective against influenza viruses. No approved use	80 mg po 1x1, 4 days
Chloroquine Hydroxychloroquine	Antimalarial	Activities shown in Vero E cells as *in vitro*. Theoretically, it has an immunomodulating effect for anti-inflammatory response to viral infections. Limited data for prevention and treatment. The results of the studies are expected. Positive effects in a limited number of studies using chloroquine and azithromycin have been reported. Both drugs can cause QTc prolongation.	Chloroquine phosphate: 500 mg oral x2/day, 10 days If <50 kg 500 mg oral x2/day for the first 3 days, then 500 mg oral one time for 3-7 days. Hydroxychloroquine (Plaquenil®): oral, 2x200 mg first day and then 1x200 mg 4 days or 2x250 mg 5 days. The dose in children is 10 mg/kg, x2/day (max: 600 mg/dose) after loading, 3 mg/kg (max: 200 mg/dose) x3/day, 4 days, total 5 days (43).
Lopinavir and Ritonavir (LPV/RTV; Kaletra®)	HIV Protease Inhibitor	It has different studies. It was found that it could not decrease clinical recovery time, could not decrease viral RNA load during viral DNA positivity, did not have any positive effect on oxygen treatment time or hospital stay and duration from diagnosis to death. More studies are needed for its combination with different drugs. The combined use with Ribavirin, Arbidol and Interferon is being studied.	Lopinavir 250 mg /Ritonavir 50 mg film tablet, oral x2/day, 5 days. Oral for 14 days-6 months with Lopinavir content of 16 mg kg. 6 months -18 years of age; for 15-25 kg oral 200 mg-50 mg; for 26-35 kg, 300 mg-75 mg, for >35 kg, 400 mg-1000 mg x2/day.

Table 4. continued

Neuraminidase inhibitors (oseltamivir, etc)	Antiviral agents against influenza viruses	Although it is widely used in confirmed or suspected COVID-19 patients, there is no study showing its effectiveness. There is no evidence that oseltamivir or zanamivir inhibits the cytopathic effect of SARS-CoV in *in vitro* cell cultures.	Oseltamivir; 3-11 months: 3 mg/kg BID oral >15 kg: 2x30 mb 15-23 kg: 2x45 mg 23-40 kg: 2x60 mg > 40 kg 2x75 mg
Remdesivir	Antiviral, unknown	It is a broad-acting antiviral against coronaviruses. It was previously investigated for SARS, MERS and Ebola and its activity as *in vitro* against SARS-CoV, SARS-CoV-2 and MERS-CoV has been demonstrated. There are phase 2 and phase 3 studies on its use.	In adult critical cases 200 mg IV 1x1, then 100 mg daily for 5-10 days. In children: If <40 kg, 5 mg/kg IV loading, then 2.5 mg/kg IV 1x1. >40 kg 200 mg IV, 100 mg IV 1x1 after loading.
Supportive agents			
Ascorbic acid	Vitamin C	Antioxidant and cofactor in many physiological reactions. It can support host defense by protecting against infection from oxidative stress.	Different doses in adults in sepsis studies; IV 50 mg/kg IV 4x1, 4 days.
Azithromycin	Macrolide	It has antibacterial effect and *in vitro* activity against some viruses (Influenza A H1N1, Zika). *In vitro* activity against corona viruses, including SARS-CoV-2, is not specified. It can have an immunomodulatory effect and anti-inflammatory effect.	1-5 months; 10 mg/kg/dose (max: 500 mg/dose), >6 months 10 mg/kg first day, single dose per day (max: 500 mg/dose), followed by 5 mg/kg once daily for 2-5 days (max: 250 mg/dose), total 5 days.
Tocilizumab (Actemra®) Sarilumab (Kefzara®)	Antirheumatoid	Recombinant human monoclonal antibody is specific to the interleukin-6 (IL-6) receptor. It is effective on cytokine release syndrome in critically ill patients. Its studies are ongoing. There are not sufficient studies on Sarilumab (Kefzara®).	Tocilizumab: IV infusion; For children: If <30 kg, dose is 12 mg/kg and if >30 kg, 8 mg/kg (max: 800 mg/dose). Infusion time should be longer than 60 minutes. If the first dose is not sufficient, it can be given again after 12 hours with the same initial dose. It is not recommended to apply for the third time.
Methylprednisolone	Anti-inflammatory antifibrotic, it prevents excessive cytokine response at low doses or accelerates the recovery of pulmonary or systemic inflammation.	Studies suggest that methylprednisolone therapy may be beneficial in patients with COVID-19 pneumonia progressing to ARDS. Chinese Thoracic Society has created a user manual according to the disease level and condition.	It is recommended as a methylprednisolone at a daily dose not exceeding 2 mg/kg (0.5-1) in short periods such as 3-5 days.
Nitric oxide (inhale)	Does selective vasodilation. Ist direct antiviral effect against SARS-CoV has also been demonstrated in *in vitro* studies.	Although it has been shown to be effective in the case of ARDS, routine use is not recommended. Studies on its use in COVID-19 continue.	It is applied as 30 ppm on the first day, 20 ppm on the 2nd day and 10 ppm on the 3rd day, and decreases with oxygenation control with 10 ppm on the 4th day.
Sirolimus	Immunosupressive mTor inhibitor	It has activity against MERS-CoV infection in *in vitro* studies. It has been found that the use of oseltamavir and corticosteroid in H1N1 pneumonia reduces the mechanical ventilation time of the patients and is useful in the treatment of hypoxia and multiorgan failure.	In the studies, it is recommended to use orally with 2 mg daily dose. It is recommended to use together with 20 mg oral prednisolone daily for 14 days and with 75 mg oseltamivir twice daily for 10 days in adults.

RNA: Ribonucleic acid, DNA: deoxyribonucleic acid, SARS: Severe acute respiratory syndrome, MERS: Middle East respiratory syndrome, COVID-19: Coronavirus disease 2019, CoV: coronavirus, ARDS: Acute respiratory distress syndrome, max: maximum, LPV: Lopinavir, RTV: Ritonavir, HIV: human immunodeficiency virus

Conditions Expected During Post-discharge and Isolation Period

The secondary effects of closed schools and having children spend long periods at home should not be forgotten. It can be predicted that this will have negative effects on children's physical and mental condition. This can result in weight gain following long screen exposure, irregular sleep, unhealthy diets and a lack of movement (111).

In a study not related to the COVID-19 outbreak, tests were conducted by interviewing 398 families, and it was found that the risk of posttraumatic stress disorder increases when children are quarantined and isolated after health-related disasters (112).

Psychological counseling; plays an important role in disease recovery. If patients (especially older children) show mood swings, fear, or psychological disorders, active psychological intervention and treatment is required.

Preventing Social Spread

Infection source control, self-isolation of supercarriers, blocking the transmission routes and infection control applications with sensitive population protection are of great importance.

Prophylaxis

WHO recommended pre-contact prophylaxis before exposure to diseases such as pandemic influenza, invasive meningococemia, or for people at high risk of infection. It is effective in preventing disease after exposure to proven infection and reducing viral load in respiratory secretions, reducing the risk of secondary spread and transmission. In pharmacological models based on invitro tests performed until now, it is predicted that prophylaxis with appropriate doses of hydroxychloroquine against SARS CoV-2 can prevent infection and reduce viral spread. This information will become clear in May 2020 with the results of the study to be carried out in the Spain-Catalonia region (113,114).

Conclusion

Close follow-up of the clinical findings of the pediatric patients and following the rules of isolation will provide a milder circumvention of the pandemic. In COVID-19; while children can usually progress with a mild clinic, children with underlying disease may have more severe pictures. More virological, epidemiological and clinical data are required for specific antiviral treatment and disease management for children.

Ethics

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - H.E.M.A., Ö.Ö.; Concept - H.E.M.A., Ö.Ö. ; Design - H.E.M.A., Ö.Ö.; Data Collection or Processing - H.E.M.A., Ö.Ö. ; Analysis or Interpretation - H.E.M.A., Ö.Ö. ; Literature Search - H.E.M.A., Ö.Ö. ; Writing - H.E.M.A., Ö.Ö.

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

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

References

1. World Health Organization. Novel coronavirus, China. 2020 https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/ (Accessed on March 19, 2020).
2. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it. WHO Technical Guidance 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it (Accessed on March 15, 2020).
3. Ashour HM, Elkhatib WF, Rahman MM, Elsabrawy HA. Insights into the Recent 2019 Novel Coronavirus (SARS-CoV-2) in Light of Past Human Coronavirus Outbreaks. Pathogens 2020; 9: 186.
4. Favre G, Pomar L, Musso D, Baud D. 2019-nCoV epidemic: what about pregnancies? Lancet 2020; 395: 40.
5. Memish Z, Perlman S, Kerkhove MDV, Zumla A. Middle East respiratory syndrome. Lancet 2020; 395: 1063-77.
6. Zhang YH, Lin DJ, Xiao MF, Wang JC, Wei Y, Lei ZX, et al. 2019-novel coronavirus infection in a three-month-old baby. Zhonghua Er Ke Za Zhi 2020; 58: E006.
7. Cai JH, Wang XS, Ge YL, Xia AM, Chang HL, Tian H, et al. First case of 2019 novel coronavirus infection in children in Shanghai. Zhonghua Er Ke Za Zhi 2020; 58: E002.
8. Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. Jama 2020;323:1335.
9. CDC COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) United States, February 12-March 16, 2020. Weekly 2020; 69; 343-6.
10. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in china: summary of a report of 72 314 cases from the chinese center for disease control and prevention. JAMA 2020; 323: 1239-42.
11. Korea Centers for Disease Control and Coordination. Updates on COVID-19 in Korea. 2020 March 14. https://www.cdc.go.kr/board/board.es?mid=a30402000000&bid=0030 (Accessed on March 18, 2020).
12. Woo PC, Huang Y, Lau SK, Yuen KY. Coronavirus genomics and bioinformatics analysis. Viruses 2010; 2: 1804-20.
13. Geller C, Varbanov M, Duval R. Human coronaviruses: insights into environmental resistance and its influence on the development of new antiseptic strategies. Viruses 2012; 4: 3044-68.
14. Perlman S. Another decade, another coronavirus. N Engl J Med 2020; 382: 760-2.
15. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382: 727-33.
16. Jubeit B, Narayan O, Johnson RT. Patognezis of human poliovirus infection in mice. Clinical and pathological studies. J Neuropathol Exp Neurol 1980; 39: 138-48.
17. Lee P. Are children less susceptible to COVID-19? Journal of Microbiol Immunol Infect 2020; 53: 371-2.
18. Gu H, Xie Z, Li T, Zhang S, Lai C, Zhu P, et al. Anjiotensin-converting enzyme 2 inhibits lung injury by respiratory syncytial virus. Scientific Reports 2016; 6: 19840.
19. Zhao Y, Zhao Z, Wang Y, Zhao Y, Ma Y. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov. BioRxiv. 2020. doi: https://doi.org/10.1101/2020.01.26.919985. [Epub ahead of print].
20. Liu J, Liu Y, Xiang P, Pu L, Xiong X, Li C, et al. Neutrophil-to-lymphocyte ratio predicts severe illness patients with 2019 Novel Coronavirus in the early stage. Med Rxiv 2020.

21. Cao Q, Chen YC, Chen LC, Chiu CH. SARS-CoV-2 infection in children: Transmission dynamics and clinical characteristics. Journal of the Formosan Medical Association 2020; 119: 670-3.
22. Doremalen VN, Bushmaker T, Morris DH, Holbrook MG, Williamson BN, Tamin A, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med 2020; 382: 1564-7.
23. Anıl M, Besli E, Duman M, Erkek N, Derinöz O, Tekin D et al. Çocuk acil servisi CoVID-19 olgu yönetim algoritmaları. Çocuk acil tıp ve yoğun bakım derneği yayınları 2020; 1: 1.
24. Chen C, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 2020; 395: 809-15.
25. Zhu H, Wang L, Fang C. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr 2020; 9: 51-60.
26. Dong L, Tian J, He S, Zhu C, Wang J, Liu C, Possible vertical transmission of sars-cov-2 from an infected mother to her newborn. research letter. JAMA 2020; 323: 1846-8.
27. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020; 382: 929-36.
28. Chan JF, Yuan S, Kok KH, To KKW, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novelcoronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020; 395: 514-23.
29. Chen C, Gao G, Xu Y, Pu L, Wang Q, Wang L, et al. SARS-CoV-2-Positive sputum and feces after conversion of pharyngeal samples in patients with COVID-19. Ann Intern Med 2020: 20-0091.
30. Wang L, Li X, Chen H, Yan S, Li Y, Li D, et al. SARS-CoV-2 infection does not significantly cause acute renal injury: an analysis of 116 hospitalized patients with COVID-19 in a single hospital, Wuhan, China. Med Rxiv 2020.
31. Liu Y, Yan L, Wan L, Xiang TX, Le A, Liu JM, et al. Viral dynamics in mild and severe cases of COVID-19. The Lancet Infect Dis 2020; 20: 656-7.
32. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith H, et al. The incubation period of 2019-nCoV from publicly reported confirmed cases: estimation and application. Med Rxiv 2020: 20-0504.
33. Lu X, Zhang L, Du H, Shao J, Peng X, Liu Z, et al. SARS-CoV-2 infection in children. N Engl J Med 2020; 382: 1663-5.
34. Liu W, Zhang Q, Chen J, Xiang R, Song H, Liang L, et al. Detection of covid-19 in children in early january 2020 in Wuhan, China. N Engl J Med 2020; 382: 1370-1.
35. Cai J, Xu J, Lin D, Yang Z, Xu L, Qu Z, et al. A case series of children with 2019 novel coronavirus infection: clinical and epidemiological features. Clin Infect Dis. 2020 February. doi:10.1093/cid/ciaa198.
36. Ji L, Chao S, Wang Y, Li XJ, Mu XD, Lin MG, et al. Clinical features of pediatric patients with COVID19: a report of two family cluster cases. World J Pediatr 2020: 1-4.
37. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in china. Pediatrics 2020.
38. Yang P, Liu P, Li D,Zhao D. Corona virus disease 2019, a growing threat to children? J Infect 2020; 80: 671-93.
39. Cui Y, Tian M, Huang D, Wang X, Yuying H, Fan L, et al. A 55-day-old female infant infected with covid 19: presenting with pneumonia, liver injury, and heart damage. J Infect Dis 2020; 221: 1775-81.
40. Available from URL: https://irannewsdaily.com/2020/03/iran-35-day-old-baby-tests-positive-for-covid-19/website. with-covid-19/6058789/ (Accessed on March 19, 2020).
41. Available from URL: https://abc11.com/health/illinois-reports-death-of-infant-with-covid-19/6058789/ (Accessed on March 19, 2020).
42. https://www.channelnewsasia.com/news/world/coronavirus-covid-19-uk-boy-dies-12596462?utm_source=headtopics&utm_medium=news&utm_campaign=2020-04-01(Accessed on March 19, 2020).
43. Zeng LK, Tao XW, Yuan WH, Wang J, Liu X, Liu ZS. First case of neonate infected with novel coronavirus pneumonia in China. Chin J Pediatr 2020; 58: 009.
44. Deng H, Zhang Y, Wang Y, Li F. Two cases of 2019 novel coronavirus infection in children. Chin Pediatr Emerg Med 2020; 27: E001-E001.
45. Shen K, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, et al. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. World J Pediatr 2020.
46. Henry BM, Lippi G, Plebani M. Laboratory abnormalities in children with novel coronavirus disease 2019. Clin Chem Lab Med 2020.
47. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020; 8: 475-81.
48. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507-13.
49. Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. Pediatr Pulmonol 2020; 55: 1169-74.
50. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.
51. Gao ZC. Efficient management of novel coronavirus pneumonia by efficient prevention and control in scientific manner. Zhonghua Jie He He Hu Xi Za Zhi 2020; 43: 163-6.
52. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 Cases. Radiology. 2020. doi: 10.1148/radiol.2020200642. [Epub ahead of print].
53. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 20: 425-34.
54. Zhou C, Gao C, Xie Y. COVID-19 with spontaneous pneumomediastinum. Lancet 2020; 20: 510.
55. Pan F, Ye T, Sun P, Gui S, Liang B, Lingli L, et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. Radiology 2020; 295: 200370.
56. Li Z, Yi Y, Luo X, Xiong N, Liu Y, Li S, et al. Development and clinical application of a rapid igm-igg combined antibody test for SARS-CoV-2 infection diagnosis. J Med Virol 2020.
57. TC Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü COVID -19 (SARS-CoV2 Enfeksiyonu) Rehberi. Bilim kurulu çalışması. 2020 Mar 23. (Accessed on March 25, 2020).
58. Sağlık Bakanlığı Ulusal CoVID-2 acile kabul algoritması, T.C. Sağlık Bakanlığı, 2020 Mar. (Accessed on March 25, 2020).
59. Sağlık Bakanlığı Ulusal CoVID-2 tanı tedavi takip algoritması, T.C. Sağlık Bakanlığı, 2020 Mar. (Accessed on March 25, 2020).
60. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance 2020 Mar 13. Avaliable fom URL: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected. (Accessed on March 15, 2020).

61. Available from URL: https://dgsurgent.sante.gouv.fr/dgsurgent/inter/detailsMessageBuilder.do?id=30500&cmd=visualiser Message (Accessed on March 19, 2020).

62. Day M. Covid-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. BMJ 2020; 368: m1086.

63. World Health Organization. Now Doesn't Recommend Avoiding Ibuprofen For COVID-19 Symptoms. Science Alert 2020. Available from URL: https://www.sciencealert.com/who-recommends-to-avoid-taking-ibuprofen-for-covid-19-symptoms. March 2020. (Accessed on March 25, 2020).

64. European Medicines Agency. EMA gives advice on the use of non-steroidal anti-inflammatories for COVID-19. Available from URL: https://www.ema.europa.eu/en/news/ema-gives-advice-use-non-steroidal-anti-inflammatories-covid-19. 2020 Mar. (Accessed on March 25, 2020).

65. Wang XF, Yuan J, Zheng YJ, Chen J, Bao YM, Wang YR, et al. Clinical and epidemiological characteristics of 34 children with 2019 novel coronavirus infection in Shenzhen. Zhonghua Er Ke Za Zhi 2020; 58: E008.

66. Wang BX, Fish EN. Global virus outbreaks: interferons as 1st responders. Semin Immunol 2019; 43: 101300.

67. Al-Tawfiq JA, Momattin H, Dib J, Memish ZA. Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: an observational study. Int J Infect Dis 2014; 20: 42-6.

68. Shen KL, Shang YX, Zhang GC, Xu BP, Fu Z, Cao L, et al. Expert consensus on rational application of interferon α in pediatrics. Chin J Appl Clin Pediatr 2018; 33: 1301-8.

69. Xu YL, Li Y, Chen YP, Xin SX, Xie L, Liang YD, et al. A multicenter controlled clinical study on the efcacy and safety of recombinant human interferon α2b spray in the treatment of hand, foot and mouth disease in children. Chin J Infect 2018; 36: 101-6.

70. Shen KL, Shang YX, Zhang H. A multicenter, randomized, controlled clinical study on the efcacy and safety of recombinant human interferon 2b spray (pseudomonas) in the treatment of acute upper respiratory tract infection in children. Chin J Appl Clin Pediatr 2019; 34: 1010-6.

71. Gao H, Zhang LL, Wei Q, Duan ZJ, Tu XM, Yu ZA, et al. Preventive and therapeutic effects of recombinant IFN-α2b nasal spray on SARS-CoV infection in Macaca mulata. Chin J Exp Clin Virol 2005; 19: 207-11.

72. Khalid M, Al Rabiah F, Khan B, Al Mobeireek A, Butt TS, Al Mutairy E. Ribavirin and interferon-α2b as primary and preventive treatment for Middle East respiratory syndrome coronavirus: a preliminary report of two cases. Antivir Ther 2015; 20: 87-91.

73. Chen ZM, Fu JF, Shu Q, Chen YH, Hua CZ, Li FB, et al. Diagnosis and treatment recommendations forpediatric respiratory infection caused by the 2019 novel coronavirus. World J Pediatr 2020: 1-7.

74. Kim UJ, Won EJ, Kee SJ, Jung SI, Jang HC. Combination therapy with lopinavir/ritonavir, ribavirin and interferon-alpha for Middle East respiratory syndrome. Antivir Ther 2016; 21: 455-9.

75. Çin Sağlık Halk Cumhuriyeti Ulusal Sağlık Kurulu. Yeni koronavirüs enfeksiyonu pnömoni tanı ve tedavi planı (deneme versiyonu 5) (2020/02/04) [2020/02/05.] http: //www.nhc.gov.cn / xcs / zhengcwj / 202001 /4294563ed35b43209b31739bd0785e67 / files / 7a9309111267475a99d4306962c8bf78.pdf (Accessed on March 20, 2020).

76. Luca DD. Managing neonates with respiratory failure due to SARS-CoV-2. Lancet 2020; 4: 8.

77. Sheahan TP, Sims AC, Leist SR, Schafer A, Won J, Brown AJ, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 2020; 11: 222-3.

78. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020; 30: 269-71.

79. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Gotte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J Biol Chem 2020; 1-13.

80. Gilead Sciences. Study to evaluate the safety and antiviral activity of Remdesivir (GS-5734) in participants with severe coronavirus disease (CoVID-2) Clinical Trials 2020 March. ClinicalTrials.gov. (Accessed on March 25, 2020).

81. Jackson Health System / University of Miami Health System .COVID-19 Confirmed or highly suspected-investigational treatment protocol, March 20,2020. https://jacksonhealth.org/coronavirus-disease-2019-covid-19/#gref (Accessed on March 25, 2020).

82. Boriskin YS, Leneva IA, Pecheur EI, Polyak SJ. Arbidol: a broad-spectrum antiviral compound that blocks viral fusion. Curr Med Chem 2008; 15: 997-1005.

83. Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). Biosci Trends 2020; 14: 69-71.

84. Stockman LJ, Bellamy R, Garner P. SARS: Systematic review of treatment effects. PLoS Med 2006; 3: 343.

85. Omrani AS, Saad MM, Baig K, Bahloul A, Abdul-Matin M, Alaidaroos AY, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. Lancet Infect Dis 2014; 14: 1090-5.

86. Shalhoub S, Farahat F, Al-Jiffri A, Simhairi R, Shamma O, Siddiqi N, et al. IFN-α2a or IFN-β1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study. J Antimicrob Chemother 2015; 70: 2129-32.

87. Morgenstern B, Michaelis M, Baer PC, Doerr HW, Cinatl J. Ribavirin and interferon-beta synergistically inhibit SARS-associated coronavirus replication in animal and human cell lines. Biochem Biophys Res Commun 2005; 26: 905-8.

88. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020; 30: 269-71.

89. Chen X, Xu Z, Zeng S, Wang S, Wang X, Liu W, et al. The molecular aspect of antitumor effects of protease inhibitor nafamostat mesylate and its role in potential clinical applications. Front Oncol 2019; 9: 852.

90. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020: 105949.

91. Michigan Medicine University of Michigan. Inpatient Guidance For Treatment of CoVID-19 in Adults and Children. http://www.med.umich.edu/asp/pdf/adult_guidelines/COVID-19-treatment.pdf. (Accessed on March 25, 2020).

92. Mehta P, McAuley FD, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020; 395: 1033-4.

93. Shakoory B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase III trial. Crit Care Med 2016; 44: 275-81.

94. World Health Organization. Coronavirus disease (COVID-19) technical guidance: Patient management. Available from URL: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/patient-management (Accessed on February 02, 2020)

95. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020; 395: 473.

96. Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet 2020; 395: 683-4.

97. Dalakas MC, Clark WM. Strokes, thromboembolic events, and IVIG: Rare incidents blemish an excellent safety record. Neurology 2003; 60: 1736-7.

98. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim WS, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015; 211: 80-90.

99. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2005; 2: 69.

100. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020; 30: 269-71.

101. Chen L, Liu P, Gao H, Sun B, Chao D, Wang F, et al. Inhalation of nitric oxide in the treatment of severely acute respiratory syndrome: a rescue trial in Beijing. Clin Infect Dis 2004; 39:1531-5.

102. Mallinckrodt Pharmaceuticals. Mallinckrodt Evaluates the Potential Role for Inhaled Nitric Oxide to Treat COVID-19 Associated Lung Complications, Engages with Scientific, Governmental and Regulatory Agencies. From the Prnewswire website. https://www.prnewswire.com/news-releases/mallinckrodt-evaluates-the-potential-role-for-inhaled-nitric-oxide-to-treat-covid-19-associated-lung-complications-engages-with-scientific-governmental-and-regulatory-agencies-301022189.html (Accessed on March 24, 2020).

103. Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F. Network-based drug repurposing for human coronavirus. Med Rxiv. Accessed on 2020 March 25. https://doi.org/10.1101/2020.02.03.20020263. [Epub ahead of print].

104. Pharmacists advancing healthcare. Assessment of Evidence for COVID-19-Related Treatments. ASHP (Pharmacists advancing healthcare) guidance. 27 March 2020. https://www.ashp.org/Pharmacy-Practice/Resource-Centers/Coronavirus (Accessed on March 29, 2020).

105. Henry BM. COVID-19, ECMO, and lymphopenia: a word of caution. Lancet Respir Med. 2020 March 13. doi: 10.1016/S2213-2600(20)30119-3. (Accessed on March 25, 2020).

106. Committee on Obstetric Practice.. ACOG committee opinion. Antenatal corticosteroid therapy for fetal maturation. American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet 2002; 78: 95-7.

107. Wang J, Qi H, Bao L, Li F, Shi Y. A contingency plan for the management of the 2019 novel coronavirus outbreak in neonatal intensive care units. Lancet Child Adolesc Health 2020; 4: 258-9.

108. Mulangu S, Dodd LE, Davey RT Jr, Mbaya OT, Proschan M, Mukadi D et al. A randomized, controlled trial of ebola virus disease therapeutics. N Engl J Med 2019; 381: 2293-303.

109. Baud D, Giannoni E, Pomar L, Qi X, Nielsen-Saines K, Musso D, et al. COVID-19 in pregnant women - Authors' reply. Lancet Infect Dis. 2020 March 17, doi: 10.1016/S1473-3099(20)30192-4. (Accessed on March 25, 2020).

110. Coronavirus (COVID-19) Infection in Pregnancy Information for healthcare professionals Version 5. 28 March, 2020 Royal College of Obstetricians and gynaecologist. Available from URL: https://www.rcog.org.uk/globalassets/documents/guidelines/2020-03-28-covid19-pregnancy-guidance.pdf (Accessed on March 29, 2020).

111. Wang G, Zhang Y, Zhao J, Zhang J, Jiang F. Mitigate the effects of home confinement on children during the COVID-19 outbreak. Lancet 2020; 395: 945-7.

112. Sprang G, Silman M. Posttraumatic stress disorder in parents and youth after health-related disasters. Disaster Med Public Health Prep 2013; 7: 105-10.

113. Mitjà O, Clotet B. Use of antiviral drugs to reduce COVID-19 transmission. Lancet Glob Health. 2020 March 19. doi: 10.1016/S2214-109X(20)30114-5. [Epub ahead of print]. (Accessed on March 26, 2020).

114. Xu X. A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19). Chinese Clinical Trial Registry (COVID-19). http://www.chictr.org.cn/showprojen.aspx?proj=49409 (Accessed on March 15, 2020).

İstanbul Med J 2020; 21(4): 258-61
DOI: 10.4274/imj.galenos.2020.78642

Evaluation of Eyelid Tumor Cases at Our Clinic

Kliniğimizde Gerçekleştirilen Göz Kapağı Tümörü Olgularının Değerlendirilmesi

Sibel Zırtıloğlu[1], Mustafa Suat Alıkma[2], Erkan Bulut[3]

[1]University of Health Sciences Turkey, İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Turkey
[2]Denizli State Hospital, Clinic of Ophthalmology, Denizli, Turkey
[3]Beylikdüzü State Hospital, Clinic of Ophthalmology, İstanbul, Turkey

ABSTRACT

Introduction: This study aimed to evaluate patients who presented with eyelid tumour and to evaluate the masses pathologically.

Methods: Between March 1, 2016- April 1, 2019, 2019, age, gender, eyelid side, pathological evaluation results and surgical margin status of the patients who presented to our clinic with eyelid mass were evaluated.

Results: During the study period, 212 patients with a mean age of 55±16 years (range, 15-85 years) who underwent surgery because of an eyelid mass were included in the study. Among these patients, 78 (37.8%), 74 (35.9%) and 54 (26.2%) underwent surgery of the right, left and both eyelids, respectively, whereas 55 (26.9%), 128 (62.7%) and 21 (10.2%) underwent surgery of the lower, upper and both lower and upper eyelids, respectively. A total of 376 eyelid mass surgeries were performed. Among these masses, 371 (98.6%) were benign and 5 (1.3%) were malignant. Regarding pathological types of benign masses, 71 (19.1%) were seborrheic keratosis, 70 (18.8%) were squamous papilloma, 53 (14.21%) were fibroepithelial polyps, 52 (14.2%) were xanthelasma, 35 (9%) were intradermal nevus, 22 (5.9%) were epidermoid cyst, 14 (3.8%) were verruca vulgaris and 51 (13.7%) were different types of tumours. Five patients were diagnosed with malignant eyelid tumours; three of them had basal cell carcinoma, one had squamous cell carcinoma and one had malignant melanoma.

Conclusion: Although eyelid tumours are mostly benign tumours, malignant tumours may be present in some cases. Pathological evaluation of valve masses obtained surgically is important to determine the prognosis of patients.

Keywords: Eyelid tumour, eyelid, pathological assessment

ÖZ

Amaç: Kliniğimize göz kapağı tümörü şikayeti ile başvuran olguların ve kitlelerin patolojik olarak değerlendirilmesi amaçlanmıştır.

Yöntemler: 01.03.2016 ve 01.04.2019 tarihleri arasında kliniğimize göz kapağı kitlesi şikayeti ile başvuran hastaların yaşları, cinsiyetleri, hangi göz kapağı olduğu, kitlelerin patolojik değerlendirme sonuçları, cerrahi sınır durumları ile klinik devamlılığı değerlendirildi.

Bulgular: Göz kapağında kitle nedeni ile ameliyat edilen yaş ortalamaları 55±16 (15-85) olan 212 hasta değerlendirmeye alındı. Çalışmaya dahil edilen hastaların 78'inin (%37,8) sağ göz kapağından, 74'ünün (%35,9) sol göz kapağından ve 54'ünün (%26,2) hem sağ hem de sol göz kapağından kitle eksizyonu yapıldı. Hastaların 55'inin (%26,9) alt göz kapağından, 128'inin (%62,7) üst göz kapağından ve 21'inin (%10,2) hem alt hem de üst göz kapağından toplam 376 adet göz kapağı kitlesi ameliyat ile alınmıştır. Alınan kitlelerin 376'sı (%98,6) benign, 5'i (%1,3) malign özellikte olarak patolojik olarak raporlanmıştır. Benign karakterdeki kitlelerden, 71 tanesi (%19,1) seboreik keratoz, 70 tanesi (%18,8) skuamöz papillom 53 tanesi (%14,21) fibroepitelyal polip, 52 tanesi ksentelazma (%14,2), 35 tanesi (%9) intradermal nevus, 22 tanesi (%5,9) epidermal kist, 14 tanesi (%3,8) verruka vulgaris ve 51 tanesi (%13,7) farklı tiplerde tümörler olarak raporlanmıştır. Hastaların 5 tanesinden 3 tanesinde bazal hücreli karsinom olmak üzere birer skuamöz hücreli karsinom ve malign melanom tiplerinde malign karakterde kapak tümörleri elde edilmiştir.

Sonuç: Kapak tümörleri çoğunlukla benign karakterde tümörler olmakla birlikte, bazı olgularda malign karakterde tümörler de olabilir. Ameliyat ile alınan kapak kitlelerinin patolojik olarak değerlendirilmesi hasta prognozu açısından önemlidir.

Anahtar Kelimeler: Kapak tümörü, göz kapağı, patolojik değerlendirme

Address for Correspondence/Yazışma Adresi: Sibel Zırtıloğlu MD, University of Health Sciences Turkey, İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Turkey
Phone: +90 505 665 99 65 **E-mail:** sibel1077@hotmail.com **ORCID ID:** orcid.org/0000-0003-1375-6643

Cite this article as/Atıf: Zırtıloğlu S, Alıkma MS, Bulut E. Evaluation of Eyelid Tumor Cases at Our Clinic. İstanbul Med J 2020; 21(4): 258-61.

Received/Geliş Tarihi: 17.01.2020
Accepted/Kabul Tarihi: 04.05.2020

Introduction

Tumors of the skin and skin appendages can be observed throughout the body, but are often observed in the head and neck area and eyelids (1). Eyelid tumors occur in 5% and 10% of superficial skin tumors throughout the body (2). Eyelid tumors have a high proportion within eyelid pathologies (3,4). These tumors are more likely to be benign tumors than malignant tumors (3,5,6). However, both benign and malignant eyelid tumors are most likely to originate from epidermal cells (7).

Eyelid tumors may also accompany systemic diseases (8). Hemotological malignancies such as non-hodking lymphoma, hodking lymphoma and chronic lymphocytic leukemia increase in benign and malignant tumoral formations of the eyelid (2,9). However, the increase in eyelid tumors is also observed in neurofibromatosis disease (10). Treatment of eyelid tumors is performed for cosmetic purposes and for the exclusion of malignancy (11). Surgical method is preferred as a priority in treatment (12). Surgical treatment varies depending on the location, depth and area of the lesion (13,14).

The aim of our study was to determine the characteristics and frequency of patients admitted to our clinic because of eyelid mass and to get an idea of the frequency of eyelid tumors in our region.

Methods

In our study, patients admitted to University of Health Sciences University Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ophthalmology Outpatient Clinic between 01.03.2016 and 01.04.2019 and operated with a pre-diagnosis of eyelid mass were evaluated retrospectively. Patients with a definitive pathological diagnosis with adequate biopsy material were included in the study. The exclusion criteria were determined as patients with a history of precancerous and cancerous systemic disease in history, inflammatory formations, and failure to make a pathologically accurate diagnosis in the samples taken. The patients' ages, gender, which eyelid was observed to have tumors, the upper and lower side of the eyelid, how many eyelid masses were surgically removed and the pathological evaluation results of the eyelid mass were recorded. Ethics Committee approval was obtained from Pamukkale University Faculty of Medicine for the study (approval no: 60116787-020/11951). The study was conducted in accordance with the Helsinki Declaration.

The patients who underwent surgical treatment due to eyelid tumor were operated by the same surgeon. After surgical site cleaning with 10% povidone iodine solution, the required amount was injected with insulin injector from jethocaine hydrochloride and epinephrine (Jethocaine® - Adeka) solution to increase the lesion slightly from the junction of the lesion and the intact eyelid. The lesion was macroscopically removed with scissors and scalpel in a depth so that no tumor lesions were left at the surgical border. After bleeding control was performed on the site where the lesion was taken, the intact skin was sutured with 8.0 vikril yarn. The removed eyelid tumor was referred for pathological examination. All patients were prescribed topical fusidic acid (Fusix® -Abdi İbrahim) for post-operative protection. All patients were called for control at 1 week (5-9 days) after the operation. As the surgical margin was found to be clean, and the malignancy was not suspected according to the pathological evaluation; patients' postoperative follow-up was terminated right after the removal of the sutures planted during the operation. In all cases, the patients who were diagnosed with malignancy in the pathology report were referred to a superior center for further examination and treatment.

Statistical Analysis

Statistical evaluation, using the SPSS 25.00 for Windows software (SPSS Inc., Chicago, Illinois, USA), was given as number and percentage for categorical variables.

Results

A total of 212 patients were enrolled in the study, including 99 men (46.7%) and 113 women (53.3%) with an average age of 55±16 (15-85). Tumor excision was performed by 78 (37.8%) right eyelid, 74 (35.9%) left eyelid and 54 (26.2%) both right and left eyelid of the patients who participated in the study. Tumor excision was performed on 55 (26.9%) lower eyelid, 128 (62.7%) upper eyelid, and 21 (10.2%) lower and upper eyelid. A total of 376 eyelid tumors, an average of 1.8±1.5 (1-10), were removed from the patients evaluated in the study, and were pathologically evaluated. According to the results of the pathological evaluation, the frequency of the masses received was reported (Table 1). When the obtained masses were examined, it was determined that 371 (98.7%) eyelid masses were of benign character and 5 (1.3%) eyelid masses were of malignant character. When all patients were examined, 376 (98.6%) of the patients had benign masses and 5 (1.3%) had malignant masses (Table 1).

In our study, 70 squamous papillomavirus histology masses were removed from 39 patients, 22 of whom were male and 17 of whom were female. The most common accompanying eyelid tumor was seboraic keratosis in patients with squamous papillomavirus excised. Seboraic keratosis was excised from 11 patients (28.2%) with squamous papilloma. In patients with squamous papillomavirus, the second most common accompanying eyelid tumor was the intradermal nevus Intradermal nevus was detected in 2 patients (5.1%) with squamous papillomavirus.

In our study, masses with 71 seboraic keratosis histology were removed from 41 patients, 22 of whom were male and 19 of whom were female. Masses diagnosed with squamous papillomavirus were found in 11 (26.8%) of patients with seboraic keratosis. Fibroepithelial polyps were found to be the second most commonly associated eyelid tumor in patients with seboraic keratosis. Fibroepithelial polyps were detected in 5 patients (12.1%) with seboraic keratosis.

In 4 out of 5 patients with malignant mass on the eyelid, surgical mass limits were reported as positive or inadequate. These two patients were referred to an superior center with an oncology unit for further examination and treatment. In 30 patients with benign mass on the eyelid, the limits of surgical material were reported positively in 11 out of 35 intradermal nevus cases (33% of the patients). In these patients, the surgical limit was extended with the second session resection and the medical intervention was terminated.

Table 1. Number and frequency of masses according to histopathological types

Diagnosis	n (%)
Seborrheic keratosis	71 (18.8)
Squamous papilloma	70 (18.6)
Fibroepithelial polyps	53 (14)
Xanthalesma	52 (13.8)
Nevus, intradermal	35 (9)
Cyst, epidermal	22 (5.8)
Verruca vulgaris	14 (3.7)
Hydrocystoma	6 (1.5)
Hyperkeratotic verrucous hyperplasia	6 (1.5)
Cyst, vellus	4 (1)
Seborrheic keratosis, acanthotic type	4 (1)
BCC*	3 (0.7)
Trichoepithelioma	3 (0.7)
Actinic lentigo	2 (0.5)
Kist, Trichilemmal	2 (0.5)
Lobular capillary hemangioma	2 (0.5)
Nevus, compaund	2 (0.5)
Nevus, epidermal	2 (0.5)
Pyogenic granuloma	2 (0.5)
Subepidermal calcified nodule	2 (0.5)
Verrucous hyperplasia	2 (0.5)
Actinic keratosis	1 (0.3)
Clear cell acanthoma	1 (0.3)
Inverted follicular keratosis	1 (0.3)
Ceratoacanthoma	1 (0.3)
Lichen planus-like keratosis	1 (0.3)
Malignant melanoma	1 (0.3)
Molluscum contagiosum	1 (0.3)
Neurome	1 (0.3)
Seborrheic keratosis, irrite type	1 (0.3)
Squamous carcinoma	1 (0.3)
Soft fibroma	1 (0.3)
Foreign body reaction	1 (0.3)

*: Basal cell carsinoma

Discussion

Tumors originated from epidermal cells are the most commonly observed benign eyelid tumors. In a study performed by Yu et al. (7), benign tumors of epidermal cell origin were listed as seboraic keratosis, squamous papillomavirus, epidermal cyst and dermoid cyst in order to be seen from the most to the least. In a study conducted by Karabulut et al. (1), they identified the most common benign eyelid tumor as the melanocytic nevus. Çağlar et al. (15), Göncü et al. (16) and Obata et al. (6) indicated the most common benign eyelid tumor as a nevus in their studies. Deprez and Uffer (17), Gundogan et al. (18), Kurt et al. (19) indicated the most common benign eyelid tumors as squamous papillomavirus and seboraic keratosis, respectively. In our study, the most common benign eyelid tumor was seborrhaic keratosis followed by squamous papillomavirus. Although Göncü et al. (16) observed squamous papillomavirus and seborrhaic keratosis less frequently in their studies, they showed both tumors among the most common tumors. Obata et al. (6) also identified the second most common benign eyelid tumor as seborrhaic keratosis. It is observed that the results of our study are compatible with other studies. Excision is prioritised because seborrheic keratosis is able to mimic malignant tumors despite being of benign character.

Göncü et al. (16), Ho et al. (20), Yu et al. (7), Asproudis et al. (21) and Pe'er (22) indicated that benign eyelid masses are more often observed in the upper eyelid. Coroi et al. (23) noted that eyelid tumors of benign character are more common in the lower eyelid. In our study, benign eyelid tumors were observed more in the upper eyelid. Göncü et al. (16), Kurt et al. (19), Hassan and Nelson (4) indicated that benign eyelid masses affect the right and left eye in approximately equal rate. Similarly, in our study, benign eyelid tumors were found to affect right (n=76, 37.4%) and left (n=73, 35.9%) eyelids at a similar rate [right: 76 (37.4%), left: 73 (35.9%)].

Salomon et al. (24) remarked that eyelid tumors were observed mostly in patients aged 60 and over. Jahagirdar et al. (25) also indicated that eyelid tumors were observed more at an advanced age. Age averages were 58.1±14.9 (15-82) in patients with squamous papilloma; 62.4±10.9 (32-81) in patients with seborrhaic keratosis; 54.3±14.4 (34-85) in patients with xentelasma; and 58.5±14.6 (23-84) in patients with fibroepithelial polyps. In our study, similar to these studies, it was determined that eyelid tumors were observed more in advanced age.

Asproudis et al. (21) noted that eyelid masses of malignant character were more likely to be seen on the lower eyelid. Wang et al. (26), Gundogan et al. (18), Silverman and Shinder (2) and Nuhoglu et al. (27) identified the most common malignant eyelid tumor as basal cell cancer. In our study, the number of cases with malignant eyelid mass excised was low, so it could not be compared with other studies.

The limitation in the study was that no excisional biopsy accompanied by frozen was performed because there was no suspicion of malignancy in the included patients. Therefore, our rate of patients with pathological positive surgery limits was found to be high.

Although we have a patient diagnosed with actinic keratosis, it is important because it is a premalignant lesion and it is not always clinically differential diagnosis with squamous cell carcinoma (28). Although we have two patients diagnosed with solar lentigo, excision is required in these lesions as malignancy cannot be completely ruled out in dermoscopical examinations in these tumors with facial placement (29).

Although the mass frequency of patients in very large populations in China and Taiwan has been looked at, there is a need for wider population studies in our country (30,31).

Conclusion

Although the character of eyelid masses is generally benign, it can also be in the malignant character. Although the purpose of surgical

treatment of this disease which affects more advanced ages is cosmetic, in some cases malignancy is excluded. It is extremely important to evaluate the eyelid masses pathologically after removal.

Ethics

Ethics Committee Approval: Ethics Committee approval was obtained from Pamukkale University Faculty of Medicine for the study (approval no: 60116787-020/11951).

Informed Consent: Informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - M.S.A.; Concept - S.Z., M.S.A.; Design - S.Z., M.S.A.; Data Collection or Processing - S.Z., M.S.A., E.B.; Analysis or Interpretation - S.Z.; Literature Search - S.Z., M.S.A., E.B.; Writing - S.Z., M.S.A.

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

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

References

1. Karabulut HH, Karabulut YY, Şenel E, Dölek Y, Uslu A, Kurşun N. Göz Kapağı Tümörlerinin Histopatolojik ve Demografik Özellikleri. Turk J Dermatol 2014; 4: 197-201.
2. Silverman N, Shinder R. What's New in Eyelid Tumors. Asia Pac J Ophthalmol (Phila) 2017; 6: 143-52.
3. Actis AG, Actis G, De Sanctis U, Fea A, Rolle T, Grignolo FM. Eyelid benign and malignant tumors: issues in classification, excision and reconstruction. Minerva Chir 2013; 68: 11-25.
4. Hassan AS, Nelson CC. Benign eyelid tumors and skin diseases. Int Ophthalmol Clin 2002; 42: 135-49.
5. Pe'er J. Pathology of eyelid tumors. Indian J Ophthalmol 2016; 64: 177-90.
6. Obata H, Aoki Y, Kubota S, Kanai N, Tsuru T. Incidence of benign and malignant lesions of eyelid and conjunctival tumors. Nippon Ganka Gakkai Zasshi 2005; 109: 573-9.
7. Yu SS, Zhao Y, Zhao H, Lin JY, Tang X. A retrospective study of 2228 cases with eyelid tumors. Int J Ophthalmol 2018; 11: 1835-41.
8. Shome D, Bell D, Esmaeli B. Eyelid carcinoma in patients with systemic lymphoma. J Ophthalmic Vis Res 2010; 5: 38-43.
9. Kyasa MJ, Hazlett L, Parrish RS, Schichman SA, Zent CS. Veterans with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) have a markedly increased rate of second malignancy, which is the most common cause of death. Leuk Lymphoma 2004; 45: 507-13.
10. Avery RA, Katowitz JA, Fisher MJ, Heidary G, Dombi E, Packer RJ, et al. Orbital/periorbital plexiform neurofibromas in children with neurofibromatosis type 1: multidisciplinary recommendations for care. Ophthalmology 2017; 124: 123-32.
11. Zielinski T, Pisera P, Siewiera I, Sporny S, Iljin A. [Surgical treatment of malignant eyelid tumors]. Pol Merkur Lekarski 2013; 34: 214-8.
12. Wójcicki P, Zachara M. Surgical treatment of eyelid tumors. J Craniofac Surg 2010; 21: 520-5.
13. Dailey RA, Chavez MR. Upper eyelid margin mass excision technique: supraciliary approach. Ophthalmic Plast Reconstr Surg 2011; 27: 48-51.
14. Fan B, Liu JJ, Wang BF, Sun YJ, Li GY. Case report repairing orbital skin defects using composite flaps after giant eyelid-derived tumor excision and orbital exenteration. Medicine Baltimore 2017; 96: e8978.
15. Çağlar Ç, Güney G, Dönmez O, Baş Y, Durmuş M. Göz Kapağı Tümörlerinde Histopatoloji Sonuçları. Turkiye Klinikleri J Ophthalmol 2017; 26: 25-31.
16. Göncü T, Çakmak S, Akal A, Oğuz H. İyi huylu göz kapağı tümörlerinin klinikopatolojik özellikleri: 101 olgunun retrospektif analizi. Turk J Ophthalmol 2014; 44: 384-7.
17. Deprez M, Uffer S. Clinicopathological features of eyelid skin tumors. A retrospective study of 5504 cases and review of literature. Am J Dermatopathol 2009; 31: 256-62.
18. Gundogan FC, Yolcu U, Tas A, Sahin OF, Uzun S, Cermik H, et al. Eyelid tumors: clinical data from an eye center in Ankara, Turkey. Asian Pac J Cancer Prev : APJCP 2015; 16: 4265-9.
19. Kurt A, Mutlu SN, Yener Hİ, Bayram N, Nazlım S. Primer göz kapağı tümörlerinde histopatoloji sonuçları. Dicle Med J 2015; 42: 72-7.
20. Ho M, Liu DT, Chong KK, Ng HK, Lam DS. Eyelid tumours and pseudotumours in Hong Kong: a ten-year experience. Hong Kong Med J 2013; 19: 150-5.
21. Asproudis I, Sotiropoulos G, Gartzios C, Raggos V, Papoudou-Bai A, Ntountas I, et al. Eyelid tumors at the university eye clinic of ıoannina, greece: a 30-year retrospective study. Middle East Afr J Ophthalmol 2015; 22: 230-2.
22. Pe'er J. Pathology of eyelid tumors. Indian J Ophthalmol 2016; 64: 177-90.
23. Coroi MC, Roşca E, Mutiu G, Coroi T, Bonta M. Eyelid tumors: histopathological and clinical study performed in County Hospital of Oradea between 2000-2007. Rom J of Morphol Embryol 2010; 51: 111-5.
24. Salomon J, Bieniek A, Baran E, Szepietowski JC. Basal cell carcinoma on the eyelids: own experience. Dermatol Surg 2004; 30: 257-63.
25. Jahagirdar SS, Thakre TP, Kale SM, Kulkarni H, Mamtani M. A clinicopathological study of eyelid malignancies from central India. Indian J Ophthalmol 2007; 55: 109-12.
26. Wang CJ, Zhang HN, Wu H, Shi X, Xie JJ, He JJ, et al. Clinicopathologic features and prognostic factors of malignant eyelid tumors. Int J Ophthalmol 2013; 6: 442-7.
27. Nuhoglu F, Abul D, Ozdemir FE, Eltutar K. Distribution of lid tumours applied surgical treatment in our clinic. MN Oftalmoloji 2013; 20: 45-9.
28. Fleming P, Zhou S, Bobotsis R, Lynde C. Comparison of the Treatment Guidelines for Actinic Keratosis: A Critical Appraisal and Review. J Cutan Med Surg 2017; 21: 408-17.
29. Evans SE, Şahin S, Özkaya O. Dermoscopic features in facial solar lentigo. Turkiye Klinikleri J Dermatol 2006; 16: 90-3.
30. Wang LY, Chen LR, Dai XZ, Cao J, Gao T, Yao K, et al. A clinicopathological classification analysis of ocular mass lesions in 7 910 cases. Zhonghua Yan Ke Za Zhi 2019; 55: 847-53.
31. Huang YY, Liang WY, Tsai CC, Kao SC, Yu WK, Kau HC, et al. Comparison of the clinical characteristics and outcome of benign and malignant eyelid tumors: an analysis of 4521 eyelid tumors in a tertiary medical center. BioMed Res Int 2015; 2015: 453091.

İstanbul Med J 2020; 21(4): 262-5
DOI: 10.4274/imj.galenos.2020.34366

Assessment of Echocardiographic Findings in Patients with Asymmetric Presentation of Retinopathy of Prematurity

Asimetrik Özellik Gösteren Prematüre Retinopatisi Olgularında Ekokardiyografik Bulguların Değerlendirmesi

Yasin Özcan[1], Hüseyin Gümüş[2], Mehmet Çıtırık[3], Murat Çiftel[4]

[1]Yeditepe University Medical School, Yeditepe Speciality Hospital, Department of Ophthalmology, İstanbul, Turkey
[2]Harran University Faculty of Medicine, Department of Children's Health and Diseases, Division of Neonatology, Şanlıurfa, Turkey
[3]University of Health Sciences Turkey, Ulucanlar Eye Training and Research Hospital Ankara, Turkey
[4]Şanlıurfa Training and Research Hospital, Clinic of Children's Health and Diseases, Division of Pediatric Cardiology, Şanlıurfa, Turkey

ABSTRACT

Introduction: This study aimed to investigate the relationship between symmetric and asymmetric retinopathy of prematurity (ROP) and echocardiographic parameters.

Methods: This prospective study included 85 premature infants classified into three groups based on the presence/absence of ROP: 32 premature infants without ROP (group A), 26 premature infants with asymmetric ROP (group B), and 27 premature infants with symmetric ROP (group C). Cardiac parameters were measured using M-mode echocardiography.

Results: The mean gestational age (GA) was 32.03±1.5 weeks in group A, 30.69±2.5 weeks in group B, and 31.5±2.9 weeks in group C. The mean birth weight (BW) was 1802±312 gram (g) in group A, 1606±470 g in group B, and 1642±456 g in group C. As a result of the one-way ANOVA, the mean GA and BW were significantly higher in group A (p=0.03). No significant differences were found in the interventricular septal wall thickness (diastolic and systolic) left ventricular internal dimension (diastolic and systolic), left ventricular posterior wall thickness (diastolic and systolic), ejection fraction, stroke volume, and fractional shortening among the three groups (p=0.12, p=0.93, p=0.64, p=0.91, p=0.48, p=0.83, p=0.56, p=0.72, p=0.32, p=0.73, p=0.21, respectively).

Conclusion: Global cardiac function does not seem to have an effect in the asymmetric presentation of the eyes in patients with ROP.

Keywords: Retinopathy of prematurity, asymmetry, echocardiography

ÖZ

Amaç: Bu çalışmada simetrik ve asimetrik özellik gösteren prematüre retinopatisi (PR) olguları ile bu olgulara ait ekokardiyografik parametreler arasındaki ilişkinin incelenmesi amaçlandı.

Yöntemler: Prospektif özellikteki bu çalışmaya, PR varlığına göre 3 gruba ayrılan toplam 85 prematüre bebek dahil edildi. PR gelişmeyen 32 hasta grup A, her iki gözde asimetrik özellikte PR gelişen 26 hasta grup B ve her iki gözde simetrik özellikte PR gelişen 27 hasta grup C olarak sınıflandırıldı. Kardiyak parametreler M-mod ekokardiyografi kullanılarak ölçüldü.

Bulgular: Ortalama (ort.) doğum haftası (DH) grup A'da 32,03±1,5 hafta, grup B'de 30,69±2,5 hafta ve grup C'de 31,5±2,9 hafta idi. Ort. doğum ağırlığı (DA) grup A'da 1802±312 gram (g), grup B'de 1606±470 g ve grup C'de 1642±456 g idi. Gruplar arasında yapılan one-way ANOVA analizinde ort. DH ve DA, grup A'da anlamlı olarak daha yüksek idi (p=0,03). Gruplar arasındaki diyastolik ve sistolik interventriküler septum duvar kalınlığı, diyastolik ve sistolik sol ventrikül internal boyutları, diyastolik ve sistolik sol ventrikül arka duvar kalınlıkları, ejeksiyon fraksiyonu, sistolik volümler ve fraksiyonel kısalma ölçümleri arasında istatistiksel olarak anlamlı bir fark saptanmadı (sırasıyla, p=0,12, p=0,93, p=0,64, p=0,91, p=0,48, p=0,83, p=0,56, p=0,72, p=0,32, p=0,73, p=0,21).

Sonuç: Genel kardiyak fonksiyonunun PR gelişen olguların gözlerinde hastalığın asimetrik olarak karşımıza çıkması üzerinde herhangi bir etkisi olmadığı gözlendi.

Anahtar Kelimeler: Prematüre retinoaptisi, asimetri, ekokardiyografi

Address for Correspondence/Yazışma Adresi: Yasin Özcan MD, Yeditepe University Medical School, Yeditepe Speciality Hospital, Department of Ophthalmology, İstanbul, Turkey
Phone: +90 216 578 51 51 **E-mail:** ozcan.yasin@yahoo.com **ORCID ID:** orcid.org/0000-0003-4536-1785

Cite this article as/Atıf: Özcan Y, Gümüş H, Çıtırık M, Çiftel M. Assessment of Echocardiographic Findings in Patients with Asymmetric Presentation of Retinopathy of Prematurity. İstanbul Med J 2020; 21(4): 262-5.

Received/Geliş Tarihi: 08.10.2019
Accepted/Kabul Tarihi: 09.05.2020

Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disorder and one of the leading causes of preventable blindness in children both in developing and developed countries (1,2). The increasing survival rate of preterm infants through advanced neonatal care has led to an increase in the incidence of ROP (3,4). Many risk factors have been identified for the development of ROP, including low gestational age (GA), low birth weight (BW), prolonged oxygen supplementation, neonatal infection, hypoxia, blood transfusion, sepsis, anaemia and apnoea that may lead to haemodynamic instability associated with the development of ROP (2,5,6). Functional echocardiography is a non-invasive method allowing the rapid assessment of cardiac output and haemodynamic status in preterm new borns. Haemodynamic assessment using echocardiography has the potential to identify the underlying cause of structural heart disease, and ventricular performance plays a significant prognostic role in the identification of clinical status and long-term outcomes in preterm neonates (7-9). Of all cardiac disorders, patent ductus arteriosus has been determined as the sole factor associated with ROP (10). Although ROP is commonly stated as a symmetric disease, a very small percentage of infants may have asymmetric presentation. Therefore, this study aimed to investigate the relationship between symmetric and asymmetric presentation of ROP in any stage and echocardiographic parameters. The hypothesis of the study was that abnormal cardiac parameters indicating haemodynamic instability that do not cause any clinical disturbance may lead to asymmetric presentation of ROP.

Methods

This single-centre, prospective study was carried out from August 2019 to October 2019 in a tertiary referral centre for ROP.

The study protocol was approved by Harran University Ethics Committee (approval number: 74059997-050.04.04), and the study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians of the patients prior to enrolment and before any measurements were taken. All patients were Turkish Caucasians.

Patients

Preterm infants with BW ≤1500 g or GA ≤32 weeks were included in this study. Infants with BW >1500 gram (g) or GA >32 weeks with a history of admission to a neonatal intensive care unit due to unstable clinical course were also included. The initial fundus examination was performed at 4-6 weeks after birth. An ophthalmologist (YO), with experience in the screening and treatment of ROP, performed all examinations. The retinal findings were classified according to the current International Classification of ROP (11). When ROP of any stage was detected, examinations were repeated at weekly or biweekly intervals depending on the retinal findings, until a completely vascularised peripheral retina was obtained. An eyelid speculum and scleral indentation were used in all examinations. The premature infants were assigned to three groups based on the presence and symmetry of ROP. Premature infants without ROP were defined as group A, those with asymmetric ROP as group B, and those with bilateral symmetric ROP as group C. Echocardiographic measurement was performed one day after the ROP screening to eliminate alterations in echocardiography outcomes caused by scleral depression and topical medications for pupil dilatation.

None of the patients had a history of heart disease or any surgery. Patients with a history of taking systemic medications, especially anticoagulants and antiplatelet drugs which may cause alterations in the cardiac output, or a history of previous blood transfusions were excluded.

Echocardiographic Examination

In all subjects, two-dimensional, M-mode, pulsed and colour flow Doppler echocardiographic examinations (Vivid 7 pro, GE, Horten, Norway, 3 MHz transducer) were performed by a cardiologist who was blinded to the clinical details and results of the other investigations of each case. During echocardiography, a 1-lead electrocardiographic recording was employed continuously. The systolic function of the left ventricle was evaluated using M-mode echocardiography in the parasternal long-axis view. Cardiac parameters were measured using M-mode echocardiography that allows evaluation of the interventricular septal (IVS) wall thickness, left ventricular internal dimension (LVID), left ventricular posterior wall (LVPW) thickness on both diastolic and systolic intervals, ejection fraction (EF), systolic volume (SV), and fractional shortening (FS).

Statistical Analysis

Data from all groups were expressed as mean ± standard deviation. The Kolmogorov-Smirnov test was used to assess the conformity of data to normal distribution. Differences in the echocardiographic parameters between the three groups were evaluated using one-way analysis of variance (ANOVA), where applicable. The Bonferroni test was used as a post hoc test after one-way ANOVA. The level of significance was set at <0.05. All statistical analyses of the study were performed using SPSS for Windows (SPSS Inc., Chicago, IL, USA).

Results

A total of 85 premature infants were divided into three groups based on the presence and symmetry of ROP. group A was composed of 32 premature infants without ROP, group B was composed of 26 premature infants with asymmetric ROP, and group C consisted of 27 premature infants with symmetric ROP.

The gender pedilection among groups was 18 boys (56%) and 14 girls (44%) in group A, 18 boys (69%) and 8 girls (31%) in group B, and 15 boys (56%) and 12 girls (44%) in group C. No difference was determined between the groups with respect to gender ($p>0.05$).

The mean GA was 32.03±1.5 weeks in group A, 30.69±2.5 weeks in group B, and 31.5±2.9 weeks in group C. The mean BW was 1,802±312 g in group A, 1,606±470 g in group B, and 1,642±456 g in group C. As a result of the one-way ANOVA, the mean GA and BW were significantly higher in group A, whereas no significant differences were found between groups B and C in terms of the mean GA and BW ($p=0.03$, 0.15, respectively).

The echocardiographic measurements of the three groups are summarised in Table 1. No significant differences in IVS (diastolic and systolic), LVID (diastolic and systolic), LVPW (diastolic and systolic), EF, SV,

Table 1. Echocardiographic measurements and comparison data of three groups of premature infants

	Group A (n=32) (mean ± SD)	Group B (n=26) (mean ± SD)	Group C (n=27) (mean ± SD)	p
IVSd (mm)	0.4±0.13	0.3±0.13	0.3±0.11	p=0.12
IVSs (mm)	0.5±0.18	0.5±0.14	0.5±0.16	p=0.93
LVIDd (mm)	2±0.37	1.9±0.42	1.9±0.36	p=0.64
LVIDs (mm)	1.2±0.29	1.2±0.32	1.2±0.25	p=0.91
LVPWd (mm)	0.4±0.11	0.3±0.15	0.4±1	p=0.48
LVPWs (mm)	0.5±0.18	0.5±0.1	0.5±0.13	p=0.83
EDV (mL)	14.5±8.38	12.3±7.9	13.3±6.8	p=0.56
ESV (mL)	4.2±2.81	3.6±2.8	4.1±2.3	p=0.72
EF (%)	71±6.80	70.5±7.3	68±9	p=0.32
SV (mL)	9.5±4.6	8.5±5.2	9.1±4.9	p=0.73
FS (%)	38.2±5.71	38±5.8	35.8±7.4	p=0.21

IVSd: Interventricular septal wall thickness (diastolic), IVSs: interventricular septal wall thickness (systolic), LVIDd: left ventricular internal dimension (diastolic), LVIDs: left ventricular internal dimension (systolic), LVPWd: left ventricular posterior wall thickness (diastolic), LVPWs: left ventricular posterior wall thickness (systolic), EDV: end-diastolic volume, ESV: end-systolic volume, EF: ejection fraction, SV: systolic volume, FS: fractional shortening, SD: standard deviation

and FS values were found between the groups (p=0.09, 0.15, 0.12, 0.93, 0.64, 0.91, 0.48, 0.83, 0.56, 0.72, 0.32, 0.73, 0.21, respectively).

Discussion

Different tools such as the measurement of blood pressure, capillary refill time, and urinary output and lactate analysis, functional echocardiography, and near-infrared spectroscopy are used to assess haemodynamic status in preterm infants at risk for haemodynamic instability (12). Clinical assessment of cardiovascular status is unreliable in neonates, while conventional echocardiography is commonly used for haemodynamic assessment (13). In this study, the investigation focused on whether haemodynamic instability may have an effect on the symmetric presentation of ROP using an echocardiographic method with different measurements. No significant difference was determined among the three groups in terms of all mean echocardiographic measurements, indicating cardiac contractibility and haemodynamic health status. No abnormal echocardiographic parameters which may indicate haemodynamic instability were detected in any of the three groups. Furthermore, neither the presence nor the asymmetry of ROP was associated with any of the echocardiographic parameters. Interestingly, on initial examination, either mild or moderate ROP was determined in patients with asymmetric presentation of ROP and no patients with symmetric ROP progressed to stage 3 disease or developed other diseases requiring treatment during the follow-up period.

Many risk factors have been identified as predisposing factors for the development of ROP. The only proven cardiological risk factor associated with the development of ROP is patent ductus arteriosus (13). In this study, no significant differences were determined in the echocardiographic parameters including IVS (diastolic and systolic), LVID (diastolic and systolic), LVPW (diastolic and systolic), EF, SV, and FS values in the three groups. Several studies have assessed different cardiac parameters in preterm and full-term infants, but none of these were designed to investigate the relationship with the presence or asymmetry of ROP (14).

Ciccone et al. (15) reported that IVS diameter, left ventricular (LV) end-systolic diameter, left atrial diameter, and EF values were not significantly different between infants born prematurely with very low BW (<1,500 g) and those born at term with weight appropriate for GA, although the size of the left ventricle and altered LV diastolic function were significant in premature infants with a very low BW. Levy et al. (16) reported that echocardiographic parameters including LV, global longitudinal strain, and global longitudinal systolic strain rates remained unchanged in both uncomplicated preterm infants and infants with bronchopulmonary dysplasia (BPD) that affects primarily right ventricular (RV) function, whereas the RV free wall longitudinal strain, RV free wall longitudinal strain rate, and IVS strain rate were significantly lower in infants with BPD.

The main limitation of this study was the use of echocardiography alone to measure reliable quantitative parameters of ventricles in preterm infants.

Conclusion

The results of this study revealed that abnormal cardiac parameters do not accompany the presence and asymmetry of ROP. Global cardiac function does not seem to have an effect on the asymmetric presentation of the eyes in patients with ROP. Echocardiographic assessment alone is not a practical method to clarify haemodynamic instability in premature infants with and without ROP. Further studies with larger patient groups are needed to confirm these findings.

Ethics

Ethics Committee Approval: The study protocol was approved by Harran University Ethics Committee (approval number: 74059997-050.04.04),

and the study was carried out in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from the parents or legal guardians of the patients prior to enrolment and before any measurements were taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - Y.Ö., Mu.Ç.; Concept- Y.Ö.; Design - Y.Ö.; Data Collection or Processing - Y.Ö., H.G., Mu.Ç.; Analysis or Interpretation - H.G.; Literature Search - H.G.; Writing - Y.Ö., M.Ç.

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

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

References

1. Gomella TL, Cunningham MD, Eyal FG, Tuttle DJ, editors. Neonatology: Management, procedures, on-call, problems. Mcgraw Hill & Lange, 2013.p.844-9.
2. Ozcan PY, Çıtırık M, Özçalışkan S. Current Epidemiology, Pathophysiology and risk Factors in retinopathy of prematurity. Ret-Vit 2016; 24: 263-70.
3. Valentine PH, Jackson JC, Kalina RE, Woodrom De. Increased survival of low birth weight infants: Impact on the incidence of retinopathy of prematurity. Pediatrics 1989; 84: 442-5.
4. Gibson DL, Sheps SB, Uh SH, Schechter MT, McCormick AQ. Retinopathy of prematurity-induced blindness: Birth weight-specific survival and the new epidemic. Pediatrics 1990; 86: 405-12.
5. Darlow BA, Hutchinson JL, Henderson-Smart DJ, Donoghue DA, Simpson JM, Evans NJ, et al. Prenatal risk factors for severe retinopathy of prematurity among very preterm infants of the Australian and New Zealand Neonatal Network. Pediatrics 2005; 115: 990-6.
6. Chen Y, Xun D, Wang YC, Wang B, Geng SH, Chen H, et al. Incidence and risk factors of retinopathy of prematurity in two neonatal intensive care units in North and South China. Chin Med J (Engl) 2015; 128: 914-8.
7. Breatnach CR, Levy PT, James AT, Franklin O, El-Khuffash A. Novel echocardiography methods in the functional assessment of the newborn heart. Neonatology 2016; 110: 248-60.
8. Lewandowski AJ, Bradlow WM, Augustine D, Davis EF, Francis J, Singhal A, et al. Right ventricular systolic dysfunction in young adults born preterm. Circulation 2013; 128: 713-20.
9. Lewandowski AJ, Augustine D, Lamata P, Davis EF, Lazdam M, Francis J, et al. Preterm heart in adult life: cardiovascular magnetic resonance reveals distinct differences in left ventricular mass, geometry, and function. Circulation 2013; 127: 197-206.
10. Mitsiakos G, Papageorgiou A. Incidence and factors predisposing to retinopathy of prematurity in inborn infants less than 32 weeks of gestation. Hippokratia 2016; 20: 121-6.
11. Fierson WM, Saunders RA, Good W, Palmer EA, et al. Screening examination of premature infants for retinopathy of prematurity. Pediatrics 2013; 131: 189-95.
12. Escourrou G, Renesme L, Zana E, Rideau A, Marcoux MO, Lopez E, et al. How to assess hemodynamic status in very preterm newborns in the first week of life?. J Perinatol 2017; 37: 987-93.
13. Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr 2010; 23: 465-95; quiz 576-7.
14. Eriksen BH, Nestaas E, Hole T, Liestøl K, Støylen A, Fugelseth D. Myocardial function in term and preterm infants. Influence of heart size, gestational age and postnatal maturation. Early Hum Dev 2014; 90: 359-64.
15. Ciccone MM, Cortese F, Gesualdo M, DI Mauro A, Tafuri S, Mancini G, et al. The role of very low birth weight and prematurity on cardiovascular disease risk and on kidney development in children: a pilot study. Minerva Pediatr 2016 Jun 29.
16. Levy PT, El-Khuffash A, Patel MD, Breatnach CR, James AT, Sanchez AA, et al. Maturational patterns of systolic ventricular deformation mechanics by two-dimensional speckle-tracking echocardiography in preterm infants over the first year of age. J Am Soc Echocardiogr 2017; 30: 685-98.

İstanbul Med J 2020; 21(4): 266-74
DOI: 10.4274/imj.galenos.2020.60343

Using Peer-based Education to Increase the Knowledge Level of Vocational High Students About Sexually Transmitted Diseases

Meslek Lisesi Öğrencilerinin Akran Temelli Eğitim ile Cinsel Yolla Bulaşan Hastalıklar Hakkındaki Bilgi Düzeyinin Artırılması

Gülay Börekçi[1,2], Derya Akdeniz Uysal[3], Arzu Özel[3], Döne Aksu[3]

[1]Mersin University Faculty of Nursing, Department of Nursing Management, Mersin, Turkey
[2]Mersin University Institute of Health Sciences, Department of Molecular Microbiology, Mersin, Turkey
[3]Mersin University Health Research and Application Hospital, Mersin, Turkey

ABSTRACT

Introduction: Sexually transmitted diseases (STDs) are one of the major health problems affecting especially young people. While the number of newly infected cases with human immunodeficiency virus (HIV), one of the STDs, is decreasing all over the world, unfortunately, it continues to increase in Turkey. Therefore, it is important to educate young people on this topic through effective methodologies. The aim of this semi-experimental study was to evaluate the effectiveness of peer-based education on increasing the knowledge levels of vocational high school students about STDs.

Methods: In this study, a peer-based training was provided to 2000 volunteer vocational high school students. Pre- and post-test questionnaire forms prepared by the researchers were filled by the students before and after the training. Of the 2000 volunteer students, the data of 620 students who completed the questionnaire forms were evaluated.

Results: The average age of the participants was 16.58±1.01 years and 61.4% of them were female, of which, 14.5% were in the 9th grade, 46.0% in the 10th, 26.5% in the 11th and 13.1% in the 12th. Moreover, 67.4% of them had not received any education on STDs before. A meaningful relationship was found between the results of the pre- and post-tests applied to the students, and the provided training was proven effective in increasing the students' knowledge levels.

Conclusion: The results of this study showed that a peer-based education model can be effective in raising awareness about STDs among youth and in creating a positive behavioural change in them.

Keywords: Sexually transmitted diseases, peer-based education, adolescence

ÖZ

Amaç: Cinsel yolla bulaşan hastalıklar (CYBH) özellikle gençleri etkileyen önemli sağlık sorunlarından biridir. CYBH'den biri olan insan bağışıklık yetmezliği virüsü (HIV) ile yeni enfekte sayısı tüm dünyada azalırken, ne yazık ki ülkemizde artmaya devam etmektedir. Bu nedenle gençleri etkili yöntemlerle eğitmek çok önemlidir. Bu yarı deneysel çalışmanın amacı, akran temelli eğitimin meslek lisesi öğrencilerinin cinsel yolla bulaşan hastalıklar konusundaki bilgi düzeylerini artırmadaki etkinliğini değerlendirmektir.

Yöntemler: Bu çalışmada, gönüllü 2000 meslek lisesi öğrencisine akran temelli eğitim verilmiştir. Araştırmacılar tarafından hazırlanan ön test ve son test soru formu, öğrencilere eğitim öncesi ve sonrasında uygulanmıştır. Veriler toplandıktan sonra, anket formunu dolduran 620 öğrencinin verileri değerlendirmeye alınmıştır.

Bulgular: Araştırmaya katılan öğrencilerin yaş ortalaması 16,58±1,01 olup, %61,4'ünün kız, %14,5'inin 9. sınıf, %46,0'ının 10. sınıf, %26,5'inin 11. sınıf ve %13,1'inin 12. sınıfta olduğu, %67,4'ünün cinsel yolla bulaşan hastalıklar konusunda daha önce hiç eğitim almadığı belirlenmiştir. Öğrencilere uygulanan ön test ve son test arasında anlamlı bir ilişki bulunmuş ve verilen eğitimin öğrencilerin bilgi düzeylerini artırmada etkili olduğu saptanmıştır.

Sonuç: Çalışma sonuçlarımız akran temelli eğitim modelinin gençlerin cinsel yolla bulaşan hastalıklar hakkındaki bilgi düzeyinin artırılmasında ve gençlerde olumlu davranış değişikliği oluşturulmasında yararlı olduğunu göstermektedir.

Anahtar Kelimeler: Cinsel yolla bulaşan hastalıklar, akran temelli eğitim, adölesan

Address for Correspondence/Yazışma Adresi: Gülay Börekçi PhD, Prof. Dr., Mersin University, Faculty of Nursing, Department of Nursing Management; Institute of Health Science, Department of Molecular Microbiology, Mersin, Turkey
Phone: +90 324 241 00 01/42 23 **E-mail:** gulay_borekci@yahoo.com **ORCID ID:** orcid.org/0000-0002-7879-7959

Cite this article as/Atıf: Börekçi G, Akdeniz Uysal D, Özel A, Aksu D. Using Peer-based Education to Increase the Knowledge Level of Vocational High Students About Sexually Transmitted Diseases. İstanbul Med J 2020; 21(4): 266-74.

Received/Geliş Tarihi: 10.07.2019
Accepted/Kabul Tarihi: 09.05.2020

Introduction

Adolescence is an important transitional period between childhood and adulthood, when the growth and development of a child is swift and the cognitive and psychosocial developments commence (1,2). In Turkey, according to the 2018 Address-based Population Registration System results, out of the total population of 81,867,223, 12,725,029 people were found to fall within the age group of 10-19 years and 6,402,806 within the 15-19 years (3). Adolescents comprise about one-sixth of the world's total population and about one-fifth of Turkey's. They are an important part of society and are most affected by any social reform or change; however, no special attention on any such accounts is paid to them (4).

The physiological and psychological changes during this transitional period can lead to behavioural changes and cause psychosocial problems among adolescents. Adolescents naturally desire to be independent and seek new environments for themselves, and in doing so, they emotionally distance themselves away from their family. This situation can bring many problems together with new experiences. Some of the common risky behaviours observed among adolescents are substance use, sexually transmitted diseases (STDs), accidents, suicides, violence and adolescent pregnancies (5).

The theme of the World Population Day 2014 was set as "Investing in Young People" by the United Nations Population Fund. And drawing attention to the sexual and reproductive health of adolescents, they stated that very little progress was made in preventing adolescent pregnancies, unsafe abortion, mother deaths, STDs and human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), and that there are important deficiencies about access to comprehensive sexual education and services and about the quality and availability of this education and these services for the young (6).

STDs are one of the most common and dangerous among infectious diseases. The most frequent STDs are gonorrhoea, syphilis, chlamydia, genital herpes, hepatitis B and HIV/AIDS. According to the WHO data, more than one million people are infected by STDs daily. Each year, 357 million new infections occur with one of the four STDs (chlamydia, gonorrhoea, syphilis and trichomoniasis); besides that, more than 500 million people have genital herpes simplex virus (HSV), and more than 290 million women have human papilloma virus (HPV) infection (7).

According to the United Nations Programme on HIV/AIDS, 36.9 million people were predicted to have HIV/AIDS in 2017; of those, 35.1 million were adults and 1.8 million were children aged under 15. People newly infected with HIV were 1.8 million in 2016, and about 940,000 people died of AIDS and AIDS-related diseases in the same year (8). While newly infected HIV/AIDS cases decrease worldwide, the number continues to rise in Turkey (9).

The insufficiency of sexual education curriculum at schools, unavailability of education to those who do not/cannot go to school, sexuality being regarded as a taboo because of sociocultural reasons, sexuality going down to early age and not knowing about or/and not applying the protection methods are some of the reasons that lead to the risky behaviours observed among adolescents in our country (10). These negligent behaviours pose a risk to their lives in terms of HIV infections and other STDs via unprotected sex or intravenous drug use. This is why educating the youth at high school age about the types of STDs and the precautions to take and using a peer-based education to do so are important. Peer education-based on social learning theory-is established on the fact that young people interact with their peers and identify with each other (11). The classical education is generally teacher-centred, where knowledge is one-way process from the educator to the student. On the other hand, in the peer education, children use similar language and influence each other creating a more positive and interactive learning environment (12). Therefore, in our study, we aimed to determine the effect of peer-based education on the knowledge levels of students about STDs.

Although, in recent years, much awareness on the topic has been created through social media, sexuality and related topics are still regarded as taboo and are not given place in education, yielding the awareness attempts on the topic so far as inadequate. Since STDs affect the age group of 15-24 the most, educating young people is especially important. However, the fact that young people do not have sufficient information about STDs at that age, that they do not obtain information from right sources and that they are misinformed cause difficulties in fighting against these diseases. It was identified through different studies in our country that students have insufficient information about STDs, and that they do not want to get information about STDs (13-17).

Mersin is a cosmopolitan tourist city with high migration rate and has been exposed to sociocultural changes since a long time. In our country, vocational high school students settle in schools with the lowest grades and their education includes mostly vocational knowledge. These students, who have more free time, are at risk for substance use and STDs. The results of our former study on this group showed that students do not have sufficient information about STDs.

Methods

This study was conducted semi-experimentally using the pre- and post-test forms in order to determine the effect of peer-based education on students' level of knowledge about STDs. A total of 20,961 students studying between the 9th and the 12th grade of 22 vocational high schools were included in this study. The sample consisted of 2,000 students selected from these vocational high schools through random sampling method. Before starting to work, ethical approval was obtained from the Clinical Research Ethics Committee of Mersin University and the other necessary permissions (governorship approval, ministry of education permission slip) were taken from related institutions.

In the first stage of the study, all 2,000 students were asked to fill a questionnaire in order to determine their level of knowledge about STDs. After that, the structure of the peer-based education, including the modes of transmission, their symptoms and prevention, was planned. Then, the educational materials (power point presentation, brochure, etc) were prepared.

In the second stage, approximately 50 university students were trained by specialists about STDs. These university students (peers) were mostly nursing department students at a university or students of other faculties who had taken lessons on STDs before.

In the third stage, a peer-based training about STDs was given to the 2,000 participating high school students by the 50 university students under the leadership of 16 researchers. Peer-based trainings on STDs were delivered in a 45 mins-long single session to groups of 20-50 students in the conference halls of the schools. Data were collected using the pre- and post-test forms prepared by the researchers. Students were asked to fill the pre-test form before and post-test form after the session. In addition, at the end of the session, students were given leaflets with information about STDs. Descriptive characteristics information form and STDs information form, prepared by the researchers in line with the literature, were used for data collection. The demographic information form included questions about the students' age, gender, school, department, and class. The STDs information form included questions about STDs, the modes of transmission of the diseases, symptoms and consequences, treatment and prevention. There were 51 questions in the survey together with their subgroups.

Finally, after the data were collected, the data of only 620 students who completed the questionnaire forms were evaluated. The data obtained were analysed using a statistics package program in computer environment. Percentage, arithmetic mean, standard deviation values, and chi-square test were used for data analysis. The results were evaluated as between 95% confidence interval and $p<0.05$ was considered as significant.

Results

The average age of the students was 16.58±1.01 years and 61.5% of them were female, of which 14.5% were in the 9th grade, 46.0% in the 10th, 26.6% in the 11th and 12.9% in the 12th. Department wise, 20.6% of the students were in child development, 20.2% in accounting, 9.2% in graphics, 8.1% in electrics-electronics and less in other departments; 67.4% of the students stated that they had not received any education about STDs.

When the pre- and post-test results of the knowledge of the students about STDs was compared, it was found that there was a statistically significant difference between before and after the education, and that the knowledge level about STDs increased after the education. The increase in the number of students who were aware of HIV/AIDS, hepatitis B, hepatitis C, syphilis, trichomoniasis and others as forms of STDs after the education was found to be statistically significant ($p<0.05$). Likewise, the number of students who knew about the different modes of transmission of STDs before and after the training increased significantly ($p<0.05$) (Table 1).

Table 1. Comparison of the pre- and post-test results of the knowledge of the students regarding the different modes of transmissions of STDs

	Pre-test n %		Post-test n %		p
Transmission through sexual intercourse					
Yes	533	86.1	578	93.8	0.001
No	11	1.8	12	1.9	
Do not know	75	12.1	26	4.2	
Transmission through cheek kissing					
Yes	148	23.9	229	37.0	0.001
No	295	47.7	335	54.1	
Do not know	175	28.3	55	8.9	
Transmission through respiration					
Yes	263	42.7	295	47.7	0.001
No	170	27.6	249	40.0	
Do not know	183	29.7	76	12.3	
Transmission through some commonly used tools (injector, razor, manicure set, etc)					
Yes	395	63.9	471	76.2	0.001
No	72	11.7	79	12.8	
Do not know	151	24.4	68	11.0	
Transmission from mother to baby during pregnancy and breastfeeding					
Yes	299	48.2	469	75.8	0.001
No	116	18.7	76	12.3	
Do not know	204	33.0	74	12.0	
Transmission through blood and organ transfusion (HIV/AIDS, hepatitis B/C)					
Yes	285	36.6	473	76.3	0.001
No	60	14.4	58	9.4	
Do not know	304	49.0	89	14.4	
Total	620	100	620	100	

p: chi-square test was used, HIV/AIDS: human immunodeficiency virus/acquired immune deficiency syndrome, STDs: sexually transmitted diseases

When the knowledge levels of students regarding the symptoms and results of STDs before and after the training were compared, it was found that their knowledge levels increased significantly after the training ($p<0.05$) (Table 2).

When the knowledge levels of students regarding the treatment of STDs before and after the training were compared, it was found that their knowledge levels increased significantly after the training ($p<0.05$) (Table 3).

As shown in Table 4, when the knowledge levels of the students related to the precautions to be taken to protect themselves against STDs before and after the training were compared, it was found that the increase in the knowledge levels after the test was statistically significant ($p<0.05$).

Table 5 shows the knowledge levels of students about vaccination against STDs before and after the training, and it was found that the increase in the knowledge levels after the training was statistically significant ($p<0.05$).

Discussion

The biggest risk that unsafe sexual life can bring is an STD. Protection is the most essential step in prevention of STDs. However, this can only be achieved if the younger population is educated on the issue and has a positive outlook towards using protection. While there are many methods of imparting education, peer-based education can be particularly effective in societies where STD is considered as a taboo. In our study, the effect of peer-based education on the knowledge levels of vocational high school students about STD was researched.

Students' knowledge on the different types of STDs increased significantly after the peer-based training. While trichomoniasis (16.5%) and Chlamydia infections (18.7%) and gonorrhoea (27.9%) were among the least known STDs before the training, a significant rise was seen in these rates after the training. Similarly, in a study of nursing school first grade students by Aşcı et al. (17), it was found that the rate of defining STDs among the risks sexual life can bring increased significantly among the participants after a peer-based training. While the rate of students viewing STDs as a risk was 67.2% before the education, it increased to 87.9% after the education. In the same study, the rate of those who knew the names of STDs other than HPV, HSV, Chlamydia and Trichomonas infections increased after the training. Furthermore, in a study by Jones et al. (18) with university students including nursing school students in the United States, an increase in the knowledge level of students about STDs was determined after a peer-based training. Also, in several other studies with university and high school students, a significant difference was found in the knowledge levels of students about STDs before and after peer-based education (19-22).

After the literature review, it was found that the studies conducted in many different countries concentrated mostly on HIV/AIDS, and that peer-based education interventions were done (23-29). A Malaysian research among medical and health school students studied the effect of peer-based education on the knowledge, attitude and risky health

Table 2. Comparison of the pre- and post-test results of the knowledge of students about the symptoms and results of STDs

	Pre-test n %		Post-test n %		p
May cause stinky secretion in sexual organs					
Yes	403	65.3	537	86.9	0.001
No	17	2.8	11	1.8	
Do not know	197	31.9	70	11.3	
May cause pain in groins					
Yes	384	62.1	518	83.8	0.001
No	19	3.1	30	4.9	
Do not know	215	34.8	70	11.3	
May cause infertility					
Yes	307	49.8	492	79.9	0.001
No	31	5.0	25	4.1	
Do not know	279	45.2	99	16.1	
May cause premature births/abortions					
Yes	315	50.9	498	80.7	0.001
No	28	4.5	36	5.8	
Do not know	276	44.6	83	13.5	
May cause death					
Yes	340	54.9	509	82.5	0.001
No	27	4.4	29	4.7	
Do not know	252	40.7	79	12.8	
Total	620	100	620	100	

p: chi-square test was used, STDs: sexually transmitted diseases

Table 3. Comparison of the pre- and post-test results of the knowledge of students about the treatment of STDs

	Pre-test		Post-test		p
	n	%	n	%	
HIV/AIDS					
Has treatment	170	27.6	217	35.6	0.001
Does not have treatment	164	26.7	297	48.7	
Do not know	281	45.7	96	15.7	
Hepatitis B					
Has treatment	218	35.4	260	42.8	0.001
Does not have treatment	82	13.3	246	40.5	
Do not know	316	51.3	101	16.6	
Hepatitis C					
Has treatment	172	28.1	245	40.4	0.001
Does not have treatment	77	12.6	237	39.0	
Do not know	364	59.4	125	20.6	
Syphilis					
Has treatment	104	17.0	291	47.8	0.001
Does not have treatment	54	8.8	119	19.5	
Do not know	453	74.1	199	32.7	
Trichomoniasis					
Has treatment	81	13.7	217	35.7	0.001
Does not have treatment	37	6.0	102	16.8	
Do not know	94.4	80.7	289	47.5	
Gonorrhoea					
Has treatment	138	22.3	293	47.3	0.001
Does not have treatment	45	7.3	102	16.5	
Do not know	429	69.2	213	34.4	
Genital wart (HPV)					
Has treatment	135	21.8	274	44.2	0.018
Does not have treatment	49	7.9	129	20.8	
Do not know	429	69.2	206	33.8	
Genital herpes					
Has treatment	141	22.7	269	43.4	0.001
Does not have treatment	47	7.6	102	16.5	
Do not know	425	68.5	238	38.4	
Chlamydia					
Has treatment	81	13.1	217	35.0	0.040
Does not have treatment	37	6.0	102	16.5	
Do not know	434	79.7	289	46.6	
Total	620	100	620	100	

p: chi-square test was used, HIV/AIDS: human immunodeficiency virus/acquired immune deficiency syndrome, STDs: sexually transmitted diseases, HPV: human papilloma virus

behaviours related to HIV, and it was found that the knowledge level of the group who received the education increased significantly compared to the control group (26). In the study of Jahanfar et al. (24), an increase in the knowledge level of the group that was given peer-based education about HIV/AIDS was found. In similar studies in Iran, after the peer-based education was given to adolescents, knowledge and attitude points of the group receiving the training on HIV/AIDS were found to increase significantly compared to the control group (27,28,30). In randomly controlled studies of Bulduk and Erdogan (31) and Calloway et al. (23), a significant increase in the HIV/AIDS knowledge levels of the group that received the training was detected.

In our study, when the knowledge levels of the students related to the modes of transmissions of STDs before and after the peer-based training was compared, the knowledge levels of students was found

Table 4. Comparison of the pre- and post-test results of the knowledge of students about the precautions to be taken against transmitted STDs

	Pre-test		Post-test		p
	n	%	n	%	
Maintaining monogamy in sexual intercourse					
Yes	301	48.5	488	79.3	0.001
No	48	7.7	37	6.0	
Do not know	271	43.7	90	14.6	
Using condom					
Yes	225	36.3	473	77.0	0.001
No	65	10.5	36	5.9	
Do not know	329	53.2	105	17.1	
Avoiding intercourse with risky people (sex workers, homosexuals)					
Yes	347	56.1	505	82.4	0.001
No	31	5.0	25	4.1	
Do not know	241	38.9	83	13.5	
Avoiding common use of tools like razor, injector, nail clipper					
Yes	386	62.7	487	79.4	0.001
No	38	6.1	46	7.5	
Do not know	195	31.5	80	13.1	
Total	620	100	620	100	

p: chi-square test was used, STDs: sexually transmitted diseases

to increase after the training ($p<0.05$). This finding matches to similar studies conducted by using peer-based education (17,22). The results obtained from our study also matches with similar studies conducted by using peer-based education (15,18). In Aşçı et al. (17) study, the number of students knowing modes of STD transmission other than vaginal intercourse increased significantly when compared with before the education. In the study of Ali et al. (29) in Sudan, the rate of the correct answer given to the question of modes of transmission of HIV increased after the peer-based education from 75.5% to 83.2%.

When the knowledge levels of students related to the symptoms and results of STDs in our study were examined, it was seen that the knowledge levels of students related to the symptoms and results of STDs increased after receiving the training. Similarly, in the study of Aşcı et al. (17), the number of students knowing the symptoms of STDs was found to increase significantly after the education compared to before the education, and the difference was found to be statistically significant.

In our study, the knowledge levels of students related to the precautions that should be taken to be protected from STDs increased significantly after the education. In the study of Kırmızıtoprak and Şimşek (22) with young people, the answers given about safe sexual intercourse as avoiding sexual intercourse, monogamy and condom usage in protection from STDs changed positively after the peer-based education. While 77%-79.9% of students did not know the precautions stated before the education, the rate of students who did not know decreased to 4.7%-6.1% after the education. In the same study, the rate of students who knew condom as the most reliable method increased significantly after the education from 31% to 60.3%. In a study by Miller et al. (25) in Kenya with university students, a significant decrease in the number of students stating that condom use is not safe in protection from HIV was detected after a peer-based education. In another study, the rate of correct answers given by students with respect to having more than one sexual partner would increase HIV/AIDS risk increased from 47.5% to 83.5% after receiving the peer-based education (29). In the study of Adeomi et al. (32), while the rate of the correct answers about the ways of protection from AIDS showed an increase in the group who was given education, the same result was not seen in the control group.

In our study, the knowledge levels of students about vaccination and treatment of STDs increased after receiving the education. In comparison of the before and after the education, a statistically meaningful difference was observed. Similar to our study, in the study of Adeomi et al. (32), the knowledge level of students about the treatment of AIDS increased compared to the control group after the education.

However, like every study, there are some limitations to this study. The study was conducted only in vocational high schools in Mersin and included students who were present in the school on the day of training and volunteered to participate in the research. Due to the large number of students and the problem of time, all students could not be reached to check the pre- and post-test forms.

Table 5. Comparison of the pre- and post-test results of the knowledge of students about the vaccination against STDs

	Pre-test		Post-test		p
	n	%	n	%	
HIV/AIDS					
Has vaccination	144	23.8	202	34.9	0.001
Does not have vaccination	79	13.1	198	34.3	
Do not know	381	63.1	178	30.8	
Hepatitis B					
Has vaccination	203	33.6	370	63.4	0.001
Does not have vaccination	43	7.1	77	13.2	
Do not know	358	59.3	137	25.5	
Hepatitis C					
Has vaccination	164	27.2	229	39.4	0.001
Does not have vaccination	46	7.6	164	28.2	
Do not know	393	65.2	188	32.4	
Syphilis					
Has vaccination	74	12.2	150	25.8	0.001
Does not have vaccination	38	6.3	153	26.3	
Do not know	493	81.5	278	47.8	
Trichomoniasis					
Has vaccination	41	6.8	126	21.7	0.001
Does not have vaccination	45	7.4	135	23.3	
Do not know	519	85.8	319	55.0	
Gonorrhoea					
Has vaccination	75	12.1	138	22.3	0.001
Does not have vaccination	46	7.4	151	24.4	
Do not know	486	78.4	290	46.8	
Genital wart (HPV)					
Has vaccination	83	13.4	203	32.7	0.018
Does not have vaccination	50	8.1	119	19.2	
Do not know	473	76.3	261	42.1	
Genital herpes					
Has vaccination	62	10.0	139	22.4	0.001
Does not have vaccination	57	9.2	143	23.1	
Do not know	489	78.9	298	48.1	
Chlamydia					
Has vaccination	49	7.9	129	20.8	0.001
Does not have vaccination	38	6.1	138	22.3	
Do not know	519	83.7	315	50.3	
Total	620	100	620	100	

p: chi-square test was used, HIV/AIDS: human immunodeficiency virus/acquired immune deficiency syndrome, HPV: human papilloma virus, STDs: sexually transmitted diseases

Conclusion

In our study, the increase in the knowledge levels of knowing the names of STDs, their symptoms and results, vaccination and treatment after the education shows that the young people do not have sufficient information related to STDs, and that the peer-based education is efficient. Especially among adolescents, who are generally under the influence of their peers in many ways including in terms of positive and negative health behaviours. Young people tend to obtain and share information about sexual health-one of the taboo topics in our society from and among individuals who are in a similar developmental stage as them (22). This is why peer-based education, where they can have comfortable sharing without being judged that can enable their knowledge levels about STDs, is an educational approach that has

been frequently used in recent times (19). We believe that peer-based education model would be beneficial in educating young people about STDs and in creating positive behavioural changes in them. It would be useful to implement and spread peer-based training in schools to prevent HIV/AIDS and STDs.

Acknowledgement

We would like to thank all the students and teachers in Vocational High School in Mersin, Turkey.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Clinical Research Ethics Committee of Mersin University and the other necessary permissions (governorship approval, ministry of education permission slip) were taken from related institutions (decision no: 78017789/050.01.04/348, date: 09.10.2015).

Informed Consent: In addition, permission was obtained from students before the questionnaires were applied.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept- G.B., D.A.U., A.Ö., D.A.; Design - G.B.; Data Collection or Processing - D.A.U., A.Ö., D.A.; Analysis or Interpretation - G.B., D.A.U., A.Ö., D.A.; Literature Search - D.A.U., A.Ö., D.A ; Writing - G.B., D.A.U., A.Ö.

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

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

References

1. Yiğit R. Growth and development in childhood. 1st ed. Ankara: Ofset Printing; 2012.
2. Güler Y, Gönener DH, Altay B, Gönener A. Obesity and nursing care in adolescents. Fırat Health Services Journal 2009; 4: 165-81.
3. TUIK. Turkey Statistical Institute Address Based Population Registration System Results in 2016. Available from: URL: http://www.tuik.gov.tr
4. Yılmaz A, Başkan S. Evaluation of primary and high school students' knowledge about AIDS. The Journal of Current Pediatrics 2014; 1: 9-15.
5. Karatay G, Kubilay G. The Determination of substance use and influenced factors at two high school; Which have different socio-economic status. Journal of Research and Development in Nursing 2004; 1: 57-70.
6. UNFPA: United Nations Population Fund (2014). World population day investment in youth. Available from: URL: http://www.un.org.tr/news/WPD2014BilgiNotu.pdf
7. WHO: World Health Organisation (2019). Sexually transmitted infections (STIs). Available from: URL: https://www.who.int/en/news-room/fact-sheets/detail/sexually-transmitted-infections-(stis)
8. UNAIDS: Global HIV&AIDS statistics-2018 fact sheet. Available from: URL: https://www.unaids.org/en/resources/fact-sheet.
9. T.C. Ministry of Health, General Directorate of Public Health, Department of Infectious Diseases. HIV-AIDS Statistics. Available from: URL: https://hsgm.saglik.gov.tr/tr/bulasici-hastaliklar/862-hiv-aids/1135-h%C4%B1v-aids-istatislik.html
10. Efetürk T, Karabacak O. Sexual health at adolescence: Risky sexual behaviour. Turkiye Klinikleri J Fam Med-Special Topics 2013; 4: 71-80.
11. Akkuş D, Eker F, Karaca A, Kapısız Ö, Açıkgöz F. High school youth peer education program an effective model to prevent substance abuse happen? Journal of Psychiatric Nursing 2016; 7: 34-44.
12. Ünver V, Akbayrak N. Peer tutoring model in nursing education. DEUHYO ED 2013; 6: 214-7.
13. Karaköse A, Aydın S. Examination of young men's knowledge about sexually transmitted diseases. New Journal of Urology 2011; 6: 33-9.
14. Beydağ KD. A group of university school for health sciences students HIV/AIDS knowledge level. TAF Preventive Medicine Bulletin 2007; 6: 59-68.
15. Özdemir L, Ayvaz A, Poyraz Ö. The level of knowledge of students in Cumhuriyet University about the sexually transmitted diseases. Journal of the Faculty of Medicine Cumhuriyet University 2003; 25: 10-4.
16. Özalp S, Tanir HM, Ilgin H, Ilgin B. Evalution of knowledge and atttitude of Eskişehir Osmangazi University Medical and Agricultural Faculty's students on sexually transmitted diseases and family planning. Duzce Medical Journal 2012; 14: 18-21.
17. Aşcı Ö, Gökdemir F, Çiçekoğlu E. Efficiency of training on reproductive health provided by peer trainers to nursing students. HSP 2016; 3: 173-83.
18. Jones SG, Patsdaughter CA, Jorda ML, Hamilton M, Malow R. SENORITAS: An HIV/sexually transmitted infection prevention project for Latina college students at a Hispanic-serving university. JANAC 2008; 19: 311-9.
19. Güçlü S, Elem E, Unutkan A. An Intervention to increase sexual health information levels of youth: Peer education project. Journal of Research in Education and Teaching 2015; 4: 56-162.
20. Dağ H, Dönmez S, Şirin A, Kavlak O. University youth reproductive and sexual health knowledge and peer education. Journal of Anatolia Nursing and Health Sciences 2012; 15: 10-7.
21. Kadıoğlu H, Yıldız A. Effects of sexual education with the peer-led and adult led on the knowledge and attitudes of the elementary school eight grade students about the sexuality. HEMAR-G 2007; 3: 28-44.
22. Kırmızıtoprak E, Şimşek Z. The effect of peer-education on sexually transmitted diseases and safer sexual life knowledge and behaviour of young people. TAF Preventive Medicine Bulletin 2011; 10: 463-72.
23. Calloway DS, Long-White DN, Corbin DE. Reducing the risk of HIV/AIDS in African American college students: An exploratory investigation of the efficacy of a peer educator approach. Health Promotion Practice 2014; 15: 181-8.
24. Jahanfar S, Lye M, Rampal L. A randomised controlled trial of peer-adult-led intervention on improvement of knowledge, attitudes and behaviour of university students regarding HIV/AIDS in Malaysia. Singapore Medical Journal 2009; 50: 173-80.
25. Miller AN, Mutungi M, Facchini E, Barasa B, Ondieki W, Warria C. An outcome assessment of an ABC-based HIV peer education intervention among Kenyan university students. J Health Commun 2008; 13: 345-56.
26. İbrahim N, Rampal L, Jamil Z, Zain AM. Effectiveness of peer-led education on knowledge, attitude and risk behaviour practices related to HIV among students at a Malaysian public university- A randomized controlled trial. Prev Med 2012; 55: 505-20.
27. Abbaspour Z, Saidian M, Abedi P. Peer education vs health provider education in knowledge and attitude about prevention and transmission of AIDS in high school students. Pak J Med Sci 2007; 23: 108-10.

28. Babazadeh T, Zibaei N, Shabani L, Moradi F. Effectiveness of educational intervention based on peer education on knowledge, attitude and behavioral intention related to HIV/AIDS in the high school female students in the region 14 of Tehran. JECH 2015; 2: 19-27.

29. Ali MHM, Osman OB, Ibrahim MAM. The effect of AIDS peer health education on knowledge, attitudes, and practices of secondary school students in Khartoum, Sudan. AIMS Public Health 2015; 2: 718-26.

30. Alizadeh Siouki H, Jadgal K, Shamaeian Razavi N, Zareban I, Heshmati H, Saghi N. Effects of health education based on health belief model on nutrition behaviors of primary school students in Torbat e Heydariyeh city in 2012. Journal of Health 2015; 5: 289-99.

31. Bulduk S, Erdogan S. The effects of peer education on reduction of the HIV/sexually transmitted infection risk behaviors among Turkish university students. JANAC 2012; 23: 233-43.

32. Adeomi AA, Adeoye OA, Asekun-Olarinmoye EO, Abodunrin OL, Olugbenga-Bello A, Sabageh AO. Evaluation of the effectiveness of peer education in improving HIV knowledge, attitude, and sexual behaviours among in-school adolescents in Osun State, Nigeria. AIDS Research and Treatment 2014; 1-10.

İstanbul Med J 2020; 21(4): 275-80
DOI: 10.4274/imj.galenos.2020.38243

What is the Frequency of Internet Searches by Patients with Rheumatic Diseases? To What Degree are the Websites They Get Information from Reliable and What is the Effect of These Websites on Their Treatment?

Romatizma Hastalarının Hastalık Araştırması İnternet Kullanım Sıklığı Nedir? Hastalıklarıyla İlgili Bilgi Aldıkları İnternet Siteleri Ne Kadar Güvenilir ve Tedavi Üzerine Etkisi Nedir?

Aysel Gürcan Atçı[1], Sena Tolu[2]

[1]Baltalimanı Metin Sabancı Bone and Joint Diseases Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, İstanbul, Turkey
[2]Medipol University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, İstanbul, Turkey

ABSTRACT

Introduction: This study aimed to determine internet use among a certain number of patients with regard to the three prevalent rheumatic diseases in clinical practice and more importantly to evaluate the quality of information available on the internet using the DISCERN scoring system.

Methods: The study population consists of patients with rheumatoid arthritis, ankylosing spondylitis and fibromyalgia. As part of this study, we conducted a survey and recorded whether or not they researched over the internet concerning their diseases. After the survey, we also tested the reliability of the websites. We analysed websites using the DISCERN scoring system in order to determine to what degree these websites contained sufficient.

Results: We found that 102 out of 173 cases (58.9%) used the internet to get information about their disease, while 71 cases (41.04%) did not conduct any internet research. According to the DISCERN scoring, the aforementioned websites were evaluated with 15 questions in the survey. Consequently, it was inferred that among these websites, 24 (27.2%) had high-level (4 to 5 points), 44 (50%) had medium-level (2 to 3 points) and 20 (22.7%) had poor-level (1 point) quality and reliability.

Conclusion: The digital interest that has gradually increased in the recent years has become a concern as patients desire to have information on the course and treatment of their rheumatic diseases. It should be acknowledged that patients with long-term treatment and follow-up processes are not and will not be guided only by their doctors. Physicians may improve the quality of life of their patients and help them

ÖZ

Amaç: Bu çalışmanın amacı poliklinikte takipli romatoloji hastalarının hastalıklarının tedavisi hakkında internette araştırma yapma oranlarını, internetin hastaların tedavi ve takiplerine etkisini araştırmak ve hastaların rehber olarak kullandıkları internet sitelerinin güvenilirliklerini belirlemektir.

Yöntemler: Çalışma popülasyonu romatoid artrit, ankilozan spondilit ve fibromiyaljili hastalardan oluşmaktadır. Bu çalışmanın bir parçası olarak, anket yapılmış ve internet üzerinden hastalara hastalıkları hakkında araştırma yapıp yapmadıklarını kayıt altına alınmıştır. Anket yapıldıktan sonra, web sitelerinin güvenilirliğini de test edilmiştir. Bu web sitelerinin hastalıklarla ilgili ne derece yeterli ve güvenilir bilgi içerdiğini belirlemek için DISCERN puanlama sistemini kullanarak web sitelerini analiz edilmiştir.

Bulgular: Yüz yetmiş üç romatoloji hastasının geneline baktığımızda 102 olgu (%58,9) hastalığı hakkında bilgi almak için interneti kullanırken, 71 olgu (%41,04) internette araştırma yapmamıştı. DISCERN skorlamasında, ankette bulunan 15 soru eşliğinde internet siteleri değerlendirildiğinde 24'ü (%27,2) yüksek düzey (4-5 puan), 44'ü (%50) orta düzey (2-3 puan), 20'si (%22,7) kötü düzey (1 puan) kaliteye ve bilgi güvenilirliğine sahipti.

Sonuç: Dijital ilgi, romatizmal hastalıkların seyri ve tedavisini irdelemek isteyen hastalar tarafından da kullanılmaktadır. Uzun soluklu tedavi ve takip süreci olan bu hastaların yönlendirilmesinde, günümüzde ve gelecekte sadece doktor kontrolü altında olamadığının bilinmesi ve mevcut websitelerinin gerek sağlık bakanlığı gerekse ilgili dernekler

Address for Correspondence/Yazışma Adresi: Aysel Gürcan Atçı MD, Baltalimanı Metin Sabancı Bone and Joint Diseases Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, İstanbul, Turkey
Phone: +90 505 496 96 45 **E-mail:** lesyag2002@yahoo.com **ORCID ID:** orcid.org/0000-0001-9490-5406

Cite this article as/Atıf: Gürcan Atçı A, Tolu S. What is the Frequency of Internet Searches by Patients with Rheumatic Diseases? To What Degree are the Websites They Get Information from Reliable and What is the Effect of These Websites on Their Treatment?. İstanbul Med J 2020; 21(4): 275-80.

Received/Geliş Tarihi: 04.02.2020
Accepted/Kabul Tarihi: 09.05.2020

avoid unnecessary anxieties, if they regard the foregoing when they inform and instruct them.

Keywords: DISCERN, information reliability, internet, fibromyalgia, rheumatoid arthritis, ankylosing spondylitis

tarafından sıkı denetim altında tutulması ile hastaların yanlış bilgilendirilmesi ve yönlendirilmesinin önüne geçilebilir.

Anahtar Kelimeler: DISCERN, bilgi güvenirliliği, internet, fibromyalji, romatoid artrit, ankilozan spondilit

Introduction

Rheumatic diseases are frequently encountered in physical medicine and rehabilitation practices. The common rheumatic diseases in society are ankylosing spondylitis (AS), rheumatoid arthritis (RA) and fibromyalgia (FM). Among the patients with spondyloarthritis, AS is most common, affecting between 0.15% and 1.8% of the white population (1). However, RA -a seropositive disease- has a prevalence of 0.5%-1.0% in most of studies conducted in northern Europe and North America (2). In the general population, the prevalence of FM is defined to be 2%-4% according to the diagnostic criteria used (3).

The patients with rheumatic diseases should be regularly checked by physicians in order to initiate proper treatment for each case; monitor the efficiency, adverse effects and disease-associated complications of treatment; apply exercise and rehabilitation treatments for possible complications and ensure that these treatments become persistent.

In Turkey, 67% (81 million) of the population are internet users, whereas only 53% of the world uses the internet (4,5). However, it is observed that patients do not primarily approach medical professionals, but seek guidance from physicians only after making an internet search and being directed by the information provided on websites. This is because the frequency of the use of tablets and smartphones has increased over the last 20 years due to technological developments and ease of internet access (6,7). In the United States, 63% of internet users turn to the internet when they are faced with a health issue (7). There are more than 70,000 websites in the United States that provide information about health (8). Although such information is of vital importance to patients, many accessible sources fail to provide correct and comprehensive information and the readability rate of quality sources is low (9,10). The reason for low readability is that quality websites do not provide information at a language level that is familiar to the general population. While informing about the treatment of diseases, some websites may claim that a certain treatment choice prevails over the others, if they have a financial interest in it.

This study therefore aimed to determine the frequency of internet use of a certain number of patients with regard to the three most prevalent rheumatic diseases in clinical practice and more importantly to evaluate the quality of information available on the internet using the DISCERN scoring system.

Methods

The study population consisted of patients with RA, AS and FM, which are the three most common rheumatic diseases in clinical practice. Diagnosis of the patients was made using the ACR/EULAR 2010 criteria for RA (11), the 1984 modified New York criteria for AS (12) and the 1990 ACR classification criteria for FM (13).

As part of this study, we conducted a survey and recorded the age, gender, follow-up period, medication compliance, exercise habit, employment status and whether or not they searched the internet concerning their disease. Subsequently, we determined the proportion of internet use for each rheumatic disease according to the education level. Information was provided while taking the pain scores of patients and conducting a survey on the internet. Written consent was not obtained because the detailed medical and identifiable information of patients were not collected.

After the survey, we also tested the reliability of the websites used by these patients. An internet search was made on Google -the most popular search engine in Turkey and all over the world (14,15). We typed "RA treatment", "FM treatment" and "AS treatment" in the search engine in Turkish and analysed the first three pages and 30 websites using the DISCERN scoring system in order to determine to what degree these websites contained sufficient and reliable information concerning these diseases (16).

The DISCERN scoring system consisted of 15 key questions (Table 1a) and each question was scored from 1 to 5. The researcher evaluated a given

Table 1a. The DISCERN® instrument

Question 1: Are the aims clear?
Question 2: Does it achieve its aims?
Question 3: Is it relevant?
Question 4: Is it clear what sources of information were used to compile the publication (other than the author or producer)?
Question 5: Is it clear when the information used or reported in the publication was produced?
Question 6: Is it balanced and unbiased?
Question 7: Does it provide details of additional sources of support and information?
Question 8: Does it refer to areas of uncertainty?
Question 9: Does it describe how each treatment works?
Question 10: Does it describe the benefits of each treatment?
Question 11: Does it describe the risks of each treatment?
Question 12: Does it describe what would happen if no treatment is used?
Question 13: Does it describe how the treatment choices affect the overall quality of life?
Question 14: Is it clear that there may be more than one possible treatment choice?
Question 15: Does it provide support for shared decision-making?
Question 16: Based on the answers to all of the above questions, rate the overall quality of the publication as a source of information about treatment choices.

website according to the questions and assigned a score from 1 to 5 (Table 1b). The 16th question attempted to reveal the total score and the reliability of a given website. Each website was separately evaluated by two researchers, independent of the other websites. The study protocol was approved by the İstanbul Medipol University Ethics Committee (decision number: 158, date: 22/02/2019).

Statistical Analysis

Data were analysed using the IBM SPSS for Windows version 23.0 software (IBM Corp. Armonk, NY, USA). Frequency, percentage, mean, standard deviation, minimum and maximum were used for descriptive statistics. A value of $p<0.05$ was considered statistically significant.

Results

This study included 73 patients (68 females and 5 males) with RA, between the ages of 26 and 73 and with a mean age of 53.47±10.17 years. Sociodemographic and disease-related characteristics of the patients are described in Table 2. The mean follow-up period was 9.28±6.18 years (range 5 months-30 years). Ninety-one percent used anti-rheumatic drugs. Fifty-four (73.9%) patients came for follow-up visits regularly. Of the patients, 34 (46.4%) had searched the internet concerning their disease (Table 2).

Fifty-six patients (52 females and 4 males) with FM, between the ages of 27 and 69 and with a mean age of 44.03±1.11 years were enrolled into the study. The mean follow-up period was 6.78±0.72 years (range 7 months-20 years). Forty-eight (85.7%) patients took medication for FM treatment and 32 (57.1%) patients complied with their follow-up visits. Forty-four (78.4%) patients did not do exercises regularly. Thirty-nine (69.6%) patients had conducted internet searches about FM (Table 2).

Forty-four patients (26 female and 18 males) with AS, between the ages of 21 and 72 and with a mean age of 40.02±1.70 years were included in the study. The mean follow-up period was 9.45±0.94 years (range 1 month- 0 years). Forty (91%) patients took medication for AS treatment and 32 (72.7%) patients complied with their follow-up visits. Half of the patients (50%) did exercises regularly. Twenty-nine (66%) patients had carried out internet searches about AS (Table 2). In total, we found that 102 (58.9%) patients out of 173 had used the internet to get information about their disease, whereas 71 (41.04%) patients did not make any search.

Table 1b. The DISCERN® Instrument-results

Low		**Moderate**		**High**
Serious or extensive shortcomings		Potentially important but no serious shortcomings		Minimal shortcomings
1	2	3	4	5

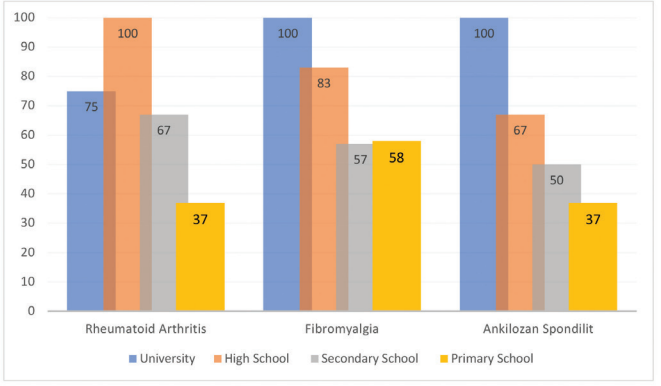
Table 2. Sociodemographic and disease-related characteristics of the patients

	Rheumatoid arthritis n=73	**Ankylosing spondylitis n=44**	**Fibromyalgia n=56**
Gender, F/M	68/5	26/18	52/4
Age, years (mean ± SD)	53.47±10.17	40.02±1.70	44.03±1.11
Educational level, n (%)			
Illiterate	7 (9.8)	1 (2.2)	-
Primary school	46 (63.0)	16 (36.3)	34 (60.7)
Secondary school	6 (8.2)	4 (9.0)	7 (12.5)
High school	10 (13.6)	12 (27.2)	12 (21.4)
University	4 (5.4)	11 (25.0)	3 (5.3)
Employment status, n (%)			
Employed	16 (22.0)	26 (59.0)	11 (19.7)
Unemployed	57 (78.0)	18 (41.0)	45 (80.3)
Exercise habit, n (%)	-	22 (50.0%)	44 (78.4)
Length of follow-up, (mean ± SD)	9.28±6.18	9.45±0.94	6.78±0.72
Patients currently taking anti-rheumatic drugs, n (%)	77 (91.8)	40 (91.0)	48 (85.7)
Compliance with follow-up visits, n (%)			
Yes	54 (73.9)	32 (72.7)	32 (57.1)
No	19 (26.1)	12 (27.3)	24 (42.9)
İnternet search for medical information, n (%)			
Yes	34 (46.4)	29 (66.0)	39 (69.6)
No	39 (53.9)	15 (34.0)	17 (30.4)

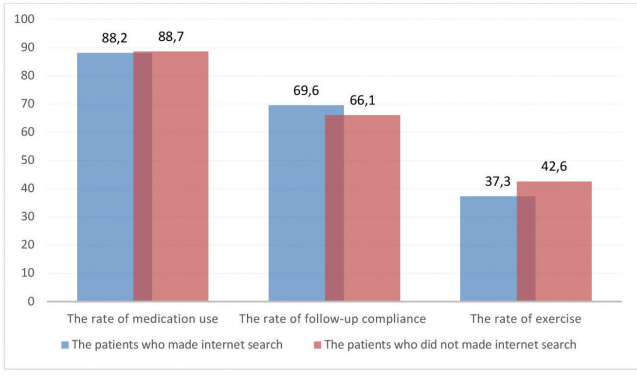
F/M: female/male, SD: standard deviation

The rate of the internet searches for the rheumatic diseases according to educational levels are shown in Graphic 1. The rate of medication use, follow-up compliance and exercise habits of the patients according to internet use are shown in Graphic 2. The question concerning exercise was only addressed to the patients with FM and AS.

We determined to what degree the websites containing information on RA, FM and AS hosted sufficient and reliable information by using the DISCERN scoring system. Out of 90 websites, 88 were used for the analysis because the other 2 websites were inaccessible. According to the search results, the top two were the websites of health institutions and physicians (Table 3). In the first part of the DISCERN scoring system, 79 (89.7%) websites out of 88 clearly defined their purpose, the information they contained or to whom they were addressed. On the contrary, only 59 (67%) websites could achieve their purpose of enlightening the patients about the treatment of rheumatic diseases. Of these, 24 (27.2%) websites could provide appropriate and accurate answers to the possible questions which might be raised by patients with rheumatic diseases. Only 15 (17.0%) websites gave references that the information provided was proven, whereas 13 (14.8%) indicated the reference publication and website revision dates. The information was consistent and neutral only on 20 (22.7%) websites. These benefited from many sources of information that were neutral and evaluated multiple treatment choices, weighing their pros and cons. However, only 8 (9%) websites directed users to other sources which could provide more detailed information concerning the treatment of rheumatic diseases.



Graphic 1. The rate of internet searches for the rheumatic diseases according to educational levels



Graphic 2. The rate of medication use, follow-up compliance and exercise habits of the patients according to internet use

Table 3. Website author classification and author definition

Author Classification	Definition	Number (%)
Healthcare	Websites affiliated with a government or private healthcare facility	27 (30.6%)
News	Websites affiliated with organisations dealing with news	21 (23.8%)
Personal	Non-physicians with no institutional or organisational affiliation	13 (14.7%)
Physician	Individual physicians with no healthcare facility affiliation	24 (27.2%)
Unidentified	Dead links or otherwise unidentifiable websites	3 (3.4 %)

In the second part of the DISCERN scoring system, it was inferred that 11 (12.5%) websites out of 88 provided descriptions of how the recommended treatment methods exerted their effect on the body. There were 6 (20.6%) websites for RA, 2 (6.6%) for AS and 2 (6.6%) for FM that gave detailed information on the benefits of each treatment method and only 10 (11.3%) websites in total, enlightened users about the risk of treatment. There were 22 (25%) websites that informed about the conditions which may arise if the patients with rheumatic diseases avoided or postponed their treatment. On the contrary, only 9 (10%) websites stated how treatment options changed the quality of life, what may arise in time and what may be the effects on family and friends. Forty-one (46.5%) websites expressed that there might be other treatment options for the three rheumatic diseases. Similarly, 25 (28.4%) websites gave descriptive information, which suggested that patients should seek help from their circle and health professionals in order to choose a treatment regime.

In the third part of the DISCERN scoring system, the aforementioned websites were evaluated using 15 questions in the survey. Consequently, it was inferred that of these websites, 24 (27.2%) had high-level (4-5 points), 44 (50%) had medium-level (2-3 points) and 20 (22.7%) had poor-level (1 point) quality and reliability.

Discussion

After being diagnosed with one of the three rheumatic diseases, the treatment processes of many patients continue throughout their lifetime. The longevity of treatments, density of medications, adverse effects that may appear because of medications and misguidance by their circle lead patients to seek alternative treatment methods and conduct internet search, which is the most easily accessible tool today. Indeed, 58% of the patients we monitored had made an internet search concerning their disease. In our study, the rate of conducting research over the internet in the FM patient group was the highest (69.6%) and the desire to learn associated with the disease in these patients could be attributed to the more common occurrence of obsessive personality structure in patients with FM compared to the general population (17).

Search engines are used to seek information over the internet. As a search engine, Google is used by more than 90% of internet users (14). It is observed that internet users generally evaluate the first three pages

and the top 30 websites when they carry out a search on any subject (18). In this study, we evaluated the top 90 websites from the first three pages that appeared on the search engine when we typed each of the aforementioned rheumatic diseases. Out of 90 websites, 88 were used for the analysis. The other 2 websites were inaccessible. However, it would have contributed to the reliability if other search engines were included and if 50 websites were scanned for each of the three diseases. In addition, the words typed by the patients in the search engine when they carried out a searched for their rheumatic disease is not clearly known. Keywords such as soft-tissue rheumatism, inflammatory articular rheumatism and inflammatory AS might have been used. In this study, we scanned Turkish websites in consideration of the patients.

According to the DISCERN scoring system, these websites had high-level (27.2%), medium-level (50.0%) and poor-level (22.7%) quality and reliability. The results demonstrated that the top two were the websites of health institutions and physicians. Nevertheless, it could be more revealing to examine the reliability and sufficiency of the websites according to their writers. In another study, physicians' personal websites showed that their ratings were higher than others (19).

As a result of the surveys that we applied to the 173 monitored patients with rheumatic diseases after website evaluations, it was seen that 102 (58.9%) patients used the internet in order to get information about their diseases. However, it was also established that internet use did not affect the follow-up of these patients who had to be checked regularly. Similarly, there was no significant difference in the rates of medication use. Exercise level -an important factor especially in the treatment of AS and FM- was 37.3% among internet users, whereas it was 42.6% among patients who did not conduct internet search for medical information. Having expressed the foregoing, there are various issues to consider about whether the websites over the internet are updated, correct, neutral and comprehensive or how they influence patients.

Conclusion

As a result, a digital interest that has gradually increased in recent years comes into question when patients desire to have information on the course and treatment of their rheumatic diseases. It should be acknowledged that patients with long-term treatment and follow-up processes are not and will not be guided only by their doctors. Therefore, it may prevent misinformation and misguidance if these websites are strictly inspected by both the Ministry of Health and relevant associations. Furthermore, physicians may improve the quality of life of their patients and help them avoid unnecessary anxieties, if they regard the foregoing when they inform and instruct them.

Ethics

Ethics Committee Approval: The study protocol was approved by the İstanbul Medipol University Ethics Committee (decision number: 158, date: 22/02/2019).

Informed Consent: Written consent was not obtained because the detailed medical and identifiable information of patients were not collected.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - A.G.A., S.T.; Concept - A.G.A., S.T. ; Design - A.G.A., S.T. ; Data Collection or Processing - A.G.A., S.T. ; Analysis or Interpretation - A.G.A. ; Literature Search - A.G.A., S.T. ; Writing - A.G.A.

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

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

References

1. Zochling J, Smith EU. Seronegative spondyloarthritis. Best Pract Res Clin Rheumatol 2010; 24: 747-56.
2. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. Autoimmun Rev 2005; 4: 130-6.
3. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken) 2010; 62: 600-10.
4. Dijilopedi. 2018 Türkiye İnternet Kullanım ve Sosyal Medya İstatistikleri. Available from URL: https://dijilopedi.com/2018-turkiye-internet-kullanim-ve-sosyal-medya-istatistikleri/ (last accessed 2019 Jan 18), 2018.
5. Dijilopedi. 2018 İnternet Kullanım ve Sosyal Medya İstatistikleri. Available from URL: https://dijilopedi.com/2018-internet-kullanimi-ve-sosyal-medya-istatistikleri/ (last accessed 2019 Jan 18), 2018.
6. Eng TR, Maxfield A, Patrick K, Deering MJ, Ratzan SC, Gustafson DH. Access to health information and support: a public highway or a private road? JAMA 1998; 280: 1371-5.
7. Pew Research Center: More online, doing more: 16 million newcomers gain Internet access in the last half of 2000 as women, minorities, and families with modest incomes continue to surge online. Available from URL: https://www.pewresearch.org/internet/2001/02/18/more-online-doing-more/ (last accessed 2016 June 26), 2001.
8. Grandinetti DA. Doctors and the web: help your patients surf the net safely. Med Econ 2000; 77: 186-8, 194-6, 201.
9. Daraz L, MacDermid JC, Wilkins S, Gibson J, Shaw L. The quality of websites addressing fibromyalgia: An assessment of quality and readability using standardised tools. BMJ Open 2011; 1: e000152.
10. Cline RJ, Haynes KM. Consumer health information seeking on the Internet: The state of the art. Health Educ Res 2001; 16: 671-92.
11. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an american college of rheumatology/european league against rheumatism collaborative initiative. Arthritis Rheum 2010; 62: 2569-81.
12. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis: a proposal for modification of the New York criteria. Arthritis Rheum 1984; 27: 361-8.
13. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the Multicenter Criteria Committee. Arthritis Rheum 1990; 33: 160-72.
14. Net Applications. Market Share Statistics for Internet Technologies. Available from: http://www.netmarketshare.com (last accessed 2016 June 26), 2014.
15. Huberman BA, Pirolli PLT, Pitkow JE, Lukose RM. Strong regularities in World Wide Web surfing. Science 1998; 280: 95-7.

16. Charnock D, Shepperd S, Needham G, Gann R. DISCERN: An instrument for judging the quality of written consumer health information on treatment choices. J Epidemiol Community Health 1999; 53: 105-11.

17. Galvez-Sánchez CM, Duschek S, Reyes del Paso GA. Psychological impact of fibromyalgia: current perspectives. Psychol Res Behav Manag 2019; 12: 117-27.

18. Samanci Y, Celik SE. Low Back Pain and Internet: Infopollution. Turk Neurosurg 2017; 27: 804-8.

19. Atci, IB, Yilmaz, H, Kocaman, U, Samanci MY. An evaluation of internet use by neurosurgery patients prior to lumbar disc surgery and of information available on internet. Clin Neurol Neurosurg 2017; 158: 56-9.

İstanbul Med J 2020; 21(4): 281-9
DOI: 10.4274/imj.galenos.2020.46667

Protective Effects of Imatinib and Ginkgo Biloba on Cisplatin-induced Ovarian Damage in Rats

İmatinib ve Ginkgo Bilobanın Sıçanlarda Sisplatin Kaynaklı Over Hasarı Üzerine Koruyucu Etkilerinin İncelenmesi

Önder Sakin[1], Ali Doğukan Anğın[1], Kazibe Koyuncu[1], Muzaffer Seyhan Çıkman[1], Kayhan Başak[2], Asuman Orçun Kaptanağası[3]

[1]İstanbul Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey
[2]İstanbul Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Pathology, İstanbul, Turkey
[3]İstanbul Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Biochemistry, İstanbul, Turkey

ABSTRACT

Introduction: In our study we aimed to observe the protective effects of imatinib and ginkgo biloba (GB) on cisplatin (CP)-induced ovarian damage in rats.

Methods: Thirty-two female rats were included and assigned to four groups. Group 1 had no medication. Their ovaries were removed for examination and the serum Anti-Mullerian hormone (AMH) levels were measured. Group 2 received a single dose of 7.5 mg/kg intramuscular CP. Group 3 received a single dose of 7.5 mg/kg oral imatinib and 30 minutes later, a single dose of 7.5 mg/kg intramuscular CP was administered. Group 4 received 80 mg/kg oral GB for 10 days. Sixty minutes after the first administration of the GB, a single dose of 7.5 mg/kg intramuscular CP was administered. The ovaries and serum AMH levels of the rats were assessed after 10 days of observation.

Results: Comparing group 1 and 2 showed that the total histopathological ovarian damage scores increased in the latter (p=0.044). This group also had decreased primordial follicles, preantral follicles and serum AMH (p=0.001, p=0.004 and p<0.001 respectively). In group 3, total histopathological ovarian damage score increased (p=0.020), and a reduction in primordial follicles (p=0.008) and serum AMH levels (p<0.001) was observed. In group 4, total histopathological ovarian damage score increased (p=0.016) as in groups 2 and 3. There was also a reduction in primordial follicles, preantral follicles and serum AMH levels (p<0.00, p=0.010 and p<0.001 respectively).

Conclusion: It was concluded that imatinib and GB were not effective in preventing CP-induced ovarian damage in rats.

Keywords: Cisplatin, imatinib, ginkgo biloba, Anti-Mullerian hormone, ovary, rat

ÖZ

Amaç: Çalışmamızda, imatinib ve ginkgo bilobanın (GB) sıçanlarda sisplatin (CP) kaynaklı over hasarı üzerindeki koruyucu etkilerini gözlemlemeyi amaçladık.

Yöntemler: Çalışmamıza toplam 32 erişkin dişi rat alındı ve 4 gruba ayrıldı. İlk gruba ilaç verilmedi. Muayene için sıçanların overleri çıkarıldı ve serum Anti-Mullerian hormon (AMH) seviyeleri ölçüldü. Grup 2'ye tek doz 7,5 mg/kg intramüsküler CP verildi. On günlük gözlemden sonra, overler ve sıçanların serum AMH seviyeleri değerlendirildi. Grup 3'e tek doz 7,5 mg/kg oral imatinib verildi ve 30 dakika sonra, tek doz 7,5 mg/kg intramüsküler CP uygulandı. Grup 4 on gün boyunca 80 mg/kg oral GB aldı. GB ilk uygulamasından 60 dakika sonra, tek bir doz 7,5 mg/kg intramüsküler CP uygulanmıştır. Gruplar ve grup 4'ün overleri ve serum AMH düzeyleri, 10 günlük gözlemden sonra değerlendirildi.

Bulgular: Grup 2'de total histopatolojik over hasarı skoru grup 1'e göre arttı (p=0,044). Ayrıca grup 2'de primordiyal foliküller, preantral foliküller ve serum AMH düzeyleri azaldı (sırasıyla, p=0,001, p=0,004 ve p<0,001), 3. grupta, aynı zamanda toplam histopatolojik over hasarı skoru (p=0,020) arttı. Primordiyal foliküllerde (p=0,008) ve serum AMH düzeylerinde azalma gözlendi (p<0,001). Grup 4'te toplam histopatolojik over hasarı skoru grup 2 ve grup 3'te olduğu gibi arttı (p=0,016). Ayrıca primordiyal foliküllerde, preantral foliküllerde ve serum AMH düzeylerinde azalma olduğu gözlendi (p<0,00, p=0,010 ve sırasıyla p<0,001).

Sonuç: İmatinib ve GB'nin sıçanlarda CP'nin neden olduğu yumurtalık hasarını önlemede etkili olmadığı sonucuna varıldı.

Anahtar Kelimeler: Sisplatin, imatinib, ginkgo biloba, Anti-Mullerian hormon, over, sıçan

Address for Correspondence/Yazışma Adresi: Önder Sakin MD, İstanbul Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey
Phone: +90 532 671 56 66 **E-mail:** sakin-onder@hotmail.com **ORCID ID:** orcid.org/0000-0001-6036-9975

Cite this article as/Atıf: Sakin Ö, Anğın AD, Koyuncu K, Çıkman MS, Başak K, Orçun Kaptanağası A. Protective Effects of Imatinib and Ginkgo Biloba on Cisplatin-induced Ovarian Damage in Rats. İstanbul Med J 2020; 21(4): 281-9.

Received/Geliş Tarihi: 01.12.2019
Accepted/Kabul Tarihi: 11.05.2020

Introduction

Cisplatin (CP) is one of the first chemotherapy drugs in cancer treatment. CP is also known as "the penicillin of cancer" as it is a widely used chemotherapeutic agent in the medical management of cancers worldwide. CP use in clinical practice has increased day by day after its approval of the Food and Drug Administration for cancer treatment in 1978 (1). Lung, head and neck, ovarian, cervical, bladder and testicular tumours are the most common tumours treated with CP (2). DNA is the main target of CP. CP interferes with DNA synthesis and repair mechanisms, causing DNA damage and subsequently inducing apoptosis in tumours. The damage in DNA synthesis affects especially blood cells, germ cells and young cells (3).

CP is one of the most effective chemotherapeutic agents especially in childhood cancers and the average cure rate is 85% in literature (4,5). On the other hand, CP has some disadvantages because it interferes with DNA repair mechanisms. The incidence of secondary tumours mostly in proliferative organs is higher in patients receiving CP, especially at young ages (6). This is one of the limiting features of CP. At this point CP-induced ovarian damage appears to be a very important side effect, especially for women who want to preserve ovarian functions (7). CP-induced ovarian damage may cause deterioration in quality of life and increase in treatment costs, from ovarian failure and infertility (8).

It is also known that CP induces the production of free oxygen radicals, which have cytotoxic effects on normal cells and causes oxidative stress throughout the body (9,10). Some evidence found that antioxidant substances reduce organ damage from oxidative stress caused by CP (11-13).

Imatinib is a competitive tyrosine kinase inhibitor (TKI) and generally used in cancer therapy (14). It is a TKI, inhibiting Abelson tyrosine kinase (c-abl), platelet derived growth factor receptor and receptor tyrosine kinase (15). Imatinib can affect all basic cellular functions (cell signalling, proliferation and differentiation), including ovarian follicles (16,17). In literature, it has been proposed as a medication to prevent primordial follicle loss induced by CP, based on its ability to inhibit c-abl kinase inhibitor (18,19). However, further studies are required on imatinib co-administration to prevent ovarian functions in CP treatment (20).

In recent studies, some antioxidant plants have been shown to have preservative effects against chemotherapy-induced reproductive organ damage (21). Ginkgo biloba (GB) has been used in traditional Chinese medicine for 5,000 years. It is a potent antioxidant and directly effective on free oxygen radicals (22). Besides the antioxidant effects of GB, its anticancer effects have been discussed in some publications (23,24).

In the current study, we aimed to investigate whether imatinib and GB, have protective effects on CP-induced ovarian damage.

Methods

This is an experimental animal study. In May 2019, the research was conducted after approval from the animal experiments local ethics committee of the Üsküdar University (no: 2019-05, date: 15.02.2019).

Animals Used in the Research

In this study, female wistar albino rats of the norvegicus species were used. The weighed from 219 to 265 grams, and were aged between 10 and 12 weeks. Four to five rats were placed in each cage. They received light for 12 hours between 8 am and 8 pm. They had unrestricted access to tap water and standard rodent pellet food at an average room temperature of 21 to 23 degrees. Humidity rate was kept between 40 and 50 percent.

Experimental Groups

Group 1 (the control group): These rats underwent a laparotomy at baseline and the ovaries were removed. Blood was drawn from the inferior vena cava for Anti-Mullerian hormone (AMH) testing.

Group 2 (the CP group): Rats received CP intramuscularly at a dose of 7.5 mg/kg at baseline (25) and underwent an oophorectomy at the end of day 10. At least 2-3 mm^3 of blood was drawn from the inferior vena cava for AMH testing.

Group 3 (the CP + imatinib group): Thirty minutes after the first dose of imatinib, rats received intramuscular CP at a dose of 7.5 mg/kg. They then received oral imatinib (Glivec®, Novartis, İstanbul, Turkey) for 10 days at a dose 7.5 mg/kg (18,20). Both ovaries were removed surgically at the end of day 10. At least 2-3 mm^3 of blood was drawn from the inferior vena cava for AMH testing.

Group 4 (the CP + GB group): Sixty minutes after the first administration of GB, rats received CP at a dose of 7.5 mg/kg intramuscularly. They additionally received GB (Ginkgo biloba leaf extract, Solgar, İstanbul, Turkey) orally, dissolved in distilled water, for 10 days at a dose 80 mg/kg (26). Both ovaries were removed surgically at the end of day 10, and at least 2-3 mm^3 of blood was drawn from the inferior vena cava for AMH testing.

Cisplatin Dose and Preparation

CP was administered intramuscularly only at baseline at a dose of 7.5 mg/kg. While preparing the drug; we used the central drug preparation unit of our hospital (with Robotic Chemotherapy Drug Preparation System) in a closed environment where microbiological contamination and employee exposure risks are eliminated under conditions that comply with national and international standards. These standards included: negative pressure indoor air environment complying with ISO 5, Class 100 and GMP Class A, double HEPA filter air cleaning system, safe waste management system, high capacity laminator current and dose sensitivity information (gravimetric and volumetric) measurement and the barcode system.

Operational Procedures

Powder free sterile latex gloves were used in all surgical procedures. After rats were decapitated, blood samples were taken for AMH hormone evaluation. Then laparotomy was performed in the supine position and oophorectomy was done. Operations were completed between 5 and 10 minutes to avoid the drying effects of room air (Figure 1).

Histopathological Examination

All examinations were performed by the same pathologist blindly. Removed ovaries were put into 10% formalin. Paraffin blocks were prepared within 24 hours after treatment. Five micrometre tissue sections were sampled and follicle examination in each ovarian tissue was made by taking five different sections. Tissues were stained with haematoxylin eosin and examined by light microscopy (Olympus Clinical Microscope, Tokyo, Japan). Paraffin blocks were sectioned using a microtome blade (Leica, Nussloch, Germany).

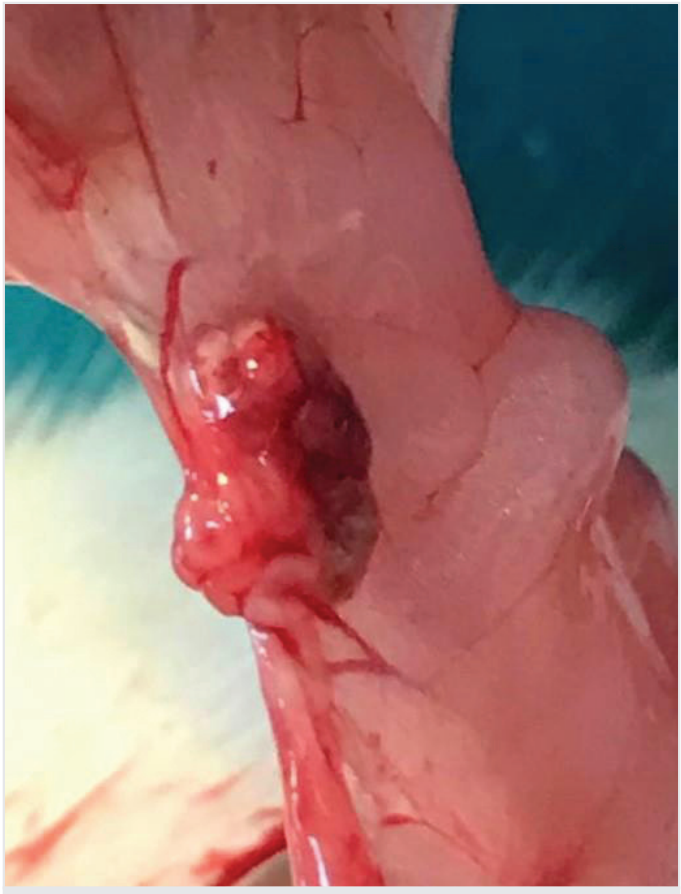


Figure 1. Excision of the ovary

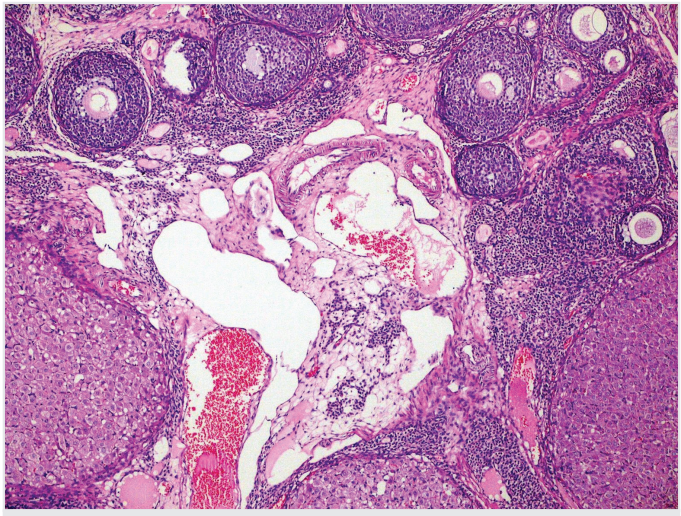


Figure 2. Oedema and vascular congestion x200 haematoxylin eosin

Histopathological injury scores were evaluated as described by Celik et al. (27). Cellular degeneration, vascular congestion, oedema, haemorrhage and inflammation were examined. The evaluations were graded from 0 to 4.

Grade 0: No abnormal findings were detected. Grade 1: mild vascular congestion, mild oedema, absence of haemorrhage or leukocyte infiltration. Grade 2: moderate vascular congestion, moderate oedema, absence of haemorrhage or leukocyte infiltration. Grade 3: severe vascular occlusion, severe oedema, minimal leukocyte infiltration and minimal haemorrhage. Grade 4: severe vascular occlusion, severe oedema, leukocyte infiltration and haemorrhage (Figure 2).

To evaluate ovarian reserves, all follicles were examined as described by Parlakgumus et al. (28). Primordial, primary, secondary (preantral), tertiary (antral) and atretic follicles were counted (Figure 3, 4). A primordial follicle was defined as oocyte with epithelial cell layer in

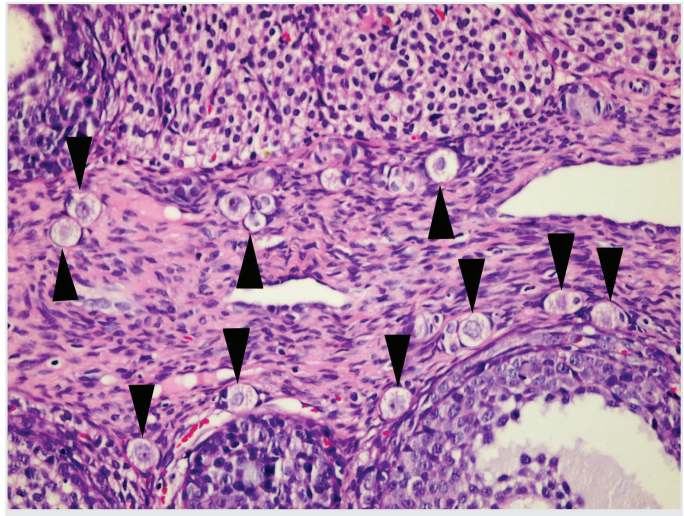


Figure 3. Primordial follicles x400 haematoxylin eosin

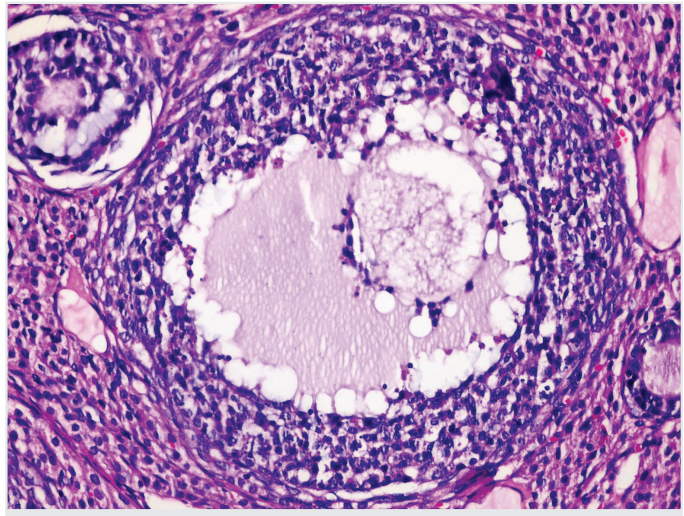


Figure 4. Degenerated follicle x400 haematoxylin eosin

only one layer. A primary follicle was defined as a follicle surrounded by one or more layers of cuboidal granulosa cells. A secondary (preantral) follicle was defined as a follicle consisting of antrum folliculi and zona pellucida surrounded by two or more cell layers. Tertiary follicles were defined as follicles with layers of antrum, stratum granulosum and surrounding cumulus oophorus. For the atretic follicle, the basement membrane that separated the oocyte from granulosa cells was often thickened to become the glassy membrane. Fibrous material replaced the granulosa cells and loss of cohesion could also be observed in granulosa cells.

Anti-Mullerian Hormone Assays

Blood samples were collected into tubes containing lithium heparin (BD Vacutainer Plasma tubes, Manchester, England). The concentration of the Lithium Heparin additive in these tubes was 17 international units of heparin/mL of blood. Blood samples were centrifuged within 30 minutes of sampling. After 15 minutes of centrifugation at 1000xg, serum was removed and remaining plasma was transferred into an eppendorf tube and stored frozen at -20 °C until the time of analysis AMH concentrations were measured in "ng/mL" of plasma using the enzyme-linked immunosorbent assay method. The rat AMH kit used in study had a sensitivity of 0.10 g/mL, a detection range of 0.16 to 10 ng/mL and a coefficient of variation less than 10% (Elabscience®, Rat AMH kit; Houston, Texas, ABD). The laboratory technician of the university hospital laboratory was blinded to the study groups All samples were analysed in the same assay.

Statistical Analysis

All the data were analysed by SPSS 25.0 (SPSS Inc., Chicago, IL, USA). Results were presented as number, percentage, average and standard deviation. One-way ANOVA, Kruskal-Wallis and Tamhane post hoc tests were used for comparison between the groups. The correlations between AMH and other variables were investigated by Spearman correlation analysis. Statistical significance level was accepted as $p<0.05$.

Results

There were no significant differences between the study groups concerning rat weights (ANOVA F=0.410; p=0.747) (minimum 219 grams, maximum 265 grams). Histopathological features of the groups were compared and shown in Table 1. The control group showed no increase in ovarian damage scores. Tamhane post hoc analysis revealed significant subgroup differences concerning oedema between the control and CP groups (p=0.032), concerning vascular congestion between control and both CP (p=0.023) and CP + GB groups (p=0.007). Also, the total damage score was significantly different between the control group and CP (p=0.044), CP + imatinib (p=0.020), as well as CP + GB groups (p=0.016). Tamhane post hoc comparisons are given in Table 2. Group 1 with normal ovaries (score: 0.13) had the lowest ovarian damage scores and group 2 with only CP had the highest scores (score: 3.47). In the follicle count, most follicles were seen in the control group (group 1), while the least follicles was seen in CP + GB group (group 4).

Follicle counts in the study groups were compared and is shown in Table 3. Tamhane post hoc analysis revealed significant subgroup differences in the number of primordial follicles between the control and CP + imatinib (p=0.008), CP alone (p=0.001), as well as CP + GB groups (p<0.001). There were significant differences in the number of secondary follicles between the control group and both CP (p=0.004) as well as CP + GB groups (p=0.010).

A significant correlation between AMH levels and over volume in the control group (Table 4). Also, positive correlations were detected between the total damage score and the number of atretic follicles in the CP group.

The mean AMH level was highest in the control group (2.73 ng/mL), and lowest in CP + GB group (0.11 ng/mL). AMH values were significantly lower in all groups compared to control rats (p<0.001 in all). A significant correlation between AMH levels and over volume in the control group (group 1). Also, positive correlations were detected between the total damage score and the number of atretic follicles in the CP group (group 3) (Table 5).

Discussion

Some chemotherapeutics used for cancer treatment are major causes of ovarian damage. Prevention of primordial follicle destruction and premature ovarian ageing will be beneficial for children, adolescents and young women with fertility desire. Primordial follicles are very sensitive to radiotherapy and chemotherapy. Follicular reserve decreases and premature ageing occurs (18), especially during chemotherapy. Both *in vitro* and *in vivo* studies have shown that CP administration clearly causes increased free oxygen radicals (9,10). In animals treated with CP,

Table 1. Comparison of histopathological damage scores of control vs Cisplatin, Cisplatin + Imatinib and Cisplatin + Ginkgo biloba groups

	Control			Cisplatin + Imatinib			Cisplatin			Cisplatin + Gingko biloba				
		Percentile			Percentile			Percentile			Percentile			
	Median	25	75	Median	25	75	Median	25	75	Median	25	75	H*	p
Oedema	0	0	0	1	0	2	2	1	2	0	0	1	12.067	0.007
Vascular congestion	0	0	0	1	0	1	2	1	2	1	1	1	12.535	0.006
Inflammation	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Cellular degeneration	0	0	0	0	0	0	0	0	1	0	0	1	3.576	0.311
Haemorrhage	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Total damage score	0	0	0	3	1	3	3	3	5	1	1	2	13.672	0.003

*Kruskal-Wallis test

free oxygen radicals cause multiple cellular changes and organ damage. Data from animal studies indicate that if oxidative stress is blocked, organs will be preserved (9,11).

In another study, imatinib was found to be effective in preventing primordial oocyte damage caused by CP or other c-abl inhibitors. Because of this, it was suggested that imatinib administration with chemotherapeutics might be considerable (5).

Imatinib acts by inhibiting c-abl, a TKI. Thus, imatinib has been shown to cause the accumulation of p63, which is an oocyte-specific homologue of p53 and activates apoptosis in DNA damage (18,29,30). Imatinib affects

Table 2. Post-hoc bi-variate comparison of the variables using the Tamhane's test

					95% Confidence Interval	
Dependent Variable	**(I) Group**	**(J) Group**	**Mean Difference (I-J)**	**p**	**Lower Bound**	**Upper Bound**
Oedema	Cisplatin + Imatinib	Cisplatin	-0.455	0.942	-1.99	1.08
		Cisplatin + Gingko biloba	0.657	0.501	-0.55	1.87
		Control	1.035	0.096	-0.16	2.23
	Cisplatin	Cisplatin + Gingko biloba	1.112	0.132	-0.24	2.47
		Control	1.490	0.032	0.13	2.85
	Cisplatin + Gingko biloba	Control	0.378	0.377	-0.28	1.03
Vascular congestion	Cisplatin + Imatinib	Cisplatin	-0.477	0.875	-1.81	0.86
		Cisplatin + Gingko biloba	-0.095	1.000	-1.19	1.00
		Control	0.892	0.108	-0.17	1.96
	Cisplatin	Cisplatin + Gingko biloba	0.381	0.909	-0.81	1.57
	Control	Control	1.369	0.023	0.20	2.54
	Cisplatin + Gingko biloba	Control	0.988	0.007	0.31	1.67
Cellular degeneration	Cisplatin + Imatinib	Cisplatin	-0.367	0.912	-1.54	0.80
		Cisplatin + Gingko biloba	-0.137	0.999	-1.11	0.84
		Control	0.244	0.695	-0.35	0.84
	Cisplatin	Cisplatin + Gingko biloba	0.230	0.995	-1.05	1.51
		Control	0.611	0.470	-0.56	1.78
	Cisplatin + Gingko biloba	Control	0.380	0.720	-0.57	1.33
Total damage score	Cisplatin + Imatinib	Cisplatin	-1.298	0.790	-4.57	1.98
		Cisplatin + Gingko biloba	0.425	0.983	-1.43	2.28
		Control	2.038	0.020	0.33	3.75
	Cisplatin	Cisplatin + Gingko biloba	1.723	0.499	-1.51	4.95
		Control	3.336	0.044	0.09	6.58
	Cisplatin + Gingko biloba	Control	1.613	0.016	0.30	2.93

Table 3. Comparison of ovarian follicle counts and Anti-Mullerian hormone levels between groups

	Control			**Cisplatin + Imatinib**			**Cisplatin**			**Cisplatin + Gingko biloba**				
		Percentile			**Percentile**			**Percentile**			**Percentile**			
	Median	**25**	**75**	**Median**	**25**	**75**	**Median**	**25**	**75**	**Median**	**25**	**75**	**H***	**p**
Number of primordial follicles	12.00	11.00	14.00	5.00	3.00	8.00	4.00	3.00	9.00	4.00	3.00	6.00	16.753	0.001
Number of primary follicles	13.00	10.00	14.00	11.00	7.00	13.00	8.00	8.00	11.00	7.00	6.00	9.00	8.659	0.034
Number of secondary follicles	10.00	8.00	10.00	7.00	5.00	8.00	5.00	5.00	8.00	5.00	3.00	8.00	13.164	0.004
Number of tertiary follicles	8.00	7.00	10.00	6.00	6.00	7.00	8.00	7.00	10.00	9.00	7.00	10.00	4.94	0.176
Number of atretic follicles	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	1.00	1.00	0.00	2.00	3.047	0.384

*Kruskal-Wallis test

early folliculogenesis in the postnatal period and decreases activation of primordial follicle pool in rat ovaries, causing an increase in the expression of AMH proteins (31). Another recent study showed a novel finding that CP-induced damage is associated with increased expression of TAp63 phosphorylated at Ser395 and Ser160/162 residues in human ovary. So, imatinib use could not provide protection for human ovarian cells. Besides, it was stated that imatinib itself may be a gonadotoxic agent for ovarian follicles (32). However, further studies are needed to investigate the long-term outcomes and their effects on fertility.

Conclusion

It is not possible to clearly describe the success of imatinib in reducing ovarian damage induced by CP. In our study, total damage score increased with the use of both CP and imatinib (group 3) compared to

Table 4. Correlations between Anti-Mullerian hormone levels and variables

			Weight (gram)	Over volume (mm^3)	Total damage score	Number of atretic follicles
Cisplatin + Imatinib	Anti-Mullerian hormone level (ng/mL)	r	-0.303	-0.354	-0.255	-0.064
		p	0.466	0.389	0.543	0.881
	Weight (Gram)	r	-	-0.340	0.568	-0.380
		p	-	0.410	0.142	0.353
	Over volume (mm^3)	r	-	-	0.013	-0.390
		p	-	-	0.976	0.340
	Total damage score	r	-	-	-	-0.325
		p	-	-	-	0.432
Cisplatin	Anti-Mullerian hormone level (ng/mL)	r	0.108	0.025	-0.313	-0.536
		p	0.799	0.953	0.450	0.171
	Weight (Gram)	r	-	-0.692	-0.248	-0.332
		p	-	0.057	0.553	0.422
	Over volume (mm^3)	r	-	-	-0.393	-0.173
		p	-	-	0.336	0.681
	Total damage score	r	-	-	-	0.877**
		p	-	-	-	0.004
Cisplatin + Gingko biloba	Anti-Mullerian hormone level (ng/mL)	r	0.494	-0.037	-0.007	0.368
		p	0.213	0.931	0.988	0.370
	Weight (Gram)	r	-	0.393	-0.308	0.032
		p	-	0.336	0.458	0.941
	Over volume (mm^3)	r	-	-	-0.508	-0.594
		p	-	-	0.199	0.121
	Total damage score	r	-	-	-	0.311
		p	-	-	-	0.454
Control	Anti-Mullerian hormone level (ng/mL)	r	-0.012	0.717*	0.412	-0.620
		p	0.978	0.046	0.310	0.101
	Weight (Gram)	r	-	0.056	0.581	0.057
		p	-	0.895	0.131	0.894
	Over volume (mm^3)	r	-	-	0.257	0.000
		p	-	-	0.539	1.000
	Total damage score	r	-	-	-	-0.293
		p	-	-	-	0.482

*: Kruskal-Wallis test, **: Spearman correlation analysis

control ovaries (group 1) (p=0.020), and the number of primary follicles in group 3 decreased compared to group 1 (p=0.008). Also, the mean AMH level (0.19 ng/mL) significantly decreased (p<0.001).

GB has been shown to be an antioxidant with protective effects on CP-induced cellular damage. In a study by Chang et al. (33), the effect of GB on total ovarian follicle count, apoptotic indices and cytoplasmic protein levels were examined and its protective effects on ovarian reserve have been showed.

On the other hand, it was reported that GB inhibits growth in ovarian cancer cells and triggers apoptosis. It has been stated that GB combination with chemotherapeutics could provide a preventive strategy for infertility (21,34,35). CP and protective agents against CP-induced organ damages are current issues in cancer treatment in patients of reproductive age, but none of the studies in literature have examined the effect of CP treatment on ovarian damage scores, AMH levels, ovarian, preantral, antral and atretic follicles. In our study, vascular congestion (p=0.007) and total damage score (p=0.016) were increased compared to control

Table 5. Correlations between rat weights, over volume, total damage score, number of atretic follicles, and Anti-Mullerian hormone levels

			Weight (gram)	Over volume (mm^3)	Total damage score	Number of atretic follicles
Cisplatin + Imatinib	Anti-Mullerian hormone level (ng/mL)	r	-0.303	-0.354	-0.255	-0.064
		p	0.466	0.389	0.543	0.881
	Weight (Gram)	r	-	-0.340	0.568	-0.380
		p	-	0.410	0.142	0.353
	Over volume (mm^3)	r	-	-	0.013	-0.390
		p	-	-	0.976	0.340
	Total damage score	r	-	-	-	-0.325
		p	-	-	-	0.432
Cisplatin	Anti-Mullerian hormone level (ng/mL)	r	0.108	0.025	-0.313	-0.536
		p	0.799	0.953	0.450	0.171
	Weight (Gram)	r	-	-0.692	-0.248	-0.332
		p	-	0.057	0.553	0.422
	Over volume (mm^3)	r	-	-	-0.393	-0.173
		p	-	-	0.336	0.681
	Total damage score	r	-	-	-	0.877**
		p	-	-	-	0.004
Cisplatin + Ginkgo biloba	Anti-Mullerian hormone level (ng/mL)	r	0.494	-0.037	-0.007	0.368
		p	0.213	0.931	0.988	0.370
	Weight (Gram)	r	-	0.393	-0.308	0.032
		p	-	0.336	0.458	0.941
	Over volume (mm^3)	r	-	-	-0.508	-0.594
		p	-	-	0.199	0.121
	Total damage score	r	-	-	-	0.311
		p	-	-	-	0.454
Control	Anti-Mullerian hormone level (ng/mL)	r	-0.012	0.717*	0.412	-0.620
		p	0.978	0.046	0.310	0.101
	Weight (Gram)	r	-	0.056	0.581	0.057
		p	-	0.895	0.131	0.894
	Over volume (mm^3)	r	-	-	0.257	0.000
		p	-	-	0.539	1.000
	Total damage score	r	-	-	-	-0.293
		p	-	-	-	0.482

*: Kruskal-Wallis test, **Spearman correlation analysis

ovaries after the use of CP in combination with GB. The mean number of ovarian follicles was the least in the CP + GB group. Both primary ($p<0.001$) and preantral follicles ($p=0.01$) decreased and AMH levels were also significantly lower in the CP + GB group ($p<0.001$).

It is important how all the apoptotic indices, cytoplasmic protein levels, antioxidant mechanisms, enzymatic changes, histopathological damage scores, follicular examinations and ovarian reserve tests help us in cancer treatment in young patients of reproductive ages. And more importantly, these parameters have real clinical implications for reproductive organs and fertility. We investigated whether follicle count and AMH levels, which are the two most used parameters in the evaluation of fertility in the clinic, can be maintained with imatinib and GB in CP-treated rats.

In our study, we concluded that imatinib and GB were not effective in preventing CP-induced ovarian damage.

Ethics

Ethics Committee Approval: The study was conducted after approval from the animal experiments local ethics committee of the Üsküdar University (no: 2019-05, date: 15.02.2019). This study was conducted at the Animal Testing Laboratory of the University after the approval of the Ethics Committee.

Informed Consent: Experimental animal study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - Ö.S., A.D.A., K.K., M.S.Ç.; Concept - Ö.S., A.D.A., M.S.Ç., K.B.; Design - Ö.S., A.D.A., K.B.; Data Collection or Processing - Ö.S., A.D.A., K.K., M.S.Ç., A.O.K.; Analysis or Interpretation - Ö.S., K.B., A.O.K.; Literature Search - Ö.S., A.D.A., K.K.; Writing - Ö.S., K.K., K.B.

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

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

References

1. Raudenska M, Balvan J, Fojtu M, Gumulec J, Masarik M. Unexpected therapeutic effects of cisplatin. Mettallomics 2019; 11: 1182-99.
2. Rybak LP, Mukherjea D, Ramkumar V. Mechanisms of Cisplatin-Induced Ototoxicity and Prevention. Hear Res 2019; 40: 197-204.
3. Cheki M, Ghasemi MS, Rezaei Rashnoudi A, Erfani Majd N. Metformin attenuates cisplatin-induced genotoxicity and apoptosis in rat bone marrow cells. Drug Chem Toxicol 2019: 1-8.
4. Ekborn A, Laurell G, Ehrsson H, Miller J. Intracochlear administration of thiourea protects against cisplatin-induced outer hair cell loss in the guinea pig. Hear Res 2003; 181: 109-15.
5. Mukherjea D, Rybak LP. Pharmacogenomics of cisplatin-induced ototoxicity. Pharmacogenomics 2011; 12: 1039-50.
6. DE Araujo JG, Serra LSM, Lauand L, Kuckelhaus SAS, Sampaio ALL. Protective Effect of Melatonin on Cisplatin-induced Ototoxicity in Rats. Anticancer Res 2019; 39: 2453-8.
7. Dayangan Sayan C, Tulmac OB, Karaca G, Ozkan ZS, Yalcin S, Devrim T, et al. Could erythropoietin reduce the ovarian damage of cisplatin in female rats? Gynecological endocrinology 2018; 34: 309-13.
8. Wallace WH, Shalet SM, Crowne EC, Morris-Jones PH, Gattamaneni HR, Price DA. Gonadal dysfunction due to cis-platinum. Medical and pediatric oncology 1989; 17: 409-13.
9. Khan R, Khan AQ, Qamar W, Lateef A, Tahir M, Rehman MU, et al. Chrysin protects against cisplatin-induced colon. toxicity via amelioration of oxidative stress and apoptosis: probable role of p38MAPK and p53. Toxicol Appl Pharmacol 2012; 258: 315-29.
10. Vijayalakshmi B, Sesikeran B, Udaykumar P, Kalyanasundaram S, Raghunath M. Chronic low vitamin intake potentiates cisplatin-induced intestinal epithelial cell apoptosis in WNIN rats. World J Gastroenterol 2006; 12: 1078-85.
11. Longo V, Gervasi PG, Lubrano V. Cisplatin induced toxicity in rat tissues: the protective effect of Lisosan G. Food Chem Toxicol 2011; 49: 233-7.
12. Chtourou Y, Aouey B, Kebieche M, Fetoui H. Protective role of naringin against cisplatin induced oxidative stress, inflammatory response and apoptosis in rat striatum via suppressing ROS-mediated NF-kappaB and P53 signaling pathways. Chem Biol Interact 2015; 239: 76-86.
13. Kaygusuzoglu E, Caglayan C, Kandemir FM, Yildirim S, Kucukler S, Kilinc MA, et al. Zingerone ameliorates cisplatin-induced ovarian and uterine toxicity via suppression of sex hormone imbalances, oxidative stress, inflammation and apoptosis in female wistar rats. Biomed Pharmacother 2018; 102: 517-30.
14. Pytel D, Sliwinski T, Poplawski T, Ferriola D, Majsterek I. Tyrosine kinase blockers: new hope for successful cancer therapy. Anticancer Agents Med Chem 2009; 9: 66-76.
15. Steeghs N, Nortier JW, Gelderblom H. Small molecule tyrosine kinase inhibitors in the treatment of solid tumors: an update of recent developments. Ann Surg Oncol 2007; 14: 942-53.
16. Nilsson EE, Detzel C, Skinner MK. Platelet-derived growth factor modulates the primordial to primary follicle transition. Reproduction 2006; 131: 1007-15.
17. Merkwitz C, Lochhead P, Tsikolia N, Koch D, Sygnecka K, Sakurai M, et al. Expression of KIT in the ovary, and the role of somatic precursor cells. Progress in histochemistry and cytochemistry 2011; 46: 131-84.
18. Gonfloni S, Di Tella L, Caldarola S, Cannata SM, Klinger FG, Di Bartolomeo C, et al. Inhibition of the c-Abl-TAp63 pathway protects mouse oocytes from chemotherapy-induced death. Nat Med 2009; 15: 1179-85.
19. Maiani E, Di Bartolomeo C, Klinger FG, Cannata SM, Bernardini S, Chateauvieux S, et al. Reply to: Cisplatin-induced primordial follicle oocyte killing and loss of fertility are not prevented by imatinib. Nat Med 2012; 18: 1172-4.
20. Kerr JB, Hutt KJ, Cook M, Speed TP, Strasser A, Findlay JK, et al. Cisplatin-induced primordial follicle oocyte killing and loss of fertility are not prevented by imatinib. Nat Med 2012; 18: 1170-2.
21. Amin A, Abraham C, Hamza AA, Abdalla ZA, Al-Shamsi SB, Harethi SS, et al. A standardized extract of Ginkgo biloba neutralizes cisplatin-mediated reproductive toxicity in rats. Journal of biomedicine biotechnology 2012; 2012: 362049.
22. Trompezinski S, Bonneville M, Pernet I, Denis A, Schmitt D, Viac J. Gingko biloba extract reduces VEGF and CXCL-8/IL-8 levels in keratinocytes with cumulative effect with epigallocatechin-3-gallate. Archives of dermatological research 2010; 302: 183-9.
23. Oliveira D, Latimer C, Parpot P, Gill CIR, Oliveira R. Antioxidant and antigenotoxic activities of Ginkgo biloba L. leaf extract are retained after in vitro gastrointestinal digestive conditions. Eur J Nutr 2020; 59: 465-76.
24. Chang L, Liu T, Chai Z, Jie S, Li Z, Liu M, et al. lincRNA-p21 Mediates the Anti-Cancer Effect of Ginkgo Biloba Extract EGb 761 by Stabilizing E-Cadherin Protein in Colon Cancer. Med Sci Monit 2018; 24: 9488-96.
25. Pandir D, Kara O, Kara M. Protective effect of bilberry (Vaccinium myrtillus L.) on cisplatin induced ovarian damage in rat. Cytotechnology 2014; 66: 677-85.

26. Yildirim N, Simsek D, Kose S, Yildirim AGS, Guven C, Yigitturk G, et al. The protective effect of Gingko biloba in a rat model of ovarian ischemia/reperfusion injury: Improvement in histological and biochemical parameters. Adv Clin Exp Med 2018; 27: 591-7.

27. Celik O, Turkoz Y, Hascalik S, Hascalik M, Cigremis Y, Mizrak B, et al. The protective effect of caffeic acid phenethyl ester on ischemia-reperfusion injury in rat ovary. Eur J Obstet Gynecol Reprod Biol 2004; 117: 183-8.

28. Parlakgumus HA, Aka Bolat F, Bulgan Kilicdag E, Simsek E, Parlakgumus A. Atorvastatin for ovarian torsion: effects on follicle counts, AMH, and VEGF expression. Eur J Obstet Gynecol Reprod Biol 2014; 175: 186-90.

29. Livera G, Petre-Lazar B, Guerquin MJ, Trautmann E, Coffigny H, Habert R. p63 null mutation protects mouse oocytes from radio-induced apoptosis. Reproduction 2008; 135: 3-12.

30. Gonfloni S. DNA damage stress response in germ cells: role of c-Abl and clinical implications. Oncogene 2010; 29: 6193-202.

31. Asadi-Azarbaijani B, Santos RR, Jahnukainen K, Braber S, van Duursen MBM, Toppari J, et al. Developmental effects of imatinib mesylate on follicle assembly and early activation of primordial follicle pool in postnatal rat ovary. Reprod Biol 2017; 17: 25-33.

32. Bildik G, Acılan C, Sahin GN, Karahuseyinoglu S, Oktem O. C-Abl is not actıvated in DNA damage-induced and Tap63-mediated oocyte apoptosıs in human ovary. Cell Death Dis 2018; 9: 943.

33. Chang Z, Wang HL, Du H. Protective effect of Ginkgo flavonoids, amifostine, and leuprorelin against platinum-induced ovarian impairment in rats. Genet Mol Res 2014; 13: 5276-84.

34. Morgan S, Lopes F, Gourley C, Anderson RA, Spears N. Cisplatin and doxorubicin induce distinct mechanisms of ovarian follicle loss; imatinib provides selective protection only against cisplatin. PloS one 2013; 8: e70117.

35. Jiang W, Cong Q, Wang Y, Ye B, Xu C. Ginkgo May Sensitize Ovarian Cancer Cells to Cisplatin: Antiproliferative and Apoptosis-Inducing Effects of Ginkgolide B on Ovarian Cancer Cells. Integr Cancer Ther 2014; 13: Np10-7.

İstanbul Med J 2020; 21(4): 290-6
DOI: 10.4274/imj.galenos.2020.26429

Assessment of Nutritional Status of Hospitalised Geriatric Patients and its Relationship with Sarcopenia

Hastanede Yatan Geriatrik Hastaların Nütrisyonel Durumlarının Değerlendirilmesi ve Sarkopeni ile İlişkisinin Saptanması

Aysun Nazlı[1], Elvan Yılmaz Akyüz[2]

[1]University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Nutrition and Dietetics, İstanbul, Turkey
[2]University of Health Sciences Turkey, Hamidiye Faculty of Health Sciences, Department of Nutrition and Dietetics, İstanbul, Turkey

ABSTRACT

Introduction: Sarcopenia and malnutrition are geriatric syndromes that reduce quality of life and muscle function in old age. This study aimed to evaluate the nutritional status of geriatric patients, determine the status of sarcopenia, and investigate the relationship between them.

Methods: The study was conducted between November 2018 and April 2019 with 100 patients aged ≥65 years who were hospitalised in University of Health Sciences Turkey, İstanbul Training and Research Hospital. The demographic characteristics of the included patients were used to evaluate nutritional status and sarcopenia. The Mini Nutritional Assessment form was used, and anthropometric measurements, bioimpedance analysis method, hand grip strength and time walk test were performed. The patients' treatment clinics, hospitalisation indications, length of hospital stay and comorbidities were determined.

Results: The mean age of the patients was 71.8±6.2 years, and 35% and 65% were women and men, respectively. Malnutrition and risk of malnutrition were observed in 8% and 50% of the patients. In addition, sarcopenia was found in 5% of the patients. A significant relationship was determined among age, weight, height, body mass index (BMI), upper arm circumference measurement and nutritional status. Muscle function adequacy (p=0.00) and hand grip strength test results (p=0.002) were lower, and time walk test results (p=0.00) were longer in malnourished patients compared with those without malnutrition (p<0.05). Weight, BMI, muscle function, and adequacy of muscle mass were significantly lower in patients with sarcopenia compared with those without sarcopenia (p<0.05). The risk of malnutrition was 60% in patients with sarcopenia, and malnutrition in 8.4% of patients without sarcopenia, and malnutrition in 47.5%. The distribution of sarcopenia did not differ based on the nutritional status (p>0.05).

Conclusion: To prevent malnutrition and sarcopenia or their progress in hospitalised patients, nutritional status

ÖZ

Amaç: Sarkopeni ve malnütrisyon, yaşlılık sürecinde yaşam kalitesini ve kas fonksiyonunu azaltan geriatrik sendromlardır. Bu çalışmada hastanede yatan geriatrik hastaların nütrisyonel durumlarının değerlendirilmesi, sarkopeni durumunun saptanması ve aralarındaki ilişkinin incelenmesi amaçlanmıştır.

Yöntemler: Çalışma Kasım 2018 - Nisan 2019 tarihleri arasında Sağlık Bilimleri Üniversitesi İstanbul Eğitim ve Araştırma Hastanesi kliniklerinde yatan ≥65 yaş 100 hasta ile yürütülmüştür. Çalışmaya dahil edilen hastaların demografik özellikleri için veri toplama formu, nütrisyonel durumları ve sarkopeni varlığını değerlendirmek için; Mini Nütrisyonel Değerlendirme formu, antropometrik ölçümler, biyoimpedans analiz yöntemi, el kavrama kuvveti ve zamanlı kalk-yürü testi uygulanmıştır. Hastaların yatarak tedavi gördükleri klinik, yatış süre ve endikasyonu, yandaş kronik hastalık varlığı sorgulanmıştır.

Bulgular: Çalışmaya katılan hastaların yaş ortalamaları 71,8±6,2 yıl ve %35'i kadın, %65'i erkektir. Hastaların %8'inde malnütrisyon ve %50'sinde malnütrisyon riski olduğu tespit edilmiştir. Hastaların %5'inde sarkopeni saptanmıştır. Hastaların yaş, ağırlık, boy, vücut kütle indeksi (VKİ), üst kol çevresi ölçümü ile nütrisyonel durumları arasında anlamlı ilişki saptanmıştır (p<0,05). Malnütrisyonu olan hastalarda olmayan hastalara göre kas fonksiyon yeterliliği daha düşük bulunmuş (p=0,00), zamanlı kalk-yürü testi sonucu daha uzun saptanmış (p=0.00) ve el kavrama kuvvet test sonucunun daha düşük olduğu tespit edilmiştir (p=0,002). Sarkopenisi olan hastalarda sarkopenisi olmayanlara göre ağırlık, VKİ, kas fonksiyonu ve kas kütlesi yeterliliği anlamlı şekilde daha düşük bulunmuştur (p<0,05). Sarkopenisi olan hastaların %60'ında malnütrisyon riski, sarkopenisi olmayan hastaların %8,4'ünde malnütrisyon ve %47,5'inde malnütrisyon riski saptanmıştır. Hastaların nütrisyonel durumlarına göre sarkopeni varlığı dağılımları farklılık göstermemiştir (p>0,05).

Sonuç: Hastanede yatan hastalarda malnütrisyon ve sarkopeni gelişmemesi veya ilerlememesi için; hastaneye yatış

Address for Correspondence/Yazışma Adresi: Aysun Nazlı, University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Nutrition and Dietetics, İstanbul, Turkey
Phone: +90 546 200 65 07 **E-mail:** aysunnazli@outlook.com **ORCID ID:** orcid.org/0000-0002-1168-6592

Cite this article as/Atıf: Nazlı A, Yılmaz Akyüz E. Assessment of Nutritional Status of Hospitalised Geriatric Patients and its Relationship with Sarcopenia. İstanbul Med J 2020; 21(4): 290-6.

Received/Geliş Tarihi: 17.01.2020
Accepted/Kabul Tarihi: 12.05.2020

and sarcopenia should be evaluated, and patients should be treated and followed up during hospitalisation. Regardless of nutritional status, all hospitalised elderly patients should be controlled for the risk of sarcopenia.

Keywords: Sarcopenia, malnutrition, nutrition, sarcopenic obesity, ageing

esnasında hastaların beslenme durumları ve kas kayıpları değerlendirilmeli, tedavi ve takibi yapılmalıdır. Nütrisyonel durumdan bağımsız olarak hastanede yatan tüm yaşlı hastalar sarkopeni riski açısından kontrol edilmelidir.

Anahtar Kelimeler: Sarkopeni, malnütrisyon, nütrisyon, sarkopenik obezite, yaşlılık

Introduction

With the improved technology and the improvement of living conditions, it has been observed that death rates on earth have decreased and life expectancy has increased. The number of geriatric patients who lack self-care, have chronic disease and need care and treatment has increased due to prolonged life expectancy and deteriorating body homeostasis with aging. The World Health Organization (WHO) has stated that the population aged ≥65 increases by about 5% per year in developing and developed countries (1,2).

With the interaction of progressive age and chronic diseases on many systems, geriatric syndromes that disrupt the comfort of life, which are not fully explained by the definition of the disease, and which can increase the mortality rate are occurring (2). These geriatric syndromes are neurological diseases, inactivity, anxiety, delirium, dementia, falls, pressure wound, osteoporosis, fragility, malnutrition and sarcopenia (3).

Malnutrition, characterized by weight loss, decreased muscle power, increased morbidity and mortality, is the occurrence of clinical pathologies in body functions as a result of deficient or excessive intake of energy, macro and micronutrients. Mental health problems, lack of self-care, skipping meals, missing nutrient intake, chronic disease, dysphagia, neurological disorders, social problems, dental problems, excessive drug use, reduced physical activity and hospital-acquired infections; are specified as conditions that cause malnutrition (4,5). A gold standard Mini Nutritional Assessment (MNA) form developed by the European Society for Clinical Nutrition and Metabolism for geriatric patients in nursing homes and hospitals is recommended for malnutrition screening (5).

Sarcopenia, which is caused by aging, decreased physical movement, malnutrition and decreased anabolic hormones, and is characterized by falling, disability, loss of mass and muscle strength, is another geriatric syndrome (6). The sarcopenia algorithm proposed by the European Working Group on Sarcopenia in Older People (EWGSOP), established by the European Union Geriatric Medicine Society, is used to determine the presence of sarcopenia. In this algorithm; sarcopenia is detected by evaluating the walking speed and muscle function of the geriatric individuals, muscle strength measurement with the hand grip force test and measuring muscle mass with the help of devices (7).

After detection and evaluation of malnutrition and sarcopenia, a multidisciplinary team (doctor, dietician, nurse) should plan effective nutritional interventions and a physical movement schedule that meets the patient's needs, including both the patient and their families/caregivers (4). In our study, it was aimed to evaluate the nutritional status of geriatric patients in İstanbul Training and Research Hospital Clinics for more than 24 hours, to determine sarcopenia status and to examine the relationship between them.

Materials and Methods

This descriptive and cross-sectional study consisted of 100 patients ≥65 years of age and who agreed to participate in the University of Health Sciences Turkey, İstanbul Training and Research Hospital clinics for more than 24 hours between November 2018 and April 2019. The study was carried out with the approval of Health Sciences University's Hamidiye Ethics Committee (decision no: 46418926-050.03.04) and with written consent from the patients.

Demographic data of the patients (age, gender), anthropometric measurements [body weight, height, body mass index (BMI), right-upper arm circumference, lower right calf circumference], Bio-impedance analysis (BIA) device measurements, hand dynamometer, timed up-and-move (3m walk test) test measurements and the MNA form scores were recorded. In addition, the duration and indications of hospitalization of patients, the service in which they received inpatient treatment, the presence of additional chronic disease were questioned.

The consciousness of the patient, sufficient walking function, lack of hand limitation and being in a position to be weighed were determined as the inclusion criteria. Patients who were in a bad condition (hemiplegic, over-edematous), unable to communicate (psychological disorders), gait disturbance, hand function limitation, previous cerebrovascular disease history, advanced dementia, Parkinson's disease and such neurological diseases were excluded from the study.

The MNA form was applied to all patients by the researcher to determine the nutritional status of the patients. According to the score on the form <17 points malnutrition, 17-23.5 points malnutrition risk and >24 points were determined as normal nutritional status (5).

The length of the patients was measured by ground-fixed, calibrated scale brand DR-MOD.85. Body weight, BMI and muscle mass measurements of the patients whose height was measured were done with BIA device (TANITA brand, SC-330 model). The skeletal muscle formula recommended by Janssen et al. (8) was used to determine the muscle mass of the patients whose weight was measured, and the muscle mass was obtained by dividing the calculated skeletal muscle amount by the square of the height length.

Hand grip test was used for muscle strength measurements. The hand grip test was carried out with the SAEHAN sh5001 model hand dynamometer. According to EWGSOP criteria, the hand grip strength required for sarcopenia was determined as cutting points; 30 kg for

men and 20 kg for women (7). The Timed Up & Go (TUG) test was used to evaluate the muscle function of the patients, and patients whose duration lasted longer than 15 seconds were considered to have decreased muscle function (2,9). EWGSOP algorithm based on TUG test, hand grip strength and muscle mass measurement was used to determine sarcopenia (7). In order to evaluate the status of sarcopenic obesity, the sarcopenia diagnostic criteria proposed by EWGSOP and the BMI values proposed by WHO were used in the evaluation of obesity. Patients with BMI greater than 30 were considered obese. Patients with obesity and sarcopenia were considered to be "sarcopenic obese patients" (1,7).

Statistical Analysis

SPSS (Statistical Package for Social Sciences) 22.0 package program was used for statistical analysis of the data. Mean, standard deviation, median lowest, highest, frequency and ratio values were used in the descriptive statistics of the data obtained from the research. The distribution of variables was measured by Kolmogorov Simirnov test. The Mann-Whitney U test was used in the analysis of quantitative independent data, the chi-square test was used in the analysis of qualitative independent data, and the Fisher exact test was used when the conditions for the chi-square test were not met.

Results

Of the total 100 patients included in the study, 35% were female and 65% were male. The mean age was 71.8±6.2 years (minimum: 65-maximum: 88). 56% of the patients included in the study were treated in physical therapy and rehabilitation, 24% in internal medicine, 8% in urology, 6% in otolaryngology and 6% in other hospital clinics.

Malnutrition was found in 8% of patients, malnutrition risk was found in 50% and normal nutrition was found in 42%. In this study, malnutrition and malnutrition risk group were discussed together. Therefore, the data were grouped and evaluated as the group of patients with malnutrition status and the group of patients without malnutrition status. 5% of patients met sarcopenia criteria, while 95% did not meet sarcopenia criteria. Sarcopenic obesity was seen in only one person (1%) out of 100 patients. The distribution of chronic disease, nutrition, sarcopenia, sarcopenic obesity and muscle adequacy of the patients is shown in Table 1.

Of the patients with malnutrition, 67.2% (n=39) were male and 32.8% (n=19) were female. Gender distribution and presence of chronic disease were not significantly different in groups of patients with and without malnutrition (p=0.581, p=0.166). Obesity is present in 51.7% of patients with malnutrition, while not present in 48.3%. Malnutrition was also detected in 1 (1%) patient with sarcopenic obesity. Sarcopenic obesity was not found in patients without malnutrition. The presence of obesity and sarcopenic obesity were not significantly different in the group with and without malnutrition (p=0.210, p=1.000) (Table 2).

While mean age of patients with malnutrition was 73.0±6.0, without malnutrition was 70.0±6.1 and significant difference was found between the groups (p=0.004). The duration of hospitalization was 6.0±5.2 in patients without malnutrition and 7.3±4.8 in patients with malnutrition and there was a significant difference between the groups (p=0.045). Anthropometric measurements of the patients according to their nutritional status are shown in Table 3.

80% of 5 patients with sarcopenia were female and 20% were male. In 80% of patients with sarcopenia, 75.8% of those without sarcopenia had chronic disease (p=1,000), (Table 4).

Mean age, duration of hospitalization and MNA scores of patients with sarcopenia were higher than those without sarcopenia, but no difference was found between them (p<0.05). Weight and BMI values of patients with sarcopenia were lower (p=0.049, p=0.028). No significant difference was observed in other anthropometric measurements (Table 5).

Sarcopenia was not seen in patients with malnutrition. The risk of malnutrition was found in 60% of patients with sarcopenia, normal nutrition in 40%; malnutrition in 8.4% of patients without sarcopenia, malnutrition risk in 47.5% and normal nutrition in 42.1%. The distribution of sarcopenia presence did not differ significantly according to the nutritional status of the patients (p=0.926).

Discussion

Sarcopenia and malnutrition are geriatric syndromes that reduce Novartis function and quality of life in old age (3). In this study, it was determined that geriatric patients in hospital may develop sarcopenia regardless of the presence of malnutrition, therefore patients should also be evaluated for sarcopenia.

One of the secondary results of sarcopenia and malnutrition is prolonged hospitalization (6). In studies where malnutrition and sarcopenia status of hospitalized patients were examined, the duration of hospitalization was found to be longer in patients with malnutrition

Table 1. Distribution of disease, nutritional status and muscle adequacies of patients

	Situation	Number (n)	Percent (%)
Chronic disease	Yes	76	76
	No	24	24
Obesity	Yes	57	57
	No	43	43
Malnutrition	Yes	8	8
	There is a risk	50	50
	No	42	42
Sarcopenia	Yes	5	5
	No	95	95
Muscle function adequacy	Yes	50	50
	No	50	50
Muscle strength adequacy	Yes	26	26
	No	74	74
Muscle mass adequacy	Yes	95	95
	No	5	5
Sarcopenic obesity	Yes	1	1
	No	99	99

and sarcopenia (10,11). In our study, different from the literature, the duration of hospitalization was significantly higher in non-malnutrition patients and did not differ according to sarcopenia status. The reason for this condition is that the majority of patients are patients with good nutritional conditions who have been in the physical therapy and rehabilitation clinic for long periods of time for treatment.

The prevalence of malnutrition or malnutrition risk in geriatric patients is between 30-60% (12,13). In one study, 26.9% malnutrition, 46.6% malnutrition risk, 26.5% normal nutrition were indicated (14). In this study, malnutrition was identified in 8% of patients, malnutrition risk in 50% and normal nutrition in 42%. We believe that the proportion of patients with malnutrition is low due to the fact that most diseases that can cause malnutrition are within the exclusion criteria.

Although sarcopenia prevalence varies according to institutions, societies, gender distribution, diagnostic tools and schemes used and age groups, a community-based study in Turkey found sarcopenia in 5.2% of geriatric individuals according to EWGSOP criteria (15). In other studies conducted according to the EWGSOP scheme, the prevalence of sarcopenia was 7.5% and 4.5% respectively (16,17). Similarly, sarcopenia was detected in 5% of patients in this study.

Low walking speed, which is positively correlated with decreased muscle function and decreased physical performance, is one of the evaluation criteria that reflects the sarcopenia and malnutrition conditions of patients. Low walking speed is thought to be related to patients with sarcopenia and malnutrition to have muscle mass lose and muscle strength loss in their lower extremities (18). In studies conducted on geriatric individuals, it was reported that walking time was longer than those without malnutrition and muscle function was lower (19,20). In geriatric patients with sarcopenia, the results of the TUG test, lower limb strength test results, and physical capacity scores reflecting muscle

Table 2. Gender, obesity, sarcopenic obesity, muscle competence according to the presence of malnutrition in patients

Number (n)		Malnutrition Yes		Malnutrition No		
		Number (%)	Percent (n)	Number (%)	Percent (%)	p
Gender	Female	19	32.8	16	38.1	0.581 $^{x^2}$
	Male	39	67.2	26	61.9	
Chronic disease	Yes	47	81	29	69	0.166 $^{x^2}$
	No	11	19	13	31	
Obesity	Yes	30	51.7	27	64.3	0.210 $^{x^2}$
	No	28	48.3	15	35.7	
Sarcopenic obesity	Yes	1	1.7	0	0	1.000 $^{x^2}$
	No	57	98.3	42	100	
Muscle function adequacy	Yes	20	34.5	30	71.4	0.000 $^{x^2}$
	No	38	65.5	12	28.6	
Muscle strength adequacy	Yes	11	19	15	35.7	0.059 $^{x^2}$
	No	47	81	27	64.3	
Muscle mass adequacy	Yes	55	94.8	40	95.2	0.926 $^{x^2}$
	No	3	5.2	2	4.8	

$^{x^2}$: chi-square test

Table 3. Anthropometric measurements of patients according to their nutritional status

	Malnutrition Yes	Malnutrition No	p
	Mean ± SD	Mean ± SD	
Body weight (kg)	72.1±13.4	80.9±11.5	0.002 ^{m}
Height (cm)	155.4±9.1	158.7±7.6	0.039 ^{m}
BMI (kg/m²)	29.9±5.7	32.2±5.2	0.049 ^{m}
Upper arm circumference (cm)	25.9±4.3	28.5±4.5	0.013 ^{m}
Lower calf circumference (cm)	37.3±4.9	47.8±56.2	0.313 ^{m}
Hand grip force (kg)	18.4±10.1	22.3±6.8	0.002 ^{m}
Timed Up & Go test (s)	18.3±8.3	13.9±3.4	0.000 ^{m}
Skeletal muscle (kg)	22.9±5.5	24.4±5.5	0.131 ^{m}
Muscle mass (kg/m²)	9.4±1.6	9.6±1.6	0.386 ^{m}

^{m}: Mann-Whitney U test, BMI: body mass index, SD: standard deviation

Table 4. Gender, obesity, sarcopenic obesity, muscle competencies according to the patients' sarcopenia status

Number (n)		Sarcopenia Yes		Sarcopenia No		
		Number (n)	Percent (%)	Number (n)	Percent (%)	p
Gender	Female	4	80	31	32.6	0.050 $^{x^2}$
	Male	1	20	64	67.4	
Chronic disease	Yes	4	80	72	75.8	1,000 $^{x^2}$
	No	1	20	23	24.2	
Obesity	Yes	1	20	56	58.9	0.086 $^{x^2}$
	No	4	80	39	41.1	
Sarcopenic obesity	Yes	1	20	0	0	0.050 $^{x^2}$
	No	4	80	95	100	
Muscle function adequacy	Yes	0	0	50	52.6	0.022 $^{x^2}$
	No	5	100	45	47.4	
Muscle strength adequacy	Yes	0	0	26	27.4	0.323 $^{x^2}$
	No	5	100	69	72.6	
Muscle mass adequacy	Yes	0	0	95	100	0.000 $^{x^2}$
	No	5	100	0	0	

$^{x^2}$: chi-square test

Table 5. Demographic characteristics and anthropometric measurements of patients with sarcopenia

	Sarcopenia Yes	Sarcopenia No	
	Mean ± SD	Mean ± SD	p
Age (Year)	73.0±4.5	71.7±6.3	0.460 ^{m}
Duration of stay (days)	6.8 ±3.6	6.5±5.1	0.575 ^{m}
Body weight (kg)	67.1±5.8	76.3±13.5	0.049 ^{m}
Height (cm)	160.0±11.2	156.6±8.5	0.491 ^{m}
BMI (kg/m^2)	26.3±2.5	31.1±5.6	0.028 ^{m}
Upper arm circumference (cm)	25.2±3.0	27.1±4.6	0.289 ^{m}
Lower calf circumference (cm)	34.0±2.9	42.1±37.7	0.064 ^{m}
Timed up & walk test (seconds)	16.3±1.5	16.4±7.2	0.472 ^{m}
Hand grip force (kg)	22.3±8.5	20.0±9.1	0.472 ^{m}
MNA score	23.5±1.6	22.0±4.4	0.511 ^{m}
Skeletal muscle (kg)	21.4±5.1	23.6±5.5	0.532 ^{m}
Muscle mass (kg/m^2)	8.2±1.0	9.5±1.6	0.131 ^{m}

m: Mann-Whitney U test, BMI: body mass index, SD: standard deviation, MNA: Mini Nutritional Assessment

functions were shown to decrease (18). In this study, similar to previous studies, muscle dysfunction was found in more than half of patients with malnutrition and in all patients with sarcopenia.

The BMI scale used in older adults was differentiated from the adults by the shortening of length due to the increase in age. BMI, which reflects malnutrition status in older individuals, is accepted as <22 kg/m^2 (5). Our study found that both malnutrition and sarcopenia patients had lower BMI than those who did not. In a study, a higher proportion of sarcopenia was found in patients with BMI below 24.99 kg/m^2 (21). In a study in which BMI values were investigated according to the nutritional status of patients, it was stated that patients' BMI was an important factor in the occurrence of malnutrition (22).

Sarcopenia is not only seen in individuals with low weight, but also in individuals with excess body weight. The condition in which sarcopenia is present alongside obesity caused by increased fat mass is called sarcopenic obesity (23). In a study investigating the prevalence of sarcopenic obesity, 12.5% of women and 5% of men were diagnosed with sarcopenic obesity (24). Another study found that out of 171 patients undergoing surgical operations, 46.8% were sarcopenic and 28.7% were sarcopenic obese. (9). In this study, obesity was found in 57% of patients and sarcopenic obesity in 1%. 51.7% of patients with malnutrition were obese, 1.7% were sarcopenic obese; 20% of patients with sarcopenia were obese and sarcopenic obese.

Hand grip strength test is often preferred to measure muscle strength in determining malnutrition and sarcopenia (7). Springstroh et al. (25) found that hand grip forces of older adults living in the community were associated with malnutrition and indicated that hand grip strength could be used to detect malnutrition. A study also found that poor nutrition causes inadequacy of muscle strength in older individuals (26). In our study, hand grip strength averages were lower in patients with malnutrition than in those without, and muscle strength inadequacy

were found in 81% of patients with malnutrition. This situation can be explained by the loss of muscle strength due to malnutrition.

It is known that the increase in physical performance assessed by the lower limb strength test and gait test reduces the need for help and improves the comfort of life during the geriatric period (18). In our study, the mean TUG test result was significantly lower in patients with malnutrition than in patients without malnutrition. Similar studies have also reported that the risk of malnutrition is directly related to slow walking speed (20,27).

Sarcopenia is characterized by loss or inability to novelize muscle mass (2). Dufour et al. (28) observed that low muscle mass, increased fat ratio and body size were associated with sarcopenia in their study. In this study, muscle mass was found to be insufficient in 5% of all patients, 5.2% of patients with malnutrition and 100% of patients with sarcopenia. Using the formula proposed by Janssen et al. (8), in geriatric individuals in Turkey in a study investigating the adequacy of muscle mass, it was found to have a higher muscle mass than expected adequacy of the patients. We think that the similar situation observed in our study is due to the high threshold value of the formula used for Turkish society.

Weight loss increases lean mass loss and sarcopenia due to aging (9). In a study, body weight was significantly lower in individuals with sarcopenia than in individuals without sarcopenia (29). Another study reported that body size should be considered in the case of sarcopenia (28). In our study, we found that patients with sarcopenia had significantly lower weight averages than those who did not. It is predicted that this is due to the loss of weight due to old age and chronic diseases, causing muscle loss.

Limitations of Research

Since the study was a cross-sectional type and single-center study, it was possible to reach a limited number of patients in a limited period of time.

Conclusion

In this study, the risk of malnutrition and malnutrition were detected in more than half of geriatric patients, and it was shown that sarcopenia may develop regardless of nutritional status. For this reason, the nutritional status of geriatric patients should be questioned in detail and risk screening should be done to prevent the early diagnosis and treatment of malnutrition and sarcopenia.

Ethics

Ethics Committee Approval: The study was carried out with the approval of Health Sciences University's Hamidiye Ethics Committee (decision no: 46418926-050.03.04).

Informed Consent: Written consent from the patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Concept - A.N., E.Y.A.; Design - A.N., E.Y.A.; Data Collection or Processing - A.N.; Analysis or Interpretation - A.N., E.Y.A.; Literature Search - A.N.; Writing - A.N.

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

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

References

1. Who Health Organization. Trends in Proportion of Older Persons- (cited 2019, April 4) Available from: URL: http://www.who.int/mediacentre/factsheets/fs404/en/
2. Sökmen ÜN, Dişcigil G. Yaşlılıkta Sarkopeni. Jour Turk Fam Phy 2017; 8: 49-54.
3. Keskiner MV, Tufan F, Oğuz A. Geriatrik Sendromlar. Okmeydanı Tıp Dergisi 2013; 29: 41-8.
4. Baz S, Ardahan M. Yaşlılarda Malnütrisyon ve Hemşirelik Yaklaşımları. Balıkesir Sağlık Bil Derg 2016; 5: 147-53.
5. Volkert D, Beck AM, Cederholm T, Jentoft AC, Goisser S, Hooper L, et al. ESPEN Guideline on Clinical Nutrition and Hydration in Geriatrics, Clin Nutr 2019; 38: 10-47.
6. Rosenberg IH. Sarcopenia: Origins and Clinical Relevance. The journal of Nutrition 1997; 127: 990-1.
7. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European Consensus on Definition and Diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010; 39: 412-23.
8. Janssen I, Heymsfield SB, Baumgartner RN, Ross R. Estimation of Skeletal Muscle Mass by Bioelectrical İmpedance Analysis. J Appl Physiol 2000; 89: 465-71.
9. Lodewick TM, van Nijnatten TJ, van Dam RM, van Mierlo K, Dello SA, Neumann UP, et al. Are Sarcopenia, Obesity and Sarcopenic Obesity Predictive of Outcome in Patients with Colorectal Liver Metastases? HPB (Oxford) 2015; 17: 438-46.
10. Saka B, Özkulluk H. İç hastalıkları polikliniğine başvuran yaşlı hastalarda nütrisyonel durumun değerlendirilmesi ve malnütrisyonun diğer geriatrik sendromlarla ilişkisi. Gülhane Tıp Derg 2008; 50: 151-7.
11. AL-Azzawi Yasir, Coukos Jennifer, Martin Alexander, Albo Betty, Howard-Wilson Sakeina R, Kroll-Desrosiers Aimee, Radcliffe David, et al. Sarcopenia Is Increased in Females and Associated With Severity of Alcoholic Hepatitis and Increased Hospital Stay. Am J Gastroenterol. 2018; 113: 503.
12. Kaiser MJ, Bauer JM, Rämsch C, Uter W, Guigoz Y, Cederholm T, et al. Frequency of Malnutrition in Older Adults: A Multinational Perspective Using The Mini Nutritional Assessment. J Am Geriatr Soc 2010; 58: 1734-8.
13. Wakimoto P, Block G. Dietary intake, dietary patterns, and changes with age: an epidemiological perspective. J Gerontol A Biol Sci Med Sci 2001; 56: 65-80.
14. Chatindiara I, Allen J, Popman A, Patel D, Richter M, Kruger M, et al. Dysphagia risk, low muscle strength and poor cognition predict malnutrition risk in older adults at hospital admission. BMC Geriatr 2018; 18: 78.
15. Şimşek Keskin H, Meseri Dalak R, Şahin S, Kılavuz A, Hopancı D, Uyar M, et al. Prevalance of sarcopenia and factors related to sarcopenia in the community-dwelling elderly. European Geriatric Medicine, 2017; 8: 108-9.
16. Yamada M, Nishiguchi S, Fukutani N, Tanigawa T, Yukutake T, Kayama H, et al. Prevalence of sarcopenia in community-dwelling japanese older adults. J Am Med Dir Assoc 2013; 14: 911-5.
17. Kemmler W, Teschler M, Goisser S, Bebenek M, von Stengel S, Bollheimer LC, et al. Prevalence of Sarcopenia in Germany and The Corresponding Effect of Osteoarthritis in Females 70 Years and Older Living in The Community: Results of The FORMoSA Study. Clin Interv in Aging 2015; 3: 1565-73.
18. Harris-Love MO, Benson K, Leasure E, Adams B, McIntosh V. The ınfluence of upper and lower extremity strength on performance-based sarcopenia assessment tests. J Funct Morphol Kinesiol 2018; 3: 53.

19. Marcell TJ. Sarcopenia: Causes, Consequences, and Preventions. J Gerontol A Biol Sci Med Sci 2003; 58: 911-6.

20. Ulusoylar Erken N, Dost Günay F. Yaşlılarda Düşük Yürüme Hızının Mini Nutrisyonel Değerlendirme ile İlişkisi. Geriatrik Bilimler Dergisi 2019; 2: 73-7.

21. Beaudart C, Reginster JY, Slomian J, Buckinx F, Dardenne N, Quabron A, et al. Estimation of Sarcopenia Prevalence Using Various Assessment Tools. Exp Gerontol 2015; 61: 31-7.

22. Yürük A, Türkoğlu İ, Yalçın T, Çerçi A, Yıldız E. Hastanede Yatan Hastaların Malnütrisyon Durumlarının Değerlendirilmesi. Hacettepe Üniversitesi Sağlık Bilimleri Dergisi 2015; 1.

23. Zamboni M, Mazzali G, Fantin F, Rossi A, Francesco V. Sarcopenic obesity: A new category of obesity in the elderly. Nutrition Metabolism Cardiovascular Disease 2008; 18: 388-95.

24. Kim TN, Yang SJ, Yoo HJ, Lim KI, Kang HJ, Song W, et al. Prevalence of sarcopenia and sarcopenic obesity in Korean adults: the Korean sarcopenic obesity study. Int J Obes 2009; 33: 885-92.

25. Springstroh KA, Gal NJ, Ford AL, Whiting SJ, Dahl WJ. Evaluation of handgrip strength and nutritional risk of congregate nutrition program participants in florida. J Nutr Gerontol Geriatr 2016; 35: 193-208.

26. Avelino-Silva TJ , Jaluul O. Malnutrition in hospitalized older patients: management strategies to ımprove patient care and clinical outcomes. International Journal of Gerontology 2017; 11: 56-61.

27. Mendes J, Borges N, Santos A, Padrão P, Moreira P, Afonso C, et al. Nutritional status and gait speed in a nationwide population-based sample of older adults. Sci Rep 2018; 9; 8: 4227.

28. Dufour AB, Hannan MT, Murabito JM, Kiel DP, McLean RR, et al. Sarcopenia definitions considering body size and fat mass are associated with mobility limitations: the framingham study. J Gerontol A Biol Sci Med Sci. 2013; 68: 168-74.

29. Aggio DA, Sartini C, Papacosta O, Lennon LT, Ash S, Whincup PH, et al. Cross-sectional associations of objectively measured physical activity and sedentary time with sarcopenia and sarcopenic obesity in older men. Prev Med 2016; 91: 264-72.

İstanbul Med J 2020; 21(4): 297-300
DOI: 10.4274/imj.galenos.2020.54037

Serum Ischaemia-modified Albumin Concentration in Hyperemesis Gravidarum

Hipermezis Gravidarumda Serum İskemi-modifiye Albümin Düzeyleri

Selen Yaman[1], Sevgi Ayhan[1], Özlem Banu Tulmaç[1], Tuba Çandar[2], Aytekin Tokmak[1], Dilek Şahin[1]

[1]University of Health Sciences Turkey, Ankara Dr. Zekai Tahir Burak Women's Health Training and Research Hospital, Clinic of Obstetrics and Gynecology, Ankara, Turkey
[2]Ufuk University Faculty of Medicine, Department of Clinical Biochemistry, Ankara, Turkey

ABSTRACT

Introduction: The role of oxidative stress in the pathogenesis of hyperemesis gravidarum (HEG) has been demonstrated in a lot of studies. The present study aimed to compare the ischaemia-modified albumin (IMA) serum levels of patients diagnosed with HEG with healthy pregnant women, and to investigate whether oxidative stress caused increased serum IMA in HEG.

Methods: Pregnant women were classified into a group diagnosed with HEG (n=45) and an age- and body mass index-matched control group without HEG (n=45). Serum IMA levels were assessed by the enzyme-linked immunosorbent assay (ELISA) method.

Results: Serum IMA levels were higher in the HEG group than the control group (HEG: 8.2±0.2 ng/mL, control: 6.9±0.3 ng/mL, p<0.001).

Conclusion: We found that HEG was related to increased maternal serum IMA levels. The high levels of IMA in HEG can be considered as a reflection of increased oxidative stress.

Keywords: Ischaemia-modified albumin, oxidative stress, hyperemesis gravidarum

ÖZ

Amaç: Birçok çalışmada hiperemezis gravidarumun (HEG) patogenezinde oksidatif stresin katkısı gösterilmiştir. Bu çalışmada, HEG tanısı konulan hastalarla sağlıklı gebe kadınların serum iskemi modifiye albümin (İMA) düzeylerini karşılaştırmak ve oksidatif stres belirteci olan İMA'nın HEG'de artıp artmadığının araştırılması amaçlanmıştır.

Yöntemler: Yaş ve vücut kitle indeksine göre eşleştirilmiş hastalar, HEG tanısı alanlar (n=45) ve sağlıklı gebe kontrol grubu (n=45) olarak ikiye ayrıldı. Serum İMA düzeyleri, her bir katılımcı için enzim bağlı immün assay (ELISA) yöntemi ile analiz edildi.

Bulgular: Serum İMA düzeyleri HEG grubunda kontrol grubuna göre daha yüksekti (sırasıyla HEG grubu 8,2±0,2 ng/mL, kontrol grubu 6,9±0,3 ng/mL, p<0,001).

Sonuç: HEG grubunda maternal serum İMA düzeyinin anlamlı yüksek olduğunu bulduk. HEG'de tanımlanan yüksek İMA seviyeleri, oksidatif stresin bir yansıması olarak düşünülebilir.

Anahtar Kelimeler: İskemi modifiye albümin, oksidatif stres, hiperemezis gravidarum

Introduction

Nausea and vomiting (NV) are common experiences in pregnancy, affecting 70%-80% of all pregnant women (1). Hyperemesis gravidarum (HEG) affects the quality of life of women during pregnancy; it is considered as the third leading cause of all hospitalisations during pregnancy (2). In other words, HEG is a serious clinical condition responsible for one-third of all hospitalisations during pregnancy (3). HEG is a severe and persistent form of NV that affects about 0.3%-2% of all pregnancies, resulting in fluid loss, electrolyte imbalance, nutrition deficiency, at least 5% weight loss and ketonuria (4). Endocrine (human chorionic gonadotropin, estradiol and progesterone), immunologic and personal factors (increased body weight) are responsible for the etiopathogenesis of the disease (5). In addition, certain pathologic factors such as lipid disorders, activation of sympathetic system, thyroid disorders, increase in systemic oxidative stress and *Helicobacter pylori* infection are frequently mentioned in the pathophysiology of the disease (6,7). However, there is no theory that explains the differences in the clinical diversity of HEG and combines various pathogenetic factors under one roof.

Ischaemia-modified albumin (IMA) is used as a biomarker in the early diagnosis of acute coronary syndrome (8), acute ischaemia that is approved by the Food and Drug Administration and is considered as a marker for elevated free radical-induced protein oxidative injury (9,10).

Address for Correspondence/Yazışma Adresi: Aytekin Tokmak MD, University of Health Sciences Turkey, Ankara Dr. Zekai Tahir Burak Women's Health Training and Research Hospital, Clinic of Obstetrics and Gynecology, Ankara, Turkey
Phone: +90 505 633 50 64 **E-mail:** aytekintokmak@gmail.com **ORCID ID:** orcid.org/0000-0001-5739-5689

Received/Geliş Tarihi: 06.07.2019
Accepted/Kabul Tarihi: 03.06.2020

Cite this article as/Atıf: Yaman S, Ayhan S, Tulmaç ÖB, Çandar T, Tokmak A, Şahin D. Serum Ischaemia-modified Albumin Concentration in Hyperemesis Gravidarum. İstanbul Med J 2020; 21(4): 297-300.

It has been observed that various ischaemic events such as stroke, acute mesenteric ischaemia and some cancer types have an effect on IMA levels (11-13). IMA is formed as an end product of modification in serum albumin caused by the reactive oxygen derivatives that emerge because of ischaemia. The amino terminus of the albumin molecule is a binding for metal ions such as nickel, cobalt and copper. However, when exposed to ischaemia, hypoxia and/or free radical damage, the amino terminus region of albumin is more susceptible to degradation when its ability to bind to metals is reduced, forming IMA. Its serum concentration is not related to age or gender (14). IMA represents 1%-2% of total serum albumin in non-pathological cases, and this ratio increases to 6%-8% during ischaemic conditions (14). Normally, pregnancy occurs in hypoxic intrauterine environment; the ensuing reperfusion and placental oxidative stress lead to the physiological development of syncytiotrophoblast. Previous studies demonstrated that IMA can be a marker for hypoxic intrauterine environment, especially in early pregnancy (15-17). In this study, we assumed that HEG was related to increased maternal serum IMA level because of oxidative stress during the early period of pregnancy. Therefore, we designed the present study to evaluate the clinical utility of IMA in HEG by comparing its serum concentrations between the HEG patients and gestational age-matched healthy pregnant women.

Methods

This study was conducted at the University of Health Sciences Turkey, Zekai Tahir Burak Women's Health Training and Research Hospital. Patients enrolled in the study were selected on the basis of their diagnosis with HEG and healthy pregnant women who were admitted to the antenatal clinic during the 6-14th week of pregnancy.

This study was approved by the local ethical committee of the hospital (decision no: 7, date: 25.05.2016), and written informed consent of all participants were obtained. The study was designed and conducted according to the principles of Helsinki Declaration (18). The participants were divided into two groups: study and control. Both groups' gestational ages (between 6- and 14 weeks' gestation) and ages (20–37 years) were matched.

The following diagnostic criteria were used for HEG: severe NV throughout the pregnancy (>3 times per day), more than 5% weight loss and at least one positive ketonuria in the urine test.

Criteria were excluded for multiple gestation, hypertensive disorders of pregnancy, diabetes mellitus, gestational trophoblastic disease, any type of existing gastrointestinal, hepatic and renal diseases or inflammatory diseases, eating disorders, psychiatric disease and other known probable vomiting causes, such as thyroid disorders.

Gestational age was calculated according to the last menstrual period or first trimester ultrasound examination of those women who did not remember their last menstrual period. Body mass index (BMI) was determined by dividing the body weight (kilograms) with the square of height in metres. All HEG patients in the study group were hospitalised for at least 24 hours for initial treatment. They were hydrated at the time of admission to avoid the possible effects of hypovolemia. It was observed that vital signs and urine output of the patients were normal before blood samples were taken. Fasting blood samples were taken from the antecubital vein without the use of anticoagulants. Serum IMA concentrations were analysed by a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Eastbiopharm Human Ischaemia Modified Albumin ELISA Kit) for IMA (Chemwell 2900, Aurenesness, USA).

Intra- and inter-assay coefficients for IMA were <10% and <12%, respectively. Blood samples were collected after an overnight fast, and centrifugation was performed at 4000 rpm for 10 minutes with the supernatant serum frozen and stored at -80 °C until analysis.

Statistical Analyses

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software (version 22, SPSS Inc., Chicago, IL). Continuous variables were demonstrated as a mean ± standard deviation or median (minimum-maximum). All normally distributed data were compared by using the Student's t-test; Data with abnormal distribution were compared by using the Mann-Whitney U test. The p value of less than 0.05 was regarded as statistically significance.

Results

This study included 90 women, 45 pregnant women diagnosed with HEG and 45 healthy pregnant women of same gestational age. Median ages of the HEG patients and the healthy pregnant women in the control group were found to be 27 (20-36) and 27 (20-37), respectively. Sociodemographic features of the patients were presented in Table 1. The groups did not show any statistical difference at the time of blood sampling with regard to age, gestational age, BMI and reproductive history (Table 1). Plasma complete blood count parameters, serum glucose, urea, creatinine, aspartate transaminase, alanine transaminase and thyroid-stimulating hormone levels of the groups were statistically

Table 1. Demographic and clinical data of the subjects

	Control (n=45)	HEG (n=45)	p
Age (year)	27 (20-37)	27 (20-36)	0.682
Body mass index (kg/m^2)	28.84 (21.3-37.3)	28.1 (21.9-36.7)	0.294
Gestational age (week)	10.24±1.09	10.28±0.94	0.238
Gravida (range)	2 (1-4)	2 (1-5)	0.825
Parity (range)	1 (0-2)	1 (0-23)	0.764

HEG: Hyperemesis gravidarum

similar (p>0.05). Serum IMA levels were found to be significantly higher among HEG patients than the control group (8.2±0.2 ng/mL vs. 6.9±0.3 ng/mL, p<0.001) (Table 2).

Discussion

In this study, we found that IMA was statistically higher in the HEG group than healthy pregnant women of the control group. Although it would not be accurate to make a clear or conclusive remark regarding the oxidative stress conditions in HEG by looking solely at the IMA levels, our results showed that the oxidative stress condition in HEG could be related to IMA levels.

Many studies elucidate the role of IMA in different diseases. IMA increase is observed in ischaemia, acidosis, free radicals and hypoxia. The studies based on literature data show that in acute coronary events, IMA has a diagnostic value of 95% when used together with troponin and electrocardiography (19,20). The diagnostic value of IMA in acute coronary events have been discussed, and evidence concerning the utility of IMA in obstetrics practice has been increasing in recent years. Prefumo et al. (15) in 2007 stated that maternal serum IMA concentrations increase during early pregnancy and normal trophoblast development is related to the hypoxic intrauterine medium. Similarly, Ustün et al. (17) stated that serum IMA levels are related to the severity of preeclampsia and preeclamptic pregnancies can be detected using a pre-determined cut-off value. In contrast to these studies, Iacovidou et al. (21) showed that IMA levels in the umbilical cord blood are same between normal pregnancies and pregnancies showing intrauterine growth retardation.

The role of IMA in perinatology practice was analysed in detail in a recently published review (22). Yarcı Gursoy et al. (22) stated that increased IMA levels in pregnancies are associated with complications such as preeclampsia, intrauterine growth retardation and diabetes mellitus; however, the results of these studies should be approached prudently

Approximately 80% of women experience a severity of NV at the time of pregnancy (23). According to the study conducted by Sari et al. (24), which is one of the very few studies in literature analysing the IMA levels of HEG patients, serum IMA levels of HEG patients were observed to be significantly higher when compared to the control group. The main cause of this increase is the hypoxic medium that develops within the uterus during the early pregnancy period. Furthermore, the authors also stated that the oxidative stress in the uterus because of the hypoxic medium is also important for physiologic trophoblast development. Although it was shown that there was no significant increase in the level of IMA of HEG patients in a smaller study by Bulanık et al. (25), in our study, serum IMA levels were found to be significantly higher when compared to the control group, similar to Sarı's study (Table 3). The actual treatment of HEG is empirical and suboptimal as the definitive aetiology is not clearly shown (26). Measurement of serum levels of IMA in these patients to guide antioxidant treatment or agents preventing reperfusion damage may be beneficial for the management of HEG.

Table 2. Laboratory findings of the subjects

	Control (n=45)	HEG (n=45)	p
WBC (x10^9/L)	8.2±1.95	8.6±1.81	0.283
Haemoglobin (g/L)	12.4±0.98	12.6±0.87	0.581
Haematocrit (%)	37.74±2.60	38.31±2.8	0.318
Platelet (x10^9/L)	238±63	243±50	0.578
Urea (mg/dL)	17±5.6	18±5.5	0.146
Creatinine (mg/dL)	0.63±0.12	0.60±0.13	0.226
TSH (µIU/mL)	1.34±0.77	1.27±0.74	0.063
AST (IU/dL)	18±6	17±7	0.659
ALT (IU/dL)	13±10	14±8	0.542
Glucose (mg/dL)	84±8.7	85±8.7	0.844
IMA (ng/mL)	6.9±0.3	8.2±0.2	<0.001

HEG: Hyperemesis gravidarum, WBC: white blood count, TSH: thyroid-stimulating hormone, AST: aspartate transaminase, ALT : alanine transaminase, IMA : ischaemia -modified albumin

Table 3. Data from previous studies of serum ischaemia-modified albumin levels in hyperemesis gravidarum patients

	Number of patients with HEG	Mean age of patients	Mean gestational age of patients	Serum IMA levels	p
Sari et al. (24)	45	26.3±5.2	9.1±2.6	6.6±0.7 ng/mL	<0.001
Bulanık et al. (25)	35	26±4.5	9.7±2.3	69.6 (40.3-400.4) ng/dL	0.136

HEG: Hyperemesis gravidarum, IMA: ischaemia-modified albumin

Study Limitations

The limitations of our study are a small number of participants, and the use of IMA levels as the only indicator of oxidative stress. In addition, as our study method is cross-sectional, IMA changes during the continuation of pregnancy were not analysed. The indicators that contribute to the evaluation of oxidative stress and inflammatory pathways would significantly increase the quality of the study. Finally, no significant difference was found between the groups in terms of biochemical parameters such as haemoglobin levels and liver and renal function tests. Although this could be considered as a factor that complicates diagnosis, it should be remembered that these biochemical parameters do not figure among the diagnostic criteria.

Conclusion

The present study demonstrated the role of IMA in the evaluation of oxidative stress, which is one of the most important factors in the pathogenesis of HEG. However, the aforementioned limitations must be considered during the evaluation of our study results, and further studies analysing the role of IMA in HEG pathogenesis should be conducted with larger patient populations.

Ethics

Ethics Committee Approval: This study was approved by the local ethical committee of the University of Health Sciences, Zekai Tahir Burak Women's Health Training and Research Hospital (decision no: 7, date: 25.05.2016).

Informed Consent: Written informed consent of all participants were obtained.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - S.Y., S.A.; Concept- S.Y., D.Ş.; Design - A.T., S.A.; Data Collection or Processing - S.Y., S.A., T.Ç.; Analysis or Interpretation - Ö.B.T., A.T., T.Ç.; Literature Search - S.Y., D.Ş.; Writing - S.A., Y.S.

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

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

References

1. Einarson TR, Piwko C, Koren G. Quantifying the global rates of nausea and vomiting of pregnancy: a meta analysis. J Popul Ther Clin Pharmacol 2013; 20:171-83.
2. Bailit JL. Hyperemesis gravidarum: epidemiologic findings from large cohort. Am J Obstet Gynecol 2005; 193: 811-4.
3. Biberoglu EH, Kirbas A, Dirican AÖ, Genc M, Avci A, Doganay B, et al. Alterations in lipid peroxidation and T-cell function in women with hyperemesis gravidarum. J Obstet Gynaecol 2016; 36: 93-6.
4. Eliakim R, Abulafia O, Sherer DM. 2000. Hyperemesis gravidarum: a current review. Am J Perinatol 2000; 17: 207-18.
5. Sun S, Qiu X, Zhou J. Clinical analysis of 65 cases of hyperemesis gravidarum with gestational transient thyrotoxicosis. J Obstet Gynaecol Res 2014; 40: 1567-72.
6. Verberg MF, Gillott DJ, Al-Fardan N, Grudzinskas JG. Hyperemesis gravidarum, a literature review. Hum Reprod Update 2005; 11: 527-39.
7. Onaran Y, Kafali H, Duvan Cİ, Keskin E, Celik H, Erel O. Relationship between oxidant and antioxidant activity in hyperemesis gravidarum. J Matern Fetal Neonatal Med 2014; 27: 825-8.
8. Shen XL, Lin CJ, Han LL, Lin L, Pan L, Pu XD. Assessment of ischemia-modified albumin concentrations for emergency room diagnosis of acute coronary syndrome. Int J Cardiol 2011; 149: 296-8.
9. Bar-Or D, Lau E, Winkler JV. A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia-a preliminary report. J Emerg Med 2000; 19: 311-5.
10. Duarte MM, Rocha JB, Moresco RN, Duarte T, Da Cruz IBM, Loro VL, et al. Association between ischemia-modified albumin, lipids and inflammation biomarkers in patients with hypercholesterolemia. Clin Biochem 2009; 42: 666-71.
11. Sinha MK, Roy D, Gaze DC, Collinson PO, Kaski JC. Role of "Ischemia modified albumin", a new biochemical marker ofmyocardial ischaemia, in the early diagnosis of acute coronary syndromes. Emerg Med J 2004; 21: 29-34.
12. Abboud H, Labreuche J, Meseguer E, Lavallee PC, Simon O, Olivot J-M, et al. Ischemia-modified albumin in acute stroke. Cerebrovasc Dis 2007; 23: 216-20.
13. Gunduz A, Turedi S, Mentese A, Karahan SC, Hos G, Tatli O, et al. Ischemia-modified albumin in the diagnosis of acute mesenteric ischemia: a preliminary study. Am J Emerg Med 2008; 26: 202-5.
14. Sbarouni E, Georgiadou P, Voudris V. Ischemia modified albumin changes - review and clinical implications. Clin Chem Lab Med 2011; 49: 177-84.
15. Prefumo F, Gaze DC, Papageorghiou AT, Collinson PO, Thilaganathan B. First trimester maternal serum ischaemia-modified albumin: a marker of hypoxia-ischaemia-driven early trophoblast development. Hum Reprod 2007; 22: 2029-32.
16. Özdemir S, Kıyıcı A, Balci O, Göktepe H, Çiçekler H, Çelik Ç. Assessment of ischemia- modified albumin level in patients with recurrent pregnancy loss during the first trimester. Eur J Obstet Gynecol Reprod Biol 2011; 155: 209-12.
17. Ustün Y, Engin-Ustün Y, Oztürk O, Alanbay I, Yaman H. Ischemia-modified albumin as an oxidative stress marker in preeclampsia. J Matern Fetal Neonatal Med 2011; 24: 418-21.
18. World Medical Association declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. JAMA 1997; 277: 925-6.
19. Dusek J, St'ásek J, Tichý M, Bis J, Gregor J, Vojácek J, et al. Prognostic significance of ischemia modified albumin after percutaneous coronary intervention. Clin Chim Acta 2006; 367: 77-80.
20. Bhagavan NV, Lai EM, Rios PA, Yang J, Ortega-Lopez AM, Shinoda H,et al. Evaluation of human serum albumin cobalt binding assay for the assessment of myocardial ischemia and myocardial infarction. Clin Chem 2003; 49: 581-5.
21. Iacovidou N, Briana DD, Boutsikou M, Sophia L, Baka S, Boutsikou T, et al. Cord blood ischemia-modified albumin levels in normal and intrauterine growth restricted pregnancies. Mediators Inflamm 2008; 2008: 523081.
22. Yarcı Gursoy A, Caglar GS, Demirtas S. Ischemia modified albumin in perinatology. Eur J Obstet Gynecol Reprod Biol 2017; 210: 182-8.
23. McCarthy FP, Lutomski JE, Greene RA. Hyperemesis gravidarum: current perspectives. Int J Womens Health 2014; 6: 719-25.
24. Sari N, Ede H, Engin-Ustun Y, Göçmen AY, Çağlayan EK. Hyperemesis gravidarum is associated with increased maternal serum ischemia-modified albumin. J Perinat Med 2017; 45: 421-5.
25. Bulanık M, Sağsöz N, Sayan CD, Yeral Mİ, Kısa Ü. Comparison of Serum Ykl-40 and Ischemia Modified Albulmin Levels Between Pregnant Women with Hyperemesis Gravidarum and Normal Pregnant Women. Med Arch 2019; 73: 97-100.
26. Sanu O, Lamont RF. Hyperemesis gravidarum: pathogenesis and the use of antiemetic agents. Expert Opin Pharmacother 2011; 12: 737-48.

İstanbul Med J 2020; 21(4): 301-6
DOI: 10.4274/imj.galenos.2020.84594

An Evaluation of the Factors Affecting Exclusive Breastfeeding

Sadece Anne Sütü ile Beslemeye Etki Eden Faktörlerin Değerlendirilmesi

Gamze Özgürhan[1], Serdar Cömert[2]

[1]İstanbul Training and Research Hospital, Clinic of Pediatrics, İstanbul, Turkey
[2]İstanbul Training and Research Hospital, Clinic of Pediatrics, Division of Neonatology, İstanbul, Turkey

ABSTRACT

Introduction: Breast milk is not only the ideal nourishment for babies, but is also unique in terms of its health benefits for mothers and economic benefits for the society. The World Health Organization and United Nations Children's Fund support exclusive breastfeeding for the first 6 months of post-natal life.

Methods: A total of 355 mothers who all delivered in our hospital were included in this study. A questionnaire was created to include questions regarding the mothers' opinions about breast milk and their reasons for continuing or discontinuing exclusive breastfeeding. We collected other data separately, including the socio-cultural and socio-economic characteristics of the mothers, fathers and babies. Using the data collected, the mothers were grouped and compared according to their breastfeeding behaviour. Fathers were also grouped according to their paternal characteristics and their potential impact on the mothers' breastfeeding behaviour was investigated.

Results: In this study, 49% of the mothers expressed the belief that breast milk is healthy and protects babies from diseases. Of the mothers who discontinued exclusive breastfeeding, 44.3% did so because they thought their milk was insufficient for their babies. In addition, 56.5% of mothers continued exclusive breastfeeding at post-natal month 4 and 35.2% at month 6. A higher percentage of mothers with a high level of education continued exclusive breastfeeding (p=0.011). There was no statistically significant difference between the different age groups in terms of breastfeeding behaviour. Mothers with healthy medical histories were found to have continued exclusive breastfeeding for longer periods than the others (p=0.037). Mothers who had help at home also continued exclusive breastfeeding for longer periods (p=0.031). Mothers using pacifiers were found to have a higher exclusive breastfeeding discontinuation rate than the others (p=0.007).

Conclusion: The leading reasons for discontinuing breastfeeding are incorrect and inadequate information about breastfeeding. Therefore, it is imperative that mothers are supported with appropriate and consistent education, both before and after birth, regarding the benefits of continued breastfeeding.

Keywords: Exclusive breastfeeding, pacifier, mother's attitude, bottle feeding, mother milk

ÖZ

Amaç: Anne sütü, bebekler için eşsiz bir besin kaynağı olmasının yanı sıra anne sağlığı ve toplum ekonomisi için de önemlidir. Dünya Sağlık Örgütü ve Birleşmiş Milletler Çocuklara Yardım Fonu ilk 6 ay sadece anne sütüyle beslenmeyi desteklemektedir.

Yöntemler: Bu çalışmaya hastanemizde doğum yapan 355 anne ve bebeği dahil edildi. Annelere uygulanan ankette; anne sütü hakkındaki düşünceleri, sadece anne sütüyle beslemeye devam etme ya da etmeme sebepleri soruldu. Anne, baba ve bebek için sosyo-kültürel ve sosyo-ekonomik özellikler dahil olmak üzere tüm sosyo-demografik veriler kaydedildi. Anneler emzirme davranışlarına göre gruplandırıldı ve karşılaştırıldı. Babaların sosyo-demografik özelliklerinin annelerin emzirme davranışları üzerine etkileri araştırıldı.

Bulgular: Çalışmadaki annelerin %49'u anne sütünün sağlıklı olduğuna ve bebekleri hastalıklardan koruduğuna inanıyordu. Emzirmeyi bırakan annelerin %44,3'ü sütlerinin bebekleri için yetersiz olduğunu düşünüyordu. Annelerin %56,5'i bebeklerini doğum sonrası ilk 4 ay sadece anne sütü ile beslerken, %35,2'si ilk 6 ay sadece anne sütü ile beslediği görüldü. Emzirme davranışı açısından farklı yaş grupları arasında istatistiksel olarak anlamlı bir fark bulunmadı. Yüksek eğitim düzeyine sahip anneler ve sağlıklı tıbbi öyküsü olan annelerin sadece anne sütü ile beslemeyi diğerlerinden daha uzun süre sürdürdüğü bulundu (p=0,011), (p=0,037). Evde yardımcısı olan anneler daha uzun süre sadece anne sütü ile beslemeye devam ettiler (p=0,031). Emzik kullanan annelerin sadece anne sütü ile beslemeyi daha önce bıraktıkları bulundu (p=0,007).

Sonuç: Emzirmeyi bırakmanın başlıca nedenleri emzirme hakkında yanlış ve yetersiz bilgilerdir. Bu nedenle annelerin, emzirmeye devam etmenin yararları konusunda hem doğumdan önce hem de sonra uygun ve tutarlı bir eğitim ile desteklenmesi zorunludur.

Anahtar Kelimeler: Sadece anne sütü ile besleme, emzik, anne davranışı, biberon ile besleme, anne sütü

Address for Correspondence/Yazışma Adresi: Gamze Özgürhan MD, İstanbul Training and Research Hospital, Clinic of Pediatrics, İstanbul, Turkey
Phone: +90 532 774 89 48 **E-mail:** gamzeozgurhan@yahoo.com **ORCID ID:** orcid.org/0000-0002-8063-1931

Cite this article as/Atıf: Özgürhan G, Cömert S. An Evaluation of the Factors Affecting Exclusive Breastfeeding. İstanbul Med J 2020; 21(4): 301-6.

Received/Geliş Tarihi: 31.05.2020
Accepted/Kabul Tarihi: 11.06.2020

Introduction

Breast milk is unique in that it provides the ideal nourishment for the growth babies and also for the development of their immune system. Its benefits are not limited to infant health, but also extend to maternal health as well as to economical saving for the society (1-4). For these reasons, many national and international institutions, including the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) advocate for the need of exclusive breastfeeding during the first 6 months following birth and the continuation of breastfeeding with necessary supplements until the age of 2 years (4,5).

Exclusive breastfeeding is defined as breastfeeding with breast milk only, without any other liquid supplements such as water or any solids (6). In many countries, most mothers start feeding their babies artificial supplements within the first 6 months of life and discontinue breastfeeding within the first 2 years. The most common reason for this behaviour is the mothers' conviction that breast milk is not sufficient for their babies or due to certain difficulties they face with breastfeeding, including not knowing how to continue breastfeeding while working outside of their homes. At other times, the reason may be as simple as that the mother does not have anyone to provide the support she needs or that the guidance and information received from health care professionals was not in support of breastfeeding (7-13).

Although breastfeeding is common in Turkey, exclusive breastfeeding dropped from 42% in 2008 to 30% in 2013, according to Turkey Population and Health Research (TPHR). This data suggests that exclusive breastfeeding is recommended, but is not widely practiced. It is common to encounter cases where babies are fed with formula or bottles. The percentage of babies receiving supplements within the first 6 months has increased from 8% in 2008 to 12% ın 2013. This ratio varies significantly across different cultures and societies (14).

The primary aim of this study was to examine the factors leading to mothers to discontinue exclusive breastfeeding within the first 6 months of life. We also assessed the reasons for continuing exclusive breastfeeding as well as opinions regarding breast milk.

Methods

This prospective and comparative study was conducted according to the principles of the Declaration of Helsinki and was approved by the Bağcılar Training and Research Hospital Non-interventional Clinical Research Ethics Committee (protocol no:2016/446, date: 17.03.2016). All the participants received oral and written information about the study and each participant provided a written informed consent.

Study Population and Design

The study included babies born in same hospital and their mothers. This hospital is the only public maternity clinic in the area with an average of 4,500 births/year and has a patient population distribution similar to that of Turkey's. Three or four cases per day were randomly selected as subjects from among the new-borns, who were born between March and July 2016 and were at 38 to 42 gestational weeks. Exclusion criteria included preterm births (<38 weeks) and unhealthy babies. All the new-borns received a comprehensive physical examination, including measuring the weight, height and head circumference (Table 1).

Data (age, type of delivery, parity, education, occupation, medical history, family type, consanguinity) was collected from the mothers via face-to-face post-natal interviews (within 3 days following delivery). Father's age, education and occupation, as well as monthly household income were also collected.

We also examined the mothers' opinions concerning breast milk and their reasons for discontinuing breastfeeding if they chose to do so. The methodology was as follows: after the mothers' opinions concerning breast milk were obtained (Table 2), they were informed about breast milk and its benefits by same specialist. At 2 weeks, 2 months, 4 months and 6 months after birth, the specialist called each mother and asked whether they have continued breastfeeding and if not, their reasons for discontinuation (Table 3). The specialist also asked whether any supplements (e.g. water, solids and formula) were given to the baby, if pacifiers/bottles were used and whether there was anyone helping the mother. Fifteen cases were excluded during follow-up because they were unreachable.

Exclusive breastfeeding is defined as breastfeeding with breast milk only, without any other liquid supplements (including water) or any solids for the first 6 months of life. Partial breastfeeding is defined as providing artificial nutrients to an infant in addition to breast milk. No breastfeeding is defined as complete cessation of breastfeeding before 6 months. The information gathered was classified according to the definitions above in Tables 4 and 5.

Mothers were classified according to their age, education, income level, medical history, occupation, consanguineous marriage, family type, helper at home, delivery method and use of pacifier (Table 5). These groups of mothers were then compared according to their exclusive breastfeeding behaviour.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20.0 for Windows (SPSS, Chicago, IL). The 1-sample Kolmogorov-Smirnov test was used to evaluate the distribution characteristics of the variables. Demographic and clinical characteristics of the Exclusive Breastfeeding and Discontinuing Exclusive Breastfeeding groups were compared using the Mann-Whitney U test for continuous variables and the χ^2 test for categorical variables. Logistic regression model was used for multivariate analysis. A $p<0.05$ was considered statistically significant.

Results

This study included 355 mothers and their babies. The mothers' breastfeeding behaviour and factors affecting this behaviour were tracked for the first 6 months of post-natal life. The demographic and clinical characteristics of the mothers and their babies are shown in Table 1.

We asked their opinions about breast milk and the mothers mentioned the following three beliefs the most: 49% of the mothers think breast milk is healthy and protects infants from diseases, 41.1% find it more nutritious than other options and 31.6% consider it the most natural food for their babies. Other opinions can be found in Table 2.

Three hundred and fifty participants (98.6% of the total participants) started breastfeeding after birth, while five participants (1.4%) did not breastfeed at all. After the first post-natal month, one third of the mothers had stopped exclusive breastfeeding (31.6%, shown in Table 4). The percentage of mothers continuing exclusive breastfeeding from month 1 to month 4 was found to be quite high (month 1, 68.4%; month 4, 56.5%). In addition, 42% of the participants who continued breastfeeding after the fourth month started including supplements in their babies' diets. The percentage of mothers who were breastfeeding exclusively by month 4 was 56.5% and 35.2% by month 6. Twenty-six participants (7.3%) fed their babies with breast milk and water within the first 6 months.

The most common three reasons given by the mothers for discontinuing exclusive breastfeeding were as follows: 44.3% said they were concerned that their milk was not sufficient for their babies, 19.1% reported that it was because their babies were not gaining weight and 13.9% mentioned that their babies did not want to breastfeed. The remaining reasons can be found in Table 3.

We found that the percentage of mothers who continued exclusive breastfeeding was significantly higher among mothers with a high level of education (p=0.011). Regarding breastfeeding behaviour, there was no statistically significant difference between the different age groups. Mothers with a certain medical condition reported discontinuing exclusive breastfeeding sooner (p=0.037) than healthy mothers. Mothers who had someone helping them at home with their baby continued exclusive breastfeeding longer than the others (p=0.031). Mothers using pacifiers were observed to have transitioned to adding supplements to their babies' diets and to have discontinued exclusive breastfeeding sooner compared to the mothers who do not use pacifiers (p=0.007). Other maternal socio-cultural and socio-economic characteristics are shown in Table 5.

In the logistic regression analysis, the presence of a helper for the mothers at home and pacifier use were found to be a factor independently affecting exclusive breastfeeding (Table 6).

Regarding paternal characteristics, there were no statistically significant differences in terms of age, education or occupation.

Discussion

Although health authorities strongly recommend exclusive breastfeeding, this advice has not been put into practice at a satisfactory level. This is the main reason why mothers' breastfeeding behaviour is supported by health policies and various educational programmes by health personnel globally (15). In our study, we found that exclusive breastfeeding occurred with 35.2% of participants. Although this percentage is higher than the country average of 30% (TPHR 2013) (14), we have a long way to go before we hit the 2025 target set by WHO and UNICEF in Global Nutrition Targets 2025: >50% exclusive breastfeeding in the first 6 months (15). In a study examining breastfeeding with and

Table 1. Demographic and clinical characteristics of the mothers and their babies

Baby	
Gender (male/female) (n)	175/180
Height (cm) (mean ± SD)	50.1±1.2
Weight (g) (mean ± SD)	3201.4±469.2
Head circumference (cm) (mean ± SD)	34.9±0.8
Mother	
Age (years) (mean ± SD)	28.3±5.2
Delivery method Vaginal/caesarean section (n)	179/176

SD: Standard deviation

Table 2. Mothers' opinions about breastfeeding

Opinions*	**(n) %**
It is healthier and protects against diseases	(174) 49.0
More nutritious	(146) 41.1
The most natural food	(112) 31.6
Affordable and hassle-free to give	(42) 11.9
To develop a close relationship with my baby	(21) 5.9
Doctor says it is better	(14) 4.0
Other opinions	(35) 9.9

*Mothers may have given more than one opinion on breastfeeding

Table 3. Reasons for discontinuing exclusive breastfeeding

Reasons*	**(n) %**
I am concerned that my milk is not sufficient for my baby	(157) 44.3
My baby is not gaining weight	(68) 19.1
My baby does not want breast milk	(49) 13.9
My baby's health has deteriorated	(46) 13.0
I wanted my baby to taste something else as well	(34) 9.6
My baby is restless and crying and I think he/she is not satisfied	(15) 4.3
Breast-related problems (mastitis, engorgement, cracked or sore nipple)	(12) 3.5
I was affected by the people around me	(9) 2.6
Breastfeeding contra-indicated	(9) 2.6
Other reasons	(9) 2.6

*Mothers who may have given more than one reason for discontinuing

Table 4. Rates of no, partial and exclusive breastfeeding from 1 to 6 month

Age (Month)	**No Breastfeeding* (n) %**	**Partial Breastfeeding** (n) %**	**Exclusive Breastfeeding*** (n) %**
1	(16) 4.5	(96) 27.1	(243) 68.4
2	(26) 7.3	(103) 28.9	(226) 63.8
3	(34) 9.6	(106) 29.9	(215) 60.5
4	(42) 11.9	(112) 31.6	(201) 56.5
5	(50) 14.1	(148) 41.8	(157) 44.1
6	(56) 15.8	(174) 49.0	(125) 35.2

*Complete cessation of breastfeeding

**Providing artificial nutrients to an infant in addition to breast milk

***Breastfeeding with breast milk only, without any other liquid supplements (including water) or any solids

without prenatal breast milk and breastfeeding training, the rates of exclusive breastfeeding at month 6 were 67.8% and 28%, respectively (16). In another national study, exclusive breastfeeding rate was 45% at month 4 (17). The importance of breastfeeding has been more widely acknowledged in low and middle-income countries; however, breastfeeding in high-income countries has been on the decline (18). Between 2006 and 2012, exclusive breastfeeding was at 25% in the WHO European Region, while it was at 43% in the WHO South-East Asia Region. More recent data (2015) from 21 countries in Europe show that exclusive breastfeeding has now dropped to 13% (19).

Table 5. Maternal socio-cultural and socio-economic characteristics

Characteristics	Discontinuing Exclusive Breastfeeding (n=230) %	Exclusive Breastfeeding (n=125) %	p
Age at delivery (Years)			
<25	(62) 26.9	(36) 28.8	ns
25-29	(71) 30.9	(41) 32.8	
30-34	(67) 29.1	(35) 28.0	
>34	(30) 13.1	(13) 10.4	
Education			
Illiterate	(19) 8.3	(7) 5.6	0.011
Primary school	(101) 43.9	(33) 26.4	
Secondary school	(79) 34.3	(41) 32.8	
High school	(23) 10.0	(29) 23.2	
University	(8) 3.5	(15) 12.0	
Monthly income (Turkish Liras)			
<1500	(160) 69.6	(88) 70.4	ns
1500-3000	(59) 25.6	(28) 22.4	
>3000	(11) 4.8	(9) 7.2	
Disease presence	(29) 12.6	(7) 5.6	0.037
Occupation	(35) 15.2	(22) 17.6	ns
Consanguineous marriage	(41) 17.8	(25) 20.0	ns
Family type			
Small*	(177) 76.9	(91) 72.8	ns
Large	(53) 23.1	(34) 27.2	
Helper at home	(35) 15.2	(29) 23.2	0.031
Delivery method			
Vaginal	(114) 49.6	(65) 52.0	ns
Caesarean section	(116) 50.4	(60) 48.0	
Pacifier use (First 1 month)	(104) 45.2	(24) 19.2	0.007

SD: Standard deviation, ns: non-significant, *Small family: mother, father and children, Statistically significant increased values (p<0.05)

Table 6. Logistic regression analysis of factors influencing exclusive breastfeeding

	β	p	OR	95% CI
Maternal education	-0.12	0.158	0.20	0.52-1.52
Maternal illness	-0.56	0.27	1.21	0.21-1.55
Helper at home	0.62	0.035	4.44	0.30-0.96
Pacifier use	0.23	0.03	1.61	0.64-1.41

β: Beta coefficient, OR: odds ratio, CI: confidence interval

The benefits of breast milk are widely known by mothers and this awareness has been the main driving factor behind breastfeeding (20). In our study, mothers predominantly believed that breast milk is healthier, protects against disease and that it is more nutritious. This by itself indicates that most of the mothers understand the importance of breast milk. However, other factors often have a negative impact on the inclination to breastfeed. The mothers' empirical decisions and values have been shown to inhibit breastfeeding (21). Mothers who are less confident about breast milk discontinue breastfeeding at earlier stages (22). In our study, the main reasons for discontinuing breastfeeding were concerns that the breast milk is not sufficient for the baby and that the baby was not gaining weight. To mitigate these concerns, education and support for breastfeeding for mothers, as well as continuous and sufficient information flow to mothers during follow-ups would boost the mothers' confidence and have a positive impact on their breastfeeding behaviour (23).

Many studies showed that maternal age and level of education has a strong positive correlation with breastfeeding in developed countries (24-26). However, in developing countries, there is an inverse correlation as we see other factors such as traditional breastfeeding behaviours and advice from family and friends becomes more dominant (27). As the age and level of education of the mother increases, so does the percentage of mothers who start and continue to breastfeed. The older the mother, the more likely she is to start and continue breastfeeding (24,28,29). Very young mothers are more likely to have lower education and a higher tendency to feed their babies formula (30). In another study, first-time mothers were found to be more likely to continue breastfeeding (31). In our study, exclusive breastfeeding was more common in mothers with high levels of education; however, there was no statistically significant difference in breastfeeding behaviour among different age groups.

Less educated and younger mothers are less likely to use alternatives to pacifiers to calm their babies and are more likely to introduce pacifiers to their babies at earlier stages. This leads to discontinuation of the exclusive breastfeeding (32). In our study, we observed that mothers who introduced pacifiers to their babies within the first month are less likely than the other mothers to continue exclusive breastfeeding.

Another major factor associated with breastfeeding is the mother's socio-economic status (occupation, household income, etc). In developed countries, there is a positive correlation between high income and breastfeeding (26-28); however, there is an inverse correlation in developing countries (29). In our study, there was no statistically significant relationship between household income/mother's occupation and breastfeeding continuation. In addition, having a helper at home is positively correlated with breastfeeding according to our findings.

Another factor influencing the breastfeeding behaviour is the health of the mother. We found that mothers with any health condition are less likely to continue exclusive breastfeeding (33-35). Also, the method of infant delivery may have an impact on breastfeeding behaviour. Pain/discomfort after a caesarean may delay breastfeeding, whereas breastfeeding can commence sooner after vaginal birth (36). In our

study, we did not come across any correlation between method of delivery and breastfeeding behaviours.

In November 2019, TPHR announced that exclusive breastfeeding as 40.7% in the first 6 months. The rate of breast-milk use decreased from 66% for one year to 34% for 2 years. The rate of feeding babies with other milk instead of breast milk is 23%. Feeding with bottle is reported as 53% in the first 2 years (37).

Our study is important because it provides some valuable results on the breastfeeding behaviours of mothers; however, it has a few limitations. The first limitation is the small sample size. Secondly, we only followed-up the participants for 6 months after birth, as we focused on exclusive breastfeeding.

Conclusion

Breast milk is the best source of nutrition during the first 6 months of life. Therefore, it is an important public health objective to increase the number of mothers who practice exclusive breastfeeding. Hospital policies and practices are essential in meeting this objective. Within the scope of the Baby-Friendly Hospital Initiative, the confidence of the mothers needs to be boosted through education about breast milk and breast feeding both in the prenatal and post-natal periods. In addition, a high level of awareness regarding the benefits of breastfeeding needs to be created among health care personnel and in the society, with education supported by factual and scientific information.

Ethics

Ethics Committee Approval: This prospective and comparative study was approved by the Bağcılar Training and Research Hospital Non-interventional Clinical Research Ethics Committee (protocol no: 2016/446, date: 17.03.2016).

Informed Consent: All the participants provided a written informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - G.Ö.; Concept - G.Ö., S.C.; Design - G.Ö., S.C.; Data Collection or Processing - G.Ö.; Analysis or Interpretation - G.Ö., S.C.; Literature Search - G.Ö., S.C.; Writing - G.Ö.

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

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

References

1. Gartner LM, Morton J, Lawrence RA, Naylor AJ, O'Hare D, Schanler RJ, et al. Breastfeeding and the use of human milk. Pediatrics 2005; 115: 496-506.
2. Kramer MS, Kakuma R. The optimal duration of exclusive breastfeeding: a systematic review. Adv Exp Med Biol 2004; 554: 63-77.
3. Gartner LM, Morton J, Lawrence RA, Naylor AJ, O'Hare D, Schanler RJ, et al. Breastfeeding and the use of human milk. Pediatrics 2005; 115: 496-506.
4. World Health Organization. Breastfeeding. Available from URL: http://www.who.int/topics/breastfeeding/en/ (accessed 14th August, 2010)
5. WHO/UNICEF. Global strategy for infant and young child feeding; World Health Organization: Geneva, Switzerland, 2003.
6. WHO. Indicators for assessing infant and young child feeding practices (Part 1) Definitions. 2008 (http://whqlibdoc.who.int/publications/2008/9789241596664_eng.pdf) (accessed 1/08/2009)
7. Essex C, Smale P, Geddis D. Breastfeeding rates in New Zealand in the first 6 months and the reasons for stopping. N Z Med J 1995; 108: 355-7.
8. Vogel A, Hutchison BL, Mitchell EA. Factors associated with the duration of breastfeeding. Acta Paediatr 1999; 88: 1320-6.
9. Avery M, Duckett L, Dodgson J, Savik K, Henly SJ. Factors associated with very early weaning among primiparas intending to breastfeed. Matern Child Health J 1998; 2:167-179.
10. Deshpande AD, Gazmararian JA. Breast-feeding education and support: association with the decision to breast-feed. Eff Clin Pract 2000; 3: 116-22.
11. Ertem IO, Votto N, Leventhal JM. The timing and predictors of the early termination of breastfeeding. Pediatrics 2001; 107: 543-8.
12. Losch M, Dungy CI, Russell D, Dusdieker LB. Impact of attitudes on maternal decisions regarding infant feeding. J Pediatr 1995; 126: 507-14.
13. Scott JA, Binns CW. Factors associated with the initiation and duration of breastfeeding: a review of the literature. Breastfeed Rev 1999; 7: 5-16.
14. Turkey Demographic and Health Survey. 2013 Report. Available from URL: www.hips.hacettepe.edu.tr/tnsa2013/rapor/TNSA_2013_ana_rapor.pdf
15. World Health Organization, UNICEF. Global Nutrition Targets 2025: Breastfeeding policy brief. 2014 Available from URL: http://www.who.int/nutrition/publications/globaltargets2025_policybrief_breastfeeding/en/
16. Onbaşı Ş, Duran R, Çiftdemir NA, Vatansever Ü, Acunaş B, Süt N. The effect of prenatal breast-milk and breast-feeding training given to expectant mothers on the behaviour of breast-feeding. Turk Arch Ped 2011; 46: 74-8.
17. Kondolot M, Yalçın SS, Yurdakök K. Sadece anne sütü alım durumuna etki eden faktörler. Çocuk Sağlığı ve Hastalıkları Dergisi 2009; 52:122-7.
18. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. Lancet 2016; 387: 475-90.
19. Regional Office for Europe of WHO. WHO European Region has lowest global breastfeeding rates. Available from: URL: https://www.euro.who.int/en/health-topics/disease-prevention/nutrition/news/news/2015/08/who-european-region-has-lowest-global-breastfeeding-rates (August-5-2015)
20. The National Information Centre, IFF Research. Infant feeding survey report 2010: Early results. 2011 Available from: URL: http://www.ic.nhs.uk/webfiles/publications/003_Health_Lifestyles/IFS_2010_early_results/IFS_2010_headline_report_tables2.pdf (accessed 16/09/2011)
21. Haku M, Ohashi K. Pursuit of factors limiting breastfeeding continuation, using Orem's dependent care model. Journal of Japan Academy of Midwifery 2004; 18: 6-18.
22. Blyth R, Creedy DK, Dennis CL, Moyle W, Pratt J, De Vries SM. Effect of maternal confidence on breastfeeding duration: an application of breastfeeding self-efficacy theory. Birth 2002; 29: 278-84.
23. Labarere J, Gelbert-Baudino N, Ayral AS, Duc C, Berchotteau M, Bouchon N, et al. Efficacy of breastfeeding support provided by trained clinicians during an early, routine, preventive visit: a prospective, randomized, open trial of 226 mother-infant pairs. Pediatrics 2005; 115: 139-46.
24. Dennis CL. Breastfeeding initiation and duration: A 1990-2000 literature review. J Obstet Gynaecol Neonatal Nurs 2002; 31: 12-32.
25. Scott JA, Landers MC, Hughes RM, Binns CW. Factors associated with breastfeeding at discharge and duration of breastfeeding. J Pediatr Child Health 2001; 37: 254-61.

26. Waldenström U, Aarts C. Duration of breastfeeding and breastfeeding problems in relation to length of postpartum stay: a longitudinal cohort study of a national Swedish sample. Acta Pediatr 2004; 93: 669-76.

27. Forman MR. Review of research on the factors associated with choice and duration of infant feeding in less-develop countries. Pediatrics 1984; 74: 667-94.

28. Haku M. Breastfeeding: factors associated with the continuation of breastfeeding, the current situation in Japan, and recommendations for further research. J Med Invest 2007; 54: 224-34.

29. Hoddinott P, Tappin D, Wright C. Breastfeeding. BMJ 2008; 336: 881-7.

30. Dubois L, Girard M. Social inequalities in infant feeding during the first year of life: The longitudinal study of child development in Quebec 1998-2002. Public Health Nutr 2003; 6: 773-83.

31. Bolling K, Grant C, Hamyln B, Thornton A. Infant feeding survey report 2005. The Information Centre, 2007. Available from URL: http://data.parliament.uk/DepositedPapers/Files/DEP2008-0853/DEP2008-0853.pdf (accessed 4/08/2010)

32. Mauch CE, Scott JA, Magarey AM, Daniels LA. Predictors of and reasons for pacifier use in first-time mothers: an observational study. BMC pediatr 2012; 12: 7.

33. Rioux FM, Savoie N, Allard J. Is there a link between postpartum anaemia and discontinuation of breastfeeding. Can J Diet Pract Res 2006; 67: 72-6.

34. Dunn S, Davies B, McCleary L, Edwards N, Gaboury I. The relationship between vulnerability factors and breastfeeding outcome. J Obstet Gynecol Neonatal Nurs 2006; 35: 87-97.

35. Galler JR, Harrison RH, Ramsey F, Chawla S, Taylor J. Postpartum feeding attitudes, maternal depression and breastfeeding in Barbados. Infant Behav Dev 2006; 26: 189-203.

36. Rondó PH, Souza MR. Maternal distress and intended breastfeeding duration. J Psychosom Obstet Gynaecol 2007; 28: 55-60.

37. Turkey Demographic and Health Survey. 2018 Report. Available from URL: http://www.hips.hacettepe.edu.tr/tnsa2018/rapor/TNSA2018_ana_Rapor.pdf

İstanbul Med J 2020; 21(4): 307–11
DOI: 10.4274/imj.galenos.2020.58224

Can Complete Blood Count Inflammation Markers Be Used to Predict Graft Success After Tympanoplasty?

Timpanoplasti Sonrası Greft Başarısını Ön Görmede Tam Kan Sayımı Enflamasyon Belirteçleri Kullanılabilir mi ?

Zehra Çınar, Özgür Yiğit, Ahmet Volkan Sünter

İstanbul Training and Research Hospital, Clinic of Otorhinolaryngology and Head and Neck Surgery, İstanbul, Turkey

ABSTRACT

Introduction: This study aimed to investigate the effect of preoperative neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), eosinophil lymphocyte ratio (ELR), basophil lymphocyte ratio (BLR) and lymphocyte monocyte ratio (LMR) on graft success after tympanoplasty.

Methods: Forty-five patients who underwent tympanoplasty with temporal fascia graft between January 2017 and December 2019 were included in this study. The patients were divided into two groups: intact (13 men, 12 women) and perforated (13 women, 7 men) according to their postoperative graft results. Demographic data and routine complete blood count parameters, such as NLR, PLR, ELR, BLR and LMR, as well as intraoperative middle ear characteristics were compared for both the groups.

Results: The following parameters did not differ significantly differ (p>0.05) in both groups: age; gender; side; middle ear condition; platelet, neutrophil, lymphocyte, eosinophil, monocyte and basophil counts; NLR; PLR; ELR; BLR and LMR.

Conclusion: From the results, it can be concluded that NLR, PLR, ELR, BLR and LMR, which are markers of inflammation in the preoperative period, cannot be used to predict graft success in patients who will undergo tympanoplasty for chronic otitis media.

Keywords: Chronic otitis media, inflammation, graft success, perforation

ÖZ

Amaç: Bu çalışmanın amacı preoperatif nötrofil lenfosit oranı (NLO), platelet lenfosit oranı (PLO), eozinofil lenfosit oranı (ELO), bazofil lenfosit oranı (BLO) ve lenfosit monosit oranı (LMO)'nın temporal fasya grefti kullanılan timpanoplasti öncesi greft başarısını ön görmede kullanılabilirliğini ortaya koymaktır.

Yöntemler: Ocak 2017-Aralık 2019 tarihleri arasında kliniğimizde kronik otitis media nedeniyle temporal fasya grefti ile timpanoplasti yapılan hastalar grefti başarılı olan intakt grup (13 erkek,12 kadın) ve grefti başarız olan perfore grup (13 kadın, 7 erkek) olmak üzere iki gruba ayrıldı. Bu iki grup yaş, taraf ve cinsiyet ile tam kan sayımında hücre sayıları ve NLO, PLO, ELO, BLO ve LMO ve orta kulağın durumu açısından karşılaştırıldı.

Bulgular: İntakt ve perfore gruplarda yaş, cinsiyet dağılımı, taraf ve orta kulağın durumu ile platelet, nötrofil, lenfosit, eozinofil, monosit, bazofil sayıları ve NLO, PLO, ELO, BLO ve LMO anlamlı (p>0,05) farklılık göstermemiştir.

Sonuç: Bu çalışmanın bulguları ışığında kronik otitis medya nedeniyle timpanoplasti uygulanacak hastalarda preoperatif dönem enflamasyon belirteçleri olan NLO, PLO, ELO, BLO ve LMO'nun greft başarısını ön görmede kullanılamayacağı sonucuna varılmıştır.

Anahtar Kelimeler: Kronik otitis media, enflamasyon, greft başarısı, perforasyon

Introduction

Otitis media is a chronic inflammation and infection of the middle ear and mastoid cavity characterized by hearing loss and ear discharge (1). Type 1 tympanoplasty is tympanic membrane perforation repair, first performed by Berthold (1878) and later popularized by wullstein and Zollner (1950) (2). Many methods and graft materials have been used in tympanic membrane perforation repair until today. The most commonly used graft material is the temporal fascia (3).

Neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), eosinophil lymphocyte ratio (ELR), basophil lymphocyte ratio (BLR) and lymphocyte monocyte ratio (LMR) are increasingly used in many medical disciplines. In chronic inflammatory pathologies, the number of neutrophils and platelets increases, while the number of lymphocytes decreases (4). The prognostic value of NLR and PLR as indicators of systemic inflammatory response in many types of cancer has found a wide range of research areas (5). On the other hand, it has been suggested

Address for Correspondence/Yazışma Adresi: Zehra Çınar MD, İstanbul Training and Research Hospital, Clinic of Otorhinolaryngology and Head and Neck Surgery, İstanbul, Turkey
Phone: +90 212 459 60 00 **E-mail:** drzehradonmez@hotmail.com **ORCID ID:** orcid.org/0000-0002-5027-4750

Cite this article as/Atıf: Çınar Z, Yiğit Ö, Sünter AV. Can Complete Blood Count Inflammation Markers Be Used to Predict Graft Success After Tympanoplasty?. İstanbul Med J 2020; 21(4): 307-11.

Received/Geliş Tarihi: 02.04.2020
Accepted/Kabul Tarihi: 11.06.2020

that the character of otitis media with effusion can be determined by calculating NLR and PLR in the preoperative period and that unnecessary surgical procedure can be avoided (6). Eosinophils and basophils are leucocytes with proinflammatory effect and multifunctional properties that are involved in the pathogenesis of parasitic and allergic diseases (4). The relationship of monocyte/lymphocyte ratio with prognosis in many types of cancer has also been investigated (7,8).

It is very important to be able to predict post-operative graft success in the preoperative period. Realistic expectations and the possibility of revision surgery can only be talked to patients in this way. In the literature, the success rate of fascia graft and tympanic membrane perforation repair ranges between 75-90%. Temporal fascia graft is the most commonly used graft material in tympanoplasty operations, but since the success rate is variable, otologists have tried to use different grafts to improve graft success (3,9,10).

The aim of this study is to determine the availability of NLR, PLR, ELR, BLR and LMR in preoperative period to predict graft success prior to tympanoplasty using temporal fascia graft.

Methods

Approval was obtained from İstanbul Training and Research Hospital Ethics Committee for this study on 07.02.2020 (decision no: 2177).

Study Design

This study is a retrospective comparative study based on the medical records of patients who underwent type 1 tympanoplasty surgery at the İstanbul Training and Research Hospital, Clinic of Otorhinolaryngology and Head and Neck Surgery (ENT-HNS) between 2017 and 2019.

Study Population

Between January 2017 and December 2019, the medical records of 769 patients who underwent tympanoplasty surgery at the İstanbul Training and Research Hospital, Clinic of ENT-HNS were reached. Patients who did not meet the criteria for inclusion in the study were excluded from the study. The patients who underwent tympanoplasty using temporal fascia graft were divided into two groups according to whether the graft was successful in the second month of post-operative: graft successful (Figure 1) group: 27 patients, graft failed (Figure 2) group: 20 patients. These two groups were compared with each other in terms of age, side, gender and middle ear condition and in terms of NLR, PLR, ELR, BLR and LMR in preoprative blood counts.

Criteria for Inclusion in the Study

Patients between the ages of 15-65 who had a persistent tympanic membrane perforation that had been dry for at least three months prior to surgery and type 1 tympanoplasty using an intraoperative fascia graft were included in the study.

Exclusion Criteria

Patients with cholesteatoma, prior autological surgery with concomitant mastoidectomy, contralateral tympanic membrane perforation, non-intact bony chain, smokers, additional disease that may disrupt middle ear pneumatization (nasal septal deviation, cleft palate,...), additional systemic disease that may trigger systemic inflammation (hypertension, cardiac diseases, oncological malignancies...), patients who were <15-years-old and >65-years-old who had type 1 tympanoplasty using a graft material other than fascia graft were excluded.

Surgery

Oral and written informed consent was obtained from all patients prior to surgery. Operation technique was standard in both groups. The temporal muscle fascia was taken using postauricular incision under general anesthesia, dried and placed using the over and underlay technique (Figure 3).

Determining Cell Rates

Preopeartive complete blood count results were used to calculate NLR, PLR, ELR, LMR and BLR. These two groups were compared statistically in terms of age, gender, location of perforation, size of perforation,

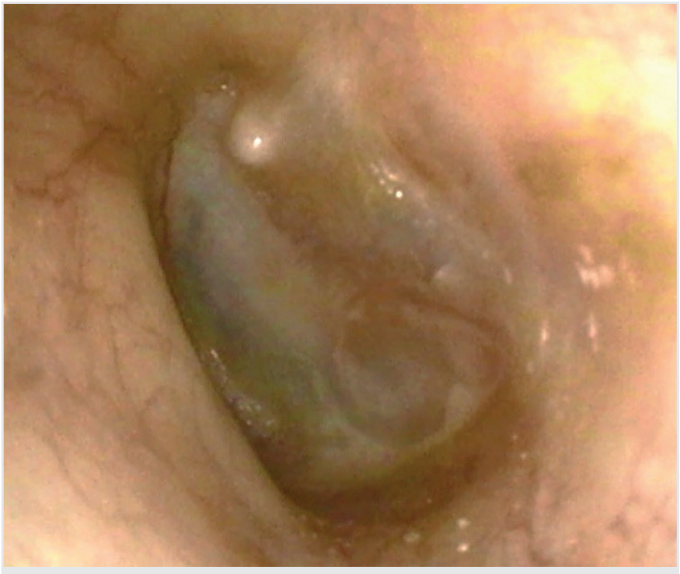


Figure 1. Graft intact after tympanoplasty

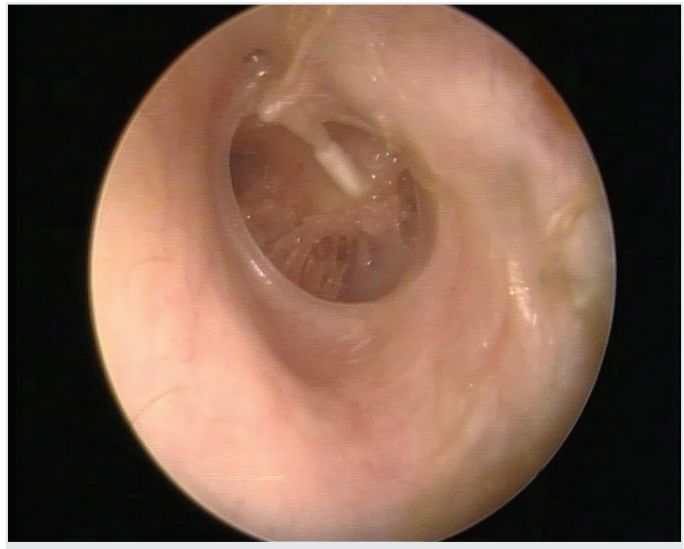


Figure 2. Graft perforated after tympanoplasty

condition of middle ear mucosa and preoperative NLR, PLR, ELR, LMR and BLR values.

Statistical Analysis

Mean, standard deviation, median lowest, highest, frequency and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured by Kolmogorov-Simirnov test. The Mann-Whitney U test and independent sample test were used in the analysis of quantitative independent data. The chi-square test was used for the analysis of qualitative independent data; the fischer excat test was used when the chi-square test conditions were not met. The SPSS 26.0 program was used in the analyses.

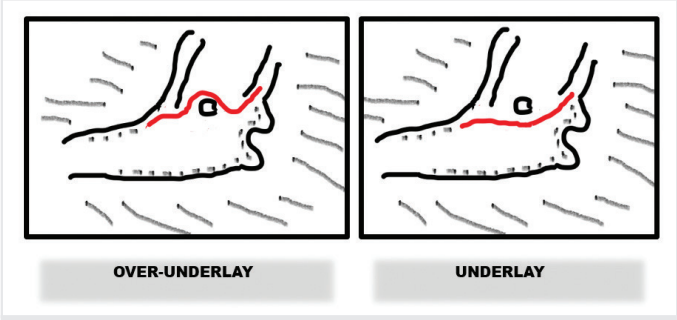


Figure 3. Overlay technic and over underlay technic

Results

The ages of the patients in the two groups with fascia graft intact and perforated after tympanoplasty, were not significantly different (p>0.05). Gender distribution and smoking rate of patients in intact and perforated graft groups did not differ significantly (p>0.05) (Table 1).

Platelet count, neutrophil count, lymphocyte count did not differ significantly (p>0.05) in groups with graft intact and perforated. The eosinophil count, monocyte count, and basophil count did not differ significantly (p>0.05) in groups with graft intact and perforated (Table 1).

PLR and NLR were not significantly different in intact and perforated graft groups (p>0.05). The ELR and BLR of patients in intact and perforated graft groups did not differ significantly (p>0.05) (Table 1). LMR was not significantly different in intact and perforated graft groups (p>0.05) (Table 1).

The right and left ear ratio of patients with intact and perforated grafts did not differ significantly (p>0.05). The middle ear condition of patients

Table 1. Comparison of groups ın terms of clinical, operation side, middle ear mucosa and cell counts and ratios in whole blood count test

		Intact		Perforated		p	
		Ave ± SD / n-%	Median	Ave ± SD / n-%	Median		
Age		34.3±12.4	36.0	32.1±12.3	30.5	0.559	t
Gender	Female	12 /48.0%		13/65.0%		0.254	X^2
	Male	13/52.0%		7/35.0%			
Cigarettes	(-)	25/100.0%		20/100.0%		1.000	X^2
	(+)	0/0.0%		0/0.0%			
Platelet count		269.3±48.5	276.0	267.1±104.1	266.0	0.404	m
Neutrophile count		4.1±0.9	4.0	4.1±1.3	4.0	0.958	t
Lymphocyte count		2.4±0.6	2.2	2.3±0.6	2.3	0.803	t
Eosinophil count		0.2±0.2	0.1	0.3±0.4	0.2	0.204	m
Monocyte count		0.6±0.2	0.6	0.6±0.1	0.6	0.438	t
Basophile count		0.0±0.0	0.0	0.0±0.0	0.0	0.482	m
Platelet lymphocyte ratio		121.0±37.7	109.9	116.2±27.6	118.6	0.636	t
Neutrophile lymphocyte ratio		1.8±0.5	1.8	1.9±0.9	1.7	0.641	t
Eosinophil lymphocyte ratio		0.1±0.1	0.0	0.1±0.1	0.1	0.157	m
Lymphocyte monocyte ratio		4.2±1.4	3.8	4.2±1.3	4.4	0.840	t
Basophobia lymphocyte ratio		0.0±0.0	0.0	0.0±0.0	0.0	0.646	t
Ear	Right	15/60.0%		8/40.0%		0.182	X^2
	Left	10/40.0%		12/60.0%			
Middle ear mucosa	Normal	23/92.0%		18/90.0%		0.814	X^2
	Hypertrophic	2/8.0%		1/5.0%			
	Sclerotic	0/0.0%		1/5.0%			

[m]Mann-Whitney U test, [X2]chi-square test, [t]Unpaired t test, Ave: average, SD: standard deviation

with intact and perforated grafts did not differ significantly (p>0.05). (Table 1).

Discussion

Tympanoplasty is a surgical procedure to close tympanic membrane perforation and improve hearing. Many graft materials have been used for tympanic membrane reconstruction so far (9,11). Temporal muscle fascia shows variable success rates but are still the most commonly used graft material (11).

The success of tympanoplasty can vary depending on the patient, the size of the middle ear pathology, the graft material and the surgical technique (9). In patients with eustachian tube dysfunction, retraction pocket, adhesive middle ear disease and subtotal or total perforation, more graft failure was revealed by temporal fascia graft (11). The success rate of the temporal fascia graft after tympanoplasty was found to be lower in young (<16-years-old) patients, patients with bilateral middle ear disease and accompanying anatomical disorder that may affect the ventilation of the middle ear, such as adenoid vegetation, cleft palate, and apparent septal deviation (3,9,10). It was stated that these patients were not suitable candidates for tympanoplasty with temporal fascia graft. Similarly, it was revealed that graft success rate with fascia graft was much lower in revision surgeries (9,10). Smoking has been reported as the solely factor associated with high graft failure in cartilage tympanoplasty (12).

Even if negative prognostic factors are eradicated, graft success after tympanoplasty with temporal muscle fascia can range between 80-97% (3,13). No useful marker has been found for predicting postopeartive tympanic membrane perforation recurrence in preoperative period except for the prognostic factors mentioned today. PLR and NLR have been used to predict prognosis and recurrence in many diseases, such as malignancies and infectious/noninfectious pathologies (14). NLR can be easily calculated from routine complete blood cell count (BCC) as a good indicator of inflammatory condition. NLR has been investigated in many diseases in otolaryngology and it has been revealed that more nasal polyp recurrence develops in patients with increased NLR compared to patients with low NLR (4). In a study by He et al. (15), in patients with nasopharyngeal cancer, increased NLR before treatment was associated with poor survival rates. In another study, higher NLR was encountared in stage IV larynx cancer compared to clinical stage III (16). Increased idiopathic sudden sensorineural hearing loss was associated with poor prognosis of increased NLR (17). In this study, no statistically significant difference was found between the intact and perforated groups in terms of NLR. PLR is another marker that can be easily calculated from a complete BCC to assess inflammatory conditions. In advanced-stage malignancies, pre-treatment high PLR was found to be associated with low survival rates (18). It has been demonstrated that increased PLR has a negative effect on prognosis in cardiovascular diseases (19). PLR is used in otolaryngology, especially in head and neck cancers. It was emphasized that increased PLR in head and neck cancers is compatible with low survival rates (20). It was also evaluated in sinonasal polyp recurrence and increased PLR was found to be associated with recurrence (21). In this study, no statistically significant difference was found between two groups with and without graft succes after tympanoplasty in terms of PLR.

ELR and BLR are other rates that present the inflammatory state and they can be easily calculated. Eosinophils and basophils are closely related to allergic conditions and parasitic infections (22,23). In the study in which Kökoğlu and Şahin (4) measured patient satisfaction after septoplasty, patient's dissatisfaction after septoplasty was found to be proportional with high ELR and BLR and high eosinophil and basophil counts. In the clinical study conducted by Kara et al. (24), a statistically significant correlation was found between nasal polyposis severity and ELR in patients with nasal polyposis. Higher ELR was found as a new inflammatory marker in smokers compared to non-smokers (25). It has been demonstrated that NLR and ELR can be used as a marker of occult inflammation and disease activity in patients diagnosed with achalasia (26). In systemic autoimmune rheumatic diseases, ELR and BLR may vary depending on the disease. It has been shown that in many systemic autoimmune rheumatic diseases, BLR is decreased, while ELR is decreased in systemic lupus erythematosus and increased in other systemic autoimmune rheumatic diseases (27). In this study, no statistically significant difference was found between the intact group whose graft was successful and the perforated group whose graft was unsuccessful in terms of ELR and BLR.

In recent years, LMR has been recognized as an important indicator of endothelial dysfunction and inflammation that have with prognostic and predictive value in different populations. Although the relationship between low LMR and increased mortality has not been fully clarified, high monocyte count or low lymphocyte count have been associated with poor prognosis in various pathologies (28,29).

A significant decrease in overall and disease-free survival was found in patients diagnosed with T-cell lymphoblastic leukemia and with LMR value ≥2.8 when evaluated together with high NLR and PLR (29). A significant correlation was found between high LMR value before treatment and overall and disease-free survival in patients with head and neck cancer (30). In this study, no statistically significant difference was found between two groups with and without graft succes after tympanoplasty in terms of LMR.

The aim of this study was to evaluate the availability of preoperative NLR, PLR, ELR, BLR and LMR values to predict graft success in patients whose operation is planned due to chronic otitis media. The results of this study showed that there was no statistically significant correlation between graft success and NLR, PLR, ELR, BLR and LMR.

Conclusion

As a result, the success rate of graft after tympanoplasty may vary depending on multifactorial causes. In the light of the findings of this study, it has been concluded that preoperative NLR, PLR, ELR, BLR and LMR cannot be used to predict graft success in patients who will undergo tympanoplasty due to chronic otitis media.

Ethics

Ethics Committee Approval: Approval was obtained from İstanbul Training and Research Hospital Ethics Committee for this study on 07.02.2020 (decision no: 2177).

Informed Consent: Oral and written informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - Z.Ç., Ö.Y., A.V.S. ; Concept- Z.Ç., Ö.Y., A.V.S. ; Design - Z.Ç., Ö.Y., A.V.S. ; Data Collection or Processing - Z.Ç., Ö.Y., A.V.S. ; Analysis or Interpretation - Z.Ç., Ö.Y., A.V.S. ; Literature Search - Z.Ç., Ö.Y., A.V.S. ; Writing - Z.Ç., Ö.Y., A.V.S.

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

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

References

1. Head K, Chong LY, Bhutta MF, Morris PS, Vijayasekaran S, Burton MJ, et al. Topical antiseptics for chronic suppurative otitis media. Cochrane Database Syst Rev 2020; 1: CD013055.
2. Dipesh S, Arun KC, Nepal A. A Comparative Study of Endoscopic versus Microscopic Cartilage Type I Tympanoplasty. Int Arch Otorhinolaryngol 2020; 24: e80-e5.
3. Sözen E, Uçal YO, Tansuker HD, Uslu CB, Korkut AY, Dadaş B. Is the tragal cartilage necessary for type 1 tympanoplasties? J Craniofac Surg 2012; 23: e280-3.
4. Kökoğlu K, Şahin MI. Use of Neutrophil, Eosinophil, Basophil, and Platelet to Lymphocyte Ratio to Predict Patient Satisfaction After Septoplasty Plus Inferior Turbinate Reduction. J Craniofac Surg 2019; 30: 1022-6.
5. Chen LC, Li SH, Lo CM, Chen YH, Huang SC, Wang YM, et al. Platelet-to-lymphocyte ratio is an independent prognosticator in patients with esophageal squamous cell carcinoma receiving esophagectomy. J Thorac Dis 2019; 11: 4583-90.
6. Boztepe OF, Demir M, Gün T, Bilal N, Ensari NA, Doğru H. A novel predictive marker for the viscosity of otitis media with effusion. Int J Pediatr Otorhinolaryngol 2015; 79: 2355-8.
7. Tan D, Fu Y, Tong W, Li F. Prognostic significance of lymphocyte to monocyte ratio in colorectal cancer: A meta-analysis. Int J Surg 2018; 55: 128-38.
8. Balta S, Demırer Z, Aparci M, Yildirim AO, Ozturk C. The lymphocyte-monocyte ratio in clinical practice. J Clin Pathol 2016; 69: 88-9.
9. Salviz M, Bayram O, Bayram AA, Balikci HH, Chatzi T, Paltura C, et al. Prognostic factors in type I tympanoplasty. Auris Nasus Larynx 2015; 42: 20-3.
10. Onal K, Arslanoglu S, Songu M, Demiray U, Demirpehlivan IA. Functional results of temporalis fascia versus cartilage tympanoplasty in patients with bilateral chronic otitis media. J Laryngol Otol 2012; 126: 22-5.
11. Jalali MM, Motasaddi M, Kouhi A, Dabiri S, Soleimani R. Comparison of cartilage with temporalis fascia tympanoplasty: A meta-analysis of comparative studies. Laryngoscope 2017; 127: 2139-48.
12. Lin YC, Wang WH, Weng HH, Lin YC. Predictors of surgical and hearing long term results for inlay cartilage tympanoplasty. Arch Otolaryngol Head Neck Surg 2011; 137: 215-9.
13. Gupta S, Harshvardhan R, Samdani S. To Study the Association of the Size and Site of Tympanic Membrane Perforation with the Degree of Hearing Loss. Indian J Otolaryngol Head Neck Surg 2019; 71: 1047-52.
14. Boztepe OF, Gün T, Demir M, Gür ÖE, Ozel D, Doğru H. A novel predictive marker for the recurrence of nasal polyposis following endoscopic sinus surgery. Eur Arch Otorhinolaryngol 2016; 273: 1439-44.
15. He JR, Shen GP, Ren ZF, Qin H, Cui C, Zhang Y, et al. Pretreatment levels of peripheral neutrophils and lymphocytes as independent prognostic factors in patients with nasopharyngeal carcinoma. Head Neck 2012; 34: 1769-76.
16. Yılmaz B, Şengül E, Gül A, Alabalık U, Özkurt FE, Akdağ M, et al. Neutrophil-lymphocyte ratio as a prognostic factor in laryngeal carcinoma. Indian J Otolaryngol Head Neck Surg 2018; 70: 175-9.
17. Kang JW, Kim MG, Kim SS, Im HI, Dong SH, Kim SH, et al. Neutrophil-lymphocyte ratio as a valuable prognostic marker in idiopathic sudden sensorineural hearing loss. Acta Otolaryngol 2019; 140: 307-13.
18. Li B, Zhou P, Liu Y, Wei H, Yang X, Chen T, et al. Platelet-to-lymphocyte ratio in advanced cancer: review and meta-analysis. Clin Chim Acta 2018; 483: 48-56.
19. Kurtul A, Ornek E. Platelet to lymphocyte ratio in cardiovascular diseases: a systematic review. Angiology 2019; 70: 802-18.
20. Bardash Y, Olson C, Herman W, Khaymovich J, Costantino P, Tham T. Platelet-lymphocyte ratio as a predictor of prognosis in head and neck cancer: a systematic review and meta-analysis. Oncol Res Treat 2019; 42: 665-77.
21. Atan D, Özcan KM, Köseoglu S, İkincioğulları A, Çetin MA, Ensari S, et al. New predictive parameters of nasal polyposis: neutrophil to lymphocyte ratio and platelet to lymphocyte ratio. Turk J Ear Nose Throat 2015; 25: 97-101.
22. Metcalfe DD, Pawankar R, Ackerman SJ, Akin C, Clayton F, Falcone FH, et al. Biomarkers of the involvement of mast cells, basophils and eosinophils in asthma and allergic diseases. World Allergy Organ J 2016; 9: 7.
23. Motran CC, Silvane L, Chiapello LS, Theumer MG, Ambrosio LF, Volpini X, et al. Helminth ınfections: recognition and modulation of the ımmune response by ınnate ımmune cells. Front Immunol 2018; 9: 664.
24. Kara A, Guven M, Yilmaz MS, Demir D, Elden H. Are neutrophil, platelet and eosinophil-to-lymphocyte ratio and red blood cell distribution width can be used for nasal polyposis? Eur Arch Otorhinolaryngol 2018; 275: 409-13.
25. Çekici Y, Yılmaz M, Seçen Ö. New inflammatory indicators: association of high eosinophil-to-lymphocyte ratio and low lymphocyte-to-monocyte ratio with smoking. J Int Med Res 2019; 47: 4292-303.
26. López-Verdugo F, Furuzawa-Carballeda J, Romero-Hernández F, et al. Hematological indices as indicators of silent inflammation in achalasia patients: A cross-sectional study. Medicine (Baltimore). 2020; 99: e19326.
27. Yang Z, Zhang Z, Lin F, Ren Y, Liu D, Zhong R, et al. Comparisons of neutrophil-, monocyte-, eosinophil-, and basophil- lymphocyte ratios among various systemic autoimmune rheumatic diseases. APMIS 2017; 125: 863-71.
28. Balta S, Demırer Z, Aparci M, Yildirim AO, Ozturk C. The lymphocyte-monocyte ratio in clinical practice. J Clin Pathol 2016; 69: 88-9.
29. Feng X, Li L, Wu J, Zhang L, Sun Z, Li X, et al. Complete blood count score model integrating reduced lymphocyte-monocyte ratio, elevated neutrophil-lymphocyte ratio and elevated platelet-lymphocyte ratio predicts inferior clinical outcomes in adult t-lymphoblastic lymphoma. Oncologist 2019; 24: e1123-e31.
30. Tham T, Olson C, Khaymovich J, Herman SW, Costantino PD. The lymphocyte-to-monocyte ratio as a prognostic indicator in head and neck cancer: a systematic review and meta-analysis. Eur Arch Otorhinolaryngol 2018; 275: 1663-70.

İstanbul Med J 2020; 21(4): 312-9
DOI: 10.4274/imj.galenos.2020.60430

A Study on Sentinel Node and Occult Lesion Localisation: Do We Really Need an Intraoperative Frozen Examination?

Sentinel Nod ve Okült Lezyon Lokalizasyonunda İntraoperatif Frozen Değerlendirme Gerekli midir?

Kivilcim Ulusan[1], Melis Baykara Ulusan[2], Mehmet Velidedeoğlu[3], Tülin Öztürk[4], Onur Erdem Şahin[5], Sina Ferahman[6], Mehmet Ferahman[3]

[1]İstanbul Training and Research Hospital, Clinic of General Surgery, İstanbul, Turkey
[2]İstanbul Training and Research Hospital, Clinic of Radiology, İstanbul, Turkey
[3]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of General Surgery, İstanbul, Turkey
[4]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Pathology, İstanbul, Turkey
[5]Sivas Numune Hospital, Clinic of Nuclear Medicine, Sivas, Turkey
[6]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of General Surgery, İstanbul, Turkey

ABSTRACT

Introduction: The sentinel node and occult lesion localisation (SNOLL) technique combines radio-guided occult lesion localisation and sentinel lymph node biopsy (SLNB) using radioisotopes. In addition to the success of the SNOLL procedure, we investigated the efficacy and necessity of intraoperative frozen pathology in terms of clear margins and reinterventions in non-palpable breast lesions (NPBLs).

Methods: The study was conducted at a single centre, in a general surgery clinic between 2006-2016. The medical records of 83 patients with NPBLs and negative axillae were acquired. Before surgery, patients were administered peritumoral and subdermal radionuclide tracer at the axillary region. All the patients underwent breast-conserving surgery and SLNB using a gamma probe following SNOLL.

Results: A malignancy was detected in 78 of 83 lesions. Analyses of intraoperative frozen sections showed that the surgical margins were clear in 35 (44.9%), close in 17 (21.7%), and involved in 26 (33.3%) patients. Patients in the latter two groups underwent intraoperative re-excision of the tumour. On the final paraffin sections, surgical margin positivity was determined in seven (9%) patients. Sentinel lymph nodes (SLNs) were detected successfully in 77 of 78 patients (98.7%). The overall success rate of the SNOLL procedure was 88.5% (69/78) in patients surgically treated in a single operation. Intraoperative re-excision was beneficial in only 3 of 78 (3.8%) patients.

Conclusion: SNOLL is a feasible, simple, and time-saving method for localising non-palpable breast cancers and SLNs. However, the contribution of margin assessment using frozen sections to the success of the method is limited.

Keywords: Sentinel lymph node, sentinel node and occult lesion localisation (SNOLL), non-palpable breast cancer, radio-guided surgery, radio-guided occult lesion localisation (ROLL)

ÖZ

Amaç: Sentinel nod ve okült lezyon lokalizasyonu (SNOLL), radyonüklid okült lezyon lokalizasyonu ve sentinel lenf nodu biyopsisinin (SLNB) birlikte kullanıldığı tekniktir. Çalışmamızda SNOLL işleminin başarısının yanı sıra palpe edilemeyen meme lezyonlarında cerrahi sınır pozitifliği ve tekrar girişim açısından intraoperative dondurulmuş patoloji gerekliliği ve yararlılığını da araştırdık.

Yöntemler: Çalışma 2006-2016 yılları arasında tek merkezde genel cerrahi kliniğimizde yapılmıştır. Palpe edilemeyen meme lezyonu olan aksillası negatif 83 hastanın kayıtları kullanılmıştır. Cerrahiden önce tüm hastalara peritümoral ve aksilla bölgesinde subdermal radyonüklid enjekte edilmiştir. Tüm hastalara SNOLL prosedürünü takiben gama prob yardımı ile meme koruyucu cerrahi ve SLNB uygulanmıştır.

Bulgular: Seksen üç hastanın 78'inde malignite tespit edilmiştir. İntraoperatif dondurulmuş incelemede 35 (%44,9) hastada cerrahi sınır negatif, 17 hastada (%21,7) yakın cerrahi sınır ve 26 (%33,3) hastada cerrahi sınır pozitif olarak gelmiştir. Son iki gruptaki hastalara intraoperatif tümör reeksizyonu yapılmıştır. Nihai paraffin incelemede 7 (%9) hastada cerrahi sınır pozitifliği tespit edilmiştir. Sentinel lenf nodları (SLN)'ler 78 hastanın 77'sinde (%98,7) başarı ile tespit edilebilmiştir. Tek operasyon ile tedavi edilen hastalarda SNOLL prosedürünün genel başarısı %88,5'tir (69/78). İntraoperatif reeksizyon hastaların sadece üçünde (%3,8) fayda sağlamıştır.

Sonuç: SNOLL; palpe edilemeyen meme kanserlerinde ve SLN'lerin lokalizasyonunda kolay uygulanabilen, basit ve zaman kazandırıcı bir yöntemdir. Ancak dondurulmuş inceleme ile cerrahi sınır değerlendirmesinin yöntemin başarısına olan katkısı sınırlıdır.

Anahtar Kelimeler: Sentinel lenf nodu, sentinel lenf nodu ve okült lezyon lokalizasyonu (SNOLL), non-palpabl meme kanseri, radyonüklid işaretleme, radyonüklid okült lezyon lokalizasyonu (ROLL)

Address for Correspondence/Yazışma Adresi: Kivilcim Ulusan MD, İstanbul Training and Research Hospital, Clinic of General Surgery, İstanbul, Turkey
Phone: +90 538 970 35 35 **E-mail:** kivilcimulusan@hotmail.com **ORCID ID:** orcid.org/0000-0002-4793-5714

Cite this article as/Atıf: Ulusan K, Baykara Ulusan M, Velidedeoğlu M, Öztürk T, Şahin OE, Ferahman S, Ferahman M. A Study on Sentinel Node and Occult Lesion Localisation: Do We Really Need an Intraoperative Frozen Examination?. İstanbul Med J 2020; 21(4): 312-9.

Received/Geliş Tarihi: 16.02.2020
Accepted/Kabul Tarihi: 12.06.2020

Introduction

Breast lesions detected incidentally in screening programmes without any findings in breast examinations are referred to as non-palpable breast lesions (NPBLs) (1). The incidence of malignancy in NPBL varies between 14% and 25% (2,3).The widespread use of screening programmes and imaging modalities to raise awareness about breast cancer, has increased the detection rates of early breast cancer and NPBLs (4,5).

Despite all these developments in the field of breast cancer, reintervention rates still vary between 20% and 50% (6). Accurate preoperative localisation is essential to prevent secondary surgeries of NPBLs (7). So far, no localisation method has been superior to the other (7). However, the most well-known among them are wire-guided localisation and radio-guided occult lesion localisation (ROLL) (8,9). The ROLL technique has increasingly been used in recent years (10). In this technique, the lesion is located by injecting a radiotracer under radiological guidance and surgical excision is performed using a handheld gamma probe.

In patients with non-palpable early breast cancer, the pathological state of the axillary lymph nodes (ALNs) is the most important determinant of staging, prognosis and the need for adjuvant therapy. Imaging techniques may show ALN involvement, but are inadequate for detecting micrometastases. Therefore, the sentinel lymh node (SLN) should be excised and examined histopathologically by SLN biopsy (SLNB).

The sentinel node and occult lesion localisation (SNOLL) technique combines ROLL and SLNB using radioisotopes. Many studies are investigating the success of the SNOLL technique (11-15). In addition to these, we investigated the efficacy and necessity of intraoperative frozen pathology in terms of clear margins and reinterventions in NPBLs from a screened population.

Methods

Prediagnostic Work-up/Demographics

At our general surgery clinic, 83 consecutive patients with NPBL detected by mammography, ultrasonography or magnetic resonance imaging (MRI) and treated using the SNOLL procedure between 2006 and 2016 were included in the study. All the patients underwent preoperative histological examination with either ultrasound-guided core needle biopsy or stereotactic biopsy. Six patients with benign biopsy results but high radiological suspicion were also included.

One patient with postoperatively proven fibroadenoma (included because of high radiological suspicion), two with complete disappearance of the lesion after neoadjuvant chemotherapy, one with a completely resected tumour after core biopsy and one in whom diffusion of the radiotracer into the ductus occurred and wire-guided localisation was performed were excluded. Thus, 78 patients were finally included. All the patients had clinically and radiologically negative ALNs (Figure 1).

Sentinel Node and Occult Lesion Localisation Procedure

All the patients were injected with 17.5-37 MBq 99mTc-labelled human albumin macroaggregate (MAA) (TechneScan MAA, Mallinckrodt Inc., St. Louis, MO, United States) intratumorally in 0.2-0.5 mL saline one day before surgery or on the morning of the procedure. Injections were performed by experienced breast radiologists under ultrasound, mammography or MRI guidance. In mammography-detectable masses, 0.2 mL radiopaque contrast material (Omnipaque; GE Healthcare, Chicago, IL, United States) was administered immediately after the radiopharmaceutical injection. The contrast covering the lesion detected by standard two-view mammography confirmed the injection of the contrast agent at the correct site. The injection was given in all the remaining cases under direct visualisation via ultrasound following the detection of changes in the lesion.

SLN detection was performed using a total of 0.2 mL 99mTc-labelled nanocolloid radiopharmaceutical (Nanocis; CIS Bio International, Gif-sur-Yvette, France) (55.5-74 MBq) at the same time as the ROLL procedure. 99mTc-labelled nanocolloid was injected into the periareolar region subdermally in all four quadrants (0.05 mL per quadrant) by a radiologist. Preoperative scintigraphy was not routinely performed.

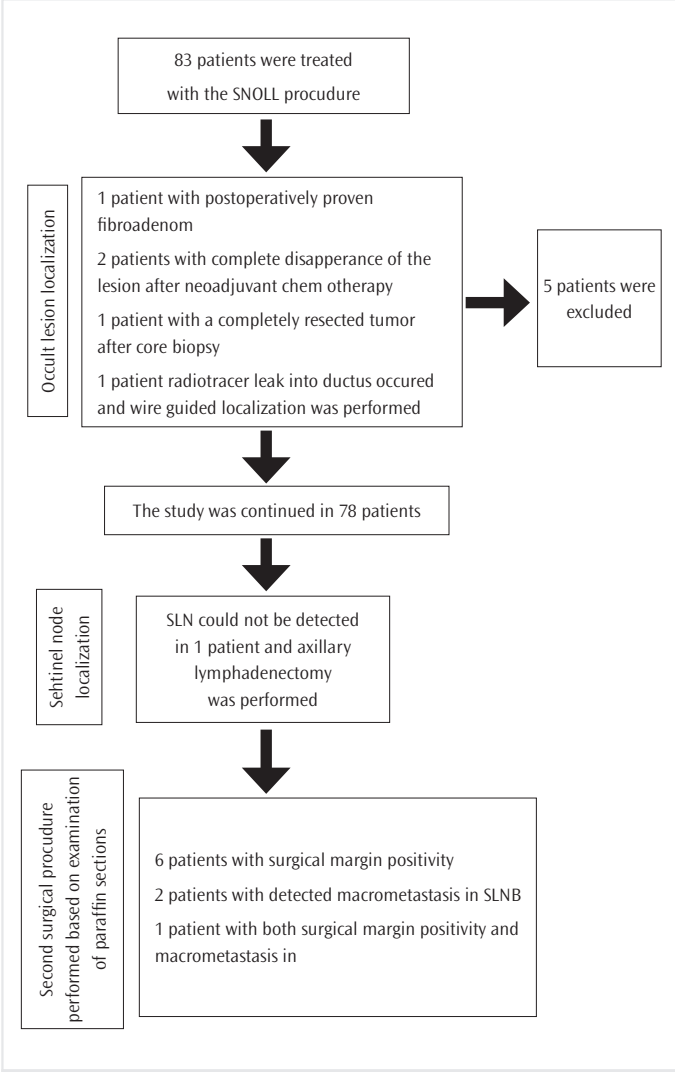


Figure 1. Study flow chart

SNOLL: Sentinel node and occult lesion localisation, SLN: sentinel lymph node, SLNB: sentinel lymph node biopsy

Surgical Procedure

A gamma probe (First Sensor; Wake Medical, Barnsley, UK and Europrobe; Eurorad, Eckbolsheim, France) was used to determine the localisation with the highest activity and the projection of the skin was marked with a pen before general anaesthesia in the operating room. After general anaesthesia, a total of 5 mL patent blue dye (Blumet; VEM, İstanbul, Turkey) was applied using a 3 mL periareolar injection and 2 mL subdermal injection into the upper outer quadrant by the surgeon. The SLNB procedure was started after 5 minute of breast massage to increase lymphatic drainage.

SLNB was attempted during the same procedure with breast surgery through a separate incision over the axillary region. The criteria for removing sentinel nodes were being hot and/or blue. Clinically suspicious LNs (palpable and firm) that were neither hot nor blue were also removed. The LNs were grouped as hot, blue and palpable, and cut into frozen sections. Patients with positive SLNB results underwent immediate axillary lymph node dissection (ALND).

For excision of the primary lesion, the skin incision was guided by the gamma probe and the radioactive area was removed. The excision was performed with the aim of a free surgical margin around the tumour bed. After excision, the remaining breast tissue was checked for further radioactivity with the gamma probe. The specimen was oriented with clips and silk sutures. If microcalcifications were present in the lesion, the specimen was X-rayed (using mammography to verify that all had been removed.) All specimens were frozen and sent to the pathology laboratory.

Pathology

To determine the pathological tumour size, the largest contiguous dimension of the tumour was taken and the pathological tumour volume and total specimen volume were calculated as the height × width × length. Patients were grouped as clear or close/involved margin according to the margin status. Margin status was defined as follows: (i) clear when at least 5 mm of normal breast tissue surrounded the carcinoma, (ii) close when less than 5 mm of normal breast tissue was found and (iii) involved when invasive carcinoma was at an inked margin. Involved and close margin patients were considered positive and intraoperative re-excision was performed. Due to differences in the breast volumes of patients and the different surgeons involved in the study, standardisation of the clear margin requiring re-excision could not be performed. All excision and re-excision materials were embedded in paraffin sections and examined with standard hematoxylin and eosin staining for the final margin evaluation.

Frozen sections of all the SLNs were analysed. According to 7th TNM staging, metastatic deposits measuring >2 mm were considered macrometastases, those from 0.2 mm to 2 mm were considered micrometastases and those <0.2 mm were considered isolated tumour cells (16). Patients with macrometastases underwent ALND.

Statistical Analyses

Baseline preoperative variables were compared via χ^2 analyses or Fisher's exact test for categorical data, where appropriate. The Mann-Whitney U test was used to compare the medians of nonparametric variables. Student's t test was used to compare parametric data between two independent groups provided that the distribution of data was normal. In all analyses, $p<0.05$ was considered statistically significant. Statistical analyses were performed using SPSS Statistics for Windows (Version 21.0; IBM, Armonk, NY).

Ethics

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study. The study was approved by the Medical Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (protocol no:83045809-604.01.02, date: 12.07.2016) and was performed in accordance with the Declaration of Helsinki.

Results

Seventy-eight female patients who underwent the SNOLL procedure between 2006 and 2016 were included in the study. The mean age of the patients was 53±8.9 years.

Of the 78 lesions detected, 48 (61.5%) were located in the upper outer quadrant. While 68 (87.2%) of the NPBLs were detected by ultrasound, 6 (7.7%) and 4 (5.1%) were detected by mammography and MRI, respectively. Invasive ductal carcinoma (IDC) was found in 57 (73.1%) patients in the preoperative histopathological diagnosis. Detailed demographic data are shown in Table 1.

The largest contiguous dimension of the tumour was taken as the pathological tumour size, and the median tumour size was 1.25 cm (range 0.6-6.5 cm). Pathological tumour volume and total specimen volume were 1.2 cm^3 (range 0.08-130 cm^3) and 140 cm^3 (range 29.7-1,174 cm^3), respectively. The mean weights of the tumour specimens were not reported in all the cases.

According to the TNM classification, 5 (6.4%) patients were classified as Tis, 27 (34.6%) as T1b, 38 (48.7%) as T1c, 7 (9%) as T2 and 1 (1.3%) as T3. Of these patients, 14 (17.9%), 42 (53.8%) and 20 (25.6%) had low-grade, intermediate-grade and high-grade tumours, respectively. At the final pathological examination, IDC was detected in 60 (76.9%) patients, while 8 (10.3%) patients had mixed type (invasive ductal + invasive lobular) carcinoma. The diagnoses of the remaining patients are shown in Table 2 along with the other histopathological data. Histopathological examination of the surgical specimen revealed lymphatic invasion of the tumour in 14 (17.9%) patients.

Analyses of intraoperative frozen sections showed that surgical margins were clear (>5 mm) in 35 (44.9%), close (<5 mm) in 17 (21.7%) and involved in 26 (33.3%) cases (Figure 2). Patients with close and involved margins (43 patients, 55.1%) underwent intraoperative re-excision.

Paraffin evaluation of 43 re-excised patients showed that:

· Three patients had tumours in the re-excision specimens, but no paraffin border positivity was detected in the total (main + re-excised) specimen (Figure 2, group A).

· Thirty five patients had no tumours in the re-excision specimens (Figure 2, group B).

· Three patients had no tumours in the re-excision specimens, but the main specimen showed paraffin border positivity (Figure 2, group C).

· Two patients had tumours in the re-excision specimens and showed paraffin border positivity (Figure 2, group D).

Group A and B together formed the clear margin group according to the final paraffin examination. This group did not undergo a secondary surgical procedure. Since group C and D showed margin positivity in the total material, they constituted the involved margin group.

On paraffin evaluation of 35 patients who were clear according to the intraoperative frozen section:

· Two patients showed paraffin border positivity (Figure 2, group E).

Table 1. Demographical data of patients

Patients	**n=78 (100%)**
Mean age (years)	53±8.9
Menopausal status	
Postmenopausal	44 (56.4%)
Premenopausal	34 (43.6%)
Referral source	
Routine screening	40 (51.3%)
Symptomatic	26 (33.3%)
Cancer follow-up	12 (15.4%)
Family history	
No	53 (67.9%)
Yes	25 (32.1%)
Primary cancer side	
Left	40 (51.3%)
Right	38 (48.7%)
Tumor location	
Upper lateral	48 (61.5%)
Lower lateral	10 (12.8%)
Upper medial	8 (10.3%)
Lower medial	6 (7.7%)
Retroareolar	6 (7.7%)
Radiological feature	
Mass	73 (93.6%)
Microcalcifications	3 (3.8%)
Stromal asymmetry	2 (2.6%)
Preoperative tumor histology	
Invasive ductal	57(73.1%)
Mixed type	4 (5.1%)
In situ carcinoma	3 (3.8%)
Tubular carcinoma	3 (3.8%)
Invasive lobular	2 (2.6%)
Mucinous carcinoma	2 (2.6%)
Papillary carcinoma	1 (1.3%)
Biopsy not malignant*	6 (7.7%)

*Biopsy not malignant but radiological high suspicious

· Thirty three patients were also clear on paraffin evaluation and showed no border positivity (Figure 2, group F).

Taken together, examination of paraffin sections to determine the final margin status revealed surgical margin positivity in seven (9%) patients (Figure 2, group C+D+E). A second surgical procedure was performed in these patients. There were no significant differences in terms of paraffin border positivity or secondary surgery rates between patients with intraoperative re-excision based on pathology.

The overall success of SLN detection was 98.7% (77/78 patients). The mean number of SLNs per case was 2.39 (range 1-5). A total of 178 LNs were harvested from 77 patients because they were hot (n=26), blue (n=9), or hot and blue (n=127). Sixteen non-hot non-blue (non-sentinel) LNs were also removed because of a high clinical suspicion (i.e., firm upon palpation). Axillary lymphadenectomy was performed in 12 patients because the LN was metastatic (hot + blue, n=10; hot, n=1; palpable, n=1) (Table 3).

According to the TNM classification, the positive SN was present in 15 (21.8%) cases (macrometastases, n=12; micrometastases, n=3 and isolated tumour cells, n=2). In addition, two more axillary lymphadenectomies were performed because the SLN could not be detected in one case and the second was according to the surgeon's preference, although the patient had micrometastases (during initial surgery, n=11; after paraffin section examination, n=3) (Table 4).

As the results were evaluated together, the success of the SNOLL procedure was 88.5% (69/78) in patients surgically treated in a single operation. Nine patients underwent supplementary surgery, including

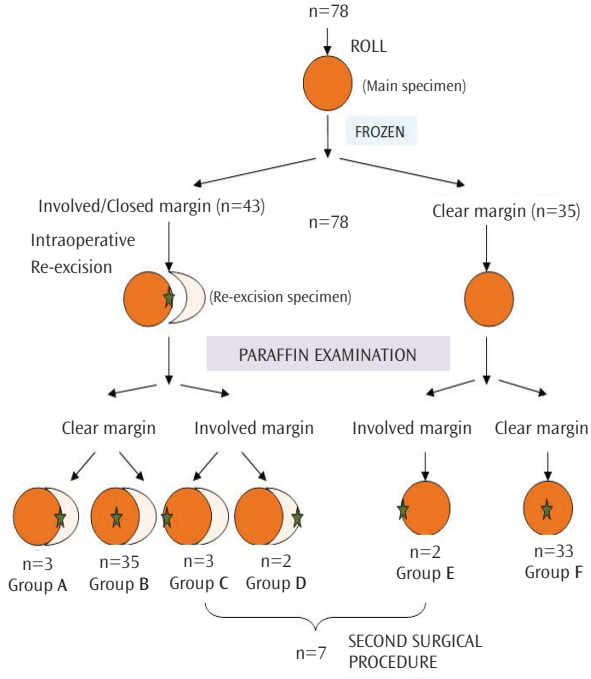


Figure 2: Pathological examination chart. ● symbol indicates the main/first excision specimen. ❨ symbol indicates the re-excision specimen. ✶ symbol indicates the tumor

ROLL: Radio-guided occult lesion localisation

breast resection in six cases, ALND in two cases and both surgical procedures in one case (Table 2).

Table 2. Tumor characteristics and margin status

Patient	**n=78**
Histopathological tumor size <2 cm/≥2 cm	Med:1.25 cm (minimum: 0.6 cm, maximum: 6.5 cm) 63 (80.8%)/15 (19.2%)
Tumor volume	Med: 1.2 cm³ (minimum: 0.08 cm³, maximum: 130 cm³)
Total specimen volume	Med: 140 cm³ (minimum: 29.7 cm³, maximum: 1,174 cm³)
T category of tumor	
Tis	5 (6.4%)
T1b	27 (34.6%)
T1c	38 (48.7%)
T2	7 (9%)
T3	1 (1.3%)
Postoperative tumor histology	
Invasive ductal	60 (76.9%)
Mixed type	8 (10.3%)
In situ carcinoma	4 (5.1%)
Tubular carcinoma	2 (2.6%)
Invasive lobular	1 (1.3%)
Mucinous carcinoma	1 (1.3%)
Papillary carcinoma	1 (1.3%)
Neuroendocrine tumor	1 (1.3%)
Lymphatic invasion	
Yes	14 (17.9%)
No	64 (82.1%)
Margin status (Frozen section)	
Involved	26 (33.3%)
Close margin	17 (21.8%)
1 mm	7 (9%)
2 mm	3 (3.8%)
3 mm	3 (3.8%)
4 mm	0 (0%)
5 mm	4 (5.1%)
Clear margin	35 (44.9%)
Margin status (Paraffin exam)	
Involved	7 (9%)
<1 cm not involved	25 (32%)
≥1 cm clear	46 (59%)
Reoperation	9 (11.5%)
Margin positivity	6 (7.7%)
SLN positivity	2 (2.6%)
Margin + SLN positivity	1 (1.3%)

Med: Median, SLN: sentinel lymph node

Total specimen volumes were significantly higher in patients without intraoperative re-excision (p=0.046). No significant correlation was found between any other parameters and intraoperative re-excision (Table 5).

Discussion

The SNOLL technique has become an accepted surgical technique for the excision of NPBLs. Although there have been many improvements in this technique, including SLNB with excision of the breast lesion, there are still different methods with regard to the use of a localisation agent (blue dye, radiotracer or both), location of the injection (periareolar, peritumoral, subareolar), timing of localisation and the axillary approach after examination of the removed LNs (17).

In recent studies, the re-excision criterion for IDC was determined as "no ink on tumour" (18,19). Due to differences in the breast volumes of patients and the different surgeons involved in the study, standardisation

Table 3. Sentinel node intraoperative findings

	SLN (-)	SLN (+)	Total
Hot	25	1	26
Blue	9	0	9
Palpable	15	1	16
Hot + blue	117	10	127
Total	166	12	178

SLN:sentinel lymph node

Table 4. Sentinel node biopsy pathological results

Patients	**n=78 (100%)**
Success of SLN detection	77 (98.7%)
Number of SLN	Mean: 2.39±0.14
0	1 (1.3%)
1	20 (25.6%)
2	31 (39.7%)
3	14 (17.9%)
4	6 (7.7%)
5	6 (7.7%)
N category of SLN	
N0	60 (76.9%)
N0 (i+)	2 (2.6%)
N1mi	3 (3.8%)
N1a	12 (15.4%)
Axillary dissection	14 (17.9%)
With frozen section	10 (12.8%)
With paraffin exam	3 (3.8%)
SLN not found	1 (1.3%)

SLN: sentinel lymph node, N0 (i+): isolated tumour cells, N1mi: micrometastases, N1a: macrometastases

of the clear margin requiring re-excision could not be performed. When cases were evaluated retrospectively, the maximum clear margin limit for re-excision was 5 mm. Margin groups were defined according to this limit. As margin positivity and reoperation rates are higher for ductal carcinoma *in situ* (DCIS), excision is performed with a wider border (20). Although it is not appropriate to evaluate IDC and DCIS patients together, our cohort included only four DCIS patients among 78 patients and it did not affect the statistics. In contrast, none of the DCIS patients in our study required re-excision or reoperation.

ALN involvement is still one of the most important prognostic factors in breast cancer and affects disease-free survival (11). The rate of SLN detection in our study was 98.7%, similar to previous studies that have used a combined radiotracer and blue dye technique (11-13). Besic et al. (21) reported a 93% SLN detection rate with the combined technique. They concluded that the lower rate was because a higher proportion of patients had hematoma due to the preoperative biopsy (21). We had better results although all of the patients underwent preoperative fine needle aspiration biopsy.

There are different opinions about the use of the combined technique for the detection of SLN. In our study, all blue nodes were also hot; therefore, the need to use blue dye can be questioned. However, the use of blue dye has been reported to increase the SN detection rate (11,22,23). Suspected palpable LNs should also be excised during the surgery. LN involvement may not be seen if the LNs are obstructed by tumour metastases (14). In our study, macrometastasis was detected in one of the non-hot non-blue nodes that were removed as palpable. Until recently, ALND was accepted as the gold standard for all patients with macrometastases in SLN and a large proportion of patients with micrometastases. Recent studies have been carried out on patients with micrometastasis in the SLN and followed-up without axillary dissection. The results of the most important randomised study in SLN^+ patients were reported in 2017 (24). In the 10-year follow-up period, there were no significant differences in locoregional recurrence in groups with and without dissection. The American College of Surgeons Oncology Group Z11 study showed that the common opinion that axillary dissection with adjuvant treatment protocols increases life expectancy is incorrect (24). Although there was insufficient data to predict survival in our study, axillary dissection was not necessary. Non-sentinel LNs were positive in only 2 of 14 patients who underwent ALND in our study. The remaining 12 patients did not have extra-SLN involvement.

The need for intraoperative excision to obtain maximum benefits with minimum tissue loss is controversial. Many authors have argued that analysing frozen sections is insufficient for detecting the negative surgical margin of non-palpable lesions due to high false-negative rates (15,21,25,26). In some cases in our study, definitive surgery for invasive carcinoma was performed with a single operation, but it did not affect the number of reoperations. Forty-three patients underwent intraoperative re-excision because frozen sections showed involved or close margins. Of these patients, 38 did not benefit from re-excision (group B+C). Two of them showed margin positivity on paraffin

Table 5. Effect of demographic and pathological parameters on intraoperative re-excision

Patients **n=78 (100%)**	**Intraoperative re-excision Yes/No** **43 (55.1%)-35 (44.9%)**	**p**
Mean age (years)	53.1±9.4/52.9±8.5	0.917[a]
Postmenopausal/Premenopausal	24 (54.5%)/20 (44.5%)-19 (55.9%)/15 (44.1%)	0.096[b]
Referral source routine screening		
Yes/No	22 (55.0%)/18 (45.0%)-21 (55.3%)/17 (44.7%)	0.981[b]
Family history		
Yes/No	11 (44.0%)/14 (56.0%)-32 (60.4%)/21 (39.6%)	0.175[b]
Primary cancer side		
Left/Right	20 (50.0%)/20 (50.0%)-23 (60.5%)/15 (39.5%)	0.350[b]
Tumour location upper lateral		
Yes/No	28 (53.8%)/20 (41.7%)-15 (50.0%)/15 (50.0%)	0.472[b]
Preoperative tumour histology		
Invasive ductal Yes/No	33 (57.9%)/24 (42.1%)-10 (47.6%)/11 (52.4%)	0.418[b]
Histopathological tumour size <2 cm/ ≥2 cm	1.4 (min: 0.7, max: 3.7)-1.2 (min: 0.6, max: 6.5) 35 (55.6%)/28 (44.4%)-8 (53.3%)/7 (44.7%)	0.792[c] 0.876[b]
Tumour volume	1.3 (min: 0.15, max: 30)-1.08 (min: 0.08, max: 130)	0.332[c]
Total specimen volume	115 (min: 30.7, max: 865)-175 (min: 29.7, max: 1.174)	0.046[c]
Postoperative tumour histology		
Invasive ductal Yes/No	33 (55.0%)/27 (45.0%)-10 (55.6%)/8 (44.4%)	0.967[b]
Lymphatic invasion		
Yes/No	8 (57.1%)/6 (42.9%)-35 (54.7%)/29 (45.3%)	0.867[b]

p: relation to intraoperative margin positivity on frozen. min: minimum, max: maximum
[a]Independent Samples test, [b]Pearson chi-square test, [c]Mann-Whitney U test

examination (group D). Although these patients seemed to benefit from frozen examination, frozen section could not prevent secondary surgery in this group. Intraoperative re-excision was beneficial in only 3 of 78 (3.8%) patients (group A) (Figure 2).

The success of intraoperative frozen section is to prevent the patient from undergoing a secondary surgery. Therefore, we think that it is not necessary to perform intraoperative re-excision based on examinations of frozen sections.

In a similar previous study, the factors affecting the involvement of the surgical margin included patient age >50 years, radiological tumour size >20 mm, surgical specimen ≥50 g and invasive ductal type carcinoma (21). In our study, there were also significant relationships between margin positivity and postoperative diagnosis of IDC and tumour size ≥20 mm.

Achieving high success rates with a single surgery, easier localisation for radiologists and surgeons, less discomfort for patients, shorter marking time and better cosmetic appearance are important advantages of the SNOLL technique (27). If the success of the SNOLL procedure is considered cure with a single surgical operation, the success rate was 88.5% in our study. A total of nine (11.5%) patients required a second surgery due to margin positivity and/or SLN positivity.

The technique also has some disadvantages, including the need for multidisciplinary work, the presence of a nuclear medicine unit, wrong injection of radionuclide material, radionuclide leakage to the duct and the need for probes (11,13). In the present study, the lesions were easily marked by ROLL in all except one patient with leakage of the radiotracer into the neighbouring ductus. This lesion was localised by wire-guided localisation and excised. In postoperative follow-up, one patient developed hematoma and two patients developed abscesses. One patient undergoing axillary dissection developed movement limitation and paraesthesia in the arm.

Study Limitations

This study was limited by its retrospective nature. In addition, as six different surgeons participated in the study, this may have caused small differences in the surgical procedure. As a 10-year period was retrospectively reviewed in this study, and changes in clinical and pathological approaches, surgical experience and guidelines vary over time, this may have affected our results.

Conclusion

SNOLL is a readily applicable and reliable method for localising non-palpable breast cancers and SLNs. The development of this technique aims to achieve better results with less tissue loss. Although the contribution of margin assessment of frozen sections to the success of the method is limited, further studies on larger populations are needed.

Ethics

Ethics Committee Approval: The study was approved by the Medical Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (protocol no:83045809-604.01.02, date: 12.07.2016).

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - K.U., M.V., O.E.Ş., S.F., M.F. ; Concept - K.U. ; Design - K.U., M.B.U. ; Data Collection or Processing - K.U., M.B.U., O.E.Ş. ; Analysis or Interpretation - K.U., M.B.U., M.V., T.Ö., M.F. ; Literature Search - K.U., M.B.U., M.V., T.Ö., O.E.Ş., S.F. ; Writing - K.U., M.B.U., M.V., T.Ö., O.E.Ş., S.F.

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

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

References

1. Veronesi U, Luini A, Botteri E, Zurrida S, Monti S, Galimberti V, et al. Nonpalpable Breast Carcinomas: Long-Term Evaluation of 1,258 Cases. Oncologist 2010; 15: 1248-52.
2. De Cicco C, Pizzamiglio M, Trifirò G, Luini A, Ferrari M, Prisco G, et al. Radioguided occult lesion localisation (ROLL) and surgical biopsy in breast cancer. Technical aspects. Q J Nucl Med 2002; 46: 145-51.
3. Ernst MF, Roukema JA. Diagnosis of non-palpable breast cancer: a review. Breast 2002; 11: 13-22.
4. Park SY, Kim HJ, Kim WH, Cheon HJ, Lee H, Park HY, et al. Feasibility of ultrasound-guided absorbable retaining thread needle localization for nonpalpable breast lesions. Ultrasonography 2019; 38: 272.
5. Follacchio GA, Monteleone F, Anibaldi P, De Vincentis G, Iacobelli S, Merola R, et al. A modified sentinel node and occult lesion localization (SNOLL) technique in non-palpable breast cancer: a pilot study. J Exp Clin Cancer Res 2015; 34: 113.
6. Corsi F, Bossi D, Combi F, Papadopoulou O, Amadori R, Regolo L, et al. Radio-guided vs clip-guided localization of nonpalpable mass-like lesions of the breast from a screened population: A propensity score-matched study. J Surg Oncol 2019; 119: 916-24.
7. Chan BK, Wiseberg-Firtell JA, Jois RH, Jensen K, Audisio RA. Localization techniques for guided surgical excision of non-palpable breast lesions. Cochrane Database Syst Rev 2015; CD009206.
8. della Rovere GQ, Benson JR, Morgan M, Warren R, Patel A. Localization of impalpable breast lesions--a surgical approach. Eur J Surg Oncol 1996; 22: 478-82.
9. Aljohani B, Jumaa K, Kornecki A, Brackstone M. Clinical utility of radioactive seed localization in nonpalpable breast cancer: A retrospective single institutional cohort study. Int J Surg 2018; 60: 149-52.
10. Paganelli G, Luini A, Veronesi U. Radioguided occult lesion localization (ROLL) in breast cancer: maximizing efficacy, minimizing mutilation. Ann Oncol 2002; 13: 1839-40.
11. Thind CR, Tan S, Desmond S, Harris O, Ramesh HSJ, Chagla L, et al. SNOLL. Sentinel node and occult (impalpable) lesion localization in breast cancer. Clin Radiol 2011; 66: 833-9.
12. Lavoué V, Nos C, Clough KB, Baghaie F, Zerbib E, Poulet B, et al. Simplified technique of radioguided occult lesion localization (ROLL) plus sentinel lymph node biopsy (SNOLL) in breast carcinoma. Ann Surg Oncol 2008; 15: 2556-61.
13. Giacalone PL, Bourdon A, Trinh PD, Taourel P, Rathat G, Sainmont M, et al. Radioguided occult lesion localization plus sentinel node biopsy (SNOLL) versus wire-guided localization plus sentinel node detection: A case control study of 129 unifocal pure invasive non-palpable breast cancers. Eur J Surg Oncol 2012; 38: 222-9.
14. Ahmed M, Douek M. Sentinel node and occult lesion localization (SNOLL): A systematic review. Breast 2013; 22: 1034-40.

15. Barros AC, Barros MA, Andrade FE, Mori LJ, Costa PA, Sheng PY, et al. Combined radioguided nonpalpable lesion localization and sentinel lymph node biopsy for early breast carcinoma. Ann Surg Oncol 2007; 14: 1472-7.

16. Edge SB, Compton CC. The american joint committee on cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010; 17: 1471-4.

17. Çelik V, Aydogan F, Yılmaz MH. Non-palpabl lezyonlara yaklaşım. Özmen V, editor. Meme Hastalıkları Kitabı. Ankara: Güneş Tıp Kitabevleri; 2012.p.345-50.

18. Pilewskie M, Morrow M. Margins in breast cancer: How much is enough?. Cancer 2018; 124: 1335-41.

19. Houssami N, Macaskill P, Marinovich ML, Morrow M. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol 2014; 21: 717-30.

20. Laws A, Brar MS, Bouchard-Fortier A, Leong B, Quan ML. Does intra-operative margin assessment improve margin status and re-excision rates? A population-based analysis of outcomes in breast-conserving surgery for ductal carcinoma in situ. J Surg Oncol 2018; 118: 1205-11.

21. Besic N, Kramaric A, Podnar B, Perhavec A, Music M, Grazio-Frkovic S, et al. Factors correlated to successful surgical treatment of 181 non-palpable invasive breast carcinomas. Breast 2009; 18: 294-8.

22. Straver ME, Meijnen P, van Tienhoven G, van de Velde CJH, Mansel RE, Bogaerts J, et al. Sentinel node identification rate and nodal involvement in the EORTC 10981-22023 AMAROS trial. Ann Surg Oncol 2010; 17: 1854-61.

23. Rodier J-F, Velten M, Wilt M, Martel P, Ferron G, Vaini-Elies V, et al. Prospective multicentric randomized study comparing periareolar and peritumoral injection of radiotracer and blue dye for the detection of sentinel lymph node in breast sparing procedures: FRANSENODE trial. J Clin Oncol 2007; 25: 3664-9.

24. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. JAMA 2017; 318: 918.

25. Cendán JC, Coco D, Copeland EM. Accuracy of intraoperative frozen-section analysis of breast cancer lumpectomy-bed margins. J Am Coll Surg 2005; 201: 194-8.

26. Osborn JB, Keeney GL, Jakub JW, Degnim AC, Boughey JC. Cost-effectiveness analysis of routine frozen-section analysis of breast margins compared with reoperation for positive margins. Ann Surg Oncol 2011; 18: 3204-9.

27. Rampaul RS, Bagnall M, Burrell H, Pinder SE, Evans AJ, Macmillan RD. Randomized clinical trial comparing radioisotope occult lesion localization and wire-guided excision for biopsy of occult breast lesions. Br J Surg 2004; 91: 1575-7.

İstanbul Med J 2020; 21(4): 320-6
DOI: 10.4274/imj.galenos.2020.39114

Assessment of Bone Mineral Density in Patients with Incidental Parathyroidectomy during Thyroidectomy

Tiroidektomi Yapılan Hastalarda İnsidental Paratiroidektominin Kemik Mineral Yoğunluğuna Etkisi

Gülay Özbölük[1], Nuri Alper Şahbaz[1], Ahmet Cem Dural[1], Cevher Akarsu[1], Deniz Güzey[1], Fatmagül Kuşku Çabuk[2], Sema Çiftçi Doğanşen[3], Serdar Altınay[2], Mehmet Karabulut[1]

[1]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Department of General Surgery, İstanbul, Turkey
[2]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Department of Pathology, İstanbul, Turkey
[3]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Department of Endocrinology and Metabolism, İstanbul, Turkey

ABSTRACT

Introduction: Thyroid surgery for benign and malign diseases is one of the most common procedures performed in surgical practice. Complication rates are higher in malignant and inflammatory diseases, recurrent surgeries and in hyperthyroid patients. Hypocalcemia is one of these complications. There are many studies investigating the effect of incidental parathyroid tissue removal on hypocalcemia in thyroidectomy operations and investigating the risk factors for incidental parathyroidectomy. However, there are no studies investigating the effect on bone mineral density (BMD). In our study, we aimed to reveal the effect of incidental parathyroidectomy during total thyroidectomy (TT) on BMD and osteoporosis.

Methods: Between January 2013 and December 2016, pathology reports of 983 patients who underwent TT, completion thyroidectomy, TT + central neck dissection, TT + functional neck dissection, TT + modified radical neck dissection were retrospectively reviewed.

Seventy-two female patients with incidental parathyroid tissue were included in the study. Demographic information, post-operative biochemical values (calcium, albumin, parathyroid hormone, vitamin D, phosphorus, alkaline phosphatase), BMD, The World Health Organization Frakture Risk Assessment Tool (FRAX) fracture risks were recorded and the relationship between them was evaluated.

Results: Patients were divided into three groups according to BMD: normal, osteopenic and osteoporotic. Patients in menopause and patients older than 45-years were more in osteopenic and osteoporotic group. Patients undergoing extended surgery had more parathyroids removed. There was no correlation between the number of parathyroid glands

ÖZ

Amaç: Benign ve malign hastalıklar için uygulanan tiroid cerrahisi, cerrahi pratiğinde en sık yapılan girişimler arasındadır. Malign hastalıklar, enflamatuvar hastalıklar, tekrarlayan cerrahiler ve hipertiroidili hastalarda komplikasyon oranları daha fazladır. Bu komplikasyonların başında hipokalsemi gelmektedir. Litaratürde tiroidektomi ameliyatlarında insidental paratiroid dokusu çıkarılmasının hipokalsemi üzerine etkisini araştıran ve insidental paratiroidektomiye neden olan risk faktörlerini araştıran pek çok çalışma mevcuttur. Ancak kemik mineral yoğunluğuna (KMY) etkisini araştıran çalışmalar yoktur. Çalışmamızda, total tiroidektomi (TT) esnasında insidental paratiroidektominin KMY'ye ve osteoporoz üzerine etkisini ortaya çıkarmaktır.

Yöntemler: Ocak 2013 ile Aralık 2016 tarihleri arasında multinodüler guatr, graves, toksik multinodüler guatr, malignite tanılarıyla TT, tamamlayıcı tiroidektomi, TT + santral boyun diseksiyonu, TT + fonksiyonel boyun diseksiyonu, TT + modifiye radikal boyun diseksiyonu ameliyatı yapılan 983 hastanın patoloji raporları retrospektif olarak incelendi. İnsidental paratiroid dokusu saptanan 72 kadın hasta çalışmaya dahil edildi. Hastaların demografik bilgileri, post-operatif biyokimyasal değerleri (kalsiyum, albümin, parathormon, D vitamini, fosfor, alkalen fosfataz), KMY, Dünya Sağlık Örgütü Kırılma Riski Değerlendirme Aracı (FRAX) fraktü riskleri kaydedilerek aralarındaki ilişki değerlendirildi.

Bulgular: Hastalar KMY'ye göre normal, osteopenik ve osteoporotik olmak üzere üç gruba ayrıldı. Menopoz ve 45 yaşın üzerinde olan hastalar osteopenik ve osteoporotik grupta daha fazlaydı. Genişletilmiş cerrahi uygulanan hastalarda

Presented in: This study was presented as a paper at the 9th National Endocrine Surgery Congress held in Antalya on 2-5 May 2019.

Address for Correspondence/Yazışma Adresi: Nuri Alper Şahbaz MD, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Department of General Surgery, İstanbul, Turkey
Phone: +90 505 557 27 62 **E-mail:** alpersahbaz@yahoo.com **ORCID ID:** orcid.org/0000-0002-0668-8382

Cite this article as/Atıf: Özbölük G, Şahbaz NA, Dural AC, Akarsu C, Güzey D, Kuşku Çabuk F, Çiftçi Doğanşen S, Altınay S, Karabulut M. Assessment of Bone Mineral Density in Patients with Incidental Parathyroidectomy during Thyroidectomy. İstanbul Med J 2020; 21(4): 320-6.

Received/Geliş Tarihi: 10.12.2019
Accepted/Kabul Tarihi: 12.06.2020

removed and hypocalcemia. After the surgery, the patients had no harmful effects on BMD and FRAX fracture risk.

Conclusion: In our study, one or two parathyroid glands were removed. No effect on BMD was detected.

Keywords: Incidental parathyroidectomy, bone mineral density, thyroidectomy

daha fazla sayıda paratiroid çıkarılmıştı. Çıkarılan paratiroid sayısıyla hipokalsemi arasında bağlantı saptanmadı.

Sonuç: Çalışmamızda, bir veya iki paratiroid bezinin çıkartılmasının KMY üzerine herhangi bir etkisi saptanmadı.

Anahtar Kelimeler: İnsidental paratiroidektomi, kemik mineral yoğunluğu, tiroidektomi

Introduction

Total thyroidectomy (TT) is the most commonly preferred method for the treatment of malignant and benign thyroid diseases. The most common complication in the post-operative period is approxiately one-third of hypocalcemia. Hypocalcemia may develop due to intraoperative manipulation of parathyroid glands, injury, accidental removal or deterioration of blood supply and is the most important factor leading to prolonged hospitalization (1-3).

Hypocalcemia that develops after TT is usually temporary. The incidence of persistent hypocalcemia depends on the experience of the clinic, but is reported between 0-13% in the literature (4).

When central neck dissection is added to TT, this rate increases to 1%-15% (5,6).

The risk of complications of TT is higher than that of limited surgery (such as lobectomy) resections. There is a higher rate of complication in diseases such as malignant diseases, inflammatory diseases, recurrent surgeries and hyperthyroidism. The experience of the surgeon performing the surgery and anatomical variations are also effective on complications (7).

Parathyroid hormone (PTH); plays an important role in the regulation of bone metabolism. PTH provides calcium balance by increasing calcium absorption through vitamin D from the intestine, reducing direct excretion from the kidney and directly increasing bone resorption (8).

Hypoparathyroidism is a factor that increases bone mineral density (BMD) (9). Although hypoparathyroidism may be idiopathic, it is often seen after thyroid surgery.

Osteoporosis is generally evaluated by the determination of BMD measured using the "Dual-Energy X-ray Absorptiometry (DEXA)" method. While it does not show other factors that may affect bone fragility, such as bone architecture and geometry, BMD is a very useful method for estimating bone strength and fracture risk (10,11).

There are many studies in the literature that investigate the effect of removal of incidental parathyroid tissue on hypocalcemia in thyroidectomy surgeries and investigate the risk factors that cause incidental parathyroidectomy. However, there are no studies investigating its effect on BMD. Our aim in this study is to reveal the effect of incidental parathyroidectomy on BMD and osteoporosis during TT.

Methods

In University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Department of General Surgery, patients diagnosed with multinodular goiter, Graves, toxic multinodular goiter and malignancy; pathology reports of 983 patients who underwent TT, complementary thyroidectomy, TT + central neck dissection, TT + functional neck dissection, TT + modified radical neck dissection surgery were analyzed retrospectively between January 2013 and December 2016.

Seventy two female patients with incidental parathyroid tissue were included in the study. The operations were performed by four experienced endocrine surgeons in the General Surgery Clinic. Post-operative pieces were evaluated by experienced pathologists in the Pathology unit. Ethics commitee approval was received for the study University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 20.03.2018, protocol no: 81). Informed consent was obtained from the patients who participated in the study.

The data of the patients were analyzed retrospectively. Patients' age, gender, body mass index (BMI), date of surgery, indication for surgery, post-operative pathology results, number of parathyroids in the pathology specimen; post-operative urea, creatinine, total protein, albumin, calcium (Ca), vitamin D, PTH, phosphorus, alkaline phosphatase (ALP), thyroid stimulating hormone (TSH), T4, BMD were evaluated using DEXA. Patients were phoned and questioned about their height, weight, medical history, family history, alcohol use, smoking, menopause status, birth, steroid use and vitamin D use. Patients were classified according to the World Health Organization (WHO) definition of osteoporosis (normal with T-score -1 or above, osteopenic with T-score -1 to -2.5, osteoporosis with T-score -2.5 or lower) (12).

A system called Fracture Risk Assessment Tool (FRAX) has been developed by the WHO's Center for Metabolic Bone Diseases cooperation to assess the 10-year fracture risk of diseases. In this system, age, gender, body weight, fracture history of patients and their parents, smoking, prolonged glucocorticoid use, rheumatoid arthritis, alcohol use, other causes of secondary osteoporosis were evaluated as the factors that determine absolute fracture risk for individuals. Finally, the WHO FRAX fracture index was calculated using https://www.sheffield.ac.uk web address.

The number of patients who underwent total tyroidectomy with clinical diagnosis of multinodular goiter, Graves' disease, toxic multinodular goiter, and malignancy and paratyhroid tissue detected in pathology reports were 107. However, 17 patients could not be reached by phone. The information in the file of thirteen patients was missing. Three patients did not want to participate in this study. Since the patient had parathyroid adenoma with thyroidectomy, 2 patients were excluded from the study and 72 women were included in the study.

Statistical Analysis

Descriptive statistics were used to define continuous variables (mean, standard deviation, minimum, median, maximum). Chi-square and Fisher exact test were used to examine the relationship between categorical variables.

Multiple linear regression analysis was applied to examine the effect of independent variables on continuous dependent variables. In order to examine the effect of independent variables on two categories of dependent variables, binary logistic regression analysis was applied. In order to study the effect of independent variables on dependent variables with more than two categories, multinomial logistic regression analysis was applied.

The statistical significance level is 0.05. The analyses were performed using Madcalc Statistical Software version 12.7.7 (MadCalc Statistical bvba, Ostend, Belgium).

Results

Seventy-two female patients were included in the study. Patients were evaluated according to WHO definition of osteoporosis. It was divided into three groups as osteoporotic, osteopenic and normal BMD. The data of the three groups were evaluated comparatively. The presence of fracture anamnesis did not make a statistically significant difference between the groups (p=0.895). Thirty five (46.6%) of the patients were premenopausal and 37 (52.4%) were postmenopausal. Sixteen (40%) of patients with normal BMD, 8 (38.1%) of patients with osteopenic BMD and 11 (100%) of patients with osteoporotic BMD were postmenopausal (p<0.001).

There was also no statistically significant difference between the groups whether the final pathology was benign or malignant (p=0.055).

The mean age of patients with normal BMD was 43.5 (20-69), the mean age of patients with osteopenic BMD was 42 (32-77), and the mean age of patients with osteoporosis was 55 (43-80) (p=0.004). Menopause was significantly higher in the osteoporosis group than in both normal and osteopenic groups (p<0.001). BMI, parathyroid count in the specimen; and albumin, Ca, vitamin D, PTH, phosphorus and ALP were also found to have no differences between the groups (Table 1).

The relationship of FRAX fracture risk to the time elapsed after surgery was observed, and the increase in the time elapsed did not increase the risk (Table 2). DEXA was taken in 25 (34.7%) patients 1-year after surgery, 21 (29.2%) 2-years after surgery, 26 (36.1%) more than 2-years after surgery. Likewise, osteopenia and osteoporosis were not related to the time elapsed after surgery (Table 2).

Patients according to the type of surgery performed were divided into two groups: Those who underwent TT and extended surgery (complementary thyroidectomy, TT + central neck dissection, TT + functional neck dissection, TT + modified radical neck dissection). FRAX fracture risk between these two groups; post-operative albumin, Ca, vitamin D, PTH, Phosphorus and ALP values and parathyroid count

Table 1. Comparison of parameters by groups

		Normal		Osteopenic		Osteoporotic		p*
		n	%	n	%	n	%	
Fracture anamnesis	Yes	5	12.5	3	14.3	2	18.2	0.895
	No	35	87.5	18	85.7	9	81.8	-
Menopause	Yes	16	40.0	8	38.1	11	100.00	<0.001
	No	24	60.0	13	61.9	0	0.0	-
Pathological diagnosis	Benign	26	65.0	7	35.0	8	72.7	0.055
	Malignant	14	35.0	13	65.0	3	27.3	-
		Ave ± SD		Ave ± SD		Ave ± SD		p**
Age		43.88±12.06		45.48±12.01		58.64±11.39		0.004
BMI		28.09±5.19		29.2±6.79		30.65±5.19		0.519
Number of parathyroid in specimen		1.15±0.36		1.14±0.36		1±0		0.399
Post-op albumin (g/dL)		4.56±0.21		4.47±0.44		4.37±0.53		0.530
Post-op Ca (mg/dL)		8.56±0.82		8.74±0.59		8.52±0.61		0.536
Post-op Vitamin D (ng/mL)		18.2±11.13		18.81±14.01		24.55±17.48		0.849
Post-op PTH (pg/mL)		37.08±20.9		40±16.24		48.3±16.9		0.088
Post-op phosphorus (mg/dL)		3.97±0.75		3.44±0.67		3.73±0.99		0.060
Post-op ALP (IU/L)		66.16±19.95		63.33±17.93		67.73±2248		0.999
Post-hoc paired comparison		**Normal - Osteopenic (p)**		**Normal - Osteoporotic (p)**		**Osteopenic - Osteoporotic (p)**		
Age		0.855		0.001		0.005		
Menopause		1.000		0.001		0.003		

*Fisher's exact test, **Kruskal Wallis-p, BMI: body mass index, PTH: parathormone, SD: standart deviation, Ave: average, Ca: calcium, ALP: alkaline phosphatase, post-op: post-operative

in pathology specimen were compared. Apart from the parathyroid number in specimen, no statistical significance was found in the others. The number of parathyroid patients in specimen was higher than in TT (p=0.006). There was no significant difference between 2 groups in terms of osteopenia and osteoprosis development (Table 3).

Discussion

Iatrogenic hypoparathyroidism is a common complication after thyroidectomy (13). To reduce this complication, it is necessary to identify the parathyroid glands during surgery and to perform dissection close to the thyroid gland capsule so that it does not disrupt its blood supply (14,15).

Hashimoto's thyroiditis (16,17) and malignancies (18-23) pose a potential risk factor for insidental parathyroidectomy. Similarly, we found an increase in incidence parathyroidectomy after surgery due to malignancy.

In the literature, incidence parathyroidectomy rate is between 8-24.9% (24,25). In many studies in the literature, one pararthyroid gland was removed (20,26,27). Similarly, most patients had a single parathyroid gland removed. Sixty-three (87.5%) patients had one parathyroid gland removed, and 9 (12.5%) patients had two parathyroid glands removed. The number of parathyroid glands three and above were not found in the specimens.

BMD is closely related to bone strength; prospective studies have shown that the risk of fracture increases with decreasing BMD and is an excellent indicator of possible future fracture risk. The risk of fracture increases twice with each standard deviation reduction in BMD (28).

Although patients with permanent hypoparathyroidism have an increase (9) in BMD, there are reports that contradict this information. Touliatos et al. (29) detected that eight patients with post-operative hypoparathyroidism have BMDs in the normal range.

In their study on 33 postmenopausal women who underwent TT, Fujiyama et al. (30) found that BMD of patients who developed hypoparathyroidism after surgery was higher than those with normal PTH levels. After this study, they concluded that hypoparathyroidism is protective against high bone mineral loss in the postmenopausal period. None of the patients we included in the study developed permanent hypoparathyroidism.

Mendonça et al. (31) did not find a significant difference between the BMDs of patients with hypoparathyroidism and patients with normal PTH levels in a controlled study conducted on 33 postmenopausal women.

Post-operative hypocalcemia is the most common complication that develops after TT and can develop due to many reasons (13).

In their study, Özden et al. (32) evaluated the temporal and permanent hypocalcemia rates in 178 patients who underwent thyroidectomy and

Table 2. Comparison of FRAX Fracture risk, osteopenic and osteoporotic BMD with the duration after the surgery

	<1 Year	1-2 Years	>2 Years	p*
	Ave ± SD	Ave ± SD	Ave ± SD	
FRAX Fracture risk	0.42±0.77	0.46±1.15	0.25±0.31	0.973
	n (%)	n (%)	n (%)	p**
Normal	13 (52%)	12 (57.1%)	15 (57.7%)	0.316
Osteoporotic	10 (40%)	5 (23.8%)	6 (23.1%)	
Osteopenic	2 (8%)	4 (19%)	5 (19.2%)	

*Kruskal Wallis test, **Mann-Whitney U test, Ave: average, SD: standard deviation, FRAX: Fracture Risk Assessment Tool, BMD: bone mineral density

Table 3. Comparison of parameters according to the type of surgery

	TT	Extended Surgery	p*
	Ave ± SD	Ave ± SD	
FRAX Fracture	0.35±0.6	0.44±1.2	0.514
Post-op Ca (mg/dL)	8.7±0.6	8.4±0.9	0.427
Post-op vitamin D (ng/mL)	18.9±13.8	20.3±11.4	0.305
Post-op PTH (pg/mL)	41.1±18.9	35.9±20	0.161
Post-op phosphorus (mg/dL)	3.8±0.8	3.7±0.7	0.995
Post-op ALP(IU/L)	65.3±20.09	66.1±15.9	0.614
Number of parathyroid in specimen	1.1±02	1.3±0.5	0.006
	n (%)	n (%)	p**
Normal	30 (75%)	10 (25%)	0.412
Osteopenic	13 (59.1)	8 (57.1)	
Osteoporotic	9 (40.9)	2 (42.9)	

*Mann-Whitney U test, **chi-square, Ca: calcium, SD: standart deviation, Ave: average, post-op: post-operative, PTH: parathormone, TT: total thyroidectomy, FRAX: Fracture Risk Assessment Tool, ALP: alkaline phosphatase

detected incidental parathyroid tissue in the pathology artery, and it was found that incidental parathyroidectomy had no effect on permanent hypocalcemia.

Manatakis et al. (33) evaluated 281 patients who underwent TT in their study. The patients were divided into two groups as those with and without incidental parathyroidectomy. Post-operative calcium levels were examined between these two groups. Hypocalcemia was observed in those who underwent incidental parathyroidectomy. However, there was no difference between the two groups in terms of symptomatic hypocalcemia.

Youssef et al. (20) included 207 patients who underwent total or unilateral thyroidectomy in their study. The patients were divided into two groups: 26 patients diagnosed with incidental parathyroidectomy and 181 patients not diagnosed incidental parathyroidectomy. Increased incidental parathyroidectomy rates were seen in surgeries where reoperation and neck dissection were also added. Post-operative hypocalcemia did not create a statistical difference between the two groups. This result was also reached in our study, and it was observed that more parathyroid tissue was removed in patients who underwent extended surgery compared to TT, and no permanent hypocalcemia occured in the patients.

Song et al. (34) examined the pathology specimens of 454 patients with TT. Incidental parathyroid tissue was detected in 19.8% of the patients in their pathology specimens. 17.6%, 1.5% and 0.7% of patients with incidental parathyroidectomy has one, two and three parathyroid tissues, respectively. It was observed that temporary hypoparathyroidism increased in proportion to the number of parathyroids removed. However, as a result, temporary or permanent hypocalcemia did not differ between these groups. In our study, hypoparathyroidism did not occur in the patients. One or two parathyroid glands were removed in our patients. Our results would have changed if three or more parathyroid glands were removed. This result, in fact, suggests that the amount of in vivo parathyroid tissue is more important.

Du et al. (35) found that surgeries in which central neck dissection was added poses a potential risk factor for incidental parathyrodectomy, in their study on 381 patients with TT and central neck dissection. Similar results were seen also in our study. The number of parathyroid glands removed in extended surgery was statistically significant (p=0.006). However, there was no effect on osteoporosis, osteopenia and FRAX fracture risk.

Zheng et al. (36) divided 548 patients who underwent total and subtotal thyroidectomy into two groups, with and without incidental parathyroid tissue. In the group where incidental parathyroidectomy was performed compared to the non-performed group; transient hypocalcemia and recurrent laryngeal nerve injury rate were increased. Also, malignancy rate was higher in the group with incidental parathyroidectomy. Therefore, central lymph node dissection was applied to more patients than the other group.

Osteoporosis is a multi-cause and most common skeletal disease characterized by increased bone fragility due to decreased bone mass and disruption of the microstructure of bone tissue (37). Age is a very important factor in bone loss. Bone loss starts around the age of 40, increases significantly in the 60s, and is even higher in the 80s (38). Low estrogen causes a decrease in bone mass. Therefore, menopause is also a risk factor for osteoporosis (39,40). One of the other risk factors is the low BMI (37). In our study, we found that menopause and advanced age are risk factors for osteoporosis in accordance with the literature. However, BMI did not make a statistical difference between our patients.

Takamura et al. (41) included 140 patients who underwent TT. These patients were divided into three groups: transient hypoparathyroidic, persistent hypoparathyroidic and normal range. 5-years after the operation, DEXA were taken to the patients and evaluated the relation of hypoparathyroidism with BMD. It is concluded that temporary hypoparathyroidism increases BMD in postmenopausal women.

In the literature, any studies investigating the effect of the number of parathyroids removed on BMD were not found, and in our study we found that the number of parathyroids does not change BMD. However, one or two parathyroid tissues were removed in our patients who did not develop hypoparathyroidism later on.

Conclusion

As a result, when the groups were evaluated, it was seen that the number of parathyroids removed was significantly higher in patients who underwent extended surgery due to malignancy. Patients with a pathological diagnosis of malignancy were 5.68 times more at risk of osteopenia than benign ones. We think that this result is due to the suppression of TSH in malignant patients.

In our study, no effect on the risk of FRAX fractures observed caused by the duration after surgery. However, FRAX scores are calculated while FRAX fracture index is evaluated as 40-years-old in patients under 40-years-old and it is a subjective evaluation, therefore it may limit the results. In our study, one or two parathyroid tissues were removed incidentally. If three or more parathyroids are removed, results may vary and prospective studies should be conducted in relation to that.

Ethics

Ethics Committee Approval: Ethics commitee approval was received for the study University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 20.03.2018, protocol no: 81).

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - N.A.Ş., A.C.D., S.Ç.D., S.A., M.K.; Concept - G.Ö., N.A.Ş., A.C.D., C.A., F.K.Ç., S.Ç.D.; Design - G.Ö., N.A.Ş., A.C.D., C.A., S.A., M.K.; Data Collection or Processing - C.A., D.G., F.K.Ç., S.Ç.D.; Analysis or Interpretation - N.A.Ş., D.G., F.K.Ç., S.Ç.D., S.A., M.K.; Literature Search - G.Ö., C.A., D.G., F.K.Ç., S.Ç.D., S.A.; Writing - G.Ö., N.A.Ş., A.C.D., D.G., F.K.Ç., M.K.

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

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

References

1. Bergamaschi R, Becouarn G, Ronceray J, Arnaud JP. Morbidity of thyroid surgery. Am J Surg 1998; 176: 71-5.
2. Parmeggiani D, De Falco M, Avenia N, Sanguinetti A, Fiore A, Docimo G, et al. Nerve sparing sutureless total thyroidectomy. Preliminary study. Ann Ital Chir 2012; 83: 91-6.
3. Bhattacharyya N, Fried MP. Assessment of the morbidity and complications of total thyroidectomy. Arch Otolaryngol Head Neck Surg 2002; 128: 389-92.
4. Uludağ M, Besler E, Aygün N, Çitgez B, Mihmanlı M, Yetkin SG, et al. Tiroid cerrahisi sonrası hipokalsemi gelişimini etkileyen faktörler. Şişli Etfal Hastanesi Tıp Bülteni 2015; 49: 101-6.
5. Clarke BL, Brown EM, Collins MT, Jüppner H, Lakatos P, Levine MA, et al. Epidemiology and diagnosis of hypoparathyroidism. J Clin Endocrinol Metab. 2016 Mar 4. doi: 10.1210/jc.2015-3908. [Epub ahead of print].
6. Shoback DM, Bilezikian JP, Costa AG, Dempster D, Dralle H, Khan AA, et al. Presentation of hypoparathyroidism: etiologies and clinical features. J Clin Endocrinol Metab. 2016 Mar 4. doi: 10.1210/jc.2015-3909. [Epub ahead of print].
7. Lal G, Clark OH. Thyroid, parathyroid, and adrenal. Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB. editors. Schwartz's Principles of Surgery. 10th ed. New York: McGraw-Hill; 2014. p.1556.
8. Lal G, Clark OH. Thyroid, parathyroid, and adrenal. Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB. editors. Schwartz's Principles of Surgery. 10th ed. New York: McGraw-Hill; 2014. p.1558.
9. Abugassa S, Nordenström J, Eriksson S, Sjödén G. Bone mineral density in patients with chronic hypoparathyroidism. J Clin Endocrinol Metab 1993; 76: 1617-21.
10. Miller PD, Bonnick SL, Rosen CJ, Altman RD, Avioli LV, Dequeker J, et al. Clinical utility of bone mass measurements in adults: consensus of an international panel. The Society for Clinical Densitometry. Semin Arthritis Rheum 1996; 25: 361-72.
11. Miller PD, McClung M. Prediction of fracture risk. I: Bone density. Am J Med Sci 1996; 312: 257-9.
12. Lal G, Clark OH. Thyroid, parathyroid, and adrenal. Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB. editors. Schwartz's Principles of Surgery 9th ed. New York: McGraw-Hill. 2010; p.2587-645.
13. Demeester-Mirkine N, Hooghe L, Van Geertruyden J, De Maertelaer V. Hypocalcemia after thyroidectomy. Arch Surg 1992; 127: 854-8.
14. Lappas D, Noussios G, Anagnostis P, Adamidou F, Chatzigeorgiou A, Skandalakis P. Location, number and morphology of parathyroid glands: results from a large anatomical series. Anat Sci Int 2012; 87: 160-4.
15. Praženica P, O'Driscoll K, Holy R. Incidental parathyroidectomy during thyroid surgery using capsular dissection technique. Otolaryngol Head and Neck Surg 2014; 150: 754-61.
16. Erbil Y, Barbaros U, Ozbey N, Aral F, Ozarmağan S. Risk factors of incidental parathyroidectomy after thyroidectomy for benign thyroid disorders. Int J Surg 2009; 7: 58-61.
17. Khairy GA, Al-Saif A. Incidental parathyroidectomy during thyroid resection: incidence, risk factors, and outcome. Ann Saudi Med 2011; 31: 274-8.
18. Ozoğul B, Nuran Akçay M, Kisaoğlu A, Atamanalp SS, Oztürk G, Aydinli B. Incidental parathyroidectomy during thyroid surgery: risk factors, incidence, and outcomes. Turk J Med Sci 2014; 44: 84-8.
19. Qasaimeh GR, Al Nemri S, Al Omari AK. Incidental extirpation of the parathyroid glands at thyroid surgery: risk factors and post-operative hypocalcemia. Eur Arch Otorhinolaryngol 2011; 268: 1047-51.
20. Youssef T, Gaballah G, Abd-Elaal E, El-Dosoky E. Assessment of risk factors of incidental parathyroidectomy during thyroid surgery: a prospective study. Int J Surg 2010; 8: 207-11.
21. Sippel RS, Ozgül O, Hartig GK, Mack EA, Chen H. Risks and consequences of incidental parathyroidectomy during thyroid resection. ANZ J Surg 2007; 77: 33-6.
22. Sorgato N, Pennelli G, Boschin IM, Ide EC, Pagetta C, Piotto A, et al. Can we avoid inadvertent parathyroidectomy during thyroid surgery?. In Vivo 2009; 23: 433-9.
23. Campos NS, Cardoso LP, Tanios RT, de Oliveiraa BC, Guimarães AV, Dedivitis RA, et al. Risk factors for incidental parathyroidectomy during thyroidectomy. Braz J Otorhinolaryngol 2012; 78: 57-61.
24. Sakorafas GH, Stafyla V, Bramis C, Kotsifopoulos N, Kolettis T, Kassaras G. Incidental parathyroidectomy during thyroid surgery: an underappreciated complication of thyroidectomy. World J Surg 2005; 29: 1539-43.
25. Applewhite MK, White MG, Xiong M, Pasternak JD, Abdulrasool L, Ogawa L, et al. Incidence, risk factors, and clinical outcomes of incidental parathyroidectomy during thyroid surgery. Ann Surg Oncol 2016; 23: 4310-5.
26. Rajinikanth J, Paul MJ, Abraham DT, Ben Selvan CK, Nair A. Surgical audit of inadvertent parathyroidectomy during total thyroidectomy: incidence, risk factors, and outcome. Medscape J Med 2009; 11: 29.
27. Lee NJ, Blakey JD, Bhuta S, Calcaterra TC. Unintentional parathyroidectomy during thyroidectomy. Laryngoscope 1999; 109: 1238.
28. Matkovic V, Colachis SC, İlich JZ. Osteoporosis: Its prevention and treatment. Braddom R, Buschacher RM, Dumitru D, Johnson WE, Sinaki M, editors. Physcial Medicine and Rehabilition. Philadephia: Saunders; 1996.p.851-76.
29. Touliatos JS, Sebes JI, Hinton A, McCommon D, Karas JG, Palmieri GM. Hypoparathyroidism counteracts risk factors for osteoporosis. Am J Med Sci 1995; 310: 56-60.
30. Fujiyama K, Kiriyama T, Ito M, Nakata K, Yamashita S, Yokoyama N, et al. Attenuation of postmenopausal high turnover bone loss in patients with hypoparathyroidism. J Clin Endocrinol Metab 1995; 80: 2135-8.
31. Mendonça ML, Pereira FA, Nogueira-Barbosa MH, Monsignore LM, Teixeira SR, Watanabe PC, et al. Increased vertebral morphometric fracture in patients with postsurgical hypoparathyroidism despite normal bone mineral density. BMC Endocr Disord 2013; 13: 1.
32. Özden S, Erdoğan A, Simsek B, Saylam B, Yıldız B, Tez M. Clinical course of incidental parathyroidectomy: Single center experience. Aurius Nasus Larynx 2018; 45: 574-7.
33. Manatakis DK, Balalis D, Soulou VN, Korkolis DP, Plataniotis G, Gontikakis E. Incidental parathyroidectomy during total thyroidectomy: risk factors and consequences. Int J Endocrinol 2016; 2016: 7825305.
34. Song CM, Jung JH, Ji YB, Min HJ, Ahn YH, Tae K. Relationship between hypoparathyroidism and the number of parathyroid glands preserved during thyroidectomy. Word J Surg Oncol 2014; 12; 200.
35. Du W, Fang Q, Zhang X, Cui M, Zhao M, Lou W. Unintentional parathyroidectomy during total thyroidectomy surgery: A single surgeon's experience. Medicine (Baltimore) 2017; 96: 6411.
36. Zheng J, Song H, Cai S, Wang Y, Han X, Wu H, et al. Evaluation of clinical significance and risk factors of incidental parathyroidectomy due to thyroidectomy: A single-center retrospective clinical study. Medicine (Baltimore) 2017; 96: 8175.
37. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO study group. 1994; 843: 1-129.

38. Bone density measurement--a systematic review. A report from SBU, the Swedish council on technology assessment in health care. J Intern Med Suppl 1997; 739: 1-60.

39. Johansson C, Mellström D. An earlier fracture as a risk factor for new fracture and its association with smoking and menopausal age in women. Maturitas 1996; 24: 97-106.

40. Concin H, Bischof HP, Taxer F, Ender K, Metka M, Heytmanek G. Menopausal bone density in healthy females of Voralberg. Lack of relation to anamnesis. Wien Med Wochenschr 1992; 142: 96-9.

41. Takamura Y, Miyauchi A, Yabuta T, Kihara M, Ito Y, Miya A. Attenuation of postmenopausal bone loss in patients with transient hypoparathyroidism after total thyroidectomy. World J Surg 2013; 37: 2860-5.

İstanbul Med J 2020; 21(4): 327-9
DOI: 10.4274/imj.galenos.2020.03453

Two Different Types of Atypical Kounis Syndrome in the Same Patient at Different Times: A Case Report

İlginç Bir Olgu: Farklı Zamanlarda İki Farklı Tipiyle Atipik Kounis Sendromu

Yavuz Furuncuoğlu[1], Başak Mert[2], Filiz Füsun Bölükbaş[1], Tayfun Gürol[3], Cengiz Bölükbaş[1]

[1]Bahçeşehir University Faculty of Medicine, Department of Internal Medicine, İstanbul, Turkey
[2]Bahçeşehir University Faculty of Medicine, İstanbul, Turkey
[3]Bahçesehir University Faculty of Medicine, Department of Cardiology, İstanbul, Turkey

ABSTRACT

Kounis syndrome (KS) is an acute coronary syndrome secondary to allergic reactions and can be triggered by many factors. It is a rare condition that is difficult to diagnose, which delays the prognosis of the disease. KS can be classified into three subtypes. In this study, we report a 57-year-old patient with a history of anaphylaxis three times, one after using Moxifloxacin and the other two following a physical activity and an application of hair dye, which were released by an intramuscular adrenalin injection. The two different types of KS occurred at different times due to different causes in the same patient. Our patient was consistent with type 2 KS at the first attack and type 1 KS at the second attack. Therefore, clinicians should not misdiagnose myocardial ischaemia in patients who present with an allergy complaint.

Keywords: Kounis syndrome, anaphylaxis, allergic angina

ÖZ

Kounis sendromu (KS) ilaçlar, çevresel etkenler ve diğer birçok durumla tetiklenebilen alerjik reaksiyonlara seconder gelişen akut koroner sendromdur. KS nadir görülmesi sebebiyle tanı konulması güç bir durumdur. Erken tanı ve tedavi ise prognoz için önem arz etmektedir. Bu olgu sunumunda 57 yaşındaki hastanın biri Moksifloksasin kullanımı sonrası, bir diğeri fiziksel aktivite sonrası olmak üzere üç anafilaksi öyküsü bulunmaktadır. Kısaca, hastada farklı zamanlarda, farklı sebeplerle gelişen iki farklı Kounis tipi mevcuttur. İlk atakta ve devamlı görülen tip 2 KS'ye, ikinci atakta tip 1 KS eklenmiştir. Klinisyenler göğüs ağrısı, yükselmiş kardiyak enzimler, elektrokardiyografi ve ekokardiyografi değişikliklerine eşlik eden alerjik reaksiyon bulgularında alerjik miyokard enfarktüsünü de akıllarına getirmeliler.

Anahtar Kelimeler: Kounis sendromu, anafilaksi, alerjik anjina

Introduction

Kounis syndrome (KS) was defined by Kounis and Zavras (1) in 1991 as a chest pain in the course of an anaphylactic reaction related to mast cell activation. It may be seen as angina pectoris or myocardial infarction (MI) with normal coronary arteries (1,2). The KS can be classified into three subtypes: type 1 patients suffer from chest pain associated with an acute allergic reaction and have no predisposing factors for coronary heart disease (3); type 2 presents in patient with primary coronary artery disease (CAD) and may cause plaque erosion or rupture (2,3) and type 3 patients suffer stent thrombosis (4). The various clinical manifestations of KS are chest pain, nausea, vomiting, syncope, pruritus, urticaria, palpitations and almost half of the patients suffer from respiratory manifestations including wheezing, stridor, rhinitis and dyspnoea (5). KS may be initiated by drugs, foreign bodies, diseases caused as a result of release of chemical mediators such as histamine, leukotrienes, chemokines and cytokines (6,7). Immunoglobulin E (IgE) and tryptase may be elevated in KS. An early diagnosis of KS is important for the prognosis and treatment of it.

Case Report

A 57-year-old woman presented with chest pain, palpitations, sweating, cough, weakness and near syncope. She had taken amoxicillin for pneumonia. She had a previous history of allergy but not of any CAD. Her history also included anaphylaxis three times, one after using Moxifloxacin and the other two following a physical activity and an application of hair dye, which were released by intramuscular adrenalin injection. Furthermore, she was allergic to Moxifloxacin, diazepam, iodine, Benzydamine oral spray, cinnamon, pistachio and peanut. Her medication included levothyroxine for the treatment of Hashimoto's thyroiditis. She was a tobacco smoker for 25 pack-years. She had a family history of Parkinson's disease, diabetes mellitus, bladder and colon cancer. Her vital signs were stable when she presented to the emergency

Address for Correspondence/Yazışma Adresi: Yavuz Furuncuoğlu MD, Bahçeşehir University Faculty of Medicine, Department of Internal Medicine, İstanbul, Turkey
Phone: +90 542 512 70 98 **E-mail:** dryavuzf@yahoo.com **ORCID ID:** orcid.org/0000-0002-6716-5577

Cite this article as/Atıf: Furuncuoğlu Y, Mert B, Bölükbaş FF, Gürol T, Bölükbaş C. Two Different Types of Atypical Kounis Syndrome in the Same Patient at Different Times: A Case Report. İstanbul Med J 2020; 21(4): 327-9.

Received/Geliş Tarihi: 21.11.2019
Accepted/Kabul Tarihi: 26.04.2020

room. She was presented with acute-onset chest pain, accompanied by allergic symptoms. Cardiac enzymes (Troponin, creatine kinase-MB) were normal. Antinuclear antibodies, anti-dsDNA, complete blood count, brain natriuretic peptide urea/creatinine, aspartate aminotransferase/alanine aminotransferase, lactate dehydrogenase/creatine phosphokinase, tryptase, antithrombin III, thyroid stimulating hormone, C3, C4 and D-dimer were normal. The abnormal test results were LDL: 157 mg/dL and IgE: 384 (n<100). Anthelmintic treatment was administered to eradicate any other possible cause of IgE elevation. Hepatitis B virus and hepatitis C virus serology were also negative. Abdominal ultrasonography and computerized tomography (CT) were normal. Thorax CT was performed showing bronchiectasis in small region.

Electrocardiography (ECG): Normal (Figure 1), echocardiography showed segmental left ventricular motion abnormality, but ejection fraction was normal, coronary angiography also revealed right coronary artery (RCA) spasm in the midportion and plaques in the left anterior descending (35%-50%) and circumflex arteries (Figures 2, 3). The RCA diameter was expanded after intravenous nitrate injection. Diltiazem, clopidogrel, statin, isosorbide mononitrate and, if necessary, isosorbide dinitrate were started as a maintenance therapy. After 15 months, the patient was readmitted with anaphylaxis-associated chest pain, amaurosis fugax and filiform pulse while dyeing her hair. She had taken nitroglycerine spray and acetylsalicylic acid when chest pain began prior to being admitted. Cardiac enzymes and transthoracic echocardiography were normal**,** ejection fraction was calculated as 55%. ECG: Normal (Figure 4), IgE: 322. Coronary angiography was performed showing no abnormal pathology. At that time, it was thought that the patient might have KS.

Parenteral H1 blocker and steroid were added to the treatment. No additional complaint was reported by the patient after being followed-up for three days. Drugs were adjusted and the patient was referred to the allergy department for allergic MI.

The patient gave a verbal and written consent before participating in the study.

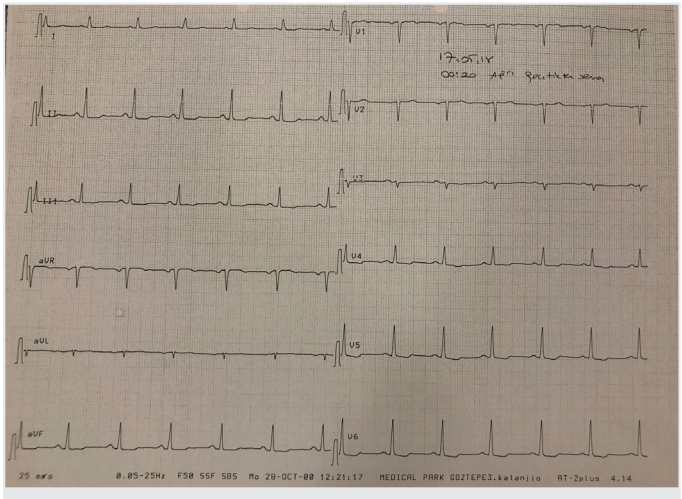


Figure 1. Normal electrocardiography of the patient when she was first admitted to the emergency service

Discussion

We present an interesting case of KS in a patient with an uncommon clinical presentation, which is significant for the awareness of KS. First, despite the recurrent anaphylaxis, there were no abnormalities in ECG and cardiac enzymes. Second, while using anti-ischaemic and anti-lipemic therapies, Kounis attacks reoccurred due to the allergic reactions

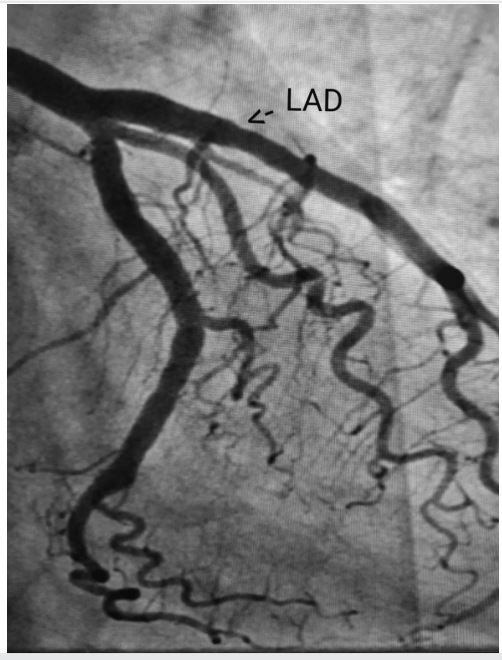


Figure 2. Coronary angiography shows non-critical plaques in the LAD (35%-50%) and Cx

LAD: left anterior descending

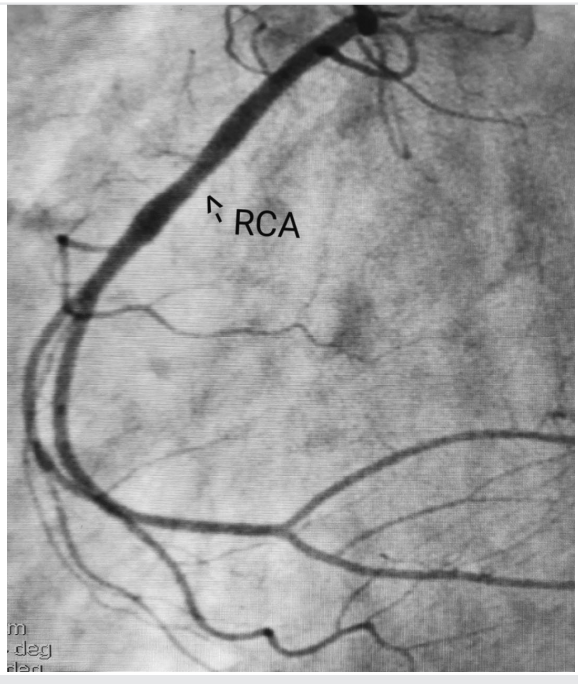


Figure 3. Coronary angiography revealed right coronary artery spasm in the midportion

RCA: right coronary artery

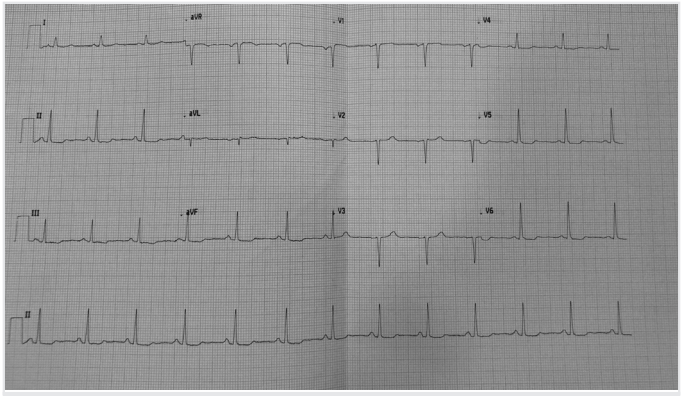


Figure 4. Normal electrocardiography of the patient after 15-months when she was readmitted to the hospital

even when narrowing disappeared. Briefly, the patient experienced two different types of KS at different times due to different causes - the consistent type 2 KS at the first attack and type 1 KS at the second.

The plaques were seen in the coronary arteries at the first coronary angiography, normal troponin but abnormal echo findings were observed, and the patient had used an antibiotic that had caused the KS. The second coronary angiography was normal when the patient had used a hair dye.

KS refers to varying degrees from myocardial ischaemia to infarction as a result of allergic and anaphylactic reactions. It could be presented as a broad clinical spectrum differing from only chest pain to ST segment elevated MI. Allergic reactions may be subclinical, acute or chronic. KS may develop for many reasons; antibiotics and other drugs (8).

Nitrates, calcium blockers, anti-histaminic and steroids are used to treat type 1 KS, whereas antithrombotic drugs are required for type 2 KS (9). Clinicians should not misdiagnose myocardial ischaemia in patients who present with an allergy complaint.

In our case, there were changes in echocardiogram (ECHO) and clinical findings considering ischaemic heart disease, however, no change in enzymes or ECG were seen. Coronary angiography was performed. Ischaemic coronary arteries and vasospasm were seen. Fifteen months later, second coronary angiography was performed due to the chest pain and anaphylaxis, but the coronary arteries were normal.

Conclusion

To conclude, we suggest that clinicians should always consider KS as a differential diagnosis if there are any signs and symptoms of allergy and ischaemic heart disease such as changes in ECG, ECHO or enzymes.

Ethics

Informed Consent: Verbal and Written informed consent was obtained from the patient.

Peer-review: Internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices- Y.F., T.G. ; Concept- Y.F., B.M., F.F.B., C.B. ; Design- Y.F., B.M., C.B ; Data Collection or Processing- Y.F., B.M., T.G., C.B ; Analysis or Interpretation- Y.F., F.F.B., T.G. ; Literature Search- Y.F., B.M. ; Writing- Y.F., B.M., F.F.B.

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

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

References

1. Kounis NG, Zavras GM. Allergic angina and allergic myocardial infarction. Circulation 1996; 94: 1789.
2. Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? Int J Cardiol 2006; 110: 7-14.
3. Kounis GN, Soufras GD, Kouni SA, Kounis NG. Hypersensitivity myocarditis and hypersensitivity coronary syndrome (Kounis syndrome). Am J Emerg Med 2009; 27: 506-8.
4. Akyel A, Murat SN, Cay S, Kurtul A, Ocek AH, Cankurt T. Late drug eluting stent thrombosis due to acemetacine: type III Kounis syndrome: Kounis syndrome due to acemetacine. Int J Cardiol 2012; 155: 461-2.
5. Kogias JS, Sideris SK, Anifadis SK. Kounis syndrome associated with hypersensitivity to hymenoptera stings. Int J Cardiol 2007; 114: 252-5.
6. Mazarakis A, Goudevenos J, Kounis NG. Coronary vasospasm induced by cytostatic drugs: Kounis syndrome seems to be the most likely culprit. Hellenic J Cardiol 2013; 54: 482-5.
7. Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? Int J Cardiol 2006; 110: 7-14.
8. Mazarakis A, Koutsojannis CM, Kounis NG, Alexopoulos D. Cefuroxime-induced coronary artery spasm manifesting as Kounis syndrome. Acta Cardiol 2005; 60: 341-5.
9. Cevik C, Nugent K, Shome GP, Kounis NG. Treatment of Kounis syndrome. Int J Cardiol 2010; 143: 223-6.

İstanbul Med J 2020; 21(4): 330–2
DOI: 10.4274/imj.galenos.2020.90699

Central Giant Cell Granuloma with Cosmetic Deformity and its Treatment without A Scar

Kozmetik Deformiteye Neden Olan Santral Dev Hücreli Granülom ve Skarsız Tedavisi

Banu Atalay Erdoğan[1,2]

[1]Bahçeşehir University Faculty of Medicine, Department of Otolaryngology, İstanbul, Turkey
[2]VM Medicalpark Pendik Hospital, Clinic of Otolaryngology, İstanbul, Turkey

ABSTRACT

Central giant cell granuloma is a non-neoplastic proliferative lesion of unknown aetiology, and may cause severe local destruction. It occurs mostly in the mandible, but can also be found in the maxilla. Surgical excision is the mainstay of treatment. We managed this case by curettage via intranasal incision without producing external scar in a young woman.

Keywords: Giant cell granuloma, maxilla, swelling

ÖZ

Santral dev hücreli granülom, etiyolojisi bilinmeyen neoplastik olmayan proliferatif lezyondur. Ciddi yerel tahribata yol açabilir. En sık mandibulada görülür, ancak maksillada da oluşabilir. Cerrahi eksizyon, tedavinin temelidir. Bu olguda, genç bir kadında yara izi oluşturmadan intranazal insizyon yoluyla kitleyi kürete etmeyi başardık.

Anahtar Kelimeler: Dev hücreli granülom, maksilla, şişlik

Introduction

Giant cell granuloma (GCG) was first described by Jaffe in 1953 (1). The etiology of GCG is uncertain but may be related to the reactive response of intraosseous haemorrhage following trauma. GCGs are most often located in the maxilla and mandible (2). The second most common locations are hands and feet bones. GCGs are seen at any age but they tend to appear between ages of 25-40 (3). Despite their benign nature, GCGs may be locally aggressive. We report a case of GCG of the anterior maxilla with cosmetic deformity.

Case Report

Written informed consent was obtained from the patient. A 17-year-old female patient presented with a swelling on the left side of the face for two months. The swelling had progressed slowly from a small lesion to the present size. She was a nonsmoker with an unremarkable medical and family history. Examination revealed a diffuse swelling on the left side of the face causing the obliteration of the nasolabial fold resulting in facial asymmetry. The overlying skin was normal. On oral examination, there was a swelling in the labial aspect extending from the midline in relation to the upper left central incisor to the second premolar posteriorly obliterating the labial sulcus. It had a smooth surface with no evidence of fluctuation on palpation. The rest of the ear, nose and throat (ENT) examination was normal. Serum calcium, phosphorus and alkaline phosphatase levels were normal.

A computed tomography (CT) scan (Figure 1) showed a 32x22 mm expansile lesion involving the left maxillary bone. It caused erosion in the anteromedial wall of left maxillary sinus and the mass reached the subcutaneous tissue. Odontogenic fibroma, odontogenic cyst, odontogenic myxoma, adenomatoid odontogenic tumour and desmoplastic ameloblastoma were considered as differential diagnosis.

The patient underwent surgical resection with an incision from the superior to the left inferior nasal concha. The thickened cyst wall was lifted from the bony walls and the mass removed completely by curettage. The bony wall remnants were curetted. Histopathologic examination revealed a fibroblastic proliferation with rich osteoclast-like polynuclear giant cells and areas of haemorrhage (Figure 2). There was no recurrence after a follow-up period of 5 years.

Discussion

The World Health Organisation defines GCG as a benign intraosseous lesion consisting of fibrous tissue containing foci of haemorrhage and haemosiderin deposits, aggregations of giant cells and reactive bone formation (4). Its aetiology is not clear but many researchers agree

Address for Correspondence/Yazışma Adresi: Banu Atalay Erdoğan MD, Bahçeşehir University Faculty of Medicine, Department of Otolaryngology; VM Medicalpark Pendik Hospital, Clinic of Otolaryngolog, İstanbul, Turkey
Phone: +90 506 248 04 66 **E-mail:** banuatalay81@gmail.com **ORCID ID:** orcid.org/0000-0002-2956-23791

Cite this article as/Atıf: Atalay Erdoğan B. Central Giant Cell Granuloma with Cosmetic Deformity and its Treatment without a Scar. İstanbul Med J 2020; 21(4): 330-2.

Received/Geliş Tarihi: 22.09.2019
Accepted/Kabul Tarihi: 11.05.2020

that they occur due to the repair process after damage (5). Giant cell reparative granuloma involves the mandible more often than the maxilla (6).

GCGs have two types; central (CGCG) or peripheral (PGCG). Central lesions develop inside the bone and peripheral lesions originate from gingiva or edentulous alveolar mucosa in the oral cavity. CGCG is rarely seen compared to PGCG (7). There is no histological difference between central and peripheral giant cell reparative granulomas. PGCG can be seen at any age, but usually, affect individuals between the ages of 40-60, and occur more frequently in females (8). CGCG affects females more often, and are encountered in individuals below 30 years of age (9). The clinical behaviour of CGCG is variable. It ranges from slow-growing, asymptomatic swellings to aggressive lesions which manifest with pain. Despite their benign nature, they may be locally aggressive. The most common presenting symptom of CGCG is a painless swelling with noticeable facial asymmetry (3).

Histopathological findings of GCG are multinucleated giant cells mixed with mononuclear stromal cells, both spindle- and round shaped cells, and found mostly in areas of haemorrhages. Radiological findings of GCG are nonspecific. It usually appears as a unilocular or multilocular radiolucency that shows variable expansion and destruction of the cortical plate (3). Magnetic resonance imaging is the best modality for evaluating the extension of the lesion.

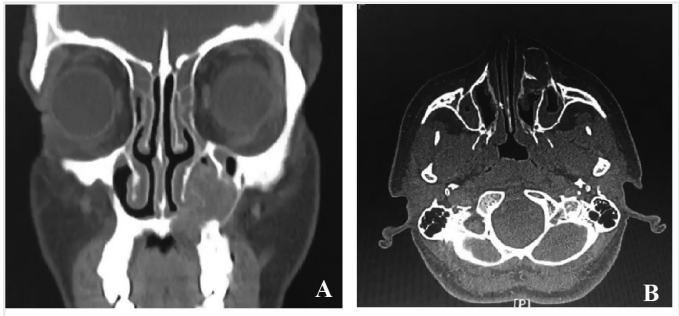


Figure 1. Computed tomography in coronal and axial sections of paranasal sinuses showing a 32x22 mm expansile lesion involving the left maxillary bone. This lesion causes an erosion in the anteromedial wall of left maxillary sinus and the mass reaches the subcutaneous tissue

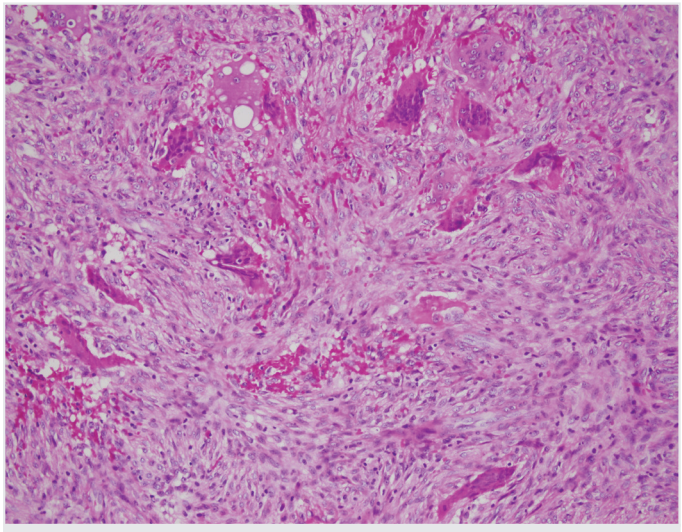


Figure 2. Histological findings of central giant cell granuloma: the tumour consists of spindled fibroblasts admixed with numerous multinucleated giant cells that tend to be arranged in small clusters

Surgery is the gold standard treatment for GCG. It ranges from curettage and simple excision to en bloc resection and reconstruction. Farrier et al. (10) suggested that complete surgical excision with curettage proved to be effective in the complete elimination of the lesion. However, it could recur after incomplete removal, ranging from 10 -15% (11). Moreover, aggressive GCG grows fast, and tends to recur. Characteristic features of aggressive GCG include maxillary location, young age, pain, paraesthesia, and tooth root and cortical erosion (12).

In this case, the mass could not be palpated through the mouth. Since the patient was a young woman, we decided to use the intranasal approach. The mass was easily reached through an incision over the inferior nasal concha, and an excision was made so the patient had no facial scar.

Medical management of GCG, as an adjunct to surgery, involves treatment with steroids or calcitonin, which inhibit osteoclastic activity (13). In addition, interferon-alpha bisphosphonates and denosumab appear to be useful in its management. Some authors have advocated the use of medical agents only for aggressive and large lesions, due to systemic side effects (14). Radiotherapy may be suggested in cases of recurrence or unresectable tumours. However, it should be noted that some GCGs are radioresistant, with sarcomatous transformation possibly taking place over time (15).

Conclusion

GCG are benign osteolytic lesions, but because of their clinical appearance, patients usually worry about the characteristic of the lesions. Surgery is the gold standard treatment modality. In this case report, we present a patient with central giant cell reparative granuloma which causes facial deformity in a young woman. We treated her with an intranasal approach without incision scar.

Ethics

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

Peer-review: Internally peer-reviewed.

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

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

References

1. Jaffe HL. Giant-cell reparative granuloma, traumatic bone cyst, and fibrous (fibro-osseous) dysplasia of the jawbones. Oral Surg Oral Med Oral Pathol 1953; 6; 159-75.
2. Boedeker CC, Kayser G, Ridder GJ, Maier W, Schipper J. Giant-cell reparative granuloma of the temporal bone: a case report and review of the literature. Ear Nose Throat J. 2003; 82: 926-37.
3. Ebrahimi H, Yazdani J, Pourshahidi S, Esmaeli F, Zenouz AT, Mehdipour M. Central giant cell granuloma of the posterior maxilla: a case report. J Dent Res Dent Clin Dent Prospects 2008; 2: 71-5.

4. Uzbek UH, Mushtaq I. Giant cell granuloma of the maxilla. J Ayub Med Coll Abbottabad 2007; 19: 93.

5. Motamedi MH, Eshghyar N, Jafari SM, Lassemi E, Navi F, Abbas FM, et al. Peripheral and central giant cell granulomas of the jaws: a demographic study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007; 103: 39-43.

6. Ishinaga H, Otsu K, Mouri G, Takeuchi K. Aggressive giant cell reparative granuloma of the nasal cavity. Case Rep Otolaryngol. 2013; 2013: 69019.

7. Cayci E, Kan B, Guzeldemir-Akcakanat E, Muezzinoglu B. Peripheral giant cell reparative granuloma of maxilla in a patient with aggressive periodontitis. Oral Health Dent Manag 2014;13: 638-41.

8. Katsikeris N, Kakarantza-Angelopoulou E. Peripheral giant cell granuloma. clinico-pathologic study of 224 new cases and 956 reported cases. Int J Oral Maxillofac Surg 1988; 17: 94-9.

9. Neville BW, Damm DD, Allen CM, Bouquot JE. Oral and Maxillofacial Pathology. 4th ed. Philadelphia: Saunders; 2002.pp.705-40.

10. Farrier SL, Farrier JN, Smart MK, Nash ES. A 10-year review of the occurrence and treatment of central giant cell granulomas, in a District General Hospital. J Oral Pathol Med 2006; 35: 332-7.

11. Günel C, Erpek G, Meteoğlu I. Giant cell reparative granuloma in the hard palate. International Journal of Pediatric Otorhinolaryngology Extra 2007; 2: 76-9.

12. Roberts J, Shores C, Rose AS. Surgical treatment is warranted in aggressive central giant cell granuloma: a report of 2 cases. Ear Nose Throat J 2009; 88: 8-13.

13. de Mendonça RP, Mitre GP, Real FH, da Silva Kataoka MS, de Melo Alves Júnior S, Vianna P, et al. Central giant cell granuloma treated with ıntralesional corticosteroid ınjections and bisphosphonates: a long-term follow-up case study. Head Neck Pathol. 2019 Jul 11. doi: 10.1007/s12105-019-01053-x. [Epub ahead of print].

14. Schreuder WH, van den Berg H, Westermann AM, Peacock ZS, de Lange J. Pharmacological and surgical therapy for the central giant cell granuloma: A long-term retrospective cohort study. J Craniomaxillofac Surg 2017; 45: 232-43.

15. Akhtar MU, Nazir A, Imtiaz M. Unusual case of maxillary giant cell granuloma: management, functional and aesthetic rehabilitation. Annals of King Edward Medical University 2014; 20: 113-6.