ISSN 2564-7784 EISSN 2564-7040

Indexed in Web of Science

European Journal of Therapeutics

OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

Formerly Gaziantep Medical Journal

VOLUME 24 ISSUE 3 SEPTEMBER 2018

eurjther.com

European Journal of Therapeutics

OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

Gaziantep Üniversitesi Tıp Fakültesi adına sahibi ve Sorumlu Yazı İşleri Müdürü/Owner on behalf of Gaziantep University School of Medicine and Responsible Manager: Mehmet Murat Sucu • Yayın türü/Publication Type: Uluslararası Süreli Yayın/International Periodical • Basım yeri Printed at: Matsis Matbaa Hizmetleri San. ve Tic.Ltd.Şti, Tevfikbey Mah., Dr. Ali Demir Cad. No: 51, 34290 Sefaköy, Turkey (+90 212 624 21 11) • Basım tarihi/Printing Date: Eylül 2018 / September 2018 • Gaziantep Üniversitesi Tıp Fakültesi tarafından yayınlanmaktadır/Published by Gaziantep University School of Medicine, Üniversite Cad, 27310 Şehitkamil, Gaziantep, Turkey (+90 342 360 60 60/77751)

AVES

Publisher
İbrahim KARA

Publication Director
Ali ŞAHİN

Finance and Administration
Zeynep YAKIŞIRER

Deputy Publication Director
Gökhan ÇİMEN

Editorial Development
Gizem KAYAN

Publication Coordinators
Betül ÇİMEN
Özlem ÇAKMAK
Okan AYDOĞAN
İrem DELİÇAY
Büşra PARMAKSIZ

Project Assistants
Ecenur ASLIM
Neslihan KÖKSAL
Cansu ASLAN

Graphics Department
Ünal ÖZER
Deniz DURAN

Contact
Address: Büyükdere Cad. 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com

European Journal of Therapeutics
OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

Aims & Scope

European Journal of Therapeutics (Eur J Ther) is the double-blind peer-reviewed, open access, international publication organ of the Gaziantep University School of Medicine. The journal is a quarterly publication, published on March, June, September, and December and its publication language is English.

European Journal of Therapeutics aims to contribute to the international literature by publishing original clinical and experimental research articles, case reports, review articles, technical notes, and letters to the editor in the fields of medical sciences. The journal's target audience includes researchers, physicians and healthcare professionals who are interested or working in in all medical disciplines.

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

European Journal of Therapeutics is indexed in Web of Science-Emerging Sources Citation Index, TUBİTAK ULAKBİM TR Index, and GALE.

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.eurjther.com. 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 Gaziantep University School of Medicine. Potential advertisers should contact the Editorial Office. Advertisement images are published only upon the Editor-in-Chief's approval.

Statements or opinions expressed in the manuscripts published in the journal reflect the views of the author(s) and not the opinions of the Gaziantep University School of Medicine, 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.eurjther.com. Printed copies of the journal are distributed to the members of the Gaziantep University School of Medicine, free of charge.

The journal is printed on an acid-free paper.

OPEN ACCESS

Editor: Prof. Murat Sucu
Address: Gaziantep University, School of Medicine, Journal Office, 27310 Şehitkamil, Gaziantep, Turkey
Phone: +90 342 3606060/77751
Fax: +90 342 3601617
E-mail: info@eurjther.com

Publisher: AVES
Address: Büyükdere Cad., 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com
Web page: avesyayincilik.com

European Journal of Therapeutics
OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

Instructions to Authors

European Journal of Therapeutics (Eur J Ther) is the double-blind peer-reviewed, open access, international publication organ of the Gaziantep University School of Medicine. The journal is a quarterly publication, published on March, June, September, and December and its publication language is English.

European Journal of Therapeutics aims to contribute to the international literature by publishing original clinical and experimental research articles, case reports, review articles, technical notes, and letters to the editor in the fields of medical sciences. The journal's target audience includes researchers, physicians and healthcare professionals who are interested or working in in all medical disciplines.

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 European Journal of Therapeutics 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. 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, releases signed by the patient or 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.

European Journal of Therapeutics requires corresponding authors to submit a signed and scanned version of the authorship contribution form (available for download through www.eurjther.com) 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.

European Journal of Therapeutics 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.

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 European Journal of Medical Sciences, authors accept to assign the copyright of their manuscript to Gaziantep University School of Medicine. If rejected for publication, the copyright of the manuscript will be assigned back to the authors. European Journal of Therapeutics requires each submission to be accompanied by a Copyright Transfer Form (available for download at www.eurjther.com). 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 European Journal of Therapeutics 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 2017 - 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.eurjther.com. 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.eurjther.com.

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: An English abstract should be submitted with all submissions except for Letters to the Editor. 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.

European Journal of Therapeutics
OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

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.

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 Presentation, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

Technical Notes: This type of manuscripts should present a new experimental, computational method, test, procedure, or comparison of methods. The method described may either be completely new, or may offer a better version of an existing method. The technical note article must describe a demonstrable advance on what is currently available. Please check Table 1 for the limitations for Technical Notes.

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
Technical Note	1500	No abstract	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

European Journal of Therapeutics
OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

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.

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: Prof. Murat Sucu
Address: Gaziantep University, School of Medicine, Journal Office, 27310 Şehitkamil, Gaziantep, Turkey
Phone: +90 342 3606060 / 77751
Fax: +90 342 3601617
E-mail: info@eurjther.com

Publisher: AVES
Address: Büyükdere Cad. 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com
avesyayincilik.com

European Journal of Therapeutics
OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

Contents

European Journal of Therapeutics

DOI: 10.5152/EurJTher.2018.344

Review

The Role of Nitric Oxide Related Therapeutics in the Treatment of Cardiovascular Pathologies

Mehmet Kürşat Derici[1], Emine Demirel Yılmaz[2]

[1]Department of Medical Pharmacology, Kırıkkale University, School of Medicine, Kırıkkale, Turkey

[2]Department of Medical Pharmacology, Ankara University, School of Medicine, Ankara, Turkey

ABSTRACT

The heart is a bio pump responsible for the provision of oxygen and nutrients to all body cells. It plays a vital role in the survival of the organism. The essential function of the heart is performed through the close interaction of the cardiac myocytes with the endocardial and capillary endothelial cells. The endothelium releases nitric oxide (NO) and modulates several physiological and pathological processes. The cardiac myocyte is also capable of NO production. Although the effect of NO on cardiac responses has been examined, data regarding the effect of NO on the heart remain controversial. The discrepancies in studies can be explained by several factors, such as different animal species, preparation, redox status, and NO concentration. However, an increasing interest in the role of NO has generated significant progress in the investigation of NO-based therapies. In this review, first, the general properties of NO are described as well as the physiological functions and pathological role in the heart. Then, an evaluation is made of several important NO-related treatment options, such as NO donors, NO synthase inhibitors, phosphodiesterase inhibitors, and soluble guanylate cyclase stimulators/activators. A summary is also given of NO-based drug candidates planned for use in clinical trials in the near future.

Keywords: Heart, nitric oxide, multiple roles, mechanism, therapeutic implication

INTRODUCTION

Nitric oxide (NO), which is both a signal molecule and an effector, plays an important role in the physiological and pathological processes of organisms. The chemical structure of NO was first discovered by an English chemist, Joseph Priestley, in 1772, and as a colorless and odorless natural gas, it is found in the upper layers of the atmosphere, vehicle exhausts, and acid rain (1). Its bioactivity has been recently more fully understood. Although the first organic nitrate, glyceryl trinitrate (GTN), was originally synthesized by an Italian chemist, Ascanio Sobrero, in 1847, it was first used as a vasodilator in 1928 (2). In 1979, nitroprusside was shown to act via NO in bovine coronary artery, and it was demonstrated that NO activates guanylate cyclase, resulting in vascular relaxation through cyclic guanosine monophosphate (cGMP) production (3). However, the in vivo relaxant effect of acetylcholine (ACh) on the vessels has not always been reproducible in in vitro conditions. In 1962, Jelliffe observed that the basic effect of ACh on the rabbit aorta is relaxation rather than contraction in in vitro conditions. A milestone in the study of NO was the work by Furchgott and Zawadzki in 1980 evaluating the effects of ACh on the rabbit thoracic aorta. Careful observation in that study found that the variability of ACh in responses in the vessel was dependent on the presence of the vascular endothelium (4). At that time, it was suggested that a substance was released from the vascular endothelium by ACh and was called endothelial-derived relaxing factor (EDRF). The candidate molecule was thought to be an unstable free radical. It was proposed that EDRF and NO were the same molecule in 1986 (5). Nowadays, NO is known to have an influential function in several biological processes in various organisms.

NO has also been shown to play an important role in the modulation of cardiac functions in physiological and pathological conditions. However, diverse responses to NO have been observed in different animal species or experimental models, such as cardiac myocytes/tissues isolated from atrial–ventricular/left–right regions of the heart. Furthermore, NO signaling pathways and the mechanism of NO actions have been poorly identified in cardiovascular studies from the perfused whole heart in in vivo examination of NO concentration and redox state.

GENERAL PROPERTIES OF NO

Endogenous NO is produced in response to several substances by NO synthase (NOS) from L-arginine (Figure 1). Three different isoforms of NOS are defined as endothelial NOS (eNOS), neuronal NOS (nNOS), and inducible NOS (iNOS). eNOS and nNOS proteins are defined as constitutive NOS (cNOS) because they are expressed in the cells in basal conditions. In the physiological

ORCID IDs of the authors: M.K.D. 0000-0002-8260-7492; E.D.Y. 0000-0002-2476-6225.

Corresponding Author: Mehmet Kürşat Derici **E-mail:** kursatderici@kku.edu.tr

Received: 19.12.2017 • **Accepted:** 15.01.2018

Figure 1. NO synthesis via the NOS enzyme from L-arginine. NOS converts L-arginine to L-citrulline using Ca–calmodulin, oxygen, nicotinamide adenine dinucleotide phosphate, tetrahydrobiopterin, and flavin adenine dinucleotide as cofactors

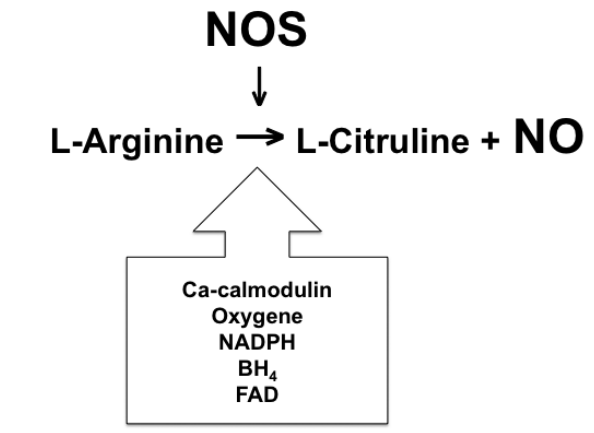
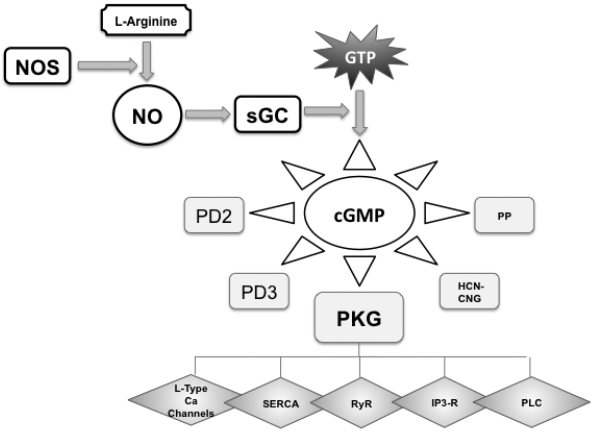


Figure 2. NO-stimulated cGMP-dependent pathway.
sGC: soluble guanylate cyclase, GTP: guanosine triphosphate, cGMP: cyclic guanosine monophosphate, PDE: phosphodiesterase enzymes, HCN-CNG: hyperpolarization-activated cyclic nucleotide-gated ion channels, PKG: protein kinase G, SERCA: sarcoplasmic reticulum Ca-ATPase, RyR: ryanodine receptor, IP3R: inositol trisphosphate receptor, PLC: phospholipase C



condition, a low level of NO is produced by the cNOSs. Several immunological agents stimulate the iNOS that generates a higher amount of NO. Basically, nNOS is found not only in the central nervous system and peripheral neurons but also in other cells. eNOS is mainly found in the endothelium, whereas iNOS is mostly found in the immune cells. Although iNOS is known to play a role in immune defense against microorganisms and tumor cells, findings have also been found that it contributes to the formation of some pathological processes, such as chronic inflammation and organ rejection (6).

In addition to NO synthesis by the NOS enzyme, NO production can also occur in the body by conversion of NO metabolite nitrite via the nitrate reductase enzyme. NO may also form spontaneously from nitrite in low pH medium (7).

Another source of NO is nitrate contained in foods. High levels of inorganic nitrate are found, especially in green leafy vegetables in daily diet. In many studies, dietary nitrate has been shown to have significant cardiovascular effects. Another foodborne group that has been proven to be related to the NO system is polyphenols that affect the reduction of nitrite to bioactive NO, thereby enhancing NO bioactivity. A low alcohol intake leads to NOS activation and increased expression of eNOS. Conversely, the chronic use of higher amounts of alcohol disrupts endothelial function and leads to a decrease in NO bioavailability (8).

Nitric oxide is metabolized to nitrite and nitrate within seconds after production. Its biological half-life may vary from approximately 6 to 50 s. Most of nitrate in the blood is excreted in the urine, but a certain amount of nitrate is converted to nitrite by oral bacteria. Nitrate in the gut is reduced to ammonia that is excreted in the urine after absorption and conversion to urea. However, in cases of oxidative stress (OS), high concentrations of the superoxide radical ($O_2^{\cdot-}$) interact with NO, and peroxynitrite anion ($ONOO^-$) is synthesized. This reaction also diminishes NO from the environment, and this NO-reducing pathway is called nitrosative stress (NS) (9).

Mechanisms of NO Action

In the target cell, NO activates soluble guanylate cyclase (sGC) and then increases the cGMP level. The main target of cGMP in the cells is protein kinase G (PKG), which regulates the activities of various proteins (Figure 2). Another important intracellular target of cGMP is phosphodiesterase (PDE) enzymes that metabolize cyclic adenosine monophosphate (cAMP) and cGMP. While cGMP activates PDE2, it inhibits PDE3, thus affecting intracellular cAMP levels. This mechanism constitutes the "cross-talk" pathway of cGMP with cAMP. In addition, cGMP can activate cyclic nucleotide-gated ion channels in the cell (10).

For many years, the effect of NO has been explained by mechanisms dependent on cGMP. However, it later became clear that there are also cGMP-independent ways. It has been demonstrated that NO primarily causes three basic chemical reactions: nitrosylation, nitrosation, and nitration (Figure 3) (11).

Nitrosylation is the binding of NO to the metal core of the functional proteins (metal nitrosylation). NO can regulate some enzyme activities by reacting with transition metals, such as iron, copper, and zinc, in the prosthetic group of proteins in the cell. The attachment of NO to heme is particularly important for the activation of the sGC enzyme. The activity of sGC is influenced by the cell's redox status. Oxidation of the heme group may render the enzyme insensitive to NO (10). NO-induced inhibition of cytochrome C enzyme is also the result of interaction with the copper core of the enzyme (11).

The nitrosation and nitration reactions of NO occur in an OS that appears in elevation of reactive oxygen species (ROS). The reaction of NO with $O_2^{\cdot-}$ gives rise to highly reactive nitrogen species, producing nitrosation and nitration of target molecules (12).

Figure 3. Brief summary of the NO-induced chemical reactions in the target cells. Interaction of NO with superoxide radical is concentration dependent. O2−•: superoxide radical

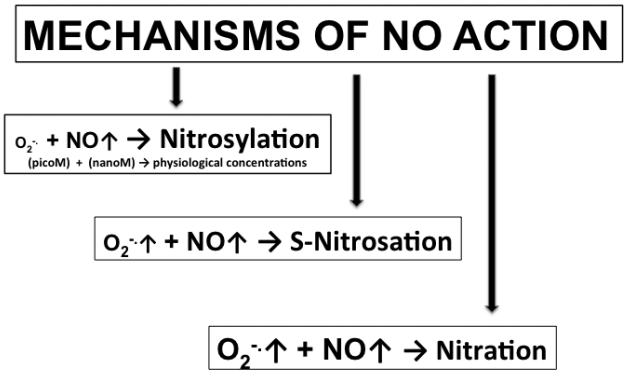
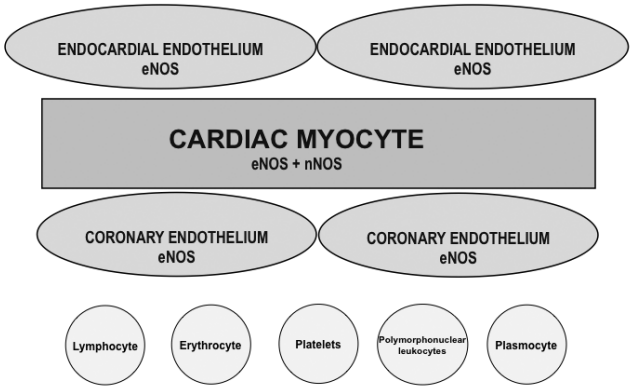


Figure 4. Close anatomic neighborhood between cardiomyocytes and endothelial cells



Nitrosation is the interaction of NO with the free thiol groups of protein cysteine residues and causes the formation of S-nitrosothiols. This mechanism is also called S-nitrosylation, and its roles have been shown with >1000 proposed targets in the heart. The inhibition of sGC by S-nitrosation may also occur, and intracellular cGMP levels can be reduced (13).

The binding of a nitroso group to the aromatic carbon of the target proteins is known as nitration. Nitration of the tyrosine residues of proteins is important for cell functions. In the case of an excessive increase of NO and $O_2^{\cdot-}$, different reactions and nitroso radicals may occur depending on the amount of oxygen and carbon dioxide and the pH in the tissue. The dominance of these three NO-induced signal transduction mechanisms depends on the redox state of the medium. In the physiological condition, NO concentration is around nanomolar level, and its increase leads to metal nitrosylation at low superoxide radical concentration (around picomolar), whereas NO formation at high $O_2^{\cdot-}$ levels causes nitrosation and nitration reactions in pathological conditions (14).

NO ACTIONS ON CARDIAC FUNCTIONS

The heart contains different cells that have different functions. While the contractile cardiomyocytes are responsible for the pumping function of the heart, pacemaker cells produce spontaneous electrical activity. The endothelial cells on the endocardium and capillary bed regulate the functions of the cardiomyocytes, and their interaction with the cells in the blood circulation is important for the critical functions of the heart (Figure 4).

The effects of the endothelium on cardiac function were first demonstrated by Brutsaert et al. (15). Both endocardial and capillary endothelial cells were shown to be directly affected by the contractile performance of the underlying cardiomyocytes.

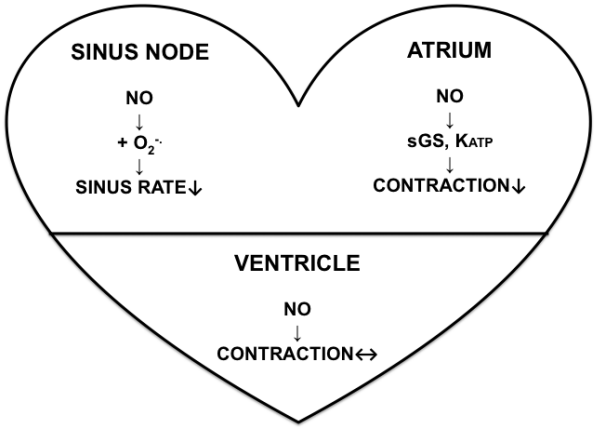
Nitric oxide is produced from the cardiac endothelial cells as well as the cardiac myocytes in the heart and regulates heart functions. While the endocardial and capillary endothelium express eNOS, both eNOS and nNOS are expressed in the cardiac myocytes. The eNOS is located in the caveolae and T-tubes, whereas the nNOS is located in the sarcoplasmic reticulum. The iNOS can be expressed in pathological conditions in both the endothelial cells and the cardiac myocytes. A high concentration of exogenous NO derived from iNOS of the immune cells may also expose the heart in pathological conditions (16).

Regulation of Cardiac Contractility by NO

Diverse responses to NO, such as positive or negative inotropy, biphasic effect, or no response, have been observed. The contribution of endogenous NO derived from the heart on cardiac contractility has been examined using selective and non-selective NOS inhibitors. The activity of eNOS inhibits beta-adrenergic inotropy, whereas the activity of nNOS may exhibit a positive inotropic effect by stimulating calcium release via the ryanodine receptor (RyR). It has been hypothesized that the negative effect of eNOS on inotropy can be compensated by nNOS. However, nNOS-derived NO may cause relaxation of the cardiomyocytes via the activation of the sarcoplasmic reticulum Ca-ATPase via the serine/threonine protein phosphatase (17).

It has also been shown that contractions of the heart change in response to the NO donors in a different manner. The NO donor, 3-morpholino-sydnonimine (SIN-1), caused a negative inotropic effect in the rat left ventricular papillary muscle (18), whereas it showed a positive inotropic activity in the cat papillary muscle. Sodium nitroprusside (SNP) caused a positive inotropic effect in the cat papillary muscle while causing a decrease in the contraction of the guinea pig heart myocytes. In some studies, it has been observed that NO and cGMP increase myocardial contractility at low concentrations, whereas a negative inotropic effect occurs at high concentrations. The amount of active NO in the target tissue can be different with different NO donors. It has been observed that organic nitrates induce a moderate increase in cGMP in the rat cardiomyocytes, leading to protein kinase A (PKA) activation and increased contraction, whereas spontaneous NO donors trigger a high level of cGMP increase, leading to PKG activation and decreased contractile response (19).

Figure 5. Region-dependent differentiation of NO action in the heart. Different mechanisms are responsible in the effects of NO on the atrium, ventricle, and sinoatrial node



It has been shown that there are histological, functional, and molecular differences between atrial and ventricular or left and right sides of the heart (20). It has been observed that NO donor diethylamine (DEA) decreases contractions of the right atrium, but there is no effect on the papillary muscles (Figure 5) (20). In addition, the PDE activities of the heart vary according to species and heart region. Thus, the PDE isoforms of the host cell can determine whether the cellular effect of NO is on the increasing or decreasing side of the cAMP (21).

The presence of pathology in the heart disrupts the association of eNOS with caveolin and nNOS with RyR, causing deviations in physiological responses. In addition to all these factors, ROS in the cardiac myocytes can reduce the effective concentration of NO in the pathological condition (9).

As can be understood from all these results, the effects of NO on cardiac contraction can be seen as both negative and positive inotropy depending on the animal species, heart preparation, and cellular situation. In addition, NO has a concentration and OS-dependent increasing or decreasing effect on heart contractions.

The negative inotropic effect of NO is explained by an increased level of cGMP. An increased cGMP activates PKG and reduces cAMP concentration by stimulating PDE2. The positive inotropic effect of NO has been explained by different mechanisms. NO-elevated cGMP inhibits the PDE3 enzyme, leading to increased intracellular cAMP concentration and hence PKA activation (22).

Regulation of Heart Rate by NO

The intrinsic activity of the sinoatrial node generates the heart rate that is regulated by the autonomic nerves and hormones in the body. The negative and positive chronotropic effects have been described using different exogenous NO donors. In the guinea pig heart, a positive chronotropic effect of NO was recorded (23). On the other hand, the intracoronary infusion of nitroprusside has been observed to cause a decrease in the rate of human heartbeat. In a study of nine heart transplant recipients, bradycardia was observed with the NOS inhibitor, whereas the NO donor SNP caused dose-dependent tachycardia (24). It has been reported that NO donor SIN-1 induces a negative chronotropic effect on the rat right atrium, and it was not reversed by sGC inhibition. Redox modulation and PDE activity have been shown to be responsible for NO action on the sinus rate (20). The regulation of NO action on heart rate by PDE3 activity has only been implemented in the right atrium of guinea pigs. In contrast, heart rate suppression induced by NO in the rat atrium was regulated by PDE1 and PDE4 activities (21).

In recent years, it has been suggested that periodic fluctuations of Ca^{2+} in the pacemaker cell may serve the spontaneous depolarization of the membranes. NO and $O_2^{\cdot-}$ increase the sinus velocity by facilitating Ca^{2+} release from the sarcoplasmic reticulum at moderate doses, but opposite effects are seen at higher doses (25).

Regulation of Coronary Vessel Tone by NO

Nitric oxide is known to be an important molecule in the regulation of the basal coronary vascular tone as well as the peripheral vascular network. Coronary vascular tone is thought to be regulated by NO secretion from the coronary endothelial cells in physiological conditions. It is understood that significant amounts of NO are released from the coronary circulation in the heart. It has been shown that sGC activation and cGMP increase in the vascular smooth muscle are the results of transient NO release from the endothelial cells. The shear stress-induced and flow-stimulated vasodilation also occurs via NO in the coronary vascular bed (26). Chronic inhibition of NO synthesis in the pig heart has been shown to impair endothelium-dependent functions of the coronary arteries (27). It has been observed that NOS inhibitor enhances basal coronary vascular resistance in isolated perfused heart preparations. Impaired cardiac angiogenesis and capillary development in studies conducted in eNOS knockout mice have also been shown (28).

ROLE OF NO IN CARDIAC PATHOLOGIES

Ischemic Heart Diseases

The main etiology for ischemic heart disease is coronary atherosclerosis originating from endothelial dysfunction of the coronary vascular bed. The endothelial cell releases important mediators that regulate vascular tone, platelet aggregation, thrombus formation, vascular smooth muscle proliferation, permeability, immune regulation, and angiogenesis in normal or pathological conditions. Endothelial dysfunction has been correlated with decreased synthesis/release or effect of NO. It is thought to be a major risk factor for cardiovascular diseases and is thought to be the earliest detectable symptom of atherosclerosis. It has been suggested that OS is closely related to the endothelial dysfunction in coronary artery disease (29). Drugs, such as statins, spironolactone, aspirin, and angiotensin-converting enzyme inhibitors, have been shown to improve endothelial function and reduce mortality.

Arginase is an important enzyme that catalyzes the conversion of arginine to ornithine and urea. The arginase enzyme competes directly with eNOS for arginine substrate, resulting in a reduction in NO production, and induces vascular dysfunction and deterioration. The inhibition of arginase activation may increase NO bioavailability and reduce OS and thus may alleviate hypertension, diastolic function, and atherosclerosis that originate from endothelial dysfunction (26).

Nitrite and nitrate levels, which are indicative of plasma NO level, have been found to be increased in studies performed in patients with coronary artery disease (30). In patients with coronary artery spasm, deterioration of both basal and stimulated NO release has been observed. The risk of myocardial infarction is thought to be increased in persons with an impaired NO-stimulated cGMP-dependent pathway (31). Spontaneous myocardial infarction and death were examined in all NOS isoform-knockout mice (32). In addition to the beneficial effects of NO, a huge amount of NO produced by iNOS in the post-ischemia–reperfusion period expands the infarct area and contributes to left ventricular dysfunction.

In organs exposed to short periods of ischemia, the increase in resistance to severe ischemia–reperfusion that develops later is known as "ischemic preconditioning." Preconditioning in the dog myocardium has been shown to relate to the arrhythmia-reducing effects of NO. A similar study was performed in pigs with NO donor pirsidomine. However, there is no increase in cGMP with NO donors as in the dog myocardium. In a similar study in the rat heart, neither NO donor nor endogenous NO could prevent ischemia-induced arrhythmias (33).

In ischemia–reperfusion injury, NO generated from eNOS and nNOS is generally positive, whereas NO produced from iNOS generally has a negative effect. In transgenic mouse models where nNOS is overexpressed, it has been shown that nNOS reduces the infarct area (34).

Heart Failure

Nitric oxide has not been shown to have a significant effect on the power–frequency relationship in healthy subjects and patients with moderate heart failure. However, a decrease in the amount of basal NO has been observed in the coronary circulation of patients with heart failure. It has been reported that this reduction may result from lack of production and/or release of NO. In patients with heart failure, an increased iNOS-mediated cardiac NO production attenuates positive inotropy in response to beta-adrenergic stimulation and accelerates relaxation. An increase in eNOS and iNOS expressions has been observed in the cardiac cells of patients with end-stage heart failure, whereas in another study, there was a decrease in eNOS expression and an increase in iNOS expression. In a congestive heart failure model created with transgenic mice, the myocardial iNOS protein levels were increased (35). In rat models of isoproterenol-induced heart failure, an increase in NO synthesis capacity was observed. Despite this increase, there was no positive effect on the contractile function of the failed heart.

Arrhythmias

It has been reported that a decreased activity of nNOS and eNOS enzymes contributes to the formation of atrial fibrillation. Therefore, it is thought that these enzymes may play a regulatory role in the electrical activity of the heart. In the presence of long-term atrial fibrillation or atrioventricular block, an increased atrial OS has been observed due to NOS uncoupling and mitochondrial oxidase activity (36). The production of atrial $O_2^{-\bullet}$ and $ONOO^-$ has been associated with an increased risk of developing atrial fibrillation. Plasma nitrite and nitrate concentrations and platelet cGMP levels have been found to be low in studies performed in patients with atrial fibrillation. The reduction in plasma NO levels is thought to be associated with hemostatic abnormalities in patients with atrial fibrillation. In the pig atrial fibrillation model, reduced atrial NOS activity and NO bioavailability have also been observed (37).

Cardiomyopathies

It has been reported that an iNOS-derived NO increase is correlated with cardiomyopathies and an increase susceptibility to complications, such as thromboembolism. An iNOS-induced NO contributes to the pathogenesis by reducing dilatation and reducing contraction in peripartum cardiomyopathies and inflammatory dilated cardiomyopathy. The elevated plasma levels of endogenous NOS inhibitors have been measured in patients with hypertrophic cardiomyopathy. In a mouse cardiomyopathy model generated by mutation of the dystrophin proteoglycan gene, the local tissue injury is the predominant characteristic of this disease. In these damaged areas, an increase in eNOS expression has been observed (38).

Inflammatory Heart Disease

Microorganism-induced or autoimmune activation of the immune cells causes an inflammatory reaction in the heart. In viral myocarditis models generated in mice and rats, viral infection has been shown to increase iNOS activation in the heart. The NO produced has an antiviral effect by inhibiting viral replication. On the other hand, iNOS causes myocardial damage through NS-induced nitrosation and nitration reactions. An increased expression of iNOS in the area of viral pericarditis and myocarditis has been found in a pig model. In autoimmune rat myocarditis models, NO derived from iNOS has been shown to react with $O_2^{-\bullet}$ and increased myocardial damage. iNOS accumulation in the lesion area in the experimental autoimmune myocarditis of rats has been observed (39).

NO-RELATED DRUGS IN CARDIOVASCULAR DISEASES

In the physiological condition, cardiovascular functions are regulated by NO, which is known as a key molecule for cardiac contraction and rate, vascular tone, and platelet aggregation. Although NO deficiency appears in some cardiovascular diseases, excess NO production causes NS and tissue damage in another group of cardiovascular pathologies. The pharmacological implication is the normalization of the NO system in the target tissues. This strategy does not work very well in all cardiac pathologies,

but with more selective inhibitors and local active NO applications, better therapeutic interventions could be achieved.

Gas NO and NO Donors

As a selective pulmonary vasodilator, gaseous NO may show a facilitating effect on postnatal pulmonary circulation adaptation. The direct use of NO inhalation is licensed as a drug to be used in the treatment of hypoxic respiratory insufficiency in newborns. Inhaled NO used in the treatment of pulmonary hypertension appears to be more advantageous due to its cheaper, less side effect profile, and ease of use (40).

L-Arginine appears to be a natural NO donor and is tested in clinical trials. However, the administration of L-arginine in patients with coronary artery disease with increased plasma arginine levels has not been shown to alter endothelial NO release. Intracoronary L-arginine infusion has not been determined to have any effect on vessel diameter. When L-arginine was administered to patients with organic erectile dysfunction, recovery of sexual function was observed in some patients (36). L-Arginine administration in rats with diabetes appears to be beneficial with respect to reducing impaired vascular responses and OS (41).

Although not recognized as an NO donor until the 1980s, GTN, an organic nitrate, has been used clinically for 150 years to relieve acute attacks of angina pectoris. Organic nitrates, such as GTN, pentaerythritol tetranitrate, isosorbide dinitrate, isosorbide 5-mononitrate, and nicorandil, are transformed into NO by bioactivation. Nitroglycerin is used effectively in the treatment of angina pectoris. SNP is used in hypertensive crisis because it causes systemic vasodilatation by reducing preload and afterload in the heart (42).

Molsidomine can be deacetylated in the liver to yield SIN-1 by successive enzymatic and non-enzymatic steps. This active metabolite SIN-1 has potent vasodilator and antithrombotic effects although molsidomine has only poorly vasoactive in vitro conditions. The main mechanism of these effects is spontaneous release of NO. Additionally, it has been shown that molsidomine decreases the venous return, cardiac output, ventricular work, and myocardial oxygen consumption in animal and human studies (42).

NONOate is a DEA/NO compound consisting of DEA and NO. Owing to their similar effects to endogenous NO, NONOates are often used as an NO donor in experimental models. It has been shown that DEA/NO decreases systemic and pulmonary arterial pressure in animals. DEA/NO and spermine (SPER)/NO inhibit platelet aggregation. Moreover, SPER/NO, dipropylenetriamine/NO, and diethylenetriamine/NO inhibit the proliferation of the vascular smooth muscle cells. Furthermore, NONOates appear superior to gas NO in pulmonary hypertension and asthma with regard to the long duration of action, stability in solid form, and no need for monitoring (43).

S-nitrosothiols are accepted as natural NO donor. They release NO when they are destroyed by enzymatic and non-enzymatic routes. They inhibit platelet activation and regulate vascular tone. However, the use of NONOates may be advantageous because NONOates are direct NO donor, but S-nitrosothiols release NO after a reduction reaction (44).

Conditions of OS can lead to an NO-resistant condition in which both endogenous and therapeutic NO effects are inactivated. This mechanism of NO insensitivity is claimed to be the reason for the reduction in the clinical effectiveness of NO treatments, such as administration of inhaled NO or direct NO donors (45).

Hybrid NO Donors

Hybrid NO donors are created by adding NO release moiety to existing drugs. Such drugs are of interest because they increase the effectiveness of the parent drug or reduce their undesirable effects. To date, the major drug group used for producing NO hybrids has been nonsteroidal anti-inflammatory drugs (NSAIDs), and preclinical studies of NO-NSAID hybrids are underway (45). A lesser known NO hybrid is latanoprost-NO, synthesized to reduce intraocular pressure.

While NO production occurs in a precisely regulated manner in natural cells, NO donors may provide an irregular dose to the entire tissue or vasculature. Therefore, maximum care should be taken when NO donors are considered as a treatment option (46).

PDE5 Inhibitors

Nitric oxide is secreted from both the endothelial cells lining the inner surface of the corpus cavernosum and the nitrergic autonomic nerve endings and causes relaxation of the corpus cavernosum smooth muscle. The enzymes responsible for the degradation of cGMP in the corpus cavernosum are PDE enzymes. PDE2, PDE3, and PDE5 have been detected in human corpus cavernosum, but the major PDE activity is linked to PDE5 (47).

Erectile dysfunction is associated with inadequate NO release in this system. The inhibition of PDE5 appears to be a reasonable approach in the treatment of erectile dysfunction. In clinical trials of patients with erectile dysfunction, an increase in erectile response has been achieved with the PDE5 inhibitor sildenafil. However, the apparent hypotensive effect of sildenafil limits its use. Another PDE5 inhibitor, vardenafil, has a more hypotensive effect than sildenafil, especially on first use. The hypotensive side effect of PDE5 inhibitors becomes even more pronounced and life-threatening when PDE5 inhibitors are used in combination with NO donors or alpha antagonists. The newest PDE5 inhibitor, avanafil, comes to the forefront in terms of its ability to initiate fast erection and fewer side effects (47). Sildenafil is also used as an alternative to conventional therapy for pulmonary hypertension for children and adults (40).

sGC Stimulators and Activators

Soluble guanylate cyclase stimulators work synergistically with NO on the heme group of sGC, whereas sGC activators work when the heme group is oxidized. Thus, they can also activate the enzyme even when there is no response to NO (48).

The first developed sGC stimulator is called "riociguat." It has been developed for the treatment of pulmonary hypertension and is a potent compound known for its powerful effects on pulmonary hemodynamics. It is licensed for the treatment of pulmonary hypertension and chronic thromboembolic pulmonary hypertension (48).

NOS Inhibitors

Studies on NOS inhibitors that can be used as drugs have focused on novel molecules that will not act on eNOS when inhibiting nNOS and/or iNOS. Several patented nNOS inhibitors have been examined for treatment of nNOS-induced NO overproduction in neurodegenerative diseases and post-stroke neuronal damage. NO produced by iNOS is involved in the pathogenesis of many diseases, such as sepsis, hemorrhagic shock, heart failure, stroke, rheumatoid arthritis, irritable colon, and even cancers (6). iNOS selective inhibitors are being designed, and there are many patents targeting iNOS inhibition. However, the side effect profile and low selectivity remain as the main problems.

Asymmetric dimethylarginine (ADMA) is an amino acid that is produced endogenously and emerges during protein degradation. It inhibits NO formation in the cardiovascular system in disorders, such as septic shock, which is the pathological excess of NO production by inhibiting NOS. Endogenous ADMA levels are metabolized by the dimethylarginine dimethylaminohydrolase (DDAH) enzyme, which has been proposed as a target for the regulation of NO bioavailability. There are continuing studies on the potential strategies to upgrade the NO levels and the methods to be used to activate DDAH (45).

New Horizons in NO-Based Treatments

As an alternative to NO donors or NOS inhibitors, the development of new treatment approaches, such as NO-donating nanoparticles and iNOS gene therapy, has recently attracted significant attention due to their interesting advantages NO-donating nanoparticle systems could localize high concentrations of NO in a sustained manner to the desired site alone to protect other organs from the effects of systemic toxicity (49). Local expression of the iNOS gene can be achieved by the use of different vectors for iNOS gene delivery. iNOS-based suicide gene therapy, which produces a huge amount of NO by this method, is a promising approach to cancer therapy (50). Studies are being planned on the use of similar methods in the cardiovascular system. However, it should be kept in mind that each of these systems should be predictive of possible effects and side effects that may arise when used.

CONCLUSION

It is well established that NO is an important biological messenger and triggers several physiological and pathological responses in numerous tissues. In the heart, NO modulates cardiomyocyte contraction, nodal rate, and tone of the coronary vascular bed in a physiological condition. In addition, the role of NO is critical in heart pathologies, such as ischemic heart diseases, arrhythmias, heart failures, cardiomyopathies, and inflammatory heart diseases.

However, there is much controversial data regarding the effect of NO on the heart. The most important reason for these contradictory results is that the effect of NO on the heart varies between species.

Experimental preparations alter the effect of NO on the heart. While hormonal and nervous systems are involved in the cardiac effect of NO in in vivo examinations of the heart, the NO action on the coronary vessels is blended with the myocardial effect of NO in the perfused whole heart. The direct effects of NO on the myocardial functions can be observed using isolated cardiac tissues, such as spontaneous beating right atrium, ventricular or atrial strips, and papillary muscles. Isolated cells are used to investigate NO actions on cellular and molecular functions of the cardiac myocytes.

An effective NO concentration in the target medium is dependent on the NOS activity and redox state and the NO-releasing capacity of the NO donors. Endogenous NOS activity can be altered by the expression of NOS variants, elevation of endogenous NOS inhibitors, NOS uncoupling, and OS. The effects of exogenous NO on the heart have been investigated using different NO donors, although the stability, lipophilicity, kinetics, and extent of the released NO and metabolites have been different among these agents. In addition to all these factors, different expressions/activities of proteins in the NO signal transduction pathways may also change the NO action on the heart.

It is believed that a detailed elucidation of the molecular mechanisms responsible for these differences will make a significant contribution to both understanding the role of NO in the progression of cardiovascular diseases and developing more effective drugs to act on the NO system.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.D.Y.; Design – M.K.D., E.D.Y.; Supervision – M.K.D., E.D.Y.; Literature Search – M.K.D.; Writing Manuscript – M.K.D., E.D.Y.; Critical Review – E.D.Y.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

REFERENCES

1. Moncada S, Palmer RMJ, Higgs EA. Nitric Oxide: Physiology pathophysiology and pharmacology. Pharmacol Rev 1991; 43: 109-42.
2. Daiber A, Wenzel P, Oelze M, Münzel T. New insights into bioactivation of organic nitrates, nitrate tolerance and cross-tolerance. Clin Res Cardiol 2008; 97: 12-20.
3. Gruetter CA, Barry BK, McNamara DB, Gruetter DY, Kadowitz PJ, Ignarro L. Relaxation of bovine coronary artery and activation of coronary arterial guanylate cyclase by nitric oxide, nitroprusside and a carcinogenic nitrosoamine. J Cyclic Nucleotide Res 1979; 5: 211-24.
4. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980 27; 288: 373-76.

5. Ignarro LJ, Byrns RE, Buga GM, Wood KS. Endothelium-derived relaxing factor from pulmonary artery and vein possesses pharmacologic and chemical properties identical to those of nitric oxide radical. Circ Res 1987; 61: 866-79.
6. Förstermann U, Sessa WC. Nitric oxide synthases: regulation and function. Eur Heart J 2012; 33: 829- 33.
7. Lundberg JO, Weitzberg E, Cole JA, Benjamin N. Nitrate, bacteria and human health. Nat Rev Microbiol 2004; 2: 593-602.
8. Gago B, Lundberg JO, Barbosa RM, Laranjinha J. Red wine-dependent reduction of nitrite to nitric oxide in the stomach. Free Radic Biol Med 2007; 43: 1233-42.
9. Thomas DD, Ridnour LA, Isenberg JS, Flores-Santana W, Switzer CH, Donzelli S, et al. The chemical biology of nitric oxide: implications in cellular signaling. Free Radic Biol Med 2008; 45: 18-31.
10. Takimoto E. Cyclic GMP-dependent signaling in cardiac myocytes. Circ J 2012; 76: 1819-25.
11. Cipak Gasparovic A, Zarkovic N, Zarkovic K, Semen K, Kaminskyy D, Yelisyeyeva O, et al. Biomarkers of oxidative and nitro-oxidative stress: conventional and novel approaches. Br J Pharmacol 2017; 174: 1771-83.
12. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y, Ali F. Atherosclerotic cardiovascular disease: a review of initiators and protective factors. Inflammopharmacology 2016; 24: 1-10.
13. Wolhuter K, Eaton P. How widespread is stable protein S-nitrosylation as an end-effector of protein regulation? Free Radic Biol Med 2017; 109: 156-66.
14. Zhang M, Shah AM. ROS signalling between endothelial cells and cardiac cells. Cardiovasc Res 2014; 102: 249-57.
15. Brutsaert DL, De Keulenaer GW, Fransen P, Mohan P, Kaluza GL, Andries LJ, et al. The cardiac endothelium: functional morphology, development, and physiology. Prog Cardiovasc Dis 1996; 39: 239-62.
16. Zhang M, Shah AM. ROS signalling between endothelial cells and cardiac cells. Cardiovasc Res 2014; 102: 249-57.
17. Zaobornyj T, Ghafourifar P. Strategic localization of heart mitochondrial NOS: a review of the evidence. Am J Physiol Heart Circ Physiol 2012; 303: H1283-93.
18. Wyeth RP, Temma K, Seifen E, Kennedy RH. Negative inotropic actions of nitric oxide require high doses in rat cardiac muscle. Pflugers Arch 1996; 432: 678-84.
19. Kojda G, Kottenberg K, Nix P, Schlüter KD, Piper HM, Noack E. Low increase in cGMP induced by organic nitrates and nitrovasodilators improves contractile response of rat ventricular myocytes. Circ Res 1996; 78: 91-101.
20. Derici K, Samsar U, Demirel-Yilmaz E. Nitric oxide effects depend on different mechanisms in different regions of the rat heart. Heart Vessels 2012; 27: 89-97.
21. Demirel-Yilmaz E, Cenik B, Ozcan G, Derici MK. Various phosphodiesterase activities in different regions of the heart alter the cardiac effects of nitric oxide. J Cardiovasc Pharmacol 2012; 60: 283-92.
22. Vila-Petroff MG, Younes A, Egan J, Lakatta EG, Sollott SJ. Activation of distinct cAMP-dependent and cGMPdependent pathways by nitric oxide in cardiac myocytes. Circ Res 1999; 84: 1020-31.
23. Francis SH, Blount MA, Corbin JD. Mammalian cyclic nucleotide phos- phodiesterases: molecular mechanisms and physiological functions. Physiol Rev 2011; 91: 651-90.
24. Chowdhary S, Harrington D, Bonser RS, Coote JH, Townend JN. Chronotropic effects of nitric oxide in the denervated human heart. J Physiol 2002; 541: 645-51.
25. Kapelko VI. Redox control of cardiac rhythm. Biochemistry (Mosc) 2012; 77: 1248-57.
26. Levy AS, Chung JC, Kroetsch JT, Rush JW. Nitric oxide and coronary vascular endothelium adaptations in hypertension. Vasc Health Risk Manag 2009; 5: 1075-87.
27. Ingram DG, Newcomer SC, Price EM, Eklund KE, McAllister RM, Laughlin MH. Chronic nitric oxide synthase inhibition blunts endothelium-dependent function of conduit coronary arteries, not arterioles. Am J Physiol Heart Circ Physiol 2007; 292: H2798-808.
28. Zhao X, Lu X, Feng Q. Deficiency in endothelial nitric oxide synthase impairs myocardial angiogenesis. Am J Physiol Heart Circ Physiol 2002; 283: H2371-8.
29. Incalza MA, D'Oria R, Natalicchio A, Perrini S, Laviola L, Giorgino F. Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. Vascul Pharmacol 2018; 100: 1-19.
30. Soydinc S, Celik A, Demiryurek S, Davutoğlu V, Tarakçıoğlu M, Aksoy M. The relationship between oxidative stress, nitric oxide and coronary artery disease. Eur J Gen Med 2007; 4: 62-6.
31. Erdmann J, Stark K, Esslinger UB, Rumpf PM, Koesling D, de Wit C, et al. Dysfunctional nitric oxide signalling increases risk of myocardial infarction. Nature. 2013; 504: 432-6.
32. Nakata S, Tsutsui M, Shimokawa H, Suda O, Morishita T, Shibata K, et al. Spontaneous myocardial infarction in mice lacking all nitric oxide synthase isoforms. Circulation 2008; 117: 2211-23.
33. Sun W, Wainwright CL. The role of nitric oxide in modulating ischaemia-induced arrhythmias in rats. J Cardiovasc Pharmacol 1997; 29: 554-62.
34. Burkard N, Williams T, Czolbe M, Blömer N, Panther F, Link M, et al. Conditional overexpression of neuronal nitric oxide synthase is cardioprotective in ischemia/reperfusion. Circulation 2010; 122: 1588-1603.
35. Funakoshi H, Kubota T, Kawamura N, Machida Y, Feldman AM, Tsutsui H, et al. Disruption of inducible nitric oxide synthase improves beta-adrenergic inotropic responsiveness but not the survival of mice with cytokine-induced cardiomyopathy. Circ Res 2002; 90: 959-65.
36. Simon JN, Duglan D, Casadei B, Carnicer R. Nitric oxide synthase regulation of cardiac excitation contraction coupling in health and disease. J Mol Cell Cardiol 2014; 73: 80-91.
37. Cai H, Li Z, Goette A, Mera F, Honeycutt C, Feterik K, et al. Downregulation of endocardial nitric oxide synthase expression and nitric oxide production in atrial fibrillation: potential mechanisms for atrial thrombosis and stroke. Circulation 2002; 106: 2854-8.
38. Dimitrow PP, Undas A, Bober M, Tracz W, Dubiel JS. Plasma biomarkers of endothelial dysfunction in patients with hypertrophic cardiomyopathy. Pharmacol Rep 2007; 59: 715-20.
39. Shin T, Tanuma N, Kim S, Jin J, Moon C, Kim K, et al. An inhibitor of inducible nitric oxide synthase ameliorates experimental autoimmune myocarditis in Lewis rats. J Neuroimmunol 1998; 92: 133-8.
40. Benedetto M, Romano R, Baca G, Sarridou D, Fischer A, Simon A, et al. Inhaled nitric oxide in cardiac surgery: Evidence or tradition? Nitric Oxide 2015; 49: 67-79.
41. Ozçelikay AT, Tay A, Güner S, Taşyaran V, Yildizoğlu-Ari N, Dinçer UD, et al. Reversal effects of L-arginine treatment on blood pressure and vascular responsiveness of streptozotocin-diabetic rats. Pharmacol Res 2000; 41: 201-9.
42. Wang PG, Xian M, Tang X, Wu X, Wen Z, Cai T, et al. Nitric Oxide Donors: Chemical Activities and Biological Applications. Chem Rev 2002; 102: 1091-134.

43. Lam CF, Sviri S, Ilett KF, van Heerden PV. Inhaled diazeniumdiolates (NONOates) as selective pulmonary vasodilators. Expert Opin Investig Drugs 2002; 11: 897-909.
44. Kim-Shapiro DB, Gladwin MT. Mechanisms of nitrite bioactivation. Nitric Oxide 2014; 38: 58-68.
45. Lundberg JO, Gladwin MT, Weitzberg E. Strategies to increase nitric oxide signalling in cardiovascular disease. Nat Rev Drug Discov 2015; 14: 623-41.
46. Mutchler SM, Straub AC. Compartmentalized nitric oxide signaling in the resistance vasculature. Nitric Oxide 2015; 49: 8-15.
47. Kotera J, Mochida H, Inoue H, Noto T, Fujishige K, Sasaki T, et al. Avanafil, a potent and highly selective phosphodiesterase-5 inhibitor for erectile dysfunction. J Urol 2012; 188: 668-74.
48. Stasch JP, Pacher P, Evgenov OV. Soluble guanylate cyclase as an emerging therapeutic target in cardiopulmonary disease. Circulation 2011; 123: 2263-73.
49. Quinn JF, Whittaker MR, Davis TP. Delivering Nitric Oxide with Nanoparticles. J. Control Release 2015; 205: 190-205.
50. Ye S, Yang W, Wang Y, Ou W, Ma Q, Yu C, et al. Cationic liposome- mediated nitric oxide synthase gene therapy enhances the antitumor effects of cisplatin in lung cancer. Int J Mol Med 2013; 31: 33-42.

How to cite:

Derici MK, Demirel Yılmaz E. The Role of Nitric Oxide Related Therapeutics in the Treatment of Cardiovascular Pathologies. Eur J Ther 2018; 24(3): 127–35.

European Journal of Therapeutics
DOI: 10.5152/EurJTher.2018.277
Original Research

Use of Subcutaneous Pedicled Rhomboid Flap Technique for Surgical Treatment of Burn Contractures

Mustafa Nihat Koç, Saffet Ulutaş, Berat Çiğdem, Serdar Kara
Department of Plastic, Reconstructive and Aesthetic Surgery, Gaziantep University, School of Medicine, Gaziantep, Turkey

ABSTRACT
Objective: Release of contractures mainly due to burn scars mandates reconstruction with a well-vascularized tissue and an aesthetically acceptable result. Many techniques of the reconstructive ladder have been applied. Local flaps are the first choice. In this study, we present a superior local flap alternative, the diamond flap (subcutaneous pedicled rhomboid flap), for the reconstruction of contractures.
Methods: In a 1-year period, 23 patients underwent contracture release using a diamond flap. The elongation of the distance between two reference points on the contracture line was measured.
Results: A total of 23 contractures due to burn scars were released via a diamond flap in 23 patients. No flap loss was seen. Patients were followed up for an average of 18 months, and no recurrence of contractures was seen. Elongation of the contracture lines was measured as the distance between two reference points preoperatively marked. We observed 60%–200% elongation of the contracture line during early postoperative measurement and 30%–125% elongation during late postoperative measurement depending on the anatomical site and original length of the contracture.
Conclusion: Diamond flap should be kept in mind as an alternative for contracture release, especially in cases of wide, long, multiple adjacent contractures located in poorly vascularized areas.
Keywords: Diamond flap, contracture, burn, Z-plasty, local flaps

INTRODUCTION

Contractures are one of the major areas of plastic surgery. The release of contractures mainly due to burn scars mandates reconstruction with a well-vascularized tissue and an aesthetically acceptable result. Many techniques of the reconstructive ladder have been applied till date, including skin grafts, Z-plasties, local flaps, and even free flaps. Grafts are not used often because they cause secondary contracture. In contrast, free flaps are better reserved for selected cases as both the procedure itself and postoperative care is arduous. Hence, local flaps are the first choice in contracture release, among which Z-plasties are most commonly used. In this study, we present a superior local flap alternative for the reconstruction of contractures (1).

The rhomboid flap was introduced by Suzuki et al. (2) in 1987, whereas the subcutaneous pedicled rhomboid flap was first used by Uzunismail et al. (3) in 1994 for contracture release. Subsequently, Askar (4) published their modification of the rhomboid flap under the name "double reverse V-Y plasty".

In the original article, the rhomboid flap is planned so that the 60° corner lies on the contracture line and the 120° corner lies perpendicular to the contracture line (5-7). However, in our study, we planned the rhomboid flap with 90° angles in an attempt to obtain greater release of the contracture.

Although it was described earlier, we believe that the subcutaneous pedicled rhomboid flap has not found its worth. We preferred to name this flap as "diamond flap" because of its shape and because we find it to be very valuable.

The diamond flap is a good alternative to Z-plasties for the reconstruction of large and long scar contractures. In this study, we aimed to present different uses and advantages of the diamond flap.

METHODS

Ethics committee approval was received for this study (Gaziantep Universiy Clinical Research Ethic Comitee, 07.01.2014 /8). In a 1-year period (Oct. 2013–Oct. 2014), 23 patients, including 14

ORCID ID of the author: M.N.K. 0000-0003-2390-3109; S.U. 0000-0002-8214-4002; B.Ç. 0000-0002-8165-4377; S.K. 0000-0001-9967-5478
This study was presented at the 38th National Congress of Turkish Society of Plastic and Estetic Surgery, 27–30 October 2016, Antalya, Turkey.
Corresponding Author: Mustafa Nihat Koç **E-mail:** mustafanihat@hotmail.com
Received: 30.11.2017 • **Accepted:** 17.03.2018

Table 1. Analysis of Results by Time

Patient	Sex	Age	Contracture localization	Preop length	Early Postop length	% of early postop gain	Late postop length	% of late postop gain
1	M	3	Antecubital	4	7	75	6.5	62.5
2	F	3	Popliteal	2	3.5	75	3	50
3	F	5	Antecubital	3	5	66	5	66
4	M	6	Axilla	3	5.6	86.6	5	66.6
5	M	8	Thumb	3.5	6.8	94	5.4	54
6	M	9	Axilla	4	7	75	6.2	55
7	M	10	Oral Commis.	1	1.6	60	1.4	40
8	F	12	First Web	6	15	150	13.5	125
9	M	13	Thumb	5	11.5	130	9.5	90
10	M	14	Antecubital	6	12	100	11	83.3
11	M	14	Axilla	7	16	128.5	13.3	90
12	F	17	First Web	3	7	133.3	5.7	90
13	F	18	Neck	3	9	200	6	100
14	M	18	Ankle	2	3.5	75	3	50
15	M	19	Antecubital	5	8	60	7.5	50
16	F	20	Neck	3	6	100	4.8	60
17	F	22	Thumb	4	8	100	7	75
18	M	23	Popliteal	3	5.5	83.3	5	66.6
19	M	25	Foot	6	13	116.6	11	83.3
20	M	27	Digit	5	9	80	5.5	30
21	F	29	Popliteal	6	13.6	126	11	83.3
22	F	29	Neck	2	5	150	3.5	75
23	M	33	Ankle	7	12.7	81.4	11	57.1

M: male; F: female

males and 9 females, underwent burn contracture release using the diamond flap. Patients' age ranged between 3 and 33 years. Informed consent was obtained from patients who participated in this study. Contracture locations and patient features are shown in Table 1. We subtracted the length of the preoperatively marked rhomboid flap (A–B) from the postoperative length provided by relaxation incisions (A_2–B_2) as shown in Figure 1. Thus, elongation of the distance between the two reference points on the contracture line was measured. Some patients had joint stiffness and were therefore referred to the physical therapy department. Patients were followed up for a mean of 18 months (12–24 months).

In its original article, the rhomboid flap is planned such that the 60° corner lies on the contracture line and the 120° corner lies perpendicular to it. Each side of this equilateral rhombus should not be longer than the contracture line. Then, two relaxation incisions are drawn externally from each 120° corner, which is no shorter than half of and no longer than one side of the rhombus. Full-thickness incisions around the flap and along the relaxation lines are completed so that an island flap is obtained. The endpoint of the relaxation incisions is pulled toward the corner of the rhomboid flap and sutured in a Y-V fashion. The 60° corners along the contracture lines are closed in a V-Y fashion (5-7). Thus, an elongation of the contracture line is obtained at the expense of lateral tissues on either side. In our series, we planned the rhombus with 90° angles in order to obtain a greater release of the contracture and eventually observed this to come off. The narrower the side angles of the rhombus, the greater the elongation in the contracture line; however, this also causes a dog ear deformity. Thus, we believe that a 90° rhomboid flap is ideal. Emphasis should be made as the incisions must be made full thickness until healthy tissue is reached, otherwise no release of the contracture will be possible (5-7).

RESULTS

A total of 23 burn contractures were released via a diamond flap in 23 patients. No flap loss was seen; however, one patient developed partial flap necrosis, which healed by secondary healing. Patients were followed up for an average of 18 months. Elonga-

Figure 1. (Above) Preoperative markings of the 90° rhomboid flap over a contracture band on the antecubital fossa. Proximal and distal ends of the flap (A–B) measured as the preoperative length of contracture band. (Below) The endpoint of the relaxation incisions is pulled toward the corner of the rhomboid flap and sutured in a Y-V fashion. Proximal and distal corners along the contracture lines are closed in a V-Y fashion. A_2–B_2 shows the early postoperative length measurement after contracture release

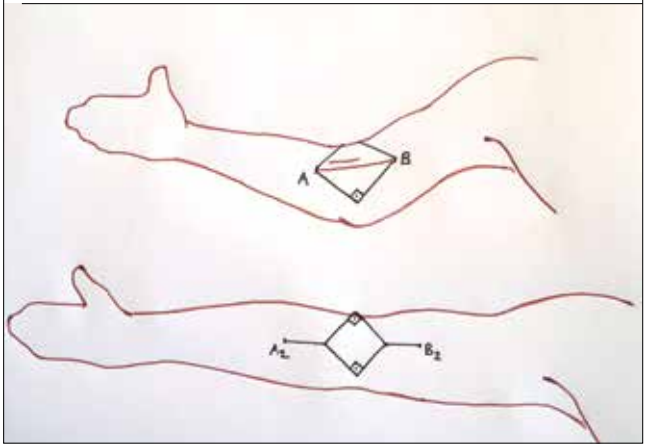
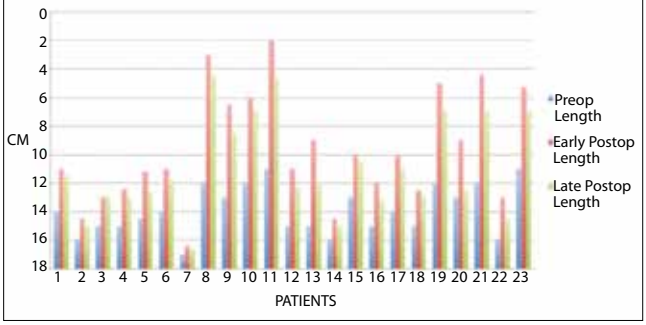


Figure 2. Preoperative, early postoperative, and late postoperative length of contracture bands of patients are shown graphically



tion of the contracture lines was measured immediately after closure and 1 year postoperatively as shown in Figure 2. Previous studies report conflicting data regarding the amount of elongation obtained with rhomboid flap. According to our results, we obtained 60%–200% elongation of the contracture line during the early postoperative measurement and 30%–125% elongation during the late postoperative measurement, depending on the anatomical site and original length of the contracture as shown in Figures 3–5.

DISCUSSION

This series includes a group of patients of heterogeneous ages, the results of whom are incomparable. There is no clear description of the locations or the size of the flaps.

Measuring only the postoperative result, only in relation to the gain of length, does not let one conclude the same growing the functional improvement of the segments operated on.

Figure 3. a-d. Preoperative planning of an 18-year-old patient with a burn scar on the neck (a), Contracture released with a 90° equilateral rhomboid flap (b), A 200% elongation distance was gained and no dog ear deformity occurred (c), Postoperative view (d)

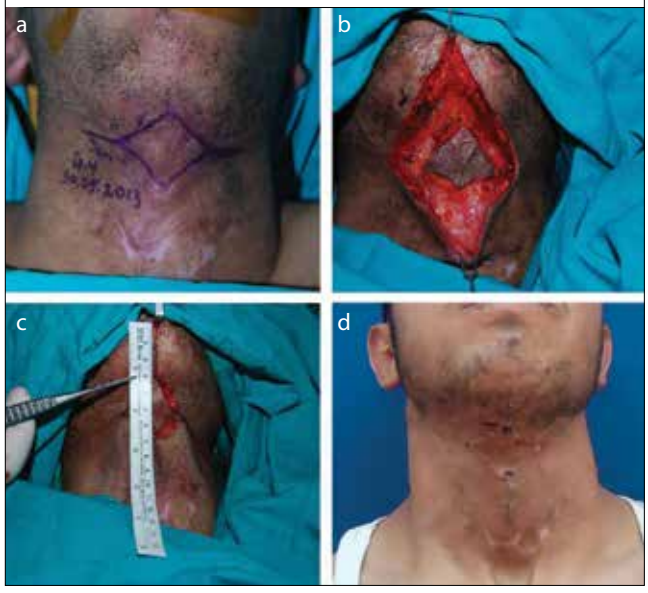


Figure 4. a-f. A 3-year-old patient with a burn contracture in the right antecubital region (a), Preoperative planning of a 90° equilateral rhomboid flap (b), A 75% elongation was gained intraoperatively (c), Postoperative view after contracture released completely with additional physical therapy (d), Late postoperative view (e), Postoperative second year; we used Z-plasties in order to change the direction of thickened scar tissue and to have a better aesthetic result (f)

There is no scientific data that compares each technique with a designated control group.

Various techniques have been used for the release of scar contractures, including split and full-thickness skin grafts (8), local flaps (9-12), and even free flaps. Grafts are not preferred as they cause secondary contraction. Free flaps, on the other hand, are difficult procedures and not cost-effective. Thus, local flaps, mainly Z-plas-

Figure 5. a-c. A 9-year-old patient with a burn scar on his right axilla (a), Contracture released with a 90° equilateral rhomboid flap (b), Postoperative view (c)

ties are the most commonly used techniques in contracture reconstruction. In this study, we aimed to offer an alternative to Z-plasty in contracture release, namely the diamond flap.

Numerous modifications of Z-plasties have been described, such as double-opposing Z-plasty; four, five, six, and seven flap Z-plasty; and unequal Z-plasty. Apart from Z-plasty, V-Y plasties and rotation flaps have also been used for the same purpose (13-18).
In 2004, Ertas et al. (19) compared Z-plasty to the diamond flap on a rat model and reported 243% elongation with Z-plasty and 327% elongation with diamond flap. In the same year, they released an experimental study on rat inguinal skin, reporting a mean elongation of 139% with the diamond flap (128%–152%) (20). In other studies by the same authors in 2004 and 2006, 75%–90% and 60%–75% elongation, respectively, were reported (1, 6). Although these results are conflicting, when a single Z-plasty and a single diamond flap with equal angles are compared, consistent data show a greater elongation with diamond flap. As previously noted, we experienced that a 90° equilateral rhomboid flap is ideal at providing contracture release and avoiding dog ear deformity at the same time.

Because the flaps have to be elevated in Z-plasties, in case of a poorly vascularized bed, distal flap necrosis can occur. On the contrary, the diamond flap is subcutaneous pedicled and does not require flap elevation; thus, it may be safely used in a scatricial, previously grafted and re-contracted bed (19, 20).

Z-plasties are superior to diamond flap in changing the direction of the contracture band. As shown in Figures 4f and 4g, in the postoperative second year, despite the fact that antecubital contracture of the patient totally released with the diamond flap, we had to use Z-plasty in order to change the direction of the thick scar tissue. Thus, we achieved a good aesthetic result by adding a sekonder Z-plasty after a diamond flap.

Five-flap Z-plasty was first introduced by Mustardee for the release of an epicanthal fold and was named as "jumping man" because of its shape. It was modified by Hirshowitz for web contractures. Theoretically, 75% is gained from Z-plasty and 50% from V-Y plasty, which amounts to 125% gain (21). Similar to Z-plasty, five-flap Z-plasty entails flap elevation, which may compromise flap circulation.

The first use of Y-V plasty for contracture release was described by Szymanowski in 1856 for oral commissure. In a long contracture line, Y-V plasty yields successful results. Contradictory data exist on the amount of elongation obtained, with various studies reporting 50%–100% release. In a well-vascularized, pliable bed, Y-V plasty yields greater gain compared with a 60° Z-plasty (22-24). It does not involve elevation of flaps, so flap compromise is rare. Short operative time is another advantage. However, a wide and scatricial bed enables only inferior results and is not suitable for such cases.

Multiple Y-V plasties were first used by Bier et al. (25) in 1922 for soft tissue defects. Although very useful in a long linear scar, it is not feasible in wide or adjacent contracture lines.

Subcutaneous pedicled rhomboid flap, named as the diamond flap, is a simple, time-consuming flap that is easy to teach and apply. Vascular compromise is not likely as it does not involve dissection and elevation of flaps. As it is devoid of wide dissections, it can be performed under local anesthesia for adult patients. It can be safely used in two or more adjacent contracture lines, in which case it would be difficult to plan Z-plasties, Y-V plasties, or other local flaps, and flap circulation is more likely to be compromised.

Another advantage of the diamond flap is its perfect fit in web spaces. Compared with five-flap Z-plasty, the operative time is much shorter and flap circulation is much more reliable.

Finally, as there is no flap transposition, anatomic lines are less violated.

CONCLUSION

The diamond flap should be kept in mind as an alternative for contracture release, especially in cases of wide, long, multiple adjacent contractures located in poorly vascularized areas. It is easy to teach and apply but is time-consuming and expensive.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University (07.01.2014/8).

Informed Consent: Written informed consent was obtained from patients or patients' parents (if under 18 years old) who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.N.K.; Design – S.U.; Supervision – M.N.K.; Resources - B.Ç.; Materials - S.K.; Data Collection and/or Processing – B.Ç.; Analysis and/or Interpretation – S.K.; Literature Search – S.K.; Writing Manuscript – S.U.; Critical Review – M.N.K.
Acknowledgements: Authors, thanks to Gaziantep University Plastic Surgery Department for their contribution.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

REFERENCES

1. Ertas NM, Kücükcelebi A, Bozdogan N, Özdil K, Celebioglu S. Treatment of recontracture with the subcutaneous pedicle rhomboid flap. Plast Reconstr Surg 2006; 117: 1590.
2. Suzuki S, Isshik N, Ishileawa K, Ogriwa Y. The use of subcutaneous-pedicle flaps in the treatment of postburn scar contractures. Plast Reconstr Surg 1987; 80: 792–8.
3. Uzunismail A, Kahveci R, Özdemir A, Bozdogan N, Yüksel F. Therhomboid release: a new approach to the management of digital burncontractures. Ann Mediterran Burns Club 1994; 8: 94–7.
4. Askar I. Double reverse V–Y-plasty in postburn scar contractures: anew modification of V–Y-plasty. Burns 2003; 29: 721–5.
5. Bozdogan N, Ertas NM, Gündeslioglu O, Celebioglu S. Release of first web space contractures using rhomboid flap. Turk J Plast Reconstr Aesthetic Surg 2002; 10: 94.
6. Ertas NM, Bozdogan N, Uscetin I , Kücücelebi A, Celebioglu S. The use of subcutaneous pedicle rhomboid flapin the treatment of postburn scar contractures. Ann Plast Surg 2004; 53: 235.
7. Ertas, NM, Kücükcelebi A, Bozdogan N, Celebioglu S. The use of subcutaneous pedicle multiple rhomboid flapsin the treatment of long postburn scar contractures. Burns 2004; 30: 594.
8. Iwnagwu FC, Wilson D, Bulre F. The use of skin grafts in postburn contracture release: a 10 year review. Plast Reconstr Surg 1999; 103: 1198–204.
9. Furnas DW. The four fundamental functions of the Zplasty. Arch Surg 1968; 96: 458.
10. Hyakusoku H, Yamamaoto T, Fumirn M. The propeller flap method. Br J Plast Surg 1991; 44: 53–4.
11. Serkan Y, Gulden A, Mithat A, Misirlioglu A, Akoz T. Antrelateralthigh flap in the treatment of postburn contractures of the knee. Plast Reconstr Surg 2003; 111: 1630–7.
12. Prakash V. A new concept for the management of post burncontracture. Plast Reconstr Surg 2000; 106: 217-37.
13. Hudson DA. Some thoughts on choosing a Z-plasty: the Z madesimple. Plast Reconstr Surg 2000; 106: 665-71.
14. Cooper MACS. The multiple Y–V plasty in linear burn scar contracturerelease. Br J Plast Surg 1990; 43: 145-9.
15. Suliman MT. Experience with the 7 flap-plasty for the release of burnscontractures. Burns 2004; 30: 374–9.
16. Goodacre T. Surgical techniques: the V to Y plasty. Repair Reconstr 2001; 2: 13.
17. Hashem AM. Use of the 5-flap Z plasty in digital flexioncontractures. Ann Plast Surg 2009; 63: 503–6.
18. Pegahmehr M, Hafezi F, Naghibzadeh B, Nouhi A. MultipleV–Y advancement flaps: a new method for axillary burncontracture release. Plast Reconstr Surg 2008; 122: 44–5.
19. Ertas NM, Kücükcelebi A, Erbas O, Bozdoğan N, Celebioglu S. Comparison of Elongation Provided by Subcutaneous Pedicle Rhomboid Flap and Z-Plasty in Rat Inguinal Skin Plast Reconstr Surg 2006; 117: 486.
20. Ertas NM, Kücükcelebi A, Bozdogan N, Erbas E, Celebioglu S. Rate of elongation provided by multiple subcutaneouspedicle rhomboid flaps: An experimental study inthe rat inguinal skin. Burns 2004; 30: 467.
21. Hirshowitz B, Karev A, Rousso M. Combined double Z-plasty and Y-Vadvancement for thumb web contracture. Hand 1975; 7: 291–3.
22. Szymanowski J. Operations on the surface of the human body. Kiev: I and A Davidenko; 1856.
23. Szymanowski J. Handbuch der Operativen Chirurgie.Braunschweig: Von Friedrich Vieweg; 1870.
24. Shaw DT, Li CS. Multiple Y-V plasty. Ann Plast Surg1979; 2: 436–40.
25. Bier A, Braun H, Kummell H. Chirurgische Operationslehre, vol. I. Leipzig: Johann Ambronius Barth; 1922.

How to cite:

Koç MN, Ulutaş S, Çiğdem B, Kara S. Use of subcutaneous pedicled rhomboid flap technique for surgical treatment of burn contractures. Eur J Ther 2018; 24(3): 136–40.

European Journal of Therapeutics DOI: 10.5152/EurJTher.2017.316

Original Research

Use of Creative Activities in Physiotherapy and Rehabilitation

Tomris Duymaz[1], Çiğdem Dikmen[2]

[1]Department of Physiotherapy and Rehabilitation, İstanbul Bilgi University, İstanbul, Turkey

[2]Department of Health Management, İstanbul Bilim University, İstanbul, Turkey

ABSTRACT

Objective: A survey was performed to study the use of creativity in the field of physiotherapy and rehabilitation. There has been little research on this topic in Turkey and only a few studies are reported to have used music therapy for children. Therefore, the present study aimed to perform a similar survey as conducted in Sweden.

Methods: In this study, we sent a survey to physiotherapists in İstanbul via email. Recorded data included sociodemographic characteristics (gender, age, and education) of the physiotherapists; where and how long they had been working; the specialties of the physicians that they work with; whether they continued training/education after graduation, and if so how did they maintain their studies; whether/how often they involve creative activities in the treatment sessions; which activities they prefer; whether they get any negative reaction from patients or colleagues while applying the creative activities; and whether they apply any treatment method other than conventional methods.

Results: According to the results of the study, 59% of the physiotherapists benefit from using creative activities during their sessions. While 21% of them use handcrafts, 19% make use of computer games, 8% take advantage of music/theater activities, 6% use exercise painting, and 2% use practice gardening.

Conclusion: There has been no previous study on this topic in Turkey, this study provides insight into existing practices and may encourage further use of creative methods in therapy. Further studies should expand on the experience of physiotherapists concerning the benefits of creative activities.

Keywords: Creativity, creative activities, physiotherapy and rehabilitation

INTRODUCTION

Creativity is a term used in various fields with broad meanings. Many theoreticians and researchers who are interested in the issue have generally defined creativity in similar ways. Creativity refers to the generation of new and valuable ideas in any field. A similar definition phrases creativity as producing and conceptualizing new and useful ideas, processes, and procedures developed either through individual effort or teamwork. The most commonly accepted definition of creativity suggests it to be a phenomenon through which new and valuable ideas are generated (1, 2).

Creativity is one's ability to see, shape, and arrange the world in a unique way. In other words, it is a process where an unprecedented synthesis is formed through a combination of independent ideas. According to the common idea stated in many recent studies, creativity involves some personality traits, such as the ability to follow a distinctive pattern in a new and unusual implementation process, to think outside the box, to see aspects that cannot be seen by others regarding the correlation of ideas, to be open to new ideas, and to never hesitate to try new ways. Newell and Simon argued that creativity is a particular kind of problem solving process. Creativity may be considered both as a process and as a unique outcome generated at the end of a process. Creativity is regarded as valuable and significant to the extent that it gives rise to ideas having the potential to create applicable and innovative solutions (3).

Creative activity in a therapeutic sense is "the art of enhancing the performance while regulating and strengthening the function in selected works in order to reduce the patient's pathology, maintain health, and ensure the adaptability and efficiency"(4). The term "creative therapy" is in this form used for "therapeutic classification services in medical rehabilitation." Creative therapies include:

- Arts and crafts therapy,
- Music therapy,
- Exercise and physical therapy (5).

Creative activities were used for the first time by nurses and psychiatrists as a part of rehabilitation during the psychotherapy process of helping wounded soldiers in World War I. Creative activities have shown a positive influence on the mental and physical health of healthcare professionals as well as members of society. Offering creative art practices, such as music or painting as

Corresponding Author: Tomris Duymaz **E-mail:** fzt_tomrisduymaz@yahoo.com

Received: 22.12.2017 • **Acceptedi:** 31.01.2018

part of nursing care promotes the quality of the care. Therefore, creative activities are recommended to be employed within the scope of nursing care (6). Creative activities may be considered as an effective tool in each stage of psychiatric treatment, namely protective, therapeutic, or rehabilitative treatment (7). In case of attempts to build social skills, patients are recommended to be assigned artistic and sporting activities designed specifically in line with their needs and interests. Such activities are regarded as substantial for strengthening patients and revealing their capabilities. Additionally, creative methods are exercised for adaptation to social life and planning and implementation of adaptation activities according to cultural characteristics. It has also been stated that healthcare professionals should apply their creativity to draw patients into treatment and ensure their therapeutic collaboration (2). For this reason, therapists not only reveal their creativity but also enhance their clients' creativity during psychotherapy.

Although therapists benefit from creative arts activities, there are only a limited number of research studies regarding this issue. Published studies have emphasized the potential contribution of creative activities for treatment and have suggested conducting similar studies on the issue (8). Despite methodological weaknesses and limitations of most of the relevant studies, there is consistency among the findings. The common conclusion from the studies suggests that creative activities positively affect behavioral changes, self-confidence, self-esteem, knowledge, and the physical activity level of the participants. Even though the studies generally present weak evidence to support these arguments, there are some cases proving that creative therapy may be a useful method for improving the knowledge and positive behavior of children and teenagers when applied as part of the treatment strategy (9, 10).

Ergotherapy (Occupational Therapy), which dates back to 100 years, has both clinical significance and a social dimension. The foundation of the profession in Turkey was first laid with the establishment of the Physical Therapy and Rehabilitation College of the Hacettepe Faculty of Medicine and Health Sciences. In 1996, occupational therapy graduate and doctorate programs were initiated at the Physical Therapy and Rehabilitation Department of Hacettepe University, Institute of Health Sciences. In 2009, the Department of Ergotherapy was established within the structure of Hacettepe University. The students graduating from the department are given the title "Occupational Therapist."

The main aim of occupational therapy is to ensure participation of individuals in daily-life activities. Occupational therapists achieve this goal by sharpening the abilities of the individuals or groups to carry out the activities that they wish or need to do or that they are expected to do; or by arranging the activity or the environment in a way that enables better participation. This is why ergotherapy focuses on arrangement of each or all of the elements, including the person, activity and environment, as well as improvement of the capacity in order to enhance social participation.

The frequent use of physical agent modalities and its importance in physical therapy were confirmed, and it was also emphasized that these modalities could be combined with creative activities (11).

Studies in physical therapy and in related areas demonstrate the benefit of creative activities and the positive impact and value that it has for human health and well-being (12).

In this day of high-tech, managed-care service delivery with an emphasis on brief treatment, it is important for physiotherapists to be aware of nontraditional treatment options that may be uniquely beneficial for some patients. It may still be considered a novelty, also to patients. According to some studies, the most commonly used forms of creative activities are arts and crafts therapy followed by music therapy, exercise, and gardening. Also exergames and virtual reality offer alternative opportunities to provide neuro-rehabilitation and exercises that are fun. With the advancement of exergame and virtual reality systems, study of players' reaction on continued involvement in a game can guide game developers to maintain freshness through game progression that preserves the patient's attentional focus, minimizes attrition, and maintains a prescribed level of energy exertion. Some physiotherapists include commercial active videogames in their therapy sessions to help make repetitive activities funny and engaging. There is a need for a wide variety of available games, music, arts, crafts, and gardening to address novelty and personal preferences. Creativity and creative activities might be one form of physiotherapy that mediates the aforementioned effects (13).

Physical therapy techniques with aspects of creative and re-creative activities are, for example, animal-assisted therapy, horticultural therapy, and caregiver singing. Animal-assisted therapy, that is, to use animals as a mediator for therapy, is receiving more interest in rehabilitation with beneficial outcomes in various areas such as the care of the elderly and alleviating the perception of loneliness and depression (14).

Another form of physical therapy is horticultural therapy, including gardening, which has been described as a valuable option for rehabilitation and has been practiced in a physical therapy context to enhance quality of life and well-being in a broad sense (15).

Various aspects of music as a therapeutic activity in physical therapy are suggested as a possibility, and care singing has been proposed as a therapeutic intervention to accompany daily occupations (16).

This variety of activities related to creativity reflects a great interest and also an ambiguity as a result of different understandings of the concept of creative activities (17).

According to a similar study in Sweden, the respondents used varied creative activities; 48% used creative activities once a week or more, 36% once a month or more, and 14% at some

point every 6 months or so. The most common type of creative activity was craft activity reported to have been used by 68% of the respondents using materials such as textile, cardboard, ceramics, and leather. The second most common types were image/painting (32%) and gardening (30%). Other activities (e.g., using computers/games, photography, or cooking/ baking) were also frequently used (19%). A smaller proportion (6%) used alternative therapy forms. Animal-assisted activities (specifically trained dogs) were used by 6% respondents, while caregiver singing was used by by 3% respondents (18).

Arts and crafts were the most engaging forms of creative activities, which may be a return to the roots of physical therapy. On the other hand, more modern and nowadays accessible activities, such as the use of computers/games and photography, were also reported as creative activities (19).

A study conducted in Sweden (8) indicated that ergotherapists utilized various creative arts as a part of their therapy. In Turkey, however, there are a very limited number of studies regarding the use of creative activities. There are only a few studies in the literature considering music therapy in children, and there is no information on where and how often creative activities are employed. Drawing inspiration from the aforementioned Swedish research, a questionnaire was prepared to investigate the issue of creativity, which is important in every field, within the scope of physiotherapy and rehabilitation. We aim to carry out a study similar to the Swedish study with the physiotherapists working in Istanbul, and thus identify the current state of occupational therapy in our country.

METHODS

This study was performed with the Approval no. 08.09.2015/37-298 of the İstanbul Bilim University Ethics Committee for Clinical Research using the data obtained via a survey method with 100 physiotherapists that were designated through simple random sampling. We obtained written consent from each subject.

Recorded data included sociodemographic characteristics (gender, age, and education) of the physiotherapists; where and how long they had been working; the specialties of the physicians that they work with; whether they continued training/education after graduation and if so how did they maintain their studies; whether/how often they involve creative activities in their treatment sessions; which activities they prefer; whether they get any negative reaction from patients or colleagues while applying the creative activities; and whether they apply any treatment method other than conventional methods.

Statistical Analysis

The recorded data were statistically analyzed. Statistical Package for the Social Sciences (SPSS version 22.0, IBM Corp.; New York, USA) was used for the statistical analyses. Descriptive statistics were made. If a p value was <0.05 with a 95% confidence interval, the values were assumed to be normally distributed.

Table 1. Socio–demographic characteristics of the physiotherapists

	Values (n=100)	Frequency (percent)
Gender	Male	30 (30%)
	Female	70 (70%)
Age	26–30	42 (42%)
	31–35	29 (29%)
	36–40	13 (13%)
	41–45	6 (6%)
	46–50	5 (5%)
	51+	5 (5%)
Education	University	51 (51%)
	Master	36 (36%)
	Phd	13 (13%)
Seniority	0–3	15 (15%)
	4–6	21 (21%)
	7–9	18 (18%)
	10+	46 (46%)
Foreign language	Not know	16 (16%)
	English	80 (80%)
	Other	4 (4%)

RESULTS

One hundred physiotherapists (30% men, 70% women) aged between 26 and 60 years old and living in Istanbul filled out the questionnaire. Thirty-six percent of these physiotherapists had completed their master's degree, and 46% of them had been working for more than 10 years. The sociodemographic characteristics of the physiotherapists included in the study are presented in Table 1.

It was found that a great number (31%) of the physiotherapists work at private training and rehabilitation centers.

It was observed that 59% of the physiotherapists work with psychiatrists. This result indicates the specialties of all the physicians that the physiotherapists work with.

In total, 85% of the physiotherapists continued training after graduation, mostly (70%) by attending courses and seminars. According to the results of the study, 59% of the physiotherapists benefit from creative activities during their sessions. While 21% of them use handcrafts, 19% make use of computer games, 8% take advantage of music/theater activities, 6% use exercise painting, and 2% practice gardening.

In total, 35% of the physiotherapists taking advantage of creative activities apply them once or twice per week. Eleven percent of

the physiotherapists reported that they were faced with criticism from the patients while applying creative activities, while 8% were met with reaction from colleagues and 9% were criticized both by patients and colleagues.

At the same time, 58% of the physiotherapists made use of methods other than conventional methods, with reflexology being the most frequently (20%) employed method.

DISCUSSION

On the grounds of the argument that creativity is a particular kind of problem solving process, creativity may be addressed both as a process and as the unique outcome of that process. Also, creativity may be defined as one's capacity to solve a problem or offer a new and acceptable product or service in her/his culture. In light of this view, creativity may be designed in organizations, generated goods, and services. Businesses, organizational units, and individuals may organize to launch innovations and creativity. Each of us can be creative enough to create unprecedented, original and useful ideas in our field of specialty. Rapidly developing technology and different living conditions have brought about the necessity for innovations in healthcare services. Healthcare professionals that continuously provide healthcare services for patients should take innovative and creative initiatives related to the treatment and care of patients. Creativity facilitates recovery of the patients while enhancing psychosocial skills and promoting abilities to cope with problems. Therefore, the significance of creative approaches increases in case of the services to be provided to individuals, whose adaptation to society has deteriorated and who experience many problems in various areas (20).

The present study, which addressed creativity through activities in physiotherapy, indicated that 59% of the physiotherapists include creative therapy once or twice per week within their sessions and often prefer activities involving handcrafts. This study shares similarity with the Swedish study regarding the finding of frequent use of handcrafts.

Further studies could better evaluate the status throughout the country by taking the activities that, have not been mentioned in this study, within the scope, as well as, examining the reasons why physiotherapists are criticized by patients and/or colleagues for using creative activities, investigating the fields where creative activities may be useful, and comparing ergotherapists with physiotherapists.

This paper emphasizes on the significance of creative approaches that increases in case of services to be provided to individuals, whose adaptation to society has deteriorated and who experience many problems in various areas. The present study, which addressed the concept of creativity through creative activities in physiotherapy, indicated that 59% of physiotherapists include creative therapy once or twice per week within their sessions and often prefer activities involving handcrafts. This study is important because there has been no previous study that has investigated the use of creative activities among physiotherapists in Turkey.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul Bilim University (no: 08.09.2015/37-298).

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – T.D., Ç.D.; Design - Ç.D.; Supervision - T.D.; Resources - T.D.; Materials - T.D.; Data Collection and/or Processing - T.D.; Analysis and/or Interpretation - T.D.; Literature Search – T.D., Ç.D.; Writing Manuscript - T.D., Ç.D.; Critical Review - T.D., Ç.D.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

REFERENCES

1. Amabile TM, Conti R, Coon H, Lazenby J, Herron M. Assessing the work environment for creativity. Acad Manage J 1996; 39: 1169-84.
2. Blomdahl C, Gunnarsson AB, Guregard S, Björklund A. A realist review of art therapy for clients with depression. The Arts in Psychotheraphy 2013; 40: 322-30.
3. Mullins LJ. Management Organizational Behavior. 2nd ed. Mishawaka, USA: Prentice Hail Press; 2002. p.367.
4. Zeki S. Artistic creativity and the brain. Science 2001; 293: 51-2.
5. Olbrich D. Kreativtherapie in der psychosomatischen Rehabilitation. Springer-Verlag 2003; 67: 883-909.
6. Lane MR. Creativity and spirituality in nursing: Implementing art in healing. Holistic Nursing Practice 2005; 19: 122-25.
7. Gillam T. Creativity and mental health care. Ment Health Practice 2013; 16: 24-30.
8. Griffiths S, Corr S. The use of creative activities with people with mental health problems: A survey of occupational therapists. Br J Occup Ther 2007; 70: 107-14.
9. Bungay H, Vella-Burrows T. The effects of participating in creative activities on the health and well-being of children and young people: a rapid review of the literature. Perspect Public Health 2013; 133: 44-52.
10. Mannerkorpi K, Henriksson C. Non-pharmacological treatment of chronic widespread musculoskeletal pain. Best Pract Res Clin Rheumatol 2007; 21: 513-34.
11. Stein F. Reflections on 50 years as an occupational therapy international. Occup Ther Int 2008; 15: 1-3.
12. Perruzza N, Kinsella EA. Creative arts occupations in therapeutic practice: a review of the literature. Br J Occup Ther 2010; 73: 261-8.
13. La Cour K, Josephsson S, Luborsky M. Creating connections to life during life-threatening illness: creative activity experienced by elderly people and occupational therapists. Scand J Occup Ther 2005; 12: 98-109.
14. Banks MR, Banks WA. The effects of animal-assisted therapy on loneliness in an elderly population in long-term care facilities. J Gerontol 2002; 57: 428-32.
15. Söderback I, Söderström M, Schalander E. Horticultural therapy: the 'healing garden' and gardening in rehabilitation measures at Danderyd Hospital Rehabilitation Clinic, Sweden. Pediatr Rehab 2004; 7: 245-60.
16. Craig DG. An overview of evidence-based support for the therapeutic use of music in occupational therapy. Occup Ther in Health Care 2008; 22: 73-95.

17. Lenkey J. The therapeutic effectiveness of creative activities on mental well-being: a systematic review of the literature. J Psyc and Ment Health Nurs 2011; 18: 501-9.
18. Müllersdorf M, Ivarsson AB. Use of creative activities in occupational therapy practice in Sweden. Occup Ther Int 2012; 19: 127-34.
19. Haltiwanger E, Rojo R, Funk K. Living with cancer: impact of expressive arts. Occup Ther in Ment Health 2011; 27: 65-86.
20. Robbins SP, Coulter M. Management. 3rd ed. Mishawaka, USA: Prentice Hail Press; 2002. p.354.

How to cite:

Duymaz T, Dikmen Ç. Use of Creative Activities in Physiotherapy and Rehabilitation. Eur J Ther 2018; 24(3): 141–5.

European Journal of Therapeutics
DOI: 10.5152/EurJTher.2017.327
Original Research

Visual Axis Opacification after Congenital Cataract Surgery and Primary Intraocular Lens Implantation: Comparison of Three Different Lenses

Alper Mete, Necdet Bekir
Department of Ophthalmology, Gaziantep University, School of Medicine, Gaziantep, Turkey

ABSTRACT
Objective: To evaluate the incidence of visual axis opacification (VAO) in children who underwent pediatric cataract surgery combined with intraocular lens (IOL) implantation.
Methods: We retrospectively evaluated 65 eyes of 49 patients (range 24–96 month) who underwent pediatric cataract surgery between 2006 and 2012. We divided the patients into groups according to the implanted IOL. In group A, an MA60BM hydrophobic; in group B, a Sensar® 40e hydrophobic; and in group C, an Eyecryl® 600 hydrophilic IOL were implanted. Patients in all groups who completed 12 months of follow-up were included in this study. The demographic data, VAO, and postoperative complications were evaluated.
Results: A total of 33 patients had unilateral and 16 had bilateral cataract surgery. The rate of VAO was 10 (45.5%) in Group A; 7 (41.2%) in Group B; and 16 (61.5%) in Group C. We determined no significant difference between the groups in terms of VAO development (p=0.353).
Conclusion: Our results demonstrated that different IOLs cause comparable VAO rates in children undergoing surgery at an older age. Based on these findings, it can be concluded that performing a posterior curvilinear capsulorhexis and anterior vitrectomy are more important than IOL design in preventing after-cataract formation in older children.
Keywords: Congenital cataract surgery, visual axis opacification, intraocular foldable lens

INTRODUCTION

Congenital and developmental cataracts are the most common treatable causes of childhood blindness (1, 2). With improvements in surgical techniques and intraocular lens (IOL) designs, primary implantation of IOLs for rehabilitation has become popular in recent years. However, implanting an IOL to pediatric eyes is still controversial because the eye globe continues to grow, and axial length and refractive values constantly change. Additionally, postoperative complications requiring secondary surgery frequently occur in younger children because of ocular inflammation during the postoperative period (3).

Visual axis opacification (VAO) is a major complication in pediatric cataract surgery. Several surgical techniques, such as posterior continuous curvilinear capsulorhexis (PCCC), anterior vitrectomy (AV), optic capture, and the bag-in-the-lens technique, can prevent this complication. However, these techniques have some limitations that still present a threat to clear visual axis because of excessive immune response and migration of lens epithelial cells (LEC) (4). Most surgeons prefer hydrophobic acrylic IOL for pediatric cataract surgery. Nevertheless, VAO has been performed with all types of IOL material (5). There are very few reports concerning the relationship between different IOLs and VAO in congenital cataract surgery with posterior capsulotomy and AV. We aim to report the VAO incidence in children who underwent cataract surgery with posterior capsulotomy, AV, and primary IOL implantation with three different IOLs.

METHODS

The parents of the children provided written informed consent approval of the ethics committee was received, and the study followed the principles of the Declaration of Helsinki. Our study is a retrospective study of 65 eyes of 49 children aged 24–96 months who underwent congenital and developmental cataract surgery at an older age in our hospital between 2006 and 2012. Preoperatively, all children had complete ophthalmic examination. In younger or uncooperative children, ocular examination was performed under general anesthesia. Eyes that had the poor red reflex were operated. The exclusion criteria were persistent hyperplastic primer vitreous, uveal inflammation or congenital glaucoma, microphthalmos, and coloboma. Children who did not complete 12 months follow-up were excluded from the study.

All surgeries were performed under general anesthesia by a surgeon. A clear 2.8 mm corneal incision was performed at 12 o'clock meridian. Anterior chamber was filled by sodium hyaluronate

ORCID IDs of the authors: A.M. 0000-0002-1712-5163; N.B. 0000-0002-6755-2550.
Corresponding Author: Alper Mete **E-mail:** dralpermete@hotmail.com
Received: 12.12.2017 • **Accepted:** 20.12.2017

Table 1. Intraocular lenses used in this study

	ALCON AcrySof® MA60BM	AMO Sensar® 40e	BIOTECH Eyecryl® 600
Material	Hydrophobic Acrylate/ Methacrylate Polymer optic, PMMA haptics (three piece)	Hydrophobic acrylic copolymer optic, PMMA haptics (three piece)	Hydrophilic Acrylic 26% CQ optic and haptic (single piece)
Optic length (mm)	6	6	6
IOL length (mm)	13.0	13.0	12.5
Optic–haptic angle	10°	5°	5°
Refractive index	1.55	1.47	1.46
Optic edge design	Square edge	Square edge	Square edge
Haptic shape	Modified C	Modified C	Optimized C
"A" constant	118.9	118.4	118.0

IOL: intraocular lens

Table 2. Demographic and clinical characteristics of groups

Characteristic	Group A	Group B	Group C	p
IOL	Alcon AcrySof® MA60BM	AMO Sensar® 40e	Biotech Eyecryl® 600	–
Number of eyes/patients	22/17	17/13	26/19	–
Age[a], months Mean+SD Range	40.9±19.9 (24–90)	44.6±21.9 (24–92)	44.7±22.5 (24–96)	0.843[b]
Sex Male/female	9/8	7/6	10/9	0.998[c]
Laterality Unilateral/Bilateral	12/5	9/4	12/7	0.881[c]

[a]: at the time of surgery; [b]: One–way ANOVA test; [c]: Chi–square test; IOL: intraocular lens; SD: standard deviation

(3.0%), and a 4.0–5.0 mm anterior continuous curvilinear capsulorhexis was performed by using a capsulorhexis forceps. After cortical hydrodissection, lens material was aspirated. Then, viscoelastic material (1.4%) was injected into the capsular bag, and a PCCC approximately 3.5 mm was performed followed by AV and foldable IOL implantation into the bag. All incisions were closed by 10.0 nylon suture after intracameral antibiotic injection.

Postoperatively, children received topical steroid and antibiotic drops eight times a day, which were tapered during the first month, and 1% cyclopentolate once a day for the first 4 weeks. Subjects were followed once a week for the next 4 weeks, every 2 months for 6 months, and 12 months after surgery. Direct and indirect ophthalmoscopic ocular examination was performed in all children to determine VAO. In younger or uncooperative children and in the suspected presence of any postoperative complication, an examination using an operating microscope was performed under general anesthesia. Postoperative complications and implanted IOL design were noted.

Based on the three different IOLs implanted, we divided children into three groups. In group A, an Acrysof® MA60BM hydrophobic three-piece IOL; in group B, Sensar® 40e hydrophobic three-piece IOL; and in group C, an Eyecryl® 600 hydrophilic single-piece IOL was implanted in the bag (Table 1).

Statistical Analysis

All data obtained from the study were analyzed using Statistical Package for the Social Sciences version 16 software (SPSS Inc.; Chicago, IL, USA). The one-way ANOVA test and Chi-square test were used to compare data among groups. Statistical significance was taken as p value <0.05.

RESULTS

A total of 65 eyes of 49 patients were included in the study. Among them, 26 (53%) were male and 23 (47%) were female. Patients were aged between 24 and 96 months, and the mean age was 43.40±21.14 months.

A total of 33 children underwent unilateral and 16 children underwent bilateral surgery. Based on the three different IOLs implanted, children were divided into three groups (Table 2).

Group A had 22 eyes, and VAO developed in 10 (45.5%) of them. Out of 17 eyes in group B, VAO developed in 7 (41.2%) of them. Group C had 26 eyes, and 16 (61.5%) of them developed VAO. The VAO rate was higher in group C than in the other groups (Table 3), but statistically significant difference was not found among the groups (p=0.353).

We observed fibrin reaction in two eyes in group A, two eyes in group B, and four eyes in group C. Two eyes in group C devel-

Table 3. Rate of complications in groups

	No(%)			
Complications	**Group A**	**Group B**	**Group C**	**p[a]**
After–cataract formation	10 (45.5)	7 (41.2)	16 (61.5)	0.353
Fibrin reaction	2 (9.1)	2 (11.7)	4 (15.4)	0.801
IOL decentration	1 (4.5)	0 (0)	2 (7.7)	0.501
Secondary glaucoma	1 (4.5)	1 (5.8)	2 (7.7)	0.902

[a]: Chi–square test; IOL: intraocular lens

oped IOL decentration. One eye in group A, one eye in group B, and two eyes in group C developed secondary glaucoma during follow-up period (Table 3). One eye in group A, two eyes in group B, and five eyes in group C underwent reoperation due to VAO development.

We did not observe other complications such as hyphema, iris prolapse, IOL drop, retinal detachment, and endophthalmitis.

DISCUSSION

Primary posterior capsulorhexis does not always guarantee a permanently clear visual axis because anterior surface of the vitreous serves chance for the LEC migration into the visual axis (6). In younger children, AV with PCCC reduces the VAO. However, it is not clear at what age AV should be performed. Basti et al. (7) performed primary posterior capsulotomy with AV in children aged less than 8 years. Vasavada and Desai (8) suggested AV with PCCC in children aged less than 5 years. In five out of eight eyes in which PCCC without AV was performed, VAO was observed, and a secondary procedure was required. Koch and Kohnen reported 20 eyes that underwent different methods of managing the posterior capsule and anterior vitreous. They found that none of the eyes that had PCCC with AV developed visually significant VAO (9). Kugelberg and Zetterström (10) reported VAO in 85 eyes that underwent cataract surgery with or without AV according to age (patients aged 0–15 years). They suggested that cataract surgery combined with AV should be performed in younger children. Dahan and Salmenson (11) recommended PCCC and AV in children aged less than 8 years. Fenton and O'Keefe (12) reported a VAO rate of 15.6% performing posterior capsulorhexis without AV. In our study group, children age range from 2 to 8 years. We performed PCCC, AV, and in-the-bag IOL implantation for all children. Most pediatric ophthalmologists agree that IOL implantation is the most suitable treatment for Aphakia rehabilitation, and primary IOL implantation has become the popular and acceptable approach in patients above 2 years of age (13).

Intraocular lens designs and materials are designed to prevent VAO (14). Wilson and Trivedi surveyed ophthalmologists about their choice of IOL for pediatric surgery (15). The AcrySof MA (Alcon Laboratories, Inc., Fort Worth, Texas, USA) series is the most preferred worldwide for sulcus fixation. For in-the-bag fixation, most surgeons prefer the MA series, whereas the SA series is more popular in the United States (16). Our results showed that VAO was the major complication in all groups. We found similar rates of VAO in groups A and B. VAO rate of group C was higher than in other groups, but we did not find a statistically significant difference in VAO among groups.

Trivedi et al. (17) showed that there was no statistically significant difference between implantation of single and three-piece IOLs in infants regarding the development of VAO. The lens design is also another critical factor in LEC migration. The square edge design of the IOLs may prevent LEC migration that is important for avoiding VAO (18–20). The three-piece IOLs provide better adhesion between the anterior and posterior capsules. The single-piece lens has bulky haptics than three-piece IOLs that may lead to LEC migration (14). The hydrophobic acrylic IOLs have less after-cataract formation rate than hydrophilic acrylic IOLs. It has been shown by previous studies that hydrophobic acrylic material contacts firmly with posterior capsule and prevents LEC migration and decreases VAO (21). High permeability of hydrophilic acrylic IOLs allows penetration of nutrients to LECs and increases VAO rate (22, 23). We thought that IOL material and design had low additional effect in reducing VAO. This may occur because of the fact that PCCC and AV eliminate the vitreous and hyaloid face as a scaffold for the LECs' migration to the visual axis.

The purpose of congenital cataract surgery is to provide a clear visual axis. However, anterior segment complications after congenital and developmental cataract surgery are more common in adults. This immune response is generally activated by the presence of an IOL, and response is more aggressive in children than in adults. With decreasing age, immune response increases (3). We observed similar rates of fibrin reaction in groups. This may be explained by no significant difference in age among groups. The similar rates of IOL dislocation between groups may also explained by in-the-bag implantation. In-the-bag placement of the IOL is preferred because it mostly eliminates the risk of lens dislocation, iris capture, and uveal inflammation. Apple et al. (24) showed the advantages of capsular bag fixation over ciliary sulcus implantation. Capsular-fixated IOLs provide less pupillary capture and pigment dispersion, elimination of ciliary body erosion. Moreover, capsular fixation provides better centration and stabilization of IOL when compared with sulcus fixation.

Kugelberg et al. (25) showed that IOL implantation protects against secondary glaucoma. The first theory is that IOL may protect the trabecular meshwork from harmful effects of vitreous chemical components. Secondly, IOLs may also provide a mechanical support for trabecular meshwork (26, 27). We observed similar rates of open angle secondary glaucoma in all groups. Longer follow-up period can increase the incidence of secondary glaucoma.

In our study, the overall rate of VAO appears high compared with existing literature. This may be because VAO was described as a fibrosis of anterior or posterior capsular opening and opacification of anterior vitreous surface that closed or threated the optic visual axis in this study. In other studies, fibrosis of anterior surface of vitreous or posterior surface of IOL that closed the visual axis, accepted as VAO or after-cataract formation (4, 5, 28, 29).

CONCLUSION

Our outcomes showed that different IOLs cause comparable VAO rate in children having undergone congenital cataract surgery at an older age. We conclude that performing a posterior curvilinear capsulorhexis and AV is more important than IOL choice in preventing VAO in late-consulted older children. Long-term studies are needed to understand the importance of IOL selection and to determine the best treatment in this age group.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University.

Informed Consent: Written informed consent was obtained from patients' parents who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.M., N.B.; Design - A.M., N.B.; Supervision A.M., N.B.; Resources - A.M., N.B.; Materials – A.M.; Data Collection and/or Processing - A.M., N.B.; Analysis and/or Interpretation - A.M., N.B.; Literature Search - A.M., N.B.; Writing Manuscript – A.M.; Critical Review - A.M., N.B.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

REFERENCES

1. Khanna RC, Foster A, Krishnaiah S, Mehta MK, Gogate PM. Visual outcomes of bilateral congenital and developmental cataracts in young children in south India and causes of poor outcome. Indian J Ophthalmol 2013; 61: 65-70.
2. Rahi JS, Dezateux C. Congenital and infantile cataract in the United Kingdom: underlying or associated factors. British Congenital Cataract Interest Group. Invest Ophthalmol Vis Sci 2000; 41: 2108-14.
3. Tuncer S, Gücükoğlu A, Gözüm N. Cataract Extraction and Primary Hydrophobic Acrylic Intraocular Lens Implantation in Infants. J AAPOS 2005; 9: 250-6.
4. Kim KH, Ahn K, Chung ES, Chung TY. Clinical Outcomes of Surgical Techniques in Congenital Cataracts. Korean J Ophthalmology 2008; 22: 87-91.
5. Lu Y, Ji YH, Luo Y, Jiang YX, Wang M, Chen X. Visual results and complications of primary intraocular lens implantation in infants aged 6 to 12 months. Graefes Arch Clin Exp Ophthalmol 2010; 248: 681-6.
6. Petric I, Lacmanović Loncar V. Surgical technique and postoperative complications in pediatric cataract surgery: retrospective analysis of 21 cases. Croat Med J 2004; 45: 287-91.
7. Basti S, Ravishankar U, Gupta S. Results of a prospective evaluation of three methods of management of pediatric cataracts. Ophthalmology 1996; 103: 713-20.
8. Vasavada A, Desai J. Primary posterior capsulorhexis with and without anterior vitrectomy in congenital cataracts. J Cataract Refract Surg 1997; 23: 645-51.
9. Koch DD, Kohnen T. Retrospective comparison of techniques to prevent secondary cataract formation after posterior chamber intraocular lens implantation in infants and children. J Cataract Refract Surg 1997; 23: 657-63.
10. Kugelberg M, Zetterström C. Pediatric cataract surgery with or without anterior vitrectomy. J Cataract Refract Surg 2002; 28: 1770-3.
11. Dahan E, Salmenson BD. Pseudophakia in children: precautions, techniques, and feasibility. J Cataract Refract Surg 1990; 16: 75-82.
12. Fenton S, O'Keefe M. Primary posterior capsulorhexis without anterior vitrectomy in pediatrics cataract surgery: longer term outcome. J Cataract Refract Surg 1999; 25: 763-7.
13. Bartholomew LR, Trivedi RH, Wilson ME. Pediatric cataract surgery and intraocular lens implantation practice styles and preferences of the 2001 ASCRS and AAPOS memberships. J Cataract Refract Surg 2003; 29: 1811-20.
14. Mian SI, Fahim K, Marcovitch A, Gada H, Musch DC, Sugar A. Nd: YAG capsulotomy rates after use of the AcrySof acrylic three piece and one piece intraoculer lenses. Br J Ophthalmol 2005; 89: 1453-7.
15. Wilson ME, Trivedi RH. Choice of intraocular lens for pediatric cataract surgery: survey of AAPOS members. J Cataract Refract Surg 2007; 33: 1666-8.
16. Lin AA, Buckley EG. Update on pediatric cataract surgery and intraocular lens implantation. Curr Opin Ophthalmol 2010; 21: 55-9.
17. Trivedi RH, Wilson ME Jr, Bartholomew LR, Lal G, Peterseim MM. Opacification of the visual axis after cataract surgery and single acrylic intraocular lens implantation in the first year of life. J AAPOS 2004; 8: 156-64.
18. Nishi O, Nishi K, Akura J, Nagata T. Effect of round-edge acrylic intraocular lenses on preventing posterior capsule opacification. J Cataract Refract Surg 2001; 27: 608-13.
19. Nishi O, Nishi K, Osakabe Y. Effect of intraocular lenses on preventing posterior capsul opacification: design versus material. J Cataract Refract Surg 2004; 30: 2170-6.
20. Findl O, Menapace R, Sacu S, Buehl W, Rainer G. Effect of optic material on posterior capsule opacification in intraocular lenses with sharp-edge optics. Ophthalmology 2005; 112: 67-72.
21. Abela-Formanek C, Amon M, Schauersberger J, Kruger A, Nepp J, Schild G. Results of hydrophilic acrylic, hydrophobic acrylic, and silicone intraocular lenses in uveitic eyes with cataract. Comparison to a control group. J Cataract Refract Surg 2002; 28: 1141-52.
22. Scaramuzza A, Fernando GT, Crayford BB. Posterior capsule opacification and lens epithelial cell layer formation. Hydrview hydrogel versus AcrySof acrylic intraoculer lenses. J Cataract Refract Surg 2001; 27: 1047-54.
23. Küçüksümer Y, Baerakfar S, Sahin S, Yılmaz OF. Posterior capsule opacification 3 years after implantation of an AcrySof and a Memory Lens in fellow eyes. J Cataract Refract Surg 2000; 26: 1176-82.
24. Apple DA, Reidy JJ, Googe JM, Mamalis N, Novak LC, Loftfield K, et al. A comparison of ciliary sulcus and bag fixation of posterior chamber intraocular lenses. J Am Intraocul Implant Soc 1985; 11: 44-63.
25. Kugelberg M, Kugelberg U, Bobrova N, Tronina S, Zetterström C. Implantation of single piece foldable acrylic IOLs in small children in the Ukraine. Acta Ophthalmol Scand 2006; 84: 380-3.
26. Kugelberg M, Shafiei K, Zetterström C. Single piece acrysof in the new born rabbit eye. J Cataract Refract Surg 2004; 30: 1345-50.
27. Asrani S, Freedman S, Hasselbad V, Buckley EG, Egbert J, Dahan E, et al. Does primary intraocular lens implantation prevent aphakic glaucoma in children. J AAPOS 2000; 4: 33-9.
28. Raina UK, Mehta DK, Monga S, Arora R. Functional outcomes of acrylic intraocular lenses in pediatric cataract surgery. J Cataract Refract Surg 2004; 30: 1082-91.
29. Vasavada AR, Trivedi RH, Nath VC. Visual axis opacification after AcrySof intraocular lens implantation in children. J Cataract Refract Surg 2004; 30: 1073-81.

How to cite:

Mete A, Bekir N. Visual Axis Opacification after Congenital Cataract Surgery and Primary Intraocular Lens Implantation: Comparison of Three Different Lenses. Eur J Ther 2018; 24(3): 146–9.

European Journal of Therapeutics
DOI: 10.5152/EurJTher.2018.438
Original Research

Relative Contribution of Apparent Diffusion Coefficient (ADC) Values and ADC Ratios of Focal Hepatic Lesions in the Characterization of Benign and Malignant Lesions

Feyza Gelebek Yılmaz[1], Abdullah Emre Yıldırım[2]
[1]Department of Radiology, Gaziantep University, School of Medicine, Gaziantep, Turkey
[2]Department of Gastroenterology, Gaziantep University, School of Medicine, Gaziantep, Turkey

ABSTRACT
Objective: The aim of the present study was to compare relative contribution of apparent diffusion coefficient (ADC) values and ADC ratios (ADC of the lesion/ADC of the neighboring hepatic parenchyma) in the differential diagnosis of benign and malignant focal hepatic lesions.
Methods: A total of 80 patients with 94 focal hepatic mass lesions (mean size, 5.3 cm; range, 1–12 cm) were evaluated retrospectively using 3 Tesla magnetic resonance imaging (MRI). The ADC values and ADC ratios were compared for different types of lesions to obtain ideal cut-off values.
Results: Mean ADC values (±SD) were 0.93±0.15, 0.95±0.48, 1.44±0.39, 1.88±0.50, and 2.94±0.75×10^{-3} mm^2/sec respectively for hepatocellular carcinoma (HCC), metastasis, focal nodular hyperplasia (FNH), hemangioma, and cysts with a mean ADC value of 1.97±0.68 for benign lesions and 0.94±0.29×10^{-3} mm^2/sec for malignant lesions. The ADC ratios of benign and malignant lesions were 1.50±0.53 and 0.80±0.20×10^{-3} mm^2/sec, respectively, and the ADC values and ratios were found to differ significantly between benign and malignant lesions. Assuming a cut-off ADC value of 1.26×10^{-3} mm^2/sec for discrimination of benign and malignant lesions provided 94% sensitivity and 92% specificity. Sensitivity of 85% and specificity of 92% were found when a cut-off ADC ratio of 0.90×10^{-3} mm^2/sec was used for discrimination of benign and malignant lesions. Compared to ADC values, ADC ratios were found to have lower sensitivity and higher specificity for discriminating between benign and malignant lesions.
Conclusion: Diffusion weighted imaging is used in combination with conventional MRI, and it enhances the diagnostic accuracy of MRI in the characterization of benign and malignant lesions.
Keywords: Diffusion weighted imaging, hepatic mass, echo-planar imaging

INTRODUCTION

Diffusion is the random microscopic motion of water molecules within the tissue. Diffusion weighted imaging (DWI) measures the movements of water molecules in extracellular, intracellular, and intravascular spaces (1). DWI is extremely sensitive to motion, and respiratory, cardiac, and peristaltic physiological movements impair the image quality considerably and make the evaluation more difficult. For this reason, DWI has been limited to brain imaging for many years. The development of echo-planar imaging (fast gradient echo sequence), a fast magnetic resonance imaging (MRI) method, eliminated prolonged imaging time and associated artifacts observed with conventional sequences and allowed use of DWI for evaluation of abdominal organs (2). The apparent diffusion coefficient (ADC) value is a mathematical representation of diffusion obtained by mapping signals lost after applying a diffusion gradient (3). ADC values are often calculated automatically by clinical MR systems. While lower ADC values indicate malignancy (hypointense with ADC, hyperintense with DWI), higher ADC values favor benignancy (hyperintense with ADC, hypointense or hyperintense with DWI). On the other hand, the ADC ratio is calculated by dividing the ADC value of a lesion by the ADC value of the adjacent liver parenchyma, and it provides more comprehensive results by eliminating differences in devices, technical approaches, and variability resulting from using different b values.

The aim of our study was to assess relative contributions of ADC values and ADC ratios to the characterization of benign and malignant hepatic lesions.

METHODS

From January 2016 to November 2016, the DWI was included in routine MRI scans. The retrospective study was performed after obtaining the approval from Gaziantep University Medical Ethics Committee with a decision number 2017/43. Patients were informed of the procedures to be used in the study, and they signed an informed consent statement.

ORCID IDs of the authors: F.G.Y. 0000-0002-9900-5981; A.E.Y. 0000-0002-4386-9297.
Corresponding Author: Feyza Gelebek Yılmaz **E-mail:** feyzagelebekyilmaz@hotmail.com
Received: 25.01.2018 • **Accepted:** 13.03.2018

Ninety-four lesions detected using the combined method in a total of 80 patients (37 males, 43 females) with primary or metastatic hepatic tumor or benign lesions were studied. The mean age of patients was 53 years (range, 11–89 years). Nine patients had simple hepatic cysts diagnosed with typical ultrasound (US) and MRI findings. Hemangioma (n=41) was confirmed by MRI and/or archived computed tomography (CT) image characteristics and typical patterns of contrast enhancement. Cases of focal nodular hyperplasia (n=10) were diagnosed on the basis of iso-hyperintense appearance obtained with a liver-specific contrast agent following the administration of 0.25 mmol/mL gadoxetic acid disodium (Primovist; Bayer) in the late phases compared to the liver parenchyma and typical dynamic images. Eleven metastatic masses were lesions diagnosed as metastatic, showing growth during routine follow-up in patients with known primary malignancy (4 cases of breast cancer, 4 cases of colon cancer, 1 cervical cancer, 1 endometrial cancer, 1 renal cell carcinoma). Out of 23 cases with lesions associated with primary hepatocellular tumors, 10 were diagnosed by histopathological features and by typical dynamic CT–MRI image characteristics in others. Overall, the diameter of 94 mass lesions ranged between 1 and 12 cm with a mean diameter of 5.3 cm. Eighty patients underwent upper abdominal MRI and DWI with 3 Tesla MR (Ingenia 3.0T; Philips Healthcare, Best, The Netherlands) using phased-array coils. Routine examination protocol consisted of axial T2-weighted TSE (Turbo Spin Echo) with fat suppression, gradient echo mode in in-phase and in opposed phase with T1-weighting, contrast-enhanced dynamic T1-weighted imaging. Diffusion weighted MR examination was performed before obtaining slices with contrast material. Diffusion weighted sequence (Repetition Time [TR]/Echo Time [TE], 1121/57; flip angle, 90°; slice thickness, 5 mm; Field of View [FOV], 250–202–230) was obtained by applying diffusion-sensitive gradients in all three directions (x,y,z) at two different b values (b=0 and b=600 mm^2/s) to single-shot echo-planar sequence in axial plane. The first series of the sequential image set consisted of echo-planar spin echo T2-weighted images (b=0); the next three series contained images with diffusion-sensitive gradients applied on the first series in x, y, and z directions with a b value of 600 mm^2/sec, and the final series consisted of isotropic images calculated from projection of diffusion vectors in three directions. Isotropic images were images created by the device by calculating the cube root of the product of signal intensities obtained in x, y, and z directions by excluding directionally sensitive signal changes. ADC maps for isotropic images were automatically constructed by the device, and average ADC values of all lesions were measured from these maps. Measurements were obtained by positioning a circular region of interest (ROI) with an approximate diameter of 1 cm on the lesions. For greater lesions, three separate ROI measurements on the same cross-section were averaged. For lesions with a heterogeneous internal structure, measurements were obtained from solid parts that showed contrast enhancement in conventional sequences and contrast-enhanced sections. The ADC value of lesions with a diameter of 1 cm was calculated using a single ROI. ADC values of normal hepatic parenchyma were also measured for 80 patients. An average ADC value was calculated from three sequential sections with measurements from the posterior segments of the right lobe of the liver by establishing 1 cm ROIs at three different locations for each section. ADC values were hepatic focal masses determined and compared between benign and malignant lesions.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Version 22.0, IBM Corp.; New York, USA) software package. Since the number of patients was sufficient in both groups (benign and malignant), comparison between the groups was done using the independent two-sample t-test. A p-value below 0.05 was considered significant. The Mann–Whitney U test was used to compare lesions because the number of cysts, hemangiomas, focal nodular hyperplasia (FNH), hepatocellular carcinoma (HCC), and metastatic lesions was insufficient and/or did not show normal distribution within groups. Additionally, for discrimination between benign and malignant lesions, cut-off values for ADC values and ADC ratios were evaluated by the Receiver operating characteristic ROC analysis, and sensitivity, specificity, and cut-off values were estimated.

RESULTS

The ADC values were 0.94±0.15, 0.95±0.48, 1.44±0.39, 1.88±0.50, and 2.94±0.75×10^{-3} mm^2/sec, respectively, for HCC, metastases, FNH, hemangiomas, and cysts, and the average ADC values were 1.96±0.68×10^{-3} mm^2/sec for benign lesions and 0.94±0.29×10^{-3} mm^2/sec for malignant lesions (Table 1).

Table 1. The number of lesions, average ADC of the mass, parenchymal ADC, and ADC ratios by the type of mass lesion

Type of mass lesion	Number of lesions	Average ADC value of the lesion mass (×10^{-3} mm^2/s)	Average parenchymal ADC value (×10^{-3} mm^2/s)	Average ADC ratio (×10^{-3} mm^2/s)
Benign	60	1.96±0.68	1.32±0.19	1.50±0.53
Simple cyst	9	2.94±0.74	1.38±0.29	2.17±0.48
Hemangioma	41	1.88±0.50	1.28±0.14	1.47±0.45
FNH	10	1.44±0.39	1.41±0.23	1.02±0.24
MALIGN	34	0.94±0.29	1.21±0.18	0.80±0.20
HCC	23	0.94±0.15	1.22±0.19	0.78±0.13
Metastasis	11	0.95±0.48	1.18±0.17	0.84±0.30

ADC: apparent diffusion coefficient; FNH: focal nodular hyperplasia; HCC: hepatocellular carcinoma

Figure 1. a-c. Boxplots for comparison between benign and malign groups: (a) mass ADC values; (b) adjacent hepatic parenchyma ADC values; (c) ADC ratio

ADC: apparent diffusion coefficient

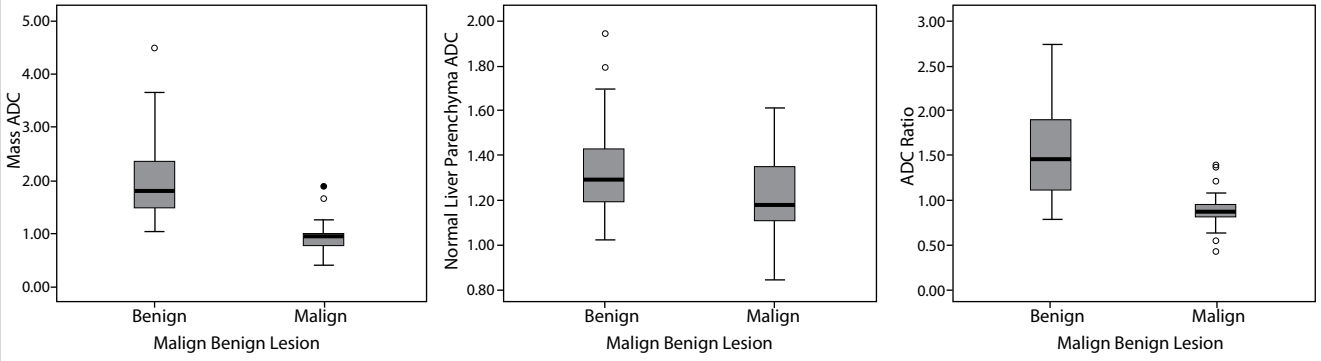


Figure 2. a, b. (a) ROC curve of the mass ADC value; (b) ROC curve of the ADC ratio

ADC: apparent diffusion coefficient

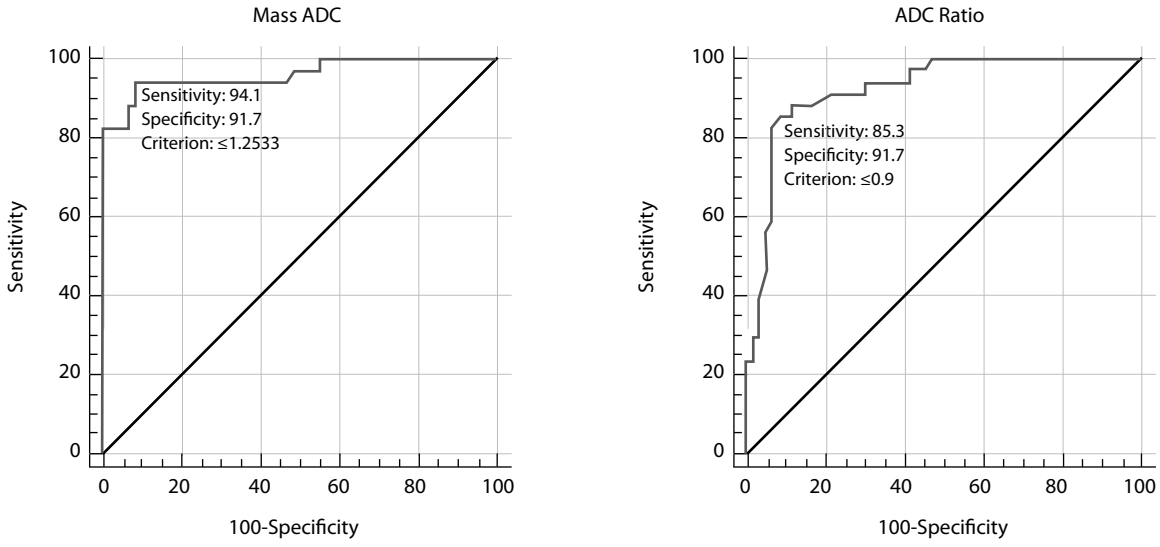


Table 2. Between-group comparison by the type of lesion. ADC measurements of mass and mass/parenchyma ratios showed a significant difference between lesion groups (p=0.001)

	Lesion		
	Malign (n=34)	**Benign (n=60)**	**p**
MASS ADC value	0.94±0.29	1.96±0.68	0.001
Normal parenchymal ADC	1.21±0.18	1.32±0.19	0.007
ADC ratio (mass/parenchyma)	0.80±0.20	1.50±0.53	0.001

ADC: apparent diffusion coefficient

The mean ADC values of adjacent hepatic parenchyma were 1.32±0.19×10^{-3} mm^2/sec for cases with benign lesions and 1.21±0.18×10^{-3} mm^2/sec for cases with malignant lesions (Table 1). The mean ADC values of cirrhotic and normal livers were 1.22±0.19 and 1.29±0.19×10^{-3} mm^2/sec, respectively.

The mean ADC ratios of benign and malignant lesions were 1.50±0.53×10^{-3} mm^2/sec and 0.80±0.20×10^{-3} mm^2/sec, respectively (Table 2) (Figure 1). Differences in the average ADC measurements, parenchymal ADC values, and ADC ratios between benign and malignant lesions were statistically significant (p<0.001) (Table 2).

The ADC values for focal hepatic masses were significant, except for metastasis–HCC, and ADC ratios were significant, except for metastasis–HCC, and metastasis–FNH (Table 3).

Sensitivity and specificity of optimal ADC and ADC ratio cut-off values for characterization of the lesions are shown in Figure

Figure 3. a-h. Hemangioma in the right lobe of the liver in a 36-year-old female patient: (a) shine-through pattern observed in DWI with b=600 s/mm2; (b) no restricted diffusion on the ADC image; (c) typical hyperintensity on T2-weighted axial image; (d) non-contrast; (e) arterial; (f) portal; (g) venous phase (h) late venous phase T1-weighted imaging after injection of contrast agent, showing typical peripheral nodular contrast-enhancement pattern

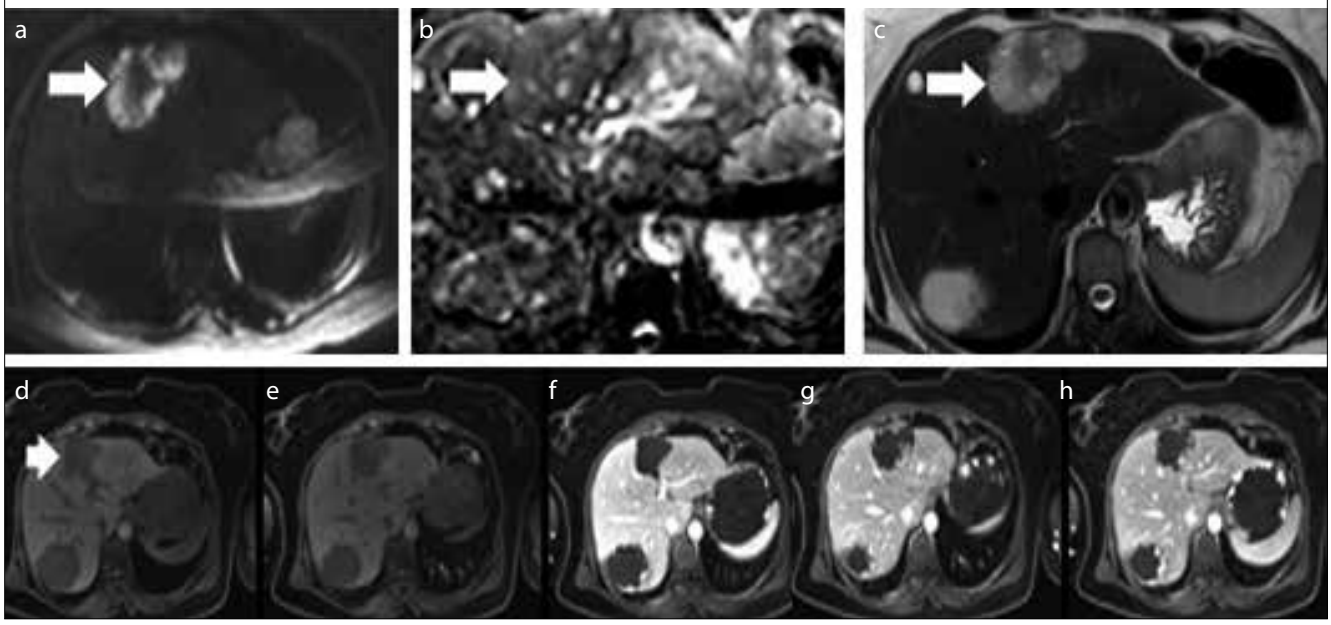
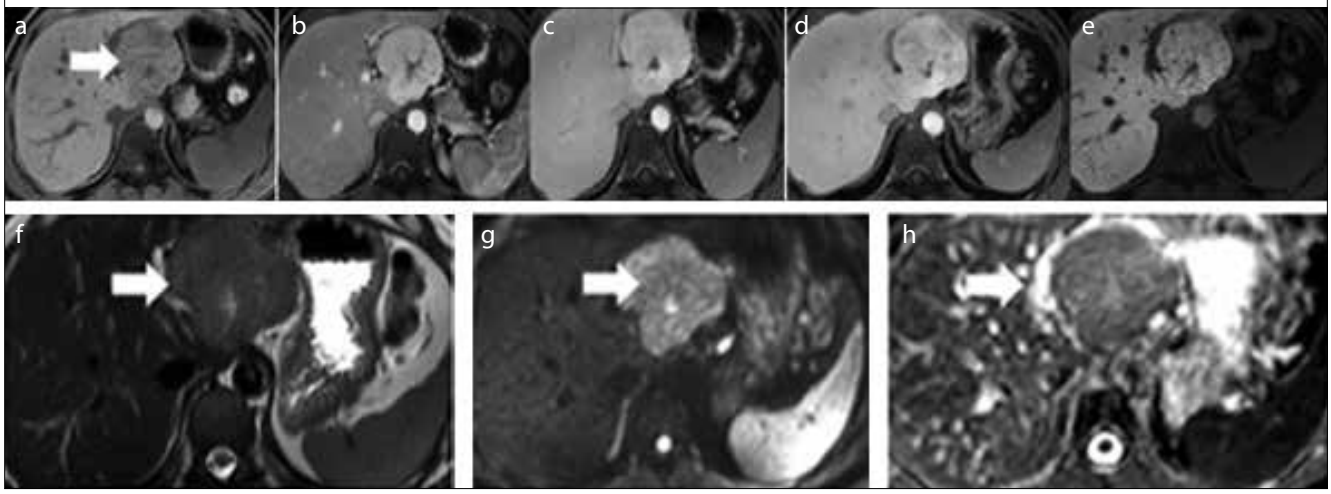


Figure 4. a-h. FNH in the left lobe of the liver of a 30-year-old male patient: (a) non-contrast; (b) arterial T1-weighted image showing marked contrast enhancement; (c) portal venous; (d) hepatic venous; (e) slight hyperintensity in T1-weighted imaging liver-specific phase at 20 minutes after injection of contrast agent; (f) typical central scar on T2-weighted axial image; (g) shine-through pattern on DWI, b=600 sn/mm^2; (h) slight restricted diffusion on the ADC image

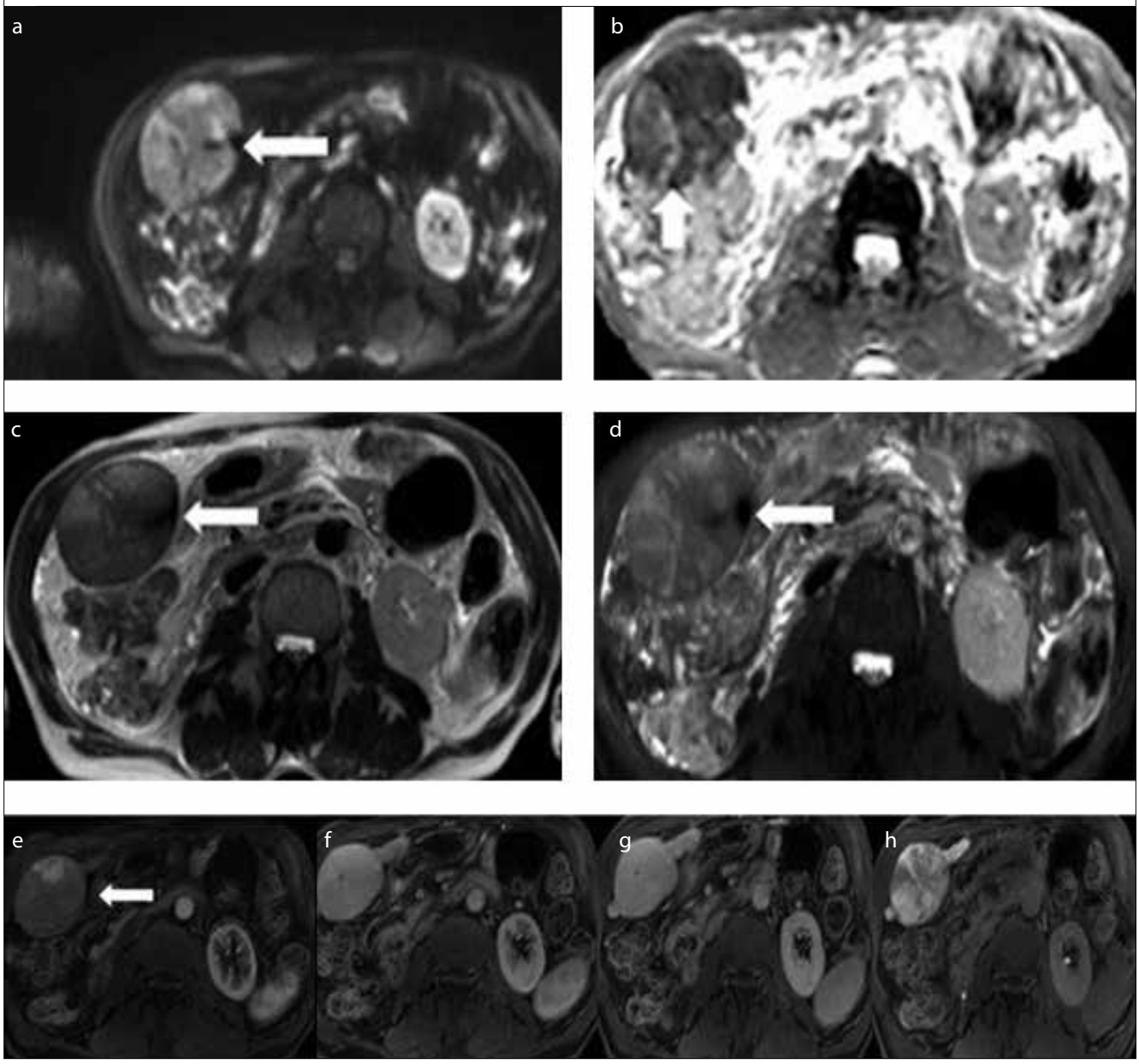


2. Lesions were accurately categorized as benign or malignant when an ADC cut-off value less than or equal to 1.26 was applied, as shown in Figure 2a. Similarly, using an ADC ratio cut-off value ≤0.9 allowed accurate classification of benign and malignant lesions, as shown in Figure 2b.

DISCUSSION

The differential diagnosis of focal hepatic masses is broad, and while most lesions show typical imaging characteristics, differential diagnosis of atypical lesions is challenging, and biopsy is often recommended. DWI has promising results in the characterization of typical lesions. Its advantages include faster acquisition of images compared to routine MR sequences and no requirement for contrast agents (4). DWI should include at least two b values when it is used to examine the abdominal region (low and high b values) (5–8). Benign hepatic lesions with fluid content (hemangioma, cyst, hydatid cyst) appear hyperintense on DWI images and ADC maps, and this pattern is called "T2 shine-through." On the other

Figure 5. a-h. HCC in the left lobe of the liver in a 49-year-old male patient; (a) shine-through pattern on DWI b=600 s/mm2; (b) periferally restricted diffusion on the ADC image; (c, d) slight hyperintensity on T2- and fat-suppressed T2-weigted axial image; (e) non-contrast; (f) arterial; (g) portal; (h) liver-specific phase in T1-weighted imaging after injection of contrast agent on dynamic imaging and hypointensity in liver-specific phase-washout in portal phase



hand, benign solid lesions cannot be differentiated clearly on DWI images with higher b values compared to adjacent liver parenchyma or they appear slightly iso-hyperintense. Malignant hepatic masses (e.g., HCC, metastasis) show restricted diffusion and appear hyperintense on DWI and hypointense on ADC maps (4).

Hemangiomas typically appear hyperintense on a T2-weighted sequence, and contrast enhancement is peripheral and nodular in early phase and usually becomes isointense to the liver in delayed phase (Figure 3). Hemangiomas have slightly lower signal intensities than cysts on ADC maps, and reduced signals are observed with increasing b values in cysts (9, 10). Cysts have significantly higher ADC values and ratios compared to other lesions, and they can be easily differentiated (10). However, some hemangiomas should be evaluated in combination with T2-weighted sequences and contrast-enhanced MRI since there is overlapping with malignant lesions when only the ADC value is used for assessment (9, 10). Similarly, highest ADC values and ratios were observed in cysts in our study, and although there were overlaps in the ADC values of hemangiomas and malignant lesions, they differed statistically significantly from all malignant and benign lesions.

Focal nodular hyperplasia is hyperintense in the arterial phase secondary to hypervascularization, and it does not show washout in portal venous or late venous phases. A typical FNH has a

Figure 6. a-g. Breast carcinoma metastasis in the right lobe of the liver in a 55-year-old female patient: (a) non-contrast; (b) arterial; (c) portal; (d) venous; (e) late venous phase T1-weighted image showing typical circular contrast enhancement on dynamic imaging after contrast injection; (f) shine-through pattern on DWI, b=600 s /mm2; (g) restricted diffusion on the ADC image

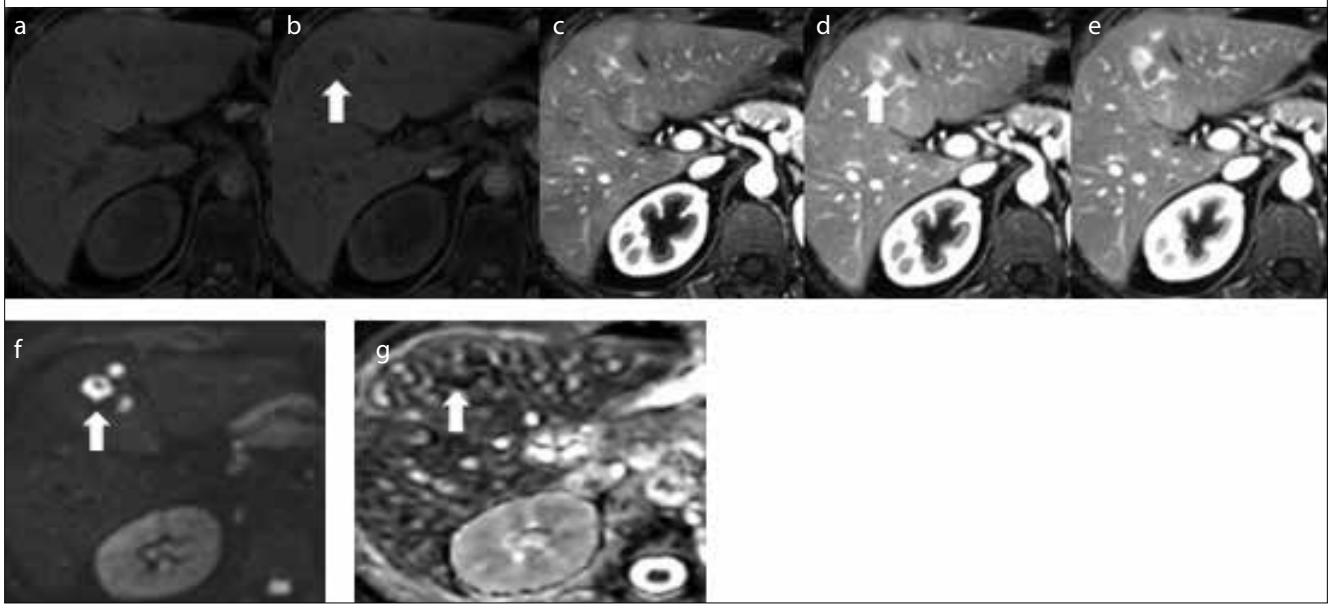


Table 3. Comparisons between lesions. Significant differences were found between lesion groups with respect to ADC values and ADC ratios (p<0.001)

Diagnosis	Type of Diagnosis	p (ADC value)	p (ADC ratio)
Cyst	Hemangioma	.001	.001
	FNH	.001	.001
	HCC	.001	.001
	Metastasis	.001	.001
Hemangioma	FNH	.006	.002
	HCC	.001	.001
	Metastasis	.001	.001
FNH	HCC	.001	.001
	Metastasis	.001	.114
HCC	Metastasis	.561	.424

ADC: apparent diffusion coefficient; FNH: focal nodular hyperplasia; HCC: hepatocellular carcinoma

central scar that is hyperintense on T2-weighted sequence and shows contrast enhancement in late venous phase. Recently, liver-specific contrast agents were introduced and iso-hyperintensity observed in the sequences obtained at least 20 minutes after injection of such a contrast agent contributes significantly to differential diagnosis (Figure 4) (11). Hepatic adenomas are frequently confused with HCC due to their atypical enhancement patterns and washout sign (12). Adenomas are rare lesions, and statistical power could not be achieved in studies due to small number of cases. However, no significant differences were found between the ADC values of FNH and adenomas in a meta-analysis, and as a group, adenomas showed variations in ADC values within different subtypes (10, 13). In our study, adenomas did not contribute to the differential diagnosis due to insufficient number of adenomas and a low ADC value. Considerable overlaps in ADC values were reported between benign solid focal liver masses including FNH and adenoma and malignant lesions (10, 14). Consistent with this finding, no statistically significant difference was found between ADC ratios of FNH and metastases. This lack of difference was considered to be due to heterogeneous nature of metastases. However, there was a statistically significant difference between the ADC values and ratios of FNH and HCC. In differential diagnosis, DWI with ADC mapping provides additional information for discrimination of FNH and HCC lesions.

In a cirrhotic liver, lesions that show contrast enhancement in the arterial phase and washout in the portal or late phase should be considered as HCC until proven otherwise (Figure 5) (15). Metastases are multiple lesions that are hypovascular and usually show peripheral "ring-like" contrast enhancement in arterial and portal phases (Figure 6). Both metastases and HCC are hypointense in hepatobiliary phase following injection of liver-specific contrast material and show restricted diffusion. DWI provides more useful data for liver metastases than for HCC because metastases have low ADC values, and signal can be more clearly observed compared to surrounding liver parenchyma (16). However, since HCC lesions often develop on a cirrhosis background and since cirrhotic hepatic parenchyma shows areas of restricted diffusion, their diagnosis and demonstration of the lesion in an ADC map is more difficult compared to metastases. Similarly, HCC lesions with a cirrhotic background could be less well discriminated by the

ADC mapping in our study. However, there were no statistically significant differences in ADC values and ratios between metastases and HCC. Metastases are a more heterogeneous group and may show lower or higher ADC values than HCC depending on the nature of the primary lesion (hypovascular or hypervascular). In a study on hypovascular and hypervascular metastases, lower ADC values were measured for hypervascular metastases, and higher ADC values were demonstrated for hypovascular metastases (17). We believe that statistically non-significant metastasis-HCC ADC values observed in our study resulted from heterogeneous nature and small sample size of the metastasis group.

Overall, benign hepatic lesions showed higher ADC values compared to malignant lesions, although a variable degree of overlapping was observed (12, 14, 16). Several cut-off values ($1.4–1.6\times10^{-3}$ mm^2/sec) are described for ADC in the literature with a reported sensitivity of 74%–100% and specificity of 77%–100% for the diagnosis of malignant lesions. Significantly high diagnostic accuracy was reported for ADC values and ADC ratios in malignant/benign lesions. Consistently, they showed high sensitivity and specificity in our study. Differential results have been reported in the literature due to the use of different MRI devices, imaging techniques, and b values. Several different cut-off values of the ADC value have been used for discrimination of malignant and benign lesions in studies, which may be explained by differences in calculation, the use of different gradients in MRI devices, and various artifact reduction methods (9). The ADC ratio is used to avoid such variations. In recent years, ADC ratios were shown to have a good diagnostic performance for prostate cancer (18). Studies have demonstrated that ADC ratios could also be used for differentiation of benign and malignant hepatic lesions (19). However, given the age-related variations in ADC values and HCCs that developed in a background of cirrhosis, ADC ratios did not provide additional information for discrimination of benign and malignant lesions beyond that provided by the ADC value in our study. It is our belief that by excluding cirrhotic liver diseases, future studies with age-matched groups may better discriminate metastases and solid/benign lesions using the ADC ratio based on the fact that metastasis is associated with parenchymal changes and systemic manifestations.

CONCLUSION

When added to conventional MRI, the ADC value and ADC ratio assessed on DWI improve the accuracy of MRI in the characterization of benign and malignant lesions. Using the ADC ratio (the ADC value of the lesion/hepatic parenchyma ADC value), higher diagnostic accuracy may be achieved for the discrimination of metastasis and benign solid lesion versus the ADC value by excluding differences in technical parameters.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.
Peer-review: Externally peer-reviewed.

Author Contributions: Concept – F.G.Y., A.E.Y.; Design - F.G.Y., A.E.Y.; Supervision – F.G.Y.; Resources - F.G.Y., A.E.Y.; Materials – A.E.Y.; Data Collection and/or Processing - F.G.Y., A.E.Y.; Analysis and/or Interpretation - F.G.Y., A.E.Y.; Literature Search - F.G.Y., A.E.Y.; Writing Manuscript – F.G.Y.; Critical Review - F.G.Y., A.E.Y.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

REFERENCES

1. Koh D, Collins D. Diffusion Weighted MRI in the Body: Applications and Challenges in Oncology. Am J Roentgenol 2007; 188: 1622-35.
2. Reimer P, Saini S, Hahn PF, Brady TJ, Cohen MS. Clinical application of abominal echoplanar imaging (EPI):optimization using a retrofitted EPI system. J Comput Asist Tomogr 1994; 18: 673-9.
3. Stejskal EO, Taner JE. Spin diffusion measurements: spin-echo in the presence of a time dependent field gradient. J Chem Phys 1965; 42: 288-92.
4. Galea N, Cantisani V, Taouli B. Liver lesion detection and characterization: role of diffusion-weighted imaging. J Magn Reson Imaging 2013; 37: 1260-76.
5. Taouli B, Koh DM. Diffusion-weighted MR imaging of the liver. Radiology 2010; 254: 47-66.
6. Taouli B, Vilgrain V, Dumont E, Daire JL, Fan B, Menu Y. Evaluation of liver diffusion isotropy and characterization of focal hepatic lesions with two single-shot echo-planar MR imaging sequences: prospective study in 66 patients. Radiology 2003; 226: 71-8.
7. Koh DM, Padhani AR. Diffusion-weighted MRI: a new functional clinical technique for tumour imaging. Br J Radiol 2006; 79: 633-5.
8. Papanikolaou N, Gourtsoyianni S, Yarmenitis S, Maris T, Gourtsoyiannis N. Comparison between two-point and four-point methods for quantification of apparent diffusion coefficient of normal liver parenchyma and focal lesions. Value of normalization with spleen. Eur J Radiol 2010; 73: 305-9.
9. Goshima S, Kanematsu M, Kondo H, Yokoyama R, Kajita K, Tsuge Y, et al. Diffusion-weighted imaging of the liver: optimizing b value for the detection and characterization of benign and malignant hepatic lesions. J Magn Reson Imaging 2008; 28: 691-7.
10. Chen ZG, Xu L, Zhang SW, Huang Y, Pan RH. Lesion discrimination with breath-hold hepatic diffusion-weighted imaging: a meta-analysis. World J Gastroenterol 2015; 21: 1621-7.
11. Zech CJ, Grazioli L, Breuer J, Reiser M, Schoenberg SO. Diagnostic performance and description of morphological features of focal nodular hyperplasia in Gd-EOB-DTPA-enhanced liver magnetic resonance imaging: results of a multicenter trial. Investig Radiol 2008; 43: 504-11.
12. Sandrasegaran K, Akisik FM, Lin C, Tahir B, Rajan J, Aisen AM. The value of diffusion-weighted imaging in characterizing focal liver masses. Acad Radiol 2009; 16: 1208-14.
13. Hennedige TP, Hallinan JT, Leung FP, Teo LL, Iyer S, Wang G, et al. Comparison of magnetic resonance elastography and diffusion-weighted imaging for differentiating benign and malignant liver lesions. Eur Radiol 2016; 26: 398-406.
14. Wei C, Tan J, Xu L, Juan L, Zhang SW, Wang L, et al. Differential diagnosis between hepatic metastases and benign focal lesions using DWI with parallel acquisition technique: a meta-analysis. Tumour Biol 2015; 36: 983-90.
15. Bruix J, Sherman M. American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020-2.

16. Kanematsu M, Goshima S, Watanabe H, Kondo H, Kawada H, Noda Y, et al. Detection and characterization of focal hepatic lesions with diffusion-weighted MR imaging: a pictorial review. Abdom Imaging 2013; 38: 297-308.
17. Schmid-Tannwald C, Thomas S, Ivancevic MK, Dahi F, Rist C, Sethi I, et al. Diffusion-weighted MRI of metastatic liver lesions: is there a difference between hypervascular and hypovascular metastases? Acta Radiol 2014; 55: 515-23.
18. Lebovici A, Sfrangeu SA, Feier D, Caraiani C, Lucan C, Suciu M, et al. Evaluation of the normal- to-diseased apparent diffusion coefficient ratio as an indicator of prostate cancer aggressiveness. BMC Med Imaging 2014; 14: 15.
19. Caraiani C, Chiorean L, Fenesan DI, Lebovici A, Feier D, Gersak M. Diffusion Weighted Magnetic Resonance Imaging for the Classification of Focal Liver Lesions as Benign or Malignant. J Gastrointestin Liver Dis 2015; 24: 309-17.

How to cite:

Gelebek Yılmaz F, Yıldırım AE. Relative Contribution of Apparent Diffusion Coefficient (ADC) Values and ADC Ratios of Focal Hepatic Lesions in the Characterization of Benign and Malignant Lesions. Eur J Ther 2018; 24(3): 150–7.

European Journal of Therapeutics

DOI: 10.5152/EurJTher.2018.445

Original Research

Effect of Combined Use of Photon-Initiated Photoacoustic Streaming and Chitosan on Smear Layer Removal

Fatih Sarı[1], Samet Tosun[2], Fatih Aksoy[3], Zübeyde Gündoğar Uçar[4]

[1]Department of Prosthodontics, Gaziantep University, Faculty of Dentistry, Gaziantep, Turkey

[2]Department of Endodontics, Pamukkale University, Faculty of Dentistry, Denizli, Turkey

[3]Department of Endodontics Adıyaman University, Faculty of Dentistry, Adıyaman, Turkey

[4]Department of Pedodontics, Gaziantep University, Faculty of Dentistry, Gaziantep, Turkey

ABSTRACT

Objective: Ethylene diamine tetraacetic acid (EDTA) is an appropriate irrigant for smear removal. This study aims to compare the smear-removing capacity of chitosan in combination with photon-initiated photoacoustic streaming (PIPS) to that of EDTA.

Methods: Forty-five human mandibular premolar teeth were included. Root canals were prepared with OneShape files. The samples were randomly divided into three equal groups. The final rinsing was done as follows. Group 1: 0.2% chitosan irrigation with PIPS irradiation; Group 2: 0.2% chitosan alone; and Group 3: 17% EDTA. All the roots were longitudinally split into two halves and examined under SEM to assess the remaining smear. A statistical analysis was performed using the Kruskal-Wallis test.

Results: In the overall evaluation, the remaining smear was significantly less for group 1 as compared to the other groups ($p<0.05$). In groups 2 and 3, the remaining smear significantly increased in the apical one-thirds, while in Group 1, the remaining smear was significantly less than the apical one-thirds of the other groups ($p<0.05$).

Conclusion: Photon-initiated photoacoustic streaming combined with 0.2% chitosan improved the removal of smear layers.

Keywords: Photon-initiated photoacoustic streaming, chitosan, ethylene diamine tetraacetic acid, scanning electron microscopy, smear layer

INTRODUCTION

The removal of smear layers during root canals is strongly recommended due to the presence of bacteria and tissue remnants in these layers (1, 2). The smear layer also reduces the penetration of irrigants, medicaments, and sealers into dentinal tubules (3, 4). There are various chemicals, including ethylene diamine tetraacetic acid (EDTA), citric acid, acetic acid, and, more recently, chitosan, that have been used to remove smear layers (5, 6). Furthermore, laser systems such as erbium-doped yttrium aluminum garnet (Er:YAG) and erbium, chromium-doped yttrium, scandium, gallium, and garnet laser (Er,Cr:YSGG) lasers are other contemporary options for the removal of smear layers.

Studies involving this subject have revealed that cleaning of the apical third is more challenging as compared to the other portions of root canals, and residual smear scores following treatment protocols increase from the coronal part toward the apical region (2, 7, 8). In order to increase the effect of irrigation solutions, particularly in the apical region and isthmuses, different systems including ultrasonic activation (2, 5), erbium-family lasers (8, 9), and photon-initiated photoacoustic streaming (PIPS) (10) have been employed. A PIPS system comprises an Er:YAG laser equipped with a specially designed tip. In this technique, the chelators and irrigants are agitated in the root canals, which enhances the antibacterial and/or chelation potential of these solutions (11).

Chitosan is obtained from the shells of shellfish (12). It is biocompatible and it has low cost and no toxicity (6, 13). Its superiority in terms of smear removal (6) and its antibacterial effects (14, 15) have been proven in earlier studies. Furthermore, chitosan improves the effects of different medicaments, pastes, and chemicals (15-17). However, in literature, information regarding the combined use of chitosan and PIPS is insufficient. Therefore, the present study aims to compare the smear removal potential of chitosan in the presence and absence of PIPS and to compare these results with EDTA. In addition, we also aimed to determine whether the PIPS technique can improve the smear removing potential of chitosan, particularly in the apical one-third of the root canals. The null hypothesis reveals that there is no difference among EDTA, chitosan, and chitosan + PIPS in both general and partial (coronal, middle apical) evaluations.

ORCID IDs of the authors: F.S. 0000-0002-4818-8562; S.T. 0000-0001-5073-2013; F.A. 0000-0002-2782-2608; Z.G.U. 0000-0002-3402-5332.

Corresponding Author: Fatih Sarı **E-mail:** fatihsa00@hotmail.com

Received: 20.02.2018 • **Accepted:** 09.04.2018

METHODS

Sample Preparation

A total of 45 sound human mandibular premolars chosen from a collection of teeth that had been extracted for periodontal or orthodontic reasons were included in the present study with the approval of the Ethics Committee Commission of Gaziantep University dated/numbered 12.01.2015/2015-3. This study is an ex vivo study and does not include human participants. Thus, no consent form was required. The teeth were randomly collected following the tooth extraction procedure of a patient who attended the clinic at the Gaziantep University, Faculty of Dentistry, Department of Oral and Maxillofacial Surgery. The study samples were radiographically controlled as they had single straight canals. The teeth with any abnormalities, such as immature apexes, calcification, cracks, or resorption, were not included in this study. The teeth were stored in 5.25% NaOCl solution for disinfection. Following the cleaning of the root surfaces of any soft tissue remnants with ultrasonic scalers, the teeth were stored in distilled water at 4°C until used. The crowns of the teeth were separated with a water-cooled diamond fissure bur, and a 13-mm root was obtained.

Root Canal Instrumentation Procedures

Working length assignment was attained by inserting a size 15 K-file until it was visible at the apex and subtracting 1 mm from this working length. Then, the root canals of the teeth were prepared with 0.06-tapered, size-25 OneShape files (Micro-Mega, Besançon, France) mounted onto an endodontic motor (VDW Reciproc, Munich, Germany) using the settings for OneShape recommended by the manufacturer (400 rpm; 2.5 N·cm). During the instrumentation process, the root canals were irrigated with 1% NaOCl: when pressure was detected, the progress of the file was stopped. The instrumentation process continued until the working length was achieved. After the completion of the canal preparation procedures, the canals were irrigated again with 1% NaOCl and dried using absorbent paper points.

Final Rinsing Protocols

The samples were randomly divided into 3 study groups, each including 15 teeth according to the final irrigation protocol.

Group 1: Chitosan solution was prepared as follows: 0.2 mg chitosan powder (Aldrich Chemistry, St. Louis, USA) was added into 100 mL 1% acetic acid and mixed under magnetic stirring at room temperature for 2 h. An Er:YAG laser with a wavelength of 2940 nm (AT Fidelis, Fotona, Ljubljana, Slovenia) was used with a special quartz tip used for PIPS (14 mm long, 300 µm diameter) (Preciso 300/14, Fotona, Ljubljana, Slovenia). The parameters of the Er:YAG laser were set as follows: 1 W, 20 Hz, and 50 mj per pulse. The water and air systems were turned off. The laser tip was placed into the canal orifice and an irrigation needle was inserted into the root canal, positioned superior to the laser tip. In the course of the irrigation process, the laser was activated for 5 s. Thus, simultaneous irrigation with chitosan solution and irradiation with PIPS was performed. This application was repeated 5 times following a 5-s break for each cycle. Therefore, simultaneous irradiation and irrigation was applied for a total of 25 s. The canals were rinsed with distilled water and dried with a paper point.

Group 2: Each root canal was slightly rinsed with 5 mL chitosan solution for 3 min. The canals were irrigated with deionized water and dried with a paper point.

Group 3: Each root canal was rinsed with 5 mL 17% EDTA (Imicryl, Konya, Turkey) solution for 3 min. The canals were irrigated with deionized water and dried with a paper point.

Sectioning and SEM Analyses

For the SEM analysis, all the roots were longitudinally separated into 2 halves (30 halves were obtained for each group). A diamond disk was used to prepare longitudinal grooves at the buccal and lingual sides of the roots: care was taken to not penetrate into the canals. The roots were split into two halves with a chisel. All the root halves were overlaid with gold and examined under SEM (magnification: 2000×). The images were taken from the 2nd, 7th, and 11th millimeter distances to the apices for the smear evaluations of the apical, middle, and coronal one-thirds, respectively (Figure 1). The smear amount was scored according to the criteria described by Hulsmann (18):

1: free of smear: all the dentin tubules are open.

2: small amount of smear: most of the dentin tubules are open.

3: nearly half the surface is coated with smear: half of the tubules are open.

4: large amount of smear: only a few tubules are open.

5: surface is totally coated with smear: no visible open tubule is present.

Statistical Analysis

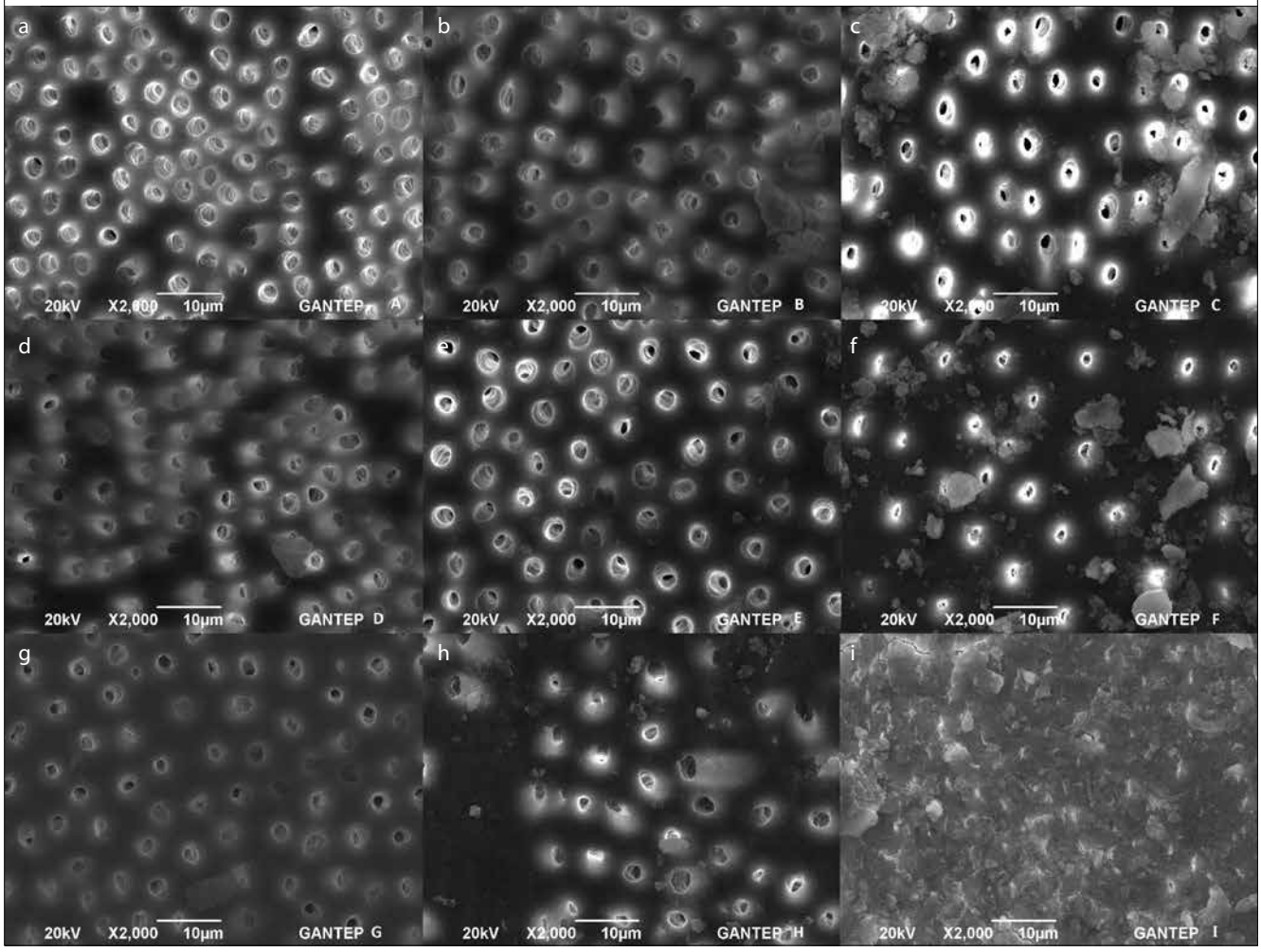
The smear scores for each group were recorded and statistically analyzed both in general and for the apical, middle, and coronal

Table 1. Mean smear score values for the groups and their standard deviations

	Coronal	Middle	Apical	Total
Group 1	$1.80\pm0.67^{A,a}$	$2.13\pm0.63^{A,a}$	$2.47\pm0.74^{A,a}$	2.13 ± 0.72^{A}
Group 2	$1.93\pm0.70^{A,a}$	$2.20\pm0.41^{A,a}$	$4.33\pm0.48^{B,b}$	2.82 ± 1.21^{B}
Group 3	$2.00\pm0.75^{A,a}$	$2.33\pm0.48^{A,a}$	$4.40\pm0.50^{B,b}$	2.91 ± 1.22^{B}

$^{A, B}$: Different uppercase letters (column) represent the statistically different groups. $^{a, b}$: Different lowercase letters (row) represent the statistically different groups

Figure 1. a-i. SEM images of the specimens (2000×). Surfaces: (a-c) Group 1: coronal, middle, and apical, respectively. (d-f) Group 2: coronal, middle, and apical, respectively. (g-i) Group 3: coronal, middle, and apical, respectively



one-thirds. The Kruskal-Wallis test was used to perform statistical analysis and the significance was set to 0.05.

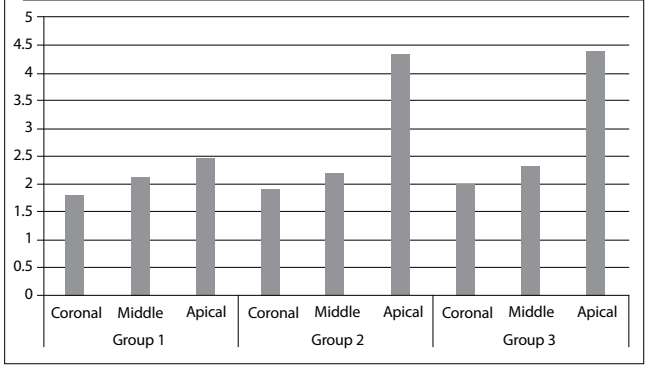
RESULTS

The mean smear scores and standard deviations (SD) are listed in Table 1 and shown in Figure 2. In the overall evaluation, group 1 (chitosan + PIPS) revealed significantly less smear scores as compared to the other groups ($p<0.05$). Groups 2 and 3 were statistically similar ($p>0.05$). In the partial evaluations, the smear scores significantly increased in the apical one-thirds as compared to the middle and coronal one-thirds ($p<0.05$), except for group 1. The apical one-third of group 1 exhibited a similar amount of smear as compared to the middle and coronal parts ($p>0.05$) and lesser amount of smear as compared to the apical one-thirds of groups 2 and 3 ($p<0.05$).

DISCUSSION

The findings did not conform to the first null hypothesis in which the smear removal efficiencies were similar among the different irrigation procedures. The presence of a smear layer in root canals may be considered as a cause of failure because it harbors bacteria and tissue remnants (2) and also reduces the penetration of irrigants, medicaments, and sealers into the dentinal tubules (3, 4). Furthermore, the penetration of resin cements used with fiber posts is interrupted by the presence of smear (5). EDTA is a widely used chemical to remove smear layers by chelating the inorganic component of the root dentin (19), while chitosan is a contemporary material used for this purpose. The optimum concentration and duration for chitosan was reported as 0.2% and 3 min, respectively, by Silva et al. (20). Furthermore, its microhardness-reducing effect—a disadvantage of chelators—is found to be not more than that of EDTA, as discussed by Pimenta et al. (21). For these reasons, 0.2% chitosan was used for 3 min in group 2. Our results are in good agreement with those of Silva et al. (6). They found that EDTA and chitosan have similar smear-removing capacities. Different from EDTA (which is not natural and is considered as a pollutant (22)), chitosan is a natural product. It is biocompatible and has no toxicity (23). It has a low cost and has chelating capacity toward various metallic ions (12). In the study of Silva et al. (6), 0.2% chitosan prepared by the mixing of chitosan powder with 1% acetic acid, as in the present study, was found to be superior to using only 1% acetic acid. Hence, they

Figure 2. Smear scores of coronal, middle, and apical one-thirds of the different groups



concluded that the chelating properties of chitosan should be attributed to chitosan rather than acetic acid. These advantageous properties make chitosan a suitable substitute for EDTA. However, it should be noted that the amount of smear increases from the coronal one-third toward the apical one-third, regardless of the chelator, as stated in the studies of Schmidt et al. (2) and Srirekha et al. (5). This is in accordance with the results of the present study for groups 2 and 3. In these groups, the amount of smear in the apical one-third was significantly higher than the coronal and middle one-thirds. These results are possibly related to the inability of EDTA and chitosan solutions to perfectly reach and affect the apical root dentin.

In order to increase the effects of irrigants and chelators, particularly in the apical portion, laser systems have been used in recent years (7). Guidotti et al. (8) revealed that Er:YAG laser irradiation with EDTA is effective in terms of smear removal even in the apical one-third. This is also verified by the study of Murugesan et al. (9), where it was found that an Er,Cr:YSGG laser increased the smear-removing capacity of EDTA in curved canals. One of these systems is PIPS, which constitutes an Er:YAG laser equipped with a special, radial tip. In the study of DiVito et al. (24), the smear-removing capacity of EDTA increased when used in combination with PIPS. The results of the present study revealed that a chitosan solution could remove smear similar to EDTA in 3 min. However, both these solutions remained inadequate for reaching the apical one-third. When used in combination with PIPS, chitosan effectively removed smear, particularly in the apical one-third. Thus, the null hypothesis was rejected. Olivi and DiVito (11) reported that PIPS strongly agitates the intra-canal irrigants and generates faster streaming of these fluids distant to the source. This mechanism explains why the apical one-third of group 1 yielded significantly less smear scores as compared to the apical parts of the other groups.

In this study, the root canals were prepared to an apical size of 25 with a 0.06 tapered instrument. It is noteworthy that preparing root canals to larger diameters may overcome the limitation of solutions by facilitating solutions to reach more areas. The disparity in the results of the present study and the study of Silva et al. (6) who found chitosan effective in both the middle and apical one-thirds may be related to the larger apical preparation size in that study. However, in the PIPS group of the present study, the smear layer in the apical portion was also effectively removed. Hence, it can be concluded that the streaming effect of PIPS mentioned above does not depend on the size of the preparation.

Teixeira et al. (25) and Lui et al. (26) found that EDTA is more capable of removing the smear layer in cases of its use in combination with 1% NaOCl. For this reason, 1% NaOCl was used during canal preparation before final rinsing in the present study.

In the study of Akcay et al. (27), an EDTA solution was refreshed when the coronal reservoir decreased during irradiation with PIPS, while in the study of DiVito et al. (24), continuous irrigation was simultaneously performed with PIPS irradiation. However, during PIPS irradiation, an accurate observation of the level of intra-canal fluids may not be possible. For this reason, we preferred to continuously irrigate the root canals during PIPS irradiation in order to maintain the irrigants at a constant level.

The present study is aimed to investigate the effectiveness of smear removal after different final rinsing protocols. Further studies are needed to examine the effect of different laser parameters and bond strength of resin cements.

CONCLUSION

Within the limitations of the present study, the following can be advised:

1) Chitosan can be used as the final irrigant, instead of EDTA, to effectively remove the smear layer at a concentration of 0.2% for 3 min.
2) Using PIPS with chitosan enhances the effect of chitosan in terms of smear removal, particularly in the apical one-third and considerably reduces the time required to obtain the expected results related to chitosan.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University (Date: 12.01.2015, Number: 2015-3).

Informed Consent: Informed consent was not obtained from patients due to this study is an ex vivo study and does not include human participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – F.S., S.T.; Design – F.S., Z.G.U.; Supervision – F.S.; Materials – F.S., S.T.; Data Collection and/or Processing – F.S., S.T., F.A., Z.G.U.; Analysis and/or Interpretation – F.S., S.T., F.A., Z.G.U.; Literature Search – F.S., F.A.; Writing Manuscript – F.S., Z.G.U.; Critical Review – F.S.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

REFERENCES

1. McComb D, Smith DC. A preliminary scanning electron microscopic study of root canals after endodontic procedures. J Endod 1975; 1: 238-42.

2. Schmidt TF, Teixeira CS, Felippe MC, Felippe WT, Pashley DH, Bortoluzzi DA. Effect of ultrasonic activation of irrigants on smear layer removal. J Endod 2015; 41: 1359-63.
3. Orstavik D, Haapasalo M. Disinfection by endodontic irrigants and dressings of experimentally infected dentinal tubules. Endod Dent Traumatol 1990; 6: 142-9.
4. Oksan T, Aktener BO, Sen BH, Tezel H. The penetration of root canal sealers into dentinal tubules. A scanning electron microscopic study. Int Endod J 1993; 26: 301-5.
5. Srirekha A, Rashmi K, Hegde J, Lekha S, Rupali K, Reshmi G. An in vitro evaluation of passive ultrasonic agitation of different irrigants on smear layer removal after post space preparation: a scanning electron microscopic study. J Indian Prosthodont Soc 2013; 13: 240-6.
6. Silva PV, Guedes DF, Nakadi FV, Pécora JD, Cruz-Filho AM. Chitosan: a new solution for removal of smear layer after root canal instrumentation. Int Endod J 2013; 46: 332-8.
7. De Moor RJ, Meire M, Goharkhay K, Moritz A, Vanobbergen J. Efficacy of ultrasonic versus laser-activated irrigation to remove artificially placed dentin debris plugs. J Endod 2010; 36: 1580-3.
8. Guidotti R, Merigo E, Fornaini C, Moritz A, Vanobbergen J. Er:YAG 2,940-nm laser fiber in endodontic treatment: a help in removing smear layer. Lasers Med Sci 2014; 29: 69-75.
9. Murugesan MS, Rajasekaran M, Indra R, Suganthan P. Efficacy of Er, Cr: YSGG Laser with Conical Tip Design in Smear Layer Removal at the Apical Third of Curved Root Canals. Int J Las Dent 2013; 3: 55-9.
10. Peters OA, Bardsley S, Fong J, Pandher G, Divito E. Disinfection of root canals with photon-initiated photoacoustic streaming. J Endod 2011; 37: 1008-12.
11. Olivi G, DiVito E. Photoacoustic endodontics using PIPS™: experimental background and clinical protocol. J Laser Health Acad 2012; 1: 22-5.
12. Kurita K. Chemistry and application of chitin and chitosan. Polymer Degradation and stability 1998; 59: 117-20.
13. Senel S, Kas H, Squier CA. Application of chitosan in dental drug delivery and therapy. Chitosan per os: from dietary supplement to drug carrier Grottammare: Atec 2000; 241-56.
14. Del Carpio-Perochena A, Bramante CM, Duarte MA, de Moura ME, Aouada FA, Kishen A. Chelating and antibacterial properties of chitosan nanoparticles on dentin. Restor Dent Endod 2015; 40: 195-201.
15. Del Carpio-Perochena A, Kishen A, Shrestha A, Bramante CM. Antibacterial Properties Associated with Chitosan Nanoparticle Treatment on Root Dentin and 2 Types of Endodontic Sealers. J Endod 2015; 41: 1353-8.
16. Barreras US, Mendez FT, Martinez RE, Valencia CS, Rodriquez PR, Rodriquez JP. Chitosan nanoparticles enhance the antibacterial activity of chlorhexidine in collagen membranes used for periapical guided tissue regeneration. Mater Sci Eng C Mater Biol Appl 2016; 58: 1182-7.
17. Shaik J, Garlapati R, Nagesh B, Sujana V, Jayprakash T, Naidu S. Comparative evaluation of antimicrobial efficacy of triple antibiotic paste and calcium hydroxide using chitosan as carrier against Candida albicans and Enterococcus faecalis: An in vitro study. J Conserv Dent 2014; 17: 335-9.
18. Hulsmann M, Rummelin C, Schafers F. Root canal cleanliness after preparation with different endodontic handpieces and hand instruments: a comparative SEM investigation. J Endod 1997; 23: 301-6.
19. Marques AA, Marchesan MA, Sousa-Filho CB, Silva-Souza YT, Souza-Neto MD, Cruz-Filho AM. Smear layer removal and chelated calcium ion quantification of three irrigating solutions. Braz Dent J 2006; 17: 306-9.
20. Silva PV, Guedes DF, Pecora JD, da Cruz-Filho AM. Time-dependent effects of chitosan on dentin structures. Braz Dent J 2012; 23: 357-61.
21. Pimenta JA, Zaparolli D, Pecora JD, Cruz-Filho AM. Chitosan: effect of a new chelating agent on the microhardness of root dentin. Braz Dent J 2012; 23: 212-7.
22. Spano JC, Silva RG, Guedes DF, Souza-Neto MD, Estrela C, Pécora JD. Atomic absorption spectrometry and scanning electron microscopy evaluation of concentration of calcium ions and smear layer removal with root canal chelators. J Endod 2009; 35: 727-30.
23. Akıncıbay H, Senel S, Ay ZY. Application of chitosan gel in the treatment of chronic periodontitis. J Biomed Mater Res B Appl Biomater 2007; 80: 290-6.
24. DiVito EE, Colonna MP, Olivi G. The photoacoustic efficacy of an Er: YAG laser with radial and stripped tips on root canal dentin walls: an SEM evaluation. J Laser Dent 2011; 19: 156-61.
25. Teixeira CS, Felippe MC, Felippe WT. The effect of application time of EDTA and NaOCl on intracanal smear layer removal: an SEM analysis Int Endod J 2005; 38: 285-90.
26. Lui JN, Kuah HG, Chen NN. Effect of EDTA with and without surfactants or ultrasonics on removal of smear layer. J Endod 2007; 33: 472-5.
27. Akcay M, Arslan H, Mese M, Sahin NN. The effect of photon-initiated photoacoustic streaming, ultrasonically and sonically irrigation techniques on the push-out bond strength of a resin sealer to the root dentin. Clin Oral Investig 2015; 19: 1055-61.

How to cite:

Sarı F, Tosun S, Aksoy F, Gündoğar Uçar Z. Effect of Combined Use of Photon–Initiated Photoacoustic Streaming and Chitosan on Smear Layer Removal. Eur J Ther 2018; 24(3): 158–62.

European Journal of Therapeutics

DOI: 10.5152/EurJTher.2018.479

Original Research

Use of Methyl Methacrylate for Small and Large Cranial Defects: A Single Institute Experience

Ziya Asan

Department of Neurosurgery, Ahi Evran University, School of Medicine, Kırşehir, Turkey

ABSTRACT

Objective: Data obtained from cases wherein methyl methacrylate was used for cranioplasty are discussed along with the literature, and methods for preventing potential complications are presented.

Methods: Records of patients who had been operated for cranioplasty between 2013 and 2017 were retrospectively analyzed. Early and late results of the cases were recorded. Area measurements of cranium defects were performed through computed tomography, scanography, or direct X-ray. The steps considered for preventing known complications are explained, and the results are discussed.

Results: Cranioplasty with methyl methacrylate was administered to areas <10 cm^2 in 29 cases, areas of 10–25 cm^2 in 25 cases, and areas >25 cm^2 in 10 cases. Cranioplasty with methyl methacrylate was performed in the supratentorial area in 57 cases and in the infratentorial area in 7 cases. In 48 cases, partial cranioplasty was performed by administering methyl methacrylate along with autograft to the craniectomy defect. A subcutaneous drain was left for 2–3 days in all cases. During this period, dual antibiotherapy was administered. Symptoms of infection were not encountered in any case. No clinical symptoms associated with cranioplasty material were discovered in the late follow-up period.

Conclusion: When methyl methacrylate is applied with appropriate methods and necessary precautions are taken, it proves as an inexpensive and effective cranioplasty material that can successfully be applied in large cranial defects, which reduces the risk of infection. This inexpensive material can be applied to repair partial craniotomy flap deformities to achieve better cosmetic outcomes.

Keywords: Cranioplasty, methyl methacrylate, calvarium, cranium, cosmetic

INTRODUCTION

In cases wherein cranial defects occur after neurological surgery, cranioplasty is performed for the conservation of the brain parenchyma and for aesthetic reasons (1, 2). Although the use of autologous bone for cranioplasty is the first choice for all neurosurgeons, cranioplasty materials made from synthetic or organic preparations can also be used. Multi-part and infected bone fractures cannot be used for cranioplasty. In this case, the bone fractures are too deformed, and it would be impossible to bring them together. Cranioplasty materials are also preferred due to ease of use in these situations (1, 3-7).

Cranioplasty materials should be tissue-compatible and easy to apply. They should not be easily infected. Unfortunately, it is predicted that none of the cranioplasty materials are as capable as autologous grafts. Various studies showed that these materials may result in graft rejection, parenchymal defects, and infection in the early or late period (8-12).

Methyl methacrylate (MM) is currently one of the most frequently used cranioplasty materials. It possesses advantages such as being easily developed and taking on the desired shape. However, it also has some disadvantages as it emits heat to the environment during its application. Additionally, it can be easily infected during the postoperative period.

In this study, the early and late results and advantages and disadvantages of MM that was used in 64 patients with calvarial defects have been discussed. Additionally, the cases wherein MM was used for cranioplasty have been presented along with comparisons with literature data.

METHODS

Records of patients who had been operated for cranioplasty between 2013 and 2017 were retrospectively analyzed. Age, sex, indications for craniectomy and cranioplasty, and follow-up period were recorded. Area measurements of the cranium defect were performed through scanography or direct X-rays obtained from the PACS software (Figures 1, 2). Localizations of cranioplasty areas were recorded. Herein, the methods to prevent known complications are explained, and the results are discussed.

Surgical Method

After the primary surgical intervention was performed and the dura was covered, the cranioplasty phase started. MM was applied to the craniectomy defect and shaped. Care was taken to

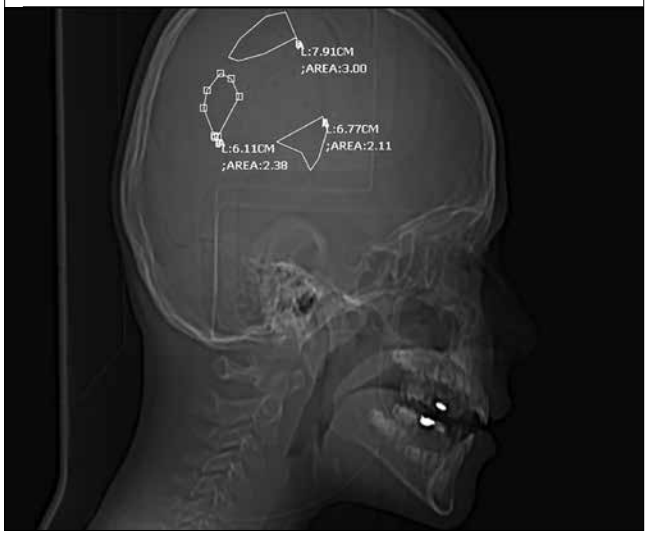
ORCID ID of the author: Z.A. 0000-0001-8468-9156.

Corresponding Author: Ziya Asan **E-mail:** ziyaasan@gmail.com

Received: 10.02.2018 • **Accepted:** 08.04.2018

Figure 1. Multi-part craniectomy defects

Figure 2. Measurements of cranioplasty areas



ensure that no dead spaces would remain in the epidural area under the cranioplasty material. Therefore, it did not matter if the cranioplasty material lacked uniform thickness over the entire region (Figures 3, 4). Later on, the MM was shaped, but suture holes were not opened to fix the cranioplasty flap (Figure 5). Edges were converted into a groove and were ensured to hold onto the cranium to attach the flap. The material was cooled by cold physiological saline solution and continuous spraying for approximately 10–15 minutes to ensure that the heat emitted after MM was administered would not damage the brain parenchyma. Later on, when the heat reaction was completed, a negative-pressure hemovac, minivac, or Jacksonian drain was placed on the cranioplasty flap, and the skin flap was sutured.

Informed consent was not required due to the retrospective nature of the study. Ethics committee approval was received for this study from Ahi Evran University Clinical Research Ethic Committee (Aprroval Date: 30.01.2018; Approval No: 2018-02/20).

Figure 3. Cranioplasty material applied to the dural surface and was not affected by the different thickness of the flap to prevent dead space

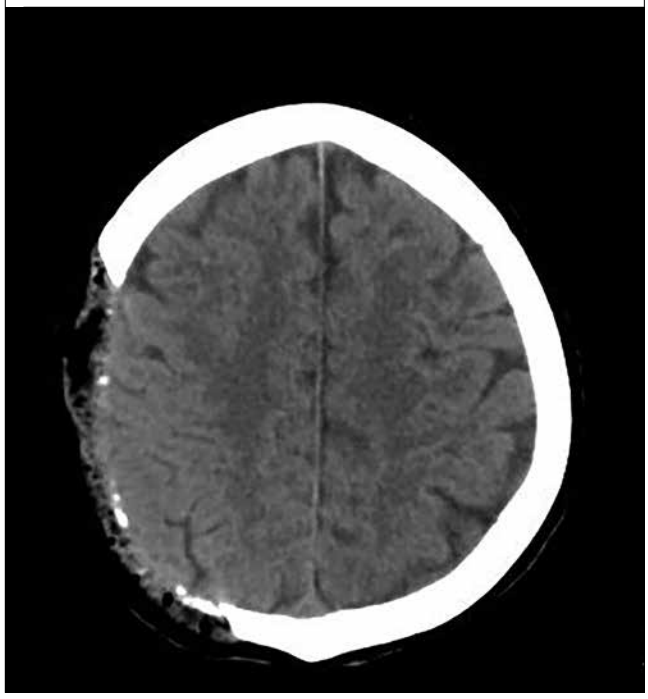
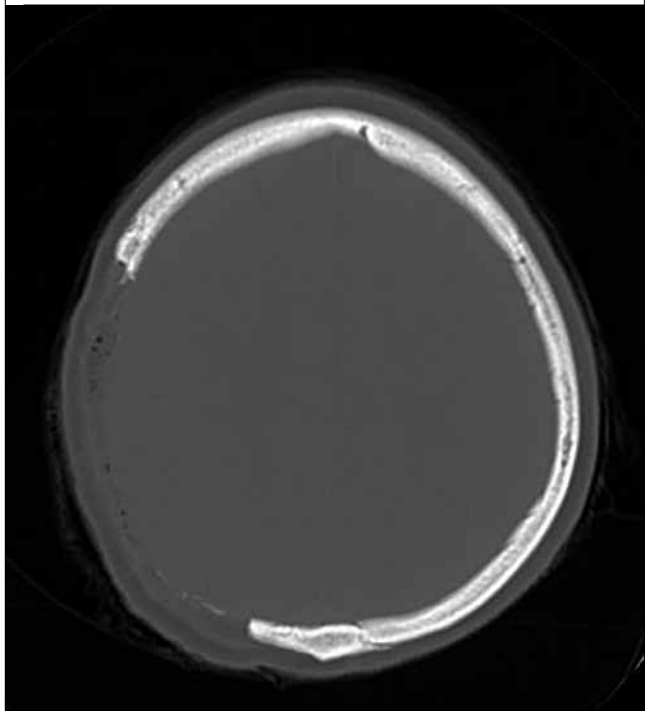


Figure 4. Postoperative 1st day of fibrous dysplasia case. Methyl methacrylate shapes do not show a density on computerized tomography



RESULTS

In total, 64 cases were evaluated in the study. The median age of the patients was 42.9 years. Overall, 52 male and 12 female patients were evaluated in the study. Craniectomy was applied

Table 1. Demographic characteristics of the cases, measurements of cranioplasty area, and late follow–up durations

Number of cases	Surgery type	Mean age (years)	Cranioplasty area (cm^2)	Mean follow–up time (months)
48	MPF	39.9	14.3	17.4
4	Decompressive craniectomy	51.7	34.6	19.5
5	Convexity/Calvarial tumor	54.8	24.2	20.5
7	Posterior fossa surgery	50.3	8.2	15.8

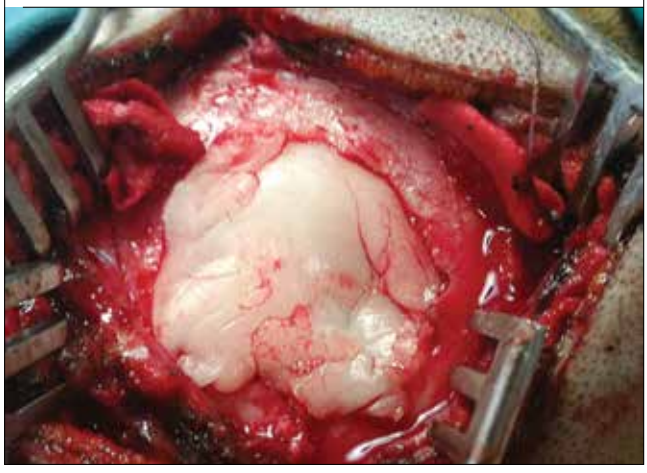
MPF: multi–part fracture

Table 2. Cranioplasty localizations and measurements of craniectomy area (*)

	<10 cm^2	10–25 cm^2	25–50 cm^2
Frontal	12	14	7
Temporal	8	5	0
Parietal	5	3	3
Occipital	4	3	0

*largest cranioplasty area was accepted for cranioplasty localization

Figure 5. Cranioplasty after suboccipital craniectomy. Edges were converted into a groove and were ensured to hold onto the cranium to fix the flap without suturization

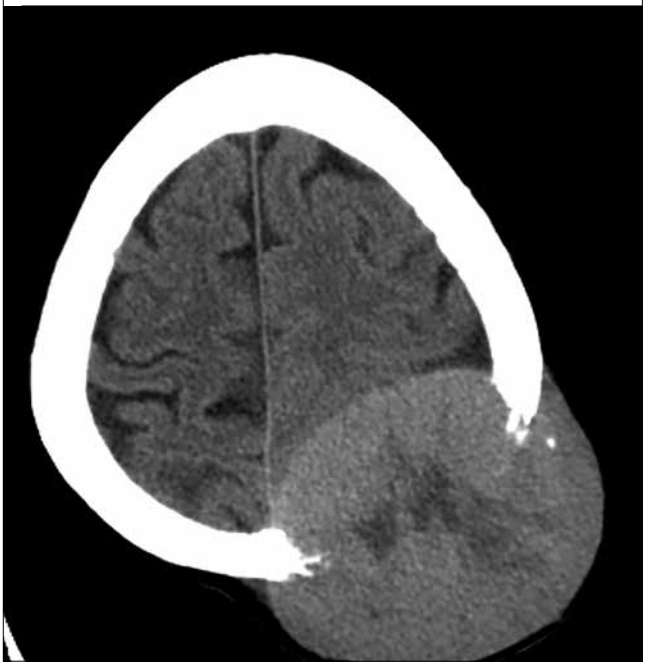


to 48 cases due to multi-part cranial fractures. Further, five cases were operated due to a convexity tumor and seven due to posterior fossa surgery; MM was used for cranioplasty. Cranioplasty was performed in four cases, on an average 85 days after decompressive surgery. Demographic analysis results of the cases are shown in Tables 1 and 2.

No findings of infection were encountered in the early or late period during the postoperative follow-up. Four cases directly died after the primary pathology in the early period during the follow-up.

One patient who had giant follicular carcinoma metastasis causing cranium defect (Figure 6) was re-operated after 15 months

Figure 6. Giant extra-axial metastasis caused large cranium defect in the left parietal region



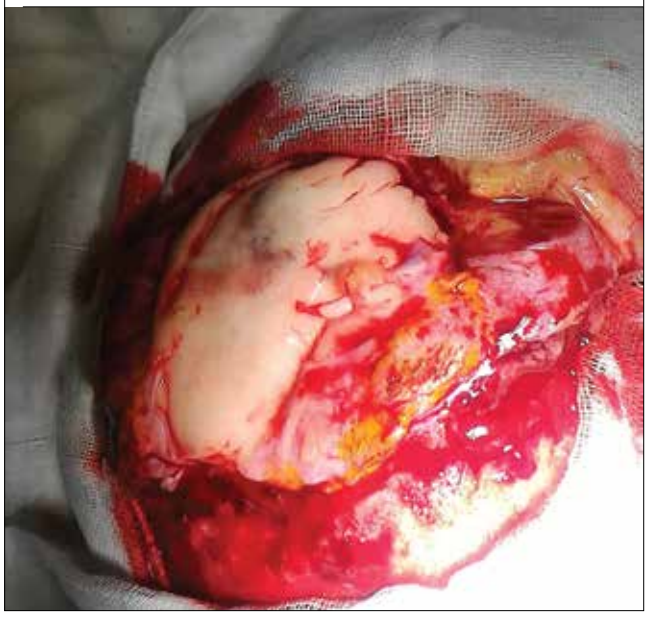
due to recurrence of the tumor (Figure 7). Tumor invasion or destruction was not observed in the cranioplasty material used for cranioplasty in the first operation. Even though the tumor tissue was seen below and over the cranioplasty material, it did not cause macroscopic flap deformation. Because the material had hardened, microscopic examination could not be performed (Figure 8). Cranioplasty was performed in the same region again with MM (Figure 9).

DISCUSSION

There are various studies in the literature about the use of MM for cranioplasty. It has been reported that the most frequent complication was an infection, and it was encountered at rates of 3.8%–14% in different series (13, 14). It was concluded that microorganisms that are frequently seen could not grow following appropriate antibiotherapy; after MM, bioactive glass and bioactive ceramic materials used for cranioplasty were left in bacterial cultures (15).

Several risk factors have been defined regarding infection encountered following cranioplasty. Factors that have been pre-

Figure 7. Tumor tissue around cranioplasty material. The tumor could not destruct cranioplasty material but could damage other tissues



viously defined include history of cranial operations, diabetes mellitus, long operative time, old age, infection in the area to be operated, and surgical indications. Another risk factor is the placement of subcutaneous drains in the area where cranioplasty material is applied (16).

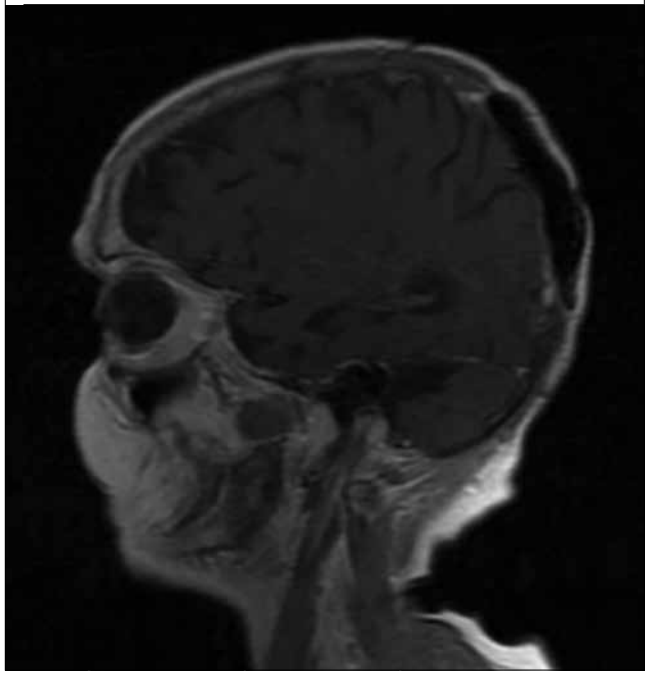
It has been known that MM causes accumulation of a significant amount of fluid under the skin after it is applied. Therefore, negative-pressure drain was left under the skin for a minimum of 2 days. The drain was removed on the 3rd day at the latest. Dual antibiotherapy comprising parenteral cefazolin and gentamicin was sustained for at least 3 days. Antibiotherapies involving three antibiotics, of which one had an anaerobic effect, was continued for 5–7 days in cranioplasty cases with a dirty wound or frontal sinus repair. The non-hemorrhagic serous fluid that filled the drainage was present since the first postoperative day. Pathogenic bacterial growth was not detected in the examinations of the liquid culture obtained from three cases.

Suboccipital craniectomy is a common procedure in posterior fossa surgery. In cases wherein craniotomy is applied, the bone is inserted in place of a flap. It may be more difficult to open the craniotomy flap on the occipital bone due to the curved structure of this area. Therefore, the use of ready-made cranioplasty materials is challenging in cases wherein suboccipital craniectomy is performed. The use of MM in this area for cranioplasty provides convenience to surgeons, and the material can be easily shaped. Hence, MM can be preferred. Furthermore, cerebrospinal fluid fistulas are often encountered after surgery in this region (17). Thus, cranioplasty application after surgery in this region will also be beneficial for protection from cerebrospinal fluid fistulas.

Figure 8. Tumor destruction was not observed in the cranioplasty material and did not macroscopically cause flap deformation

Figure 9. Cranioplasty material on the parietal region is shown at a sagittal section of MRI

MRI: magnetic resonance imaging



Especially following supratentorial surgeries, defects associated with craniectomy performed when craniotomy is not of adequate size, has irregular loss of bone tissue at the borders of craniotomy, and has burr-hole defects may result in noticeable cosmetic problems beneath the scalp. Even in cases wherein there are several defects, their coverage by administering MM leads to better cosmetic results. The combined use of MM during the use of autologous grafts or application of craniotomy flap in the late period for cranioplasty and in the cases of reduction of the flap in size or coverage of other bone defects leads to more favorable cosmetic outcomes.

One of the alternative materials used for cranioplasty is the porous polyethylene implant. The shaping of this material during surgery takes a long time when compared with MM. Although the desired cosmetic results may be achieved when it is applied, dead spaces between the material and brain parenchyma are probable as the material is of the same thickness all over the defect. Presence of dead spaces may lead to infection or bleeding in the form of oozing in the area (18).

It should be noted that in case wherein ready-made cranioplasty materials or MM is administered after being shaped and hardened before application on the dura, they may cause pressure on the brain parenchyma if the lower surface is thick. However, if it is prepared in a more cambered form, it may cause the formation of dead space in the epidural area. Therefore, we believe that it is more reliable to continuously wash MM with cold water immediately after it is prepared and completely solidified to protect it from the heat generated while attaching it to the cranium by making edges groove. We believe that the attachment of cranioplasty flap with auxiliary materials such as sutures or titanium plates will increase the number of foreign bodies in the region and, thus, will provoke the possibility of infection due to tissue reaction.

CONCLUSION

Methyl methacrylate is an easily applicable cranioplasty material, even in wide craniectomy defects. Its shaping after it is administered in the defect site prevents formation of a dead space. It is one of the cost-effective preparations in cases wherein autologous graft cannot be administered.

Ethics Committee Approval: Ethics Committee approval was received for this study from Ahi Evran University Clinical Research Ethics Committee (Approval Date: 30.01.2018; Approval No: 2018-02/20).

Informed Consent: Informed consent was not received due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author has no conflicts of interest to declare.

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

REFERENCES

1. Marchac D, Greensmith A. Long-term experience with methylmethacrylate cranioplasty in craniofacial surgery. J Plast Reconstr Aesthet Surg 2008; 61: 744-52.
2. Andrabi SM, Sarmast AH, Kirmani AR, Bhat AR. Cranioplasty: Indications, procedures, and outcome-An institutional experience. Surg Neurol Int 2017; 8: 91.
3. Aydin S, Kucukyuruk B, Abuzayed B, Aydin S, Sanus GZ. Cranioplasty: Review of materials and techniques. J Neurosci Rural Pract 2011; 2: 162-7.
4. Khader BA, Towler MR. Materials and techniques used in cranioplasty fixation: A Review. Master Sci Eng C Mater Biol Appl 2016; 66: 315-22.
5. Ernst G, Qeadan F, Carlson AP. Subcutaneous bone flap storage after emergency craniectomy: cost-effectiveness and rate of resorption 2018; 5: 1-7.
6. Edwards MS, Outhershout OK. Autogenic skull bone grafts o reconstructed large or complex skull defects in children and adolescent. Neurosurgery 1987; 20: 273-80.
7. Hammon WM, Kempe LG. Methylmetacrylate cranioplasty. Acta Neurochir 1971; 25: 69-77.
8. Kaneshiro Y, Murata K, Yamauchi S, Urano Y. Fatal cerebral swelling immediately after cranioplasty: A case report. Surg Neurol Int 2017; 8: 156.
9. Maugeri R, Giammalva RG, Graziano F, Basile L, Gulì C, Giugno A, et al. Never say never again: A bone graft infection due to a hornet sting, thirty-nine years after cranioplasty. Surg Neurol Int 2017; 8: 189.
10. Ma IT, Symon MR, Bristol RE, Beals SP, Joganic EF, Adelson PD, et al. Outcomes of Titanium Mesh Cranioplasty in Pediatric Patients. J Craniofac Surg 2018; 29: 99-104.
11. Kato A, Morishima H, Nagashima G, Unexpected complications immediately after cranioplasty. Acute Med Surg 2017; 4: 316-21.
12. Frassanito P, Tamburrini G, Massimi L, Peraio S, Caldarelli M, Di Rocco C. Problems of reconstructive cranioplasty after traumatic brain injury in children. Childs Nerv Syst 2017; 33: 1759-68.
13. Han SE, Lim SY, Pyon JK, Mun GH, Bang SI, Oh KS. Aesthetic refinement of secondary cranioplasty using methyl methacrylate bone cements. Aesthetic Plast Surg 2013; 37: 592-600.
14. Ergin N, Kadioglu HH. Kraniyal Kemik Defektlerinin Onariminda Akrilik, Otolog ve Homolog Kemik Greftlerin Kullanimi. Türk Nöroşir Derg 1996; 6: 24-7.
15. Temiz C, Tehli O, Kural C, Solmaz I, Gumral R, Bedir O, et al. Comparison of the Efficacies of Methyl Methacrylate, Bioactive Ceramic and Bioactive Glass on the Prevention of Cranioplasty Infections: An In Vitro Laboratory Study. Turkiye Klinikleri J Neur 2014; 9: 93-9.
16. Shibahashi K, Hoda H, Takasu Y, Hanakawa K, Ide T, Hamabe Y. Cranioplasty Outcomes and Analysis of the Factors Influencing Surgical Site Infection: A Retrospective Review of More than 10 Years of Institutional Experience. World Neurosurg 2017; 101: 20-2.
17. Kehler U, Hirdes C, Weber C, Spuck S, Tronnier V, Kundt G, et al. CSF leaks after cranial surgery - a prospective multicenter analysis. Innovative Neurosurgery 2013; 1: 49-53.
18. Wang JC, Wei L, Xu J, Liu JF, Gui L. Clinical outcome of cranioplasty with high-density porous polyethylene. J Craniofac Surg 2012; 23: 1404-6.

How to cite:

Asan Z. Use of Methyl Methacrylate for Small and Large Cranial Defects: A Single Institute Experience. Eur J Ther 2018; 24(3): 163–7.

European Journal of Therapeutics
DOI: 10.5152/EurJTher.2018.487
Original Research

Anatomical and Clinical Relevance of the Thyroid Foramen

Bülent Yalçın[1], Sedat Develi[1], R. Shane Tubbs[2], Necdet Kocabıyık[1], Selda Yıldız[1], Nurcan Ercıktı[1]

[1]Department of Anatomy, University of Health Sciences, Gülhane School of Medicine, Ankara, Turkey
[2]Division of Pediatric Neurosurgery, Children's Hospital of Alabama, Birmingham, AL, USA

ABSTRACT

Objective: The thyroid foramen (TF) is an opening on the lamina of the thyroid cartilage. It may be located on the posterosuperior part of the lamina or below the superior tubercle. The aim of the present study was to determine the incidence of the foramen in an adult Turkish population and the morphometry, topography, and structures within it, thereby aiding surgeons working in this area.

Methods: In 57 formalin-fixed cadaveric laryngeal specimens, 113 (56 right and 57 left) sides were dissected using a surgical microscope.

Results: The TF was observed in 6 out of 57 (10.5%) specimens. It was bilateral in 3 (5.3%) specimens; thus, it was observed in 9 sides. It was located at (33.3%) or posterior to (66.7%) the oblique line and below the superior tubercle. It was crossed by only a nerve in 2 (22.2%) left sides, an artery with a vein in 2 (22.2%) sides, or a neurovascular bundle in 5 (55.6%) sides.

Conclusion: The TF is a variation located on the lamina of the thyroid cartilage with an incidence of 2% to 57% in adults. Neurovascular structures can pass through it. It is important in two aspects: surgical exposure and spread of laryngeal tumors.

Keywords: Thyroid cartilage, thyroid foramen, superior laryngeal nerve

INTRODUCTION

The thyroid cartilage is the most prominent cartilage of the larynx. It consists of two hyaline cartilage flats called laminae. The apparent protrusion of the anterior fusion of these laminae is called laryngeal prominence. On the lateral side of each lamina, a slight crest extending from the superior thyroid tubercle to the inferior thyroid tubercle is called the oblique line. The posterior borders of the laminae do not fuse and deviate laterally. The superior and inferior extensions seen on the posterior border are called superior and inferior cornu (1).

The thyroid foramen (TF) is an opening located in one or both posterosuperior parts of the lamina of the thyroid cartilage and below the superior tubercle. Its presence over the thyroid cartilage lamina becomes apparent from the middle of the first trimester and closes during the subsequent trimesters. If there is a problem at the conjunction point of the cartilage tissue between the 4th and the 6th pharyngeal arches, the foramen can remain open (2, 3). The incidence of the TF has been variously reported, ranging from 2% to 57% in adults (4, 5). It is sometimes double but is more often seen in single form (3, 6, 7). Its location has been reported as posterior or anterior to the oblique line and below the superior tubercle. The foramen might contain only a nerve or vessel or house a neurovascular bundle. The nerve anastomoses between the external branch of the superior laryngeal nerve (ebSLN) and the internal branch of the superior laryngeal nerve (ibSLN) (3, 6–8) or between the ebSLN and the recurrent laryngeal nerve (9, 10). The arterial branch is usually an aberrant superior laryngeal artery (SLA) (3, 6, 9). The foramen is rarely covered only by the connective tissue with no content.

The TF is generally found incidentally during imaging examinations, larynx surgery or dissection of the neck. Its presence and content can be clinically important. Surgeons should be careful to avert from iatrogenic damage to the nerve or bleeding of the vessel when they place a surgical retractor or reflect the soft tissue around the larynx.

The aim of the present study was to determine the incidence of the TF in an adult Turkish population and the morphometry, topography, and structures within it, thereby aiding surgeons working in this area.

METHODS

The study was conducted with 57 formalin-fixed cadaveric laryngeal specimens. A total of 113 (56 right and 57 left) sides were investigated. Dissections were made using a Zeiss OpM1 surgical microscope (OpM1; Carl Zeiss, Oberkochen, Germany). One right

The study has been presented in 7th International Symposium of Clinical and Applied Anatomy (ISCAA) meeting hold on 17–20 September 2015 in Bratislava.

ORCID IDs of the authors: B.Y. 0000-0003-1653-3701; S.D. 0000-0002-3712-7510; R.S.T.0000-0003-1317-1047; N.K. 0000-0003-2164-9231; S.Y. 0000-0002-7324-7165; N.E. 0000-0002-7836-0095.

Corresponding Author: Bülent Yalçın **E-mail:** bulent.yalcin@sbu.edu.tr

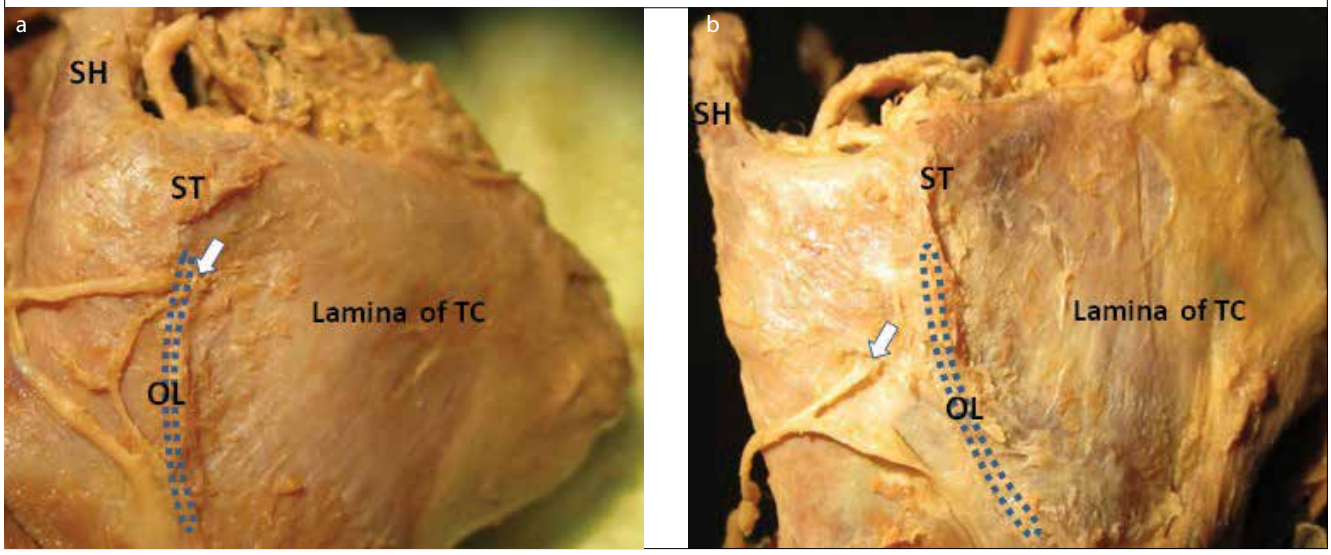
Received: 13.02.2018 • **Accepted:** 04.04.2018

Table 1. Mean values of the measurements of the TF (mm)

Vertical distance of the outer side of the foramen	Horizontal distance of the outer side of the foramen	Vertical distance of the inner side of the foramen	Horizontal distance of the inner side of the foramen	Distance between the superior tubercle and the TF
2.3±1.0	2.2±0.9	3.1±0.9	2.4±0.7	6.7±2.9

Figure 1. a, b. Right laminae of the thyroid cartilage. The thyroid foramen (white arrow) was located at (a) or posterior (b) to the oblique line. It was below the superior tubercle

TC: thyroid cartilage; OL: oblique line; SH: superior horn



side was not suitable for dissection. After the soft tissue around the larynx was removed, the strap muscles were exposed. The muscle parts attaching to the thyroid cartilage were incised to expose the lamina of the cartilage and TF clearly. The soft tissue occupying the outer and inner openings of the foramen and surrounding its content was also cleaned to measure its dimensions and to follow the contents to their origin points. The inferior constrictor muscle was subsequently incised at the midline to view inside the lamina of the thyroid cartilage. This enabled us to follow the contents throughout their length. The incidence, location, contents, and diameters of the TF were recorded. Finally, the structure was documented using a high-resolution photography. The vertical length of the TF was regarded as the widest site of the foramen. The horizontal length of the foramen was considered as the longest distance between the superior and the inferior edges of the foramen. Measurements were made using a digital vernier caliper (D&W Measuring-1kds15, China). The local ethics committee approved the study (University of Health Sciences, Gülhane School of Medicine-2016-16), patient approval was not necessary since the current study was conducted on cadaveric specimens.

Statistical Analysis

Descriptive analyses were made for all variables. Statistical results represented as mean ± standard deviation. Statistical analyses of data were performed using Statistical Package for the Social Sciences for Windows, version 16.0. (SPSS Inc.; Chicago, IL, USA), at a statistical significance set at $p<0.05$.

RESULTS

The TF was observed in 6 out of 57 (10.5%) specimens. It was bilateral in 3 (5.3%) specimens, suggesting that it was observed in 9 out of 113 (7.9%) sides. Table 1 shows the mean values of the horizontal and vertical diameters of the outer and inner openings of the TF and the distance between the superior tubercle and the TF.

The TF was located at (33.3%, Figure 1a) or posterior to (66.7%, Figure 1b) the oblique line and below the superior tubercle in all nine sides.

The foramen was crossed by only a nerve originating from the ebSLN. This was observed in 2 (22.2%, Figure 2a) sides. After passing, it anastomosed with the ibSLN in all 9 sides (Figure 2b). The foramen was also crossed by an artery with a vein observed in 2 (22.2%, Figure 3a) sides. The artery originated directly from the superior thyroid artery (STA). No SLA was observed. After passing through the foramen, the artery spread to the area supplied by the SLA (Figure 3b). Finally, the foramen was crossed by a neurovascular bundle observed in 5 (55.6%, Figure 4a) sides. The nerve of the bundle emerged from the ebSLN and anastomosed with the ibSLN in all cases. The artery of the bundle originated from the STA directly or from its glandular branches. After passing through the foramen, the artery anastomosed with the SLA. If no SLA was observed (in two sides), the area normally supplied by the SLA was supplied by the artery passing through the TF (Figure 4b).

Figure 2. a, b. (a) Outer and (b) inner surface of the right lamina of the thyroid cartilage. The thyroid foramen (white arrow) was crossed by only a nerve originating from the external branch of the superior laryngeal nerve. After passing, the nerve anastomosed with the internal branch of the superior laryngeal nerve

TC: thyroid cartilage; n: nerve; ebSLN: external branch of the superior laryngeal nerve; ibSLN: internal branch of the superior laryngeal nerve; SH: superior horn

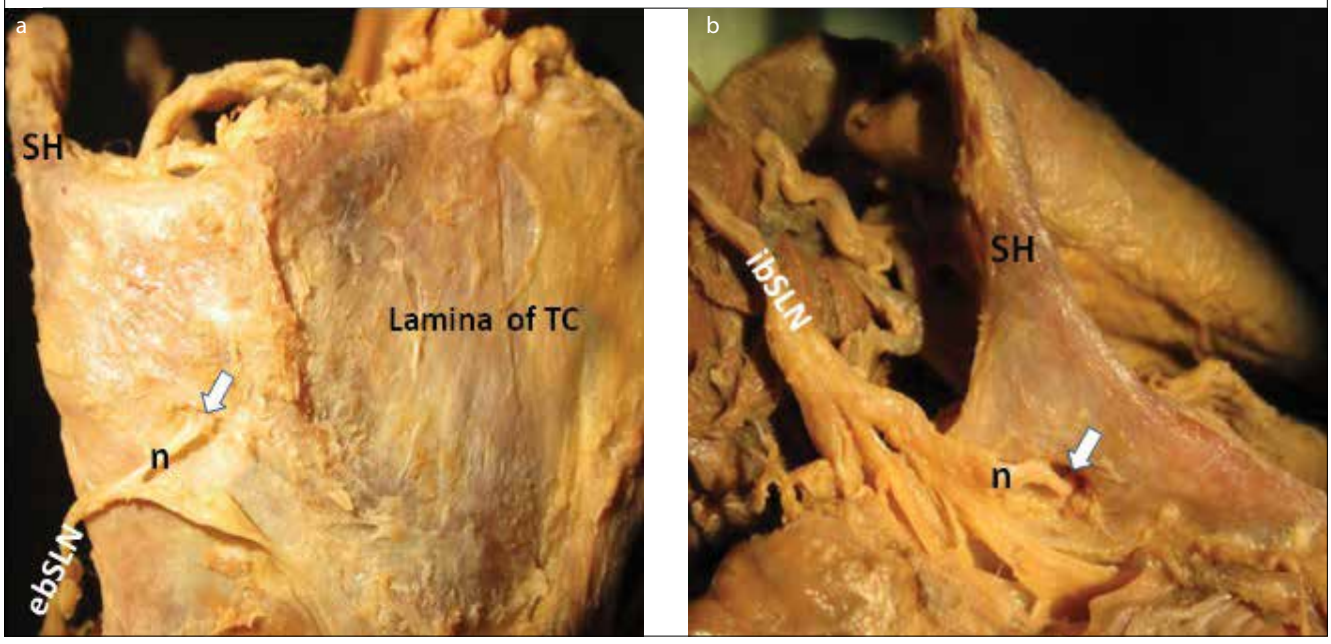
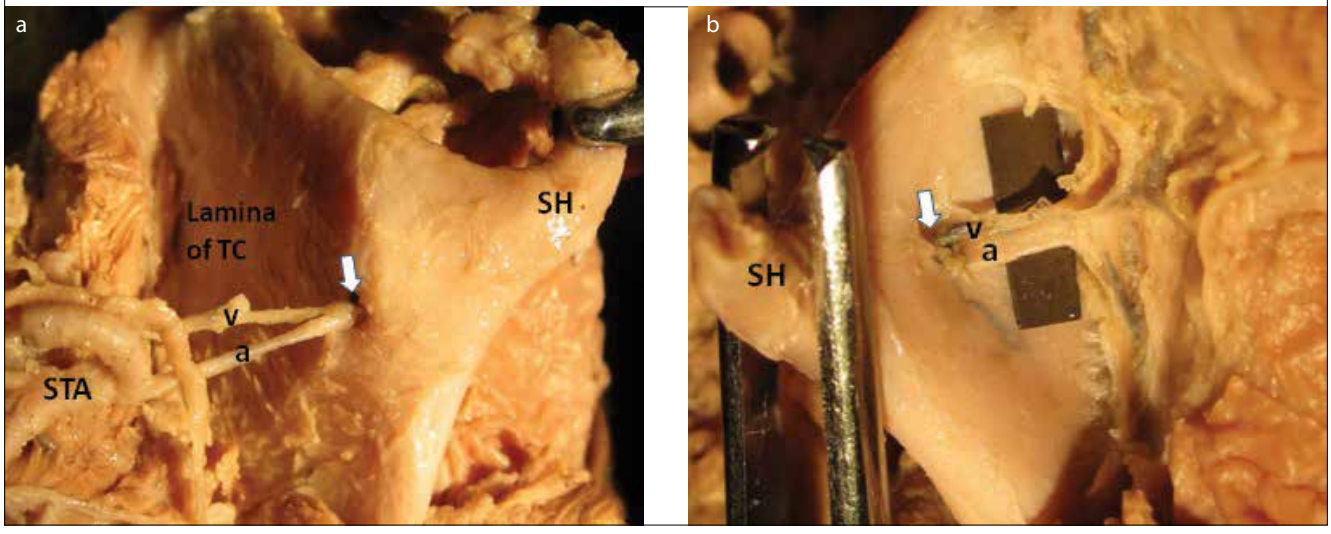


Figure 3. a, b. (a) Outer and (b) inner surface of the left lamina of the thyroid cartilage. The thyroid foramen (white arrow) was crossed by an artery with a vein. The artery originated directly from the superior thyroid artery

TC: thyroid cartilage; a: artery; v: vein; STA: superior thyroid artery; SH: superior horn



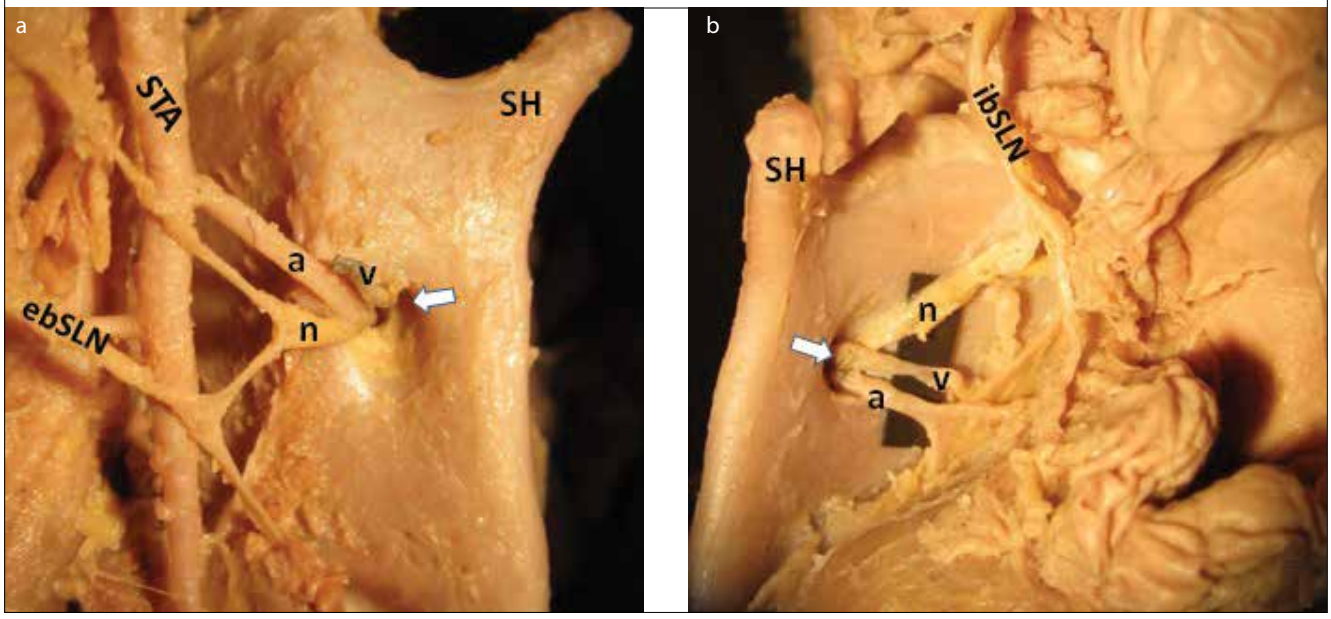
DISCUSSION

The embryological development of the TF is controversial. The embryonic draft of the thyroid laminae begins to develop in the first trimester as quadrilateral plates with a foramen. In the following stages of embryogenesis, the TF closes. However, hesitation or distortion of the fusion of the cartilaginous tissue between the fourth and the sixth pharyngeal arches may lead to the foramen to remain open (2, 3). Other studies have indicated that the shape of the TF is formed due to the content of the foramen, affecting the proper chondrification of the thyroid lamina (6). This satisfactorily explains why the TF is almost always located on the posterosuperior aspect of the laminae, in the neighborhood of the superior thyroid tubercle (3, 6). Muller et al. (11) reported that the descent of the ebSLN over the thyroid cartilage during the development of the larynx results in the formation of the foramen.

This incidence of the TF has been variously reported as ranging from 2% to 57% in adults and from 12.5% to 76.9% in fetuses. Its incidence differs greatly among the adult population: 33%–57%

Figure 4. a, b. (a) Outer and (b) inner surface of the left lamina of the thyroid cartilage. The thyroid foramen (white arrow) was crossed by a neurovascular bundle. The nerve of the bundle emerged from the external branch of the superior laryngeal nerve and anastomosed with the internal branch of the superior laryngeal nerve. The artery of the bundle originated from the superior thyroid artery directly or from its glandular branches

TC: thyroid cartilage; n: nerve; ebSLN: external branch of the superior laryngeal nerve; ibSLN: internal branch of the superior laryngeal nerve; a: artery; STA: superior thyroid artery; SH: superior horn



in the USA, 2%–55% in Europe, 10%–16% in India, 27.3%–50% in Japan, and 7.5%–17.3% in South Africa (3). Ortug et al. (12) observed the TF in 12% of 50 Turkish cadavers, and it was found in 10.5% of 57 cadaveric laryngeal specimens in the present study.

The foramen appears solitary and unilateral in 0% to 42.9% of cases but bilateral in 0% to 31.3% (4, 9, 13). An equal incidence of the unilateral and bilateral TFs was also reported (3). There are few studies of double TFs in the literature (6, 7). There were bilateral TFs in 5.3% of specimens in the present study, but no double ones were observed.

The foramen was located posterior to the oblique line in 60% and 61.9%, at the oblique line in 14.3% and 20%, or anterior to it in 20% and 23.8% (3, 14). Ramsaroop et al. (7) stated that it was most often located anterior to the linea obliqua. It has also been reported as located below the oblique line in 68.29%, above it in 21.95%, and right at the upper end in 9.76% of cases (6). In the present study, it was found to be at the oblique line in 33.3% and posterior to it in 66.7%. It was located below the superior tubercle in all nine sides. The distance between the foramen and the superior tubercle was reported as 10 mm (9) and found to be 6.7±2.9 mm in the present study.

The diameter of the TF ranged from 0.5 to 9 mm (3, 9). It was reported as 0.5–6 mm in males and 0.45–6.5 mm in females (15). The mean horizontal and vertical diameters were reported as 2.8 and 3.3 mm on the right side and 3.1 and 3.4 mm on the left side, respectively (14). According to our results, the outer vertical and horizontal diameters were 2.3±1.0 and 2.2±0.9 mm, respectively, whereas the inner vertical and horizontal diameters were 3.1±0.9 and 2.4±0.7 mm, respectively.

The TF passed by neurovascular structures 6.5% to 83.3% was crossed by only a nerve originating from the ebSLN and anastomosing with the ibSLN inside the larynx (8, 12). In the present study, the same variation was observed in 2 (22.2%) sides. The TF passed by neurovascular structures 7% to 33% was crossed by only an artery, usually a communicating branch between the SLA and the cricothyroid vessels or an aberrant SLA (3, 6, 12, 16). In contrast, the TF was crossed by an artery with a vein in 2 (22.2%) sides. The artery originated directly from the STA. No SLA was observed. Since the artery spread to the area supplied by the SLA, it was regarded as an aberrant SLA. The TF passed by neurovascular structures 16.7% to 100% was crossed by a neurovascular bundle (4, 6–9, 12, 13). In the present study, a neurovascular bundle coursing through the TF was observed in 5 (55.6%) sides. Its nerve originated from the ebSLN and anastomosed with the ibSLN in all cases. Its artery originated from the STA directly (aberrant SLA) or from its glandular branches.

Partab et al. (10) reported an interesting case of double neural anastomosis running through the TF. In this case, two neural loops were observed. The proximal loop was reported to be between the ebSLN and ibSLN, whereas the distal loop was reported to be between the ebSLN and the recurrent laryngeal nerve.

The existence of the TF is most likely to be asymptomatic, but it is very significant in surgeries of the larynx, such as partial laryngectomy or partial reconstruction. Its location and contents

are important for surgeons performing laryngeal procedures (3). Since the artery passing through the TF supplies the area of the SLA when the SLA is absent, surgeons should remember the aberrant artery to avoid injury. Another way in which the TF is important concerns the spread of tumors: a TF containing neurovascular structures is a possible pathway for tumor spread (12).

CONCLUSION

The TF was observed in 6 out of 57 (10.5%) specimens. It was bilateral in 3 (5.3%) specimens. It was situated at (33.3%) or posterior to (66.7%) the oblique line and below the superior tubercle. The foramen was crossed by only a nerve (22.2%), only a vessel(s) (22.2%), or a neurovascular bundle (55.6%). The nerve extended between the ebSLN and the ibSLN in all cases. The artery originated from the STA directly or from its glandular branches. Surgeons should be aware of the unusual course of the neurovascular structures on the surface of the thyroid cartilage to avoid injuring the nerve and artery passing through the TF.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University of Health Sciences, Gülhane School of Medicine (No: 2016-16).

Informed Consent: Informed consent was not necessary since the current study was conducted on cadaveric specimens.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – B.Y., S.D.; Design – B.Y., S.D.; Supervision – R.S.T., N.K.; Resources – N.K., S.Y., N.E.; Materials - N.K., S.Y., N.E.; Data Collection and/or Processing – B.Y., S.D., R.S.T.; Analysis and/or Interpretation – B.Y., S.D., R.S.T.; Literature Search – N.K., S.Y., N.E.; Writing Manuscript – B.Y., S.D., R.S.T.; Critical Review – R.S.T., N.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

REFERENCES

1. Standring S. Gray's anatomy : the anatomical basis of clinical practice. Forty-first edition. ed. New York: Elsevier Limited; 2016.
2. Gilliam C, Renner G. The thyroid foramen: a case report and literature review of a largely unrecognized laryngeal anomaly. Ear Nose Throat J 2009; 88: E4-7.
3. Raikos A, Paraskevas GK. The thyroid foramen: a systematic review and surgical considerations. Clin Anat 2013; 26: 700-8.
4. He X, Ye C, Carrat X, Traissac L. Anatomical study of the thyroid foramen in human larynx: a study of 100 dissections. Rev Laryngol Otol Rhinol (Bord) 1999; 120: 127-9.
5. Kirchner JC, Kirchner JA, Sasaki CT. Anatomic foramina in the thyroid cartilage: incidence and implications for the spread of laryngeal cancer. Ann Otol Rhinol Laryngol 1989; 98: 421-5.
6. Leon X, Maranillo E, Mirapeix RM, Quer M, Sanudo JR. Foramen thyroideum: a comparative study in embryos, fetuses, and adults. Laryngoscope 1997; 107: 1146-50.
7. Ramsaroop L, Hurrinarain K, Partab P, Satyapal K. The Incidence of the Foramen Thyroideum in the South African Population. Int J Morphol 2010; 28: 433-8.
8. Sanudo JR, Maranillo E, Leon X, Mirapeix RM, Orus C, Quer M. An anatomical study of anastomoses between the laryngeal nerves. Laryngoscope 1999; 109: 983-7.
9. Tanaka S, Shoumura S, Chen H, Nakatani T, Mizukami S. Aberrant branch of the superior laryngeal nerve passing through the thyroid foramen: a macroscopical study. Kaibogaku Zasshi 1997; 72: 251-6.
10. Partab P, Hurrinarain K, Ramsaroop L, Satyapal KS. Atypical anastomosis of laryngeal nerves. Clin Anat 2006; 19: 651-6.
11. Muller F, O'Rahilly R, Tucker JA. The human larynx at the end of the embryonic period proper. I. The laryngeal and infrahyoid muscles and their innervation. Acta Otolaryngol 1981; 91: 323-36.
12. Ortug C, Gunduz T, Sam B. The incidence of the foramen thyroideum in Turkish population. Surg Radiol Anat 2005; 27: 491-4.
13. Rusu MC, Nimigean V, Banu MA, Cergan R, Niculescu V. The morphology and topography of the superior laryngeal artery. Surg Radiol Anat 2007; 29: 653-60.
14. Joshi MM, Joshi SS, Joshi SD. The presence of the foramen thyroideum: A cadaveric study in western region of the India. Calicut Med J 2011; 9: e3.
15. Zemlin WR, Simmon A, Hammel D. The frequency of occurrence of foramen thyroideum in the human larynx. Folia Phoniatr (Basel) 1984; 36: 296-300.
16. Silva RB, Dias MVF, Fernandes RMP, Babinski MA. A unilateral anomaly of the superior laryngeal artery passing through the thyroid cartilage lamina. Braz J morphol Sci 2005; 22: 41-2.

How to cite:

Yalçın B, Develi S, Tubbs RS, Kocabıyık N, Yıldız S, Ercıktı N. Anatomical and Clinical Relevance of the Thyroid Foramen. Eur J Ther 2018; 24(3): 168–72.

European Journal of Therapeutics

DOI: 10.5152/EurJTher.2018.607

Original Research

Relationship between Thyroid Volume and Baseline Vitamin D Levels in New-Onset Graves Disease

Gülşah Yenidünya Yalın[1], Hüseyin Çelik[2], Fuat Cenik[3], Serkan Feyyaz Yalın[4]

[1]Division of Endocrinology and Metabolism Disorders, Başkent University, School of Medicine, İstanbul, Turkey

[2]Clinic of Endocrinology and Metabolism Disorders, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey

[3]Clinic of Internal Medicine, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey

[4]Clinic of Nephrology, Kartal Dr. Lütfi Kırdar Training and Research Hospital, İstanbul, Turkey

ABSTRACT

Objective: Serum vitamin D is shown to be decreased and associated with higher thyroid volumes in Graves disease (GD). We aimed to investigate the relationship between thyroid volume and baseline serum vitamin D status in newly diagnosed GD patients.

Methods: This was a single-center cross-sectional study with a total of 61 new-onset GD patients (n=61, F: 40, M: 21) who were divided into two groups, according to baseline serum vitamin D levels, as Group-1 (vitamin D <20; n: 42) and Group-2 (vitamin D ≥20; n=19). Thyroid volume (mL) and isthmus measurements (mm) were compared between the two groups.

Results: There was an inverse correlation between the baseline serum vitamin D levels and thyroid volume, thyroid receptor autoantibodies (TRAb), free triiodothyronine (fT3), and parathyroid hormone (PTH) levels (p=0.02, r=-0.31; p=0.005, r=-0.36; p=0.04, r=-0.26; p=0.02, r=-0.32, respectively). Thyroid volume was also correlated with serum free thyroxine (fT4), fT3, TRAb, and thyroid peroxidase autoantibodies (TPOAb; p=0.001, r=0.426; p=0.001, r=0.50; p=0.04, r=0.26; p=0.001, r=0.42, respectively). Low vitamin D and high thyroglobulin antibody (TgAb) levels were significantly associated with thyroid volume based on a regression analysis (p=0.03, odds ratio [OR]:18.7, 95% confidence interval [CI]: 1.34-260.91 and p=0.04, OR: 16.6, 95% CI: 1.07-255.64, respectively).

Conclusion: Baseline serum vitamin D levels are inversely related with thyroid volumes, fT3, and TRAb levels in new-onset GD. In addition to several advantages, optimization of vitamin D levels would also be beneficial in the surveillance of these patients. However, larger scale studies are required to make further suggestions.

Keywords: Autoimmune disorders, 25 (OH) vitamin D, TRAb, Graves disease, thyroid volume

INTRODUCTION

Vitamin D is as a pro-hormone in the regulation of calcium and phosphate levels, and therefore it is particularly essential for bone and mineral metabolism. However, in recent years, many studies have been demonstrating an effect of vitamin D deficiency in several diseases, such as cancer, hypertension, cardiovascular diseases, and diabetes mellitus as well as autoimmune thyroid disorders (1). Although vitamin D levels of over 20 ng/mL are considered sufficient for its skeletal effects, values over 30 ng/mL are required to avoid manifestation of vitamin D deficiency in the organs outside the skeletal system (2).

Vitamin D mediates its effects on autoimmune disorders by triggering immune responses through its receptors on macrophages, dendritic cells, and T and B lymphocytes. Thus, the relationship between vitamin D deficiency and autoimmune thyroid disorders may also be related with vitamin D receptor (VDR) gene polymorphisms as well as environmental factors. Recently, Graves disease (GD) has been associated with vitamin D deficiency (3-6). Serum 25(OH)D levels were shown to be significantly lower and inversely correlated with thyroid volume in patients with new-onset GD compared to control subjects (7). Vitamin D deficiency was also reported to be associated with lower remission rates in GD (8, 9). In this study, we aimed to investigate the impact of baseline vitamin D levels on thyroid volume in patients with new-onset GD.

METHODS

Study Group

The patients who were admitted to the endocrinology and metabolism outpatient clinic with a diagnosis of new-onset GD were included in the study (n=61, F: 40, M: 21). The serum vitamin D levels were measured using the competitive protein--binding

ORCID IDs of the authors: G.Y.Y. 0000-0002-9013-5237; H.Ç. 0000-0003-0775-5978 ; F.C. 0000-0003-2063-541X; S.F.Y. 0000-0002-8146-6966.

Corresponding Author: Gülşah Yenidünya Yalın **E-mail:** gulsah_y@hotmail.com

Received: 20.03.2018 • **Accepted:** 02.04.2018

assay. The vitamin D status was defined as deficient, inadequate, and sufficient for vitamin D levels of <20 ng/mL, 20-30 ng/mL, and >30 ng/mL, respectively (1). According to the baseline serum vitamin D status at the time of diagnosis, the patients were divided into three groups: vitamin D deficient group (Group-1; n: 42, F/M: 31/11), vitamin D inadequate group (Group-2; n=10, F/M: 4/6), and vitamin D sufficient group (Group-3; n: 9, F/M: 5/4). The diagnosis of GD was based on the standard clinical criteria, thyroid function tests with autoantibody levels, and thyroid scintigraphy imaging. The serum free triiodothyronine (fT3) and free thyroxine (fT4) levels were measured using a competitive enzyme immunoassay. Serum thyroid stimulating hormone (TSH), thyroid receptor autoantibodies (TRAb), thyroid peroxidase autoantibodies (TPOAb), and thyroglobulin antibody (TgAb) levels were measured using a two-site immunoenzymetric assay. Thyroid volume (mL) and isthmus measurements (mm) were compared between each group. Thyroid volume was calculated ~~with~~ using the following standardizsed formula (10).

Thyroid Volume (mL)=0.479×[Right lobe depth × width × length(cm)]+0.479 × [Left lobe depth × width × length(cm)]

Thyroid ultrasonography imaging for the calculation of thyroid volumes (mL) and isthmus measurements (mm) were performed by the same physician using Logic 7, General Electric, Milwaukee, Wiskonsin. Patients with a history of thyroidectomy, renal disease, hepatic disease, or malignancy or those under medications that affect vitamin D status and having prior replacement of vitamin D in the last 6 months were excluded from the study. The patients younger than 18 years and older than 75 years were also not included in the study groups.

This study was approved by the ethics committee of Kanuni Sultan Süleyman Training and Research Hospital on 17.06.2016 (2016/16) and written informed consent was obtained from all patients. All procedures were performed in accordance with the Declaration of Helsinki.

Statistical Analysis

The distribution of variables was evaluated using the Kolmogorov-Smirnov test and a histogram analysis. The mean±standard error of the mean (SEM) and frequency values are reported for each data. The three groups were compared using ANOVA, Kruskal-Wallis, and Mann-Whitney U tests, with the post-hoc Bonferroni adjustment as appropriate: for statistically significant results. Categorical variables were processed using the chi-square test. The Pearson and Spearman correlation analysis was performed for normally and non-normally distributed data, respectively. A statistical significance was accepted at a p value of <0.05. Statistical calculations were performed using the Statistical Package for Social Sciences 22.0 software (SPSS IBM Corp.; Armonk, New York, USA).

RESULTS

A total of 61 patients were included in the study (F: 40, M: 21). The serum TSH levels were below 0.005 μIU/mL, and the fT4 and fT3 levels were above upper limit of normal (1.71 ng/dL, 4.4 pg/mL) in all the patients. The mean age and vitamin D levels of the patients were 34.8±1.2 years (18-61) and 13.8±1.3 (2.5-39), respectively, (mean±SEM [min-max]). The distribution of the clinical features according to vitamin D levels are shown in Table 1. Thyroid volumes and isthmus measurements did not show significant difference according to the baseline serum vitamin D levels at the time of diagnosis (p=0.8 and p=0.1, respectively; Table 1).

Table 1. Distribution of clinical features according to the vitamin D status

	Group-1 (vit D <20 ng/mL)	Group-2 (vit D >20 ng/mL)	p
Age (mean±SEM)	36.2±1.5	35.1±2.0	0.05
BMI	23.7±0.7	22.5±3.1	0.3
fT4	4.4±0.3	4.3±0.7	0.9
fT3	15.2±1.3	13.7±2.3	0.6
TRAb	9.4±1.4	9.1±4.5	0.5
TPOAb	335.6±38.6	317.9±89.7	0.5
TgAb	573±170	606±434	0.6
vit D	7.9±4.6	26.6±3.5	0.001
Ca	9.5±0.6	9.7±0.14	0.3
P	3.7±0.1	4.1±0.2	0.2
PTH	52±2.2	35.1±4.1	0.05
Thyroid Volume (mL)	31.9±2.7	26.8±5.0	0.3
Isthmus (mm)	4.8±0.4	3.7±0.8	0.1

BMI: body mass index, fT4: free thyroxine; fT3: free triiodothyronine; TRAb: thyroid receptor antibody; TPOAb: thyroid-peroxidase antibody; TgAb: thyroglobulin antibody; vit D: vitamin D; Ca: calcium, P: phosphorus; PTH: parathyroid hormone; SEM: standard error mean

The presence of Graves ophthalmopathy was similar between the three groups (p=0.7). Thyroid volume was higher in males and in patients with body mass index (BMI) >25 (p=0.001 and 0.04, respectively). The thyroid volume did not show significant difference according to presence of Graves ophthalmopathy (Table 2).

There was a positive correlation between thyroid volume and serum fT4, fT3, TRAb, TPOAb, and TgAb levels (p=0.001, r=0.426; p=0.001, r=0.50; p=0.04, r=0.26; p=0.001, r=0.42; p=0.001 r=0.42; respectively; Table 3). There was an inverse correlation between serum vitamin D levels and thyroid volume, TRAb, fT3, and parathyroid hormone (PTH) levels (p=0.02, r=-0.31; p=0.005, r=-0.36; p=0.04, r=-0.26; p=0.02, r=-0.32; respectively; Table 4).

Low baseline vitamin D and high TgAb levels were significantly associated with higher thyroid volume in a logistic regression analysis (p=0.03, odds ratio [OR]: 18.7, 95% confidence interval [CI]:1.34-260.91; p=0.04, OR: 16.6, 95% CI: 1.07-255.64, respectively; Table 5).

DISCUSSION

The major effect of vitamin D is on the regulation of bone and mineral homeostasis; however, it has been recently shown that hypovitaminosis D is also associated with extraskeletal disorders,

Table 2. Relationship of thyroid volume with categorical variables

	Thyroid Volume (mean±SEM)	p
Gender		
Female	25±2.8	0.001
Male	40±2.7	
Ophthalmopathy		
Absent	28.7±2.5	0.1
Present	35.8±4.3	
Age, years		
<40	31.1±2.8	0.8
>40	30.2±3.4	
BMI		
<25	28.3±2.5	0.04
>25	39.4±5.2	

Chi-square; SEM: standard error mean; BMI: body mass index

Table 3. Correlation of thyroid volume and isthmus thickness with clinical features

	Thyroid Volume		Isthmus Thickness	
	p	r	p	r
Age, years	0.7	0.04	0.6	0.07
BMI	0.2	0.15	0.04	0.27
fT4	0.001	0.45	0.001	0.52
fT3	0.001	0.50	0.001	0.55
TRAb	0.04	0.26	0.001	0.40
TPOAb	0.001	0.42	0.1	0.21
TgAb	0.001	0.42	0.8	-0.02
Vit D	0.02	-0.31	0.3	-0.12
Ca	0.1	0.21	0.6	0.06
PTH	0.3	0.13	0.9	-0.004
P	0.7	0.03	0.1	-0.21

Pearson, Spearman; BMI: body mass index; fT4: free thyroxine; fT3: free triiodothyronine; TRAb: thyroid receptor antibody; TPOAb: thyroid-peroxidase antibody; TgAb: thyroglobulin antibody; vit D: vitamin D; Ca: calcium; P: phosphorus; PTH: parathyroid hormone

Table 4. Correlation of vit D levels with clinical features

	Vit D	
	p	r
Age, years	0.1	-0.11
BMI	0.7	-0.04
fT4	0.2	-0.16
fT3	0.04	-0.26
TRAb	0.01	-0.33
TPOAb	0.1	-0.11
TgAb	0.1	-0.11
Thyroid volume	0.02	-0.31
Ca	0.1	0.21
PTH	0.02	-0.32
P	0.04	0.28

BMI: body mass index; fT4: free thyroxine; fT3: free triiodothyronine; TRAb: thyroid receptor antibody; TPOAb: thyroid-peroxidase antibody; TgAb: thyroglobulin antibody; vit D: vitamin D; Ca: calcium, P: phosphorus; PTH: parathyroid hormone

Table 5. Logistic regression analysis of risk factors asociatedassociated with thyroid volume

	Thyroid volume		
	p	OR	CI 95%
Vitamin D	0.03	18.7	1.34-260.91
Age, years	0.8	1.19	0.19-7.2
BMI	0.1	0.14	0.18-1.11
Gender	0.002	142.85	0.0-0.15
fT4	0.5	0.38	0.01-9.33
fT3	0.1	13.9	0.68-285,67
TRAb	0.4	0.30	0.02-4.25
TPOAb	0.4	0.47	0.07-3.04
TgAb	0.04	16.6	1.07-255.64

BMI: body mass index; fT4: free thyroxine; fT3: free triiodothyronine; TRAb: thyroid receptor antibody; TPOAb: thyroid-peroxidase antibody; TgAb: thyroglobulin antibody; vit D: vitamin D; PTH: parathyroid hormone; OD: odds ratio; CI: confidence interval

such as hypertension, diabetes mellitus, malignancy, cardiovascular and autoimmune thyroid diseases (1). Vitamin D regulates inflammatory cytokine production and inhibits the proliferation of proinflammatory cells through its receptors on lymphocytes and macrophages (11). The effects of vitamin D on monocytes and macrophages is in favor of activating the innate immune system;, however, there is an inhibitory effect on the acquired immune response (12). These effects represent the immunomodulatory action, which results in an association between vitamin D deficiency and autoimmune disorders. Vitamin D inhibits the production of Th1 cells by suppressing the function of interleukin (IL)-2, IL-12, and interferon (IFN)-γ and stimulating IL-4, thereby shifting the polarization of T cells towards the Th2 phenotype (13). The decrease in this inhibitory effect on Th1 production is related to an increase in the autoimmune thyroid disorders with vitamin D deficiency (1).

The relationship between low vitamin D levels and GD has been previously reported (14, 15). GD is characterized by a loss of im-

mune tolerance to thyroid antigens leading to the inflammation of thyroid gland (3). Thus, the decreased inhibitory effect on the immune system caused by hypovitaminosis D is thought to act as a further reinforcement in the development of GD. Vitamin D levels were shown to be decreased and related with thyroid volume in patients with new-onset GD (7). Furthermore, lower levels of vitamin D were reported to be associated with lower rates of remission in patients with GD (8). To the best of our knowledge, this is the first study investigating the change in thyroid volumes according to the baseline serum vitamin D levels among patients with new-onset GD. In our study, the mean thyroid volume and isthmus measurements did not show significant difference between the three groups according to the vitamin D status. However, thyroid volumes had an inclination to be higher in patients with lower vitamin D levels revealing a negative correlation between the two parameters. In contrast, thyroid volumes showed positive correlation with thyroid hormones and autoantibody levels. Higher autoantibody levels causing enhanced stimulation of thyroxine synthesis, accompanied with a further increase in the volume of thyroid gland, is the possible explanation of this relation.

In an animal in vivo autoimmune thyroiditis model, vitamin D treatment is shown to reduce the severity of inflammatory lesions in the thyroid gland (16). It is also reported that lower vitamin D levels are associated with higher thyroid autoantibody levels (17, 18). In our study, there was an inverse correlation between baseline vitamin D levels and serum TRAb titers. This may be associated with the lack of an inhibitory action on the immune system due to decreased vitamin D levels. In our study, there was a tendency to higher fT3 levels in patients with lower levels of vitamin D, which may be related with the increased TRAb titers and further stimulation of the inflammatory changes in the thyroid gland.

In addition to vitamin D deficiency due to environmental factors, vitamin D receptor (VDR) polymorphism is also reported to be an important cofactor in the development of GD (19). In a recent meta-analysis, significant difference in the association of vitamin D levels and GD has been reported in African and Asian patients, while no significant difference was found in the European population (20). These differences might be related with the VDR polymorphisms among different ethnic populations. The increased prevalence of autoimmune thyroid disorders according to VDR polymorphisms has been reported in several studies (19, 21). The most common polymorphisms are reported as ApaI and FokI polymorphisms in Hashimoto disease and TaqI polymorphism in GD (22). In a study performed in the Turkish population, TaqI and FokI genotypes were shown to be associated with higher prevalence of Hashimoto thyroiditis (23). Despite the negative correlation of vitamin D and thyroid volumes, the lack of difference in the mean thyroid volumes between the three groups in our study may be due to the presence of these polymorphisms; however, further studies are needed to demonstrate the VDR genotypes related with GD in the Turkish population.

In our study, thyroid volume was higher in male patients accompanied with higher BMI values, which was also related with an increased gland size. There was no significant difference in the rates of ophthalmopathy development according to the vitamin D levels, and the thyroid volumes were similar in patients with and without Graves ophthalmopathy. Previous studies have shown that there was no difference in the severity of GD according to the vitamin D status (7, 24). However, higher fT3 and TRAb levels were observed with lower vitamin D levels in our study. Nevertheless, the ophthalmopathy presence was similar between the three groups. The higher fT3 and TRAb levels may also be the reason for lower remission rates of GD in vitamin D deficiency, which has been previously reported (8).

The limitation to our study is that it was a single-center cross-sectional study with a limited number of patients. Prospective larger scale studies with vitamin D treatment and follow-up for the onset of remission are needed to make definitive suggestions. Studies of vitamin D receptor polymorphisms associated with GD among different population groups would also be beneficial for further conclusions.

CONCLUSION

Vitamin D deficiency is an important risk factor in the development of autoimmune thyroid disorders. Baseline serum vitamin D levels are inversely related to fT3, TRAb levels, and thyroid volumes, which are related to the adverse outcomes in GD. Therefore, in addition to several advantages, optimization of vitamin D levels would also be beneficial on the surveillance of these patients. However, larger scale studies on different ethnic populations are required to make further suggestions.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kanuni Sultan Süleyman Training and Research Hospital.

Informed Consent: Written informed consent was obtained from all patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - G.Y.Y.; Design - H.Ç.; Supervision - G.Y.Y.; Materials - F.C.; Data Collection and/or Processing - S.F.Y.; Analysis and/or Interpretation - G.Y.Y.; Literature Search - H.Ç.; Writing Manuscript - G.Y.Y.; Critical Review - G.Y.Y.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

REFERENCES

1. Bizzaro G, Shoenfeld Y. Vitamin D and autoimmune thyroid diseases: facts and unresolved questions. Immunol Res 2015; 61: 46-52.
2. Vondra K, Starka L, Hampl R. Vitamin D and Thyroid Diseases. Physiol Res 2015; 64: 95-100.
3. Kivity S, Agmon-Levin N, Zisappl M, Shapira Y, Nagy EV, Danko K et al. Vitamin D and autoimmune thyroid diseases. Cell Mol Immunol 2011; 8: 243-7.
4. Kurylowicz A, Ramos-Lopez E, Bednarczuk T, Badenhoop K. Vitamin D-binding protein (DBP) gene polymorphism is associated with Graves' disease and the vitamin D status in a Polish population study. Exp Clin Endocrinol 2006; 114: 329-35.

5. Abd el Gawad SS, Samee Er Abdul, Metwali AA, Abd el Gawad MS. Vitamin D receptor gene polymorphism and its association with 1,25-dihydroxyvitamin D in patients with Graves disease in an Egyptian population: a pilot study. Endocr Pract 2012; 18: 132-9.
6. Ramos-Lopez E, Kurylowicz A, Bednarczuk T, Paunkovic J, Seidl C, Badenhoop K. Vitamin D receptor polymorphisms are associated with Graves' disease in German and Polish but not in Serbian patients. Thyroid 2015; 15: 1125-30.
7. Yasuda T, Okamoto Y, Hamada N, Miyashita K, Takahara M, Sakamoto F. Serum vitamin D levels are decreased and associated with thyroid volume in female patients with newly onset Graves' disease. Endocrine 2012; 42: 739-41.
8. Yasuda T, Okamoto Y, Hamada N, Miyashita K, Takahara M, Sakamoto F, et al. Serum vitamin D levels are decreased in patients without remission of Graves' disease. Endocrine 2013; 43: 230-2.
9. Hollick MF. Vitamin D deficiency. N Engl J Med 2007; 357: 266-81.
10. Shabana W, Peeters E, De Maeseneer M. Measuring thyroid gland volume: should we change the correction factor? AJR Am J Roentgenol 2006; 186: 234-6.
11. Yin K, Agrawal DK. Vitamin D and inflammatory diseases. J Inflamm Res 2014; 7: 69-87.
12. Bouillon R. Vitamin D: from photosynthesis, metabolism and action to clinical applications. In: Endocrinology, Jameson JL, De Groot LJ, Saunders Elsevier, Philadelphia 2010.
13. Baeke F, Takiishi T, Korf H, Gysemans C, Mathieu C. Vitamin D: modulator of the immune system. Curr Opin Pharmacol 2010; 10: 482-96.
14. Li YB, Xue XH, Liu SW, Xi GX, Zhao LX, Zhang XL. Clinical research of serum vitamin D in early Graves disease. Chin Rem Clin 2014; 14: 242-3.
15. Miao W, Ma J, Guo R, Wang YJ, Wang G, Guan HX. Research about the correlation between Serum 25(OH)D with Graves' disease. Chin. J Pract Internal Med 2013; 33: 394-95.
16. Fournier C, Gepner P, Sadouk M. In vivo beneficial effects of cyclosporin A and 1,25-dihydroxyvitamin D3 on the induction of experimental autoimmune thyroiditis. Clin Immunol Immunopathol 1990; 54: 53-63.
17. Choi YM, Kim WG, Kim TY. Low levels of serum vitamin D3 are associated with autoimmune thyroid disease in pre-menopausal women. Thyroid 2014; 24: 655-61.
18. Zhang H, Liang L, Xie Z. Low vitamin D status is associated with increased titers of thyroid stimulating hormone receptor antibodies in Graves disease. Endocr Pract 2015; 21: 258-63.
19. Feng M, Li H, Chen SF. Polymorphisms in the vitamin D receptor gene and risk of autoimmune thyroid diseases: a meta-analysis. Endocrine 2013; 43: 318-26.
20. Xu MY, Cao B, Yin J, Wang DF, Chen KL, Lu QB. Vitamin D and Graves' Disease: A Meta-Analysis Update.Nutrients 2015; 7: 3813-27.
21. Effraimidis G, Wiersinga WM. Mechanisms in endocrinology: autoimmune thyroid disease: old and new players. Eur J Endocrinol 2014; 170: 241-52.
22. Inoue N, Watanabe M, Ishido N. The functional polymorphisms of VDR, GC and CYP2R1 are involved in the pathogenesis of autoimmune thyroid diseases. Clin Exp Immunol 2014; 178: 262-9.
23. Yazici D, Yavuz D, Tarcin O. Vitamin D receptor gene ApaI, TaqI, FokI and BsmI polymorphisms in a group of Turkish patients with Hashimoto's thyroiditis. Minerva Endocrinol 2013; 38: 195-201.
24. Pantazi H, Papapetrou PD. Changes in parameters of bone and mineral metabolism during therapy for hyperthyroidism. J Clin Endocrinol Metab 2000; 83: 1099-106.

How to cite:

Yenidünya Yalın G, Çelik H, Cenik F, Yalın SF. Relationship between Thyroid Volume and Baseline Vitamin D Levels in New–Onset Graves Disease. Eur J Ther 2018; 24(3): 173–7.

European Journal of Therapeutics
DOI: 10.5152/EurJTher.2018.666
Original Research

Our Experiences with Vertebral Artery Stents

Yusuf İnanç[1], Semih Giray[1], Yılmaz İnanç[2]
[1]Department of Neurology, Gaziantep University, School of Medicine, Gaziantep, Turkey
[2]Department of Neurology, Kahramanmaraş Sütçü İmam University, School of Medicine, Kahramanmaraş, Turkey

ABSTRACT
Objective: This study aimed to evaluate the success and clinical outcomes of endovascular stent treatment in vertebral artery (VA) occlusive lesions.
Methods: A total of 103 patients who underwent endovascular treatment due to VA constriction were included in this study. The patients were diagnosed on the basis of their clinical manifestations (vertigo, visual complaints, syncope, ataxia, drop attack, ischemic stroke, and transient ischemic attack (TIA)), neurological examinations, Doppler ultrasonography examination, and digital subtraction angiography (DSA). For angiographic evaluation, all patients underwent four vessel angiographies including the aortic arch, VA, and carotid artery. Anterior circulation, posterior circulation, and the Willis polygon were evaluated for all patients. During the procedure, the patients were not sedated, and neurological findings were continuously monitored.
Results: Thirty-six patients had stents implanted in their right vertebral arteries, 16 patients in their left vertebral arteries, and 3 patients in both vertebral arteries. During the procedure, bradycardia developed in three cases, and atropine was administered for its intervention. Hypotension developed in two cases, and dopamine along with 0.9% NaCl was administered for its intervention. One of the patients developed a speech disorder along with a complaint of imbalance 24 hours after the procedure. A magnetic resonance imaging (MRI) examination revealed an infarct on the left posterior inferior cerebellar artery (PICA) supply area. The patients' symptoms subsided with minimal sequelae. Two patients had TIAs with complaints of dizziness and weakness on the left side. Hemorrhage and hematoma developed in the femoral artery region 2 hours after the stent implantation in two cases. One unit transfusion was applied.
Conclusion: Vertebral artery stenosis is one of the correctable causes of posterior systemic stroke and can now be diagnosed with more ease with the use of modern imaging methods. Balloon angioplasty or stent-assisted endovascular treatment is an effective treatment with low morbidity and mortality for patients with a single VA or who do not respond to medical treatment due to cerebral vascular pathology.
Keywords: Vertebral artery, stenosis, stent

INTRODUCTION

In Western societies, stroke is a major cause of death and hospitalization and is the second most common cause of fatalities worldwide. Twenty-five percent of ischemic strokes are caused by the vertebrobasilar system, whereas approximately one-fifth of posterior strokes are due to vertebral artery (VA) constrictions. Unlike for anterior circulation, no definitive treatment strategies have been established for symptomatic posterior circulation stenosis yet. Drug therapy alone can reduce the risk of strokes in these patients, but there is no definitive study in this regard. Surgical treatment of VA occlusive lesions is very limited, and endovascular treatment methods and technological improvements have rendered almost all surgical treatment options (1-3) obsolete. This study aimed to evaluate the success and clinical outcomes of endovascular stent treatment in VA occlusive lesions.

METHODS

A total of 103 patients who underwent endovascular treatment between 2014 and 2017 due to VA constriction were included in this study. Gaziantep University School of Medicine Ethics Committee's approval (date:01/18//2018, decision no:2018/27) was obtained for the study. The patients were diagnosed on the basis of their clinical manifestations (vertigo, visual complaints, syncope, ataxia, drop attack, ischemic stroke, and transient ischemic attack (TIA)), neurological examinations, Doppler ultrasonography examination, and digital subtraction angiography (DSA). The patients and their relatives were informed about the risks and possible complications before undergoing the procedure and were given an informed consent form to sign. To reduce the risk of thrombosis following stent implantation and to speed up the endogenous clearance phase of the lesion's thrombus component, the patient was put on a dosage of 100–300 mg/day of acetylsalicylic acid and 1×75 mg/day of clopidogrel 1week before the procedure. A few days before the procedure, the patients were evaluated with a full blood count, coagulation tests, and a biochemical panel. The patients were told not to eat on the day of the procedure. For angiographic evaluation, all patients underwent four vessel angiographies including the aortic arch, VA, and carotid artery. Anterior circulation, posterior circulation, and the Willis polygon were evaluated for all the patients.All patients

ORCID IDs of the authors: S.G. 0000-0002-0722-3181; Y.İ. 0000-0002-0423-0941.
Corresponding Author: Yusuf İnanç **E-mail:** drinancc@gmail.com
Received: 07.04.2018 • **Accepted:** 06.06.2018

received 5,000–10,000 unit of heparin after arterial intervention to maintain an active clotting time (250 s). Endovascular therapy was performed for all patients under local anesthesia following insertion of a subclavian arterial 6-F 100-cm-long guide catheter (Guider Softip, Boston Scientific Target, Fremont, Boston, USA) using stents with a monorail system dilated with a balloon using a 0.014 guide wire (TransendEx 0.014 inch, Boston Scientific Target, Fremont, Boston, USA). Patients developing bradycardia (pulse rate of <40 or a decrease of ≤50% for up to 24 hours) or hypotension (systolic blood pressure of <90 mmHg or mean arterial pressure of <50 mmHg) during and after the stenting procedure were recorded. At the end of the procedure, anterior posterior and lateral cranial angiographic imaging were performed, and the procedure was ended. During the procedure, the patients were not sedated, and neurological findings were continuously monitored. Double antiplatelet therapy (aspirin and clopidogrel) was applied for at least 3 months after the procedure.

Statistical Analysis

The Statistical Package for the Social Sciences 22 (SPSS, IBM Corp;, Armonk, New York, USA) package program was used for data analysis. Descriptive statistics were given as mean values, standard deviations, and the frequency distribution in percentages. The Chi-Square Test was used for categorical data and the significance level was accepted as $p<0.05$ in statistical analysis.

RESULTS

Out of 103 patients, 71 (68.9%) were male and 32 (31.1%) were female. The mean age of the patients was 68.5. Of the103 patients, 33 had type 1 arch, 30 had type 2 arch, and 16 had type 3 arch (Table 1). The risk factors were ischemic cerebrovascular diseases in 55 (53.4%) patients, hypertension in 56 (54.4%), hyperlipidemia in 22 (21.4%), diabetes in 33 (32.0%), and atrial fibrillation in 1 (1.0%). Further, 64 patients (62.1%) had vertigo, 20 (19.4%) had visual symptoms, 5 (4.8%) had syncope, 6 (5.8%) had TIAs, and 2 (1.9%) had ischemic strokes (Table 2).

The left VA origin stenosis degree revealed that 14 (13.5%) patients had <50%, 11 (10.6%) had 50%–69%, 21 (20.3%) had 70%–99%, 4 (3.8%) had near occlusion, and 5 (4.8%) had total occlusion (Table 3). Thirty-six patients had stents implanted in their right vertebral arteries, 16 in their left vertebral arteries, and 3 in both vertebral arteries (Table 4). The mean age of patients who had stent implantations was 65.97±7.9 years. Twenty-three patients (48.9%) who had stent implantations had type 1 arch. During the procedure, bradycardia developed in three cases, and atropine was administered for its intervention. Hypotension developed in two cases and dopamine along with 0.9% NaCl was administered for its intervention. One of the patients developed a speech disorder alongwith a complaint of imbalance 24 hours after the procedure. A magnetic resonance imaging (MRI) examination revealed an infarct on the left posterior inferior cerebellar artery (PICA) supply area. The patients' symptoms subsided with minimal sequelae. Two patients had TIAs along with complaints of dizziness and weakness on the left side. Hemorrhage and hematoma developed in the femoral artery region 2 hours after the stent implantation in two cases. One unit transfusion was applied (Table 5).

Table 1. Arcus types

Arcus types	n=103	Percent
Type1	33	32.0
Type2	30	29.1
Type3	16	15.5
Type1 bovine	14	13.6
Type2 bovine	6	5.8
Type3 bovine	4	3.9
Total	103	100.0

Table 2. Patient characteristics

Patients	Total n=103(%)
Age (years)	68.5
Indication for procedure	
Vertigo	64 (62.1%)
Visual disturbance	20 (19.4%)
Syncope	5 (4.8%)
CVA/TIA	6 (5.8%)
Ataxia	4 (3.8%)
Drop attack	2 (1.9%)
Comorbidities	
History of stroke	55 (53.3)
Hypertension	56 (54.3)
Diabetes	33 (32)
Hyperlipidemia	22 (21.3)
Smoking	8 (7.7)
Heart failure	8 (7.7)
Atrial fibrillation	1 (0.9)
Coronary artery disease	29 (28.1)

Values are mean±SD or n (%). CVA: cerebrovascular accident; TIA: transient ischemic attack

DISCUSSION

Vertebral artery stenosis is among the most common causes of posterior ischemic symptoms. VA stenosis may be intra- or extracranial, but it frequently occurs at the subclavian artery exit level. VA stenosis is one of the correctable causes of posterior systemic stroke and can now be diagnosed with more ease through the use of modern imaging methods such as computerized tomography (CT), MRI angiography, and DSA.

Vertebral artery stenoses reduce posterior cerebral perfusion causing vertebrobasilar insufficiency. They are also an important embolic source for posterior circulation. The risk of recurrent stroke after 5 years of vertebrobasilar TIA or strokes is reported to

Table 3. Patients' intracranial and extracranial stenosis grades

Angiography stenosis level	Left vertebral artery origin n (%)	Left vertebral artery intracranial n (%)	Right vertebral artery origin n (%)	Right vertebral artery intracranial n (%)
No stenosis	48 (46.6)	89 (86.4)	40 (38.8)	99 (96.1)
<50%	14 (13.5)	10 (9.7)	15 (14.5)	3 (2.9)
50%–69%	11 (10.6)	2 (1.9)	8 (7.7)	1 (0.9)
70%–99%	21(20.3)	2 (1.9)	29 (28.1)	0 (0)
Near occlusion	4 (3.8)	0 (0)	7 (6.7)	0 (0)
Occlusion	5 (4.8)	0 (0)	4 (3.8)	0 (0)

Table 4. Patients implanted with stents

Stent–implanted patients	n=103	Percent
Left vertebral artery	16	15.5
Right vertebral artery	36	35.0
Both vertebral arteries	3	2.9

Table 5. Procedural complications

Procedural complications	n=103	Percent
Bradycardia	3	2.91
Hypotension	2	1.94
Stroke	1	0.97
Transient ischemic attack	2	1.94
Hematoma/bleeding requiring transfusion	3	2.91

be 22%–35% (4-7). Medical, surgical, and endovascular methods are used for treating VA stenosis.

Surgical treatment has been abandoned because of complications such as Horner's syndrome (15%–28%) and laryngeal nerve injury (2%) (5).

Endovascular treatment should be considered the first option for patients with asymptomatic bilateral carotid occlusion where VA enables the collateral circulation or in the case of posterior strokes developing despite appropriate medical treatment. Technical success varies according to the risk factors of patients, the state of the endovascular treatment materials, the degree of stenosis, the type of arch, and the experience of the interventionalist neurologist performing the procedure (8, 9).

Arcus aorta typing, determined by the distance of the point where the truncus brachiocephalicus originates from the arcus aorta to the arcus aorta peak point, is important for intravenous procedures for diagnosis and treatment of supra-aortic and cerebral vessels, which are becoming increasingly more common (10). As one goes from type 1 to type 3, catheterization of the supra-aortic vessels and the planned procedures afterwards become more complicated. For this reason, knowing the aortic arch type is important in the planning of intravenous procedures. Overall, 32% of the patients had type 1 arch, 29.1% type 2 arch, 15% type 3 arch, 13.6% type 1 bovine arch, 5.8% type 2 bovine arch, and 3.9% type 3 bovine arch.

In terms of risk factors that play an important role in technical success and prognosis, ischemic cerebrovascular diseases were found in 53.4% patients, hypertension in 54.4%, hyperlipidemia in 21.4%, diabetes in 32%, a history of smoking in 7.8%, cardiac insufficiency in 7.8%, atrial fibrillation in 1%, and coronary artery disease in 28.2% patients.

In a study by Stayman et al. (11) focusing on endovascular treatment of extracranial VA stenosis, the rate of strokes was 1.1% and that of TIAs was 0.8%. In our study, the ischemic stroke rate was 1%, and the transient ischemic stroke rate was 3.6%.

The technical success rate in a stent implantation study by Motarjeme et al. (12) for 39 patients' vertebral orifice was 92.3%. In our study, endovascular treatment was successful for 55 patients who had stent implantations, implyinga 100% technical success.

CONCLUSION

Vertebral artery stenosis is one of the correctable causes of posterior systemic stroke and can now be diagnosed with more ease through the use of modern imaging methods. Balloon angioplasty or stent-assisted endovascular treatment is an effective treatment with low morbidity and mortality for patients with a single VA or who do not respond to medical treatment due to cerebral vascular pathology.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University School of Medicine (date:01/18//2018, decision no:2018/27).

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Yı.İ., Yu.İ.; Design – Yı.İ., Yu.İ., S.G.; Supervision – S.G.; Data Collection and/or Processing – Yu.İ., S.G.; Analysis and/or Interpretation – Yı.İ., Yu.İ., S.G.; Literature Search – Yı.İ., Yu.İ., S.G.; Writing Manuscript – Yı.İ, Yu.İ.; Critical Review – Yı.İ.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

REFERENCES

1. Coward LJ, McCabe DJ, Ederle J, Featherstone RL, Clifton A, Brown MM. Long-term outcome after angioplasty and stenting for symptomatic vertebral artery stenosis compared with medical treatment in the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomized trial. Stroke 2007; 38: 1526-30.
2. Compter A, van der Worp HB, Schonewille WJ, Vos JA, Boiten J, Nederkoorn PJ, et al. Stenting versus medical treatment in patients with symptomatic vertebral artery stenosis: a randomised open-label phase 2 trial. Lancet Neurol 2015; 14: 606-14.
3. Drazyk AM, Markus HS. Recent advances in the management of symptomatic vertebral artery stenosis. Curr Opin Neurol 2018; 31: 1-7.
4. Markus HS, Larsson SC, Kuker W, Schulz UG, Ford L, Rothwell PM, et al. Stenting for symptomatic vertebral artery stenosis The Vertebral Artery Ischaemia Stenting Trial. Neurology 2017; 89: 1229-36.
5. Jenkins JS, White CJ, Ramee SR, Collins TJ, Chilakamarri VK, McKinley KL, et al. Vertebral artery stenting. Catheter Cardiovasc Interv 2001; 54: 1-5.
6. Savitz SI, Caplan LR. Vertebrobasilar disease. N Engl J Med 2005; 352: 2618-26.
7. Jenkins JS, Stewart M. Endovascular treatment of vertebral artery stenosis. Prog Cardiovasc Dis 2017; 59: 619-25.
8. Wehman JC, Hanel RA, Guidot CA, Guterman LR, Hopkins LN. Atherosclerotic occlusive extra cranial vertebral artery disease: indications for intervention, endovascular techniques, short-term and long-term results. J Interv Cardiol 2004; 17: 219-32.
9. Henry M, Polydorou A, Henry I, Polydorou A, Hugel M. Percutaneous transluminal angioplasty and stenting of extracranial vertebral artery stenosis. The Carotid and Supra-Aortic Trunks: Diagnosis, Angioplasty and Stenting, 2nd Edition, 2003; 458-72.
10. Patil ST, Meshram MM, Kamdi NY, Kasote AP, Parchand MP. Study on branching pattern of aortic arch in Indian. Anat Cell Biol 2012; 45: 203-6.
11. Stayman AN, Nogueira RG, Gupta R. A systematic review of stenting and angioplasty of symptomatic extracranial vertebral artery stenosis. Stroke 2011; 42: 2212-6.
12. Motarjeme A, Keifer JW, Zuska AJ. Percutaneous transluminal angioplasty of the vertebral arteries. Radiology 1981; 139: 715-7.

How to cite:

İnanç Y, Giray S, İnanç Y. Our Experiences with Vertebral Artery Stents. Eur J Ther 2018; 24(3): 178–81.

European Journal of Therapeutics

DOI: 10.5152/EurJTher.2018.237

Case Report

Effects of IVIG and Pulse Steroid Therapy in a Case of Allopurinol Induced DRESS Syndrome

Selma Korkmaz[1], Elif Günay[2], Nuray Can[3], Sezin Fıçıcıoğlu[4], Süleyman Pişkin[4]

[1]Department of Dermatology, Süleyman Demirel University, School of Medicine, Isparta, Turkey

[2]Clinic of Dermatology, Kaçkar State Hospital, Rize, Turkey

[3]Department of Pathology, Trakya University, School of Medicine, Edirne, Turkey

[4]Department of Dermatology, Trakya University, School of Medicine, Edirne, Turkey

ABSTRACT

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a drug reaction that causes peripheral eosinophilia and primarily renal and hepatic insufficiency and dysfunction of other visceral organs with skin rash as noticeable symptom. Early diagnosis and discontinuation of the culprit drug along with rapid treatment are required to reduce mortality rate. Herein, a case of allopurinol-induced DRESS syndrome is presented in which the patient was resistant to medium dose systemic steroid therapy and was treated with pulse steroid and IVIG treatment successfully. Pulse steroid therapy may be an alternative treatment option in refractory DRESS syndrome.

Keywords: DRESS syndrome, allopurinol, pulse steroid

INTRODUCTION

"Drug Reaction with Eosinophilia and Systemic Symptoms" (DRESS) is a drug reaction that causes peripheral eosinophilia and primarily renal and hepatic insufficiency and dysfunction of other visceral organs with skin rash as noticeable symptom. Miscellaneous drugs such as anticonvulsants, sulphonamids, dapson, allopurinol, minocycline, fluoroquinolone, and gold salts may cause this reaction. The symptoms are initial fever manifestation, skin rash, lymphadenomegaly, lymphocytosis, and eosinopilia, which emerge within in 2–8 weeks after the therapy (1-3). The other symptoms include primarily hepatic, renal, cardiac, and pulmonary failure. The mortality rate of the disease is higher than 10%, which is usually caused due to hepatic failure. Skin findings vary from maculopapular rash to erythroderma.

Rash, fever, and visceral organ failure are the major manifestations of the disease, which can also be seen primarily in infections and many other diseases. The early and accurate differential diagnosis of DRESS syndrome is important because of organ failures and skin symptoms (4). Although allopurinol-induced DRESS syndrome generally responds to corticosteriod therapy, there could be some cases resistant to steroid. Herein, a case of allopurinol-induced DRESS syndrome is presented in which the patient was resistant to steroid therapy but responded to IVIG and pulse steroid treatment, as given in the literature.

CASE PRESENTATION

A 45-year-old woman with extended skin rashes on the body surface and fever was admitted to our clinic. Her body temperature and blood pressure were 39℃ and 120/80 mmHg, respectively. She had edema and maculopapular rash on face, erytematous maculopapular and locally targetoid rash on neck and trunk, membranous secretion on conjunctiva, superficial ulcerations on oral mucosal surfaces, and fissures and hemorrhagic crusts on lips (Figure 1). There were locally targetoid and consolidated erytematous macular rash on forearms, legs, and back. There was no lesion on palmoplantar regions. Her medical history included bipolar effective disorder for 28 years, type 2 diabetes mellitus for 15 years, and chronic renal insufficiency for 6 months; she had been consuming lithium and oral antidiabetic drugs for these diseases. Additionally, she started allopurinol dosage of 300 mg/day 15 days ago.

Eosinophilia, trombocytopenia, increase in hepatic transaminases and renal function parameters, and inflammatory markers (erytrocyte sedimentation rate and C-reactive protein) were also observed. No infectious focus relating to fever could be determined. Viral markers such as anti-HCV, HBSAg, anti-Hep B IgM, anti-CMV IgM, and anti EBV IgM were negative. The blood and urine cultures were also negative. Superficial ultrasound examination revealed 2 cm size lymph nodes in both axillary and inguinal regions. Her echocardiography and electrocardiogram were normal. The histological view of punch

ORCID IDs of the authors: S.K. 0000-0003-3877-3976; E.G. 0000-0002-9943-0355; N.C. 0000-0003-2554-6432; S.F. 0000-0002-7934-3633; S.P. 0000-0002-0999-2267.

This case was presented as a poster at the congress of Aegean Dermatology Days in 2015 (5–10 May 2015, Fethiye, Turkey).

Corresponding Author: Selma Korkmaz **E-mail:** selmakorkmaz35@gmail.com

Received: 15.10.2017 • **Accepted:** 11.05.2018

biopsy revealed patterns of interphase reaction, including lymphocyte egzocytosis, basal liquefactive changes, epidermal necrosis indicating Steven–Johnsons syndrome/toxic epidermal necrosis, and dermal perivascular inflammation composed of lymhocytes, histiocytes, and eosinophil leukocytes (Figure 2a, b).

The patient was diagnosed with allopurinol-induced DRESS syndrome in accordance with these clinical and histophatological findings, so the use of allopurinol was stopped immediately. 1 mg/kg/day methylprednisolone therapy was started. She responded for the first 5 days but then her general state deteriorated leading to increased fever, tachycardia, tachypnea, and hypotension. No infectious symptoms were found to explain this condition. It was assumed to be due to steroid resistance, and we gave intravenous immunoglobulin 0.5 mg/kg/day for 3 days together with 500 mg pulse methylprednisolone twice a day. On the second day of treatment, her general state was stabilized, the fever reduced, respiration became normal, and urine excretion was increased in addition to amelioration in hepatic and renal function parameters. On the third day of therapy, steroid dose was decreased to 1 mg/kg/day. After skin lesions dissolved, methylprednisolone dose was reduced and then stopped within 3 weeks. Her skin rash totally disappeared with fine desquamation on follow-up visits (Figure 3). Written informed consent was taken from the patient. No relapse was observed on follow-ups.

Figure 1. There are erythematous maculopapular rashes on forearms, legs, and trunk in addition to facial edema

DISCUSSION

Drug Reaction with Eosinophilia and Systemic Symptoms syndrome is an acute and severe drug reaction presented with fever, systemic symptoms, marked eosinophilia, and commonly maculopapular skin rashes with a wide range of clinical presentation variating from toxic epidermal necrolysis, erytema multiforme, exfoliative dermatitis to erythroderma (1, 2). This condition develops within 2–6 weeks after starting the drug. It has 8–10% mortality ratio. The most initial finding is persistent fever. Facial edema and maculopapular skin rashes start from trunk and expand to face, and extremities are seen in 90% of the cases. In this case, there was fever resistant to antibiotics along with widely erytematous maculopapular polimorphous skin rash similar to the cases in other literature. DRESS syndrome affects many visceral organs, primarily liver and kidney. Mild increase in transaminases and haematological abnormalities such as eosinophilia and atypical lymphocytes are shown in half of the cases (4, 5). In our case, increase in transaminases and eosinophilia is observed too but no atypical lymphocytes were seen in peripheral blood.

The most frequently responsible agents in DRESS syndrome are aromatic anticonvulsants (e.g., carbamazepine), allopurinol, sulphonamides, minocycline, other antibiotics, antiretroviral agents, and dapsone (1, 2, 4). Allopurinol-induced DRESS syndrome occurs more frequently in older patients with renal dysfunction. It is

Figure 2. a, b. Interphase reaction, including lymphocyte egzocytosis, basal liquefactive changes, epidermal necrosis, and dermal perivascular inflammation composed of lymhocytes, histiocytes, and eosinophil leukocytes (HE×100)

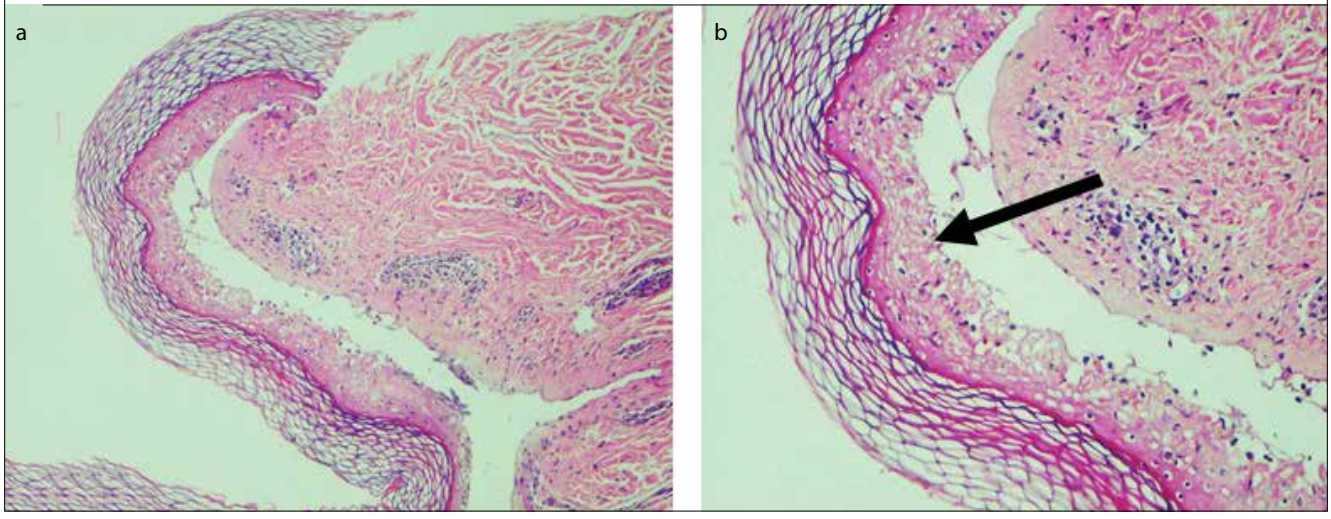


Figure 3. Skin rash disappeared totally after therapy

suggested that in allopurinol-induced DRESS syndrome oxypurinol, a metabolite of allopurinol, is less excreted so it accumulates, then stimulates CD4 (+) and CD8 (+) T lymphocytes, and then increases interleukin 5 which triggers the inflammatory cascade stimulating eosinophils and therefore initiating tissue damage (6, 7). In this case, chronic renal insufficiency might have facilitated the development of allopurinol toxicity. Singer and Wallace had established Allopurinol Hypersensitivity Syndrome criteria for evaluating allopurinol-related reactions (8). In this case, in addition to the first two criteria, all of last criteria were positive.

Drug Reaction with Eosinophilia and Systemic Symptoms syndrome could mimic several disorders because of the involvement of various organs; therefore, it could be diagnosed solely by excluding many clinical entities. A standard scoring system was assessed with the study RegiSCAR, which was a polycentral study, to build a consensus on diagnosis. With this scoring system, cases can be classified as "definite DRESS, highly probable, probable DRESS, and no DRESS" (1).

In DRESS syndrome, liver and lymph node involvements are reported more frequently than cardiac and pulmonary involvements (2). In this case, hepatic, renal, and haematological involvements were determined.

It is reported that reactivation of Ebstein-Barr Virus, HHV-6, HHV-8, and CMV might frequently worsen this condition, and the syndrome could be intensified with viral replication (1, 2, 4, 5, 8). However, the viral markers were negative in our case.

The initial approach on DRESS syndrome should be to stop the use of the culprit drug. It is suggested to continue systemic corticotherapy for 6–8 weeks to treat skin and visceral infections and to prevent the relapses. IVIG, plasmapheresis, rituximab, and valgancyclovir are recommended in the cases resistant to corticosteroid therapy (8-10). It is shown that IVIG therapy could be useful in DRESS syndrome triggered by anticonvulsants (11, 12). To the best of our knowledge, usage of IVIG therapy in allopurinol-induced DRESS syndrome has not been reported in the literature yet. In this case, because of the resistance to steroid therapy, 0.5 mg/kg/day IVIG therapy was given for 3 days and 500 mg/day pulse methylprednisolone for 2 days. From the second day of this regimen, clinical and laboratory findings were ameliorated rapidly.

CONCLUSION

As the result, the first step of the therapy for allopurinol-induced DRESS syndrome is discontinuing the use of allopurinol and starting systemic corticosteroid therapy. Nevertheless in cases resistant to these implications, we suggest that pulse steroid and IVIG could be an alternative treatment option.

Informed Consent: Written informed consent for photography and publishing was obtained from patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.K.; Design – S.K., N.C.; Data Collection and/or Processing – E.G.; Analysis and/or Interpretation – S.K., E.G., S.F., S.P.; Writing Manuscript – S.K.; Critical Review – S.F.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

REFERENCES

1. Kardaun SH, Sekula P, Valeyrie -Allanore L, Liss Y, Chu CY, Creamer D, et al. RegiSCAR study group. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adevrse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol 2013; 169: 1071-80.
2. Bakkal SU, Tufan ZK, Bulut C, Boyraz S, Vahaboğlu G. A case of DRESS Syndrome mimicking Sepsis. Klimik Derg 2011; 24: 132-4.
3. Alkhateeb H, Said S, Cooper CJ, Gaur S, Porres-Aguilar M. DRESS syndrome following ciprofloxacin exposure: An unusual association. Am J Case Rep 2013; 4: 526-8.
4. Emre S, Akoğlu G, Metin A, Demirseren DD, Kurtoğlu G. Evaluation of clinical features of 11 cases with DRESS syndrome. Turkderm 2013; 47: 218-22.
5. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, Roujeau JC. The DRESS syndrome: a literature review. Am J Med 2011; 124: 588-97.
6. Erturan İ, Başak PY. A case of Allopurinol Induced Dress Syndrome. Turk J Dermatol 2013; 7: 100-2.
7. Guleria VS, Dhillon M, Gill S, Naithani NJ. Res Pharm Pract. Ceftriaxone induced drug rash with eosinophilia and systemic symptoms. 2014; 3: 72-4.
8. Singer JZ, Wallace SL. The allopurinol hypersensitivity syndrome. Unnecessary morbidity and mortality. Arthritis Rheum 1986;29:82-7.
9. Fernando SL. Drug-reaction eosinophilia and systemic symptoms and drug-induced hypersensitivity syndrome. Australas J Dermatol 2014; 55: 15-23.
10. Kito Y, Ito T, Tokura Y, Hashizume H. High-dose intravenous immunoglobulin monotherapy for drug-induced hypersensitivity syndrome. Acta Derm Venereol 2012; 92: 100-1.
11. Santhamoorthy P, Alexander KJ, Alshubaili A. Intravenous immunoglobulin in the treatment of drug rash eosinophilia and systemic symptoms caused by phenytoin. Ann Indian Acad Neurol 2012; 15: 320-2.
12. Dredge DC, Parsons EC, Carter LP, Staley KJ. Anticonvulsant hypersensitivity syndrome treated with intravenous immunoglobulin. Pediatr Neurol 2010; 43: 65-9.
13. Comfere NI, Sartori-Valinotti JC, Bruce AJ, Drage LA. Successful treatment of lamotrigine-associated drug hypersensitivity syndrome with intravenous IgG. J Am Acad Dermatol 2012; 66: 249-50

How to cite:

Korkmaz S, Günay E, Can N, Fıçıcıoğlu S, Pişkin S. Effects of IVIG and pulse steroid therapy in a case of allopurinol induced DRESS syndrome. Eur J Ther 2018; 24(3): 182–4.

European Journal of Therapeutics
DOI: 10.5152/EurJTher.2017.266
Case Report

Tuberculous Arthritis in the Elbow Joint in an Adolescent

Mehmet Öztürk[1], Ayşenur Akatlı[2], Ahmet Sığırcı[3], Nusret Akpolat[2]
[1]Department of Radiology, Selçuk University School of Medicine, Konya, Turkey
[2]Departments of Pathology, İnönü University School of Medicine, Malatya, Turkey
[3]Division of Pediatric Radiology, İnönü University School of Medicine, Malatya, Turkey

ABSTRACT
Musculoskeletal system tuberculosis (TB) accounts for approximately 10% of all TB cases, excluding those involving pulmonary TB. Elbow TB is extremely rare and is seen in 2%–5% of musculoskeletal system cases. The diagnosis of TB arthritis is very difficult because its onset is insidious and progress is slow and there are nonspecific local and systemic symptoms. A delay in treatment can result in irreversible osteoarticular destruction. This paper presents the clinical and radiological findings of a 12-year-old adolescent patient with elbow TB arthritis.
Keywords: Adolescent, tuberculosis, elbow joint

INTRODUCTION

Tuberculosis (TB) arthritis is generally seen in weight-bearing joints or joints exposed to repeated trauma. Vertebrae are affected in half of the cases, and the hip and knee joints can be affected, although less frequently. Upper extremity joint involvement is extremely rare (1, 2).

In as many as half of TB arthritis cases, no proof of active infection, previous infection, or history of exposure to infection can be found. In addition, diagnosis can be delayed because of a negative tuberculin skin test that does not discount diagnosis and when the clinical and radiological findings are similar to those of a number of joint diseases (3). As morbidity and mortality increases when treatment is delayed, timely diagnosis is of the greatest importance. Appropriate and sufficient radiological evaluation plays a key role in early diagnosis.

The aim of this paper is to present the clinical and radiological findings of a case involving a 12-year-old adolescent who had TB arthritis in the elbow joint.

CASE PRESENTATION

A 12-year-old girl presented to our hospital with complaints of pain and swelling in the left elbow for the last 2 months. Any previous occurrence of TB was unknown, and there was no history of any disease that had suppressed the immune system or of any trauma or arthritis. Physical examination revealed that there was swelling, restricted movement, increased temperature, and sensitivity in the left elbow joint. The laboratory values included an erythrocyte sedimentation rate of 38 mm/s, C-reactive protein level of 5.5 mL/L, and leukocytes of 6.7×10^9/L. The skin tuberculin test, TB blood culture, and real-time polymerase chain reaction were reported as positive. Acido-resistant staining was negative. A written informed consent was obtained from the patient's parents.

The lateral and anterior–posterior (AP) radiographs of the left elbow revealed widespread, nonsclerotic, and lytic areas with irregular borders, encompassing the epicondyles, ulna and radial head, and lytic foci in the cortex contours. These radiographs also showed separation of the humerus periosteum and periarticular osteoporosis (Figure 1).

Computed tomography (CT) of the left elbow revealed effusion in the joint space, lytic areas destroying the cortex in the humerus epiphysis, proximal and metaphyseal sections of the ulna and radius, and fluid collection extending to the soft tissue (Figure 2).

Magnetic resonance imaging (MRI) of the left elbow showed increased effusion in the joint space, synovial thickening and disrupted cortical integrity together with contrast in the bone structures, and widespread bone marrow edema. In addition, fluid collection was observed, showing contrast extending to the soft tissue, which was disrupting the cortical integrity in the distal ulna (Figure 3).

Thoracic CT revealed nodular lesions in the posterior of the right lung superior lobe, the largest lesion measuring 19×13 mm. There were calcifications in the middle lobe medial segment as

ORCID IDs of the authors: M.Ö. 0000-0001-5585-1476; A.A. 0000-0002-9677-2456; A.S. 0000-0001-9221-0002; N.A. 0000-0002-9138-2117.
This study was presented at the 36th National Radiology Congress, 21–25 October 2015, Antalya, Turkey.
Corresponding Author: Mehmet Öztürk **E-mail:** drmehmet2121@gmail.com
Received: 25.11.2017 • **Accepted:** 03.02.2018

Figure 1. a, b. On the lateral (a) and AP (b) radiographs of the left elbow, widespread, nonsclerotic, lytic areas with irregular borders were seen in the epicondyles and ulna and radial head, and there was thickening of the surrounding soft tissue

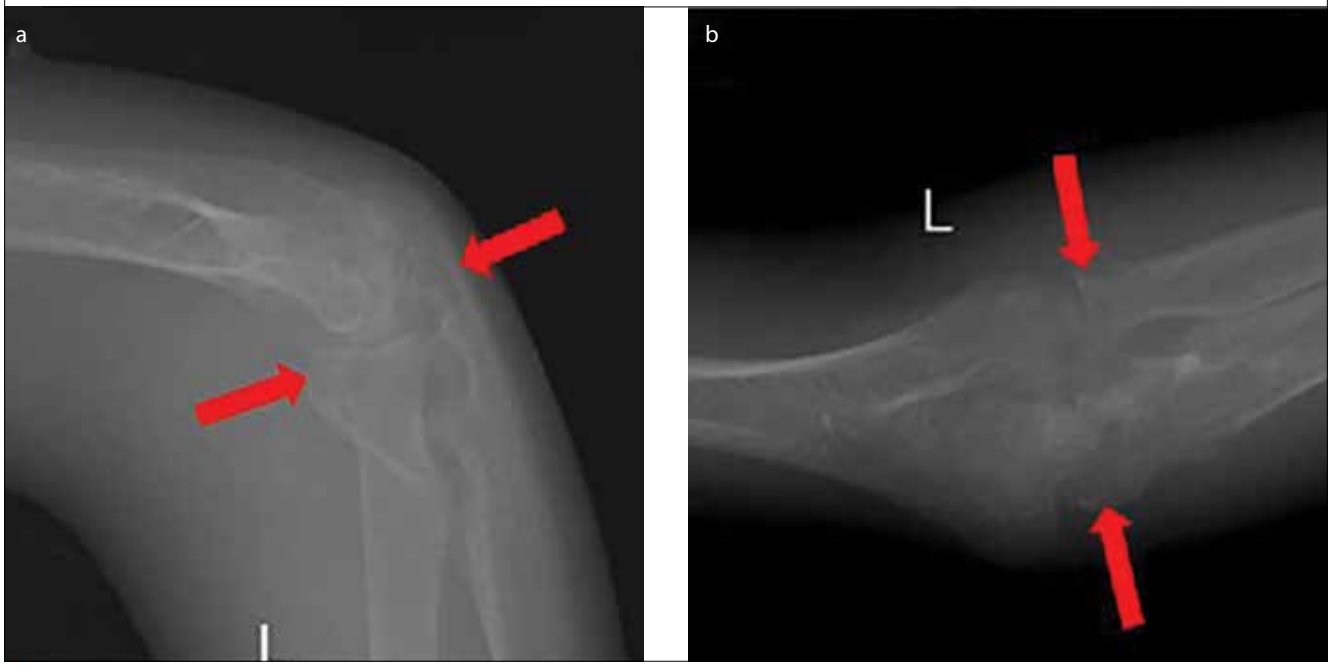
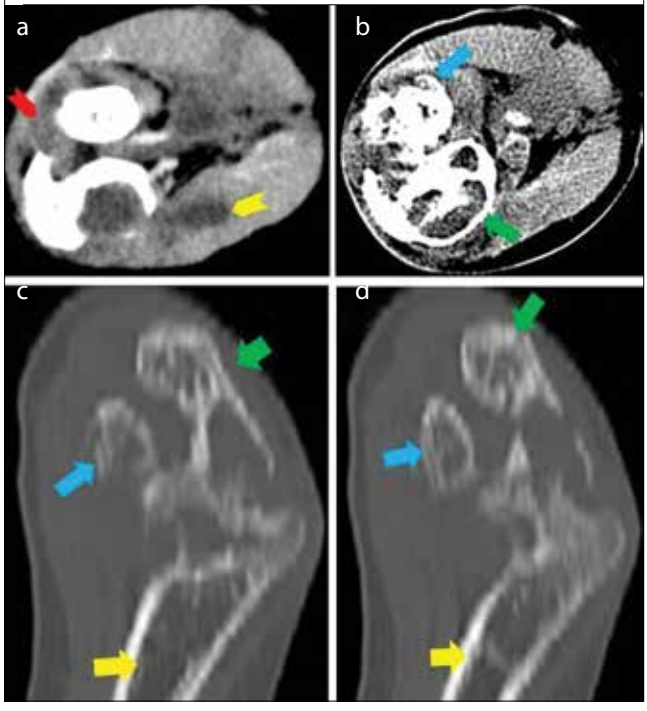


Figure 2. a-d. On CT of the left elbow, in the axial slices, (a) effusion was seen in the joint space (red arrow head), with locular collection extending to the soft tissue (yellow arrowhead), (b) the lytic areas were destroying the cortex in the proximal sections of the ulna (green arrow) and radius (blue arrow), and (c, d) on the coronal sections of the olecranon–distal humerus (yellow arrow), widespread lytic areas were destroying the cortex in the proximal sections of the ulna (green arrow) and radius (blue arrow)



well as calcified lymph nodes in the paratracheal, pretracheal, and right hilum (Figure 4).

Synovectomy was performed by an orthopedic surgeon. Subsequent histological examination of the joint synovial membrane showed granulomatous inflammation (Figure 5). Anti TB treatment started.

DISCUSSION

Osteoarticular TB is usually monoarticular and is polyarticular in only 10%–15% of cases. It is rarely seen in non-weight-bearing joints such as the elbow. In the upper extremity, the shoulder is most often affected, followed by the elbow (4). In addition to reaching the joint space by the adjacent hematogenous and lymphatic pathways, bacteria may settle by direct inoculation. In terms of pathogenesis, juxta-articular demineralization, local bone destruction, and periosteal new bone formation occur because of reactive hyperemia at the beginning of the disease. When the disease reaches the subchondral region, there is separation in the articular cartilage, resulting in cartilage and bone erosion, destruction, and effusion. When the process is prolonged, fibrinous material spreads through necrotic cartilage to the synovial space, tendon sheath, and bursae. If treatment is not given in the early period, para-articular soft tissue mass, cold abscess, and sinus tract can form (4, 5).

Clinically, articular TB is extremely difficult to diagnose. The most frequent findings are pain, swelling, and restricted movement in the early stage and deformity and loss of function in the later stage. A delay in diagnosis may lead to septic arthritis and irreversible osteolytic complications. There may not be a history of either TB or exposure to TB, and in half of the cases, pulmonary

Figure 3. a, b. On MRI of the left elbow, (a) fat-suppressed coronal image revealed disrupted cortical integrity in the proximal ulna (yellow arrow) and fluid collection, showing contrast extending to the soft tissue (pink arrow), and (b) synovial thickening and contrast were found on the T1-weighted axial post-contrast image (blue arrow)

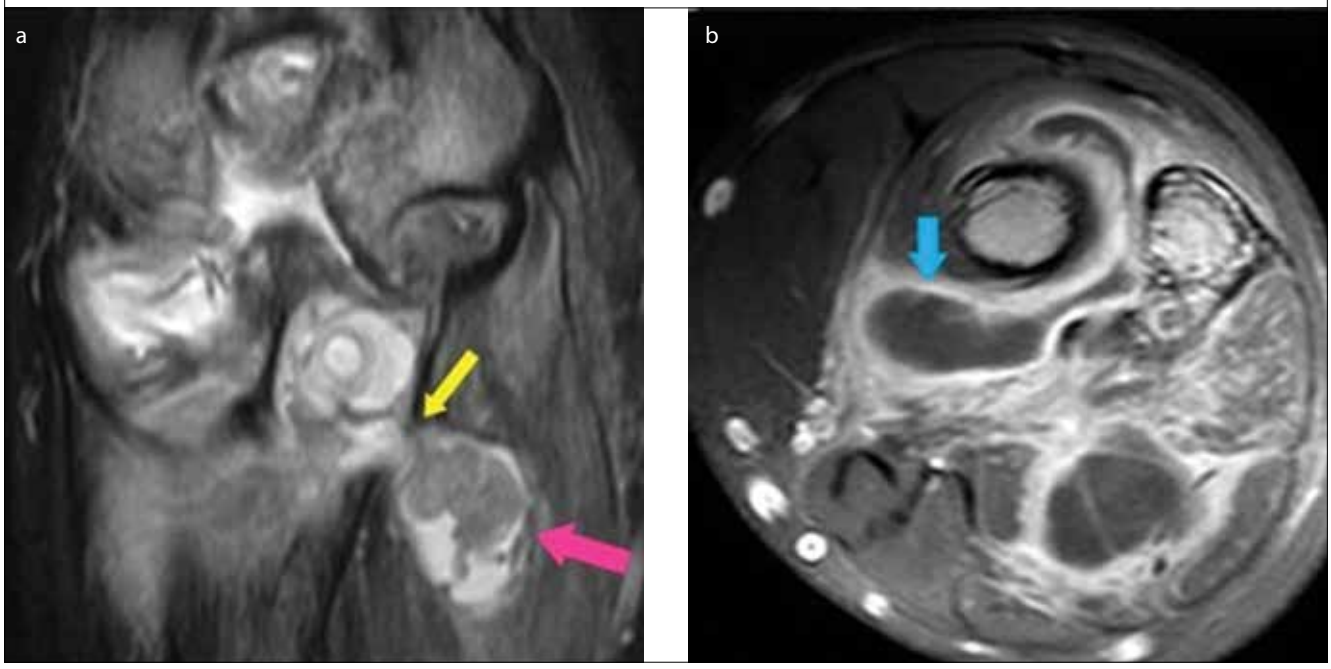
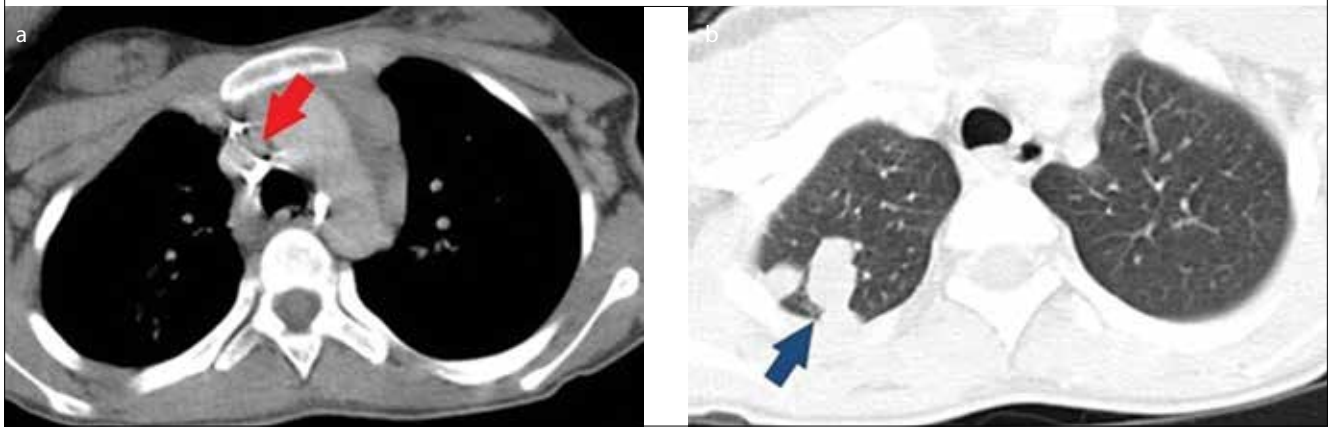


Figure 4. a, b. On thoracic CT, (a) there was a mediastinum window axial slice and calcified lymph nodes in the left paratracheal, pretracheal, and right hilum (red arrow), and (b) a parenchyma window axial slice and nodular lesions in the posterior of the right lung superior lobe (blue arrow)

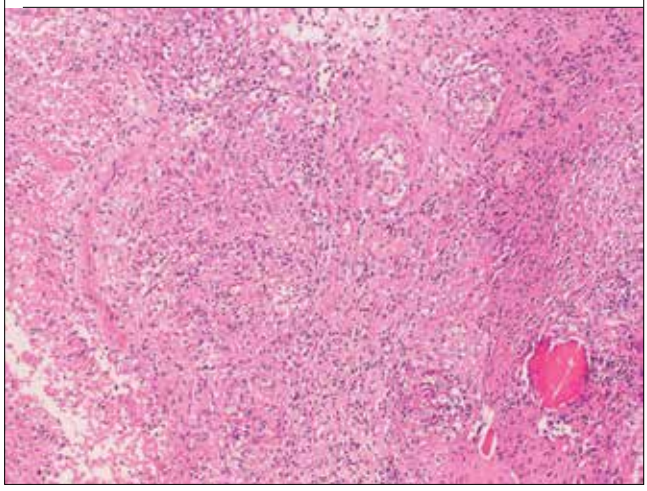


involvement cannot be determined radiologically (6). In the current case, no findings of deformity were determined in the postoperative 6-month follow-up examination. Lung radiograph and thoracic CT showed parenchymal consolidation and calcified lymph nodes, which are compatible with previous primary pulmonary TB.

During the early stage of TB arthritis, radiographic findings are not specific and the first lesions can easily be overlooked. Soft tissue edema or effusion may also be seen. On progression of the disease, periarticular osteopenia develops, and varying degrees of cartilage and periarticular bone destruction start occurring in the chronic phase (7). On direct radiographs, the triad of Phemister is seen, comprising osteoporosis around the joint, peripheral bone erosions, and narrowing of the joint space (8). The distal humerus and proximal ulna are most frequently affected. Especially in children, the "ice-cream scoop" appearance in the proximal ulna on direct radiographs is significant in terms of TB. As long as there is no additional pyogenic infection, periosteal reaction is rarely seen (9). In the current case, bone erosion and periarticular osteoporosis together with soft tissue swelling were observed as the late-stage findings.

Computed tomography evaluation of the degree of bone destruction, spread to soft tissue, and formation of sequestrum is useful (10). MRI is extremely effective in showing osteomyelitis

Figure 5. Histopathological report of synovial membrane of the left elbow joint showing multiple granulomas, some with areas of necrosis



and bone marrow edema, chondral and subchondral bone erosion, synovial thickening, joint effusion, narrowing of the joint space, and spread to the surrounding soft tissue. Bone marrow edema is hypointense on T1-weighted images and hyperintense on T2-weighted images and is seen after intravenous gadolinium enhancement. Synovial thickening in TB arthritis is seen as hypointense on T2-weighted images, which is different from other synovial arthropathies (11, 12). No sequestrum was determined on CT in the current case. Synovial thickening and spread to the soft tissue were clearly seen on MRI.

Radiological imaging provides useful information about the findings and spread of the disease in elbow TB (13, 14). However, aspiration or synovial biopsy is necessary for a definitive diagnosis.

Pyogenic arthritis, pigmented villonodular synovitis, hemophilic arthropathy, rheumatoid arthritis, osteochondromatosis, and neoplasms should be considered in the differential diagnosis of patients with elbow involvement (15).

CONCLUSION

Tuberculosis arthritis should be considered in the differential diagnosis for adolescent patients who present with complaints of pain and swelling in the elbow. Sufficient and appropriate clinical and radiological evaluation is extremely important for preventing morbidity and mortality related to TB arthritis.

Informed Consent: Written informed consent was obtained from patients father who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept – M.Ö.; Design - A.S.; Supervision – A.A.; Resource – MÖ., A.A.; Materials – A.S.; Data Collection and/or Processing – N.A.; Analysis and/or Interpretation – N.A.; Literature Search – M.Ö, A.A; Writing – A.S.; Critical Reviews – N.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

REFERENCES

1. Akgun U, Erol B, Cimsit C, Karahan M. Tuberculosis of the knee joint: a case report. Acta Orthop Traumatol Turc 2008; 42: 214-8.
2. Yazıcı A, Kayan G, Yaylacı S, Demir MV, Karakeçe E, Tamer A, et al. Tuberculous arthritis of the elbow joint: A case report. Eur J Rheumatol 2016; 3: 142-3.
3. Agarwal A, Rastogi A. Tuberculosis of the Elbow Region in Pediatric Age Group - Experiences from a Single Centre. J Hand Surg Asian Pac Vol 2017; 22: 457-63.
4. Aggarwal A, Dhammi I. Clinical and radiological presentation of tuberculosis of the elbow. Acta Orthop Belg 2006; 72: 282-7.
5. Lupatkin H, Brau N, Flomenbergh P and Simberkoff MS. Tuberculosis abscesses in patients with AIDS. Clin Infect Dis 1992; 14: 1040-4.
6. Kramer N, Rosenstein ED. Rheumatologic Manifestations of tuberculosis. Bull Rheum Dis 1997; 46: 5-8.
7. Haygood TM, Williamson SL. Radiographic findings of extremity tuberculosis in childhood: back to the future? Radiographics 1994; 14: 561-70.
8. Domingo A, Nomdedeu M, Tomas X, Garcia S. Elbow tuberculosis: An unusual location and diagnostic problem. Arch Orthop Trauma Surg 2005; 125: 56-8.
9. Agarwal A, Mumtaz I, Kumar P, Khan S, Qureshi NA. Tuberculosis of the elbow joint in children: a review of ten patients who were managed nonoperatively. J Bone Joint Surg Am 2010; 92: 436-41.
10. Stabler A, Reiser MF. Imaging of spinal infection. Radiol Clin North Am 2001; 39: 115-35.
11. Hong SH, Kim SM, Ahn JM, Chung HW, Shin MJ, Kang HS. Tuberculous versus pyogenic arthritis: MR imaging evaluation. Radiology 2001; 218: 848-53.
12. Sanghvi DA, Iyer VR, Deshmukh T, Hoskote SS. MRI features of tuberculosis of the knee. Skeletal Radiol 2009; 38: 267-73.
13. Domingo A, Nomdedeu M, Tomas X, Garcia S. Elbow tuberculosis: An unusual location and diagnostic problem. Arch Orthop Trauma Surg 2005; 125: 56-8.
14. Watts HG, Lifeso RM. Tuberculosis of bones and joints. J Bone Joint Surg Am 1996; 78: 288-98.
15. Suh JS, Lee JD, Cho JH, Kim MJ, Han DY, Cho NH. MR imaging of tuberculous arthritis: clinical and experimental studies. J Magn Reson Imaging 1996; 6: 185-9.

How to cite:

Öztürk M, Akatlı A, Sığırcı A, Akpolat N. Tuberculous Arthritis in the Elbow Joint in an Adolescent. Eur J Ther 2018; 24: 185–8.

European Journal of Therapeutics

DOI: 10.5152/EurJTher.2018.312

Case Report

Unusual Presentation of Bilaterally Symmetrical Gout Tophi on Elbows

Ahmet Fevzi Kekeç[1], Bilgin Bozgeyik[2], Selçuk Yılmaz[3]

[1]Clinic of Orthopedic and Traumatology, Necmettin Erbakan University, Meram School of Medicine, Konya, Turkey

[2]Clinic of Orthopedic and Traumatology, Dörtyol State Hospital, Hatay, Turkey

[3]Clinic of Orthopedic and Traumatology, University of Health Sciences Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, Ankara, Turkey

ABSTRACT

Gout is a crystal deposition rheumatic disease. It is a more common inflammatory arthritis in men, characterized by formation of monosodium urate crystals in the synovial fluid of joints and in other tissues. It commonly deposits in the feet, ankles, knees, hands, wrists, and elbows. A 54-year-old male presented with big symmetrical masses developed gradually on both the elbows over the last 4 years. Radiographs of both the elbows showed soft tissue swellings with no involvement of bones. Masses were of intermediate signal intensity on T1-weighted magnetic resonance images and high signal intensity on T2-weighted images. Fine needle aspiration cytology was performed in masses on both the elbows. Light microscopy of the Giemsa- and Papanicolaou-stained smears demonstrated abundant granular amorphous material and scattered stacks of slender needle-shaped crystals, associated with chronic inflammatory infiltrate. Based on the above findings, a diagnosis of gout tophi was made. After informed consent with the patient under general anesthesia, marginal resection of tophi were performed in the same session with clear margins. We describe the treatment of a patient with long-standing chronic gout tophus located bilaterally at the elbow joint complicated by bursal deposit with rapid progression during the last 4 years. To the best of our knowledge, our case presentation may be the first case report where huge tophi were symmetrical and bilaterally presented on both the elbows.

Keywords: Gout, elbow, tophi

INTRODUCTION

Gout is a crystal deposition rheumatic disease. It is an inflammatory arthritis which is characterized by the formation of monosodium urate (MSU) crystals in the synovial fluid and in other tissues, and is more common in men (1). It commonly deposits in the feet, ankles, knees, hands, wrists, and elbows. Generally disease progresses through four clinical stages if left untreated. These stages are asymptomatic hyperuricemia, acute gout, intercritical or interval gout, and chronic tophaceous gout (2). The major risk factors for gout are high purine consumption, ethanol use, and elevated body weight (3). In this report, we described the rare presentations of symmetrical, bilateral, extensive, and neglected tophi on both elbows.

CASE PRESENTATION

A 54-year-old male presented with big symmetrical masses on both elbows which had developed gradually over the last 4 years (Figure 1). Physical examination revealed limited range of motion of both elbow joints; approximately 15 degrees both in flexion and extension. These masses were firm, semimobile, and nontender. The patient refused to refer to a specialist before, as the masses were painless. Radiographs of both the elbows showed soft tissue swellings without involvement of bony cortex. Masses were of intermediate signal intensity on T1-weighted magnetic resonance (MR) images and high signal intensity on T2-weighted MR images (Figure 2). Tru-cut biopsy was performed on both the elbows, and light microscopy of the Giemsa- and Papanicolaou-stained smears demonstrated abundant granular amorphous material and scattered stacks of slender needle-shaped crystals, associated with chronic inflammatory infiltrate (Figure 3). In the light of these findings, gut disease "tophi" was diagnosed. Blood count was in normal ranges. Serum uric acid was 6.0 mg/dL (2.5–7 mg/dL). Serum electrolytes, thyroid and parathyroid hormones, and renal function tests (albümin, creatinin, and urea) were within normal limits. A 24-hour urine analysis was done to rule out other pathologies. Different tests to exclude connective tissue diseases (ANA, antinuclear antibody) were performed.

After written informed consent was obtained from the patient, under general anesthesia, marginal resection of tophi were performed bilaterally in the same session with clear margins (Figure 4). No wound problem or recurrence was recorded in the postoperative period. The patient had painless range of motion of 120 degree flexion at the first week of surgery. At the third year of operation, he had no pain or motion limitation in his elbows and no recurrence was noted.

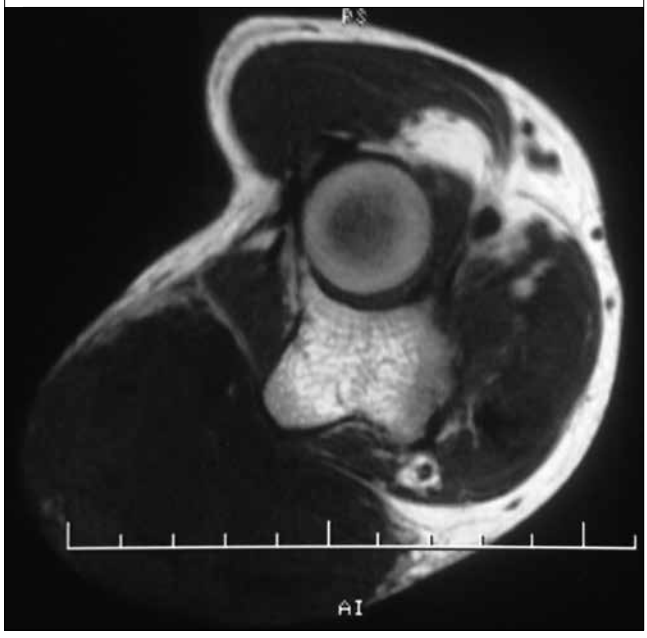
ORCID IDs of the authors: A.F.K. 0000-0003-2045-4686; B.B. 0000-0001-9459-6535; S.Y. 0000-0003-2508-8558.

Corresponding Author: Ahmet Fevzi Kekeç **E-mail:** afkekec@hotmail.com

Received: 07.12.2017 • **Accepted:** 28.03.2018

Figure 1. Clinical presentation of the patient with bilateral symmetric elbow masses

Figure 2. Axial T1-weighted MRI scan revealing extensive tophus extending ventrally



DISCUSSION

In this case report, treatment of a patient with long-standing chronic gout tophus located bilaterally at the elbow joints, which was complicated by bursal deposit and rapid progression during the last 4 years, was reported.

Gout is a metabolic disease affecting 0.3% of the population in Europe and North America (4). It is characterized by an elevated serum urate concentration and recurrent attacks of arthritis and MSU crystals in synovial fluids (5). In chronic tophaceous gout, MSU is deposited in articular cartilage, the periarticular soft tissue, synovium, and joint capsule. The period for the formation of tophi following the first episode of the acute gout arthritis is estimated at an average of 11.6 years (6). Tophi are seen in approximately 50% of 10-year cases (7). If the hyperuricemia is left untreated for many years, painless subcutaneous or bursal deposits of aggregated crystals of MSU or tophi form, and the patient develops nephropathy and urolithiasis. The essential lesion of tophaceous gout is the deposition of crystals in cartilage, synovial membrane, periosteum, subchondral bone, bone marrow, tendons, ligaments, bursae, subcutaneous fat, and skin (8-10). In the upper extremity, tophi are usually located in the subcutaneous tissues, more commonly around the elbow and proximal interphalangeal joints (11).

Figure 3. Histologic examination revealed abundant granular amorphous material and scattered stacks of slender needle-shaped crystals, associated with chronic inflammatory infiltrate

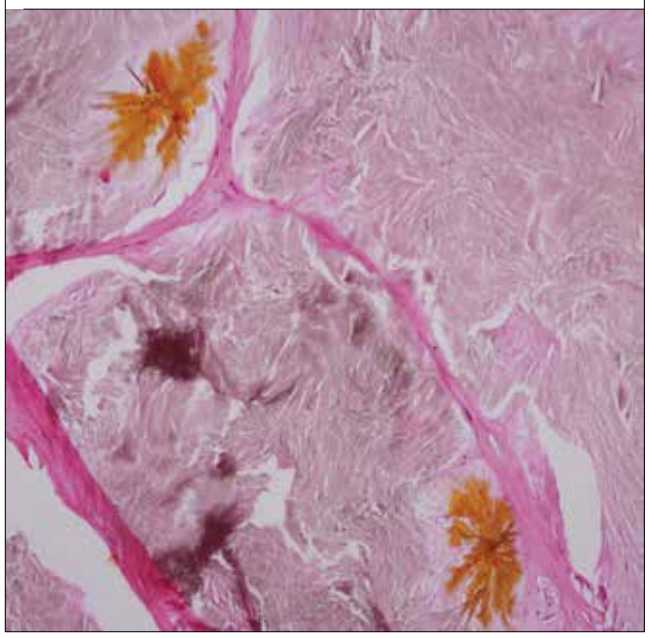
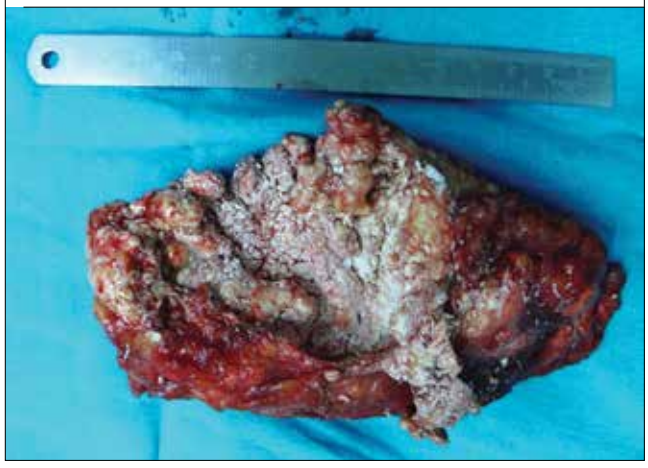


Figure 4. Macroscopic appearance showing bursal deposition of gout tophi in the resected specimen after surgery



Gouty arthritis has characteristic radiographic manifestations. Although plain radiographs are less sensitive than other imaging techniques, they remain the imaging technique of choice for initial evaluation of gouty arthritis. The use of MR imaging and Computed Tomography, and ultrasound is seldom necessary; however, occasionally a tophus has an unusual presentation

mimicking a neoplasm or infection (12). In 2005, Carnero et al. (13) reported a case report of a malignant fibrous histiocytoma arising in a gouty tophus at the second metacarpophalangeal joint. Although its radiological findings strongly suggest the gout tophus, we performed open biopsy before the surgical treatment to eliminate any probable malignancy. In gout, most relevant lesions are near the skin surface (14) like our presented case. Bilateral symmetrical elbow involvement as in our case is very uncommon and review literature revealed no reports of symmetrical and huge gout tophi manifestations in either adolescents or adults.

The articular spaces are usually preserved for a long time, before destruction is caused by crystal deposition in the hyaline cartilage and synovial membrane, which lead to degeneration and ankylosis (11). In our patients there were no joint degeneration or ankylosis but limited range of motion that was resolved after surgery with physiotherapy, which was probably because of the mass that stretched the joint capsule.

CONCLUSION

Gout tophi can reach large size when neglected and can cause painless joint limitation. To the best of our knowledge, our case presentation may be the first case report where huge tophi were symmetrical and bilaterally presented on both the elbows.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.F.K.; Design – B.B.; Supervision – A.F.K.; Resources – B.B.; Materials – S.Y.; Data Collection and/or Processing – S.Y.; Analysis and/or Interpretation – B.B.; Literature Search – S.Y.; Writing Manuscript – S.Y., A.F.K.; Critical Review – A.F.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

REFERENCES

1. Smith EU, Díaz-Torné C, Perez-Ruiz F, March LM. Epidemiology of gout: an update. Best Pract Res Clin Rheumatol 2010; 24: 811-27.
2. Koley S, Salodkar A, Choudhary SA, Singhania K, Choudhury M. Tophi as first manifestation of gout. Indian J Dermatol Venereol Leprol 2010; 76: 393-6.
3. Falasca GF. Metabolic diseases: gout. Clin Dermatol 2006; 24: 498-508.
4. Grahame R, Scott J T. Clinical survey of 354 patients with gout. Ann Rheum Dis 1970; 29: 461-8.
5. Nishioka N, Mikanagi K. Clinical features of 4000 gouty subjects in Japan. Adv Exp Med Biol 1980; 122: 47-54.
6. Kelley WN, Schumacher HR. Crystal-associated synovitis-gout. In: Kelly WN, Harris ED, Ruddy S (eds). Textbook of Rheumatology, vol 2, 4th edn. Saunders, Philadelphia, 1993; 1291-336.
7. Hasturk AE, Basmaci M, Canbay S, Vural C, Erten F. Spinal gout tophus: a very rare cause of radiculopathy. Eur Spine J 2012; 21: 400-3.
8. Nishioka N, Mikanagi K. Clinical Features of 4,000 Gouty Subjects in Japan. Adv Exp Med Biol 1980; 122: 47-54.
9. Nakayama DA, Barthelemy C, Carrera G, Lightfoot RW, Wortmann RL. Tophaceous Gout: A Clinical and Radiographic Assessment. Arthritis Rheum 1984; 27: 468-71.
10. Resnick D, Niwayama G. Gouty arthritis. Resnick D, editor. Diagnosis of bone and joint disorders. 3rd ed. Philadelphia: W.B. Saunders Company, 1995; 1511-55.
11. Schuind FA, Van Geertruyden J, Stallenberg B, Remmelink M, Pasteels JL. A rare manifestation of gout at the wrist--a case report. Acta Orthop Scand 2002; 73: 594-6.
12. Dhanda S, Jagmohan P, Quek ST. Tian, A re-look at an old disease: A multimodality review on gout. Clin Radiol 2011; 66: 984-92.
13. Carnero S, Terán P, Trillo E. Malignant fibrous histiocytoma arising in a gouty tophus at the second metacarpophalangeal joint. J Plast Reconstr Aesthet Surg 2006: 59: 775-8.
14. Dalbeth N, Doyle AJ. Imaging of gout: An overview. Best Pract Res Clin Rheumatol 2012; 26: 823-38.

How to cite:

Kekeç AF, Bozgeyik B, Yılmaz S. Unusual Presentation of Bilaterally Symmetrical Gout Tophi on Elbows. Eur J Ther 2018; 24: 189–91.