MIDDLE BLACK SEA JOURNAL OF HEALTH SCIENCE

MAY 2022 VOLUME 8 ISSUE 2

ISSN 2149-7796

MIDDLE BLACK SEA JOURNAL OF HEALTH SCIENCE (MBSJHS)

The Middle Black Sea Journal of Health Science, which is international journal, is published by Ordu University Institute of Health Sciences on behalf of the Middle Black Sea Universities Collaboration Platform

e-ISSN 2149-7796

Middle Black Sea Journal of Health Science

Editorial Office

Ordu University

Institute of Health Sciences

Cumhuriyet Campus

52200, Ordu, TURKEY

Tel: +90 (452) 234 5010-6105

Fax: +90 (452) 226 52 28

E-mail: ukaraman@odu.edu.tr

Correspondence Address: Ulku KARAMAN, PhD, Assoc. Prof. Dr.
Institute of Health Sciences,
Ordu University,
Cumhuriyet Campus,
52200 Center/ Ordu TURKEY

Phone: +90 452 234 50 10
Fax: +90 452 226 52 55
Email: ukaraman@odu.edu.tr
ulkukaraman44@hotmail.com

Web site: https://dergipark.org.tr/en/pub/mbsjohs

Sort of Publication: Periodically

Publication Date and Place: 31 / 05/ 2022, ORDU, TURKEY

Publishing Kind: Online

Indexing: *Turkey Citation Index, SOBIAD, Rootindexing, Academic Resource ındex, Fatcat index, Researcgate, EuroPub, Gooogle Scholar, Turk Medline, Index Copernicus*

The Middle Black Sea Journal of Health Science, which is international journal, is published by Ordu University Institute of Health Sciences on behalf of the Middle Black Sea Universities Collaboration Platform

Aims and Scope

Middle Black Sea Journal of Health Science is an international journal that publishes original clinical and scientific research. Middle Black Sea Journal of Health Science, published by Ordu University, publishes basic innovations in health education, case reports, reviews, letters to the editor, case reports and research articles.

The aim of the journal is to contribute to the international literature with clinical and experimental research articles, case reports, reviews and letters to the editor in the field of health sciences.

The target audience of the journal is all scientists working in the field of health, graduate students and researchers in this field.

Middle Black Sea Journal of Health Science is an open access, independent and impartial, international journal based on double-blind peer-reviewed principles.

The publication language of the journal is English. The journal is published every three months, in February, May, August and November, and four volumes are completed.

Middle Black Sea Journal of Health Science - adheres to the standards of publication ethics in health science research, Higher Education Council's Scientific Research and Publication Ethics Directive, Committee on Publication Ethics (COPE), Directory of Open Access Journals (DOAJ), Open Access Scholarly Publishers It also adopts the ethical publishing principles published by the Association (OASPA) and the World Association of Medical Editors (WAME).

No fee is charged from the authors for the evaluation and publication of the article.

Publication Ethics Statement

Middle Black Sea Journal of Health Science - adheres to the standards of publication ethics in health science researches, Higher Education Council's Scientific Research and Publication Ethics Directive, Committee on Publication Ethics (COPE), Directory of Open Access Journals (DOAJ), Open Access Scholarly Publishers It also adopts the ethical publishing principles published by the Association (OASPA) and the World Association of Medical Editors (WAME); The address for the principles expressed under the Principles of Transparency and Best Practice in Scholarly Publishing is given below.

https://publicationethics.org/resources/guidelines-new/principles-transparency-and-best-practice-scholarly-publishing

Submitted research is original, has not been published before and should not be in the evaluation process of another journal. Each article is double blinded by one of the editors and at least two referees. Plagiarism, duplication, fraudulent authorship / denied authorship, research / data fabrication, article slicing, slicing publishing, copyright infringement and concealing conflict of interest are considered unethical behavior.

All articles that do not comply with ethical standards are removed from publication even if they are accepted. This situation is valid for articles containing possible irregularities and inconveniences detected after publication.

Research Ethics

• The authors are responsible for the compliance of the articles with the ethical rules.

• Ethical standards of the Declaration of Helsinki must be followed in human studies.

• Attention should be paid to ethical principles in designing, reviewing and conducting the research.

• The research team and the participants should be fully informed about the purpose of the research, the participation rules and, if any, the risks involved.

• Confidentiality of the information and answers given by the research participants should be ensured. Research should be designed in a way that preserves the autonomy and dignity of its participants.

• Participants in the research should take part in the research voluntarily and should not be under any coercion.

• The research should be planned in a way that does not put the participants at risk.

• Be clear about research independence; If there is a conflict of interest, it should be indicated.

• In experimental studies, written informed consent must be obtained from the participants who decide to participate in the research. The legal guardian's consent must be obtained for children, those under guardianship and those with confirmed mental illness.

• If the study is to be carried out in an institution or organization, the necessary approval should be obtained from this institution or organization.

• In studies with a human element, it should be stated in the "method" section that "informed consent" was obtained from the participants and the ethics committee approval was obtained from the institution where the study was conducted.

Authors' Responsibility

The authors are responsible for the compliance of the articles with scientific and ethical rules. The author should provide assurance that the article is original, has not been published elsewhere, and is not being reviewed for publication elsewhere, in another language. Copyright laws and treaties in practice must be observed. Corresponding materials (eg tables, figures or large quotations) should be used with necessary permissions and acknowledgments. Work or sources of other authors, contributors should be appropriately used and cited in references.

All authors should have a direct contribution in academic and scientific terms in the submitted article, accordingly, the "author" is someone who contributes to the conceptualization and design of a published research, obtaining, analyzing or interpreting data, writing the article or reviewing it critically in terms of content. Other conditions for being an author are planning or executing and / or revising the work in the article.

Funding, data collection, or general supervision of the research group alone does not provide authorship rights. All individuals designated as authors must meet all the criteria listed, and any individual who meets the above criteria can be shown as an author. The name order of the authors should be a joint decision. All authors must indicate the author order signed on the

Copyright Agreement Form.

All individuals who do not meet the sufficient criteria for authorship but contributed to the study should be listed in the "thank you" section. Examples of these are people who only provide technical support, help with writing or just provide general support, financial and material support.

All authors must declare financial relationships, conflicts of interest and competition of interest that have the potential to affect the results of the research or scientific evaluation. If writer detects a significant error or inaccuracy in his published manuscript, he / she bears the responsibility to immediately contact and cooperate with the editor for correction or retraction of these inaccuracies.

Editor and Referee Responsibilities

The editor-in-chief evaluates the articles regardless of the authors' ethnicity, gender, sexual orientation, nationality, religious belief, and political philosophy. It ensures that the articles submitted for publication go through a fair double-blind peer review. It guarantees that all information about the submitted articles will remain confidential until the article is published. The editor-in-chief is responsible for the overall quality of the content and publication. It should publish an error page or make a correction when necessary.

Editor in Chief; It does not allow any conflict of interest between authors, editors and referees. It has full authority to appoint a referee and is responsible for making the final decision on the articles to be published in the journal.

Reviewers should not have conflicts of interest with the authors and / or financial supporters of the research. They should reach an impartial judgment as a result of their evaluation. They must ensure that all information regarding submitted articles is kept confidential and report to the editor if they notice any copyright infringement or plagiarism on the part of the author. In cases where the subject of the article is not his area of expertise or cannot return on time, the referee should inform the editor of this situation and state that he cannot be a referee.

Referees and editorial board members cannot discuss articles with other people. Care should be taken to keep the identity of the referees anonymous. In some cases, with the decision of the editor, the relevant referees' comments on the article may be sent to other referees who interpret the same article.

Publication Policy

Authors undertake that their publications are created in accordance with all universal ethical rules and research is accepted accordingly.

Authors are responsible for all statements in their work. Submitted studies should be prepared in line with the journal's writing rules. Studies that do not comply with the spelling rules are rejected or sent back to the authors for correction.

The journal has the right to make corrections in the accepted works without changing the content and meaning.

The journal accepts the research provided that it has not been published in another journal or publication.

All authors should indicate their relationships with individuals or organizations that may have conflicts of interest. Support received for the study, if any, should be stated in detail. Conflicts of interest should also be indicated on the title page.

In the management and publication processes of the journal, attention is paid to the publishing principles of "International Committee of Medical Journal Editors (ICMJE)" and "Committee on Publication Ethics (COPE)".

Evaluation process

-Only articles uploaded to the journal's system are evaluated. Studies sent via e-mail are not considered.

- All submitted studies go through pre-evaluation, language editor, statistical editor and referee evaluation processes. The evaluation process is carried out by the editor of the journal.

Pre-Evaluation Process

After the article is uploaded to the journal, the pre-evaluation process begins. At this stage, the editor examines the article in terms of content, form, purpose and scope of the journal. As a result of this thinning

• Decides that the work is not suitable for the journal and declines the work.

• Resend the work to the responsible author for corrections.

• The study sends to the language editor and can request a correction.

• The study is evaluated by sending it to a statistics advisor. After this evaluation, the author may ask for a correction.

• Can direct the article to the referees and initiate the referee evaluation process.

Referee Evaluation Process

All articles in the journal are double-blind peer-reviewed. In order to ensure the impartial evaluation process, each article is evaluated by at least two independent referees who are experts in their fields. If there is no consensus among the referees, the article is evaluated by the third referee. The editor in chief makes the final decision in the decision-making process of all articles.

Revision

Authors should mark the changes they made in the main text in color while submitting the article revision files. The responses to the referees should be specified in a separate Word file. Revised articles should be submitted to the journal within one month following the decision letter. If the revised version of the article is not uploaded within the specified time,

the revision option can be canceled. If the authors need additional time for revision, they must submit their publication requests to the journal before the end of one month.

Articles accepted for publication are checked again for grammar, punctuation and format.

Accepted articles are edited in accordance with the journal's publication format and the final version is sent to the responsible author in pdf format before publication, and approval is obtained for publication. Authors should review the article and approve for publication. If the article requires any correction other than the publication format, the request for correction is notified to the editor at ulkukaraman44@hotmail.com. Requests for correction are evaluated by the editor and notified to the responsible author. Articles that are not approved by the corresponding author are not published.

Plagiarism

The similarity rate of the articles should be made over iThenticate and should be at most 20%, excluding the "References" section.

The journal is published online only.

The journal is free and does not require any publication fee from researchers.

GENERAL RULES

Middle Black Sea Journal of Health Science publishes experimental and observational research articles, clinical reviews, case reports and review articles on health science. Manuscripts must be submitted online at https://dergipark.org.tr/en/login

All submissions must be accompanied by a signed statement of scientific contributions and responsibilities of all authors and a statement declaring the absence of conflict of interests.

Any institution, organization, pharmaceutical or medical company providing any financial or material support, in whole or in part, must be disclosed in a footnote. Manuscripts must be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (updated in December 2013 - http://www.icmje.org/icmje-recommendations.pdf).

An approval of research protocols by an ethical committee in accordance with international agreements (Helsinki Declaration of 1975, revised 2002 - available at http://www.vma.net/e/policy/b3.htm, “Guide for the care and use of laboratory animals - www.nap.edu/catalog/5140.html/) is required for experimental, clinical and drug studies. A form stating that the patients have been informed about the study and consents have been obtained from the patients is also required for experimental, clinical and drug studies. All

submissions must be accompanied by a letter that states that all authors have approved the publication of the paper in the Middle Black Sea Journal of Health Science.

Submission of the studies requiring ethical committee decision must be accompanied by a copy of the submission to the ethical committee.

SUBMISSION POLICY

Submission of a paper to Middle Black Sea Journal of Health Science is understood to imply that it deals with original material not previously published and is not being considered for publication elsewhere. Manuscripts submitted under multiple authorships are reviewed on the assumption that all listed Authors concur with the submission and that a copy of the final manuscript has been approved by all Authors. After acceptation of an article, it should not be published elsewhere in the same form, in either the same or another language, without the written consent of the Editors and Publisher.

If excerpts from other copyrighted works are included, the Author(s) must obtain written permission from the copyright owners and credit the source(s) in the article.

The layout and style should adhere strictly to the instructions. No revisions or updates will be incorporated after the article has been accepted and sent to the Publisher (unless approved by the Editors).

SUBMISSION PROCEDURE

The Middle Black Sea Journal of Health Science welcomes submitted manuscripts online at http://dergipark.gov.tr/login Manuscripts submitted online are received on the day of submission and quickly assigned to reviewers. Through individual Author Centers on this website, authors can view the status of their manuscripts as they progress through the review process. Notification of the disposition of each manuscript will be sent by e-mail to the corresponding author on the day of decision.

To establish your account for online submission, go to http://dergipark.gov.tr/register/ Authors are encouraged to check for an existing account. If you are submitting for the first time, and you do not have an existing account, then you must create a new account. If you are unsure about whether or not you have an account, or have forgotten your password, enter your e-mail address into the Password Help section on the log-in page. If you do not have an account, click on the Create Account link on the top right of the log-in page. You then will be able to submit and monitor the progress of your manuscripts. Once you have logged

in, you will be presented with the Main Menu and a link to your Author Centre. Submit your manuscript from the Author Centre. At the end of a successful submission and you will receive an e-mail confirming that the manuscript has been received by the journal. If this does not happen, please send an e-mail to ulkukaraman44@hotmail.com

To submit your manuscript online, please prepare the text and illustrations according to the instructions listed below. You may enter and exit the manuscript submission process at the completion of each step. After submission of the manuscript, however, you will not be able to edit it.

Web submission is required- instructions are available for downloading on the website https://dergipark.org.tr/en/pub/mbsjohs/writing-rules

COPYRIGHT TRANSFER AGREEMENT

A signed COPYRIGHT RELEASE FORM by all authors of the manuscript should be sent during manuscript submission. http://mbsjohs.odu.edu.tr/files/copyright_transfer_form_1.pdf

Middle Black Sea Journal of Health Science

Editorial Office

Ordu University, Institute of Health Sciences

Cumhuriyet Campus

52200, Ordu, TURKEY

Tel: +90 (452) 226 52 14-5234

Fax: +90 (452) 226 52 28

E-mail: ulkukaraman44@hotmail.com

Authors should write their information exactly (Full address, telephone and fax numbers, e-mail address).

PREPARING ELECTRONIC MANUSCRIPTS

In the writing of words for the studies, "Oxford English Dictionary (https://www.oed.com)" should be taken as a reference. The symbols of the units used in the text should be given according to the http://www.bipm.org/en/si/

Author should submit manuscript in both ways as explain in below:

1- The text must be single-spaced, 12-point font (except with URL addresses); and all illustrations, figures, and tables must be placed within the text at the appropriate points, rather than at the end.

2- Files you need to add:

Title Page,

Full Text,

Tables,

Figures,

Images,

Copyright Form,

Similarity Report (Similarity should be at most 20%.).

Cover Letter

Ethics Committee Approval.

3- Please insert all attachments that are tables, figures and graphics into the text file in appropriate place.

When mentioning parasites, bacteria, virus and fungi in the main text and references, the genus and species names must be italicized, and the genus name must be written with an initial capital letter.

Abbreviations should be expanded at first mention and used consistently thereafter.

Graphic files: Each figure should be a separate file.

All figure files must be submitted in sufficiently high resolution.

Electronic submission of articles via the Web

http://dergipark.gov.tr/mbsjohs

Full instructions for uploading data and files etc. are given on the website when submitting a manuscript. It is the responsibility of the Authors to create the proper files as instructed above for the electronically submitted manuscript. The editorial office cannot make conversions beyond the supported file types.

ORGANIZATION OF THE ARTICLE

Manuscripts should be prepared electronically using "Time News Roman" font, formatted according to A4 page size, single-spaced from beginning to end, 2.5 cm margins on all sides and 12-point font. Words should not be hyphenated to fit on a line. Pages should be numbered.

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

The title page should include full and short title English.

Meeting and congress presentations of the manuscript must be stated, if any.

Name(s), affiliations, highest academic degree(s) and ORCID ID's of the author(s),

Example: Ulku Karaman[1], Yeliz Kasko Arici[2], Cemil Colak[3]

[1]Institution of the first author, e -mail, orcid no

[2]Second Author's Institution, e -mail, orcid no

[3]Third Author's Institution, e -mail, orcid no

Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,

Ethics Committee Approval: Ethics committee approval was received for this study from ……. Clinical Research Ethics Committee of …… University (No…….).

Author Contributions: Concept: …….., Design: …….., Literature search:……..... Data Collection and Processing: ……..., Analysis and Interpretation:……, Writing - …….

Acknowledgements:

Conflict of Interest:

Financial Disclosure:

Note: Kongress participation……..

In the article sent, the sections that should be below are listed.

1. Abstract, 2. Keywords, 3. Introduction, 4. Methods, 5. Results, 6. Discussion, 7. Conclusion, 8. References, Tables and Figures sections.

1. Abstract Page: The first page should include abstracts written English, and key words. The abstract of Original Articles should be structured with subheadings (Objective, Methods, Results, and Conclusion) (average 200-400 word).

2. Keywords: Provide at least 3-6 keywords and avoiding general and plural terms and multiple concepts. These keywords will be used for indexing purposes. Key words in should follow the abstract. Please select keywords in Turkish Science Terms (http://www.bilimterimleri.com).

3. Introduction: The objectives of the research should be clearly stated in this section. Relevant background information and recent published studies should be described concisely and be cited appropriately.

4. Methods: This section should contain all the details necessary to reproduce the experiments. Avoid re-describing methods already published; only relevant modifications should be included in the text. Experimental subjects when human subjects are used, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and written consent of each subject.

When experimental animals are used, the methods section must clearly indicate that adequate measures were taken to minimize pain or discomfort.

5 Results: These sections should present the results and interpret them in a clear and concise manner. Results should usually be presented descriptively and be supplemented by figures.

6. Discussion: Extensive citations and discussion of published literature should be being used.

7. Conclusion: In this section, the results obtained from the article should be written.

8. Literature references:

Care should be taken to cite Turkey-based studies and journal of national during the granting of resources (www.atifdizini.com).

References should be listed according to the order of appearance in the text, and "in parentheses" should be indicated in the relevant places. References should be written according to the "Vancouver" system of the American National Library of Medicine (U.S. National Library of Medicine; http://www.nlm.nih.gov/).

Examples: Hypotension is one of the most common and critical problems in hemodialysis patients (1,2).

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.

The accuracy of references is the responsibility of the author. The references should include only articles that are published or in press.

Unpublished data, submitted manuscripts, or personal communications should be cited within the text only. Personal communications should be documented by a letter of permission.

All items in the list of references should be cited in the text and, conversely, all references cited in the text must be presented in the list.

The abbreviations of journal titles should conform to those adopted by the List of Serial Title Word Abbreviations, CIEPS/ISDS, Paris, 1985 (ISBN 2-904938-02-8).

Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed.

For citation of references with one to six authors, the names of all authors should be included, and for the articles with more than six authors, “et al.” should be written after typing the six names. The surnames of authors should be written exactly, and the initials of their names should be indicated with capital letter without any punctuation mark.

Please use the following style for references:

Examples

Journal: Stephane A. Management of Congenital Cholesteatoma with Otoendoscopic Surgery: Case Report. J Med Sci 2010;30(2): 803-7.

Levine WC, Pope V, Bhoomkar A, Tambe P, Lewis JS, Zaidi AA, et al. Increase in endocervical CD4 lymphocytes among women with nonulcerative sexually transmitted diseases. J Infect Dis. 1998;177(1):167–174.

Chapter in Edited Book: Hornbeck P. Assay for antibody production. In: Colign JE. Kruisbeek AM, Marguiles DH, editors. Current Protocols in Immunology. New York: Greene Publishing Associates; 1991. p. 105-32.

Book with a Single Author: Fleiss JL. Statistical Methods for Rates and Proportions. Second Edition. New York: John Wiley and Sons; 1981. p. 105-32.

Editor(s) as Author: Balows A. Mousier WJ, Herramaflfl KL, editors. Manual of Clinical Microbiology. Fifth Edition. Washington DC: IRL Press. 1990. p. 105-32.

Conference Paper: Entrala E, Mascaro C. New structural findings in Cryptosporidium parvum oocysts. Eighth International Congress of Parasitology (ICOPA VIII); October 10-14; Izmir-Turkey: 1994. p. 1250-75

Thesis: Erakinci G. Searching for antibodies against parasites in donors. Izmir: Ege University Health Sciences Institute. 1997.

Article in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) l995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

ILLUSTRATIONS AND TABLES

Illustrations:

The illustrations should be numbered in Arabic numerals according to the sequence of appearance in the text, where they are referred to as Figure. 1, Figure. 2, etc.

If illustrations (or other small parts) of articles or books already published elsewhere are used in papers submitted to MBSJHS, the written permission of the authors and publisher concerned must be included with the manuscript. The original source must be indicated in the legend of the illustration in these cases.

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. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm).

Tables: Tables should be so constructed together with their captions and legends.

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. Tables of numerical data should each be typed (with one-spacing) and numbered in sequence in Arabic numerals (Table 1, 2, etc.). They are referred to in the text as Table 1, Table 2, etc. The title of each table should appear above it. A detailed description of its contents and footnotes should be given below the body of the table.

Revisions: Authors should mark the changes they made on the main text in color while submitting their article revision files. The responses to the referees should be specified in a separate Word file. Revised articles should be sent to the journal within one month following the decision letter. If the revised version of the article is not uploaded within the specified time, the revision option may be canceled. If the authors need additional time for revision, they are required to submit their extension requests to the journal before the end of one month.

PROOFS, OFFPRINTS, MISCELLANEOUS

Proofs

Proofs will be sent by e-mail, as a pdf. Only printer's errors may be corrected; no change in, or additions to, the edited manuscript will be allowed at this stage. It should be kept in mind that proofreading is solely the authors' responsibility. A form with queries from the copyeditor may accompany the proofs. Please answer all queries and make any corrections or additions required. Corrections to the proofs must be returned by e-mail within 48 hours after receipt. If the publisher receives no response from the authors after 3 days, it will be assumed that there are no errors to correct and the article will be published.

Page charges

The journal is free and does not require any publication fee from the authors.

The journal is only published online.

The similarity rate of the articles should be done through iThenticate and should be at most 20% excluding the "References" part.

The editorial board has the authority to make necessary revisions in the format of the manuscript (without making any revision in the context) that does not comply with the above-mentioned requirements.

TYPES OF ARTICLES

The studies submitted to the Journal are accepted in Original research, Short papers, Case report, Review articles,

a) Original research: Prospective, retrospective and all kinds of experimental studies

Structure

Title

Abstract should be structured with subheadings (Objective, Methods, Results, and Conclusion) (average 200-400 word)

Key words

Introduction

Methods

Results

Discussion

Conclusion

Acknowledgements

References (most 40)

Whole text should not exceed 4500 words except for resources and English summary.

b) Short papers: Prospective, retrospective and all kinds of experimental studies

Structure

Title

Abstract should be structured with subheadings (Objective, Methods, Results, and Conclusion) (average 200-400 word)

Key Words

Introduction

Methods

Results

Discussion

Conclusion

Acknowledgements

References (most 20)

Whole text should not exceed 2700 words except for resources and English summary.

c) Case Report: They are rarely seen articles which differs in diagnosis and treatment. They should be supported by enough photographs and diagrams.

Structure

Title

Abstract (average 100-300 word)

Key words

Introduction

Case report

Discussion

Conclusion

Acknowledgements

References (most 20)

Whole text should not exceed 2200 words except for resources and English summary.

d) Review articles

Structure

Title

Abstract (average 200-400 word)

Key words

Introduction

The compilation text also including appropriate sub-headings,

Conclusion

Acknowledgements

References (most 50)

Whole text should not exceed 6550 words except for resources and English summary.

May 2022 **VOLUME 8** **ISSUE 2**

CONTENTS

EDITORIAL

Our new issue

We are proud to publish the second issue of 2022, which we started to publish four issues a year. We are delighted to bring together multidisciplinary and interesting research with you.

We would like to express our sincere thanks to all the researchers who contributed.

Hope to meet you in new numbers.

PhD, Assoc. Prof. Ülkü KARAMAN

Editor

Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci **May 2022; 8(2):187-201**

RESEARCH ARTICLE **DOI:** 10.19127/mbsjohs.980157

Emotion Regulation Difficulties and Childhood Trauma are Associated with Alcohol Use Severity: A Comparison with Healthy Volunteers

Atila Gurgen[1](ID) , Demet Gulec Oyekcin[2](ID) , Deniz Deniz Ozturan[3](ID)

[1]Ordu State Hospital, Department of Mental Health and Diseases Ordu, Turkey
[2]18 Mart University, Faculty of Medicine, Department of Mental Health and Diseases, Çanakkale, Turkey
[3]Ordu University, Faculty of Medicine, Department of Mental Health and Diseases, Ordu, Turkey

Received: 10 December 2021, Accepted: 22 February 2022, Published online: 31 May 2022

Abstract

Objective: Emotion regulation difficulties and the effect of childhood traumas on the etiology of alcohol use disorder are an important topic in the literature. This study aimed to evaluate patients with alcohol use disorder in terms of emotional control and childhood trauma and the difficulty in trauma and emotion regulation as a risk factor.

Methods: In this study, 37 patients with alcohol use disorder (AUD) and 37 healthy volunteers were included. The participants were assessed with a 35-item sociodemographic data form, Severity of Alcohol Dependence Questionnaire (SADQ-C), Childhood Trauma Questionnaire (CTQ-28), and Difficulties in Emotion Regulation Scale (DERS). All participants were interviewed based on DSM-5.

Results: Participants with AUD had more difficulty in regulating emotions in all areas. clarity, awareness, impulse, nonacceptance, objectives, and strategies were deteriorated ($p < 0.05$). Patients with AUD had more childhood traumas. All trauma types, especially physical neglect and emotional abuse were more common in participants with AUD. Assessment of the traumas and emotion regulation revealed that emotional abuse increased the risk of AUD by 1.6 times (95% CI 1.025–2.801) and maladaptive emotion regulation strategies are linked to addiction severity.

Conclusion: The maladaptive emotional strategies of patients with AUD were worse than those of healthy volunteers. Patients with AUD experienced more childhood traumas. Particularly, emotional abuse increased the risk of AUD. As a result, childhood traumas were more severe in patients with AUD, and they adversely affected emotion regulation strategies and increased addiction severity.

Keywords: Alcohol Use Disorder; Childhood Trauma; Emotion Regulation.

Suggested Citation: Gurgen A, Oyekcin DG, Ozturan DD. Emotion Regulation Difficulties and Childhood Trauma are Associated with Alcohol Use Severity: A Comparison with Healthy Volunteers. Mid Blac Sea Journal of Health Sci, 2022;8(2):187-201

Address for correspondence/reprints:
Deniz Deniz Ozturan
Telephone number: +90 (505) 241 91 49
E-mail: dr.denizdeniz@gmail.com

INTRODUCTION

Emotion regulation is the awareness and understanding of emotions, the ability to control impulsive behaviors and behave in accordance with desired goals when experiencing negative emotions, and the ability to use situationally appropriate emotion regulation (1). Emotion regulation strategies are classified under five categories: state choice, state adjustment, paying attention, cognitive change, and reaction change (2).

Difficulties in emotion regulation are defined as the absence or deficiency of any or all of these abilities. These difficulties may occur in six separate dimensions, including (a) lack of awareness of emotional responses, (b) lack of clarity of emotional responses, (c) nonacceptance of emotional responses, (d) limited access to emotion regulation strategies perceived as effective, (e) difficulties controlling impulses when experiencing negative emotions, and (f) difficulties engaging in goal-directed behaviors when experiencing negative emotions (3).

Difficulties in emotion regulation are central to the development and maintenance of psychopathology. The use of strategies (e.g., rumination, suppression, and avoidance) to regulate emotion has been found to be associated with a broad range of mental, mood, anxiety, personality, and addictive disorders (4). Emotion regulation difficulties are also a key characteristic of alcohol use disorder (AUD). Patients have difficulties in identifying emotions in themselves/others, and these emotional impairments elicit difficulties in interpersonal relationships, which may trigger further drinking behavior and relapse (5). These deficits in adaptive emotion regulation skills also predict AUD (6).

Knowledge of the mechanisms involved in the difficulties of emotion regulation may contribute to a better understanding of childhood trauma-alcohol association. A history of childhood trauma can affect the development, severity (amount of alcohol consumption, early-onset drinking), treatment outcomes, and course of AUD. Patients exposed to childhood trauma have been reported to develop AUD at an earlier age and show more severe alcohol abuse characteristics compared with patients without childhood trauma (7–9). In particular, childhood traumas may be associated with a greater severity of alcohol dependence (10) and defined as one of the most important risk factors for AUD (11).

The high rates of childhood trauma among these patients have been associated with the self-medication hypothesis. This hypothesis suggests that individuals may consume alcohol or other substances to cope with psychological distress, thereby alleviating negative emotional states and evoking positive emotions (12). Affective processes play a crucial role in substance use. Substance use can serve as an emotion regulation strategy (13). Therefore, exposure to early childhood maltreatment can lead to early

emotion regulation difficulties or emotion dysregulation in later life.

The patterns of emotion regulation difficulties are associated with higher levels of internalizing and externalizing psychopathology, suggesting a transdiagnostic pathway linking childhood maltreatment to psychopathology through disruptions in emotion regulation (14). In addition to biological, psychological, and social factors (15), both childhood traumas and difficulties in emotion regulation have been suggested to play a role in the severity of AUD (5).

The aim of the current study was to examine emotion regulation difficulties and childhood traumas, which are associated with the severity of alcohol use, by comparing patients with AUD with healthy volunteers. First, we hypothesized that patients with AUD may have more emotion regulation difficulties and childhood traumas. Second, the severity of alcohol use may be associated with certain types of emotion regulation strategies and childhood traumas. Third, the childhood traumas may contribute to emotion regulation difficulties in AUD.

METHODS

Participants

Our study was approved by the Ethics Committee of Onsekiz Mart University Rectorate, Faculty of Medicine, Clinical Research Ethics Committee, dated 13.04.2016 and numbered 07-09, and was approved by the Faculty Administrative Board dated 28.06.2016 and numbered 2016/27. The total sample group consisted of 74 participants (37 patients and 37 healthy volunteers), who were age/gender-matched. Patients admitted to the Psychiatry Addiction Department of Çanakkale Onsekiz Mart University (Medical Faculty) between April 2016 and January 2017 were enrolled in the study. A total of 37 healthy participants, randomly selected to age/gender-matched with the patients, those were above the age of 18 and agreed to participate in the study. Those who had no substance use disorder/AUD, were included in the study as the control group. . The sample size consists of all patients who were admitted to the hospital during the study period, except for the exclusion criteria.

Patients under the age of 18, those could not fill out the scales due to illiteracy, those diagnosed with dementia, psychosis, or mental retardation, those with bipolar disorder in an episodic period, those with addictive substance use disorder other than alcohol, those who refused to participate in the study, and those using drugs such as benzodiazepine (which affects cognitive functions) were excluded from the study.

Data Collection Tools

Demographic Data

A sociodemographic data form consisting of 35 questions about information such as name, surname, gender, age, place of residence, occupation, marital status, monthly income,

education status, and alcohol use was given to all the participants.

Severity of Alcohol Dependence Questionnaire (SADQ-C)

The SADQ-C is a Likert-type scale with 20 questions. The scale score is obtained as the sum of individual item scores. In this study, a form based on the DSM-5 diagnostic criteria from a validity and reliability study was used (16,17).

Childhood Trauma Questionnaire (CTQ-28)

The subscale and total scores of traumatic experiences were evaluated with CTQ-28 (18). In this study, we used a form from a previous validity and reliability study, which assessed five factors including physical abuse, sexual abuse, emotional abuse, physical neglect, and emotional neglect (19).

Difficulties in Emotion Regulation Scale (DERS)

The DERS consists of 36 items under the headings lack of awareness of emotional reactions (awareness), lack of emotional clarity (clarity), impulsivity (impulse), unacceptance of emotional reactions (nonacceptance), limited access to effective emotion regulation strategies (strategies), and difficulty in exhibiting goal-oriented behaviors while experiencing negative emotions (goals). It is a Likert-type self-rating scale (20).

Diagnostic Interview

In accordance with DSM-5 diagnostic criteria, psychiatric interviews were held with patients in an outpatient setting, and other comorbid psychiatric disorders of the patients were investigated

Statistical Analysis

Categorical variables are presented as % (n) and compared using the Chi-squared test. In addition, non-categorical (quantitative) (variables of the demographic data, DERS, and CTQ scores were applied to the Shapiro-Wilk normality test and compared using the Mann-Whitney U test, which are presented as the median (min–max). Although the median values were the same in the CTQ score comparison, there was a significant difference in the control group because of the difference between the distributions and means. For this, the average ± STD values were included in the CTQ score comparison. An average of ± STD (min–max) was used in the clinical description of the patient group. The Spearman correlation test was performed to investigate the correlation of the DERS, CTQ, SAQD-C, and clinical variables of the AUD group. Logistic regression analysis was performed to determine the AUD risk factors, and the CTQ and DERS subscales were included in the model. SPSS 19.0 was used, and $p < 0.05$ was defined as statistically significant.

RESULTS

Demographic Findings

In the patient and control groups, there were more male than female participants [91% (n:34) and 89.2% (n:33), respectively]. There was no significant difference between the patient and control groups in terms of age, monthly income,

and occupational status (p = 0.449, p = 0.065, and p = 0.117, respectively). The education level was lower in the patient group than in the control group (p = 0.009). The divorce rates were higher [18.9% (n:7)] in the patient group than in the control group (p = 0.005). Demographic data are presented in Table 1 and 2.

Table 1. Mann-Whitney U Test of the Sociodemographic Characteristics of Participants

	Mean	Standard deviation (SD)	Median	Min–max	p
Age					
Patient	41.8	12.7	41.0	18–68	0.449
Control	39.9	13.6	39.0	19–66	
Income per month (US Dollar)					
Patient	605.9	522.7	569.8	0–2859.0	0.065
Control	819.3	721.0	569.8	0–5273.5	
Education level (year)					
Patient	9.7	3.0	11.0	5–15	***0.009***
Control	11.8	3.8	13.0	5–21	

Table 2. Chi-Square Test of the Sociodemographic Characteristics of Participants

	AUD		Control		
	n	%	n	%	p
Gender					
Female	3	8.1	4	10.8	1.000
Male	34	91.9	33	89.2	
Marital status					
Married	21	56.8	24	64.9	***0.005***
Non-married	9	24.3	13	35.1	
Divorced	7	18.9	0	0	
Occupation status					
Working	19	51.4	27	73	0.117
Not working	8	21.6	3	8.1	
Retired	10	27	7	18.9	

AUD: alcohol use disorder, n: number, %: column percentage

Clinical Characteristics of Participants

No participants in the control group had a history of hospitalization, suicide attempts, and substance use. The use of cigarettes and the history of alcohol abuse in the family were more prevalent in the patient group (p < 0.001 and p = 0.006, respectively). The clinical features are shown in Figure 1.

Evaluation of the DERS of Participants

The median value of the DERS total score of the patient group was 104 (68–171), which was significantly higher than the median value of the

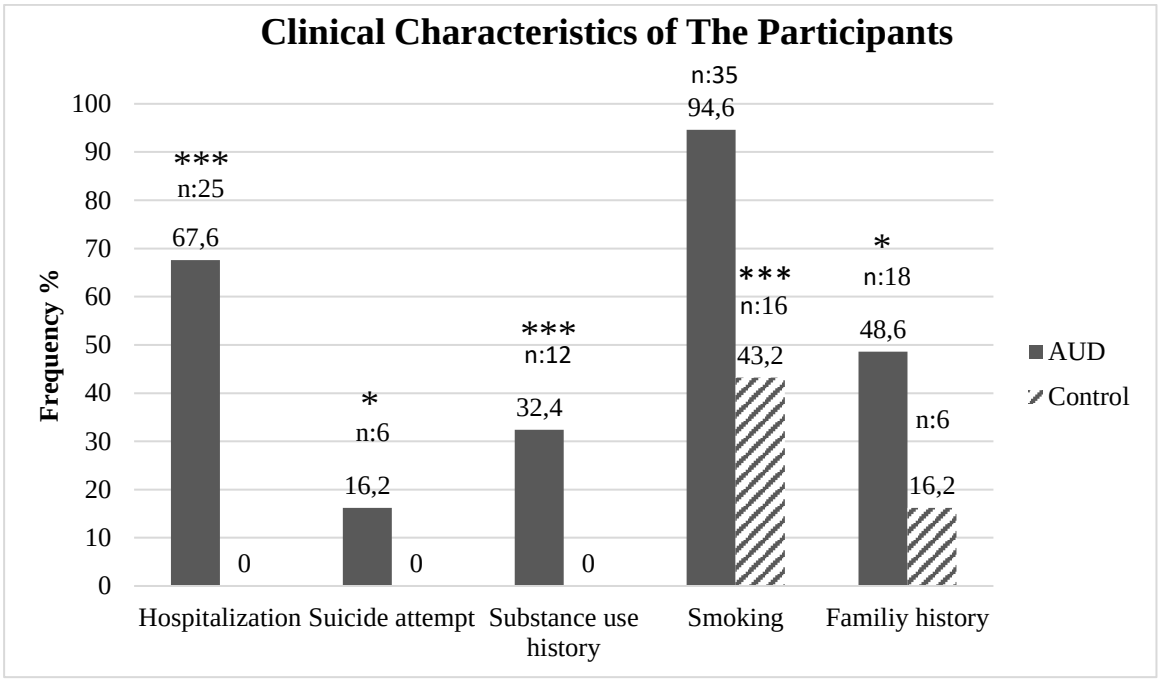

Figure 1. Frequency of the clinical characteristics of the participants. *Statistically significant difference between groups at $p < 0.05$; ***Statistically significant difference between groups at $p < 0.001$; Chi-square test

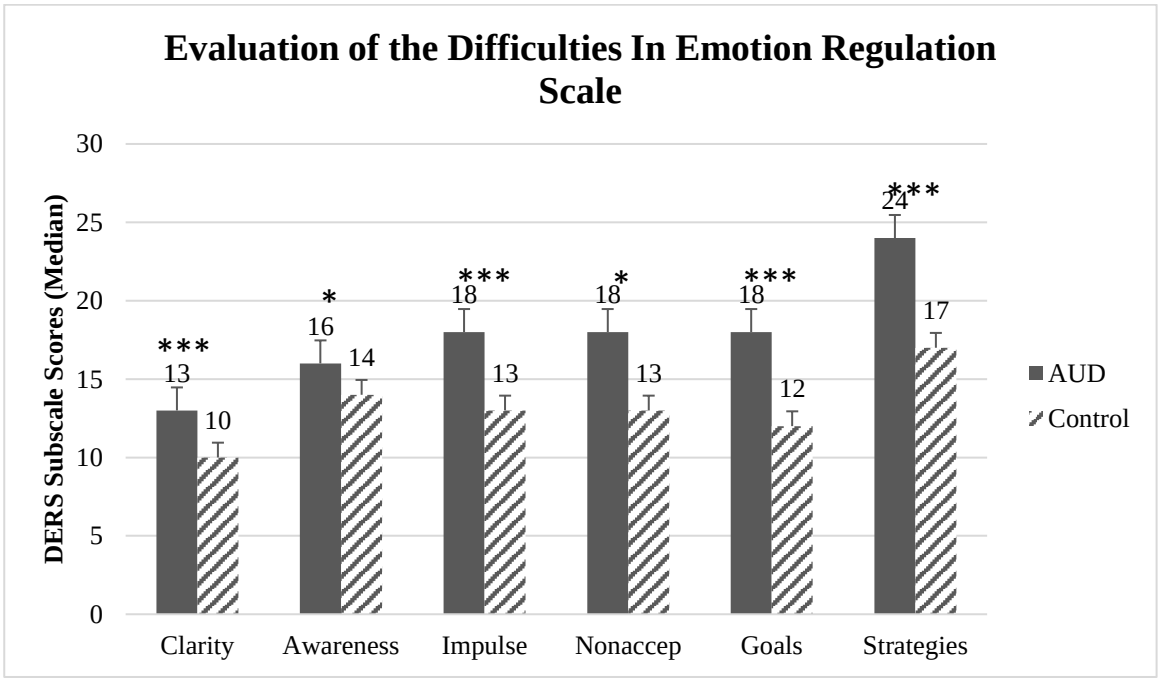

Figure. 2. Evaluation of the Difficulties in Emotion Regulation Scale (DERS). *Statistically significant difference between groups at $p < 0.05$; ***Statistically significant difference between groups at $p < 0.001$; Mann-Whitney U test.

control group [83 (51–173)] ($p < 0.001$). The AUD group's clarity13.0 (6–25), awareness 16.0 (11–30), impulse 18.0 (6–30), nonacceptance 18.0 (8–30), goals 18.0 (5–25), and strategies 24.0 (12–40) median (min–max) scores were respectively, and the median (min–max) scores

of the control group were clarity 10.0 (5–24), awareness 14.0 (6–25), impulse 13.0 (6–30), non-acceptance 13.0 (6–30), goals 12.0 (5–25), and strategies 17.0 (8–40) respectively. The AUD group's clarity, awareness, impulse, nonacceptance, objectives, and strategies median (min–max) scores were higher than the scores of the control group ($p < 0.001$, $p = 0.027$, $p < 0.001$, $p = 0.001$, $p < 0.001$, and $p < 0.001$, respectively). The DERS scores are summarized in Figure 2.

Evaluation of the CTQ Scale of Participants

The total CTQ score of the control group was 35 (26–76), and the total CTQ score of the patient group was 49 (25–89), which was significantly higher ($p < 0.001$).

The total CTQ score of the AUD group was 48.0 ± 9.7, whereas that of the control group was 37.3 ± 9.2. The median total CTQ (min–max) score of the AUD group was 49.0 (25–84), whereas that of the control group was 35.0 (26–76). The average values of emotional neglect 16.1 ± 5.4, physical neglect 5.9 ± 2, , sexual abuse 12.0 ± 4.6, , physical abuse 5.2 ± 1.3, and emotional abuse were 8.6 ± 3.9, in the AUD group and emotional neglect 10.4 ± 3.4, physical neglect 6.8 ± 3.7, sexual abuse 7.6 ± 2.8, physical abuse 5.6 ± 1.4 and emotional abuse were 6.1 ± 1.6 respectively in the control group. The median (min–max) values of emotional neglect 18.0 (5-24), physical neglect 10.0 (5-18), sexual abuse 5.0 (5-15), physical abuse 5.0 (5-25), and emotional abuse were 8.0 (5-25) in the AUD group and emotional neglect 12.0 (5–24), physical neglect 7.0 (5–18), sexual abuse 5.0 (5–13), physical abuse 5.0 (5–10) and emotional abuse were 5.0 (5–10) in the control group. The median emotional neglect, physical neglect, and emotional abuse values were significantly higher in the AUD group than in the control group ($p = 0.001$, $p < 0.001$, and $p < 0.001$, respectively). The median values of sexual abuse and physical abuse were the same. On the other hand, the average values of sexual abuse and physical abuse were higher in the AUD group than in the control group ($p = 0.014$ and $p = 0.031$, respectively). The results are summarized in Figure 3.

The prevalence of childhood traumas was higher in the AUD group than in the control group ($p < 0.05$). The frequencies of emotional neglect, physical neglect, sexual abuse, physical abuse, and emotional abuse were higher in the AUD group ($p = 0.005$, $p = 0.001$, $p = 0.024$, $p = 0.024$, and $p = 0.003$, respectively). Neglect experiences were the most frequent in the AUD and control groups. Emotional abuse was the most common type of abuse in the AUD group, and physical abuse was the most frequent type of abuse in the control group. The prevalence of childhood traumas is summarized in Figure 4.

Clinical Characteristics of AUD

The average age of the patients was 23.3 ± 8.7 years (13–51), the average alcohol use duration was 18.5 ± 10.8 years (3–45), the average amount of alcohol use was 71.3 ± 49.2 standard drinks

per week (6–210), the average duration of abstinence was 92.6 ± 203.1 days (10–912), and the average duration of remission was 24.5 ± 50.8 months (0–300).

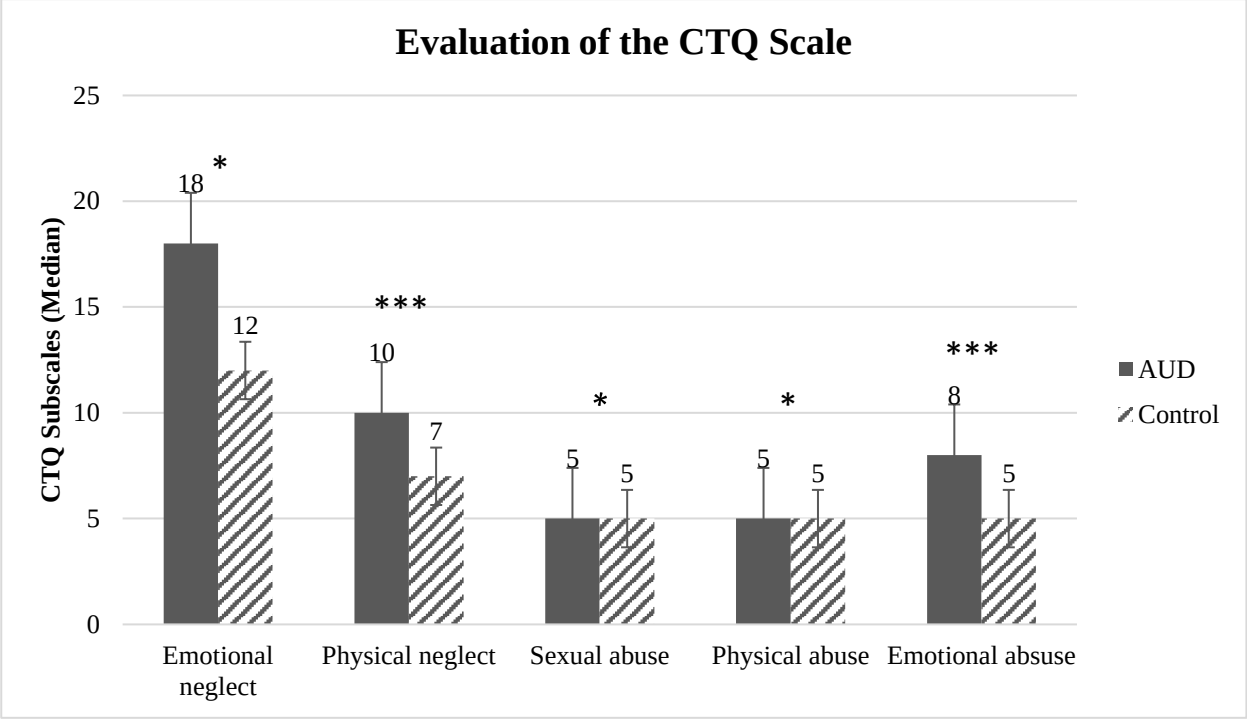

Figure 3. Evaluation of the CTQ scale. *Statistically significant difference between groups at $p < 0.05$; ***Statistically significant difference between groups at $p < 0.001$; Mann-Whitney U test.

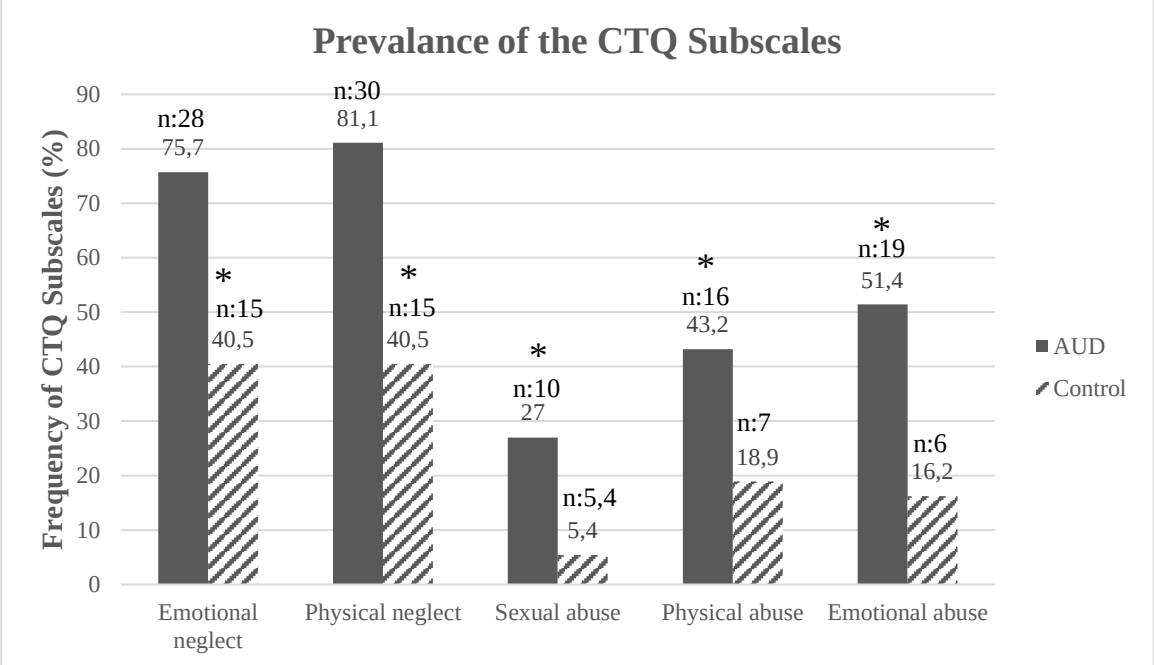

Figure. 4. Prevalance of the CTQ subscales. *Statistically significant difference between groups at $p < 0.05$; ***Statistically significant difference between groups at $p < 0.001$; Chi-square test.

Evaluation of Alcohol Addiction Severity

The SADQ-C score of the patients was 23.1 ± 13.5 (0–51). The severity of addiction was categorized as mild (32.4%), moderate (35.1%), and severe (32.4%).

Analysis of Correlation

The impulsivity subscale of DERS was positively correlated with the SADQ-C scores (r = 0.376, p = 0.022). In addition, impulsivity was correlated with the scores of physical abuses (r = 0.343, p = 0.037) and emotional abuse (r = 0.358, p = 0.030). The number of forensic cases was positively correlated with the awareness score (r = 0.673, p < 0.001). The score of goals was positively correlated with the duration of abstinence (r = −0.372, p = 0.023). The scores of objectives (r = 0.387, p = 0.018) and strategies (r = 0.391, p = 0.391) were positively correlated with emotional abuse. There was a significant positive correlation between SAQC-C scores and emotional abuse (r = 0.469, p = 0.003). The scores of physical neglect (r = 0.354, p = 0.031) and sexual abuse (r = 0.391, p = 0.017) showed a positive correlation with the number of suicide attempts.

Risk Factors for AUD

Logistic regression analysis was performed to evaluate the factors affecting AUD. DERS subscales and CTQ subscales were included in the model. Among the subscales, emotional abuse was identified as a risk factor for AUD (1.6 times higher risk) (p = 0.040). The risk factors of AUD are summarized in Table 3.

Table 3. Assessment of Alcohol Use Disorder (AUD) Risk Factors

	Beta	Odds ratio (95% CI)	p
Emotional neglect	0.116	1.123 (0.969–1.302	0.124
Physical neglect	−0.076	0.927 (0.713–1,205)	0.569
Sexual abuse	−0.171	0.843 (0.491–1.446)	0.534
Physical abuse	−0.221	0.803 (0.483–1.334)	0.396
Emotional abuse	**0.527**	***1.694* (*1.025–2.801)****	**0.040**
Clarity	0.110	1.117 (0.882–1.414)	0.360
Awareness	0.001	1.001 (0.827–1.212)	0.991
Impulse	0.200	1.222 (0.976–1.530)	0.081
Nonacceptance	0.039	1.040 (0.880–1.230)	0.647
Goals	0.048	1.049 (0.857–1.284)	0.644
Strategies	−0.180	0.835 (0.696–1.001)	0.052

Logistic regression analysis, * = *p < 0.005, model of p = 0.038.*

DISCUSSION

We examined the associations of emotion regulation difficulties and childhood traumas with alcohol use severity in a sample of patients and healthy volunteers. As expected, patients with AUD had more emotion regulation difficulties and childhood traumas (Fig. 2-3). The patients had difficulties in all of the six domains of emotion regulation.

The results showed that individuals with AUD exhibited limited access to emotion regulation strategies perceived as effective, difficulties engaging in goal-directed behaviors, difficulties in controlling impulses, and nonacceptance of emotional responses. Consistent with the primary hypothesis, there was a significant association between difficulties controlling impulsive behaviors and alcohol use severity. The literature suggests that a variety of emotion regulation difficulties, which emerge in AUD, could lead to difficulties in relationships, poor prognosis, worse treatment outcomes, and relapse (21). Maladaptive emotion regulation strategies have been linked to addiction severity and minimal positive affects (22). Furthermore, cross-sectional studies of emotion regulation have identified a relationship between addiction severity and the greater use of maladaptive emotion regulation strategies (4).

Emotion regulation strategies in alcohol-dependent patients include a higher response modulation and lower cognitive change. Cognitive change has been associated with greater positive effects, better interpersonal functioning, and greater well-being, and the use of response modulation has been associated with lower emotional functioning (23). In some studies, cognitive change has been linked to prolonged excessive alcohol drinking, which causes prefrontal impairment, affecting the neural region of emotion regulation (24). The prefrontal cortex is also the origin of impulse regulation. Therefore, addicted individuals may have higher impulsivity, which is linked to maladaptive emotion regulation strategies. Studies have revealed that the subdomains of impulsivity such as cognitive, attentional, and motor impulsivity are higher among individuals with AUD than among healthy individuals, and persistent impulse-related problems during abstinence may render patients susceptible to poor decision-making and increased vulnerability to relapse (25). Ethanol results in structural and functional impairments in the frontal cortex and consequently deteriorates emotional and behavioral regulation (26). Consistent with the literature, we found that impulsivity (the subdomain of emotion regulation strategies) was associated with addiction severity. These results provide robust evidence that emotion regulation difficulties could be higher in cases of alcohol use in adults compared with healthy controls, and impulsivity may explain at least some of the features of addiction severity.

There was a negative correlation between the duration of abstinence and score of goals. In this case, it can be assumed that if there is a problem in the DERS (goals), the duration of abstinence could be decreased. Based on the literature, we did not find any data showing the relationship between the subscale areas of the DERS and the duration of abstinence.

The second hypothesis of this study was that childhood traumas may contribute to emotion

regulation difficulties in AUD. The frequencies of childhood traumas, emotional abuse, physical abuse, sexual abuse, physical neglect, and emotional neglect were higher among patients with AUD than among healthy controls. The most prevalent childhood traumas were emotional neglect, physical neglect, and emotional abuse. These types of childhood traumas have been reported to be highly prevalent among alcohol-dependent patients, and a history of childhood trauma could have an effect on the development, severity, and course of AUD (10). Accordingly, individuals may consume alcohol or other substances to cope with psychological distress and trauma experiences, thereby alleviating negative emotional states and evoking positive emotions (27). The self-medication hypothesis can explain the relationship between emotion and trauma. A previous study found that compared with healthy controls, children who have experienced neglect or some kind of abuse are less able to understand negative emotions and exhibit fewer adaptive emotion regulation skills (1). Therefore, childhood maltreatment may result in maladaptive emotion regulation strategies, which are closely associated with addiction severity.

The childhood trauma profiles of patients were significantly associated with specific dimensions of emotion regulation strategies. We found that emotional abuse correlated with engagement in goal-directed behaviors and emotion regulation strategies. Furthermore, physical and emotional abuse was associated with impulsivity, which is defined as a dimension of emotion regulation strategies. The correlational findings implicated emotion dysregulation as a mediating mechanism in the association between childhood maltreatment and AUD. This finding suggests that there might be a common underlying factor between the dimensions of childhood traumas and emotion regulation strategies.

We also found a significant association between the number of suicides attempts and the sexual abuse and physical neglect scores. Self-harm behaviors such as suicide attempts have been reported to be more frequent among these individuals with AUD (28). In addition, impulsivity has been reported to be associated with suicide attempts in AUD (21). These clinical factors may be related to alcohol addiction severity.

The third hypothesis of the current study attempted to explain the severity of alcohol use, which may be associated with certain types of emotion regulation strategies and childhood traumas. The results demonstrated that addiction severity was correlated with impulsivity, emotion regulation difficulties, and childhood emotional and physical abuse. Several studies have reported that childhood traumas could increase the risk of alcohol dependence (29,30). Similarly, we identified childhood traumas such as emotional abuse as a risk factor for AUD, which increased the risk by 1.6-fold.

This study has some limitations, which include a small sample size, a predominantly male sample, cross-sectional measurements, and reliance on self-report measures. In addition, cognitive and emotional skills were not evaluated concurrently for emotion regulation strategies. Follow-up studies may be considered for further investigation of emotion regulation difficulties in AUD.

CONCLUSION

As expected, our results showed the higher maladaptive strategies of patients with AUD compared with healthy volunteers. Patients with AUD experienced more childhood traumas. Particularly, emotional abuse increased the risk of AUD. As a result, childhood traumas were more severe in patients with AUD, and they adversely affected emotion regulation strategies and increased the severity of addiction.

ACKNOWLEDGMENTS

First, we would like to thank our nurse of ROP unit, Merve Şura Yayla, for her great sacrifice in the operation of the CEKUS reports. We would also like to thank the director of Public Health Services of Ordu Provincial Health Directorate dealing with the CEKUS unit, Fatih Aydın, MD, for taking responsibility for the follow up of babies that were not brought in. Finally, we would like to thank all the CEKUS team and family physicians who ensured the referral of all patients to the ROP unit.

Ethics Committee Approval: Ethics committee approval was received for this study from Çanakkale Onsekiz Mart University School of Medicine (2016/27)

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: AG, DGO; Design: AG, DGO; Literature search: AG,DGO; Data Collection and Processing: AG,DGO,DDO; Analysis or Interpretation AG,DGO,DDO; Writing: AG, DGO,DDO.

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

Financial Disclosure: The authors also decline any financial support neither from any pharmaceutical company, nor from a company that provides or produces medical instruments and materials.

REFERENCES

1. Dutcher CD, Vujanovic AA, Paulus DJ, Bartlett BA. Childhood maltreatment severity and alcohol use in adult psychiatric inpatients: The mediating role of emotion regulation difficulties. Gen Hosp Psychiatry 2017;48:42–50.
2. Gross JJ, Richards JM, John OP. Emotion regulation in everyday life. Emot Regul couples Fam Pathways to Dysfunct Heal 2006;2006:13–35.
3. Gratz KL, Roemer L. Multidimensional assessment of emotion regulation and dysregulation: Development, factor structure, and initial validation of the difficulties in emotion regulation scale. J Psychopathol Behav Assess 2004;26(1):41–54.

4. Sloan E, Hall K, Moulding R, Bryce S, Mildred H, Staiger PK. Emotion regulation as a transdiagnostic treatment construct across anxiety, depression, substance, eating and borderline personality disorders: A systematic review. Clinical Psychology Review Pergamon 2017; 57: 141–63.

5. Petit G, Luminet O, Maurage F, Tecco J, Lechantre S, Ferauge M, et al. Emotion regulation in alcohol dependence. Alcohol Clin Exp Res 2015; 39(12):2471–79.

6. Berking M, Margraf M, Ebert D, Wuppermann P, Hofmann S, Junghanns K. Emotion regulation skills as a predictor of relapse during and after treatment of alcohol dependence. J Consult Clin Psychol 2011; 79(3):307–18.

7. Greenfield SF, Kolodziej ME, Sugarman DE, Muenz LR, Vagge LM, He DY, et al. History of abuse and drinking outcomes following inpatient alcohol treatment: a prospective study. Drug Alcohol Depend 2002;67(3):227–34.

8. Schwandt ML, Heilig M, Hommer DW, George DT, Ramchandani VA. Childhood trauma exposure and alcohol dependence severity in adulthood: mediation by emotional abuse severity and neuroticism. Alcohol Clin Exp Res 2013; 37(6):984–92.

9. Huang M-CMM-C, Schwandt MLM, Ramchandani VA, George DT, Heilig M, M.-C. H, et al. Impact of Multiple Types of Childhood Trauma Exposure on Risk of Psychiatric Comorbidity Among Alcoholic Inpatients. Alcohol Clin Exp Res 2012; 36(6):1099–107.

10. Lotzin A, Haupt L, von Schönfels J, Wingenfeld K, Schäfer I. Profiles of Childhood Trauma in Patients with Alcohol Dependence and Their Associations with Addiction-Related Problems. Alcohol Clin Exp Res 2016; 40(3):543–52.

11. Walsh K, McLaughlin KA, Hamilton A, Keyes KM. Trauma exposure, incident psychiatric disorders, and disorder transitions in a longitudinal population representative sample. J Psychiatr Res 2017 ;92:212–18.

12. Khantzian EJ. The self-medication hypothesis of substance use disorders: a reconsideration and recent applications. Harv Rev Psychiatry 1997; 4(5):231–44.

13. Wolff S, Holl J, Stopsack M, Arens EA, Höcker A, Staben KA, et al. Does Emotion Dysregulation Mediate the Relationship between Early Maltreatment and Later Substance Dependence? Findings of the CANSAS Study. Eur Addict Res 2016 ;22(6):292–300.

14. Heleniak C, Jenness JL, Stoep A Vander, McCauley E, McLaughlin KA. Childhood Maltreatment Exposure and Disruptions in Emotion Regulation: A Transdiagnostic Pathway to Adolescent Internalizing and Externalizing Psychopathology. Cognit Ther Res 2016; 40(3):394–415.

15. Nieratschker V, Batra A, Fallgatter AJ. Genetics and epigenetics of alcohol dependence. J Mol psychiatry 2013; 1(1):1.

16. Stockwell T, Murphy D, Hodgson R. The severity of alcohol dependence questionnaire: its use, reliability and validity. Addiction 1983; 78(2):145–55.

17. Akyel B, Aldemir E, Altıntoprak E. Turkish Validity and Reliability of The Severity of Alcohol Dependence Questionnaire 2015; 90(12):33–34.

18. Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, et al. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. Child Abuse Negl 2003; 27(2):169–90.

19. Yargıç LI, Tutkun H, Şar V. Childhood traumatic experiences and dissociative symptoms in adults. J Psychiatry, Psychol Psychopharmacol 1994; 2:338–48.

20. Ruganci RN, Gençöz T. Psychometric properties of a Turkish version of the Difficulties in Emotion Regulation Scale J Clin Psychol 2010; 66(4):442-55.

21. Ghorbani F, Khosravani V, Sharifi Bastan F, Jamaati Ardakani R. The alexithymia, emotion regulation, emotion regulation difficulties, positive and negative effects, and suicidal risk in alcohol-dependent outpatients. Psychiatry Res 2017; 252:223–30.

22. Watkins LE, Schumacher JA, Coffey SF. A preliminary investigation of the relationship between emotion dysregulation and partner violence perpetration among individuals with PTSD and alcohol dependence. J Aggress Maltreatment Trauma 2016; 25(3):305–14.

23. Mauss IB, Cook CL, Cheng JYJ, Gross JJ. Individual differences in cognitive reappraisal: experiential and physiological responses to an anger provocation. Int J Psychophysiol 2007; 66(2):116–24.

24. Kober H. Emotion regulation in substance use disorders. In: Handbook of emotion regulation. New York, NY, US: Guilford Press; 2014.p.428–46.

25. Lejuez CW, Magidson JF, Mitchell SH, Sinha R, Stevens MC, De Wit H. Behavioral and Biological Indicators of Impulsivity in the Development of Alcohol Use, Problems, and Disorders. Alcohol Clin Exp Res 2010; 34(8):1334–45.

26. Jakubczyk A, Trucco EM, Kopera M, Kobyliński P, Suszek H, Fudalej S, et al. The association between impulsivity, emotion regulation, and symptoms of alcohol use disorder. J Subst Abuse Treat 2018; 91:49–56.

27. Holl J, Wolff S, Schumacher M, Höcker A, Arens EA, Spindler G, et al. Substance use to regulate intense posttraumatic shame in individuals with childhood abuse and neglect. Dev Psychopathol 2017; 29(3):737–49.

28. Glassman LH, Weierich MR, Hooley JM, Deliberto TL, Nock MK. Child maltreatment, non-suicidal self-injury, and the mediating

role of self-criticism. Behav Res Ther 2007; 45(10):2483-90.

29. Wu NS, Schairer LC, Dellor E, Grella C. Childhood trauma and health outcomes in adults with comorbid substance abuse and mental health disorders. Addict Behav 2010; 35(1):68–71.

30. Edwards VJ, Holden GW, Felitti VJ, Anda RF. Relationship between multiple forms of childhood maltreatment and adult mental health in community respondents: results from the adverse childhood experiences study. Am J Psychiatry 2003; 160(8):1453–60.

Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci **May 2022; 8(2):202-207**

RESEARCH ARTICLE **DOI:** 10.19127/mbsjohs.1001931

YY1 and NFYA: Potential tr-KIT Specific Transcription Factors in Prostate Cancer

Sercan Ergun[1(ID)], Ferda Arı[2(ID)] , Erdal Benli[3(ID)], Diler Us Altay[4(ID)], Tevfik Noyan[5(ID)], Havva Erdem[6(ID)], Yeliz Kaşko Arıcı[7(ID)]

[1]Department of Medical Biology, Faculty of Medicine, Ondokuz Mayis University, Samsun, Turkey
[2]Department of Biology, Faculty of Arts and Science, Uludag University, Bursa, Turkey
[3]Department of Urology, Faculty of Medicine, Ordu University, Ordu, Turkey
[4]Department of Nutrition and Dietetics, Faculty of Health Sciences, Ordu University, Ordu, Turkey
[5]Department of Medical Biochemistry, Faculty of Medicine, Ordu University, Ordu, Turkey
[6]Department of Medical Pathology, Faculty of Medicine, Ordu University, Ordu, Turkey
[7]Department of Biostatistics, Faculty of Medicine, Ordu University, Ordu, Turkey

Received: 30 August 2021, Accepted: 23 December2021, Published online: 31 May 2022

Abstract

Objective: Via the use of an alternative promoter, a truncated c-KIT protein (tr-KIT) of 30-50 kDa is generated, lacking extracellular and transmembrane domains. Moreover, over-expression of tr-KIT, a stronger activator than c-KIT, appears to be specific to prostate cancer (PCa). Also, Imatinib, a tyrosine kinase inhibitor, blocks the activity of full-length c-KIT but has no effect on tr-KIT in PCa. Tr-KIT has its own nuclear factor binding site. However, the transcription factors (TFs) binding to this region specific to tr-KIT are not known yet. This study was conducted to define the most potential TFs specific for tr-KIT via in silico analysis.

Methods: Tr-KIT potential TF binding sequence was uploaded into Tfsitescan database. Five TFs with the highest potential binding to this sequence were selected. Transcriptomic data of LNCaP (PCa expressing tr-KIT), PC3 (PCa not expressing tr-KIT) and RWPE-1 (normal prostate) cell lines (GSM1647378, GSE36022 and GSM738189, respectively) from Gene Expression Omnibus (GEO) database were compared for gene expression levels of pre-defined potential tr-KIT specific TFs using DESeq package of R-program. Finally, two TFs having higher expression levels in both LNCaP and PC3 compared to RWPE-1 and higher expression levels in LNCaP compared to PC3 were detected.

Results: Five TFs having the highest potential were selected as: YY1, c-MYB, IL8, NFYA and TCF3. Via in silico analysis performed, it was found that YY1 and NFYA have the highest potential to be tr-KIT specific TFs in PCa, among them.

Conclusion: YY1 and NFYA TFs may take a role in formation of tr-KIT in PCa.

Key words: Prostate cancer, transcription factors, gene expression regulation

Suggested Citation: Ergun S, Ari F, Benli E, Us Altay D, Noyan T, Erdem H, Kasko Arici Y. YY1 and NFYA: Potential tr-KIT Specific Transcription Factors in Prostate Cancer. Mid Blac Sea Journal of Health Sci, 2022;8(2):202-207.

Address for correspondence/reprints:
Sercan Ergun

Telephone number: +90 (554) 921 7482
E-mail: sercan.ergun@omu.edu.tr

INTRODUCTION

Prostate cancer (PCa) is the most widespread internal organ tumoral formation in men and the second most widespread type of cancer worldwide (1). C-KIT (CD117) is an oncogenic receptor tyrosine kinase overexpressed in PCa cases. Moreover, c-KIT regulates cell proliferation in the prostate and plays an important role in the pathophysiology of benign prostatic hyperplasia (BPH). In addition, c-KIT expression in PCa patients has been found to correlate with disease relapse. That provided c-KIT to be considered as a choice for anti-cancer therapies. Currently, inhibitors of c-KIT interfering with c-KIT signaling pathways are options for the treatment of PCa, gastrointestinal cancers and leukemia, and in the assessments of other cancer types (2). Via an alternate promoter, a truncated c-KIT protein (tr-KIT) of 30-50 kDa is formed, not having the transmembrane and extracellular domains (3). Tr-KIT is a stronger activator of Src kinases in comparison with the full length c-KIT protein. Higher Src efficiency was detected in PCa tissues and cells expressing tr-KIT. The markedly increased transcriptional activity of tr-KIT with PCa aggression provides it to be considered as a pharmacological target (4, 5).

Imatinib is a tyrosine kinase inhibitor that has the ability to slow and stop tumor formation by targeting the extracellular part of c-KIT, which is overexpressed in PCa cases, by suppressing it. Imatinib arrests the efficiency of full-length c-KIT however doesn't have influence on tr-KIT. This explains the ineffectiveness of this agent in the therapy of PCa, and the discrepancy between in vitro test results and clinical findings. Moreover, vascular endothelial growth factor (VEGF), an angiogenesis factor, represented a marked reaction to Imatinib in DU145 and PC3 cells. Imatinib treatment reduced VEGF expression levels in DU145 cells, while an opposite effect was observed in PC3. Those adverse influences of Imatinib in different cell lines might conduce to explain the lack of efficiency of that anti-tumor agent to control prostate tumor development and increase anxiety about the induction and progression of metastasis in case of administering imatinib therapy in PCa patients. As a result, the transcriptional activities of tr-KIT and c-KIT in PC3 and DU145 cell lines identify the variable influences seen in response to Imatinib with decreased full-length c-KIT expression and rised tr-KIT expression. Overall, the available information and the data obtained above support more comprehensive studies aimed specifically at defining agents blocking tr-KIT (6). So, it is crucial to understand tr-KIT activation mechanism in PCa.

Tr-KIT possesses its own transcription factor binding region (a site in the 16th intron of the c-KIT) (4, 7). Even so, transcription factors (TFs) targeting to that site particular to tr-KIT are not defined still. This study was performed to define the most probable TFs in silico by analyzing the potential TF binding site for tr-KIT

METHODS

Sequence based potential TF analysis

Firstly, we have to mention that this is an in silico study so there is no need for Ethics Committee Approval.

Potential TF binding sequence specific to tr-KIT was loaded into database of Tfsitescan (8). The nucleotide sequence of tr-KIT-specific possible TF binding region in the 16th intron of c-KIT gene (NC_000004.12) is as follows:

>gi|568815594|ref|NC_000004.12|:54732094-54732264 Homo sapiens chromosome 4, GRCh38.p12 Primary Assembly

5'-
TAGTTAAAATGCAGAATGTCATTTTGAAGTG
TGGTAACCAAAAGCAGAG
GAAATTTAGTTTCTTCATGTTCCAACTGCTGT
CTCTTTGGAATTCCTGTTCTAATTTATAAGCT
GTAAAGTACAAGCCTGTCTAAATGAGTTTTT
CTATGAATATTCTTTTATATGCAGTGA-3'

Five TFs with the highest binding probability to that region were chosen.

Comparison of transcriptomic data and statistical analysis

From Gene Expression Omnibus (GEO) database, transcriptomic data of LNCaP (PCa expressing tr-KIT), PC3 (PCa not expressing tr-KIT) and RWPE-1 (normal prostate epithelium) cell lines (GSM1647378, GSE36022 and GSM738189, respectively) were compared with respect to gene expression levels of five pre-defined potential TFs using DESeq package of R-program. For differential gene expression analysis, the number of reads mapped to each pre-defined potential TFs was calculated and presented utilizing the HTseq package, and the output data was processed as input data for statistical computations. The Q-value obtained from statistical approaches were utilized to assess gene expression differing between cell lines (9).

Consequently, this analysis presented that two TFs with higher transcriptional activity in both PC3 and LNCaP in comparison with RWPE-1 and with higher transcriptional activity in LNCaP in comparison with PC3 were obtained

RESULTS

Having the highest potential binding to tr-KIT-specific possible TF binding region sequence according to sequence based potential TF analysis, five TFs selected as follows: c-MYB, YY1, NFYA, TCF3 and IL8.

As a result of in silico comparsion of LNCaP (PCa expressing tr-KIT), PC3 (PCa not expressing tr-KIT) and RWPE-1 (normal prostate epithelium) cell lines' transcriptomic data (Figure 1), we detected only Yin Yang 1 (YY1) and Nuclear Transcription Factor Y Subunit Alpha (NFYA) TFs provided the condition with higher transcriptional activity in both LNCaP and PC3 in comparison with RWPE-1 and with higher transcriptional activity in LNCaP in comparison with PC3. So, YY1 and NFYA TFs defined to possess the highest potency to become TFs particular to tr-KIT.

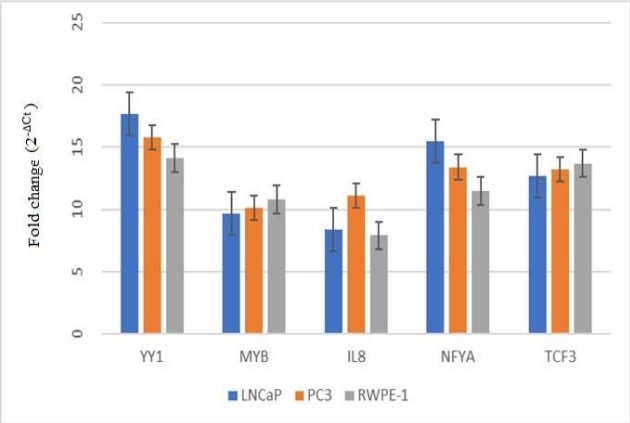

Figure 1. Comparison of transcriptomic data

DISCUSSION

Tr-KIT is a strınger activator of Src kinases in comparison with the full length c-KIT protein. Higher Src efficiency was detected in PCa tissues and cells expressing tr-KIT. Tr-KIT activation mechanism is very important to understand PCa and imatinib resistance better. Yet, tr-KIT specific TFs are not known. In this study, we defined two TFs with the

highest probability to become tr-KIT specific TFs, YY1 and NFYA. This shows potential oncogenic roles of YY1 and NFYA for PCa as activators of tr-KIT. As presented below, the findings related with YY1 and NFYA with respect to their potential to activate PCa are so convincing.

Heterogeneous nuclear ribonucleoprotein M (hnRNPM) can bind to cis-acting elements or various proteins and implement variety of biological functions in different cells. HnRNPM has a lower transcriptional activity both in PCa tissue compared to benign prostate hyperplasia (BPH) tissue and in neuroendocrine prostate cancer (NEPC) tissue compared to adenocarcinoma tissue. Yang et al. showed that YY1 overexpression might trigger epithelial-mesenchymal transition (EMT) by decreasing hnRNPM transcriptional activity in PCa cells (10). Also, XAF1 having absent or low transcriptional activity in cancer is a tumor suppressor gene product. Ectopic-mediated expression or transcriptional reactivation of XAF1 suppresses cancer progression. Camacho et al. reported that YY1 could suppress tumor suppressor gene XAF1 through HDAC1 downregulation or inhibition and because of mutation at the YY1-binding region in XAF1 promoter in PCa (11). Moreover, the high expression of miR-146a affects PCa cells with respect to progression, viability, and apoptosis. Huang et al. expressed that YY1 depletion suppressed PCa cell proliferation and viability, and triggered apoptosis via miR-146a assistance (12).

Protein arginine methyltransferase 5 (PRMT5) add methyl groups to non-histone protein substrates and arginine residues of histones in parallel and mediates various cellular functions via epigenetic control of post-translational modification of signaling molecules or target gene expression. The latest evidence proposes that PRMT5 can serve as an oncogene and its excessive expression causes the formation and progression of many different human cancers. Zhang et al. found that PRMT5 regulated the effect of NFYA to activate cell grown in LNCaP prostate cancer cells (13). Also, Chan et al. indicated that the phosphorylation of NFYA regulated the transcriptional expression of G2 checkpoint mediators (cyclin B1, cyclin A2, cdc2, and cdc25c) through binding to CCAAT motif in their promoters in PCa cells (14).

These studies support our findings giving potential oncogenic roles to YY1 and NFYA and increasing their clinical significance for PCa as activators of tr-KIT.

Some limitations of this study should be noted. First, tr-KIT potential TF binding sequence was used to determine tr-KIT specific TFs (4, 7). However, there may be other genomic regions that have not been identified as tr-KIT specific TF binding site yet. So, we can just analyze the region identified up to now. Second, we defined potential tr-KIT specific TFs, YY1 and NFYA, upon transcriptomic data of PCa cell lines. But, for now, we don’t know their validity in PCa cancer patients although it is within our future plans.

CONCLUSION

All in all, YY1 and NFYA TFs might take a function in production and activity of tr-KIT in PCa and provide clinically significant information about PCa progression and Imatinib resistance via tr-KIT activation. More universal research is required to figure out the functions of NFYA and YY1 TFs in PCa progression via higher tr-KIT transcriptional activity.

Ethics Committee Approval: Clinical Studies Ethics Committee of Ordu University, Faculty of Medicine was not needed.

Peer-review: Externally peer-reviewed.

Author Contributions:

Concept: S.E., Design: S.E, F.A.; Literature search: S.E., D.U.A, Data Collection and Processing: S.E. F.A., E.B., D.U.A., T.N, H.E., Analysis or Interpretation: S.E., F.A., D.U.A, Y.K.A., Writing: S.E.

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

Financial Disclosure: This study was carried out within the scope of TUBITAK 3501 project, numbered 119Z574.

REFERENCES

1. Wu P, Cao Z, Wu, S. New progress of epigenetic biomarkers in urological cancer. Dis Markers 2016; 9864047.
2. Imura M, Kojima Y, Kubota Y, Hamakawa T, Yasui T, Sasaki S, Hayashi Y, Kohri K. Regulation of cell proliferation through a KIT-mediated mechanism in benign prostatic hyperplasia. Prostate 2012; 72(14): 1506-1513.
3. Cardoso HJ, Figueira MI, Socorro S. The stem cell factor (SCF)/c-KIT signalling in testis and prostate cancer. Cell Commun Signal 2017; 11(4): 297-307.
4. Paronetto MP, Farini D, Sammarco I, Maturo G, Vespasiani G, Geremia R, Rossi P, Sette C. Expression of a truncated form of the c-Kit tyrosine kinase receptor and activation of Src kinase in human prostatic cancer. Am J Pathol 2004; 164(4): 1243-1251.
5. Ergun S, Altay DU, Gunes S, Buyukalpelli R, Karahan SC, Tomak L, Abur U. Tr-KIT/c-KIT ratio in renal cell carcinoma. Mol Biol Rep 2019; 46(5): 5287-94.
6. Mol CD, Dougan DR, Schneider TR, Skene RJ, Kraus ML, Scheibe DN, Snell GP, Zou H, Sang BC, Wilson KP. Structural basis for the autoinhibition and STI-571 inhibition of c-Kit tyrosine kinase. J Biol Chem 2004; 279(30): 31655-31663.
7. Albanesi C, Geremia R, Giorgio M, Dolci S, Sette C, Rossi P. A cell-and developmental stage-specific promoter drives the expression of a truncated c-kit protein during mouse spermatid elongation. Development 1996; 122(4): 1291-1302.
8. Ghosh D. Object-oriented transcription factors database (ooTFD). Nucleic Acids Res 2000; 28(1): 08-310.
9. Anders S, Huber W. Differential expression analysis for sequence count data. Genome Biol 2010; 11(10): R106.
10. Yang T, An Z, Zhang C, Wang Z, Wang X, Liu Y, Xu Y. HnRNPM is a potential mediator of YY1 which promotes EMT in prostate cancer cells. Prostate 2019; 79(11): 1199-1210.
11. Camacho-Moctezuma B, Quevedo-Castillo M, Melendez-Zajgla J, Aquino-Jarquin G, Martinez-Ruiz, GU. YY1 negatively regulates the XAF1 gene expression in prostate cancer. Biochem Bioph Res Co 2019; 508(3): 973-979.
12. Huang Y, Tao T, Liu C, Guan H, Zhang G, Ling Z, Chen M. Upregulation of miR-146a by YY1 depletion correlates with delayed progression of prostate cancer. Int J Oncol 2017; 50(2): 421-431.

13. Zhang HT, Zhang D, Zha ZG, Hu CD. Transcriptional activation of PRMT5 by NF-Y is required for cell growth and negatively regulated by the PKC/c-Fos signaling in prostate cancer cells. BBA Gene Regul Mech 2014; 1839(11): 1330-1340.

14. Chan QK, Lam HM, Ng CF, Lee AY, Chan ES, Ng HK, Lau KM. Activation of GPR30 inhibits the growth of prostate cancer cells through sustained activation of Erk1/2, c-jun/c-fos-dependent upregulation of p21, and induction of G 2 cell-cycle arrest. Cell Death Differ 2010; 17(9): 1511-1523.

Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci **May 2022; 8(2): 208-222**

RESEARCH ARTICLE **DOI:** 10.19127/mbsjohs.1015480

Turkish Validity and Reliability Study of the Pregnancy Stress Rating Scale

Ozlem Akin[1](ID), Nulufer Erbil[2](ID)

[1]Department of Obstetrics and Gynecologic Nursing, Faculty of Health Sciences, Recep Tayyip Erdogan University, Rize, Turkey
[2]Department of Obstetrics and Gynecologic Nursing, Faculty of Health Sciences, Ordu University, Ordu, Turkey

Received: 28 October 2021, Accepted: 09 January 2022, Published online: 31 May 2021

Abstract

Objective: This study was conducted to evaluate the reliability and validity by adapting to Turkish of the Pregnancy Stress Rating Scale (PSRS-36).

Methods: The sample of this methodological study included 360 volunteer pregnant women. The data were collected with questionnaire form and Turkish version of the Pregnancy Stress Rating Scale. In data analysis were used Cronbach's alpha coefficient, explanatory, and confirmatory factor analysis (CFA) after the language and content validity of Pregnancy Stress Rating Scale. For CFA one of the concordance models of structural equality, LISREL, was used.

Results: As a result of the explanatory factor analysis, it was found that the Pregnancy Stress Rating Scale had five sub dimensions structure as in the original form, and the factor loads of the model changed between 0.453-0.807. Cronbach's alpha coefficient of Turkish version of total Pregnancy Stress Rating Scale was 0.92. Cronbach's alpha values of subdimensions of Pregnancy Stress Rating Scale. Turkish version was between 0.81 and 0.86. Of these x2/SD value 2.18, GFI 0.95, AGFI 0.94, CFI 0.95, RMSEA 0.077 and SRMR 0.075 were identified.

Conclusion: The Turkish version of Pregnancy Stress Rating Scale (PSRS-36) was determined a valid and reliable measurement tool for Turkish society. The Turkish version of Pregnancy Stress Rating Scale (PSRS-36) be used as data collection tool to determine pregnancy stress by midwives and nurses.

Key words: Nurse, pregnancy, reliability, stress, scale, validity

Suggested Citation: Akin O, Erbil N. Turkish validity and reliability study of the Pregnancy Stress Rating Scale. Mid Blac Sea Journal of Health Sci, 2022;8(2):208-222.

Address for correspondence/reprints:

Ozlem Akin
Telephone number: +90 (464) 214 10 59-3908
E-mail: akinozleem@gmail.com

INTRODUCTION

The concept of stress is a bodily and psychosocial situation causing tension in a person, leading to psychological and physiologic discomfort in individuals (1). Stress is more commonly encountered in women due to expectations about undertaking the load of family life. Women were identified to encounter stressful life events at rates of 53.5% for pregnancy, 49.6% marriage, 44.5% differences in sleep quality, 36.5% inclusion of a new member into the family, and 31.6% changes in eating habits (2). Though pregnancy is a natural life event, it is a situation causing physiologic, psychologic and social changes (3). Stress is experienced during pregnancy due to reasons such as previous personal experiences, interfamily relationships, cultural level, attitude of partner and family toward the pregnancy, maternal age, size of family, not wanting the pregnancy, and not having social support (4).

Reasons for increased stress during the pregnancy period include physiologic changes in the woman's body, expectations of the mother, situations threatening the health of the unborn baby, expectations about taking on a new role, and society's expectations about being a flawless mother (5). Additionally, general physiologic and psychological changes like disrupted body image, unwanted pregnancy, not adapting to the pregnancy, anxiety about the fetus, little social support, financial issues, not being prepared for parenthood, increased numbers of pregnancies, not knowing the sex of the baby, the pregnancy not being planned, and pain or hemorrhage occurring are situations causing stress during pregnancy (6,7). Pregnant women may not be informed about the birth and experience stress due to labor pains and this situation may cause complications during pregnancy and birth. Pain experienced during labor significantly increases the mother's stress levels and causes anxiety. Extreme stress during pregnancy affects fetal circulation, increasing the levels of various maternal hormones and neurotransmitters that modulate fetal development (8). The stress and anxiety experienced by the pregnant women may negatively affect the blood pressure and heart rate of the fetus and cause negative effects on the baby at birth and while newborn like preterm labor, development retardation or low birth weight (5).

Good mental status during the pregnancy period is important for maternal and fetal health. Psychological diseases in pregnancy affect the psychological status of the pregnant person, may cause negative situations, and are known to increase rates of maternal and fetal morbidity and mortality of mothers who don't receive care. It is necessary to initially determine the risk group to prevent stress related to pregnancy. A holistic approach is important with medical examination of pregnant cases during follow-up including psychosocial evaluation in addition to physical examination. Emotional stress, anxiety and depression experienced in this period require diagnosis and treatment as they can cause complications in pregnancy, affect the health of the fetus and mother, cause preterm birth, low birth weight and intrauterine growth retardation in the fetus, and also due to the tendency toward postnatal depression in the mother (9).

Nurses and midwives should prepare pregnant people very well so they experience for this process in the healthiest way, developing the mother's coping skills for problems encountered will ensure this period passes with higher quality (10). In addition to

the physical care services that nurses, and midwives provide to mothers, they should reduce stress levels by giving additional education and counseling services. Studies in Turkey in different fields have observed the use of newly developed scales or scales adapted to Turkish. In Turkey, commonly used scales for anxiety and depression include the State and Trait Anxiety Inventory (11), Beck Anxiety Inventory (12) Beck Depression Inventory (13), Fear of Childbirth and Postpartum Period Scale (14), Edinburgh Postnatal Depression Scale (15) and the Tilburg Pregnancy Distress Scale (16). These scales are generally about identifying a single problem and the number of scales specific to pregnancy is limited.

The study aims to determine translate the Pregnancy Stress Rating Scale, measuring anxiety and stress related to pregnancy among pregnant women developed by Chung-Hey Chen in Chinese with validity and reliability studies completed among Taiwanese pregnant women, into Turkish and perform validity and reliability studies on the Turkish version.

METHODS

Study Design And Participants

The methodological study was completed in the obstetrics clinic of a university hospital in the Black Sea region in Turkey.

Research data were collected from October 16, 2017, to February 26, 2018. Inclusion criteria for the sample in the study were being pregnant, aged at least 18 years, voluntary participation in the research, primary school graduate at least, married, able to form verbal communication, and living with their partner. Exclusion criteria for the research were history of chronic diseases, history of psychiatric diseases, and any problem with the baby. For determination of the numbers in samples for methodological studies in the literature, it is recommended they be at least 5-10 times the number of items on the scale (17). In this study, as the scale contained 36 items, the number in the sample was 10 times that at 360 pregnant women.

Data Collection

Data in the research were collected with a personal information form, and the Pregnancy Stress Rating Scale-36 Turkish version with linguistic and scope validity performed on the scale developed by Chen (2015) (18). Data were collected in the obstetrics clinic in the hospital. Pregnant women included within the scope of the research were given information about the research and completing the personal information form and scale. Pregnant women read and completed the information form and scale themselves. Answering the personal information form and scale questions took about 20-25 minutes in a quiet-calm section of the outpatient clinic.

Evaluation Tools

Personal Information Form

The personal information form encompasses questions about the sociodemographic features of the pregnant women. In this form includes questions about age, years of marriage, number of children, week of pregnancy, education level, occupation, partner education level, partner occupation, family type and family income levels.

The Pregnancy Stress Rating Scale-36 Turkish Version

Developed by Chen (2015) (18) the PSRS-36 is a scale used to define stress factors linked to pregnancy in pregnant cases comprising 5 subdimensions and 36 items. The PSRS-36 includes the subdimensions

"Stress from seeking safe passage for mother and child through pregnancy, labor, and delivery" subdimension (items 1-9); "Stress from baby care and changing family relationships" subdimension (items 10-18); "Stress from maternal role identification" subdimension (items 19-26); "Stress from social support seeking" subdimension (items 27-30); and "Stress from altered physical appearance and function" subdimension (items 31-36). The scale items have a 5-point Likert response. The worry, distress, and anxiety experienced by the pregnant case is graded as "definitely not", "mildly", "moderately", "severely" or "very severely" with points given from 0 to 4. The lowest points that can be obtained are 0, with highest points of 144 from the PSRS-36. The scale is used to identify stress factors linked to pregnancy in pregnant people. As points obtained from the scale increase, the stress is interpreted to increase.

The PSRS-36 Turkish Version Cross-Cultural Adaptation Process

Developed by Chung-Hey Chen (2015) (18) with validity and reliability studies in Taiwanese pregnant women and original version in Chinese, the PSRS-36 had translation-retranslation performed by English linguistic scientists to test linguistic equivalence. After the items on the PSRS-36 were translated into Turkish, the retranslation into English was performed by two linguistic scientists who knew both languages. After the translation procedure, similar results were obtained by the translators. After completing translation-retranslation procedures, expert opinions were sought from 11 faculty member employed in the Gynecology and Obstetrics Nursing and Midwifery Departments in the university for scope validity of the PSRS-36. The expert lecturers investigated the scale for cultural appropriateness and comprehensibility and reported their opinions. Experts were requested to evaluate the appropriateness and comprehensibility for the aim by giving each item points as 1: not appropriate, 2: slightly appropriate, 3: quite appropriate and 4: very appropriate.

After scope validity, factor analysis was performed to determine the construct validity of the PSRS-36 and obtain clearer data. Before factor analysis, with the aim of evaluating the sample sufficiency and fit of data for factor analysis, the Kaiser-Meyer-Olkin (KMO) and Bartlett's tests were applied. The KMO value was identified as 0.888 and this shows it is appropriate for basic component analysis. Similarly, the Bartlett test results ($x2 = 6657.871$, $p>0.001$) show the data are correlated with each other and that it is appropriate for factor analysis.

Statistical Analysis

Normal distribution of data was evaluated with the skewness and kurtosis coefficients. Appropriateness of the sample size and data set for factor analysis were evaluated with the KMO index and Bartlett test (19). To determine the construct validity of the PSRS-36, Exploratory Factor Analysis (EFA) and Confirmatory Factor Analysis (CFA) were performed. For EFA, basic component analysis, varimax transformation and Scree Plot test were performed (20). For CFA, the x2/SD value, GFI, AGFI, CFI, RMSEA and SRMR fit indices and PATH diagram were used. To measure the internal consistency and homogeneity of the PSRS-36, the item total point correlations and Cronbach alpha coefficient were used (21). For CFA one of the concordance models of structural equality, LISREL, was used (22, 23).

RESULTS

Participant

The mean age of pregnant women included in the scope of the research was 27.90±3.99 years (range 18-41), mean years of marriage was 5.58±4.99 years (range 1-26), number of pregnancies was 2.22±1.20 (range 0-7), number of surviving children was 0.92±0.96 (range 0-5 children), and week of pregnancy was 27.81±10.67 weeks (range 0-41). Of pregnant cases, 28.6% were high school graduates, 76.4% were housewives, 34.7% had partners who were high school graduates, and 31.9% had partners who were laborers. Of pregnant women 82.8% lived in a nuclear family, while 90.8% stated they had "moderate" income levels (Table 1).

Table 1. Distribution of pregnant women according to their characteristics (n=360)

Characteristics of pregnant women	n	%
Education status		
Primary school	60	16.6
Secondary school	101	28.1
High school	103	28.6
University	96	26.7
Employment status		
Housewife	275	76.4
Offier	27	7.5
Worker	29	8.1
Self-employment	8	2.2
Other (farmer etc.)	21	5.8
Spouse's education level		
Primary school	55	15.3
Secondary school	84	23.3
High school	125	34.7
University	96	26.7
Spouse's employment status		
Offier	54	15.0
Worker	115	31.9
Farmer	18	5.0
Self-employment	109	30.3
Unemployed	64	17.8
Family type		
Nuclear family	298	82.8
Extended family	62	17.2
Family income level		
Low	26	7.3
Medium	327	90.8
Good	7	1.9

Validity of the PSRS-36 Turkish Version

Validity of the Language

For linguistic equivalence of the PSRS-36 in Turkish, translation from English to Turkish was performed and then the Turkish scale items were retranslated into English.

Content Validity

After ensuring linguistic equivalence for the Turkish version of the PSRS-36, for scope validity opinions were sought from 11 faculty member working in the Gynecology and Obstetrics Nursing and Midwifery Departments in the university. The expert faculty member investigated the scale for cultural appropriateness and comprehensibility and reported their opinions. Experts were requested to evaluate the appropriateness and comprehensibility for the aim by giving each item points from 1: not appropriate, 2: slightly appropriate, 3: quite appropriate and 4: very appropriate. According to the responses of experts about the PSRS-36 items, the scale had scope validity assessed with the Davis technique. The Scope Validity index (SVI) scores for all items varied from 0.80-1.00, so there was no need to remove any item from the scale due to scope/content validity and the SVI for all items on the scale was found to be 0.952 (24).

Construct Validity

After scope validity, factor analysis was performed to determine the construct validity of the PSRS-36 and obtain clearer data. Before factor analysis, with the aim of evaluating the sample sufficiency and fit of data for factor analysis, the KMO and Bartlett's tests were applied. The KMO value was identified as 0.888 and this shows it is appropriate for basic component analysis. Similarly, the Bartlett test results (x2= 6657.871, p=0.000) show

the data are correlated with each other and that it is appropriate for factor analysis.

Table 2. Factor pattern of the Pregnancy Stress Rating Scale-36 of Turkish version

Item no	Item description	Factor 1[a]	Factor 2[b]	Factor 3[c]	Factor 4[d]	Factor 5[e]
Item 1	Abnormal or difficult birth	0.616				
Item 2	Safe labor and delivery for my sake	0.654				
Item 3	Safe delivery for my baby's sake	0.669				
Item 4	Doctor may not arrive on time at delivery	0.687				
Item 5	Premature labor	0.635				
Item 6	Doctor attitudes during labor and delivery	0.742				
Item 7	Nurse attitudes during labor and delivery	0.751				
Item 8	Husband's absence during labor	0.515				
Item 9	Unbearable labor pain	0.561				
Item 10	Breast or bottle feed my baby		0.654			
Item 11	Ability to breastfeed succesfully		0.791			
Item 12	Ability to raise my baby succesfully		0.793			
Item 13	Naming my baby		0.644			
Item 14	Sexual activity during pregnancy		0.403			
Item 15	Loss of free time after birth		0.475			
Item 16	Acceptance of the child by significant others		0.651			
Item 17	Increased financial burden		0.440			
Item 18	Support from family members or husband		0.725			
Item 19	Baby's appearance					0.572
Item 20	Baby's birth weight					0.651
Item 21	Baby's gender					0.435
Item 22	Baby's health					0.532
Item 23	Concern about status of fetal movement					0.559
Item 24	Adhering to traditional pregnancy mores					0.481
Item 25	Maternal behavior influencing the fetus					0.532
Item 26	Preparation of clothes and newborn supplies for baby					0.537
Item 27	Finding a qualified baby-sitter				0.688	
Item 28	Deciding who will help take care of the baby				0.807	
Item 29	Choosing a place to "do-the-month"				0.674	
Item 30	Arranging for someone to handle housework during labor				0.719	
Item 31	Altered body shape during pregnancy			0.760		
Item 32	Controlling weight during pregnancy			0.755		
Item 33	Mobility difficulties due to altered body shape			0.779		
Item 34	Returning to prenatal body shape and weight during postnatal period			0.779		
Item 35	Dark brown areas appearing on the skin			0.656		
Item 36	Sleep quality			0.488		
Described Variances (%)		12.90	13.68	10.78	8.35	8.06
Total Described Variance %				**53.805**		

Factor analysis showed the PSRS-36 Turkish version comprised five subdimensions, similar to the original structure, and all items had factor loads above 0.40 (Table 2). The variances explained by the PSRS-36 Turkish version were determined to be 12.908 for the 1st subdimension of "Stress from seeking safe passage for mother and child through pregnancy, labor, and delivery"; 13.684 for the 2nd subdimension of "Stress from baby care and changing family relationships"; 10.789 for the 3rd subdimension of "Stress from maternal role identification"; 8.358 for the 4th subdimension of "Stress from social support seeking"; and 8.066 for the 5th subdimension of "Stress from altered physical appearance and function". The variance explained by the total PSRS-36 Turkish version was determined to be 53.805 (Table 2).

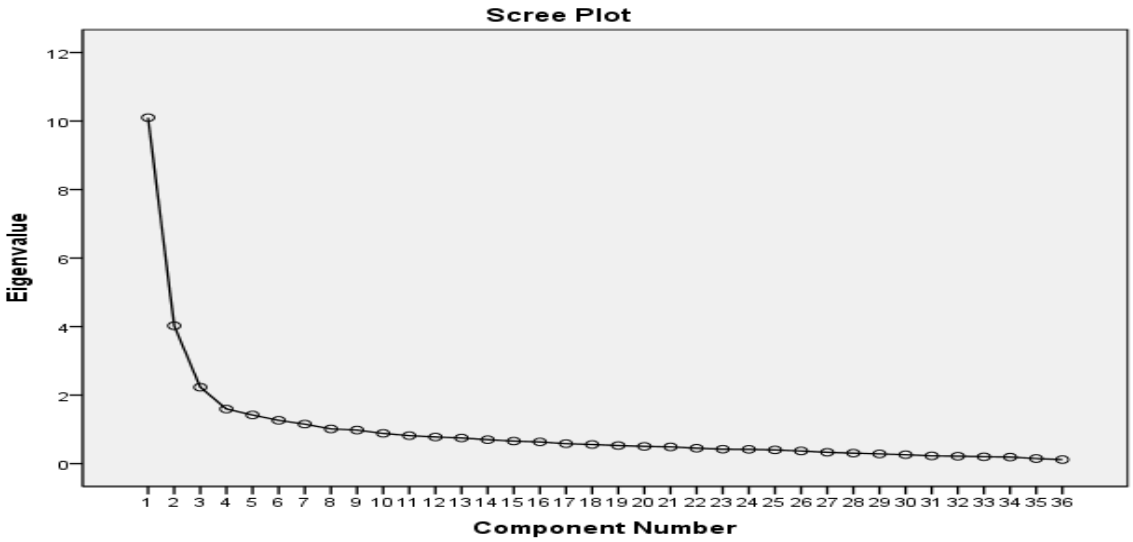

Figure 1. Eigenvalue scree plot for the PSRS-36 Turkish form after applying Varimax rotation

Table 3. Fit Indexes Values, Normal and Acceptable Values of PSRS-36

Index	Normal values	Acceptable values	Fit Indexes values
x^2/SD	<2	<5	2.18
GFI	>0.95	>0.90	0.95
AGFI	>0.95	>0.90	0.94
CFI	>0.95	>0.90	0.95
RMSEA	<0.05	<0.08	0.077
SRMR	<0.05	<0.08	0.075

The cut-off points for the five dimension structure of the PSRS-36 Turkish version appeared to have eigenvalue above 1 (Figure 1). The PSRS-36 Turkish version with five sub-dimensions was confirmed.

After explanatory factor analysis for the PSRS-36 Turkish version, structural equivalence modelling was used for confirmatory factor analysis. There are many indices used to investigate the fit of the model to PSRS-36 Turkish version. Here the x2/SD value was 2.18, GFI 0.95, AGFI 0.94, CFI 0.95, RMSEA 0.077 and SRMR 0.075 were identified (Table 3).

As seen on the PATH diagram, the factor loads for the PSRS-26 Turkish version and subdimensions were acceptable for the original structure without applying any modification to the model (Figure 2). The factor loads for the model varied from 0.42 to

0.83, and the "t" value for all items was above 1.96 (16).

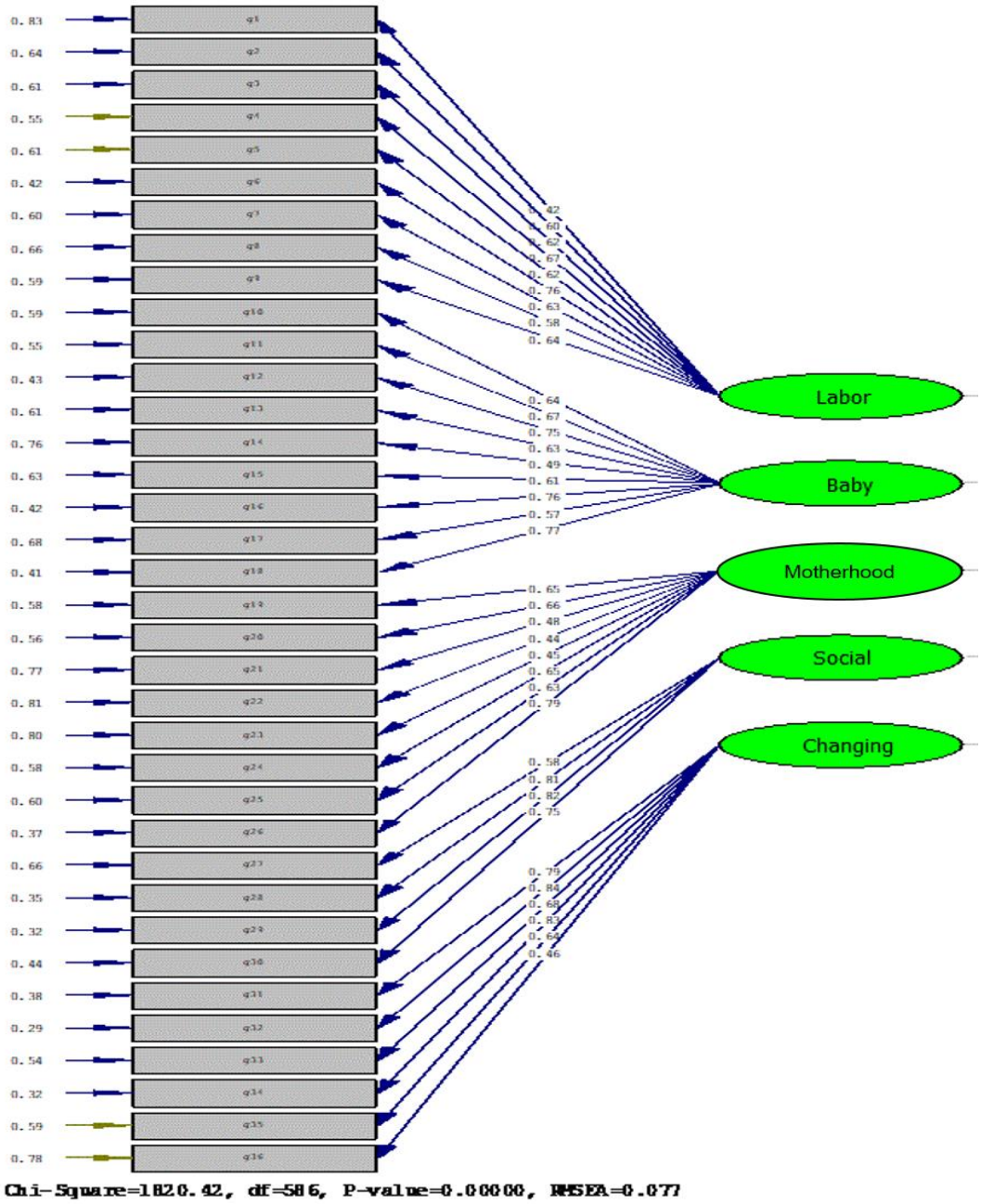

Figure 2. PATH Diagram of the Turkish Version of PSRS-36

Reliability of the PSRS-36 form in Turkish

Corrected Item-Total Correlation and Cronbach's Alpha Reliability Coefficient

The item total points correlation and Cronbach alpha coefficient were used to measure the internal consistency and homogeneity of the PSRS-36 Turkish version. Item total correlations for all items on the scale had positive values and item correlation coefficients were between r=0.230-0.647 (Table 4). Removing any item from the PSRS-36 did not cause a significant increase in the Cronbach alpha coefficient of the scale. As a result, no items were removed from the scale at this stage (Table 4).

Table 4. Total Item Correlations and Cronbach α Coefficients of PSRS-36

Item no	Item description	n	Mean	SD*	ITC**	if the item is deleted Cronbach α
Item 1	Abnormal or difficult birth	360	2.20	1.29	0.230	0.92
Item 2	Safe labor and delivery for my sake	360	2.32	1.26	0.376	0.92
Item 3	Safe delivery for my baby's sake	360	2.49	1.29	0.382	0.92
Item 4	Doctor may not arrive on time at delivery	360	2.41	1.40	0.422	0.92
Item 5	Premature labor	360	2.10	1.39	0.389	0.92
Item 6	Doctor attitudes during labor and delivery	360	2.55	1.25	0.477	0.92
Item 7	Nurse attitudes during labor and delivery	360	2.69	1.20	0.359	0.92
Item 8	Husband's absence during labor	360	2.10	1.49	0.398	0.92
Item 9	Unbearable labor pain	360	2.49	1.29	0.429	0.92
Item 10	Breast or bottle feed my baby	360	1.62	1.40	0.552	0.92
Item 11	Ability to breastfeed succesfully	360	1.65	1.43	0.558	0.92
Item 12	Ability to raise my baby succesfully	360	1.69	1.56	0.614	0.91
Item 13	Naming my baby	360	1.16	1.32	0.492	0.92
Item 14	Sexual activity during pregnancy	360	1.09	1.18	0.395	0.92
Item 15	Loss of free time after birth	360	1.42	1.26	0.523	0.92
Item 16	Acceptance of the child by significant others	360	0.90	1.37	0.609	0.91
Item 17	Increased financial burden	360	1.49	1.32	0.489	0.92
Item 18	Support from family members or husband	360	1.18	1.44	0.596	0.92
Item 19	Baby's appearance	360	0.51	1.00	0.372	0.92
Item 20	Baby's birth weight	360	1.04	1.27	0.519	0.92
Item 21	Baby's gender	360	2.87	1.25	0.411	0.92
Item 22	Baby's health	360	2.28	1.46	0.428	0.92
Item 23	Concern about status of fetal movement	360	1.68	1.40	0.555	0.92
Item 24	Adhering to traditional pregnancy mores	360	1.31	1.23	0.558	0.92
Item 25	Maternal behavior influencing the fetus	360	0.99	1.28	0.533	0.92
Item 26	Preparation of clothes and newborn supplies for baby	360	1.11	1.39	0.647	0.91
Item 27	Finding a qualified baby-sitter	360	0.48	1.10	0.357	0.92
Item 28	Deciding who will help take care of the baby	360	0.80	1.25	0.505	0.92
Item 29	Choosing a place to "do-the-month"	360	0.64	1.15	0.541	0.92
Item 30	Arranging for someone to handle housework during labor	360	0.76	1.16	0.483	0.92
Item 31	Altered body shape during pregnancy	360	1.25	1.30	0.557	0.92
Item 32	Controlling weight during pregnancy	360	1.35	1.31	0.585	0.92
Item 33	Mobility difficulties due to altered body shape	360	1.79	1.31	0.511	0.92
Item 34	Returning to prenatal body shape and weight during postnatal period	360	1.47	1.43	0.575	0.92
Item 35	Dark brown areas appearing on the skin	360	1.06	1.32	0.500	0.92
Item 36	Sleep quality	360	1.97	1.34	0.328	0.92

**SD: Standard deviation **ITC: Item total correlation*

The lowest, highest and mean points obtained by pregnant cases included in the scope of the research for the PSRS-36 Turkish version and subdimensions and the Cronbach alpha coefficients are presented in Table 5. Pregnant cases obtained points of 21.35±7.96 for the "Stress from seeking safe passage for mother and child through pregnancy, labor, and delivery" subdimension; 12.19±8.59 for the "Stress from baby care and changing family relationships" subdimension; 11.78±6.80 for the "Stress from maternal role identification" subdimension; 2.67±3.81 for the "Stress from social support

seeking" subdimension; 8.89±6.11 for the "Stress from altered physical appearance and function" subdimension; and 56.88±24.59 for the whole PSRS-36 scale (Table 5).The Cronbach alpha coefficient for all items on the PSRS-36 Turkish version was 0.92, with Cronbach alpha coefficients for the subdimensions of PSRS-36 Turkish version 0.84, 0.86, 0.81, 0.83, and 0.85, respectively (Table 5).

Analysis results comparing the upper and lower 27% of the PSRS-36 Turkish version showed the differences were statistically significant (p<0.001). This value proves that the scale can be used for differentiation (Table 6).

Table 5. Item number, lower-upper values, mean, standard deviation and Cronbach alpha coefficients of sub-dimensions and the PSRS-36 Turkish version

Subdimension No	Definition of Subdimensions	Items	Lower-Upper Values	Mean	SD	Cronbach's Alpha
1.	Stress from seeking safe passage for mother and child through pregnancy, labor, and delivery	1-9	0-36	21.35	7.96	0.84
2.	Stress from baby care and changing family relationships	10-18	0-34	12.19	8.59	0.86
3.	Stress from maternal role identification	19-26	0-32	11.78	6.80	0.81
4.	Stress from social support seeking	27-30	0-16	2.67	3.81	0.83
5.	Stress from altered physical appearance and function	31-36	0-24	8.89	6.11	0.85
	Total PSRS-36	1-36	1-124	56.88	24.59	0.92

Table 6. Comparison of lower 27% and upper 27% points of the PSRS-36 Turkish version

PSRS-36 Turkish version	n	Mean	SD*	Test and p
Lower 27%	93	27.56	9.13	t=-39.683 **p>0.001**
Upper 27%	94	89.47	12.03	

**SD: Standard deviation*

DISCUSSION

Evaluating stress levels related to pregnancy can determine stress factors in the early period and plan appropriate interventions. For this, it's necessary to use valid and reliable scale tools. In this research, the aim was to adapt the PSRS-36, developed by Chen (2015) (18) to determine stress levels experienced by the pregnant person during pregnancy, to Turkish and perform validity and reliability studies. In this section, the findings about the Turkish language equivalence, scope validity, construct validity, internal consistency, pregnancy variables, and comparison of mean points on the PSRS-36 are discussed for the PSRS-36 comprising 36 items and 5 factors.

In the guide published by the International Testing Commission (ITC, 2018) on scale adaptation, the first items are language and culture adaptation. For

language adaptation of the PSRS-36, translation from English to Turkish, then from Turkish to English was used to ensure linguistic equivalency (26).

Identification of scope validity is a necessary study for scale development studies. When adapting scale tools developed in any language into Turkish, scope validity must be tested. For scope validity of the PSRS-36 Turkish version, opinions were sought from 11 teaching staff in the university's Gynecology and Obstetrics Nursing and Midwifery Departments. Expert lecturers investigated the cultural appropriateness, fit for the aim and comprehensibility of the scale and evaluations were sought according to the Davis technique. The expressions in items "2, 4, 6, 7, 8, 9, 11, 12, 15, 16, 17, 23, 24, 25, 29, 30, 31, 34 and 35" were reorganized.

According to the Davis technique, the SVI score of scale items analyzed was between 0.80 and 1.00. The SVI score being 0.80 means it has acceptable levels (27). This finding shows the PSRS-36 has sufficient scope validity.

Construct validity is the degree to which the items on a prepared scale measure a generally abstract concept. Factor analysis, comparison of contrasting or known groups, hypothesis testing, multivariate-multimethod matrix approach methods may be used to test construct validity (28-30). The most commonly used method is factor analysis. Factor analysis is a technique used to determine whether there is a pattern among responses to items on a scale tool by responders (27). In this study, factor analysis was used to investigate the construct validity of the PSRS-36. Before factor analysis with the aim of evaluating the sample, sufficiency and fit of data for factor analysis, the KMO and Bartlett's tests were applied. The KMO value was identified as 0.888. The Bartlett test result ($x2 = 6657.871$, $p > 0.001$) obtained showed that the data were appropriate for factor analysis. When the explanatory factor analysis results for the PSRS-36 Turkish version are investigated, the eigenvalue was larger than 1 and the scale was determined to have similar structure to the original scale. The five-factor scale explained 53.80% of the variance. A breakpoint corresponding to component 5 was seen in the graph after applying the Varimax rotation (Figure 1).

The results of explanatory factor analysis for PSRS-36 identified the PSRS-36 had five subdimensions similar to the original PSRS-36, with the variances explained by subdimensions varying from 8.06-13.68, with total scale explaining 53.80% of variance and the results were identified to be sufficient (Table 2). While 0.30 is sufficient for the variance explained by a single factor scale, values from 0.40-0.60 are sufficient for multifactor scales (31). No item in the Turkish PSRS-36 was removed as none had a factor loading of less than 0.40. A nine-item first factor, nine-item second factor, eight-item third factor, four-item fourth factor and six-item fifth factor were determined. The PSRS-36 Turkish version was determined to have five factors like the original form of the scale.

After explanatory factor analysis, a structural equivalence model was created with confirmatory factor analysis to obtain more definite results. Many indices were used to investigate the fit of the model belonging to PSRS-36. Of these x2/SD value 2.18, GFI 0.95, AGFI 0.94, CFI 0.95, RMSEA 0.077 and SRMR 0.075 were identified (Table 3). In the literature, it is reported that the RMSEA and SRMR value should be below 0.08, while the GFI, AGFI, and CFI values should be above 0.90 (32, 33). The results

of the fit index values found the 36-item 5 subdimension PSRS-36 Turkish version did not require any changes compared to the original and the model was acceptable. Finally, it was determined that the results obtained from confirmatory factor analysis of the 36 item PSRS-36 fit the original five factor PSRS-36 developed by Chen (2015) and that construct validity was determined (Figure 2).

The item total points correlation and Cronbach alpha reliability coefficient were used to measure the internal consistency and homogeneity of the PSRS-36 Turkish scale (29). When the internal consistency of a scale is examined whether or not all subdimensions measure the same traits is examined. The Cronbach alpha reliability coefficient has a value between 0 and 1 with the higher coefficients determining consistent items measuring the same trait elements on the scale. If the Cronbach alpha reliability coefficient is close to 1, it shows the items on the scale are compliant and consistent (34, 35). In this study, the PSRS-36 had Cronbach alpha coefficient of 0.92 for all items.

Pregnant women obtained points of 21.35±7.96 for the "Stress from seeking safe passage for mother and child through pregnancy, labor, and delivery" subdimension; 12.19±8.59 for the "Stress from baby care and changing family relationships" subdimension; 11.78±6.80 for the "Stress from maternal role identification" subdimension; 2.67±3.81 for the "Stress from social support seeking" subdimension; 8.89±6.11 for the "Stress from altered physical appearance and function" subdimension; and 56.88±24.59 for the whole PSRS-36 scale (Table 4). Considering the lowest points that can be obtained from the PSRS-36 are 36 and highest points are 144, it appears the points obtained by pregnant cases in this study had moderate values. In the original study, the mean points were found to be 53.96±21.04 (18). The results of this study are similar to the results of the original study for PSRS-36.

The Cronbach's alpha coefficients of the PSRS-36 Turkish version and subdimensions were between 0.81 and 0.92 (Table 4). The Cronbach's alpha value between 0.60-0.80 indicates that it is quite reliable (36). The item total correlations for all items on the scale have positive values and no removal of any item caused significant increases in the Cronbach alpha coefficient (Table 4). In this study, the Cronbach alpha coefficients were found to have sufficient levels. The item total point correlations used to measure the internal consistency explains the relationship between points obtained from items on the scale and total points on the scale. If item total correlations are positive and high, the items display similar behavior, and the scale has high internal consistency (31). For the analysis test points, the use of corrected total points is recommended. For acceptance of an item, the item total correlation coefficient should be at least 0.20. Values of 0.20 and less are items that should be excluded from the study (37). In this study, the item total coefficients varied from 0.230-0.647 (Table 4). These values show the scale items have sufficient reliability.

Another route used in the scope of item analysis is to test the differences between the upper 27% and lower 27% item mean points according to total points with the unrelated t test. If the differences observed between the groups is significant, it may be assessed as a marker of the internal consistency of the scale. The analysis results show the degree to which the items distinguish individuals in terms of the measured behavior (37). In this study, the difference between

mean points for the upper 27% and lower 27% groups for the PSRS-36 Turkish version was determined to be statistically significant (t=-39.683, p=0.000) (Table 6). The results show the scale has high internal consistency and that items measure the same behavior.

CONCLUSIONS

In conclusion, the PSRS-36 Turkish version was found to be a valid and reliable scale appropriate for Turkish culture. It is recommended that the scale be used as data collection tool to determine pregnancy stress in different samples by midwifery and nursing, for experimental studies related to pregnancy stress, with valid and reliable scales for stress, anxiety and depression related to pregnancy, and to repeat validity and reliability in different sample groups.

Acknowledgements

The authors thank to pregnant women participated to this study and permission given to adapt of the Scale Chung-Hey Chen. This study was accepted as master thesis of Ozlem Akın.

Ethics Committee Approval: This study was approved by Ordu University Clinical Research Ethics Committee (12.10.2017/121).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: O.A, N.E; Design: O.A, N.E; Literature Search: O.A, N.E; Data Collection and Processing: O.A, N.E; Analysis or Interpretation: O.A, N.E; Writing: O.A

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

Financial Disclosure: The author declared that this study hasn't received no financial support.

REFERENCES

1. Unsal P. Perception of Work Stress and the Role of Individual Differences in Coping, Behavior in Working Life, Current Approaches. Askin Keser, Gozde Yilmaz, Senay Yurur, editor. Izmit, Turkey: Umuttepe Publications; 2012. p. 387-422.
2. Bayik A, Altug Ozsoy S, Ardahan M, Ozkahraman S, Iz F. The situations of meeting stressor life events by women. Journal of Anatolia Nursing and Health Sciences. 2006; 9 (2): 1-12.
3. Yanikkerem E, Altiparmak S, Karadeniz G. The determination of the pyhsical health problems experienced during pregnancy summary. Family and Community Education Culture and Research Journal. 2006;3(10):35–42.
4. Donmez S, Yeniel OA, Kavlak O. Comparison of strait anxietylevels of pregnant women who have vaginal of cesarean delivery. Gumushane University Journal of Health Sciences. 2014;3(3):908-920.
5. Sahin EM, Kilicarslan S. Depressive, anxiety levels and affecting fcators of third trimester pregnant women. Medical Journal of Trakya University. 2010;27(1):51-58.
6. McCrory C, McNally S. The effect of pregnancy intention on maternal prenatal behaviours andparent and child health: results of an Irish cohort study. Pediatric and Perinatal Epidemiology. 2013;27(2):208–215. doi: 10.1111/ppe.12027
7. Ust Z, Pasinlioglu T, Ozkan H. Investigation of anxiety levels of pregnant women in labor. Journal of Anatolia Nursing and Health Sciences. 2013;16:110-115.
8. Nagle K, Green J, Walker K. The link between brain development, neonatal outcomes and

maternal stress states. Journal of Neonatal Nursing. 2017;23(6):282–5.

9. Dastan N, Deniz N, Sahin B. The determination of mental status of pregnants by home visiting in Kars. Journal of Psyhiatric Nursing. 2015;6(2):71-78.

10. Ozturk S, Erci B. The effect of training provided the primiparas in the postpartum period for motherhood and neonatal care on maternal selfconfidence. Gumushane University Journal of Health Siences. 2016;5(2):25-31.

11. Oner N, Le Compte A. The State-Trait Anxiety Inventory Handbook. Istanbul, Turkey: Bogazici University Publication, 1985.

12. Ulusoy M, Sahin N, Erkman H. Turkish version of the beck anxiety inventor, psychometric properties. Journal of Cognitive Psychotherapy: An International Quartery. 1988;12 (2):28-35.

13. Hisli N. Validity and reliability of Beck Depression Inventory for university students. Turkish Journal of Psychology. 1989;7(23):3-13.

14. Kitapcioglu G, Yanikkerem E, Sevil U, Yuksel D. Fear of childbirth and the postpartum period: A scale development and validation study. Journal of Adnan Menderes University Medical Faculty. 2008;9(1):47-54.

15. Engindeniz AN, Kuey L, Kultur S. Validity and reliability study of Edinburgh postpartum depression scale Turkish form. Spring Symposium 1st Book. Ankara. Psychiatric Association Publications; 1996. p:51-52.

16. Capik A, Pasinlioglu T. Validity and Reliability Study of the Tilburg Pregnancy Distress Scale into Turkish. Journal of Psychiatric and Mental Health Nursing. 2015;22(4);260-269.

17. Akgul A. Statistical Analysis Techniques used in Medical Studies. 2nd ed. Ankara, Turkey: Emek Ofset Ltd. Sti; 2003. p. 86-92.

18. Chen CH. Revision and validation of a scale to assess pregnancy stress. Journal of Nursing Research. 2015;23(1):25-32. doi: 10.1097/jnr.0000000000000047

19. Ozdamar K. Statistical Analysis with Software Packages. 5th edn. Eskisehir, Turkey: Kaan Publishing House; 2004. p. 450-455.

20. Tabachnick BG, Fidel LS. Using Multivariate Statistics. (Baloglu, M., Cev. Ed.). Ankara: Nobel Yayincilik, 2015.

21. Polit DF, Beck CT. Essentials of nursing research: Appraising evidence for nursing practice. 7th ed. Philadelphia, USA: Wolters Kluwer and Lippincott Williams and Wilkins; 2010.

22. Aksu G, Eser MT, Guzeller CO. Structural equation modeling applications with exploratory and confirmatory factor analysis. Ankara: Detay Publishing; 2017.

23. Civelek ME. Structural Equality Modeling Methodology. 1st edition. Istanbul: Beta Publishing; 2018.

24. Taskin C, Akat O. Structural Equality Modeling in Research Methods. Bursa: Ekin Publishing House; 2010.p. 16-26.

25. International Test Commission (ITN). Guidelines for translating and adapting tests. International Journal of Testing. 2018;18(2),101–134. http://dx.doi.org/10.1080/15305058. 2017.1398166

26. Gozum S, Aksayan S. A guide for trans-cultural adaptation of the scale I: Psychometric characteristics and cross-cultural comparisons. Journal of Research and Development in Nursing. 2002; 4 (1): 9-14.

27. Karakoc FY, Donmez L. Basic Principles of Scale Development. Medical Education World. 2014; 13(40): 39-49.

28. Erefe I. The nature of the data collection instruments. In Erefe I, (editor) Research in Nursing. Istanbul, Turkey: Odak Press; 2002. p. 169-88.

29. Sencan H. Reliability and validity in social and behavioral measurements. Ankara, Turkey: Seckin Publishing, 2005.

30. Burns N, Grove SK. The practice of nursing research: Appraisal, synthesis, and generation of evidence. 6th ed. St Louis, USA: Saunders & Elsevier; 2009.

31. Buyukozturk S. Data Analysis Handbook for Social Sciences (7th). Ankara, Turkey: Pegem Ak Publishing; 2007. p. 167-182.

32. Schumacker RE, Lomax RGA. Beginner's Guide to Structural Equation Modeling (3rd Edition). New York: Routledge/Taylor & Francis Group, 2010.

33. Wang J, Wang X. Structural equation modeling: applications using mplus: methods and applications. West Susex: John Wiley & Sons, 2012. p. 5-9.

34. Gozum S, Aksayan S. A guide for trans-cultural adaptation of the scale II: Psychometric characteristics and cross-cultural comparisons. Journal of Research and Development in Nursing. 2003; 5(1): 3-33.

35. Tavsancil E. Attitude Measurement and Data Analysis with SPSS (4th ed.) Istanbul, Turkey: Nobel Broadcast Distribution; 2010.p. 5-200.

36. Karagoz Y. SPSS 22 Applied Biostatistics (2nd ed.) Ankara, Turkey: Nobel Publishing; 2015.

37. Buyukozturk S. Manual of data analysis for social sciences. (21st Edition). Ankara: Pegem Publications. 2015.

Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci **May 2022; 8(2):223-232**

RESEARCH ARTICLE **DOI:** 10.19127/mbsjohs.1104293

The Effect of Intracranial Hemorrhage and SARS-CoV-2 Association on Mortality

Yavuz Erdem[1(ID)] , Samet Dinc[2(ID)] , Adem Kurtulus[2(ID)]

[1]Neurosurgery Department, Health Sciences University, Ankara Health Practice and Research Center, Ankara, Turkey

[2]Neurosurgery Department, Afyonkarahisar State Hospital, Afyonkarahisar, Turkey

Received: 15 April 2022, Accepted: 28 April 2021, Published online: 31 May 2022

Abstract

Objective: SARS-CoV-2 is a pandemic that still causes high mortality and morbidity in our world. We observed and wanted to examine the high mortality and morbidity rates of SARS-CoV-2 due to lung and other organ involvement, and even more mortality in the presence of accompanying intracranial events.

Methods: This study is a single-center retrospective cohort study. Patients who applied to Afyonkarahisar State Hospital between June 2020 and June 2021, who were evaluated as SARS-CoV-2 in their current state and who were found to have an intracranial hemorrhage, were evaluated.

Results: Of the 13 patients in our cohort, 7 (54%) had comorbidities such as hypertension, diabetes mellitus, and chronic renal failure. The intraparenchymal hematoma was observed in 5 patients, chronic subdural hematoma in 2 patients, acute subdural hematoma in 1 patient, and subarachnoid hemorrhage in 4 patients. Decompressive craniectomy and hematoma evacuation were performed on 5 patients in our study. Nine of the patients included in our study died as a result of their follow-up and treatment in the intensive care unit, and the mortality rate was 69%.

Conclusion: Intracranial hemorrhages may occur rarely in patients with SARS-CoV-2 infection, and it is observed that intracerebral hemorrhages, which are already quite mortal, are more mortal. In addition, COVID-19 infection is thought to be a risk factor for intracranial hemorrhages.

Keywords: Intracranial Hemorrhages, Anticoagulants, Covid-19, Mortality

Suggested Citation: Erdem Y, Dinc S, Kurtulus A. The Effect of Intracranial Hemorrhage and SARS-CoV-2 Association on Mortality. Mid Blac Sea Journal of Health Sci, 2022;8(2):223-232.

Address for correspondence/reprints:
Adem Kurtulus
Telephone number: +90 (507) 169 94 61
E-mail: dr.ademkurtulus@gmail.com

INTRODUCTION

"Severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) is a pandemic that still causes high mortality and morbidity in our world. Cases of intracranial events are seen in the literature in patients who are active or have had SARS-CoV-2 active recently. In a study conducted in Wuhan, the incidence of neurological symptoms in patients with SARS-CoV-2 infection was 36.4%, and the rate of acute cerebrovascular disease was 5.7% (1). Although many factors are blamed for this, it is argued that SARS-CoV-2 causes endothelial cell damage and endotellitis and may cause thrombosis in the venous and arterial system with the effect of platelet activation and stasis in blood flow (2,3). At the same time, there is an opinion in the literature that it predisposes to bleeding due to depletion of coagulation factors (4,5). In addition, anticoagulant treatment regimens are used to prevent thrombosis in the current guideline of SARS-CoV-2 treatment, and it is known that anticoagulant treatments increase intracranial bleeding. And it is argued that this may be a predisposing factor for intracranial hematomas in patients with SARS-CoV-2 (6). Intracerebral hematomas constitute 10-15% of all ischemic brain diseases, and 1-year mortality rates range from 51% to 65% (7). In the study of Cheruiyot et al. (8), the mortality rate of SARS-CoV-2 and the intracerebral hematoma was found to be 48.6%. We observed and wanted to examine the high mortality and morbidity rates of SARS-CoV-2 due to lung and other organ involvement, with a more mortal course in the presence of accompanying intracranial events.

METHODS

This study is a single-center retrospective cohort study. Ethics committee approval was obtained from Afyonkarahisar Health Sciences University on 06.08.2021 with the decision numbered 427.

Patient Population

In our study, between June 2020 and June 2021, intracranial hemorrhage was detected in the application to Afyonkarahisar State Hospital, followed up and treated in our hospital, and evaluated as SARS-CoV-2 in its current state (with positive nasopharyngeal SARS-CoV-2 polymerase chain reaction (PCR) test and/or patients with typical radiological thoracic computed tomography (CT) findings) or patients who were admitted to our hospital again within 1 month after discharge were included. Traumatic intracranial hemorrhages and patients under 18 years of age were not included in the study.

Data Collected

The patient data used were obtained from Afyonkarahisar State Hospital's electronic health records and patient files. Demographic characteristics of the patients (age, gender), comorbidities and related anticoagulant drug use, complaint at admission, SARS-CoV-2 diagnosis time, anticoagulant drug use after SARS-CoV-2 diagnosis, intracranial bleeding time (if detected at the time of application It was evaluated as "initial apply", it was evaluated as "late apply" if it was detected after re-admission within 1 month after SARS-CoV-2 treatment), anticoagulant drug use after intracranial hemorrhage, an antiviral medication used after SARS-CoV-2 diagnosis, intracranial treatment for

bleeding (surgery/follow-up) and mortality were evaluated.

Clinical Evaluation

SARS-CoV-2 treatment was arranged according to the general conditions, respiratory parameters, vital signs, and thorax CT evaluations of the patients, and the need for mechanical ventilator/non-invasive mechanical ventilation was evaluated. In terms of cranial, Surgery/follow-up decision was made according to brain CT/MRI evaluations. In patients with intracranial hematoma, the surgical intervention was decided considering the location of the hematoma, the amount of hematoma, the midline shift effect, herniation findings, and the general condition of the patient. Patients who did not undergo surgical treatment were followed up closely in our intensive care unit clinically, neurologically, and radiologically.

Radiological and Laboratory Evaluation

The patients included in our study were patients who applied to our emergency department with neurological and respiratory symptoms and had intracranial hemorrhage findings according to brain computed tomography (CT) or brain magnetic resonance (MR) imaging. Nasopharyngeal SARS-CoV-2 PCR test and thoracic CT are taken routinely from all patients who are planned to be hospitalized in the intensive care unit in our hospital. Thoracic CT scans were evaluated using the "Radiological Society of North America (RSNA) Chest CT Classification System" and the "COVID-19 Reporting and Data System (CO-RADS)" (9,10). These classifications were used both for diagnosis and for predicting the severity of the infection. Intracranial hemorrhage findings were classified as intraparenchymal, subarachnoid, and subdural hemorrhage according to the type of hemorrhage. In laboratory findings, white blood cell (WBC), hemoglobin (Hb), urea, creatinine, platelet, prothrombin time (PT), active partial thromboplastin time (aPTT), international normalized ratio (INR), C-reactive protein (CRP), sedimentation, ferritin values were checked.

Anticoagulant Use

As is known, SARS-CoV-2 infection generally predisposes to thrombosis. For this reason, anticoagulant therapy is often started in patients with risk factors. Although the use of anticoagulant drugs is contraindicated in patients with intracranial bleeding; Considering the general condition of the patient clinically and radiologically, it can be given by close neurological and radiological follow-up according to the benefit-harm ratio. We evaluated the previous use of anticoagulant medication and the initiation/continuation of anticoagulant therapy after intracranial hemorrhage, depending on SARS-CoV-2 infection or the type of bleeding in our cohort.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 22.0 (IBM Corporation, Armonk, NY). Frequency analysis was used for demographic analyses. In descriptive statistics, the data were presented as mean ± standard deviation for parametric, median (range) for non-parametric continuous, and number (percentage) for categorical variables.

RESULTS

Demographic Findings and Comorbid Diseases

The demographic information of the patients is summarized in Table 1. The mean age was 66.5 ± 20.2 (median 66, range 25-91). 61% of the patients

were female (n=8). Seven of the patients in our cohort (54%) had comorbidities such as hypertension (HT), diabetes mellitus (DM), and chronic renal failure (CRF). Only 1 patient had used clopidogrel for cardiac reasons unrelated to SARS-CoV-2 infection.

Anticoagulant Use

Three patients included in the study were diagnosed with hemorrhagic cerebrovascular accident (CVO) accompanied by subarachnoid hemorrhage; Vascular pathology was not considered because of the location and clinic of the bleeding. The therapeutic dose of enoxaparin Na was started in these 3 patients, taking into account the benefit-risk ratio, for close clinical and radiological follow-up. In addition, 1 patient in our study was started on a prophylactic dose of enoxaparin Na due to SARS-CoV-2 in the last 1 month and was discharged; In the next period, he applied to the emergency department with the complaint of left hemiparesis and was operated with the diagnosis of right temporoparietal intraparenchymal hematoma. For this reason, the patient's anticoagulant treatment was discontinued. Other patients in our cohort were not given anticoagulant therapy after detecting intracranial hemorrhage. Information on the use of anticoagulant drugs is shown in Table 1.

Clinical Findings

The most common reason for admission of patients in our cohort was the loss of consciousness with 54% (n=7). In addition, 5 patients (38%) were admitted to the hospital with neurological symptoms such as hemiparesis and headache. Only 1 patient (7%) was admitted to the hospital due to dyspnea. When we consider patients diagnosed with COVID-19 for the first time; We see that 91% of them present with neurological symptoms.

Decompressive craniectomy and hematoma evacuation were performed on 5 patients in our study. Anticoagulant treatment was not given to any of the patients who underwent surgery in the postoperative period. Patients who were not planned for surgery were followed closely clinically and radiologically. Cranial surgery was not required in the follow-up of all patients who did not undergo surgery at the first admission. Considering the general clinical condition, respiratory parameters, and imaging findings of the patients, 9 (69%) patients were followed up with a mechanical ventilator.

All patients newly diagnosed with SARS-CoV-2 were started on favipiravir treatment as an antiviral treatment. 2 patients in our study; Since favipiravir treatment was given for SARS-CoV-2 within 1 month and SARS-CoV-2 infection was not considered clinically, laboratory and radiologically in her current application, favipiravir was not started.

Nine of the patients included in our study died as a result of their follow-up and treatment in the intensive care unit, and the survival rate in our cohort was 31%. The clinical findings of the patients are summarized in Table 1.

Radiological Findings

CO-RADS and RSNA classifications were used in the diagnosis of SARS-CoV-2 infection and the evaluation and prediction of clinical progression of the patients. These classifications are shown in Table 2 and Table 3. As it is known, there is a possibility that the SARS-CoV-2 PCR test may be false-negative, and although the PCR test is negative in some cases, the diagnosis can be made clinically and

Table 1. Baseline Demographic, Clinic, and Radiological Characteristics

Demographic characteristics	**Mean age ± SD** 66.5 ± 20.2 (median 66, range 25-91) **Gender (female)** 61% (n=8)												
	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**	**Patient 7**	**Patient 8**	**Patient 9**	**Patient 10**	**Patient 11**	**Patient 12**	**Patient 13**
Age	87	82	66	63	91	83	84	47	78	40	63	25	56
Gender	M	M	F	F	F	F	M	F	M	F	F	F	M
Comorbidity	-	DM	CRF	HT	DM	DM	HT, CRF	-	-	-	-	-	HT, CRF
Use of anticoagulant	-	-	-	-	-	-	-	-	-	-	-	-	Clopidogrel
Clinical characteristics													
COVID time	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Late apply	Late apply	Initial apply
Presenting complaint	unconsciousness	Unconsciousness	Unconsciousness	Unconsciousness	Unconsciousness	Dyspnea	Unconsciousness	Headache	Left hemiparesis	Headache	Left hemiparesis	Right hemiparesis	unconsciousness
Haemorrhage time	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Initial apply	Late apply	Late apply	Initial apply
COVID medication	Favipiravir	Favipiravir	Favipiravir	Favipiravir	Favipiravir	Favipiravir	Favipiravir	Favipiravir	Favipiravir	Favipiravir	-	-	Favipiravir
Anticoagulant initiated with COVID	-	-	-	Enoxaparin Natrium	-	Enoxaparin Natrium	-	-	-	Enoxaparin Natrium	Enoxaparin Natrium	-	-
Use of anticoagulant after haemorrhage	-	-	-	Enoxaparin Natrium	-	Enoxaparin Natrium	-	-	-	Enoxaparin Natrium	-	-	-
Surgery	-	+	-	-	+	-	-	-	+	-	+	+	-
Mortality	+	+	+	+	+	-	+	+	-	-	+	-	+
Radiological characteristics													
RSNA	İndeterminate	İndeterminate	İndeterminate	Typical	Typical	Typical	Typical	Negative	Negative	Typical	Negative	Negative	Typical
CO-RADS	4	6	4	6	5	5	5	6	6	5	1	1	6
Pneumonia	+	+	+	+	+	+	+	-	-	+	-	-	+
Type of intracranial haemorrhage	ICH	Acute SDH	Spontaneous SAH	Haemorrhagic stroke	Acute SDH	Haemorrhagic stroke	ICH	ICH	Chronic SDH	Haemorrhagic stroke	ICH	Chronic SDH	ICH
Haemorrhage localization	Left temporal and intraventricular	Left frontotemporal	Diffuse Fisher Grade 4 SAH	Left occipital	Left frontotemporal	Left parietal	Left thalamic	Left thalamic	Left frontoparietal	Left parietal	Right parietal	Left temporoparietal	Left parietooccipital
Laboratory characteristics													
Hb	13,9	12,1	10,6	15	11,6	12	13	14,3	12	12	14	12	14,7
WBC	12,8	4,3	5,7	8,3	25	6	8	9	9	6	5	7	16,1
Platelet	124	104	270	299	300	368	102	291	316	443	384	318	107
PT	11,3	12,7	11,3	13,1	10,1	11,1	11,1	12,2	14,5	12	11	11,3	12,4
aPTT	24,3	27	25,3	26,1	20,4	20,1	23,8	23,6	27,7	22,9	25,2	29,9	35,7
Creatinine	0,95	1,04	5,37	1,03	1,53	0,89	1,02	0,64	0,62	0,45	0,66	0,72	4,8
CRP	304	80	39,4	205	119	72	182	7	58	25	1	6,8	57,1
Sedimentation	36	53	61	43,5	71	28	76	17	85	61	14	13	36
INR	1,3	1,2	1,1	1,3	1,3	1,1	1,2	1,1	1,2	1,1	1,1	1,1	1,3
Ferritin	-	208	1708	1668	505	-	799	47,4	576	331	-	-	531
COVID-19 PCR	Negative	Positive	Negative	Positive	Negative	Negative	Negative	Positive	Positive	Negative	Negative	Negative	Positive

DM: Diabetes Mellitus, HT: Hypertension, CRF: Chronic Renal Failure, ICH: Intracerebral Haemorrhage, SDH: Subdural Haemorrhage, SAH: Subarachnoid Haemorrhage, Hb: Hemoglobin, WBC: White Blood Cell, PT: Prothrombin Time aPTT: Active Partial Thromboplastin Time, CRP: C-Reactive Protein, INR: International Normalized Ratio

Table 2. RSNA Classification

COVID-19 pneumonia imaging classification	Rationale	CT Findings
Typical appearance	Commonly reported imaging features of greater specificity for COVID-19 pneumonia	Peripheral, bilateral, GGO* with or without consolidation or visible intralobular lines ("crazy-paving") Multifocal GGO of rounded morphology with or without consolidation or visible intralobular lines ("crazy-paving") Reverse halo sign or other findings of organizing pneumonia (seen later in the disease)
Indeterminate appearance	Nonspecific imaging features of COVID-19 pneumonia	**Absence of typical features AND** **Presence of:** Multifocal, diffuse, perihilar, or unilateral GCO with or without consolidation lacking a specific distribution and are non-rounded or non- peripheral. Few very small GCO with a non-rounded and non-peripheral distribution
Atypical appearance	Uncommonly or not reported features of COVID-19 pneumonia	**Absence of typical or indeterminate features AND** **Presence of:** I solated lobar or segmental consolidation without GCO Discrete small nodules (centrilobular, "tree-in-bud") Lung cavitation Smooth interlobular septal thickening with pleural effusion
Negative for pneumonia	No features of pneumonia	No CT features to suggest pneumonia

**GGO: Ground Glass Opacity*

Table 3. CO-RADS Classification

	Level of suspicion for pulmonary involvement of COVID-19	Summary
CO-RADS 0	Not interpretable	Scan technically insufficient for assigning a score
CO-RADS 1	Very low	Normal or non-infectious
CO-RADS 2	Low	Typical for other infection but not COVID-19
CO-RADS 3	Equivocal/unsure	Features compatible with COVID-19, but also other diseases
CO-RADS 4	High	Suspicious for COVID-19
CO-RADS 5	Very high	Typical for COVID-19
CO-RADS 6	Proven	RT-PCR positive for SARS-CoV-2

radiologically (11). In this context, CO-RADS and RSNA classifications are frequently used in current clinical practice. Eight of the patients in our cohort who were diagnosed with SARS-CoV-2 had a negative PCR test. Two of these patients had SARS-CoV-2 infection in the last 1 month, and it is normal for the PCR test to be negative.

However, the other 6 patients were diagnosed with SARS-CoV-2; The patients' history, clinical evaluation, and thorax CT scans were placed according to CO-RADS and RSNA classifications. Figure 1 shows typical SARS-CoV-2 involvement in patient 4's thorax ct examination.

When the patients with the first diagnosis of SARS-CoV-2 were evaluated according to the RSNA classification, the findings of 54% of the patients were considered "typical" (n=6). When the same patients were evaluated according to the CO-RADS classification, it was seen that 82% of the patients had high-risk thoracic CT findings in terms of COVID-19 or the PCR test was positive. The evaluations of the patients in our study according to these classifications are summarized in Table 1.

In our cohort, 5 patients had intraparenchymal hematoma, 2 patients had a chronic subdural hematoma (SDH), 1 patient had acute SDH, and 4

patients had subarachnoid hemorrhage (SAH). In Figure 2 brain ct images of patient 11, patient 2, and, patient 12 are shown, respectively. The bleeding of 3 of the patients with SAH was thought to be clinically and radiologically related to hemorrhagic SVO.

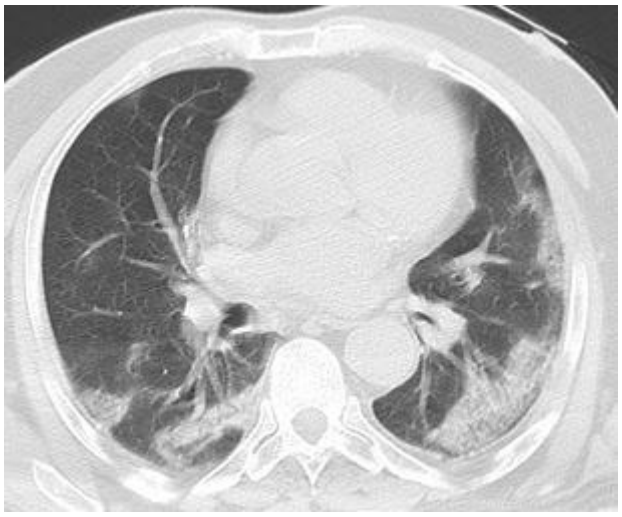

Figure 1. Thorax tomography of fifth patient

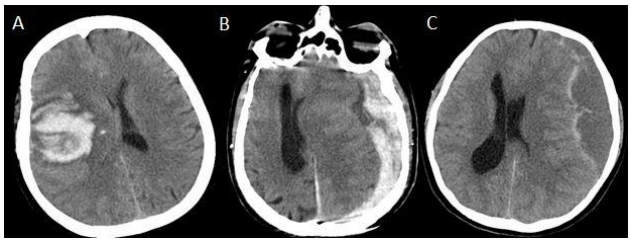

Figure 2. Brain CT images of patient 11, 2 and 12 shown respectively

Aneurysmal SAH was considered in 1 patient, but an advanced radiological examination could not be performed because the patient's general condition was not suitable. These findings are summarized in Table 1.

Laboratory Findings

Routine complete blood count, biochemistry tests, PT, aPTT, INR, and acute phase reactants (CRP, sedimentation, ferritin) were evaluated at the time of admission of the patients in our study. D-Dimer could not be used in our study because it could not be checked in our hospital. It was observed that acute phase reactants, especially CRP and ferritin, were high in patients infected with the newly diagnosed SARS-CoV-2. No bleeding diathesis was observed in any of the patients in our cohort. The creatinine elevation in our 2 patients was associated with the CRF present in these patients. Laboratory parameters are summarized in Table 1.

DISCUSSION

SARS-CoV-2 infection is more common in the advanced age group, as is the case with intraparenchymal hemorrhages. At the same time, according to studies, the association of intracranial hemorrhage in patients with COVID-19 infection is also seen more frequently in the elderly patient group (8). The mean age of the patients in our study was 66.5 ± 20.2 (median 66, range 25-91). 61% of the patients were female (n=8). In the study of Altschul et al. (12), the mean age was 67.03 ± 15.5 years, and 40% were female. In the study of Melmed et al. (13), the mean age was 61.6 ± 11.2 years and the female gender ratio was 21.1%. Our study observed that the mean age was similar, but the female sex ratio was higher.

Especially in the elderly patient group, comorbidities such as HT and DM are more common than in the normal population. At the same time, the symptoms of infection are more severe in these patients. In this context, elderly patients with comorbidities in COVID-19 infection were accepted as a risk group (13,14). 54% of our patients had at least one comorbidity. In one patient, clopidogrel was used before bleeding due to cardiac reasons. In the study of Mishra et al. (15), the comorbidity rate was 81% and 3 patients were using

antiplatelet/anticoagulant drugs before intracranial hemorrhage. In the study of Nawabi et al. (16), the rate of having at least one comorbidity was 83.3% and the rate of using anticoagulant/antiplatelet medication was 50%. As it is known, comorbidities such as HT, DM, and CRF and the use of antiplatelet/anticoagulant drugs increase the frequency of intracranial bleeding. In our study, the rate of both comorbid disease and anticoagulant/antiplatelet drug use was found to be lower.

As it is known, favipiravir in SARS-CoV-2 infection; is an antiviral agent used to provide effective treatment, reduce mortality, and accelerate discharge (17).

When we evaluate the laboratory findings in our study, we see that acute phase reactants, especially ferritin and CRP, are high in patients with newly diagnosed SARS-CoV-2 infection. Although this situation is primarily related to the picture of infection, acute phase reactants may increase especially in the early period in cases of intracranial hemorrhage. In the current situation, it is difficult to distinguish this. However, high CRP negatively affects mortality (18,19). On the other hand, none of the patients in our cohort had bleeding diathesis, which would be a predisposing factor for bleeding.

It is known that the use of anticoagulants/antiaggregants increases the frequency of intracranial bleeding, especially in elderly patients (20). Pavlov et al. also explained in their study the close association of advanced age COVID-19 patients with comorbidities with intracranial hemorrhage (21). In this context, in the study of Melmed et al. (13), it was found that the use of anticoagulant drugs is closely associated with intracerebral hemorrhage in COVID-19. In our study, only 1 patient had anticoagulant drug use before COVID-19 for cardiac reasons. In addition, one patient, who was accepted as a late admission, was started, and currently using enoxaparin Na at a prophylactic dose as an anticoagulant treatment due to COVID-19 due to risk factors. As seen in the literature, the bleeding diathesis seen in COVID-19 can create a cranial destructive process (13,22). In this context, the rate of anticoagulant use in our cohort was 15.3% (n=2). In the study of Mishra et al. (15), the use of anticoagulant drugs was 54.5%. The rate of use of anticoagulant drugs in our cohort was found to be lower. When we look at the mortality rates, the 1-year mortality rate is 50% in patients with non-traumatic intracerebral hemorrhage (23). In this study, the mortality rate was found to be 69%. According to the literature, although the rate of use of anticoagulant drugs in our study was low, mortality rates were higher than those of intracerebral hematomas, especially independent of COVID-19 infection. In our opinion, the risk of intracranial hemorrhage and mortality increases due to SARS-CoV-2 infection. Although the literature supports this, the rate of use of anticoagulant drugs in our study was low. This situation led us to consider the increased risk of intracranial hemorrhage and mortality rates due to SARS-CoV-2 infection, even without the use of anticoagulants.

CONCLUSION

The SARS-CoV-2 pandemic continues its effectiveness worldwide. In addition to its pulmonary effects, extrapulmonary complications are also present and are still under investigation. In these

patients, intracranial hemorrhages may occur, albeit rarely, and are quite mortal. It is thought that intracerebral hemorrhages, which are already quite mortal, are more mortal due to SARS-CoV-2 infection. In addition, COVID-19 infection is thought to be a risk factor for intracranial hemorrhages. However, further studies involving larger patient groups are needed on this subject.

ACKNOWLEDGMENTS: The authors thank all hospital staff who provided careful treatment and care for the patient.

Ethics Committee Approval: Ethical approval was obtained from Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (Decision No: 2021-9).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: A.K Design: A.K, Y.E Data Collection and Processing: S.D Analysis or Interpretation: S.D; Writing: Y.E

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

Financial Disclosure: The authors also decline any financial support neither from any pharmaceutical company, nor from a company that provides or produces medical instruments and materials.

REFERENCES

1. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020;77(6):683-690. doi:10.1001/jamaneurol.2020.1127
2. Unüvar A. COVID-19 and Coagulopathy COVID-19 and Coagulopathy COVID-19 Associated Coagulopathy. Journal of Health Science Advanced Studies. 2020;3:53-62. doi:10.26650/JARHS2020-S1-0007
3. Sharifi-Razavi A, Karimi N, Rouhani N. COVID-19 and intracerebral haemorrhage: causative or coincidental? New Microbes New Infect. 2020;35:0-1. doi:10.1016/j.nmni.2020.100669
4. Benger M, Williams O, Siddiqui J, Sztriha L. Intracerebral haemorrhage and COVID-19: Clinical characteristics from a case series. Brain Behav Immun. 2020;88(June):940-944. doi:10.1016/j.bbi.2020.06.005
5. Thachil J, Tang N, Gando S, Falanga A, Jattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020;18(5):1023-1026. doi:10.1111/jth.14810
6. Dogra S, Jain R, Cao M, Bilaloglu S, Zagzag D, Hochman S, et al. Hemorrhagic stroke and anticoagulation in COVID-19. J Stroke Cerebrovasc Dis. 2020;29(8):104984. doi:10.1016/j.jstrokecerebrovasdis.2020.104984
7. Rymer MM. Hemorrhagic stroke: intracerebral hemorrhage. Mo Med. 2011;108(1):50-54.
8. Cheruiyot I, Sehmi P, Ominde B, Bundi P, Mislani M, Ngure B, et al. Intracranial hemorrhage in coronavirus disease 2019 (COVID-19) patients. Neurol Sci. 2021;42(1):25-33. doi:10.1007/s10072-020-04870-z
9. Prokop M, Everdingen W Van, Vellinga T van R, Ufford HQ Van, Stöger L, Beenen L, et al. CO-RADS-A categorical CT assessment scheme for patients with suspected COVID-19: definition and evaluation original research. Radiology. 2020;(1):1-37.
10. Jaergere T, Krdzalic J, Fasen B, Kwee R. Radiological Society of North America Chest Classification System for Reporting COVID-19 Pneumonia: Interobserver Variability and Correlation with RT-PCR. Radiol Cardiothorac Imaging. Published online 2020. https://doi.org/10.1148/ryct.2020200213
11. Arevalo-Rodriguez I, Buitrago-Garcia D, Simancas-Racines D, Zambrano-Achig P, Campo R, Ciapponi A,

et al. False-negative results of initial RT-PCR assays for COVID-19: A systematic review. PLoS One. 2020;15(12 December):1-19. doi:10.1371/journal.pone.0242958

12. Altschul DJ, Unda SR, de La Garza Ramos R, Zampolin R, Benton J, Holland R, et al. Hemorrhagic presentations of COVID-19: Risk factors for mortality. Clin Neurol Neurosurg. 2020;198(June):106112. doi:10.1016/j.clineuro.2020.106112

13. Melmed KR, Cao M, Dogra S, Zhang R, Yaghi S, Lewis A, et al. Risk factors for intracerebral hemorrhage in patients with COVID-19. J Thromb Thrombolysis. 2021;51(4):953-960. doi:10.1007/s11239-020-02288-0

14. Erol TA, Asar S, Sabaz SM, Bilgin OB, Cukurova Z. Risk Factors for 28-day Mortality Among COVID-19 Patients in an Intensive Care Unit of a Tertiary Care Center in Istanbul.Med J Bakirkoy 2021;17(1):100-7

15. Mishra S, Choueka M, Wang Q, Hu C, Visone S, Silver M, et al. Intracranial Hemorrhage in COVID-19 Patients. J Stroke Cerebrovasc Dis. 2021;30(4):105603. doi:10.1016/j.jstrokecerebrovasdis.2021.105603

16. Nawabi J, Morotti A, Wildgruber M, Boulouis G, Kraehling H, Schlunk F, et al. Clinical and Imaging Characteristics in Patients with SARS-CoV-2 Infection and Acute Intracranial Hemorrhage. J Clin Med. 2020;9(8):2543. doi:10.3390/jcm9082543

17. Ghasemnejad-Berenji M, Pashapour S. Favipiravir and COVID-19: A Simplified Summary. Drug Res (Stuttg). 2021;71(3):166-170. doi:10.1055/a-1296-7935

18. Yüksel U, Ogden M, Akkurt I, Bakar B, Kısa U, Ozveren MF. Biochemical Markers in the Prognosis of Intracranial Hemorrhages. Cukurova Med J. 2018;43(2):350-359.doi:10.17826/cumj.341851

19. Napoli M Di, Parry-Jones AR, Smith CJ, Hopkins SJ, Slevin M, Masotti L, et al. C-reactive protein predicts hematoma growth in intracerebral hemorrhage. Stroke. 2014;45(1):59-65. doi:10.1161/STROKEAHA.113.001721

20. Macdonald RL. Management of Intracranial Hemorrhage in the Anticoagulated Patient. Neurosurg Clin N Am. 2018;29(4):605-613. doi:10.1016/j.nec.2018.06.013

21. Pavlov V, Beylerli O, Gareev I, Torres Solis LF, Herrera AS, Aliev G. COVID-19-Related Intracerebral Hemorrhage. Front Aging Neurosci. 2020;12(October):1-6. doi:10.3389/fnagi.2020.600172

22. Abdulazim A, Ebert A, Etminan N, Szabo K, Alonso A. Negative Impact of the COVID-19 Pandemic on Admissions for Intracranial Hemorrhage. Front Neurol. 2020;11(September):1-5. doi:10.3389/fneur.2020.584522

23. Hostettler IC, Seiffge DJ, Werring DJ. Intracerebral hemorrhage: An update on diagnosis and treatment. Expert Rev Neurother. 2019;19(7):679-694. doi:10.1080/14737175.2019.1623671

Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci **May 2022; 8(2): 233-241**

RESEARCH ARTICLE **DOI:** 10.19127/mbsjohs.1012580

Our Surgical Technique and Results About Undescended Testis at Ordu University

Ahmet Yuce[1(ID)], Nurullah Kadim[2(ID)], Mevlut Keles[2(ID)], Erdal Benli[2(ID)], Abdullah Cirakoglu[2(ID)], Ibrahim Yazici[2(ID)]

[1]Darende Hulusi Efendi State Hospital Malatya, Türkiye
[2]Ordu Üniversitesi Tıp Fakültesi, Üroloji Ana Bilim Dalı, Ordu, Türkiye,

Received: 20 October 2021, Accepted: 23 December 2021, Published online: 31 May 3022

Abstract

Objective: Undescended testis is one of the most common congenital anomalies among the children. It is very important to treat this disease at the appropriate time in experienced centers. The aim of this study is to share the experience and results of our clinic on undescended testicular surgery and discuss with literature.

Methods: The results of 38 patients who were operated with the diagnosis of primary undescended testis in our clinic and whose data were available were used. Patients' ages, sides, follow-up times, and results were recorded. Remaining of the testis in the scrotum after the procedure, increase of size in the follow-ups were used as success criteria.

Results: The mean age (median ± IQR) of our patients was 60.97±12.29 (7-230) months. While 20 (52.6%) of the patients applied with the diagnosis of undescended testis, 18 (47.4%) patients were diagnosed during the examination performed for other reasons. Hernia sacs were detected in 32 (84.2%) of the patients during surgery. Recurrence was observed in two cases, positive results were obtained in 36 (94.7%) cases. In the surgeries performed in our clinic, the success rate for undescended testis was 94.7%.

Conclusion: As a result of this study, the success rates in undescended testicular surgery were found to be satisfactory. An important finding in this study was that most of these patients were diagnosed late. For this reason, we think that it is important to raise awareness and education of the society about personal testicular examination.

Key words: Undescended Testis, Surgical treatment, Success

Suggested Citation: Yuce A, Kadim N, Keles M, Benli E, Cirakoglu A, Yazici I. Our Surgical Technique and Results About Undescended Testis at Ordu University. Mid Blac Sea Journal of Health Sci, 2022;8(2):233-241.

Address for correspondence/reprints:

Ahmet Yuce
Telephone number: +90 (506) 217 6164
E-mail: ahmetyuce7@gmail.com

INTRODUCTION

Undescended testis is one of the most common congenital anomalies in children. It affects approximately 2-9% of term neonatals. When children reach the age of 1, the rate gradually decreases and is observed around 0.8-1%. As with preterms, the risk increases as the week of birth is early and the weight decreases (1). In a significant part of the cases, approximately 30-43% of the cases, the testis descends into the scrotum over time for unknown reasons. This descent event often occurs within 3-6 months after birth. Close follow-up of these children is important, as relapses occur in approximately 22% of cases (2).

Early recognition and treatment of this pathology is essential. Delays in this matter can lead to very important problems such as infertility, tumor development, testicular torsion, exposure to trauma as a result of compression of the testis in the inguinal canal (3). In addition, parents are seriously worried about the future of their children. For these reasons, the aim of treatment is to lower the testis into the scrotum with medical or surgical treatment. However, surgical treatment is still the gold standard method in the treatment of these patients, as there are problems with medical treatment and the possibility of recurrence is high. It is critical for the effectiveness of the treatment that this procedure is carried out in specialized clinics and by meticulously following certain rules. Otherwise, patients and their relatives may encounter problems such as unsuccessful treatment, loss of testis, and repeat surgery. The aim of this study is to describe the surgical technique we used in our clinic during undescended testicular surgery and to share our surgical results.

METHODS

Study Design

Patient data were obtained retrospectively from patient records. The results of 38 patients who were operated in the Urology Clinic of Ordu University Training and Research Hospital between April 2016 and April 2021 and whose data were accessed were used. Suspected cases such as previous scrotal surgery, relapse cases, previous medical treatment, and retractile testis were excluded. Demographic characteristics, history, physical examination findings, side of pathology and surgical results of the patients were recorded.

Clinical Evaluation

All patients were evaluated by anamnesis and physical examination. Physical examination was performed in frog position in a calm and warm room to prevent cremaster reflex in young children. When the testis could not be palpated during the examination, radiological studies such as ultrasonography were performed. In retractile or suspicious testicles, the families were taught the examination method, and they were asked to examine the testicles at regular intervals and record which region they were in. From these records, it was tried to determine the rate at which the testis was detected in the scrotum. In all cases, the diagnosis of undescended testis was not included in the treatment program without clarification. In all patients, surgery was delayed until 1 year of age due to the possibility of spontaneous testicular descent. Surgical procedure after 1 year, tried to be done as soon as possible. Success after surgery was accepted as the testis remaining in the scrotum and reaching a size close to the contralateral testis or at least above its initial size.

Surgical Technique

Relatives of patients who were scheduled for surgery were informed in detail about treatment options and outcomes. Written informed consent was obtained from all patients. The surgical procedure was performed with general anesthesia. Physical examination was performed again with anesthesia. In this way, important information was provided especially in non-palpable testicles. In order to reduce the need for anesthetic and postoperative analgesics, local anesthesia or caudal block was applied in appropriate cases.

The surgical procedure was initiated with a 3-5 cm inguinal incision parallel to the skin lines (From the edge of the rectus muscle, between the spina iliaca anterior superior, the inguinal canal is easily reached). If the testis is not palpable, the incision was modified slightly above. Then the champer and scarpa fascia were separated with scissors and the external obliq muscle was exposed. It is especially important that this be as lateral to the inguinal ligament as possible. Then, it was lifted with a curved clamp and the superficial fascia was opened. At this time, the testis, which is on the surface in the inguinal canal, should be kept in mind. In the meantime, pressing the abdomen may facilitate easy viewing of the testis at the level of the internal ring. The external obliq fascia is then sharply opened and terminated in the external ring. In the meantime, damage to the ilioinguinal nerve and its branches in the lower part should be avoided. The internal oblique fascia is then opened, and the testis is exposed within the tunica vaginalis.

The testicular tissue is gently lifted and separated from the surrounding cremasteric fibers and smooth muscle structures by blunt and sharp dissection. At this time, it is important to completely cut the cremaster muscle fibers. We spend a lot of time in our applications to cut this structure exactly. We think that the complete separation of this structure from the cord elements is one of the key points in surgical success. The testis is released from the gubernaculum, then with gentle traction the proximal connections of the spermatic cord are separated. The peritoneal connections on the cord were released and pushed into the internal inguinal ring. Then the tunica vaginalis opens anteriorly. If seen, the appendix testis and appendix epididymis are cauterized so that these structures do not later mimic testicular torsion. The cord is separated from the surrounding tissues until sufficient cord length is assured. Tunica vaginalis (peritoneal layer) is held close to the internal ring. The hernia sac is carefully separated from the vessel and cord structures with scissors or a hemostatic clamp. Meanwhile, the most difficult issue, especially for those who do not have sufficient experience in this surgery, is the separation of the sac. The tunica vaginalis may appear to surround the cord. The easiest way to separate the sac from the cord and vessels just below the internal ring is to dissect it alternately from the lateral and medial margins. The very delicate free edges of the sac are cut and held until the mosquito is separated with clamps. Then, the posterior and lateral connections of the internal spermatic fascia, which hold the sheath, are separated. The pouch must be completely separated. The edges are held with a mosquito clip and the peritoneal opening is closed as if closing the mouth of the bag. Sometimes this pouch is so thin that it can be easily torn. In this case, the peritoneal opening can be closed continuously with absorbable sutures.

At the same time, a very important point in surgical success is the clear separation of the cord from the peritoneal connections during high ligation

both above and above the internal ring. The cord is measured over the symphysis pubis, if it is not sufficient to reach the scrotum, the cremasteric and tunica vaginalis fibers should be carefully distinguished on the cord by working close to the internal ring. However, care should be taken in terms of cord and epididymal damage at this time. The use of cauterizing devices should be restricted as much as possible. Dissection in the retroperitoneum, separation of the lateral spermatic fascia allows medial movement of the cord.

A transverse incision is then made on the scrotal skin, creating a space between the skin and the dartos layer. A gap is created in the dartos layer through which the testis will pass. With a clamp extended from the outside of the scrotum, the testis is placed in this pouch without torsion through the inguinal canal. Dartos is narrowed with sutures on both sides to prevent the testicle from refluxing.

Postoperatively, the layers were closed anatomically. The scrotum was closed with minimal compression. The patients were discharged on postoperative day 1 when there was no problem, and they were called for control 10 days later. Then, 3 months later, the patients were included in the follow-up program.

Statistical analysis

Normal distribution of continuous data was checked with the Shapiro-Wilk test, while homogeneity of group variance was checked with Levene test. Comparison of variables abiding by assumptions was performed in two groups with the student t test and data are expressed as mean ± standard deviation. Variables not abiding by assumptions were compared in two groups with the Mann-Whitney U test and data are expressed as median [interquartile range (IQR)]. Categoric variables are expressed as frequency and analyzed with Pearson chi-square analysis. All calculations were performed with SPSS v.25 (IBM corp, Chicago, IL, USA) statistical program. Statistical significance used $p<0.05$.

RESULTS

Data of 38 patients were used in the study. The mean age (median ± IQR) was calculated as 60.97±12.29 (7-230) months. While 20 (52.6%) of the patients applied with the diagnosis of undescended testis, 18 (47.4%) patients were diagnosed during the examination performed for other reasons. When classified as undescended testis, it was observed as right in 19 (50%) patients, left in 3 (7.9%) and bilateral in 16 (42.1%) patients. While the testicles were palpable in 30 (78.9%) of the patients who were found to be undescended, they were not palpable in 8 (21.1%) patients. In 6 of the non-palpable cases, the testis was palpated after anesthesia.

Table 1. Demographic Characteristics of the Patients

Age (month)	60.97±12.29 (7-230)[a]
Outpatient clinic application due to undescended testis n (%)	20 (%52,6)
Diagnosed during examination n (%)	18 (%47,4)
Primary case n (%)	38 (100)
Number of patients with palpable testis n (%)	30 (78.9)

a = median ± IQR

When the preoperative cases were classified according to whether they were circumcised or not, 22 (57.9%) patients were uncircumcised, and 16 (42.1%) patients had been circumcised before. Retractile testis was detected in 11 (28.9%) of the patients. While hernia sac was detected in 32 (84.2%)

patients during surgery, it was not detected in 6 (15.8%) patients. The surgical procedure was terminated with dartos pouch in 35 (92.1%) cases, high scrotal insertion in 2 (5.3%) cases, and fowler stephans procedure in 1 (2.6%) case. Orchiectomy was not performed in any patient. The cases were followed up for a mean of 13.19±9.11 (2-36) months. During this period, 2 recurrences were observed, and the desired result was achieved in 36 (94.7%) cases. In surgeries performed in our clinic, the success rate for undescended testis was 94.7%.

Table- 2: Surgical Results

Cases that have been circumcised Before n (%)	16 (42.1)
Retractile testis n (%)	11 (28.9)
Presence of hernia n (%)	32 (84.2)
Surgically placed in the dartos Pouch	35 (92.1)
Fowler Stephans	1 (2.6)
Follow-up (month)	13.19±9.11 (2-36)
Success n (%)	36 (94.7)

DISCUSSION

Undescended testis is a common pathology in the community and associated with important problems when its treatment is delayed. Surgery is the gold standard method of treatment. The aim of this study was to present the surgical technique and results that we applied in our clinic during undescended testicular surgery. The most important finding in this study is that undescended testicular surgery has near perfect results in experienced clinics. In addition, it was found that most of the patients were diagnosed in the late period, beyond the ideal age.

In the prenatal period, the testis begins to develop in the intra-abdominal region. In other words, as we can understand from here, the testis is an intra-abdominal organ at first. However, in order to maintain normal functions such as spermatogenesis, it must migrate into the scrotum, which has a lower temperature than body temperature. Until the 7th month of antenatal development, the testis, which is in the intra-abdominal distance, then enters the inguinal canal. It often descends into the scrotum in prenatal term. Any problem during the descent of the testis results in the test is not descending into the scrotum. The exact reason for this is not known exactly, there are hypotheses put forward on this subject (4,5). When the testicles cannot descend into the scrotum, where they should normally settle, they cannot show their normal development and functions. Changes in germ cells adversely affect fertility and spermiogram pathologies are often detected in these patients (6,7). Cases that occur at older ages, especially after marriage, can be quite impressive in terms of their effects. For this reason, testicles that have not completed the descent process should be lowered into place at the most appropriate time.

Treatment options include medical and surgical treatment. The rationale for medical treatment is the thought that this descent is due to hormone deficiency. For this purpose, HCG and LHRH were used. There are doubts about its reliability, insufficient treatment results, and long-term effectiveness. For this reason, it could not find enough supporters for its use. Studies have reported low success rates up to 20% (8). Another problem is the lack of a common follow-up period for the studies on this subject. In addition, the long follow-up results of these patients are unknown. In our literature review, we could not find any information on the results of lifelong follow-up. In short, information on long follow-up results of these patients is lacking (9).

In the longest follow-up study on this subject, patients were followed for 4 years after medical treatment. As a result of the study, treatment failure was observed in 35% of the cases (10).

Considering the literature, medical treatment is not offered as the first treatment option in cases of undescended testis, except in special cases (11). This is our daily practice as well. We offer surgical treatment as the first choice and reserve medical treatment for a very limited patient group. We definitely do not use medical treatment, especially in cases where we consider open processus vaginalis or in newborns. Due to some of the side effects that can be important, the family should be informed about the side effects and results of the treatment when starting hormonal therapy. Another problem with this treatment is that the disease can recur. Therefore, even if the patient benefits from medical treatment, it should be monitored for recurrence. It is important that parents are informed about this issue and that they are trained to follow the child's test. Medical treatment may not be appropriate if problems are suspected in follow-up or immediate results are expected.

Surgical lowering of the testis into the scrotum is a very effective and successful technique. In cases diagnosed early, it is important to apply surgical treatment, especially in the 6-18 months period, to preserve the fertility potential (12). Because from this moment on, the number of germ cells begins to deteriorate. However, as seen in our study, most of the patients are diagnosed at a later age. The mean age of the patients at the time of surgery was 61 months. We do not know the exact reason for this delay. The reason for this may be that the hospital we are in addresses a large area and a significant part of these regions are located in rural areas. In a study conducted by Yildiz et al., the ages of 240 patients who applied for undescended testicular surgery in different regions of our country were examined (13). In this study, the mean age at surgery was 56.4 months. These results were very close to our results. Unfortunately, many patients are diagnosed late for various reasons. This age seems to be quite far from the ideal age (<2 years) recommended for surgery. This age limit is a very important threshold. Studies in children with undescended testicles have shown that if left untreated, germ cells, which are normal in the newborn period, decrease rapidly after 2 years of age. In addition, interstitial fibrosis and deterioration of tubular structures were also revealed (14). In the study of Wenzler et al., they found that the spontaneous descent of testicles was very low after 6 months in children with undescended testicles. Therefore, operation is recommended after 6 months, especially around 1 year of age. It was stated that surgery performed at this age is more suitable for both fertility and psychosocial aspects (14,15). These results have been confirmed by other studies in the literature. In this study, it was reported that surgery performed within 6-12 months is the most appropriate time for fertility and malignancy (16) Another important result in our study was that 47.4% of these patients were detected during the examination performed for another reason. For this reason, raising awareness and training of health workers and parents on this issue seems to be very important. The most important process is the diagnosis stage. Most of these patients are successfully treated after diagnosis.

In our patient group, the success rate for undescended testis was 94.7%. These results are similar to the rates reported in the literature (89-

100%) (17). None of the patients experienced testicular loss or any significant surgery-related complication. Problems such as pain in the postoperative period were resolved with simple measures. No patient encountered a problem such as reoperation or death in the early postoperative period. Surgical outcomes seem to be quite high compared to medical treatment. In a study on this subject, it was found that 52% of the patients who received medical treatment had testes in the scrotum after 9 years. Half of the patients were unsuccessful in treatment (18). It was not fully specified in this study how many patients had truly retractile or true undescended testicles. In addition, the results after 9 years are not known. In our study, cases with retratile testis were not included in the study and all of them consisted of true undescended testicles. It is very important to follow the basic rules during surgery. We think that the most important point in success is to lower the testis with sufficient length into the scrotum. This is possible in most cases. In cases where sufficient length cannot be achieved, it should be kept in mind that sufficient release may not have been made on the cord. Especially cremaster, spermatic fascia, peritoneal adhesions are the most limiting factors. In addition, hernia sac, which is very common (90%) in these patients, is an important limiting factor (19). If the sac is released from the cord elements, especially at the level of the internal ring, it can be seen more clearly. The very thinness of the sac can lead to dissection difficulties. Often the pouch is easily separated by gentle and unhurried dissection. It should be observed that the cord and the vascular structure diverge at the level of the internal ring. Care should be taken to preserve the vascular structures during dissection and insertion of the testis into the scrotum.

CONCLUSION

When the undescended testis is left untreated, it can lead to important problems, especially cancer development and infertility. It is important to diagnose these patients in the early period and to treat them as early as possible (6-18 months) in terms of preserving fertility and preventing malignant events. In particular, awareness and education of parents and healthcare professionals on this issue is very important in terms of diagnosis. In fact, the necessary information and training should be provided for everyone to examine their own testicles. It has been shown in many studies that significant changes in the testis begin after the age of 2 years. As seen in the results of our study, surgical treatment is quite effective and complication rates are negligible. We think that sufficient experience and experience is important in this regard.

Ethics Committee Approval: Ethics committee approval was received for this study from Ordu University Clinical Research Ethics Committee (2021/209)

Peer-review: Externally peer-reviewed.

Author Contributions:

Concept: E.B, A.Y, Design: E.B., A.Ç., A.Y; Literature search: E.B., A.Ç, Data Collection and Processing: E.B., A.Ç.; Analysis or Interpretation: Y.K.A., Writing: A.Y., I.Y.

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

Financial Disclosure: The authors declared that this study hasn’t received no financial support.

REFERENCES

1. Snodgrass W, Bush N, Holzer M, Zhang S. Current referral patterns and means to improve accuracy in diagnosis of undescended testis. Pediatrics 2011;127(2):e382-8.
2. Elder JS. Surgical Management of the Undescended Testis: Recent Advances and Controversies. Eur J Pediatr Surg 2016;26(5):418-26.
3. Abaci A, Catli G, Anik A, Bober E. Epidemiology, classification and management of undescended testes: does medication have value in its treatment? J Clin Res Pediatr Endocrinol 2013;5(2):65-72.
4. Sijstermans K, Hack WW, Meijer RW, van der Voort-Doedens LM. The frequency of undescended testis from birth to adulthood: a review. Int J Androl 2008;31(1):1-11.
5. Berkowitz GS, Lapinski RH, Godbold JH, Dolgin SE, Holzman IR. Maternal and neonatal risk factors for cryptorchidism. Epidemiology 1995;6(2):127-31.
6. Fedder J, Cruger D, Oestergaard B, Petersen GB. Etiology of azoospermia in 100 consecutive nonvasectomized men. Fertil Steril 2004;82(5):1463-5
7. Kollin C, Karpe B, Hesser U, Granholm T, Ritzén EM. Surgical treatment of unilaterally undescended testes: testicular growth after randomization to orchiopexy at age 9 months or 3 years. J Urol 2007;178(4):1589-9.
8. Ritzén EM, Bergh A, Bjerknes R, Christiansen P, Cortes D, Haugen SE, et al. Nordic consensus on treatment of undescended testes. Acta Paediatr 2007;96(5):638-43.
9. Hadziselimovic F. Is Hormonal Treatment of Congenital Undescended Testes Justified? A Debate. Sex Dev 2019;13(1):3-10.
10. Hadziselimovic F, Gegenschatz-Schmid K, Verkauskas G, Demougin P, Bilius V, Dasevicius D, et al. GnRHa Treatment of Cryptorchid Boys Affects Genes Involved in Hormonal Control of the HPG Axis and Fertility. Sex Dev 2017;11(3):126-36.
11. Cho A, Thomas J, Perera R, Cherian A. Undescended testis. BMJ 2019;364:l926.
12. Kim SO, Hwang EC, Hwang IS, Oh KJ, Jung SI, Kang TW, et al. Testicular catch up growth: the impact of orchiopexy age. Urology 2011;78(4):886-9.
13. Yildiz T, Keles I, Metin M, Dumlupinar Y, Arpacik M, Aydinc M, et al. Age of Surgery of Undescended Testis in Turkey; Does it Show Health Care Level? Konuralp Medical Journal 2014;6(2):29-33.
14. Kokorowski PJ, Routh JC, Graham DA, Nelson CP. Variations in timing of surgery among boys who underwent orchidopexy for cryptorchidism. Pediatrics 2010;126(3):e576-82.
15. Wenzler DL, Bloom DA, Park JM. What is the rate of spontaneous testicular descent in infants with cryptorchidism? J Urol 2004;171(2):849-51.
16. Chan E, Wayne C, Nasr A; FRCSC for Canadian Association of Pediatric Surgeon Evidence-Based Resource. Ideal timing of orchiopexy: a systematic review. Pediatr Surg Int 2014;30(1):87-97.
17. Kolon TF, Herndon CD, Baker LA, Baskin LS, Baxter CG, Cheng EY, et al. Evaluation and treatment of cryptorchidism: AUA guideline. J Urol 2014;192(2):337-45.

18. Waldschmidt J, Doede T, Vygen I. The results of 9 years of experience with a combined treatment with LH-RH and HCG for cryptorchidism. Eur J Pediatr 1993;152(2):34-6.

19. Simpson M, Sundaram V. Urologic Conditions in Infants and Children: Inguinal Hernia, Hydrocele, and Cryptorchidism. FP Essent 2020;488:16-20.

Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci **May 2022; 8(2): 242-248**

RESEARCH ARTICLE **DOI:** 10.19127/mbsjohs.1062196

Evaluation of Optic Nerve Diameter Measurement: According to Bleeding Subtypes in Patients with Non-Traumatic Intracranial Hemorrhage in the Emergency Department

Seyda Tuba Savrun[1](ID), Bilge Sezin Akhan[2](ID), Halil Arslan[3](ID)

[1]Ordu University, Faculty of Medicine, Department of Emergency Medicine, Ordu, Turkey
2 Gemlik State Hospital, Radiology Clinic, Bursa, Turkey
3. Health Ministry of Turkish Republic Ankara City Hospital, Department of Radiology, Ankara, Turkey

Received: 31 January 2022, Accepted: 22 February 2022, Published online: 30 May 2022

Abstract

Objective: Nontraumatic intracranial hemorrhage is an important cause of adult death and disability. The optic nerve sheath is surrounded by cerebrospinal fluid. Therefore, the increase in intracranial pressure; causes a diameter change in the optic nerve sheath. In this direction, to determine the changes in optic nerve diameter measurements according to the bleeding subtypes of patients diagnosed with non-traumatic intracranial hemorrhage in the emergency department. Thus, it is aimed to assist in early diagnosis and treatment.

Methods: The study is retrospective and includes 136 patients diagnosed with non-traumatic intracranial hemorrhage, who applied to the 3rd level university hospital emergency department between January 01/ 2015 and June 01/ 2017. The parameters of each patient at the time of first admission and at eight hours were checked. These were subtypes of bleeding in brain tomography, amount of bleeding, optic nerve diameter measurements, Glasgow coma scales and demographic characteristics.

Results: 136 patients were included in the study. The mean age of the patients was 64.5 ± 17.8 years, 47.1% were female (n=64), 52.9% were male (n=72). Intracranial hemorrhage was 64.7% (n=88), subdural hemorrhage was 29.4% (n=40), and epidural hemorrhage was 5.9% (n=8) ($p<0.001$). In addition, the patients showed a significant increase in both the right and left optic nerve diameter at the 8th hour ($p<0.001$). Bleeding diameter increased in parallel with the increase in right and left optic nerve diameter. Similarly, a significant decrease was observed in Glasgow Coma Scales at the 8th hour (13.0 (2)) compared to the first admission (14.0 (1)) ($p<0.001$).

Conclusion: When evaluating brain tomography of patients with nontraumatic intracranial hemorrhage; In addition to the existing parameters, it is recommended to look at the optic nerve diameter change.

Keywords: Non-traumatic, intracerebral hemorrhage, optic nerve diameter, glaskow coma scale

Suggested Citation: Savrun S T, Akhan B S, Arslan H. Evaluation of Optic Nerve Diameter Measurement:According to Bleeding Subtypes in Patients with Non-Traumatic Intracranial Hemorrhage in the Emergency Department. Mid Blac Sea Journal of Health Sci, 2022;8(2):242-248.

Address for correspondence/reprints:
Şeyda Tuba Savrun
Telephone number: +90 (553) 370 40 09

E-mail: dr.seyda.tuba@gmail.com
Note: This article is produced from the author's specialist thesis

INTRODUCTION

Intracranial hemorrhage is a clinical picture that can be treated, its progression can be prevented. Otherwise, it can cause serious morbidity and mortality (1). Dramatic increase in intracranial pressure (IP) of patients with intracerebral hemorrhage; associated with deaths (2).

IP measurement is important in terms of patient follow-up and prognosis. IP is measured by interventional methods such as lumbar puncture or ventriculostomy. At the same time, changes in IP affect the optic nerve sheath diameter (ONSD) via cerebrospinal fluid (CSF). Especially since this pressure increase can cause enlargement in the retrobulbar segment, this region is used in measurements. (3). ONSD; it is an anatomical structure that continues from the intracranial area and is surrounded by CSF. Thus, the increase in ONSD is used to detect IP.

The gold standard method for measuring IP is ventricular catheterization. However, the invasiveness of these methods, the need of a neurosurgeon to perform the intervention, technical difficulties, infection, hemorrhage, contraindications of the procedure such as coagulopathy and thrombocytopenia are limiting factors in the application of the method (4). It is thought that IP in patients diagnosed with intracranial hemorrhage can be evaluated with ONSD without using an invasive method. In this study, the aim of this study is to evaluate the changes in ONSD according to the subtypes of intracranial hemorrhage in patients diagnosed with nontraumatic intracranial hemorrhage, early and without any interventional procedure.

METHODS

Before starting the study, ethical approval was obtained from Ankara Yıldırım Beyazıt University Faculty of Medicine Clinical Research Ethics Committee (Decision No. 46, dated February 17, 2016). Since the presented study was retrospective and observational, informed consent was not obtained from the participants. However, all authors paid attention to its compliance with the Declaration of the World Medical Association of Helsinki.

Study Population

Inclusion criteria: Statistical analysis

All cases with nontraumatic intracranial hemorrhage, aged 18 years and over, who applied to Ankara Yıldırım Beyazıt University Hospital Emergency Medicine Clinic between the specified dates, and whose data could be accessed, were included.

Exclusion criteria

Patients with a history of trauma, eye or orbital diseases such as glaucoma, optic neuritis, ischemic optic neuropathy, lens opacity, history of malignancy, pregnancy and trauma were not included in the study.

Data Collection

Demographic data of the patients included in the study, both Glasgow coma scale (GCS) and brain tomography (CCT) images at the time of first admission and eight hours later were analyzed retrospectively. In cases where the patient does not have sudden changing clinical findings, the control CCT scan time is applied as the 8th hour in our center. According to CCT images, it was analyzed by dividing into 3 classes as intracerebral hemorrhage (ISH), subdural hemorrhage (SH) and epidural hemorrhage (EH). subarachnoid hemorrhage (SAH)

patients in our hospital were excluded from the study because it was determined that it developed secondary to trauma. The amount of bleeding in the patients CCT was measured after determining the widest part of the bleeding area. In addition, the ONSD of each patient's first admission and eighth hour CCT scans were measured separately in both the right and left eyes. Measurements were made in the axial and sagittal planes of both eyes, 2-3 mm behind the optic disc, at 5 times magnification. All CCT evaluations were made by the radiologist and recorded in the data collection forms.

Statistical Analysis

The analysis of the study was performed using SPSS 21.0 package program. Descriptive statistics of the variables (Frequency, Percentages, Mean ± Standard Deviation, Median (IQR) were given with tables. Shapiro-Wilk tests were used to determine whether the variables met the parametric test assumptions, and it was determined that they did not fit the normal distribution ($p< 0.05$) The difference between dependent groups was determined by Wilcoxon signed rank test. A p value of <0.05 was considered statistically significant.

RESULTS

136 patients were included in the study. The mean age of the patients was 64.5 ± 17.8 years, with 47.1% female (n=64) and 52.9% male (n=72). ICH 64.7% (n = 88), SH was 29.4% (n = 40) and additional 5.9% (n = 8) (Table 1) first admission median (IQR) values of bleeding diameters in CCTs at 8 hours were 23.3 (24.4) and 27.9 (31.2), respectively. And this increase at 8 hours was statistically significant ($p<0.001$). At the 8th hour, the right ONSD (5.2 (0.6)) showed a significant increase in the moment (4.5 (0.6)) ($p <0.001$). Similarly, the left ONSD was significantly higher than the 8th time (5.2 (0.7)) of first admission ($p <0.001$). Parallel to the increase in hemorrhage diameter, right and left ONSD, a significant decrease was observed in GCS at 8 hours (13.0 (2)) compared to the time of admission (14.0 (1)) ($p<0.001$) (Table 2).

Table 1. Demographic and clinical characteristics of the patients

Parameter	
Age (years)	
Mean±SD	64.5 ± 17.8
Median (IQR)	65.0 (25.8)
Gender	
female; % (n)	%47.1 (64)
male; % (n)	%52.9 (72)
Diagnosis	
ISH; % (n)	%64.7 (88)
SH; % (n)	%29.4 (40)
EH; % (n)	%5.9 (8)

ISH; Intracerebral Hemorrhage, SH; Subdural Bleeding, EH; Epidural Bleeding.

Table 2. Comparison of changes in repeated measured parameters in all patients.

Variable	**first admission Median (IQR)**	**8 hours Median (IQR)**	***p***
Bleeding Diameter	23.3 (24.4)	27.9 (31.2)	**<0.001**
Right ONSD	4.5 (0.6)	5.2 (0.6)	**<0.001**
Left ONSD	4.5 (0.6)	5.2 (0.7)	**<0.001**
GCS	14.0 (1)	13.0 (2)	**<0.001**

Wilcoxon signed rank test
ONSD; optic nerve sheath diameter, GCS; Glasgow coma scale.

The median (IQR) values of the bleeding diameters in the 8th hour CCT of the patients with ISH, SH, and EH were found to be 35.8 (25), 13 (7.7) and 17.7 (19.2), respectively. Moreover, these values were found at the time of admission (30.8 (19.9), 9.1 (7.7) and 12.7 (6.5)), there is a statistically significant increase ($p<0.001$; $p<0.001$; $p=0.011$, respectively) (table 3).

Right ONSD median (IQR) values in the 8th hour CCT of the patients with ICH, SH, and EH were 5.2

(0.5), 5 (0.8), and 5.25 (1), respectively. There is a statistically significant increase compared to (4.5 (0.5), 4.3 (0.6) and 4.5 (0.9)) at the time of arrival (p<0.001; p<0.001; p=0.012, respectively).

Left ONSD median (IQR) values in the 8th hour CCT of the cases with ICH, SH, and EH were 5.2 (0.5), 4.95 (0.8), .3 (1.1), respectively, at the time of arrival (4.5 (0.5), 4.3 (0.5), 4.6 (0.9)), there is a statistically significant height (p<0.001; p<0.001; p=0.012, respectively).

The median GCS (IQR) values of patients with ICH and SH at the eighth hour CCT were 14.0 (1.8), 12.0 (3.0), respectively, and there was a statistically significant decrease compared to the GCS values at the time of admission (14.0 (1.0), 14.0 (2.0). (p<0.001; p<0.001 respectively) In the EH group, there was no significant difference in GCS care between arrival and 8th hour (p=0.066). 0.047)

Table 3. The relationship between bleeding subtypes and GCS, optic nerve diameter and bleeding diameter.

Variable		first admission Median (IQR)	8 hours Median (IQR)	p
Bleeding diameter	**ISH**	30,8 (19.9)	35.8 (25)	**<0.001**
	SH	9.1 (7.7)	13 (7.7)	**<0.001**
	EH	12.7 (6,5)	17.7 (19.2)	**0.011**
Right ONSD	**ISH**	4.5 (0.5)	5.2 (0.5)	**<0.001**
	SH	4.3 (0.6)	5 (0.8)	**<0.001**
	EH	4.5 (0.9)	5.25 (1)	**0.012**
Left ONSD	**ISH**	4.5 (0.5)	5.2 (0.5)	**<0.001**
	SH	4.3 (0.5)	4.95 (0.8)	**<0.001**
	EH	4.6 (0.9)	5.3 (1.1)	**0.012**
GKS	**SH**	14.0 (1.0)	14.0 (1.8)	**<0.001**
	SH	14.0 (2.0)	12.0 (3.0)	**<0.001**
	EH	14.5 (1.8)	12.0 (5.0)	0.066

1: Wilcoxon signed rank test
ONSD; optic nerve sheath diameter, GCS; Glasgow coma scale, ICH; Intracerebral hemorrhage, SH; Subdural bleeding, EH; epidural bleeding

DISCUSSION

In this study, the effect of ONSD on patients diagnosed with nontraumatic intracranial hemorrhage in the emergency department was investigated between the time of first admission to the hospital and the eight-hour follow-up period. In the eight-hour follow-up of the patients, a significant increase was found in the bleeding diameter and ONSD value in all three bleeding subtypes compared to the value at the time of admission. In the evaluation, it was determined that both the right eye and the left eye had a significant increase in ONSD. The level of consciousness is the first and important finding that informs the change in the neurological status of the patient. GCS is a scoring method that shows the level of consciousness and brain damage (5,6). Accordingly, in parallel with the increase in bleeding diameter, right and left ONSD, a significant decrease was observed in GCS at 8 hours (13.0 (2)) compared to the time of admission (14.0 (1)) (p<0.001) This situation can be explained by the fact that when the increase in ONSD is observed, it is thought that GCS may decrease, and the patient can be followed in this direction.

According to the available source information, it has been shown that there is dilatation of ONSD in cases with increased intracranial pressure. In addition, investigators reported that in cases where intracranial pressure increases, ONSD increases significantly (7,8). Similarly, in the presented study, it was found that ONSD increased in the following hours due to the increase in IP. This can be explained as the increase in the diameter of bleeding may lead to an increase in intracranial pressure.

In studies, ONSD has been suggested as an indirect and alternative parameter for the detection of increased intracranial pressure. However, in the source information reached, no research was found regarding the examination of ONSD according to the

bleeding subtypes. Accordingly, ONSD was evaluated according to bleeding subtypes in patients with non-traumatic intracranial hemorrhage, considering that ONSD may vary according to its subtypes and may guide the diagnosis and treatment in this situation. In the study, the relationship between nontraumatic intracranial hemorrhage (ICH) subtypes (ICH, SH, and EH) and SAH was investigated, but SAH was excluded because it was traumatic. It was determined that the ONSD of all cases with ICH, SH and EH increased statistically significantly. A significant decrease was observed in the median GCS (IQR) at the eighth hour in patients diagnosed with ICH and SH. In the EH group, there was no significant difference in GCS care between arrival and 8th hour. This situation can be explained as the low number of patients in the EH group.

In the literature, frequent follow-up of patients with non-traumatic intracranial hemorrhage is recommended (9,10,11). In the presented study, a significant decrease in GCS values was found in patients with ICH and SH at the eighth hour. It can be explained as the need for rapid intervention, as it can cause serious complications in patients with a diagnosis of ICH and SH if it is waited for eight hours. In different studies, Geeraerts et al. reported that there is a significant relationship between GCS and IP (12). Similarly, Karakitsos et al. reported that there is a significant relationship between IP and GCS. In addition, while the ONSD was 5.8 ± 1.1 mm in patients with moderate and severe coma with GCS <13, it was found to be 4.9 ± 0.8 mm in patients with mild coma. Researchers have reported that there is a statistically significant relationship between GCS and ONSD(13). Besides, IP can be evaluated by measuring the noninvasive and easy method (ONSD). 14,15). Patients with IP had increased ONSD and its measurement using CCT has been reported to be important(16,17). In the presented study, it is thought that the bleeding diameters of the cases increased at the 8th hour, and accordingly, IP and GCS decreased. The significant relationship between the increase in ONSD and decrease in GCS is; It was thought that the increase in IP and the increase in ONSD may occur.

Study Limitation

Since the study is retrospective, the data obtained are limited to file information.

CONCLUSION

In cases with non-traumatic ICH, the change in the ONSD level and the change in GCS score should be checked in the first admission to the hospital and in the eighth hour control brain tomography. It was concluded that this situation could be effective in reducing mortality and morbidity by detecting IP change. Accordingly, when evaluating the brain tomography of patients with non-traumatic ICH;in addition to the existing parameters, it was suggested that optic nerve diameter change should also be considered.

Ethics Committee Approval: Ethical approval was obtained from Ankara Yıldırım Beyazıt University Faculty of Medicine Clinical Research Ethics Committee (Decision No. 46, dated February 17, 2016).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept and Design: STS, BSA, HA Data Collection: STS, BSA, HA , Literature search: STS, BSA, HA, Analysis or Interpretation, Writing: STS, BSA, HA

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

Financial Disclosure: The authors also decline any financial support neither from any pharmaceutical company, nor from a company that provides or produces medical instruments and materials.

REFERENCES

1. Gonzalez-Duarte A, Cantu C, Ruiz-Sandoval JL, Barinagarrementeria F. Recurrent Primary Cerebral Hemorrhage Frequency, Meohanisms, and Prognosis. Stroke. 1998;29:1802-1805.
2. Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R. 'Malignant' middle cerebral artery territory infarction: clinical course and prognostic signs. Arch Neurol. 1996;53:309-315.
3. Hansen HC, Helmke K. The subarachnoid space surrounding the optic nerves. An ultrasound study of theoptic nerve sheath. Surg Radiol Anat. 1996;18 (4) :323-8.
4. Rickert K, Sinson G. Intracranial pressure monitoring. Oper Tech Gen Surg. 2003;5:170-175.
5. Vavilala MS, Lujan SB, Qiu Q, Petroni GJ, Ballarini NM, Guadagnoli N, et al. Benchmarking Prehospital and Emergency Department Care for Argentine Children with Traumatic Brain Injury: For the South American Guideline Adherence Group PLoS One. 2016;11 (12) :e0166478.
6. Bombacı E, Boztepe A, Cizen A, Cevik Z, Çolakoglu S, Yollu Atakan T. The relationship between bispectral index monitoring and modified Glasgow coma and Ramsay sedation scale scores in unconscious intensive care patients. Bakirköy Medical Journal. 2005;1 (3):90-4.
7. Hayreh SS. Pathogenesis of edema of the optic disc. Doc Ophthalmol. 1968;24:289-411
8. Amini A, Kariman H, Dolatabadi AA, Hatamabadi HR, Derakhshanfar H, Mansouri B, et al. Use of the sonographic diameter of optic nerve sheath to estimate intracranial pressure. Am J Emerg Med. 2013;31 (1) :236-9.
9. Sekhon MS, McBeth P, Zou J, Qiao L, Kolmodin L, Henderson WR, et al. Association between optic nerve sheath diameter and mortality in patients with severe traumatic brain injury. Neurocritical care. 2014;21 (2) :245-52.
10. Karasu A, Sabancı PA, Cansever T, Hepgül KT, Imer M, Dolaş I, et al. Epidemiological study in head injury patients. National Journal of Trauma Emergency Surgery. 2009;15 (2) :159-163.
11. Cokuk A, Kozaci N, Ay MO, Acikalin A, Seviner M, Satar S. Evaluation of Head Trauma Cases in the Emergency Department. Cukurova Medical Journal. 2013;38;63-71.
12. Thomas Geeraerts, Sybille Merceron, Dan Benhamou, Bernard Vigue, Jacques Duranteau. Non-invasive assessment of intracranial pressure using ocular sonography in neurocritical care patients. Intensive Care Med. 2008;34:2062-67.
13. Karakitsos D, Soldatos T, Gouliamos A, Armaganidis A, Poularas J, Kalogeromitros A, et al. Transorbital sonographic monitoring of optic nerve diameter in patients with severe brain injury. Transplant Proc. 2006;38:3700-6.:963-7.
14. Guzelda S, Yılmaz G, Tuna M, Altuntas M, Ozdemir M. Measuring the Optic Nerve Sheath Diameter with Ultrasound in Acute Middle

Cerebral Artery Stroke Patients. Journal of Stroke and Cerebrovascular Diseases,2021,30.2: 105523.

15. Celik K, Demiryurek B. E.The association between intracranial pressure and optic nerve sheath diameter on patients with head trauma. Arq Neuropsiquiatr 2021;79(10):879-885

16. Kim D Y, Kim S Y, Hong D Y, sung B Y, Lee S, Paik J H et all. Comparison of ultrasonography and computed tomography for measuring optic nerve sheath diameter for the detection of elevated intracranial pressure. Clinical Neurology and Neurosurgery 204 (2021) 106609

17. Altayar A S, Abouelela A Z, Abdelshafey E E, Mohammed K S, Hassan A A, Khattab M A et all. Optic nerve sheath diameter by ultrasound is a good screening tool for high intracranial pressure in traumatic brain injury. Ir J Med Sci (2021) 190:387–393

Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci **May 2022; 8(2): 249-257**

RESEARCH ARTICLE **DOI:** 10.19127/mbsjohs.1051424

Clinical Evaluation of Injection of Corticosteroid and Prolotherapy in the Treatment of Plantar Fasciitis

Emre Calısal[1](ID), Selami Karadeniz[1](ID), Ismail Murad Pepe[2](ID)

[1]Amasya University, School of Medicine, Department of Orthopaedics and Traumatology, Amasya, Turkey.
[2]Antalya Bilim University, MedStar Antalya Hospital, Department of Orthopaedics and Traumatology, Antalya, Turkey.

Received: 30 December 2021, Accepted: 28 April 2022, Published online: 31 May 2022

Abstract

Objective: Plantar fasciitis is one of the primary causes of heel pain. Several treatment methods are substantial. This study was aimed to evaluate the clinical results of corticosteroids and prolotherapy injection therapies.

Methods: The gender, age, time of symptoms, BMI (body mass index) were specified in 60 patients with symptomatic chronic plantar fasciitis disorder between 2019 and 2020. The patients were randomly divided into two groups as prolotherapy and corticosteroid groups. Foot pain and disability were evaluated via a visual analog scale (VAS) and foot function index (FFI) that interpreted the clinical scores measured at baseline and three months after the injections.

Results: The distribution of age, gender, BMI, and duration were similar between groups. The mean VAS scores and FFI scores of all the groups were not significantly different in the baseline time ($p > 0.05$). A significant improvement was observed in the FFI and VAS scores of the patients in both injection groups ($p < 0.05$). The post-treatment VAS scores decreased from 8.03 to 4.93 (p=.003) and 7.76 to 4.23 (p=.002), respectively, in the prolotherapy and corticosteroid groups. The post-treatment FFI scores decreased from 176.1 to 126.9 (p=.004) and 181.5 to 121.1 (p=.002), respectively, in the prolotherapy and corticosteroid groups. The percentile decreases in VAS and FFI scores between groups were higher in favor of the corticosteroid group.

Conclusion: Prolotherapy and corticosteroid injection treatments provide significant functional outcomes in short-term follow-up of the treatment of plantar fasciitis. Corticosteroid injection results in superior clinical healing than prolotherapy.

Keywords: Plantar fasciitis, Corticosteroid, Prolotherapy

Suggested Citation: Calisal E, Karadeniz S, Pepe IM. Clinical Evaluation of injection of Corticosteroid and Prolotherapy in the Treatment of Plantar Fasciitis. Mid Blac Sea Journal of Health Sci, 2022;8(2): 249-257.

Address for correspondence/reprints:
Selami Karadeniz

Telephone number: +90 (506) 599 35 38
E-mail: drskaradeniz@hotmail.com

INTRODUCTION

Plantar fasciitis is a primary cause of inferior heel pain. 11 to 15 percent of adults with foot symptoms are thought to have been examined by a physician (1). It is at a peak level in adults over 40 years of age and young athletes compared to the general population (2). Characteristic complaints are morning pain, standing pain after periods of immobility (3). Numerous treatments methods such as rest, stretching exercises, weight loss, heel cups, night splints with medical treatment have been described, and approximately 90% of patients respond to conservative treatment (4). Although, in the remaining 10% of patients, less invasive ways such as injection therapy, extracorporeal shockwave therapy, and aggressive procedures such as surgical releasing of the plantar fascia, if not responding to less invasive treatment, can be performed (5). There are different injectable ingredients such as corticosteroid, prolotherapy, platelet-rich plasma, lidocaine needling. The superiority and effectiveness of injection treatments are controversial and limited (6-8).

Corticosteroid injection therapy is the most widely used method of plantar fasciitis. However, corticosteroid injection has a risk of fat pad atrophy and plantar fascia rupture (9, 10).

Prolotherapy is known as regenerative injection treatment based on the injection of generating materials via high-density dextrose into ligaments and tendons (11-13). Dextrose solution provides fibroblast proliferation and collagen synthesis in response to the departure of various growth factors (14). All of these stimuli improve functional outcomes by reducing chronic musculoskeletal pain (15).

Although prolotherapy and steroid injection treatments are studied in the treatment of plantar fasciitis separately, to the best of our knowledge, there is a limited study comparing only these two injection methods in the literature (16). Considering the complications of corticosteroid injection, we hypothesized that prolotherapy was as effective as a steroid in the treatment of plantar fasciitis. We aimed to compare the clinical results of corticosteroid and prolotherapy injection therapies.

METHODS

Patients, Study Design and Evaluation

The local ethics committee at Amasya University approved this retrospective study (2021/134). Informed consent was obtained from all patients included in the current study. Patients admitted to Amasya University outpatient clinic between 2019 and 2020 for heel pain and clinically and radiographically diagnosed as plantar fasciitis were recruited in the study. Plain radiography was taken in all patients to exclude unsuitable patients. Patients undergoing previous heel injections or surgery, foot bone tumors and bone fractures, chronic systemic diseases (cardiovascular, renal, or hepatic disease), vascular insufficiency, peripheral neuropathy, diabetes, high unknown infection markers levels were excluded from the study. The vaid participants were clarified about all injection procedures. Institutional Review Board approval and informed consent were obtained for a total of 60 patients who met the conditions of participation. The patients were re-evaluated three months after the injections.

Foot pain and disability were evaluated via visual analog scale (VAS) and foot function index (FFI) that interpreted the clinical scores evaluated at baseline and three months after the first treatment by an author

who was blinded to the injection type. Heel pain intensity was evaluated using a visual analog scale (VAS) scale from 0 to 10. On this scale, while 0 was described as “no pain at all,” 10 was described, “my pain is as bad as it could be.” A Foot Function Index (FFI), which inclusion 23 self-reported items, has measured the effects of foot disturbance on function in terms of pain, disability, and activity restriction (17).

The demographics of each group, including age, height, weight, body mass index (BMI), and the period of foot pain, were received (Table 1).

Preparation And Application of Injections

The injections were applied to all patients who included unilateral foot symptoms and didn't respond to conservative treatment for at least six months. Medial calcaneal tuberosity and the origin of the plantar fascia, which was the most painful point before injection, were marked with palpation. The area to be injected was cleaned with an antiseptic povidone-iodine solution. A total of 60 patients were separated into two groups, including thirty patients each. In the prolotherapy group, 2 ml 15% dextrose and 2 ml 2% prilocaine were mixed and administered to the patients. Patients received the second dose on the 15th day after the first prolotherapy injection. In the corticosteroid group, patients were treated with a single dose injection using 2 mL 2% prilocaine and 2 mL 40 mg methylprednisolone. The patients in both groups were given a six-week exercise program, including stretching exercises for the gastrocnemius and soleus muscles and plantar fascia. None of the patients used oral medication after injections.

Statistical Analysis

All statistical analyses were evaluated using SPSS software (version 21.0). Descriptive data that were shown in number with or without mean ± standard deviation (SD) was tested for normality using the Kolmogorov–Smirnov and Shapiro-Wilk tests. While an independent samples t-test was used for between-group comparisons in the normal distribution, the Mann–Whitney U test was performed if the distribution was not normal. Intra-group analyses were exerted using a paired t-test. The P-value was 0.05 or less were considered significant differences.

RESULTS

The demographic characteristics of the patients participating in our study are shown in table 1. The distribution of age, gender, BMI, and duration were similar between groups (Table 1).

The mean VAS scores and FFI scores of all the groups were not significantly different in the baseline time ($p > 0.05$). A significant improvement was observed in the FFI and VAS scores of the patients in both injection groups ($p < 0.05$). The post-treatment VAS scores decreased from 8.03 to 4.93 (p=.003) and 7.76 to 4.23 (p=.002), respectively, in the prolotherapy and corticosteroid groups (Table 2). The post-treatment FFI scores decreased from 176.1 to 126.9 (p=.004) and 181.5 to 121.1 (p=.002), respectively, in the prolotherapy and corticosteroid groups (Table 3). The percentile decreases in VAS and FFI scores between groups were higher in favor of the corticosteroid group.

Table 1. The demographic characteristics of the patients

Characteristic	Group		P values
	prolotherapy (n = 30)	**corticosteroid (n = 30)**	
Gender. M/F	12/18	14/16	.610
	prolotherapy (mean ± SD)	**corticosteroid (mean ± SD)**	
Age (years)	54.13 ± 9.38	47.46 ±6.74	.170
Height (cm)	166.23 ± 6.51	164.73 ± 8.61	.450
Weight (kg)	86.93 ± 10.84	86.36 ± 10.54	.838
Time of symptoms (years)	2.4 ± 1.40	1.8 ±0.80	.121
BMI (kg / m^2)	31.57 ± 4.58	32.02 ± 4.89	.714

*P<0.05 values were considered statistically significant

Table 2 VAS score results on the affected foot before and after treatment

Group	No.	VAS score (mean ± SD)		P values
		Baseline	3 Months	
prolotherapy	30	8.03± 1.09	4.93± 1.11	.003
corticosteroid	30	7.76± 0.93	4.23 ± 0.62	.002

**P<0.05 values were considered statistically significant*

Table 3 FFI score results on the affected foot before and after treatment

Group	No.	FFI score (mean ± SD)		P values
		Baseline	3 Months	
prolotherapy	30	176.1±16.9	126.9±17.4	.004
corticosteroid	30	181±13.9	121.1±16.1	.002

*P<0.05 values were considered statistically significant

DISCUSSION

In the present study, we compared the results of prolotherapy and corticosteroid administration in patients with chronic plantar fasciitis. Pain, disability, and activity limitations were evaluated with VAS and FFI scores before and three months after injection. Post-treatment clinical scores in the third month were lower in both groups than pre-treatment. Also, the increase in clinical results was higher in the corticosteroid group than in the prolotherapy group.

Local injections relieve heel pain by reducing inflammation (18, 19). It is reported that injection-based invasive methods can be used in patients with plantar fasciitis if symptoms are present for more than six months (2, 10, 20). Similarly, we included patients with symptoms lasting longer than six months in our study. Prolotherapy is an injection procedure in which a solution of proliferant is administered to the ligament and muscle injuries (14, 21). There are no formal practice guidelines about the procedure of the prolotherapy method, the density of the solution, the frequency, and the number of sessions in the clinical practice. Usually, prolotherapy injection can often be administered through a few injections' sessions every two or more weeks (22). We performed two doses (at 0-, 2- week intervals) with two-week intervals. Although there is no known side effect of the high dose dextrose solution, the most widely used

concentration of prolotherapy in clinical administration dextrose was varying between 12.5% to 25% (23). We used a solution containing 15% dextrose density, as described by Kim and Lee (24).

The superiority of sonographically-guided injections compared to palpation-guided injections is still controversial. In the meta-analysis study that was conducted in 2014 about this topic, even though ultrasound-guided injections were advocated to be more effective, further studies are required to attain this outcome (25). However, Kane et al concluded that there was no significant difference between the two-application guide technique (26). We administered the injections with the palpation-guided method in both groups.

Ersen et al. (27) found that prolotherapy application significantly improved in VAS and FFI scores at three months in the treatment of plantar fasciitis. Kim and Lee conducted a randomized controlled study, and they compared the effectiveness of autologous PRP versus dextrose prolotherapy treatments. Each treatment resulted in better initial clinical improvement via Foot Functional Index measurement at two- and six-month follow-ups (24). Ryan et al. argued that prolotherapy injection is superior to corticosteroid injection because it provides tissue healing and regeneration like Platelet-Rich Plasma (PRP). They recorded VAS at baseline and the final at the end of an 11-month follow-up treatment consultation and concluded that prolotherapy injections indicated an excellent clinical response with chronic plantar fasciitis (3). Besides, the complication rate of prolotherapy is lower and more cost-effective than corticosteroid (28). Many studies have shown that the effectiveness of corticosteroids in the treatment of plantar fasciitis, relieves pain, especially in the three months after injection. (29-31). Fat pad atrophy, calcaneal osteomyelitis, rupture of the plantar fascia are long-term complications of corticosteroid injection (32-34). In a placebo-controlled corticosteroid injection trial, the authors found that there was a significant difference in VAS scores between the groups at 6 and 12 weeks after injections (35). Crawford et al. reported a significant reduction in heel pain at one month in the steroid injection independent of affected by anesthesia of the heel (36). Mahindra et al. reported that the mean VAS score in the corticosteroid groups decreased from 7.72 preinjection to 3.64 at the final follow-up in three months ended (37). In a study conducted by Shetty et al., a total of 60 patients who injected PRP and corticosteroids found a significant improvement in VAS scores in the 3rd month (38). Ball EM et al. reported that steroid injection presented a clear advantage over the placebo at 12 weeks. Also, according to VAS scores, there was no significant difference following steroid injection between the ultrasound-guided and palpation groups (35). Compared to all these studies, we found significant improvement in VAS scores in the 3rd month in corticosteroid injections with the palpation guide method.

In a study by Raissi et al., ultrasound-guided prolotherapy and corticosteroid injection therapy used in the treatment of plantar fasciitis were compared. Compared with dextrose prolotherapy, corticosteroid injection was found to be superior at 2 weeks after injection, but results were similar outcomes at 12 weeks post-injection (16). In the

current study, the corticosteroid injection was superior to the prolotherapy injection in the 12th week.

To the best of our knowledge, there are not enough articles comparing prolotherapy and corticosteroid injections for the treatment of plantar fasciitis (16). The current study has some limitations. The main limitations of this study were the small sample size and the short duration of follow-up. Also, there was no placebo control group in the present study. Therefore, further, large-scale studies are required to compare the effect of prolotherapy and corticosteroid injections on the treatment of plantar fasciitis.

CONCLUSION

Prolotherapy and corticosteroid injection treatments provide significant functional outcomes in short-term follow-up of the treatment of plantar fasciitis. Contrary to our study hypothesis, corticosteroid injection results in superior clinical healing than prolotherapy.

Ethics Committee Approval: This retrospective study was approved by the local Ethics Committee (Amasya University, 2021/134, Amasya, Turkey).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept and Design: E.Ç., S.K., M.P. Data Collection: E.Ç., S.K., M.P. Literature search: E.Ç., S.K., M.P. Analysis or Interpretation, Writing: E.Ç., S.K., M.P.

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

Financial Disclosure: The authors also decline any financial support neither from any pharmaceutical company, nor from a company that provides or produces medical instruments and materials.

REFERENCES

1. Buchbinder R. Plantar fasciitis. N Engl J Med. 2004;350(21):2159-66. doi: 10.1056/NEJMcp032745
2. Rompe JD. Plantar fasciopathy. Sports medicine and arthroscopy review. 2009;17(2):100-4. doi: 10.1097/JSA.0b013e3181a3d60e
3. Ryan MB, Wong A, Gillies J, Wong J, Taunton J. Sonographically guided intratendinous injections of hyperosmolar dextrose/lidocaine: a pilot study for the treatment of chronic plantar fasciitis. British journal of sports medicine. 2009;43(4):303-6. doi: 10.1136/bjsm.2008.050021
4. Diaz-Llopis IV, Rodriguez-Ruiz CM, Mulet-Perry S, Mondejar-Gomez FJ, Climent-Barbera JM, Cholbi-LLobel F. Randomized controlled study of the efficacy of the injection of botulinum toxin type A versus corticosteroids in chronic plantar fasciitis: results at one and six months. Clinical rehabilitation. 2012;26(7):594-606. doi: 10.1177/0269215511426159
5. Scioli MW. Platelet-rich plasma injection for proximal plantar fasciitis. Techniques in Foot & Ankle Surgery. 2011;10(1):7-10. doi:10.1097/BTF.0b013e31820b4b63
6. Jahangiri A, Moghaddam FR, Najafi S. Hypertonic dextrose versus corticosteroid local injection for the treatment of osteoarthritis in the first carpometacarpal joint: a double-blind randomized clinical trial. J Orthop Sci. 2014;19(5):737-43. doi: 10.1007/s00776-014-0587-2
7. Cole C, Seto C, Gazewood J. Plantar fasciitis: evidence-based review of diagnosis and therapy.

Am Fam Physician. 2005;72(11):2237-42. https://www.aafp.org/afp/2005/1201/p2237.html

8. League AC. Current concepts review: plantar fasciitis. Foot & ankle international. 2008;29(3):358-66. doi: 10.3113/FAI.2008.0358
9. Puttaswamaiah R, Chandran P. Degenerative plantar fasciitis: A review of current concepts. The Foot. 2007;17(1):3-9. doi:10.1016/j.foot.2006.07.005
10. Crawford R. Diagnosis and treatment of plantar fasciitis. Am Fam Physician. 2011;84(6):676-82. https://www.aafp.org/afp/2011/0915/afp20110915p676.pdf
11. Yildiz Y, Apaydin AH, Seven MM, Orscelik A. The effects of prolotherapy (hypertonic dextrose) in recreational athletes with patellofemoral pain syndrome. Journal of Experimental & Integrative Medicine. 2016;6(2). doi: 10.5455/jeim.210616.or.152
12. Bae G, Kim S, Lee S, Lee WY, Lim Y. Prolotherapy for the patients with chronic musculoskeletal pain: systematic review and meta-analysis. Anesthesia and Pain Medicine. 2021;16(1):81. doi: 10.17085/apm.20078
13. Lai W-F, Yoon CH, Chiang MT, Hong Y-H, Chen H-C, Song W, et al. The effectiveness of dextrose prolotherapy in plantar fasciitis: A systemic review and meta-analysis. Medicine. 2021;100(51). doi: 10.1097/MD.0000000000028216
14. Jensen KT, Rabago DP, Best TM, Patterson JJ, Vanderby Jr R. Early inflammatory response of knee ligaments to prolotherapy in a rat model. J Orthop Res. 2008;26(6):816-23. doi: 10.1002/jor.20600
15. Rabago D, Best TM, Beamsley M, Patterson J. A systematic review of prolotherapy for chronic musculoskeletal pain. Clin J Sport Med. 2005;15(5):E376. doi: 10.1097/01.jsm.0000173268.05318.a4
16. Raissi G, Arbabi A, Rafiei M, Forogh B, Babaei-Ghazani A, Khalifeh Soltani S, et al. Ultrasound-guided injection of dextrose versus corticosteroid in chronic plantar fasciitis management: a randomized, double-blind clinical trial. Foot & Ankle Specialist. 2021:1938640020980924. doi: 10.1177/1938640020980924
17. Budiman-Mak E, Conrad KJ, Roach KE. The Foot Function Index: a measure of foot pain and disability. J Clin Epidemiol. 1991;44(6):561-70. doi: 10.1016/0895-4356(91)90220-4
18. Akpancar S, Seven MM, Tuzun HY, Gurer L, Ekinci S. Current concepts of prolotherapy in orthopedic surgery. Arch Trauma Res. 2017;6(2):e40447. doi: 10.5812/atr.40447
19. Rabago D. Slattengren A. Zgierska A. Prolotherapy in primary care. Primary Care Clin Office Pract. 2010;37:69-80. doi: 10.1016/j.pop.2009.09.013.
20. Healey K, Chen K. Plantar fasciitis: current diagnostic modalities and treatments. Clin Podiatr Med Surg. 2010;27(3):369-80. doi: 10.1016/j.cpm.2010.03.002
21. Liu YK, Tipton CM, Matches RD, Bedford TG, Maynard JA, Walmer HC. An in-situ study of a sclerosing solution in rabbit medial collateral ligaments and its junction strength. Connect Tissue Res. 1983;11(2-3):95-102. doi: 10.3109/03008208309004846

22. Rabago D, Slattengren A, Zgierska A. Prolotherapy in primary care practice. Primary Care: Clinics in Office Practice. 2010;37(1):65-80. doi: 10.1016/j.pop.2009.09.013

23. Distel LM, Best TM. Prolotherapy: a clinical review of its role in treating chronic musculoskeletal pain. PM&R. 2011;3:S78-S81. doi: 10.1016/j.pmrj.2011.04.003

24. Kim E, Lee JH. Autologous platelet-rich plasma versus dextrose prolotherapy for the treatment of chronic recalcitrant plantar fasciitis. PM&R. 2014;6(2):152-8. doi: 10.1016/j.pmrj.2013.07.003

25. Li Z, Xia C, Yu A, Qi B. Ultrasound-versus palpation-guided injection of corticosteroid for plantar fasciitis: a meta-analysis. PLoS One. 2014;9(3). doi: 10.1371/journal.pone.0092671

26. Kane D, Greaney T, Shanahan M, Duffy G, Bresnihan B, Gibney R, et al. The role of ultrasonography in the diagnosis and management of idiopathic plantar fasciitis. Rheumatology. 2001;40(9):1002-8. doi: 10.1093/rheumatology/40.9.1002

27. Ersen O, Koca K, Akpancar S, Seven MM, Akyildiz F, Yildiz Y, et al. A randomized-controlled trial of prolotherapy injections in the treatment of plantar fasciitis. Turkish Journal of Physical Medicine and Rehabilitation. 2018;64(1):59. doi: 10.5606/tftrd.2018.944

28. Lana J, Santana M, Belangero W, Luzo A. Platelet-rich plasma. Lecture Notes in Bioengineering, doi. 2014;10:978-3.

29. Tsai W-C, Wang C-L, Tang F-T, Hsu T-C, Hsu K-H, Wong M-K. Treatment of proximal plantar fasciitis with ultrasound-guided steroid injection. Arch Phys Med Rehabil. 2000;81(10):1416-21. doi: 10.1371/journal.pone.0092671

30. Kane D, Greaney T, Bresnihan B, Gibney R, FitzGerald O. Ultrasound guided injection of recalcitrant plantar fasciitis. Ann Rheum Dis. 1998;57(6):383-. doi: 10.1136/ard.57.6.383

31. Roberts WO. Plantar fascia injection. The Physician and sportsmedicine. 1999;27(9):101-2. doi: 10.3810/psm.1999.09.1014

32. Acevedo JI, Beskin JL. Complications of plantar fascia rupture associated with corticosteroid injection. Foot & Ankle International. 1998;19(2):91-7. doi: 10.1177/107110079801900207

33. Sellman JR. Plantar fascia rupture associated with corticosteroid injection. Foot & ankle international. 1994;15(7):376-81. doi: 10.1177/107110079401500706

34. Gidumal R, Evanski P. Calcaneal osteomyelitis following steroid injection: a case report. Foot & ankle. 1985;6(1):44-6. doi: 10.1177/107110078500600109

35. Ball EM, McKeeman HM, Patterson C, Burns J, Yau WH, Moore OA, et al. Steroid injection for inferior heel pain: a randomised controlled trial. Ann Rheum Dis. 2013;72(6):996-1002. doi: 10.1136/annrheumdis-2012-201508

36. Crawford F, Atkins D, Young P, Edwards J. Steroid injection for heel pain: evidence of short-term effectiveness. A randomized controlled trial. Rheumatology. 1999;38(10):974-7. doi: 10.1093/rheumatology/38.10.974

37. Mahindra P, Yamin M, Selhi HS, Singla S, Soni A. Chronic plantar fasciitis: effect of platelet-rich plasma, corticosteroid, and placebo. Orthopedics.

2016;39(2):e285-e9. doi: 10.3928/01477447-20160222-01

38. Shetty VD, Dhillon M, Hegde C, Jagtap P, Shetty S. A study to compare the efficacy of corticosteroid therapy with platelet-rich plasma therapy in recalcitrant plantar fasciitis: a preliminary report. Foot and Ankle Surgery. 2014;20(1):10-3. doi: 10.1016/j.fas.2013.08.002

Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci **May 2022; 8(2):258-268**

RESEARCH ARTICLE **DOI:** 10.19127/mbsjohs.1039087

Does Preoperative Vitamin D Level Effect Acute Postoperative Pain After Hip Arthroplasty Surgery

Nilay Tas[1(ID)], Ali Altınbas[2(ID)], Murat Cihan[3(ID)], Yunus Guzel[4(ID)], Tevfik Noyan[5(ID)]

[1]Ordu University, Faculty of Medicine, Department of Anesthesiology and Reanimation, Ordu, Turkey
[2]Ministry of Health-Training and Research Hospital, Department of Anesthesiology and Reanimation, Ordu, Turkey
[3]Ministry of Health-Ordu University Training and Research Hospital, Department of Biochemistry, Ordu, Turkey
[4]Inova Private Hospita, Department of Orthopaedics and Traumatology, Aksaray, Turkey
[5]Ordu University, Faculty of Medicine, Department of Biochemistry, Ordu, Turkey

Received: 20 December 2021, Accepted: 22 February 2021, Published online: 31 May 2022

Abstract

Objective: 25-OH Vitamin D is well known that has an important role in the perception of pain. Vitamin D insufficiency is important health problem all over the world. Most of the research related to vitamin D and pain is about chronic pain. In this study, it was investigated whether there is an association between Vitamin D levels and acute postoperative pain.

Methods: Preoperative Vitamin D levels were measured in patients who underwent elective hip replacement. Patients undergoing spinal anesthesia were administered patient-controlled analgesia (PCA). Patients whose pain assessment was performed with the postoperative visual analog scale (VAS), the time of initial analgesic administration, the number of analgesic needs, the number of bolus opioid use and additional NSAID use were evaluated.

Results: It has seen that a negative correlation between the vitamin D values and postoperative VAS scores. It was determined that patients with low vitamin D had earlier postoperative first analgesic administration time. It was also determined that as the vitamin D values decreased, the number of bolus opioids and total analgesic requirements used was higher.

Conclusion: In postoperative pain, low preoperative vitamin D level caused an increase in VAS scores and analgesic need and patients have low vitamin D also had earlier analgesic administration time.

Keywords: 25-OH Vitamin D, acute postoperative pain, hip arthroplasty, VAS

Suggested Citation: Tas N, Altınbas A, Cihan M, Guzel Y, Noyan T. Does preoperative Vitamin D level effect acute postoperative pain after hip arthroplasty surgery. Mid Blac Sea Journal of Health Sci, 2022;8(2):258-268.

Address for correspondence/reprints:

Nilay Taş
Telephone number: +90 (452) 225 23 44
E-mail: drnil.anest@hotmail.com

INTRODUCTION

25-Dihydroxyvitamin D3 (25-OH Vitamin D) plays an important role in the pathophysiology of critical diseases and acute stress conditions. It also has important role in defense against pathogens, immunomodulation, and skeletal muscle function (1,2). Vitamin D insufficiency is important health problem all over the world, and it has been shown that low Vitamin D levels are associated with bad consequence in hospitalized patients (3,4). Vitamin D deficiency is present in more than half of all hospitalized patients and it is associated with muscle weakness, especially much more in the proximal muscle groups (5,6). There are clinical studies on hypovitaminosis D on many systems such as the musculoskeletal system, respiratory system, and cardiovascular system, but it is seen that the number of studies on this subject is low, especially on surgical patients. Most of these studies are related to specific issues and situations such as postoperative cardiac morbidity, postoperative infection, or the period after liver transplantation (7-9). Malnutrition and vitamin deficiencies are common among geriatric patients undergoing elective orthopedic surgery and are known to be independent risk factors for postoperative side effects (10). It is well known that Vitamin D has a significant role in the perception of pain and Vitamin D deficiency is associated with higher opioid use in patients with chronic pain syndromes and cancer. Studies have found that vitamin D levels are lower than normal in patients with pain (11,12). Hip arthroplasty surgery is one of the most frequently performed surgery in orthopedics practice and postoperative pain is one of the most important factors that impair patient comfort after surgery. It's known that postoperative pain delays mobilization and recovery. In this study, we aimed to examine the effect of preoperative vitamin D values on postoperative pain levels after hip arthroplasty.

METHODS

This prospective study was approved by the local Ethics Committee (Ordu University, 2017/116-118, Ordu, TURKEY) and patient consent forms was obtained from all patients. The study included 53 patients in the ASA I-III (American Society of Anesthesiologists risk score) group over the age of 18, who will undergo elective hip replacement surgery due to coxarthrosis. The probability sampling method (simple random sample) was used. Patients that were on vitamin D treatment, who had used analgesics in the previous 24 hours, patients who could not be reached, patients that have used opioids for a long period, and those with any neuromuscular disorder were excluded from the analysis. When the patients came to the operating room, electrocardiography, pulse oximetry, and noninvasive blood pressure monitoring were performed. Venous cannulation was performed on the appropriate side of the dorsum of the hand, and a 5 ml blood sample was taken and sent to the laboratory for vitamin D measurement. Then, 0.9% isotonic NaCl infusion was started through the opened venous access. After these procedures, following appropriate field sterilization and covering, 0.5% hyperbaric bupivacaine (Marcaine Spinal Heavy) was applied to patients in a sitting position by using a 25 gauge spinal needle from the L3-4 interval; spinal anesthesia was applied with 3 mL-15 mg. The sensory block was evaluated with the pinprick test, while the motor block was evaluated with the Bromage scale (0: Can move the leg, foot, and knee easily, 1: Knee and foot

movements are normal, but cannot lift the leg straight, 2: Cannot flex the knee, 3: Cannot move the foot and knee) Surgery was allowed when the sensory block level was T10 and the Bromage scale was 3. At the end of the surgery, the PCA device prepared with tramadol HCL was attached and the loading dose was administered to the patients who were taken to the postoperative recovery unit before being sent to the room (Tramadol PCA Protocol: Loading dose 50 mg, bolus dose 20 mg, lockout time 20 minutes and basal infusion dose 10 mg/hour). VAS values were recorded by the visual analog scale at postoperative 30th minute, 1st, 2nd, 4th, 6th, 8th, 12th, and 24th hours for pain assessment. Dexketoprofen trometamol 50 mg was administered intravenously to patients with a VAS value of 4 and above during postoperative follow-up. Patients' time of first analgesic administration, the total number of analgesic needs, the number of PCA bolus opioid use, and the number of additional NSAID use were recorded. The study was completed in a double-blind manner by ensuring the patient and the researchers evaluating the pain were not aware of the vitamin D level. The primary output measurements of this study are VAS scores, vitamin D level and the total number of analgesic needs.

Sample Size and Power Analysis

At least 52 patients with low and high levels of vitamin D were calculated as an alpha value of 0.05 and power 80% (13).

Vitamin D analysis:

Cobas Vitamin D assay: 25-OH Vitamin D (electrochemiluminescence binding assay) on the Roche Cobas e601 instrument. Elecsys uses a competitive immunoassay for the detection of total vitamin D (25-OH).

Statistical Analysis

For vitamin D values, the Shapiro Wilk test was used to check normality assumption in terms of values such as demographic data, time of first analgesic administration, and the total number of analgesic needs. Differences in vitamin D values in terms of analgesic requirement time, the total number of analgesic needs, and time of first analgesic administration were evaluated using the student's t-test and Mann-Whitney U test. The Chi-Square test was used for qualitative data comparison and Pearson correlation analysis was used to evaluate data correlation. Statiscal significance level was accepted as $p<0.05$. All statistical calculations were made in SPSS 20.0 (for Windows; SPSS Inc., Chicago, IL, USA) statistics package program.

RESULTS

A total of 53 patients, 19 female, and 34 males, were included in our study. The mean age of the patients was 61.25±9.83 for women, and 59.94±10.42 for men. In Table 1, the mean age, vitamin D and PTH values of the patients participating in the study as well as the mean duration of the regional block, the duration of the surgery, and the time of first analgesic administration are shown. The mean vitamin D values of the patients were 14±67 µg / L and it was statistically significantly lower in women (12.04±4.69, p=0.004, Table 2). It was determined that the sensory block ending time was longer in male patients (p=0.027, Table 2). It was determined that female patients needed analgesic earlier than male patients (p=0.006, Table 2). Female patients had higher VAS values than men (p=0.041, p=0.035,

p=0.013, p=0.021, Table 3). Also, the total number of analgesic needs needed and the number of additional NSAID use was higher in women than men (p=0.008, P=0.007, Table 3). In our study, we determined that as the vitamin D values of the patients decreased, the sensory block ending time also shortened (p=0.000, Table 4). In addition, it was observed that there was a negative correlation between the vitamin D values of the patients and their VAS scores (p=0.000, p=0.000, p=0.000, p=0.048, p=0.000, Table 4). It was observed that patients with low vitamin D levels had earlier first analgesic administration time (p=0.001, Table 4).

Table 1. Age, Vitamin D, PTH values, durations of regional blockade, surgery and first analgesic administration time of all patients

	Mean	Std. deviation	Min.	Max.
Age (year)	**61,25**	**9,83**	**38**	**78**
Vitamin D (µg/L)	**14,67**	**5,04**	**6,43**	**25,18**
PTH (pg/ml)	**39,17**	**20,20**	**7,31**	**94,22**
Time to reach T10 of sensory block (min)	**4,26**	**1,19**	**2**	**6**
Time to reach Bromage 3 (min)	**6,75**	**1,07**	**5**	**9**
Surgery duration (min)	**57,92**	**5,41**	**50**	**75**
Sensory block end time (min)	**156,89**	**13,84**	**135**	**190**
First analgesic administration time (min)	**115,57**	**11,42**	**90**	**140**

Table 2. Age, Vitamin D, PTH values, durations of regional blockade, surgery and first analgesic administration time in female and male patients

	Female	Male	P
Age (year)	63,58 ± 8,45	59,94 ± 10,42	P>0,05
Vitamin D (µg/L)	12,04 ± 4,69	16,13 ± 4,68	P=0,004*
PTH (pg/ml)	34,51 ± 16,96	41,78 ± 21,61	P>0,05
Time to reach T10 of sensory block (min)	4,32 ± 1,10	4,24 ± 1,25	P>0,05
Time to reach Bromage 3 (min)	6,53 ± 1,02	6,88 ± 1,09	P>0,05
Surgery duration (min)	58,16 ± 5,82	57,79 ± 5,25	P>0,05
Sensory block end time (min)	151,32 ± 11,76	160,00 ± 14,08	P=0,027*
First analgesic administration time (min)	109,47 ± 12,00	118,97 ± 9,67	P=0,006*

Statiscal significance level was accepted as p<0.05

Table 3. VAS scores, total number of analgesic needs, PCA bolus opioid use and additional NSAID use in female and male patients

	Female	Male	P
Postoperative 30th min VAS score	0	0	P>0,05
Postoperative 1st hour VAS score	2	0	P=0,041*
Postoperative 2nd hour VAS score	6	5	P=0,035*
Postoperative 4th hour VAS score	4	4	P>0,05
Postoperative 6th hour VAS score	5	5	P=0,013*
Postoperative 8th hour VAS score	4	4	P>0,05
Postoperative 12th hour VAS score	3	3	P>0,05
Postoperative 24th hour VAS score	2	2	P=0,021*
Total number of analgesic needs	2	1	P=0,008*
Number of PCA bolus opioid use	1	0	P>0,05
Number of additional NSAID use	1	1	P=0,007*

Statiscal significance level was accepted as p<0.05

It was also determined in our study that as the Vitamin D values of the patients decreased, the number of bolus opioid and total analgesic requirements used was higher (p=0.000, Table 4). In our study, a statistically significant negative correlation was found between vitamin D values and VAS values at postoperative 1st and 6th hours in female patients (p=0.018, p=0.020, Table 5). In addition, as the vitamin D values increased, it was observed that the number of bolus opioid and total

analgesic needs decreased (p=0.001, p=0.025, Table 5). In male patients, a negative correlation was found between vitamin D values and postoperative VAS scores (p=0.012, p=0.001, p=0.020, p=0.001, Table 6). In addition, it was determined that as vitamin D values increased in male patients, the time of first analgesic administration was also prolonged (p=0.036, Table 6).

Table 4. Correlation of age and vitamin D values in all groups

		Sensory block end time	Postop. 1st hour VAS	Postop. 2nd hour VAS	Postop. 4th hour VAS	Postop. 6th hour VAS	Postop. 8th hour VAS	Postop. 12th hour VAS	Postop. 24th hour VAS	First analg. admin. time	Total analgesic needs	PCA bolus opioid use	Add. NSAID use
Age	r value	-0,024	0,115	0,035	-0,039	-0,165	-0,336 *	-0,003	0,054	0,125	-0,006	0,103	-0,099
	p value	>0,05	>0,05	>0,05	>0,05	>0,05	0,014 *	>0,05	>0,05	0,371	0,968	0,465	0,479
Vit D	r value	0,585 **	-0,519 **	-0,548 **	-0,22	-0,554 **	-0,273 *	-0,265	-0,567 **	0,452 **	-0,658 **	-0,579 **	-0,202
	p value	0,000	0,000	0,000	>0,05	0,000	0,048	>0,05	0,000	0,001	0,000	0,000	0,147

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

Table 5. Correlation of age and vitamin D values in female patients

		Sensory block end time	Postop. 1st hour VAS	Postop. 2nd hour VAS	Postop. 4th hour VAS	Postop. 6th hour VAS	Postop. 8th hour VAS	Postop. 12th hour VAS	Postop. 24th hour VAS	Total analgesic needs	PCA bolus opioid use
Age	r value	-0,411	0,289	0,027	0,224	-0,280	-0,119	0,175	0,082	-0,061	0,283
	p value	0,081	0,231	0,911	0,357	0,245	0,628	0,473	0,739	0,804	0,240
Vit D	r value	0,535*	-0,535*	-0,399	0,073	-0,527*	-0,252	-0,155	-0,363	-0,511*	-0,720**
	p value	0,018	0,018	0,091	0,765	0,020	0,298	0,526	0,127	0,025	0,001

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

Table 6. Correlation of age and vitamin D values in male patients

		Sensory block end time	Postop. 1st hour VAS	Postop. 2nd hour VAS	Postop. 4th hour VAS	Postop. 6th hour VAS	Postop. 8th hour VAS	Postop. 12th hour VAS	Postop. 24th hour VAS	Total analgesic needs	PCA bolus opioid use	First analg. admin. time
Age	r value	0,172	-0,025	-0,026	-0,217	-0,273	-0,509**	-0,158	-0,021	-0,101	-0,018	0,451**
	p value	0,331	0,890	0,883	0,218	0,119	0,002	0,372	0,907	0,571	0,919	0,007
Vit D	r value	0,501 **	-0,426*	-0,536 **	0,003	-0,396*	-0,112	-0,149	-0,560**	-0,719**	-0,532**	0,361*
	p value	0,003	0,012	0,001	0,988	0,020	0,528	0,399	0,001	0,000	0,001	0,036

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

DISCUSSION

Vitamin D deficiency is an important cause of concern for human health. Especially the elderly people are at high risk for deficiency (6,14). In our study, the average vitamin D values of our patients were found to be below our reference laboratory

values of 20-32 µg/L and were significantly lower in women (12.04±4.69) compared to men (16.13±4.68). Our study has resulted in a similar way in this respect with studies in the literature showing a higher rate of moderate vitamin D insufficiency in women (15-17). Low vitamin D levels in the body are known to be associated with many diseases such as osteoporosis, heart disease, and type I diabetes (18). Vitamin D has a major role in the perception of pain. Low level of Vitamin D has been associated with headache, abdominal pain, back pain, musculoskeletal pain, and fibromyalgia. Pain pathways associated with hormonal, immunological, and neuronal changes are affected by vitamin D levels (11,12,19). Inadequate treatment of postoperative pain delays patient recovery. Although the importance of effective pain control is acknowledged, 70% of patients still complain of moderate or severe pain after surgery (20). Hip arthroplasty is associated with high degree postoperative pain. Effective postoperative pain management leads to early recovery and reduces hospital stay (21,22). In our study, it was found that there was a negative correlation between the vitamin D values of our patients and the postoperative VAS scores at the 1st, 2nd, 6th, 8th, and 24th hours, and the VAS score increased as the vitamin D level decreased. The effect of gender differences on clinical pain conditions is well known. In many studies, it has been found that women have more severe pain than men and consume more morphine in the postoperative period (23,24). Female patients have a higher incidence of pain than men in terms of acute pain as well as chronic pain (25). Similarly in our study, it was seen that the female patients needed analgesic earlier than male patients, and female patients had higher VAS values than men at the 1st, 2nd, 6th, and 24th hours postoperatively. In the analysis performed in patients who underwent major surgical interventions by Kim et al., it was found that patients with low vitamin D levels had both 1.7 days more opioid use in the postoperative period compared to patients with adequate 25-OH vitamin D levels and found that they used a higher dose of analgesic equivalent to a high morphine milligram (26). There is an independent relevance between low vitamin D level and hospitalization of older adults. Nawabi et al. (27) reported that preoperative low vitamin D levels cause negative consequences after hip arthroplasty, and therefore, studies on vitamin D, which is a relatively basic and inexpensive method to correct, would be useful. In the study of Mak et al., (28) on 218 patients over 65 years with hip fracture, it was reported that the postoperative pain levels evaluated with the Verbal Rating Scale (VRS) were found to be lower in patients with high baseline levels. Also in our study, we found that patients with low vitamin D levels had higher VAS scores. In our study there was a negative correlation between the vitamin D values of our patients and their VAS scores at the postoperative 1st, 2nd, 6th, 8th, and 24th hours, and the VAS score increased as the vitamin D level decreased. In addition, the duration of the first analgesic administration was determined earlier in patients with low vitamin D levels than patients with high vitamin D levels. The study of Xu et al. conducted on 360 patients who underwent lumbar spine surgery, showed that patients with high serum vitamin D levels had better results in terms of postoperative VAS scores. Researchers stated that severe pain scores were among the significant

predictors of vitamin D deficiency (29). In our study, when we evaluated it in terms of analgesic needs, we found that as the vitamin D values of our patients decreased, the number of bolus opioid and total analgesic needs was higher. In pain management, recent findings of vitamin D-mediated prostaglandin E2 inhibition provide a reliable mechanical explanation for the role and mechanism of vitamin D in pain management (30). In the geriatric age group, musculoskeletal pain due to osteomalacia may be due to the formation of a spongy matrix beneath the periosteal membranes caused by demineralization. Expansion of this collagen matrix causes throbbing bone pain (31). Vitamin D deficiency is associated with musculoskeletal pain refractory to drugs (32). These kinds of findings are important in pain medicine because they indicate that vitamin D deficiency is potential comorbidity with pain. Chriss Wall et al. reported that there are a number of modifiable factors, such as anemia, malnutrition, and vitamin D deficiency, that increase the risk of postoperative complications following arthroplasty, and that optimizing these factors in the preoperative period may reduce the risk of adverse outcomes (33). It is known that vitamin D deficiency is observed more frequently in female patients and that there is a positive relationship between this deficiency and various nonspecific bone pain, especially in female patients (16,34). Also in our study, the vitamin D levels of our female patients were statistically significantly lower than those of men. It was also observed that female patients needed analgesic earlier than male patients. Although the total number of analgesic needs needed and the number of additional NSAID use is still not clearly explained in women compared to men, the relationship between vitamin D and pain is still not clearly explained, but it is thought that the most likely mechanism of vitamin D to reduce pain is through its anti-inflammatory effect. Adequate vitamin D levels lead to less inflammation and lower inflammatory cytokine and prostaglandin levels (30). As is known, one of the most important elements of patient comfort after surgery is undoubtedly pain reduction. In our study, there was a negative correlation between vitamin D values and postoperative VAS scores in patients who underwent hip arthroplasty, and patients with low vitamin D values were found to need analgesics earlier. There are also publications in the literature investigating the relationship between low vitamin D levels and high pain scores and reporting that there is no relationship between these two conditions. Bose et al. evaluated the relationship between vitamin D levels and the time-weighted pain scores and whole opioid usage in their analysis of the data of 185 patients with bariatric surgery but reported that they could not find a relationship between preoperative vitamin D levels and postoperative pain scores / opioid consumption in these patients (35). Lee et al. reported that as vitamin D levels decreased in patients with neuropathic pain, pain intensity increased according to the McGill pain questionnaire (MPQ) and VAS scores, and with vitamin D supplementation in both VAS and MPQ there was significant decrease in pain scores of -48.5% and -39.4%, respectively. (36). Low vitamin D level has been associated with poor outcomes, such as long-term hospital stay after hip arthroplasty surgery and measures of quality of life (37). Anna Lee et al. showed that patients with low vitamin D levels in patients who underwent knee arthroplasty had higher

postoperative pain scores. The researchers also stated that the postoperative persistent pain scores for the period 3 months after surgery were also significantly higher in patients with insufficient vitamin D levels. According to results of this study, preoperative hypovitaminosis D has been observed as a risk factor for moderate to severe persistent pain (11). Vitamin D deficiency in geriatric patients is a dominant poor factor for postoperative side effects. Meyer et al. discovered that patients with vitamin D deficiency were more likely to have poor postoperative outcomes in a study on patients who had undergone elective orthopedic surgery. Re-operation rates and hospital readmission rates were observed to be higher in these patients (10). In a study conducted by Heidari et al. (34) on 276 patients with pain in different parts of the skeletal system, found a positive relationship between non-specific pain such as leg pain, arthralgia, rib pain, and low vitamin D levels (<20 ng/ml). Larrosa et al. (38) evaluated parameters such as fracture type, comorbidities, and osteoporosis history in 324 hip fracture patients in their study, and reported that patients who received vitamin D supplements had less severe fractures in fracture grading. Again, several randomized controlled studies in the literature have shown that addition of vitamin D make better pain management and leads to a significantly lower pain score in patients with chronic pain as compared to placebo (39). The main limitation of this study is that the vitamin D levels of the patients were always measured in the same season and another limitation is that the patients VAS scores were evaluated only rest time.

CONCLUSION

In our study, low vitamin D levels in patients who underwent hip arthroplasty surgery were found to be associated with an increase in VAS score, earlier analgesic requirement, and an increase in the amount of total analgesic and bolus opioids used. Considering the frequency of hip arthroplasties in the geriatric population and that this age group is in the high-risk group for D hypovitaminosis, the importance of early diagnosis and treatment of low vitamin D levels becomes evident. It is obvious that any additional medication required for the patient's various needs during the postoperative period will result in additional costs. Considering correctable factors in the preoperative period, especially when it comes to analgesic consumption, can be considered as a safe and low-cost method to overcome these and similar problems. Given the positive effects of vitamin D on bones, muscles, and general health, we believe it is critical to conduct vitamin D screening tests at appropriate intervals determined by health policies and to supplement vitamin D care, especially for individuals in the geriatric age group.

Ethics Committee Approval: This prospective study was approved by the local Ethics Committee (Ordu University, 2017/116-118, Ordu, TURKEY).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept and Design: N.T., A.A., Y.G. Data Collection: N.T., A.A., M.C. Literature search: N.T., A.A., M.C. Analysis or Interpretation, Writing: N.T., A.A., Y.G., T.N.

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

Financial Disclosure: The authors also decline any financial support neither from any pharmaceutical

company, nor from a company that provides or produces medical instruments and materials.

REFERENCES

1. Banerjee A, Panettieri R Jr. Vitamin D modulates airway smooth muscle function in COPD. Curr Opin Pharmacol 2012; 12(3):266-74.
2. Quraishi SA, Camargo CA Jr. Vitamin D in acute stress and critical illness. Curr Opin Clin Nutr Metab Care 2012; 15(6):625-34.
3. Damera G, Fogle HW, Lim P, Goncharova EA, Zhao H, Banerjee A et al. Vitamin D inhibits growth of human airway smooth muscle cells through growth factor-induced phosphorylation of retinoblastoma protein and checkpoint kinase 1. Br J Pharmacol 2009; 158(6):1429-441.
4. Zosky GR, Berry LJ, Elliot JG, James AL, Gorman S, Hart PH. Vitamin D deficiency causes deficits in lung function and alters lung structure. Am J Respir Crit Care Med 2011; 183(10):1336-343.
5. Turan A, Hesler BD, You J, Saager L, Grady M, Komatsu R et al. The association of serum vitamin D concentration with serious complications after noncardiac surgery. Anesth Analg 2014; 119(3):603-12.
6. Janssen H, Samson MM, Verhaar JJ H. Vitamin D deficiency, muscle function, and falls in elderly people. Am J Clin Nutr 2002; 75:611–15.
7. Doi J, Moro A, Fujiki M, Eghtesad B, Quintini C, Menon KVN et al. Nutrition Support in Liver Transplantation and Postoperative Recovery: The Effects of Vitamin D Level and Vitamin D Supplementation in Liver Transplantation. Nutrients 2020 Nov 28; 12(12):3677.
8. Ney J, Heyland DK, Amrein K, Marx G, Grottke O, Choudrakis M et al. The relevance of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentration for postoperative infections and postoperative organ dysfunctions in cardiac surgery patients: The eVIDenCe study 2019 Dec; 38(6):2756-2762.
9. Quraishi SA, Bittner EA, Blum L, Hutter MM, Camargo JA Jr. Association Between Preoperative 25-Hydroxyvitamin D Level and Hospital-Acquired Infections Following Roux-en-Y Gastric Bypass Surgery. JAMA Surg 2014; 149(2):112–118.
10. Meyer M, Leiss F, Greimel F, Renkawitz T, Grifka J, Maderbacher G et al. Impact of malnutrition and vitamin deficiency in geriatric patients undergoing orthopedic surgery. Acta Orthop 2021 Feb 4; 1-6.
11. Lee A, Chan Cheong SK, Samy W, Chiu CH, Gin T. Effect of Hypovitaminosis D on Postoperative Pain Outcomes and Short-Term Health-Related Quality of Life After Knee Arthroplasty: A Cohort Study. Medicine (Baltimore) 2015 Oct; 94(42):e1812.
12. Shipton EA, Shipton EE. Vitamin D and Pain: Vitamin D and Its Role in the Aetiology and Maintenance of Chronic Pain States and Associated Comorbidities. Pain Res Treat 2015; 2015:904967.
13. Zang L, Fu P, Huang YQ, Wu M, Li L, Zang J et al. Vitamin D deficiency and carotid artery intima-media thickness and coronary calcification in patients with diabetic nephropathy. Sichuan Da Xue Xue Bao Yi Xue Ban 2012 May; 43(3):420-4, 450.

14. Holick MF, Chen TC. Vitamin D deficiency; a worlwide problem with health consequences. Am J Clin Nutr 2008; 87(4):1080S-6S.

15. Wei Q, Chen Z, Tan X, Su H, Chen X, He W et al. Relation of Age, Sex and Bone Mineral Density to Serum 25-Hydroxyvitamin D Levels in Chinese Women and Men. Orthop Surg 2015; 7(4):343-9.

16. Hovsepian S, Amini M, Aminorroaya A, Amini P, Iraj B. Prevalence of Vitamin D Deficiency among Adult Population of Isfahan City, Iran. J Health Popul Nutr 2011 ;29(2):149-55.

17. Daly RM, Gagnon C, Lu ZX, Magliano DJ, Dunstan DW, Sikaris KA et al. Prevalence of vitamin D deficiency and its determinants in Australian adults aged 25 years and older: a national, population-based study. Clin Endocrinol (Oxf) 2012; 77(1):26-35.

18. Mosekilde L. Vitamin D and the elderly. Clinical Endocrinology 2005; 62:265–28.

19. Lot A, Abdel-Nasser AM, Hamdy A, Omran AA, El-Rehany MA. Hypovitaminosis D in female patients with chronic low back pain. Clin Rheumatol 2007; 26(11):1895-901

20. Pyati S, Gan TJ. Perioperative pain management. CNS Drugs 2007; 21(3):185-211.

21. Fujino T, Odo M, Okada H, Takahashi S, Kikuchi T. Continuous pericapsular nerve group block for postoperative pain management in total hip arthroplasty: report of two cases. JA Clin Rep 2021; 7(1):22.

22. Gotz JS, Leiss F, Maderbacher G, Meyer M, Reinhard J, Zeman F et al. Implementing fast-track in total hip arthroplasty: rapid mobilization with low need for pain medication and low pain values: Retrospective analysis of 102 consecutive patients. Z Rheumatol 2021 Mar 11. doi: 10.1007/s00393-021-00978-5.

23. Pereira MP, Pogatzki-Zahn E. Gender aspects in postoperative pain. Curr Opin Anaesthesiol 2015 Oct;28(5):546-58.

24. Cepeda MS, Carr DB. Women experience more pain and require more morphine than men to achieve a similar degree of analgesia. Anesth Analg 2003; 97(5):1464-8.

25. Aasvang E, Kehlet H. Chronic postoperative pain: the case of inguinal herniorrhaphy. Br J Anaesth. 2005; 95(1):69-76.

26. Kim Y, Zhang F, Su K, LaRochelle M, Callahan M, Fisher D et al. Perioperative Serum 25-Hydroxyvitamin D Levels as a Predictor of Postoperative Opioid Use and Opioid Use Disorder: a Cohort Study. J Gen Intern Med 2020; 35(9):2545-2552

27. Nawabi DH, Chin KF, Keen RW, Haddad FS. Vitamin D deficiency in patients with osteoarthritis undergoing total hip replacement: a cause for concern? J Bone Joint Surg Br 2010; 92(4):496-9.

28. Mak JC, Klein LA, Finnegan T, Mason RS, Cameron ID. An initial loading-dose vitamin D versus placebo after hip fracture surgery: baseline characteristics of a randomized controlled trial (REVITAHIP). BMC Geriatr 2014; 14:101–9.

29. Xu HW, Shen B, Hu T, Zhao WD, Wu DS, Wang SJ. Preoperative vitamin D status and its effects on short-term clinical outcomes in lumbar spine surgery. J Orthop Sci 2020; 25(5):787-792.

30. Helde-Frankling M, Björkhem-Bergman L. Vitamin D in Pain Management. Int J Mol Sci 2017; 18(10):2170.

31. Shinchuk LM, Holick MF. Vitamin d and rehabilitation: improving functional outcomes. Nutr Clin Pract 2007; 22(3):297-304.

32. Turner MK, Hooten WM, Schmidt JE, Kerkvliet JL, Townsend CO, Bruce BK. Prevalence and clinical correlates of vitamin D inadequacy among patients with chronic pain. Pain Med 2008; 9(8):979-84.

33. Wall C, de Steiger R. Pre-operative optimisation for hip and knee arthroplasty: Minimise risk and maximise recovery. Aust J Gen Pract 2020; 49(11):710-714.

34. Heidari B, Shirvani JS, Firouzjahi A, Heidari P, Hajian-Tilaki KO. Association between nonspecific skeletal pain and vitamin D deficiency. Int J Rheum Dis 2010; 13(4):340-6.

35. Bose S, Khanna A, You J, Arora L, Qavi S, Turan A. Low serum vitamin D levels are not associated with increased postoperative pain and opioid requirements: a historical cohort study. Can J Anaesth 2015; 62(7):770-6.

36. Lee P, Chen R. Vitamin D as an analgesic for patients with type 2 diabetes and neuropathic pain. Arch Intern Med 2008; 168(7):771-2.

37. Morrison RJM, Bunn D, Gray WK, Baker PN, White C, Rangan A et al. VASO (Vitamin D and Arthroplasty Surgery Outcomes) study - supplementation of vitamin D deficiency to improve outcomes after total hip or knee replacement: study protocol for a randomised controlled feasibility trial. Trials. 2017; 18(1):514.

38. Larrosa M, Gomez A, Casado E, Moreno M, Vázquez I, Orellana C et al. Hypovitaminosis D as a risk factor of hip fracture severity. Osteoporos Int 2012; 23(2):607-14.

39. Wu Z, Malihi Z, Stewart AW, Lawes CM, Scragg R. Effect of Vitamin D Supplementation on Pain: A Systematic Review and Meta-analysis. Pain Physician 2016; 19(7):415-27.

Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci **May 2022; 8(2):269-278**

RESEARCH ARTICLE **DOI:** 10.19127/mbsjohs.1066185

Women's Feeling of Discomfort During Vaginal Examination and Related Factors

Zeynep Bal[1](ID), Tuba Ucar[1](ID) , Ezgi Can Kantar[2](ID)

[1]Inönü University, Faculty of Health Sciences, Department of Midwifery, Malatya Turkey

[2] Malatya Training and Research Hospital, Maternity and Children's Hospital, Malatya Turkey

Received:31 January 2022, Accepted: 14 April 2022, Published online: 31 May 2022

Abstract

Objective: This study aimed to identify the level of women's feeling of discomfort during the vaginal examination and associated factors.

Methods: Designed as cross-sectional research, the study was performed with 386 women who had a vaginal examination at a public hospital in Malatya province of Turkey in August-November 2018. The Personal Information Form, the Visual Analog Scale (VAS), and the Impact of Event Scale were used in the collection of research data.

Results: The mean of VAS scores was 2.86±3.52 points for the discomfort felt by participant women from the vaginal examination, and 22.8% of participant women (n=88) felt discomfort from the vaginal examination (VAS≥6 cm). Participant women who had no post-traumatic stress symptoms (79.3%), to whom the doctor made explanations during the examination (82.2%), to whom the doctor made explanations after the examination (83.3%), who found the post-examination explanation adequacy (80.2%), who were examined by the doctor (85.1%), who were examined by male health staff (86.6%), and who had the vaginal examination due to pregnancy (86.9%) felt lower levels of discomfort from the vaginal examination, and these differences from corresponding groups of participant women were statistically significant ($p<0.05$).

Conclusion: It was identified that participant women felt low-level discomfort from the vaginal examination, approximately one-fifth of them had the feeling of discomfort, and the post-traumatic stress and health staff's approaches toward the woman in the vaginal examination affected the woman's feeling of discomfort.

Keywords: Vaginal Examination, Stress, Feeling of Discomfort, Gynecology

Suggested Citation: Bal Z, Ucar T, Kantar EC. Women's feeling of discomfort during vaginal examination and related factors. Mid Blac Sea Journal of Health Sci, 2022;8(2):269-278.

Address for correspondence/reprints:
Zeynep Bal
Telephone number: +90 (506) 940 47 82
E-mail: zeynepp_ball@hotmail.com

INTRODUCTION

Vaginal examination is an important part of reproductive health services and is one of the most commonly applied procedures (1). Many women in the world experience one or more vaginal examinations throughout their lives, from youth to old age (2). Although vaginal examination takes a shorter time than many other examinations, studies have shown that most of the women do not like vaginal examination, are embarrassed and feel uncomfortable with the examination (1,3,4). Although vaginal examination takes a shorter time than many other examinations, studies have shown that most of the women do not like vaginal examination, are embarrassed and feel uncomfortable with the examination (3,4).

Among all medical interventions, vaginal examinations are one of the most common causes of anxiety and discomfort. In studies conducted on the subject, it was reported that 26% of women felt uncomfortable during the examination, 25% of them embarrassment, 23% of them stress and 20% of them anxiety (4,5). The vulnerability of private parts of the body along with the loss of control during the vaginal examination can lead to psychological disorders besides the feeling of physical discomfort (6,7). In addition, other reasons for the feeling of discomfort experienced in the vaginal examination; Lack of information about the examination, insufficient privacy, the approach of health professionals, the young age of the woman, the lack of examination experience, examination position, the gender of the examining health professional and previous negative examination experiences (4,5,8).

The feeling of discomfort experienced during a vaginal examination can cause feelings ranging from mild anxiety to high stress in women. The case in which the vaginal examination leads to stress symptoms in women as a negative experience can give rise to reluctance in women to attend vaginal examinations and cause delays or absenteeism in examinations, which has potentially harmful health effects (9,10). For this reason, analyzing the factors inducing women to have the feeling of discomfort during the vaginal examination can help women avoid having a negative experience in the vaginal examination by putting these factors under control (9). Thus, the impediments dissuading women from regularly having vaginal examinations, which are important to the protection of the woman's health, can be eliminated. In this respect, this study aimed to identify the level of the woman's feeling of discomfort during the vaginal examination and associated factors.

Research Questions

1. What is the level of the feeling of discomfort in women during the vaginal examination?

2. What are the related factors that are associated with the feeling of discomfort during the vaginal examination?

METHODS

Research Type and Sample

Designed as cross-sectional research, the study was performed with women who had a vaginal examination at polyclinics of a public hospital in Malatya province of Turkey in August-November 2018. At the hospital, there are six polyclinics, and women can apply to these polyclinics due to gynecological and obstetric reasons. According to hospital records, approximately 7550 women annually were admitted to polyclinics for vaginal examination.

The research population was composed of women who applied to polyclinics of the public hospital. In the selection of women from the population to the sample, the simple random sampling method was used. OpenEpi 3.0, an open-source statistical software, was utilized in the calculation of the sample size (http://www.openepi.com). As per the power analysis, the sample size was calculated as a minimum of 366 women with a 5% margin of error, a 95% confidence interval at the two-tailed significance level, and an 80% power. A total of 386 women who volunteered to participate in the research by filling in the informed consent form were included in the study. The criteria designated for women to be included in the research were to have no communication problem and to be aged above 18 years whereas the criteria designated for women to be excluded from the research were to have a history of any psychological disease, to have a vaginal infection, and to have an anatomical or functional disorder in reproductive organs (on grounds that these conditions were likely to raise the level of discomfort felt during the vaginal examination). Only women who applied for pregnancy and postpartum control and routine gynecological control were included in the study. The women who had vaginal bleeding and menstrual bleeding during the examination, and infertility or history of vaginismus were not included in the study.

Data Collection Tools

Researchers collected the data from women by using the face-to-face interview method. Data were collected in patient rooms when women and researchers were left alone in order to protect women's privacy and prevent women from being influenced by others. The Personal Information Form, the Visual Analog Scale, and the Impact of Event Scale were used in the collection of research data.

Personal Information Form: Researchers created this form in light of the review of the relevant literature. The form has questions addressing participant women's certain descriptive characteristics (age, education level, employment status, income level, and so on) and examination-related characteristics (whether the woman had a vaginal examination in the past, whether the doctor made any explanation about the examination to the woman before/during/after the last examination, the title and gender of the health staff who conducted the vaginal examination, and so on). In the Personal Information Form, there are five questions about descriptive characteristics and nine questions about examination-related characteristics.

Visual Analog Scale (VAS): In the research, the VAS was utilized to identify the feeling of discomfort experienced by women during the vaginal examination. The VAS is a 10 cm measure starting from 0 (not severe at all) to 10 points (unbearably severe). Across the VAS, the woman herself can tick off the level of her feeling of discomfort during the vaginal examination. When the marking on the scale is divided into two according to the score close to the 75% percentile; a score of 5 or less was defined as "no discomfort", and a score of 6 or more as "discomfort" (11).

Impact of Event Scale (IES): The IES that is utilized to evaluate traumatic stress symptoms was developed by Horowitz et al. (12). The IES has a total of 22 items, and each IES item is scored from 0 to 4. Minimum and maximum total scores to be obtained from the IES are respectively 0 and 88 points. A high IES total score shows that the respondent has high-

level stress. Besides, the cut-off point for the IES is 33, and a total IES score of 33 points or above is in support of the probable diagnosis of post-traumatic stress symptoms. Çorapçıoğlu et al. (2006) performed the validity and reliability study for the IES in Turkish, and Cronbach's alpha coefficient as the measure of internal consistency was found as 0.93 for the IES (13). In the current study, Cronbach's alpha coefficient was calculated as 0.92 for the IES.

Statistical Analysis

The data collected during the research were evaluated by using the Statistical Package for Social Science (SPSS) 20.0 for Windows. The research data were expressed as numbers, percentages, means, and standard deviations. The chi-squared test and Fisher's exact test were used in the evaluation of categorical data in statistical analysis. In the research, the statistical significance was identified if the p-value was below 0.05 ($p<0.05$).

RESULTS

The data collected from 386 participant women who were included in the research were evaluated, and the breakdown of participant women's descriptive characteristics was exhibited in Table 1. In this regard, participant women had a mean age of 30.56±8.43 years, and of all participant women, 25.4% were high school graduates, 84.2% did not work, 72.8% had incomes equaling their expenses, and 71.8% were multiparous (Table 1).

Besides, in the research, the mean of VAS scores was 2.86±3.52 points (range: 0-10 points) for the discomfort felt by participant women from the vaginal examination, and 77.2% of the participant women (n=298) felt no discomfort from the vaginal examination (VAS<6 cm) whereas 22.8% of the participant women (n=88) felt discomfort from the vaginal examination (VAS≥6 cm) (Figure 1).

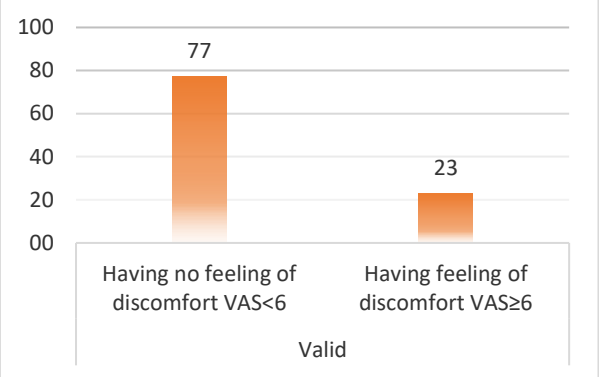

Figure1. Rate of discomfort in gynecological examination in women

Moreover, inter-group comparisons of participant women's discomfort levels during the vaginal examination as per their descriptive characteristics were indicated in Table 2. Participant women who exhibited no post-traumatic stress symptoms (79.3%) felt a lower level of discomfort from the vaginal examination than those who had post-traumatic stress symptoms, and the difference between the two groups was statistically significant ($p<0.05$).

Tablo 1. Distribution of introductory characteristics of women (n=386)

Variables	**n**	**%**
Age (year) (Ort ± SS) 30.56 ± 8.43		
Education level		
Primary school	104	26.9
Secondary school	93	24.1
High school	98	25.4
University	91	23.6
Occupational status		
Working	61	15.8
Not working	325	84.2
Income level		
Low	41	10.6
Moderate	281	72.8
Good	64	16.6
Parite		
Nullipar	35	9.1
Primipar	74	19.1
Multipar	277	71.8

SS: Standart Sapma

Tablo 2. Comparison of discomfort during gynecological examination according to the introductory characteristics of women (n=386)

Variables	Having no feeling of discomfort (VAS < 6 cm)	Having feeling of discomfort (VAS ≥ 6 cm)	Test and p value
Age (year)			
≤ 35	220 (74.8)	74 (25.2)	χ^2=3.944
> 35	78 (84.8)	14 (15.2)	p=0.051
Education level			
Primary school	85 (81.7)	19 (18.3)	χ^2=2.968
Secondary school	67 (72.0)	26 (28.0)	p=0.397
High school	74 (75.5)	24 (24.5)	
University	72 (79.1)	19 (20.9)	
Occupational status			
Working	47 (77.0)	14 (23.0)	χ^2=0.001
Not working	251 (77.2)	74 (22.8)	p=0.975
Income level			
Low	33 (80.5)	8 (19.5)	χ^2=0.651
Moderate	214 (76.2)	67 (23.8)	p=0.722
Good	51 (79.7)	13 (20.3)	
Parite			
Nullipar	33 (94.3)	2 (5.7)	χ^2=6.456
Primipar	55 (74.3)	19 (25.7)	p=0.051
Multipar	210 (75.8)	67 (24.2)	
PTSB			
Yes	22 (57.9)	16 (42.1)	χ^2=8.927
No	276 (79.3)	72 (20.7)	**p=0.007**

Lastly, inter-group comparisons of participant women's discomfort levels during the vaginal examination as per their examination-related characteristics were exhibited in Table 3. Participant women to whom the doctor made explanations during the examination (82.2%), to whom the doctor made explanations after the examination (83.3%), who found the post-examination explanation adequacy (80.2%), who were examined by the doctor (85.1%), who were examined by male health staff (86.6%), and who had the vaginal examination due to pregnancy (86.9%) felt lower levels of discomfort from the vaginal examination, and these differences from corresponding groups of participant women were statistically significant (p<0.05).

DISCUSSION

Vaginal examination is a process that is utilized regularly to protect the woman's health and identify the woman's sexual problems; however, it triggers negative feelings in most women. In this study, we aimed to identify the level of the woman's feeling of discomfort during the vaginal examination and associated factors. In our study, it was found that participant women felt low-level discomfort from the vaginal examination (2.86±3.52 points) and approximately one-fifth of them (22.8%) had the feeling of discomfort. In previous studies, this percentage was identified as 17.9% for Danish women (14), 51% for Swiss women (15), and 68% for Palestinian women (16). In studies performed in Turkey, Erbil et al. put forward that woman experienced medium-level anxiety, embarrassment, and distress before vaginal examination (17), Gunes and Karacam found 26.3% of the women described discomfort during vaginal examinations (9), and Demiray et al. asserted that women had mild anxiety in association with the examination, and 15% of the women felt uneasy and 21.7% of the women felt embarrassment and distress during the examination (18). In light of these findings, it can be said that women had negative feelings during the examination even if they felt different levels of discomfort.

Another reason for women to feel different levels of discomfort during the examination may be the fact that the feeling of discomfort is a subjective experience and is measured by using different measurement tools in different communities.

Tablo 3. Comparison of the discomfort during the gynecological examination according to the characteristics of the examination (n=386)

Variables	Having no feeling of discomfort (VAS < 6 cm)	Having feeling of discomfort (VAS ≥ 6 cm)	Test and p value
History of gynecological examination			
Yes	293 (76.9)	88 (23.1)	
No	5 (100)	0	χ^2=1.496* p=0.593
State of making a statement before the examination			
Yes	131 (74.4)	45 (25.6)	χ2=4.081
No	133 (82.1)	29 (17.9)	p=0.130
Partially	34 (70.8)	14 (29.2)	
Person making a statement during the examination			
Midwife	45 (57.7)	33 (42.3)	χ2=15.728
Doctor	120 (82.2)	26 (17.8)	**p<0.001**
State of making a statement after the examination			
Yes	200 (83.3)	40 (16.7)	χ2=26.144
No	38 (54.3)	32 (45.7)	**p<0.001**
Partially	60 (78.9)	16 (21.1)	
Adequacy of the explanation made after the examination			
Yes	146 (80.2)	36 (19.8)	χ2=10.963
No	82 (67.2)	40 (32.8)	**p=0.004**
Partially	70 (85.4)	12 (14.6)	
Number of previous gynecological examinations			χ2=3.743
1-5 times	109 (72.2)	42 (27.8)	p=0.154
6-10 times	51 (78.5)	14 (21.5)	
11-15 times	138 (81.2)	32 (18.8)	
Medical personnel examining			
Midwife	54 (62.8)	32 (37.2)	
Nurse	5 (26.3)	14 (73.7)	χ2=47.943
Doctor	239 (85.1)	42 (14.9)	**p<0.001**
Gender of the examining health personnel			χ2=37.385
Woman	78 (59.1)	54 (40.9)	**p<0.001**
Man	220 (86.6)	34 (13.4)	
Reason for inspection			
Pregnancy control	133 (86.9)	20 (13.1)	χ2=41.753
Gynecological reasons	131 (80.4)	32 (19.6)	**p<0.001**
Postpartum control	34 (48.6)	36 (51.4)	

VAS: Visual Analog Skala, *Fisher kesin ki-kare testi sonucu

Moreover, in our study, it was found that the title of the health staff who conducted the vaginal examination and made explanations during the examination affected levels of discomfort felt by women. In this respect, it was discerned that women to whom the doctor made explanations during vaginal examination felt a lower level of discomfort than those to whom the midwife made explanations. In the study by Erbil et al., women put forward that the doctor conducting the gynecological examination should be first of all well-informed and talented (63.8%) and should provide information (44.6%), and also, in the same study, 37.5% of women stated that they did not want anyone else, except the doctor, to be with them in the examination room during the gynecological examination (17). This finding may have been obtained due to the women's perception of firstly the doctor and then successively the midwife

and nurse as experts in the field of gynecology as indicated in our study.

Furthermore, in our study, it was identified that women to whom the doctor made explanations after the examination and who found the post-examination explanation adequacy felt lower levels of discomfort from the vaginal examination respectively than those to whom the doctor made no explanation after the examination and who found the post-examination explanation inadequacy. In the study by Demir and Yesiltepe Oskay, it was identified that 69.7% of the women expected that necessary information would be given, and explanations would be made in the gynecological examination (19). In the study by Altay and Kefeli, it was stated that among women's expectations was that the health staff would provide information (20). In the qualitative study performed by Gunes and Karacam with women who had a vaginal examination, it was discerned that women's expectations were to be treated more kindly and to obtain information about the vaginal examination (1). In the literature, it has been reported that informing women during the vaginal examination process by a health professional will reduce anxiety and fear and provide a positive experience. Having a positive communication with the woman after gynecological examination and informing the woman about the administered procedure and her health status can eliminate negative experiences to be faced by the woman during the examination (1,19).

Next, one of the factors associated with the level of discomfort felt by women in the vaginal examination is the examiner's gender. In our study, it was found that women who were examined by female health staff felt a higher level of discomfort than those examined by male health staff. In the study by Gunes and Karacam, the majority of women asserted that they wanted to be examined by a female midwife/doctor and felt higher levels of diffidence and embarrassment in examinations conducted by male health staff (1). In the study by Yanikkerem et al., it was discerned that, when women were asked about their preferences for the doctor's gender, 45.5% of the women wanted to be examined by a female doctor, 4.2% of them preferred a male doctor, and the rest of them (49.9%) did not have any particular preference (21). In the study by Szymoniak et al., 56% of the women wanted to be examined by female health staff, 37% of them wanted to be examined by male health staff, and 7% of them told that being examined either by female or by male health staff was not important at all (22). These findings differ from our study result. This may be due to the fact that the women we sampled consisted of women who only came for routine controls.

Lastly, in our study, it was identified that women who had the vaginal examination in the context of the postpartum control felt a higher level of discomfort from the vaginal examination than those having the vaginal examination due to gynecological control and pregnancy. Vaginal examination in the postpartum period is conducted after a few weeks following childbirth, and thus, for the woman, this means being re-examined at an interval of a few weeks. It is thought that, in comparison to routine controls, the vaginal examination conducted more frequently in this period may have increased the feeling of discomfort in women. As a matter of fact, the finding of the study by Esencan indicating that the rate of having routine vaginal examinations after the last

childbirth was low (19.2%) (23) is in support of this thought.

In this study, discomfort from vaginal examination was also evaluated in women with and without post-traumatic stress symptoms. It was discerned that women who felt discomfort from the vaginal examination had post-traumatic stress symptoms more than those who felt no discomfort from the vaginal examination. Swahnberg et al. stated that the feeling of discomfort during the vaginal examination was associated with traumatic stress disorder and the negative emotional state (24). Also, Hilden et al. found that women who felt discomfort during the vaginal examination later had stress symptoms and sadness (14). Along with these findings, it can be put forward that woman could have post-traumatic stress symptoms due to perceiving the vaginal examination as a traumatic experience, or women with post-traumatic stress symptoms felt higher levels of discomfort during the vaginal examination.

CONCLUSION

In this study, it was found that participant women felt low-level discomfort from the vaginal examination and approximately one-fifth of them had the feeling of discomfort. Besides, it was discerned that the participant women who had no post-traumatic stress symptoms, who found the post-examination explanation adequacy, who were examined by the doctor, to whom the doctor made explanations during the examination, who were examined by male health staff, and who had the vaginal examination due to pregnancy felt lower levels of discomfort from the vaginal examination.

Ethics Committee Approval: Ethical approval was obtained from İnönü University Health Sciences Scientific Research and Publication Ethics Committee (Decision No: 2018/3-16).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept and Design: TU, Data Collection: ZB, ECK, Literature search: TU, ZB, ECK, Analysis or Interpretation: TU, ZB, ECK, Writing: TU, ZB, ECK;

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

Financial Disclosure: The authors also decline any financial support neither from any pharmaceutical company, nor from a company that provides or produces medical instruments and materials.

REFERENCES

1. Gunes G, Karacam Z. Vaginal examination experiences of postpartum women: a qualitative study. Dokuz Eylül University Faculty of Nursing Electronic Journal 2018;11(2):87-95.
2. Erkek ZY, Ozer S. Views of mothers on vaginal examination during labor. Anatolian Journal of Nursing and Health Sciences 2020;23(1):9-16.
3. Ozbek H, Sumer H. The effect of supportive midwifery approach on the anxiety level of women who come to pelvic examination. Journal of Cumhuriyet University Institute of Health Sciences 2019;4(1):45-54.
4. Aksu S, Turgut B. Anxiety level of women before gynecological examination and affecting factors. Journal of İnönü University Vocational School of Health Services 2020;8(3):688–700.

5. Ozcan H, Dagli A, Kocak DY. Experiences of women who had gynecological examination: The case of Gümüshane. Journal of Health Academics 2020;7(3):188–195.
6. Calim SI, Ulas SC, Suluden E, Atac S, Gocer S, Yurekli ZN. Determining the gynecological examination experiences and expectations of academic women. Adnan Menderes University Faculty of Health Sciences Journal 2022;6(1):125-134.
7. Skär L, Grankvist O, Soderberg S. Factors of importance for developing a trustful patient-professional relationship when women undergo a pelvic examination. Health Care for Women International 2020;41(8):869-882.
8. Saleh N, Abu-Gariba M, Yehoshua I, Peleg, R. Barriers to implementation of a pelvic examination among family doctors in primary care clinics. Postgraduate Medicine 2018;130(3):341–347.
9. Gunes G, Karacam Z. The feeling of discomfort during vaginal examination, history of abuse and sexual abuse and post-traumatic stress disorder in women. Journal of Clinical Nursing 2017;26(15-16):2362-2371.
10. Mrayan L, Alnuaimi K, Abujilban S, Abuidhail J. Exploring Jordanian women's experience of first pelvic examation. Applied Nursing Research 2017;38(September):159–162.
11. Noble B, Clark D, Meldrum M, Have H, Seymour J, Winslow M, Paz S. The Measurement of Pain, 1945–2000, Journal of Pain and Symptom Management 2005;29(1):14-21.
12. Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: A measure of subjective stress. Psychosomatic medicine 1979; 41(3):209-218.
13. Corapcioglu A, Yargic I, Geyran P, Kocabasoglu N. The validity and reliability of Turkish version of "Impact of Event Scale-Revised" (IES-R). New Symposium Journal 2006;44(1):14–22.
14. Hilden M, Sidenius K, Langhoff-Roos J, Wijma B, Schei B. Women's experiences of the gynaecologic examination: Factors associated with discomfort, A.O.G.S. 2003; 82(11):1030−1036.
15. Neuhaus LR, Memeti E, Sch äaffer M-K, Zimmermann R, Schäaffer L. Using a wrap skirt to improve the pelvic examination experience. Acta Obstet Gynecol Scand 2016;95:534–540.
16. Hassan S, Sundby J, Husseini A, Bjertness E. Palestinian women's feelings and opinions about vaginal examinations during normal childbirth: an exploratory study. The Lancet Journal 2012;380:35.
17. Erbil N, Senkul A, Saglam Y, Ergul N. Determination of attitudes with gynecologic examination and anxiety of turkish women before gynecologic examination. International Journal of Human Sciences 2008;5(1):1-5.
18. Demiray A, Akin Korhan E, Cevik K, Khorshid L, Yucebilgin MS. Comparison of state anxiety related to gynecological examination in patients admitted to public and private institutions. Electronic Journal of Vocational Colleges 2014;4(4):122-129.
19. Demir S, Yesiltepe Oskay U. The experiences of women who have had a gynecological

examination and their expectations from the health professional. Kashed 2014;1(1):68-79.

20. Altay B, Kefeli B. Anxiety level of women who come to gynecological examination and some affecting factors. Dokuz Eylul University Faculty of Nursing Electronic Journal 2012;5(4):134–141.
21. Yanikkerem E, Ozdemir M, Bingol H, Tatar A, Karadeniz G. Women's attitudes and expectations regarding gynaecological examination. Midwifery 2009;25(5):500-508.
22. Szymoniak K, Cwiek D, Berezowska E, Branecka-Woźniak D, Dzióbek I, Malinowski W. Women's opinions regarding gynaecological examination in a hospital. Ginekol Pol 2009;80:498–502.
23. Esencan TY. Evaluation of women's attitudes and behaviors in the use of gynecological early diagnosis methods. Zeynep Kamil Medical Bulletin 2009;40(2):63-66.
24. Swahnberg K, Wijma B, Siwe K. Strong discomfort during vaginal examination: why consider a history of abuse. European Journal of Obstetrics and Gynecology and Reproductive Biology 2011;157:200–205.

Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci **May 2022; 8(2): 279-285**

RESEARCH ARTICLE **DOI:** 10.19127/mbsjohs.1095041

Uniportal VATS Pleural Biopsy: Analysis of 50 Cases Is It Safe and Effective?

Baris Hekimoglu[1](ID)

[1]Ordu University, Faculty of Medicine, Department of Thoracic Surgery, Ordu, Turkey

Received: 29 March 2022, Accepted: 16 May 2022, Published online: 31 May 2022

Abstract

Objective: Pleural effusion may occur in patients due to benign or malignant processes. This study aimed to evaluate the efficacy and safety of Uniportal Video-Assisted Thoracoscopic Surgery (VATS) operation in the diagnosis processes of patients with pleural effusion.

Methods: The data of 50 patients who underwent diagnostic Uniportal VATS pleural biopsy between November 2018 and April 2021 were retrospectively analyzed. The patients' age, gender, postoperative hospital stay, operation-related complications, and pathology results of the pleural tissues were recorded.

Results: Thirty-five (70%) cases were male, 15 (30%) were female, mean age was 52.58 ± 20.1, mean operative time was 56.1 ± 16.8 minutes, and mean postoperative hospital stay was 2.64 ± 0.89 days. 48 (96%) of the patients were operated on under general anesthesia and 2 (4%) under sedative anesthesia. All patients were operated on with the Uniportal VATS technique. The postoperative treatment process was carried out with service follow-up without requiring intensive care follow-up. Twenty-eight (56%) patients were operated on from the right and 22 (44%) patients from the left hemithorax. When the pleural biopsy results were examined, malignancy was detected in 18 (36%) patients and tuberculosis in 8 (16%). Malignancies: 6 were adenocancer metastases (2 stomachs, 2 breast, and 2 colon cancers), 5 malignant mesotheliomas, 4 epidermoid cancer metastases (2 ovarian and 1 breast and 1 malignant melanoma), 2 lung adenocarcinoma infiltration, and 1 chondrosarcoma metastasis. No postoperative complications were observed in any of the patients.

Conclusion: Uniportal VATS is an easy-to-apply, safe, effective, and rapid method for diagnosing pleural effusion.

Keywords: Minimally invasive surgery; pleural effusion; uniportal VATS

Suggested Citation: Hekimoglu B. Uniportal VATS Pleural Biopsy: Analysis of 50 Cases Is It Safe and Effective? Mid Blac Sea Journal of Health Sci, 2022;8(2): 279-285.

E-mail: drbarishekimoglu@yahoo.com

Address for correspondence/reprints:

Baris Hekimoglu
Telephone number: +90 (505) 751 06 89

INTRODUCTION

Video-Assisted Thoracoscopic Surgery (VATS) has become the most frequently applied technique in operations performed in worldwide thoracic surgery clinics. The indications of uniportal, that is, operations performed from only one incision, are gradually expanding (1). The rapid and reliable diagnosis with the Uniportal VATS method, with almost no complications, has been evaluated as an indispensable method for investigating the etiological causes of pleural effusions (2).

Many benign and malignant diseases cause pleural effusion. While pleural effusion may occur due to primary diseases of the lung and pleura, it can also be seen frequently as a result of other system malignancies and other systemic diseases (3).

This study has aimed to share the efficacy and safety of Uniportal VATS pleural biopsy operation in patients with pleural effusion.

METHODS

The approval of the local ethics committee was obtained (Approval number: 2021/194). The authors confirmed compliance with the World Medical Association Declaration of Helsinki on the ethical conduct of research involving human subjects.

The data of 50 patients who underwent pleural biopsy with diagnostic Uniportal VATS operation between November 2018 and April 2021 were reviewed retrospectively. Patients' age, gender, postoperative hospital stays, operation-related complications, operation time, anesthesia type, Adenosine Deaminase (ADA) value of pleural effusion, and pleural pathology results were recorded. Preoperative thoracentesis results of all patients were exudative according to Light's criteria. Thoracentesis and pretreatment cytology findings revealed no cancer in any patient's pleural fluid.

All patients were operated on with the Uniportal VATS technique. In the operations, assistive hand tools, which are used both to take a biopsy and to control bleeding, with video-thoracoscope were used with a single incision made from the 7th-9th rib intervals. The same thoracic surgeon performed all operations. Due to advanced age and other conditions, two of the patients could not have general anesthesia, so the treatment was performed with sedation and a local anesthetic agent. The other 48 operations were performed under general anesthesia.

Statistical Analysis

Statistical analysis was performed using the "IBM SPSS Statistics for Windows Version 22.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)" program. Descriptive statistics of the study were presented with frequency and percentage for categorical variables and mean and standard deviations for numerical variables. Independent group analyses were performed using Mann-Whitney U, and a $p<0.05$ value was considered significant.

RESULTS

Of the 50 patients in the study, 35 (70%) were male, 15 (30%) were female, with a mean age of 52.58 ± 20.1 (range: 18-81). The mean age of male patients was 51.37 ± 21.8 (range: 18-81), and the mean age of female patients was 55.4 ± 19.9 (range: 35-75), but there was no statistically significant difference between the two groups.

Twenty-eight (56%) patients were operated on from the right and 22 (44%) patients from the left hemithorax. While 19 male patients had surgery on the right hemithorax and 16 on the left, 9 female

patients had surgery on the right and 6 on the left. Although effusions originating from the right hemithorax were relatively common, no statistically significant difference was found in this group comparison.

The operation of 48 patients was performed under general anesthesia. Of these, 38 (76%) were performed with single-lumen intubation and 10 (20%) double-lumen intubations. The operations of 2 patients were performed with sedation and local anesthetic application.

When the operation time was calculated as the time spent by the patient on a mechanical ventilator under intubation, it was determined as 56.1 ± 16.8 minutes (range: 35-130). In the operations of 2 patients, which lasted 110 and 130 minutes, it was observed that the pouches due to empyema were opened, and partial decortication was performed. The pathology results of these two patients were reported as benign (Table 1).

All patients were followed up in the thoracic surgery service postoperatively. There was no indication for follow-up in the intensive care unit. The mean stay in the service after the operation was determined as 2.64 ± 0.89 days (range: 2-10). No complications developed in any of the patients in the postoperative period. The 2 patients with prolonged hospitalizations lasting 9 and 10 days were the same two cases above with a prolonged operative course. It was determined that the length of hospital stay was prolonged due to the long air leak caused by partial decortication and pouches opening due to empyema (Table 1).

Table 1. General Characteristics of Patients who underwent Uniportal VATS Pleural Biopsy Operation

	Mean or N(%)
Gender	
Male	35 (70%)
Female	15 (30%)
Age	52.5
Male	51.4
Female	55.4
Operation Side	
Right	28 (56%)
Left	22 (44%)
Operation Time (min.)	56.1
Type of Anesthesia	
Single-lumen Intubation	38 (76%)
Double-lumen Intubation	10 (20%)
Non-entubated VATS	2 (4%)
Type of Surgery	
Uniportal (single incision)	50 (100%)
Bi/Triportal	0
Postoperative Complication	0
Postoperative follow-up (day)	2.64

There was no patient with a suspected or definite diagnosis of malignancy in the cytology examinations performed before the surgery. Diagnostic surgery indications of all patients were determined regarding exudative fluids (suspicion of malignancy, suspicion of Tuberculosis-Tbc, additional malignant disease, etc.) that did not resolve despite conventional antibiotic therapy. Pathological examination revealed 32 (64%) benign and 18 (36%) malignant cases. When the benign pathology results of the patients were examined; chronic nonspecific pleuritis 22 (44%) (2 cases due to empyema), tuberculous pleuritis 6 (12%), granulomatous inflammation compatible with tuberculosis 2 (4%) (total number of cases referred to tuberculosis treatment 8) and foreign body type granulation 2 (2%) were determined as cases (sailor and miner) (Figure 1 and 2). When the malignancy results were examined, 6 (12%)

adenocarcinoma metastases (2 breast, 2 stomachs, and 2 colon cancers), 5 (10%) malignant mesotheliomas, 4 (8%) epidermoid cancer metastases (2 ovarian cancer and 1 breast and 1 malignant melanoma) metastasis), 2 (4%) lung adenocarcinoma infiltration and 1 (2%) sarcoma metastasis (Table 2).

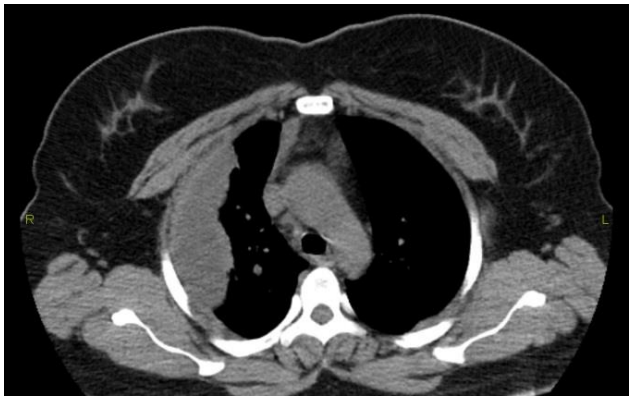

Figure 1. Thorax CT image of a 21-year-old female patient diagnosed with tuberculous pleuritis with the Uniportal VATS.

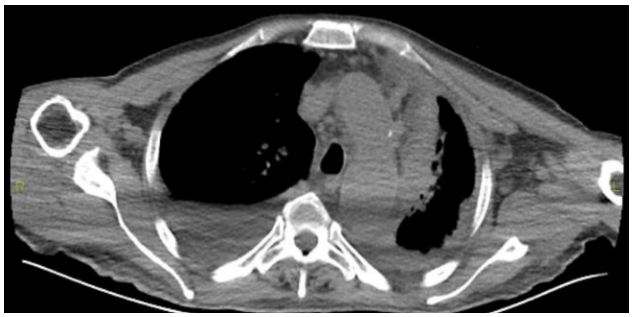

Figure 2. Thorax CT image of a 74-year-old male patient diagnosed with Primary Lung Adenocancer Infiltration with the Uniportal VATS.

In our study, tuberculosis was diagnosed in 8 patients as a result of postoperative pathology, and anti-Tbc treatment was given by this way. None of the tuberculosis diagnosed patients had preoperative ADA results. When the cut-off value for the ADA examination was taken as 40 U/L (the reference value of the working center), it was noted that 3 patients were found to be below this value and negative with an average of 23 U/L (18, 24, 27 U/L).The other 5 patients were considered positive with a mean value of 54.2 U/L (40, 42, 50, 61, 78 U/L). In summary, ADA positivity was also present in 5 of 8 patients diagnosed with tuberculosis and confirming the diagnosis.

Except for 1 patient who was diagnosed with malignant melanoma metastasis, all patients diagnosed with metastatic cancer were diagnosed with primary organ cancer such as colon, stomach, breast, etc., except lung. The case of malignant melanoma was diagnosed as a new diagnosis as a result of our operation. Patients diagnosed with malignant mesothelioma and lung adenocancer infiltration were also diagnosed after our operation. Intraoperative pleurodesis with sterile talc was performed on patients diagnosed with malignancy due to the evaluation of the biopsy taken during the operation with frozen section or who were suspected of having severe malignancy due to anamnesis and macroscopic findings.

When these pathological results were examined, the correct diagnosis rate was 100% in benign and malignant disease groups. We would like to state that no recurrence or malignancy was detected in the first 6 months of follow-up of the last benign case.

DISCUSSION

The etiology of pleural effusion is the most common indication for VATS operation (2). Thoracentesis and closed pleural biopsy performed in diagnosing patients with pleural effusion have a low diagnostic value and a higher complication rate than VATS (1,2). VATS has been defined as a minimally invasive surgical procedure that provides an early diagnosis of pleural effusion (4). Moreover, Uniportal VATS is a primary diagnostic method, especially in terms of etiological investigation of pleural effusion,

because it can be diagnosed quickly, reliably, and clearly without causing complications (2).

Table 2. Uniportal VATS Pleural Biopsy Results

Benign	N	Malignant	N
Chronic Nonspecific Pleuritis	22	Metastasis of Adenocancer	6
Tuberculous Pleuritis	8	Malignant Mesothelioma	5
Foreign Body Type Granulation	2	Metastasis of Epidermoid Cancer	4
		Primary Lung Adenocancer Infiltration	2
		Metastasis of Sarcoma	1
Total	32	**Total**	18

In the study of Kurkcuoglu et al., the diagnostic success rate of VATS was found to be 97.9% (4). In the study of Buyukkarabacak et al. on pleural effusions with a single port VATS approach, an accuracy of 100% was found in the malignancy group (5). Confirming the above studies, we found the correct diagnosis rate to be 100% in pleural biopsies performed with Uniportal VATS. Therefore, we think that Uniportal VATS is an extremely effective method for diagnostic pleural biopsy.

Postoperative hemorrhage, prolonged air leakage due to lung parenchymal injury, and other complications in pleural biopsy surgeries performed with the Uniportal VATS method have become rare conditions due to developing camera technologies and assistive hand tools (1). In our study, no postoperative complications were observed in any patients. We observed that the reliability of Uniportal VATS against complications is high.

In parallel with the increase in uniportal minimally invasive surgical methods used in other surgical branches, uniportal VATS is rapidly becoming widespread in thoracic surgery (1). It has been reported that the Uniportal VATS procedure, performed with only one incision to be used for tube thoracostomy, is less invasive, less painful, performed in a shorter time, and has a shorter postoperative hospital stay compared to the conventional VATS procedure performed through three separate ports (1,2,5,6). In addition, the Uniportal VATS application can be easily performed by a single thoracic surgeon, unlike the classical 3-port VATS application. In our study, it was seen that the operation time of the patients was as short as 56.1 minutes on average, they stayed in the hospital for an

average of 2.64 days after the operation, and all patients could be followed directly in the service without the need for the intensive care unit after the operation. They could be discharged from the hospital without complications.

When the literature is evaluated in terms of the pathology results of the pleural tissue obtained during the operation, it is seen that there are series with quite different weights for the rates of benign and malignant diseases. It has been published in different series that a varying range of malignancies was detected with a rate of 15-53% (4,5,8,9). In our study, malignant pleural tissue results were encountered with 36%. There may be many reasons for the different malignancy rates in these studies. The differences in the regions where the studies were conducted, for example, in regions where mesothelioma is more common, it is possible that malignancy will be detected more frequently. In addition, even if the initial fluid biochemistry is exudative as a result of the preoperative evaluation, patients who do not find any evidence of malignancy in the beginning patient evaluation can be followed up under medical treatment. Thus, the probability of possible benign patients diagnosed with non-VATS methods will increase. Therefore, we believe that the differences in the centers where the studies were conducted, clinical experience, and approach may result in the different malignancy rates summarized above.

Tuberculosis, one of the causes of pleural effusion, is an ongoing health problem in our country (10). Radiologically, it may present with classical cavitation findings and pleural effusion alone (3,4). In different studies, tuberculous pleuritis has been reported with 5.7-17% (4,5,8,11). In our study, the rate of tuberculosis pleuritis was 16%, and this result was found at a similar rate to the studies in our country. Six of the eight patients with tuberculosis in our study were under 35. In the light of this data, we think that the possibility of tuberculosis should be evaluated more carefully in pleural effusions seen in young adults.

Study Limitation

The fact that the study was conducted retrospectively in a single center and the small number of cases are limiting the study.

CONCLUSION

We think that the Uniportal VATS procedure, a minimally invasive surgical method, is an easy-to-apply, safe, effective, and fast-response operation for diagnosing pleural effusion.

Ethics Committee Approval: The study was approved by the decision of Ordu University Clinical Research Ethics Committee dated 26/08/2021 with the decision number 194.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: B H , Design: B H, Literature search: B H

Data Collection and Processing: B H, Analysis or Interpretation: B H, Writing: B H

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

Financial Disclosure: The authors also decline any financial support neither from any pharmaceutical company, nor from a company that provides or produces medical instruments and materials.

REFERENCES

1. Gonzalez-Rivas D, Yang Y, Ng C. Advances in Uniportal Video-Assisted Thoracoscopic Surgery: Pushing the Envelope. Thorac Surg Clin. 2016;26:187-201. Doi: 10.1016/j.thorsurg.2015.12.007.
2. Hashimoto M, Sato A, Kuroda A, Nakamura A, Nakamichi T, Kondo N, et al. Clinical Feature of Diagnostic Challenging Cases for Pleural Biopsy in Patient with Malignant Pleural Mesothelioma. Gen Thorac Cardiovasc Surg. 2020;68:820-827. Doi: 10.1007/s11748-020-01295-5.
3. Atalay F, Ernam D, Atikcan S. Lung Cancer and Pleural Effusion. Respiratory Diseases. 2001; 12: 274-78.
4. Kurkcuoglu C, Karaoglanoglu N, Eroglu A,Unlu M. Videothoracoscopy for pleural effusion: A review of 47 cases. Turk Gogus Kalp Dama. 2000;8:712-4.
5. Buyukkarabacak YB, Sengul AT, Celik B, Pirzirenli MG, Surucu P, Gurz S, et al. The effectiveness of single port thoracoscopic approach in pleural effusions. Dicle Med J. 2014; 41: 738-742.
6. Alar T, Ozcelik C. Single-incision Thoracoscopic Surgery of Pleural Effusions for Diagnostic and Treatment. Surg Endosc 2013;27:4333-6.
7. Boutin C, Astroul P, Seitz B. The Role Of Thoracoscopy in the Evaluation and Management of Pleural Effusion. Lung. 1990;168:1113-21.
8. Eren S, Balci EA, Ulku R, Esme H, Eren MN. Role of Video-Assisted Thoracoscopic Surgery (VATS) in Pleural Effusions. Tuberk Toraks. 2002;50:53-8.
9. Dumanli A, Oz G. Vats Plevra Biopsy Experiences: Analysis Of 35 Cases. Med J SDU.2020;27:261-6. Doi: 10.17343/sdutfd.565162.
10. Yilmaz S, Daharli KE. Evaluation of tuberculosis cases followed in Erzurum tuberculosis dispensary between 2012-2018 . Turk J Public Health. 2021;19:106-115.
11. Tuluce K, Sevilgen G. Effectiveness of VATS in Pleural Diseases. Med J SDU 2021;28:269-74. Doi: 10.17343/sdutfd.837596

Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci **May 2022; 8(2): 286-296**

RESEARCH ARTICLE **DOI:** 10.19127/mbsjohs.1068103

The Relationship Between Women's Birth Beliefs and Their Depression, Anxiety, Stress, and Pregnancy Avoidance

Sumeyye Barut[1](ID), Esra Guney[2](ID), Tuba Ucar[3](ID)

[1]Fırat University, Faculty of Health Sciences, Department of Midwifery, Elazığ, Turkey
[2]İnönü University, Faculty of Health Sciences, Department of Midwifery, Malatya, Turkey
[3]İnönü University, Faculty of Health Sciences Department of Midwifery, Malatya, Turkey

Received:06 February 2022, Accepted: 22 April 2022, Published online: 31 May 2022

Abstract

Objective: This study was conducted to determine the relationship between women's birth beliefs and their depression, anxiety, stress, and pregnancy avoidance.

Methods: This web-based study was conducted in Turkey between September 2021 and October 2021. The study was completed with 619 participants. Personal Information Form, Birth Beliefs Scale (BBS), Depression Anxiety Stress Scale-Short Form (DASS), and Desire to Avoid Pregnancy (DAP) were used to collect the data.

Results: The mean scores of women in the Natural and Medical Process Birth Belief (NPBS/MPBS) were determined as NPBS 4.31±0.68, MPBS 3.65±0.69 respectively. It was determined that there was a weak positive relationship between MPBS and DASS-Depression/Anxiety/Stress, and that this relationship was statistically significant (r=0.107, r=0.081, r=0.100, respectively; $p<0.05$). That the mean MPBS scores of the women who had a low level of education and a high income and were unemployed, and the women using modern family planning methods were statistically higher ($p<0.05$).

Conclusion: In the study, it was determined that there was a positive relationship between depression, anxiety and stress levels of women who considered birth as a medical process, and that women's medical beliefs about birth affected their education and income levels, employment status and the use of modern family planning.

Keywords: Birth beliefs, Depression, Anxiety, Stress, Pregnancy Intention, Pregnancy Preferences, Woman

Suggested Citation: Barut S, Guney E, Ucar T. The Relationship between Women's Birth Beliefs and their Depression, Anxiety, Stress, and Pregnancy Avoidance. Mid Blac Sea Journal of Health Sci, 2022;8(2): 286-296.

Address for correspondence/reprints:
Sumeyye Barut

Telephone number: +09 (538) 618 88 63
E-mail: sbarut@firat.edu.tr

Note: the study was presented as an oral presentation at the "6th ASIA PACIFIC International Modern Sciences Congress"

INTRODUCTION

Although pregnancy and birth are biological and physiological processes, they may arouse the feelings of fear, excitement and happiness in women (1). Women's thoughts about birth are usually clear before pregnancy (2). Sociocultural beliefs, women's obstetric history, perception of birth, fear of birth, psychological state are some of the factors that affect women's birth beliefs. These factors are effective on the health behaviors of the individual (3). Women may consider birth as a medical or natural process (4). "Dysfunctional health beliefs" formed by the society's impact generally consist of beliefs that are idle, rigid, extreme (5). Women have a role in the transfer of health beliefs to the individual, family and society due to their roles as both "wives" and "mothers". Dysfunctional beliefs are used by women in the society in every field and affect women's attitudes towards pregnancy process from generation to generation (6).

The fact that birth is considered to be medical may affect the women's birth preferences and may lead to cesarean. Women's beliefs and attitudes towards a particular mode of delivery are strongly affected by the stories and recommendations they hear from their relatives and friends. For instance, a negative experience from a previous birth may affect a woman's choice of a particular mode of delivery for subsequent births due to the belief that negative experience may occur again (7). If there is a family history of poor obstetric outcomes, the pregnant women may also be anxious. Women turn to an alternative mode of delivery after hearing negative stories about a particular mode that raises concerns that they might have the same experience when they give birth (8). The beliefs about birth may lead to avoidance of vaginal delivery and conception, impaired sexual desire, and the feeling of guilt by causing anxiety and fear. The recommendations from healthcare professionals such as midwives and doctors greatly affect a woman's understanding and choice of a particular mode of delivery (9). Therefore, it is important to determine whether women's birth beliefs are medical or natural and to determine their effects on women's psychology and reproductive health. It is important to know the community served well and to determine the needs and effects on the subject in ensuring the effectiveness of health services. Beliefs create attitudes, and attitudes create behaviors. Therefore, the way to create behavior change in individuals is to determine and correct their beliefs.

No study examining the relationship between birth beliefs and women's psychological state and pregnancy avoidance was found in the literature. Therefore, in our study, it was aimed to determine the relationship between women's birth beliefs and their depression, anxiety, stress, and pregnancy avoidance.

METHODS

This web-based study was conducted in Turkey between September 2021 and October 2021. The data were collected using a web-based online survey through women's groups on social media (Facebook). Online data collection was used because of its many advantages such as convenience, low cost, faster data collection, and comprehensiveness (10). Women who were aged between 15 and 49 years, were sexually active, were not pregnant, could read Turkish and agreed to participate in the study were invited to the study. 848 women participated in the study. The study was completed with 619 participants by excluding

229 women who had missing data and did not meet the inclusion criteria. Before the study, ethical approval was obtained from "XXX" Non-Interventional Research Ethics Committee (Decision No: 2021/2449; Date: 21.09.2021). Voluntary consent was obtained from the participants online before answering the questionnaire forms.

Data Collection Tools

Personal Information Form, Birth Beliefs Scale (BBS), Depression Anxiety Stress Scale-Short Form (DASS), and Desire to Avoid Pregnancy (DAP)were used to collect the data.

Personal Information Form

The Personal Information Form includes a total of 13 questions created by the researchers by reviewing the literature (11). While questions 1-6 were aimed at evaluating the demographic data of women (age, education, employment status, income level, family type, place of living), questions 9-13 were for obstetric data (pregnancy status, miscarriage, giving birth, last mode of delivery, the use of family planning method).

Birth Beliefs Scale

The scale, that evaluates women's basic beliefs about birth, was developed by Preis and Benyamini in 2017 (12). Its Turkish validity and reliability study was conducted by Ahsun (4). The scale has 2 sub-dimensions evaluated as Natural Process Belief Scale (NPBS) (items 1, 2, 4, 6, 9, 10) and Medical Process Belief Scale (MPBS) (items3, 5, 7, 8, 11). The responses to the items are scored from 1 to 5 (1 - strongly disagree - 5 - strongly agree). The scores obtained from the items for each sub-dimension are added and divided by the number of sub-dimension items, and the dimension with a high mean score determines the woman's birth belief. The Cronbach's alpha reliability coefficient of the scale was determined as 0.89 for the NPBS sub-dimension and 0.86 for the MPBS sub-dimension (4). In this study, the Cronbach's alpha reliability coefficient of the scale was determined as 0.82 for the NPBS sub-dimension and 0.86 for the MPBS sub-dimension.

Depression Anxiety Stress Scale-Short Form

It is an assessment tool created by abbreviating the 42-item scale, which was developed by Lovibond and Lovibond to evaluate the depression, anxiety and stress levels of individuals (13). The Turkish validity and reliability study of the scale was conducted by Sarıçam (14). The scale has 3 sub-dimensions in the scale, including depression, anxiety and stress. The scale, which has 7 items to evaluate each sub-dimension, consists of a total of 21 items. The items of the four-point Likert scale are scored between 0 (Never) and 3 (Always). The scores obtained from the subscales are collected within themselves for the scoring of the scale, and high scores indicate an increase in symptoms in the sub-dimension. The Cronbach's alpha internal consistency coefficient of the scale was determined as 0.87 for the depression subscale, 0.85 for the anxiety subscale, and 0.81 for the stress subscale (14). In this study, the Cronbach's alpha internal consistency coefficient of the scale was determined as 0.88 for the depression subscale, 0.81 for the anxiety subscale, and 0.88 for the stress subscale.

Desire to Avoid Pregnancy

It was developed by Rocca et al. in 2019 (15). The Turkish validity and reliability study of the scale was conducted by Karataş Okyay, Güney, and Uçar in 2021 (16). The scale was developed to prospectively

measure the preference range of sexually active women for a possible future pregnancy and aimed to determine women's desire to avoid pregnancy. While the first 5 items of the fourteen-item scale are related to feelings and thoughts about the idea of becoming pregnant in the next 3 months, the remaining items are related to feelings and thoughts about having a baby next year. Items 3, 7, 9, 11, 12, 13, 14 in the scale are reverse scored. The statements of the five-point Likert-type scale are scored as 0 “strongly agree”, 1 “agree”, 2 “undecided”, 3 “disagree”, 4 “strongly disagree” according to their agreement with the items. After the reverse scored items are normalized, all items are summed up and divided by 14 to get a mean score. A high item total score indicates a high desire to avoid pregnancy. The Cronbach's alpha reliability coefficient of the scale was found to be 0.94 (16). In this study, the Cronbach's alpha internal consistency coefficient of the scale was found to be 0.94.

Collection of Research Data

The data of the study were collected using a web-based online survey through women's groups on social media (Facebook). The survey forms developed by using the Google forms application (Google LLC, Mountain View, CA, USA) was delivered to women on social media by sending an online link via an online survey link. Before filling out survey forms, the women were briefly informed about the study online.

Statistical Analysis

The statistical analyses of the data obtained from the study were performed using the SPSS 22.0 (Statistical Packet for the Social Science) program. Numerical data were shown as mean and standard deviation, the nominal data were shown as frequency and percentage. In the evaluation of numerical data, the Kolmogorov-Smirnov test was first used to determine whether the variables met the parametric test conditions. It was determined that the data met the parametric test conditions, the t-test was used for the comparison of two groups, and the One-Way ANOVA Test was used for the comparison of more than two groups. Tukey test, which is a post-hoc test, was used to determine which group caused the difference between groups. The results were evaluated at a significance level of $p<.05$.

RESULTS

The comparison of the mean scores of women of the natural process belief and medical process belief according to some descriptive characteristics is presented in Table 1. It was determined that the difference between the mean scores of the medical process belief and age, family type, place of living, pregnancy status, miscarriage/curettage status, delivery status and last mode of delivery was not statistically significant ($p>0.05$). Nevertheless, it was determined that the difference between education level and the mean scores of the medical process belief was statistically significant, that women considered birth as a medical process as the education level decreased, and that the difference within the group was between those with a university or higher education level and those with a lower than high school education ($p<0.05$, a>c). It was determined that unemployed women considered birth as a medical process compared to employed women and that the difference between the groups was statistically significant ($p<0.05$). It was determined that women with a high level of income considered

Table 1. Comparison of the mean scores of women of the Natural Process Belief and Medical Process Belief according to some descriptive characteristics (n=619)

Variables		Natural Process Belief		Medical Process Belief	
	n(%)	Mean± SD	Test	Mean± SD	Test
Age					
19-29 years	298(48.1)	4.32±0.65		3.64±0.69	
			F=0.828		F=1.091
30-39 years	212(34.2)	4.33±0.72	p=0.438	3.62±0.73	p=0.336
40 years and above	109(17.6)	4.23±0.66		3.73±0.58	
Education status					
High school below[a]	204(33.0)	4.29±0.67		3.73±0.65	
			F=2.021		F=3.481
High School[b]	167(27.0)	4.24±0.73	p=0.133	3.67±0.67	**p=0.031** a>c
University and above[c]	248(40.0)	4.37±0.65		3.56±0.72	
Employment status					
Yes	193(31.2)	4.30±0.74	t=-0.198	3.55±0.74	t=-2.446
No	426(68.8)	4.31±0.65	p=0.843	3.69±0.66	**p=0.015**
Income status					
Low[a]	90(14.5)	4.32±0.59	F=0.343	3.70±0.61	F=3.990
Medium[b]	489(79.0)	4.30±0.70	p=0.710	3.62±0.69	**p=0.019** c>b
High[c]	40(6.5)	4.39±0.56		3.92±0.69	
Family type					
Nuclear family	528(85.3)	4.31±0.68	t=-0.089	3.63±0.69	t=-1.765
Extended family	91(14.7)	4.31±0.69	p=0.929	3.77±0.66	p=0.078
Country Of Residence					
State	412(66.6)	4.31±0.70	t=0.717	3.63±0.71	t=0.476
County	207(33.4)	4.36±0.63	p=0.474	3.67±0.67	p=0.634
The state of undergoing pregnancy					
Yes	517(83.5)	4.31±0.69	t=0.396	3.65±0.69	t=0.255
			p=0.692		p=0.799
No	102(16.5)	4.28±0.64		3.63±0.66	
Miscarriage/curettage status					
Evet	186(30.0)	4.27±0.75	t=-0.817	3.70±0.68	t=1.143
Hayır	433(70.0)	4.32±0.65	p=0.414	3.63±0.69	p=0.254
The state of giving birth					
Yes	495(80.0)	4.32±0.69	t=0.761	3.66±0.70	t=1.090
No	124(20.0)	4.27±0.65	p=0.447	3.59±0.65	p=0.276
The last form of childbirth (n=495)					
Vaginal delivery					
	258(41.7)	4.34±0.63	t=0.739	3.61± 0.64	t=-1.545
Cesarean	237(38.3)	4.29±0.76	p=0.460	3.71± 0.74	p=0.123
Using family planning status					
Those who use;					
The modern method	296(47.8)	4.31±0.66		3.71±0.64	
The traditional method			F=1.189		F=3.736
	166(26.8)	4.36±0.70	p=0.305	3.53±0.76	**p=0.024** a>b
Do not use the method	157(25.4)	4.24±0.70		3.65±0.68	

Modern methods: Oral contraceptive, IUD, condom, tubal ligation, emergency contraception, injection, vasectomy, Traditional methods: Withdrawal, calendar method

Table 2. Distribution of the mean scores of women from the scales (NPBS, MPBS, DASS and DAP)

Scales	Mean± SD	Min-max points that can be obtained from the scale	Min-max scores taken from the scale
NPBS	4.31±0.68	5-25	5-25
MPBS	3.65±0.69	6-30	8-30
DASS - Depression	5.82±3.89	0-21	0-20
DASÖ - Anxiety	5.58±3.50	0-21	0-18
DASÖ - Stress	8.07±3.96	0-21	0-21
DAP	2.16±1.04	0-4	0-4

NPBS: Natural Process Belief Scale, MPBS: Medical Process Belief Scale, DASS: Depression Anxiety Stress Scale, DAP: Desire to Avoid Pregnancy

Table 3. Relationship between women's perception of natural belief and medical belief about birth and depression, anxiety, stress and pregnancy avoidance

	NPBS		MPBS	
Variables	**r**	**p**	**r**	**p**
DASS - Depression	0.013	0.751	0.107	**0.008**
DASÖ - Anxiety	-0.034	0.399	0.081	**0.044**
DASÖ - Stress	-0.005	0.903	0.100	**0.013**
DAP	-0.064	0.109	0.041	0.310

r: Pearson Correlation analysis, NPBS: Natural Process Belief Scale, MPBS: Medical Process Belief Scale, DASS: Depression Anxiety Stress Scale, DAP: Desire to Avoid Pregnancy

birth as a medical process and that the difference within the group was between those with a high level of income and those with a moderate level of income ($p<0.05$, c>b). It was determined that the difference between the use of family planning and the mean scores of the medical process belief was statistically significant, that the women using modern methods considered birth as a medical process, and that the difference within the group was between those using modern methods and those using traditional methods ($p<0.05$, a>b). It was determined that the difference between age, education level, employment status, income level, family type, place of living, pregnancy status, miscarriage/curettage status, delivery status, last mode of delivery, and the use of family planning and the mean scores of the natural process belief was not statistically significant ($p>0.05$).

The distribution of the mean scores of the women participating in the study from the scales is presented in Table 2. Accordingly, the mean scores were found to be NPBS 4.31±0.68, MPBS 3.65±0.69, DASS -Depression5.82±3.89, DASS -Anxiety 5.58±3.50, DASS -Stress 8.07±3.96 and DAP 2.16±1.04, respectively.

The relationship between women's perception of natural belief and medical belief about birth and depression, anxiety, stress and pregnancy avoidance is presented in Table 3. Accordingly, it was determined that the relationship between NPBS and DASS (depression, anxiety, stress) and DAP was not statistically significant ($p>0.05$). It was determined that there was a weak positive relationship between MPBS and DASS -Depression, DASS -Anxiety and DASS -Stress ($r=0.107$, $r=0.081$, $r=0.100$, respectively), and that this relationship was statistically significant ($p<0.05$), however, the relationship between MPBS and DAP was not statistically significant ($p>0.05$).

DISCUSSION

In this study in which women's beliefs about birth were examined, it was determined that women who had a low level of education and a high income and were unemployed and the women using modern family planning methods perceived birth as medical. Accordingly, these women who considered birth as a medical process had beliefs such as the fact that birth is dangerous and risky, it can be considered safe only by looking at past experiences, labor pain is an unnecessary discomfort and needs to be resolved pharmacologically, and it is necessary to give birth under the supervision of a medical professional due to faulty anatomy of the body, and they formed their expectations in this direction. In the literature, there are several study results that support our results or have different results. In their study, Dinç and Karataş Okyay examined the factors affecting the perception

of traumatic birth in women, it was determined that those with low education levels had higher medical beliefs about birth (17). According to the result of the qualitative study conducted by Preis et al. to determine the basic birth beliefs of women, it was determined that women with low education levels obtained higher scores in medical process beliefs (18). These results can be interpreted that the high level of education positively affects the perception of birth.

According to the result of our study, it was determined that women with a high level of income and unemployed women perceived birth as medical. Although it is possible to explain this finding as that woman with high income levels have easier access to health services, it cannot be said to be compatible with the literature. Because high income and working status are often paralleled. Indeed, in a thematic study conducted to evaluate women's birth experiences, it was determined that women with a low level of income and unemployed women wanted to give birth at home and did not prefer the hospital because they had financial difficulties (19). In a cross-sectional study conducted to determine the birth beliefs of women admitted to gynecology clinic and the related factors, women's natural and medical process beliefs were evaluated according to their demographic characteristics, and it was determined that women with a high level of income considered birth as a medical process, which supports the result of our study (2).

According to another result of our study, it was determined that women using modern family planning methods perceived birth as medical. Although there are no studies in the literature evaluating birth beliefs according to the use of family planning, the reason why women using modern methods have high medical birth beliefs may be explained that they consider birth as dangerous and risky and therefore they prefer modern methods with higher protection. In a study in the literature that supports this result, the beliefs of women who gave birth for the first time were evaluated two months after their childbirth, and it was determined that the beliefs of the women in the study that the birth was medical became stronger (18).

According to another result of our study, it was determined that women who considered birth as a natural process had a positive relationship with depression and a negative relationship with anxiety, stress and pregnancy avoidance, however, this relationship was not statistically significant. Accordingly, women who considered birth as a natural process exhibited less pregnancy avoidance behavior. The beliefs about birth in these women represent the expectations that birth should be a normal and safe process, that the female body should be designed for birth, that the woman should trust her body's ability to do it, that pain should be an essential part of childbirth, and that birth should not be intervened except when it is not necessary. It can be considered that women's positive birth experiences contributed to these beliefs. In a study, it was determined that the experience in birth showed that the beliefs were strengthened when the women met their expectations about the birth being satisfactory, natural or medical, and the moderator effect was observed in this regard (18). The World Health Organization (20), stating that increasing the positive experience of mothers at birth is related to reducing

the rates of postpartum depression, has published a global list of recommendations for increasing the positive birth experience. Accordingly, with suggestions such as supporting women during births in the hospital and taking an active role in making decisions about themselves and their birth, stress, anxiety and depression that women will experience will be reduced, their satisfaction with birth will increase, and therefore their belief in considering birth as a natural process will also increase. In a study conducted by Hildingsson, Johansson, Karlström and Fenwick (2013) in Sweden, it was determined that receiving high-quality and individualized maternity care during childbirth was associated with very high birth satisfaction (21). Furthermore, it is indicated in the literature that good care support provided by health personnel is coded as a positive birth experience in women's long-term memory, no matter how complex and difficult the birth process is during childbirth (22). It is thought that women who consider that birth is a natural process will exhibit less pregnancy avoidance behaviors since they believe in the woman's body's ability to do it rather than being a dangerous and risky process.

According to another result of our study, it was determined that women who considered birth as a medical process had a positive and significant relationship with depression, anxiety and stress, however, there was a positive and insignificant relationship with their pregnancy avoidance. When it is considered that women's experience during birth affect their natural or medical beliefs about birth, it can be said that women with negative experiences have negative birth beliefs, which is related to depression, anxiety and stress situations. In the studies, it was determined that low birth satisfaction was associated with an increase in postpartum depression (23, 24), and the risk of experiencing postpartum depression was higher in women who had an interventional delivery (25-27). It is considered that these women will exhibit pregnancy avoidance behavior and will prefer to use effective family planning methods. In the studies, it was revealed that women with a negative birth experience had a decreased desire to have more children, and the desire of these women to give birth by cesarean section increased in their subsequent pregnancies (28, 29).

Limitations of the study

The study has some limitations. One of them is that the study was conducted online. Although online studies have advantages, they also have disadvantages such as carelessness. Another limitation is that the long-term consequences of positive and negative birth experiences on next pregnancy preferences could not be evaluated.

CONCLUSION

In this study conducted to determine the relationship between women's beliefs about birth and their depression, anxiety, stress and pregnancy avoidance, it was determined that there was a positive and significant relationship between medical belief about birth in women and depression, anxiety and stress, and also, women's medical beliefs about birth were affected by education and income level, employment status and the use of modern family planning. When these results are referenced, it can be said that natural birth beliefs about birth will increase with the increase in the education level of women and their participation in business life. Both the result of the study and other reference studies suggest that the

perceptions of birth may change after an objective or subjective birth experience. Therefore, it can be said that midwives play a very important role in increasing women's positive experiences of birth and natural birth beliefs by providing good care to them, thus in whether they want their next pregnancies. Thus, it is very important to support midwives with in-service training so that they can take an active role in this field and manage depression, anxiety and stress well.

Ethics Committee Approval: Ethical approval was obtained from İnönü University Health Sciences Non-Interventional Research Ethics Committee (Decision No: 2021/2449; Date: 21.09.2021).

Author Contributions: Concept and Design: SB, TU Data Collection: SB, EG. Literature search: SB, EG. Analysis or Interpretation, Writing: SB, EG.

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

Financial Disclosure: This study was not supported by any funding.

REFERENCES

1. Vatansever Z, Okumus H. The Study of Decision Making About the Delivery Type of Pregnant Women. DEUHFED. 2013;6(2):81-87.Retrieved from: https://dergipark.org.tr/tr/pub/deuhfed/issue/46814/587060
2. Alp Yilmaz F, Durgun Ozan Y. "Women's birth beliefs and associated factors in an obstetrics clinic in the Southeastern Anatolian Region of Turkey", J Health Res. 2020;34(4):345-351. https://doi.org/10.1108/JHR-07-2019-0166
3. Cook K, Loomis C. The Impact of Choice and Control on Women's Childbirth Experiences. JPE. 2012;21(3):158–168. https://doi.org/10.1891/1058-1243.21.3.158
4. Ahsun S. Validity and Reliability Study of the Turkish Form of the Birth Beliefs Scale (thesis). Department of Obstetrics and Gynecology, Institute of Health Sciences, Izmir, Turkey, Ege Univ; 2018. Retrieved from: https://tez.yok.gov.tr/UlusalTezMerkezi/tezDetay.jsp?id=_8YmvCxeooOmaJ2bBFyDLg&no=PC68T3vWexBrnNa9zF4IEg
5. McDevitt-Petrovic O, Kirby K. Assessing the Effectiveness of Brief and Low Intensity Psychological Interventions for Medically Unexplained Symptoms and Health Anxiety: A Systematic Review of the Literature. Psychosomatic Medicine. 2020. doi: 10.5772/intechopen.93912
6. Preis H, Chen R, Eisner M, et al. Testing a biopsychosocial model of the basic birth beliefs. Birth. 2018;45(1):79-87. doi: 10.1111/birt.12313.
7. Suwanrath C, Chunuan S, Matemanosak P, et al. Why do pregnant women prefer cesarean birth? A qualitative study in a tertiary care center in Southern Thailand. BMC Pregnancy Childbirth. 2021;21(1):1-6. https://doi.org/10.1186/s12884-020-03525-3
8. Muslu A, Yanikkerem E. Turkish Form Validity and Reliability of the Childbirth Expectations and Experiences Scale. DEUHFED. 2020;13(4):231-244.
9. Haines H, Rubertsson C, Pallant JF, Hildingsson I. Womens' attitudes and beliefs of childbirth and association with birth preference: a comparison of

a Swedish and an Australian sample in mid-pregnancy. Midwifery. 2012;28(6):e850-6. doi: 10.1016/j.midw.2011.09.011.

10. J. de Winter M, Kyriakidis D, Dodou R. Happee Using crowdflower to study the relationship between self-reported violations and traffic accidents. Procedia Manuf. 2015;3:2518-2525. https://doi.org/10.1016/j.promfg.2015.07.514

11. Preis H, Gozlan M, Dan U, Benyamini Y. A quantitative investigation into women's basic beliefs about birth and planned birth choices. Midwifery. 2018;63:46-51. doi: 10.1016/j.midw.2018. 05.002.

12. Preis H, Benyamini Y. The birth beliefs scale – a new measure to assess basic beliefs about birth. J Psychosom Obstet Gynecol. [Internet] 2017;38(1):73–80. Available at: doi: 10.1080/0167482X.2016.1244180

13. Lovibond SH, Lovibond PF. Manual for the Depression Anxiety Stress Scales (2nd ed.). Sydney: Psychology Foundation; 1995.

14. 14.Sarıçam H. The psychometric properties of Turkish version of Depression Anxiety Stress Scale-21 (DASS-21) in health control and clinical samples. JCBPR. 2018;7(1):19-30. https://doi.org/10.5455/JCBPR.274847

15. Rocca C. H, Ralph L.J, Wilson M, Gould H, Foster D. G. Psychometric Evaluation of an Instrument to Measure Prospective Pregnancy Preferences: The Desire to Avoid Pregnancy Scale. Medical care. 2019;57(2):152–158. https://doi.org/10.1097/MLR.0000000000001048

16. Karataş Okyay E., Güney E, Uçar T. Turkish adaptation of the pregnancy avoidance scale: Validity and reliability study. World Woman Conference–II, Online, Azerbaijan. 11-12 February 2021. (Verbal Presentation).

17. Dinç B, Karataş Okyay E. Women's birth beliefs and affecting factors. Anatolian Journal of Health Research 2021;2(2):57-63. doi : 10.29228/anatoljhr.52200

18. Preis H, Pardo J, Peled Y, Benyamini Y. Changes in the basic birth beliefs following the first birth experience: Self-fulfilling prophecies? PLoS ONE. 2018;13(11):e0208090. https://doi.org/10.1371/journal.pone.0208090

19. Calis G, Ozsoy S.A. Birth at Home Experiences of Women: Phenomenological Study. JEUNF. 2021; 37(1): 23-38. Retrieved from https://dergipark.org.tr/tr/pub/egehemsire/issue/62035/613962

20. WHO Recommendations: Intrapartum Care for a Positive Childbirth Experience. World Health Organization; Geneva, Switzerland: 2018.

21. Hildingsson I, Johansson M, Karlström A, Fenwick J. Factors associated with a positive birth experience: An exploration of Swedish women's experiences. Int. J. Childbirth. 2013;3:153–164. doi: 10.1891/2156-5287.3.3.153

22. Stadlmayr W, Amsler F, Lemola S, Stein S, Alt M, et al. Memory of childbirth in the second year: the long-term effect of a negative birth experience and its modulation by the perceived intranatal relationship with caregivers. JPOG. 2006;27:211-224. https://doi.org/10.1080/01674820600804276

23. Graham JE, Lobel M, DeLuca RS. Anger after childbirth: An overlooked reaction to postpartum stressors. Psychol Women Q. 2002;26:222–233. https://doi.org/10.1111/1471-6402.00061

24. Bell AF, Andersson E. The birth experience and women's postnatal depression: A systematic review. Midwifery. 2016;39:112–123. doi: 10.1016/j.midw.2016.04.014

25. Smarandache A, Kim THM, Bohr Y, Tamim H. Predictors of a negative labour and birth experience based on a national survey of Canadian women. BMC Pregnancy Childbirth. 2016;16:114. doi: 10.1186/s12884-016-0903-2

26. Unsal Atan Ş, Ozturk R, Gulec Satir D, Ildan Çalim S, Karaoz Weller B, et al. Relation between mothers' types of labor, birth interventions, birth experiences and postpartum depression: A multicentre follow-up study. Sex Reprod Healthc. 2018;18:13–18. doi: 10.1016/j.srhc.2018.08.001

27. Smorti M, Ponti L, Pancetti F. A comprehensive analysis of post-partum depression risk factors: The role of socio-demographic, individual, rational, and delivery characteristics. Front. Public Health. 2019;7:295. doi: 10.3389/fpubh.2019.00295

28. Gottvall K, Waldenstrom U. Does a traumatic birth experience have an impact on future reproduction? BJOG. 2002;109:254-260. doi: 10.1111/j.1471-0528.2002.01200.x

29. Pang MW, Leung TN, Lau T.K, Hang Chung T.K. Impact of first childbirth on changes in women's preference for mofe of delivery: follow-up of a longitudinal observational study. Birth. 2008;35:121-128. doi: 10.1111/j.1523-536X.2008.00225.x

Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci **May 2022; 8(2): 297-304**

RESEARCH ARTICLE **DOI:** 10.19127/mbsjohs.1070107

Investigation of The Effect of Serum Homocysteine Level on Cognitive Functions in Multiple Sclerosis Patients

Tuba Gul[1(ID)], Musa Kazim Onar[2(ID)]

[1]Ordu University, Faculty of Medicine, Department of Department of Neurology, Ordu, Turkey

2 Ondokuz Mayis University, Faculty of Medicine, Department of Neurology, , Samsun, Turkey

Received: 08 February 2022, Accepted: 18 May 2022, Published online: 31 May 2022

Abstract

Objective: In this study, we aimed to investigate whether serum homocysteine level was higher in patients with MS, and evaluate the effect of this situation on cognitive functions. In addition, we aimed to determine whether high blood homocysteine level is associated with socio-demographic and clinical features and determine the affected cognitive functions with neuropsychological tests.

Methods: We looked at changes in the levels of vitamin B12 and folic acid associated with high levels of serum homocysteine levels. Cognitive performance, and laboratory values of 60 cases with Relapsing-remitting MS (RRMS) patient, and 30 healthy volunteers were compared. The frontal lobe activities, information processing speed, flexibility, and the ability of the calculation, as well as cognitive functions of attention and visuospatial perception and construction of complex skills were also evaluated. For these purposes, Paced Auditory Serial Addition Test (PASAT), Line Orientation Test (LOT) and Stroop Test were used.

Results: Test performance for all of the test steps were found to be defective in MS group more than the control group subjects. In addition, all steps of the test performance were found to be impaired in both patients and healthy subjects with high levels of homocysteine($p<0.001$).

Conclusion: In this study visual memory processes, visual-spatial functions, construction skills, planning, programming and executive functions were found to be significantly deteriorated and the reaction time prolonged in RRMS patients with high levels of homocysteine compared with healthy control group

Keywords: Multiple sclerosis, cognitive impairment, serum homocysteine levels

Suggested Citation: Gul T, Onar MK. Investigation of The Effect of Serum Homocysteine Level on Cognitive Functions in Multiple Sclerosis Patients. Mid Blac Sea Journal of Health Sci, 2022;8(2): 297-304.

Address for correspondence/reprints:
Tuba Gul

Telephone number: +90 (505) 313 18 72
E-mail: tglyzc@hotmail.com

INTRODUCTION

MS is a chronic inflammatory, demyelinating and neurodegenerative disease accompanied by focal demyelinating plaques and axonal degeneration that may affect cortex and deep gray matter, primarily white matter in the central nervous system (CNS) (1,2). The disease manifests itself with symptoms associated with the involved CNS region.

Impairment of memory and cognitive performance is an important problem affecting functionality in patients. This is thought to be caused not only by MS itself, but also by other underlying damage mechanisms. Studies have shown that the neurotoxic effects of homocysteine may be associated with thrombosis, central nervous system (CNS) developmental disorders and neurodegenerative diseases, psychiatric disorders such as depression and schizophrenia, and some cancers (3).

The main purpose of this study was to investigate the relationship between homocysteine levels and impaired cognitive performance in MS patients. In this context, to investigate whether blood homocysteine levels increase in MS patients and its effect on cognitive functions. Sociodemographic characteristics related to high levels of serum homocysteine, EDSS score, as well as hyper-homocysteinemia, which impaired cognitive functions and which functional brain regions are most affected by neurocognitive tests are our secondary goals. It is also aimed to investigate the changes in vitamin B12 and folic acid levels simultaneously with high blood homocysteine levels. The results obtained will provide important information on the etiology of cognitive impairment in MS patients and whether treatments to reduce homocysteine levels can be effective.

METHODS

Between January 2012 and October 2012, 61 RRMS patients admitted to the MS Outpatient Clinic of Neurology Department of Ondokuz Mayıs University Medical Faculty Hospital were included in the study. The control group consisted of 32 healthy volunteers. 2012/451 was approved by the ethics committee of Ondokuz Mayıs University Medical Faculty Hospital dated 23.02.2012 and numbered B.30.2.ODM.0.20.08 / 949.

Informed consent form was obtained from all MS cases and healthy volunteers included in the study. Patients aged between 18-55 years who were diagnosed with MS according to McDonald's criteria were included in the study. Patients with clinical features compatible with secondary progressive, primary progressive, and other demyelinating diseases, those who use drugs such as B12 and / or folic acid that may affect blood homocysteine levels, those who have a disease that may cause neuroleptic, antipsychotic, antidepressant-like drug use, and those who may use such cognitive functions. Illiteracy, patients with definite diagnosis of MS were not included in the study. During the outpatient controls, detailed neurological examination was performed. Patients who had received an attack treatment were enrolled in the remission period at least six weeks after treatment. Healthy control group was formed; Those who used drugs that could affect blood homocysteine levels such as B12 and / or folic acid, who had any disease that could affect cognitive functions, or those who could use drugs that could

affect cognitive functions, illiterate, and any known chronic diseases were excluded from the study.

Depression affects many cognitive functions such as working memory, information processing speed, learning and memory functions in MS patients (4,5). In addition, antidepressants, anticonvulsants, neuroleptics and glucorticocytoids may negatively affect cognitive performance (6).

Hamilton Depression Scale (HDRS) was applied to all MS cases. Neuropsychometric examination was performed by excluding depression in patients who had a score below seven points. After the antidepressant treatment, neuropsychometric examination was performed for individuals above seven points of HDS when they scored less than seven points of HDS. Patients using antidepressants, anticonvulsants, neuroleptics, and glucorticocytoid for these or other reasons were not included in the study because their cognitive performance could be affected.

Neurological disabilities of the patients were taken into consideration when creating a neuropsychometric battery. Patients with severe visual impairment and impaired speech function were excluded from the study.

MS patients who had normal and high homocysteine levels were compared with; Age, education level, EDSS, disease duration, vitamin B12, folate levels, PASAT, Line direction Determination Test (LDDT) and Stroop test performances. The data obtained were evaluated statistically. All data analyzed for MS patients were also examined in the healthy control group.

Pearson chi-square test and Spearman correlation analysis were applied to the parameters in the MS and healthy control groups, whether they were parametric or not. Each parameter was considered a constant variable and the effects and significance levels of the other variables were examined.

Three neurocognitive tests and EDSS scales lasting approximately one hour in total were administered to the patient and control groups. It basically measures the activities of the frontal lobe; Stroop Test, which demonstrates the ability to change perceptual set-up in line with changing demands and under a “disruptive effect,, the ability to suppress a habitual behavior pattern and to conduct unusual behavior; The Paced Auditory Serial Addition Test (PASAT), a test that measures attention, as well as information processing speed, flexibility, and computational ability, has recently been used frequently to assess cognitive abilities in MS patients; Line Perception Detection Test (BIMC), which assesses the viscospasial perception and construction skills, also called complex perceptual functions.

Stroop test considerations: The time periods during which the test steps are applied and the time differences between them and the number of errors and corrections made. On the other hand, the number of correct answers is important in LDDT and PASAT.

Determination of plasma homocysteine levels; Chromsystems Diagnostics devices and kits were studied. In the isocratic system, the fluorescence detector was measured by HPLC (high performance liquid chromatography) method and the results were obtained in µmol / L. In this method, plasma is separated from whole blood by centrifugation at 4000 rpm for 5 minutes. Precipitant is added to plasma to remove proteins. The resulting supernatant is treated by derivatization and reduction to give homocysteine.

In our study, blood samples were taken at least 12 hours after fasting. The samples were centrifuged as soon as possible after blood collection. In our study, we accepted that the limit at which cognitive influences started, that is, 10 µmol / L and higher, was high homocysteine. Plasma B12 levels below 197 pg / ml and blood folic acid levels below 4.6 ng / ml were considered low.

Statistical Analysis

If the probability of error (p) obtained as a result of statistical analysis is less than 0.05, the result was considered statistically significant, and SPSS (ver. 15.0) program was used in all statistical calculations.

Descriptive statistics of the obtained data are given in tables as mean ± standard deviation (SD), number and% value. In the normality test of numerical variables, Kolmogorov-Smirnov test was used if the number of individuals examined was> 50 and Shapiro-Wilk test was used if the number of individuals examined was <50. In the comparison of patient and control groups in terms of numerical variables showing normal distribution (parametric), hypothesis test and T test of the difference between two independent sample means were used. Mann-Whitney U test was used to compare these two groups in terms of numerical variables that do not show normal distribution (non-parametric).

In addition, Pearson chi-square test was used for parametric data and Spearman correlation analysis was used for non-parametric data in the analysis of the relationship between categorical data and disease and linear relationships between numerical variables. Homocysteine, B12 vitamin, folic acid levels, PASAT, Stroop and Line orientation tests were evaluated separately by using in-group and inter-group data. When evaluating the data, the data that corresponds to the normal distribution are expressed as mean ± standard deviation, and the frequency data are expressed as a percentage.

RESULTS

61 RRMS patients were included in the study. The control group consisted of 32 healthy volunteers. 42 of the patients were female (68.9%), 19 were male (31.1%), 22 of the controls were female (68.8%) and 10 (31.3%) were male. The mean age of the MS patients was 35.2 ± 9.53 years and the mean age of the control group was 36.1 ± 10.59 years. There was no significant difference between the groups in terms of gender and age (p = 0.992, p = 0.690). The mean disease duration was 8.3 ± 5.88 years. The mean EDSS score was 1.7 ± 1.63 (0-6). 38 (62.3%) patients were classified as 0-2, 18 (29.5%) were classified as 2.5-4, 5 (8.2%) were classified as> 4.

Homocysteine levels were significantly higher in MS patients than in the control group (p = 0.044). There was no statistically significant difference between the mean values of blood homocysteine levels in MS (50.05) and control groups (41.19) (p = 0.133).

When MS and control groups were compared with B12 vitamin and folic acid levels by logarithmic statistical analysis, no statistically significant difference was found between B12 vitamin levels (p = 0.209) and folic acid levels (p = 0.125).

PASAT test scores were significantly lower (p <0.001) in patients with high homocysteine levels than the normal group.

It was found that the BICT scores were significantly different in patients with high

homocysteine levels compared to those with normal homocysteine levels (p <0.001).

In the evaluation of data between homocysteine levels and Stroop test performances in MS patients; Card reading times and time differences were longer in MS patients with higher homocysteine levels than those with normal homocysteine levels. The number of errors and corrections was higher than the homocysteine normal group. The p values obtained for all stroop test steps were found to be less than 0.05, meaningful. There were no significant differences between the levels of serum homocysteine, age, disease duration, EDSS, educational level, and vitamin B12 levels (p> 0.05).

There was a negative correlation between homocysteine levels and vitamin B12 (r = -0.364, p = 0.004) and folic acid (r = -0.408, p = 0.001) levels. As vitamin B12 and folate levels decrease, homocysteine levels increase.

In both patients and healthy controls, the test performance was found to be impaired for all test steps in individuals with high homocysteine levels (Table 1-2).

Table 1. Comparison of the data of individuals in the healthy control group with high homocysteine levels and normal in terms of different variables and p values obtained

HEALTHY CONTROL GROUP		HOMOCYSTEINE LEVEL (µmol / l)		
		Normal Average ± ss	High Average ± ss	P Value
AGE		35.7 ± 10.83	37.5 ± 10.27	0.725
VITAMIN B12 (pg / ml)		257.2 ± 97.68	275.3 ±182.63	0.735
FOLATE (ng / ml)		9.3 ± 3.27	8.8 ± 5.05	0.247
PASAT		44.0 ± 10.49	27.0 ± 14.95	**0.002**
LDDT		27.2 ± 2.33	19.3 ± 6.25	**0.004**
STROOP TEST	1.Card time / sec	13.7 ± 3.21	24.6 ± 9.87	**0.042**
	3.Card time / sec	18.2 ± 5.53	33.8 ± 13.27	**0.013**
	5.Card time / sec	28.0 ± 11.17	64.1± 31.3	**0.005**
	5-1 Card time / sec	14.3 ± 8.64	39.5 ± 22.42	**0.005**
	5-3 Card time / sec	9.8 ± 6.36	30.3 ± 19.52	**0.005**
	5.Card correction	0.85 ± 1.08	3.0 ± 1.09	**0.001**
	5.Card error	0.15 ± 0.36	2.1 ± 0.98	**<0.001**

Table 2. Comparison of the data of MS cases with high and normal homocysteine levels in terms of different variables and p values obtained

HEALTHY CONTROL GROUP		HOMOCYSTEINE LEVEL (µmol / l)		
		Normal Average ± ss	High Average ± ss	P Value
AGE		35.7 ± 8.50	34.4 ± 11.09	0.596
DISEASE DURATION		8.7 ± 6.32	7.6 ± 5.21	0.568
VITAMIN B12 (pg / ml)		312.4 ±133.63	253.0 ± 99.12	0.098
FOLATE (ng / ml)		8.9 ± 3.61	7.1 ± 2.33	**0.036**
PASAT		36.9 ± 12.7	23.0 ± 10.64	**< 0.001**
LDDT		25.9 ± 3.12	20.4 ± 5.91	**< 0.001**
STROOP TEST	1.Card time / sec	12.7 ± 5.96	19.1 ± 9.60	**0.044**
	3.Card time / sec	19.0 ± 8.55	29.6 ± 15.38	**0.021**
	5.Card time / sec	37.0 ± 21.44	65.0 ± 39.33	**0.007**
	5-1 Card time / sec	24.3 ± 17.48	45.8 ± 30.97	**0.010**
	5-3 Card time / sec	18.0 ± 14.58	35.3 ± 25.16	**0.008**
	5.Card correction	1.7 ± 1.70	2.7 ± 1.53	**0.015**
	5.Card error	0.59 ± 1.14	1.5 ± 1.47	**0.003**

DISCUSSION

In most studies, high homocysteine levels were found to be associated with cognitive impairment in MS patients. Our study was conducted on Turkish population with similar characteristics. Different cognitive functions will be evaluated by different cognitive tests, and folic acid and B12 levels were evaluated simultaneously, which distinguishes our study from other studies.

In a study, the relationship between cognitive functions and homocysteine, vitamin B12 and folic acid levels was investigated using multiple neuropsychiatric tests. 93 MS and 53 healthy controls were taken, and there was no difference between B12 and folic acid levels between control and MS groups. It was shown that homocysteine levels were higher in MS patients compared to the control group and cognitive performance was significantly impaired in those with high homocysteine levels (Russo et al., 2008). Similarly, in our study, homocysteine levels were found to be significantly higher in MS patients compared to the control group, and test performance for all PASAT, LDDT scores, and Stroop test steps was found to be poor in individuals with high homocysteine levels.

Durga et al. and Brattstorm and Wilcken, in their critical review of studies, have stated that there is sufficient evidence supporting a relationship between white matter and homocysteine (7,8). Increased homocysteine levels disrupt the endothelial structure, causing spasm and ischemia (9,10). In another study, homocysteine has been shown to induce apoptosis in neuronal cell cultures with copper and beta amyloid-peptide-mediated toxic effects (11). It is known that the earliest and lasting disorder in the pathogenesis of MS is the structural alteration of blood brain barrier and perivenular lymphocyte accumulation (12). The role of homocysteine on neurodegenerative processes in MS can be explained by these mechanisms.

In one study, healthy elderly individuals, patients with Alzheimer's Dementia and Parkinson's, and other patients with cognitive impairment and MS patients were evaluated to investigate the effect of homocysteine in various conditions. After all; It was found that high homocysteine concentration was significantly associated with impaired cognitive performance at 6 years of follow-up in normal aging population and was higher in Parkinson's patients than in normal population. It was found that there was no significant elevation in dementia patients and higher homocysteine levels in MS patients than in the normal population. This was found to be significantly associated with impaired cognitive and motor performance. This shows us that homocysteine has a neurotoxic effect under all conditions and this effect is obvious enough to be clinically detectable (13).

In a study by Aksungar et al., It was stated that the blood homocysteine levels of MS patients were significantly higher than those of healthy individuals and serum B12 and folate levels were not correlated with homocysteine (14). Despite this study, in another study, Vrethem et al. reported that vitamin B12, folate and serum methylmalonic acid levels did not decrease in MS patients (15). There are other studies with low correlation between B12 and homocysteine ratio (16).

Despite normal B12 levels measured in serum, intracellular levels of vitamin B12 decrease as age progresses. As in this study, the normal B12 and folate levels despite homocysteine elevation may be due to a polymorphism in the MTHFR gene coding in

MS patients or due to any enzyme defect in the transsulfurization pathway. MTHFR and other regulatory enzymes in the transsulfurization pathway are required for methylenetetrahydrofolate regeneration and normal homocysteine metabolism. In our study, the absence of a correlation between homocysteine levels and vitamin B12 levels may be due to such an underlying pathology. however, the fact that we could not perform MTHFR gene analysis, and we could not determine it precisely may be a shortcoming of our study.

In a study conducted with 35 MS patients and 30 healthy controls, Kocer et al. Found that homocysteine levels were normal in the control group and high in 20% of the MS group. Vitamin B12 levels were found to be lower in MS patients with prolongation of VEP, posterior tibial SEP P1 and P2 latencies compared to MS patients with normal latency. It was stated that there was a close relationship between MS and vitamin B12 deficiency, and homocysteine elevation was due to vitamin B12 deficiency.

Last studies about reduction of plasma homocysteine levels and increase of B12 levels in impaired cognition patients, taking vitamins B6, B12, and/or folic acid supplements, at least 1 month of supplementation, findings support that reduce homocysteine levels and elevated plasma B12 levels. Thus, the cognitive impairment caused by high homocysteine levels can treated like this way as possible as (17).

Ethics Committee Approval: 2012/451 was approved by the ethics committee of Ondokuz Mayıs University Medical Faculty Hospital dated 23.02.2012 and numbered B.30.2.ODM.0.20.08 / 949.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: TG, MKO; Design: TG, MKO; Literature search: TG, MKO, Data Collection and Processing: TG, Analysis or Interpretation: TG, MKO Writing: TG, MKO

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

Financial Disclosure: The authors declared that this study has /hasn't received no financial support.

REFERENCES

1. Lassmann H, Brück W, Lucchinetti CF. The immunopathology of multipl sclerosis: an overview. Brain Pathol 2007; 17(2):210-8.
2. Trapp BD, Stys PK. Virtual hypoxia and chronic necrosis of demiyelinated axons in multipl sclerosis. Lancet Neurol 2009; 8(3):280-91.
3. Mattson MP, Kruman II, Duan W. Folic acid and homocysteine in age-related disease. Ageing Res Rev 2002; 1: 95-111. Review.
4. Chiaravalloti ND, Deluca J. Cognitive impairment in multiple sclerosis. Lancet Neurol 2008; 7(12):1139-1151.
5. Siegert RJ, Abernethy DA. Depression in multiple sclerosis: a review. J Neurol Neurosurg Psychiatry 2005 Apr;76(4):469-75.
6. Engel C, Greim B, Zettl UK. Diagnostics of cognitive dysfunctions in multiple sclerosis. J. Neurol. 2007; 254: II/30–II/34.
7. Brattstrom L, Wilcken DE. Homocysteine and cardiovascular disease: cause or effect? Am J Clin Nutr 2000;72: 315–23.
8. Durga J, Verhoef P, Bots ML, Schouten E. Homocysteine, and carotid intima-media

thickness: a critical appraisal of the evidence. Atherosclerosis 2004;176:1–19.

9. Di Minno G, Davi G, Margaglione M. Abnormally High Thromboxane Biosynthesis in Homozygous Homocystinuria. J Clin Invest 1993; 92: 1400-1406.

10. Tsai JC, Peralla MA, Yarkizumi M. Promotion of vascular smooth muscle cell growth by homocysteine a link to atherosclerosis. Proc Natl Acad Sci USA.1994; 91: 6369-6373.

11. White AR, Huang X, Jobling MF, et al. Homocysteine potentiates copper and amyloid beta peptide-mediated toxicity in primary neuronal cultures: possible risk factors in the Alzheimer's-type neurodegenerative pathways. J Neurochem 2001; 76: 1509-20.

12. Vural A, Tuncer Kurne A, Karabudak R. Immüpatholegenesis of Multiple Sclerosis Part 1: Are all the plaques the same? Ankara University Faculty of Medicine Journal. 2016;69(2):1-6.

13. Teunissen CE, van Boxtel MP, Jolles J, de Vente J, Vreeling F, et al. Homocysteine in relation to cognitive performance in pathological and non-pathological conditions. Clin Chem Lab Med 2005; 43(10):1089-95.

14. Aksungar FB, Topkaya AE, Yildiz Z, Sahin S, Turk U. Coagulation status and biochemical and inflammatory markers in multiple sclerosis. J Clin Neurosci 2008; 15: 393–397.

15. Vrethem M, Mattsson E, Hebelka H, et al. Increased plasma homocysteine levels without signs of vitamin B12 deficiency in patients with multiple sclerosis assessed by blood and cerebospinal fluid homocyteine and methylmalonic acid. Mult Scler 2003; 9: 239–45.

16. Baig SM, Qureshi G. Homocysteine and vitamin B12 in multiple sclerosis. Biogenic Amines 1995; 11: 479–85.

17. Olaso-Gonzalez, Gloria, Et Al. Impact Of Supplementation With Vitamins B6, B12, And/Or Folic Acid On The Reduction Of Homocysteine Levels İn Patients With Mild Cognitive İmpairment: A Systematic Review. Iubmb Life 2022; 74.1: 74-84.

Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci **May 2022; 8(2): 305-313**

RESEARCH ARTICLE **DOI:** 10.19127/mbsjohs.1079414

Evaluation Medicine Management of Elderly During COVID-19: Descriptive Cross-Sectional Research Study

Kazım Bas[1]

[1]Munzur University, Tunceli Vocational School, Department of Medical Services, Tunceli, Turkey

Received: 25 February 2022, Accepted:18 May 2022, Published online: 31 May 2022

Abstract

Objective: It has been reported that medication adherence and routine controls of elderly and chronic patients are important during the COVID-19 pandemic. The research was conducted to evaluate medicine management and the opinions of elderly people during the pandemic.

Methods: The research was conducted with 410 individuals, aged 65 and over, in a province in the east of Turkey, between May and August 2021. The research data were collected online using a questionnaire through Google forms. The data obtained were analyzed by using numbers and percentiles in the SPSS 24 package program.

Results: Of the individuals with an average age of 73.09±7.76 years, 52.2% was female, 22.4% was literate, 67.6% had one or more chronic diseases, and 64.6% was taking medicine continuously. Of elderly people, 42.9% had problems accessing health services during the pandemic, 29.7% had problems accessing medicines, and 44.1% has obtained his/her medicines from pharmacies through his/her children. Of elderly, 40.7% has met the need for medicines from the pharmacy during the COVID-19 process, and 56.1% reported that social support for elderly is insufficient.

Conclusion: According to the study results, most elderly people were found to have chronic diseases and take medication regularly, and experienced problems with medication management and elderly need more support during the COVID-19 pandemic.

Keywords: Covid-19, Elderly, Elderly health, Health management, Medication management.

Suggested Citation: Bas K. Evaluation of Medicine Management of Elderly During Covid-19: Descriptive Cross-Sectional Research Study. Mid Blac Sea Journal of Health Sci, 2022;8(2): 305-313.

Address for correspondence/reprints:
Kazım Baş

Telephone number: +90 (428) 213 17 94
E-mail: kbas@munzur.edu.tr

INTRODUCTION

It is observed that the elderly population is gradually increasing due to the increased longevity around the world. Aging is considered to be a public health problem, and diseases and health problems, seen in line with increasing age, negatively affect the quality of life of elderly and increase mortality rates (1,2).

Elderly individuals may use numerous medicines due to their health problems. While the average number of drugs used is 3 to 4 in the 65-70 age group, the average increases up to 3 to 6 in the 70 and older age group (3). Failure to correctly manage multidrug use during increased chronic diseases in the elderly may adversely affect treatment and cause some problems related to unwanted adverse effects of the drug (2,4,5). The new type of COVID-19 disease, which first appeared in China in 2019 and spread worldwide in 2020 as a pandemic, continues to adversely affect people's entire lives, especially their health, to this day. Along with the measures implemented to prevent the epidemic, hospitals have closed most of their wards for routine patient admission to treat patients with coronavirus. During the rapid spread of the epidemic, normal patient admissions were postponed in hospitals, and it was stated that difficulty in accessing a physician for routine treatments would pose serious problems, especially for chronic and elderly patients (6). Medication adherence and management are important in the treatment of chronic and elderly diseases (i.e. diabetes). It has been reported that individuals with COVID-19 disease have an increased chance of survival when the optimal level of medication adherence is maintained in the treatment of chronic disease. It has also been reported that increased stress during the treatment of patients, which does not receive adequate support due to the restriction/prohibition measures applied throughout the epidemic, has a negative effect on medication adherence and treatment (7,8). It has been stated that physicians can reduce the potential risks that may occur in patients taking multiple drugs by controlling prescribed drugs during the COVID-19 pandemic with effective drug management (9). This study was conducted with the aim of evaluating the opinions and medicine management of elderly during the COVID-19 pandemic.

METHODS

Study Design

This study has a cross-sectional and descriptive research design.

Study Population and Sample

The study population was consisted of elderly people aged 65 and over who were living in the central neighborhoods of a province located in the eastern Turkey. Without performing a sample selection, 410 elderly individuals, who agreed to participate voluntarily in the study and were reached between May-August 2021, constituted the sample of the study.

Data Collection

The questionnaire used in the research was developed by the researcher based on the literature (9–12). The first part of the 24-item, the two-part questionnaire consists of eight items on socio-demographic characteristics, and the second part consists of 18 items that determine the status of taking medicine and the opinions of elderly regarding drug management during the COVID-19 pandemic.

Purposive sampling method was used to reach the participants. The research data were collected online from the participants through the Google forms, using a questionnaire developed by the researcher.

Statistical Analysis

SPSS Version 24.00 for Windows (IBM, Armonk, New York, USA) was used for the statistical analysis of the study data. Obtained data were entered into the SPSS package program in a computer environment. Percentage, mean and standard deviation were used in the evaluation of the data.

RESULTS

It was determined that 52.2% of elderly people with an average age of 73.09±7.76 was female, 22.4% was illiterate, 91.5% was not working in an income-generating job, 65.2% lives with his/her spouse, and 58.4% had expenses less than the average monthly income (Table 1).

Table 1. Descriptive Characteristics of Elderly

Characteristics	N	%
Age (X±SD)	73.09±7.76 (Min=65, Max=95)	
Gender		
Female	214	52.2
Male	196	47.8
Education status		
Illiterate	33	8.0
Literate	92	22.4
Primary school	86	21.0
Secondary School	63	15.4
High school	84	20.5
Bachelor's degree and above	52	12.7
Employment status		
Working	35	8.5
Nonworking	375	91.5
Perceived average monthly income		
Lower than expenses	229	55.8
Balanced	150	36.6
Higher than expenses	31	7.6
The people who he/she lives together (n=376)		
Spouse	245	65.2
Children, grandchildren, sibling	82	21.8
Alone	31	8.2
Caregiver	18	4.8

Table 2. Distribution Medicine Management and Taking Medication Statuses of Elderly During the COVID-19 Pandemic
* Number of respondents giving more than one answer

Characteristics	N	%
Chronic disease		
Yes	275	67.6
No	135	32.4
Diseases *		
Hypertension	147	56.8
Diabetes	83	32.0
Asthma	20	8.2
Chronic Obstructive Pulmonary Disease (COPD)	13	5.4
Renal problem	29	11.8
Heart diseases	63	25.2
Joint disease	49	19.8
Stomach disease	25	6.1
Ophthalmic diseases	39	9.5
Cancer	19	4.4
Mental problem	18	4.4
Regular use of medication		
Yes	262	64.6
No	145	35.4
Number of medicine taken	3.67±1.59	
Taking medicine other than those that are used constantly		
Yes	72	17.6
No	338	82.4
If yes, the types of medicine (n=72)		
Painkiller	51	70.8
Physician's prescription	17	23.6
Vitamin	4	5.6
How the medicines are procured (n=174)		
I bought them myself at the pharmacy	53	30.5
My children bought them at the pharmacy	78	44.8
My relatives bought them at the pharmacy	36	20.7
My caregiver bought them at the pharmacy	4	2.3
I couldn't buy them	3	1.7
Where the medicines are stored (n=197)		
At room temperature	157	79.7
In the refrigerator	40	20.3
Problems with access to medicines		
Yes	122	29.7
No	288	70.3
The problem experienced in accessing to medicines (n=122)		
I didn't get any information from the physician since I couldn't leave the house	101	82.8
I had no one to bring medicine	17	13.9
I didn't know how to buy my medication	4	3.3

Of elderly, 67.6% had one or more chronic diseases, 64.6% were on medication all the time. During the coronavirus pandemic, 44% of elderly people reported that his/her children bought medicines at the pharmacy, 79.7% kept their medicines at room temperature, and 29.7% had problems accessing the medicines (Table 2).

During the COVID-19 pandemic, 42.9% of elderly people had problems accessing health services, only 32.9% had visited family medicine for an examination, 88.2% had received information to protect themselves from the epidemic, and the source of information was the media (56.1%), a physician (46.3%), and close circle (40.7%), respectively (Table 3).

Table 3. Access of Elderly to Health Services and Getting Information During the COVID-19 Pandemic

Characteristics	N	%
Problems with access to health services		
Yes	176	42.9
No	234	57.1
The status of examination by a specialist physician		
Yes	54	13.2
No	356	86.8
The status of examination by a primary care physician		
Yes	135	32.9
No	275	67.1
Getting information for protection from Covid-19		
Yes	362	88.2
No	48	11.8
From whom he/she received information*		
Media	230	56.1
Physician	190	46.3
Close circle	167	40.7
Did any institution provide information about Covid-19?		
Yes	104	32.2
No	306	67.8
Who informed (n=102)		
Governor's office (authorized services)	57	55.8
Primary care provider	45	44.2

* Number of respondents giving more than one answer

Table 4. Distribution of opinions and recommendations on health services provided to the elderly during the COVID-19 pandemic

Characteristics	N	%
The status of success of the services provided during the epidemic		
Successful	230	56
Unsuccessful	180	44
Access to medicines		
We met the need for medicines from the pharmacy during the pandemic	167	40.7
Delivery of medicines from the pharmacy without visiting a physician facilitated access	93	22.6
Social support status		
Sufficient	180	43.9
Insufficient	230	56.1
Opinions and recommendations on the epidemic process *		
Social and economic support for the elderly should be increased	191	46.6
The personnel needs of the units dealing with the elderly should be met	173	42.3
Governorship and municipality should cooperate regarding the services for the elderly	160	39.0
Health care professionals should bring medicines to home and provide information about them	145	35.4

* Number of respondents giving more than one answer

Of elderly, 40.7% has met the need for medicines from the pharmacy during the COVID-19 process, and 56.1% reported that social support for the elderly is insufficient. Opinions and suggestions of elderly people about the epidemic process were as follows: social and economic support for the elderly should be increased (46.6%), the personnel need of units related to the elderly should be met (42.3%), the governor's office and the municipality should cooperate regarding the services for the elderly (39%), and health care professionals should bring medicines and provide information to the elderly (Table 4).

DISCUSSION

Along with the COVID-19 pandemic, restriction and prohibition measures have been implemented throughout the countries in order to prevent and control the disease. It has been reported that patients with chronic diseases and elderly patients had difficulty in accessing health services, and medication controls have also been disrupted along with their treatment due to the restrictive measures (such as staying at home) applied during the pandemic. It has also been reported that the pandemic has affected other vulnerable groups more, along with the elderly, by increasing social inequalities in various dimensions, especially health services, in all countries (13–15). Therefore, it has been emphasized that solidarity with the elderly is important during the epidemic, and it has been reported that the social support that will be provided together with the protection and support will positively affect the health of elderly (11,16). In this study, the fact that the monthly incomes of elderly were less than their expenses, more than three-quarters was unemployed, and the majority have a low level of education indicate that they are a disadvantaged group that could be affected negatively by the epidemic, in line with the literature.

Aging is considered a public health problem worldwide and chronic diseases seen in the ever-increasing elderly population have been reported to negatively affect the quality of life of elderly and increase mortality rates (1,2). It was determined that there was an increase in the number of drugs used with age and that 65-70-year-old patients take an average of 3-4 drugs while those aged 70 and older take an average of 3-6 drugs (3). It has been emphasized that the habits of taking medications have increased and drug controls have been disrupted in line with the sale of over-the-counter and unsafe medications to patients, without visiting a physician (12). In a study conducted in Turkey, it was reported that 90% of people aged 65 years and over had at least one chronic disease, 35% had two chronic diseases, 23% had three chronic diseases, and 14% had four or more chronic diseases, and that the increase in chronic diseases also increases drug use (17,18). It has been found that COVID-19 increases the risk of mortality in the elderly and those with chronic diseases (hypertension, diabetes mellitus, coronary artery disease, chronic lung disease, obesity, cancer), as well as individuals taking multiple medications (18–20). It has been stated that good management of multidrug use together with the management of nutritional problems, movement restriction, depression, and social problems in elderly individuals during the epidemic will have a positive effect on elderly health (4,21). It has been reported that adequate preventive measures and appropriate medication follow-up are necessary for elderly people who are at risk during the pandemic (12). Regulations on the use and management of drugs in the coronavirus process have also been implemented in Turkey. The regulation made by the Ministry of Health states that medicines without a report can be prescribed by a family physician by phone, and medicines with a report can be purchased from pharmacies without a prescription (22). The importance of pharmacists and health care providers to cooperate in drug management in order to protect chronic and elderly patients, who use multiple drugs during the epidemic, from the undesirable effects of

drugs has been emphasized (23). It has been reported that physicians can reduce the potential risks of patients using multiple drugs during the epidemic by following up and controlling the results of prescribed drugs in addition to effective drug management during the epidemic (2,9). Similar to the above-mentioned results, it was found in this study that most of elderly people (67.6%) have at least one or more chronic diseases and take medication regularly (64.6%). In the study, about a third (29.7%) of elderly was found to experience problems with the supply of medicines during the COVID-19 pandemic and missed their health checks. It is understood that pharmacists and service providers, especially health care professionals, can play an important role in eliminating these problems. It has been reported that restrictive measures applied to control the COVID-19 pandemic (including the inability to leave the house) will disrupt chronic disease control in the elderly, make it difficult to access medications, and increase anxiety, stress, and loneliness levels. For this reason, it has been emphasized that health and care services and social support to be provided to the elderly have become important in all countries because of the epidemic (24–26). In addition, another study has emphasized that non-pharmaceutical treatment methods also have a positive effect on the lives of elderly in cases of diseases that adversely affect their long-term health that requires medication (5).

It has been stated that half of elderly people in some developing countries of the world did not have access to basic health services before the COVID-19 pandemic and that this will worsen with the pandemic. In addition, it has been stated that there are double disease burdens (infectious, chronic diseases) in these countries and that individuals who have a lot of disease burden will have more significant health risks (10,27). It has been reported that the disadvantaged groups in societies will be affected more in line with the COVID-19 crisis and that the crisis will lead to unemployment, reduced income, poor health conditions, and increased social and economic problems more in these groups (28). During the epidemic, it has been noted that elderly people living at home and elderly people in need of prolonged care were not adequately supported, and there were some problems in care services due to the insufficient number of personnel who provide care for the elderly (29). In addition, it has been observed that the physician visits of elderly for medical purposes have also decreased during the COVID-19 epidemic (30). It has been stated that the most important source of information for individuals forced to stay at home during the pandemic is the mass media. Another study states that unconfirmed information disseminated through media organizations negatively affects individuals at the start of the pandemic (7). Similar to these results, a significant part of elderly (42.9%) participating in the study research that they had problems accessing health services during the pandemic and received information from the media (56.1%), physicians (46.3%), and their relatives (40.7%), respectively, to protect themselves against the pandemic. More than half of elderly (56.1%) stated that social support was insufficient for the elderly, nearly half (46.6%) recommended increasing economic and social support for elderly people, more than a third (%42.3) has stated that the personnel need of the units that provide services for the elderly should be met.

Study Limitation

This research has some limitations. Firstly, the study data is based on self-reports of elderly individuals. Other limitation is that the study data were obtained in only one province.

CONCLUSION

The implementation of policies that will contribute to the healthy aging of elderly along with social and economic support during the COVID-19 pandemic and its aftermath will have a positive impact on the lives of elderly people.

Ethics Committee Approval: Ethical approval was obtained from Munzur University of Non-Interventional Research Ethics Committee with decision No:3, 03 November 2020.

Peer-review: Externally peer-reviewed.

Author Contributions: Study design, data collection and analysis and manuscript preparation: KB.

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

Financial Disclosure: The author received no financial support for the research, authorship and/or publication of this article

REFERENCES

1. Bakir G, Akin S. Factors associated with management of chronic diseases in elderly. Health and Society. 2019;29(2):17–25.
2. Nouira N, Bahria W, Hamdi D, Lahouegue A, Demni W, Cheikh M Ben. Medication adherence in elderly during Covid-19 pandemic: What role can the emergency department play? Pan Afr Med J. 2021;38.
3. Smaje A, Weston-Clark M, Raj R, Orlu M, Davis D, Rawle M. Factors associated with medication adherence in older patients: A systematic review. Aging Med. 2018;1(3):254–66.
4. Palmer K, Monaco A, Kivipelto M, Onder G, Maggi S, Michel JP, et al. The potential long-term impact of the COVID-19 outbreak on patients with non-communicable diseases in Europe: consequences for healthy ageing. Aging Clin Exp Res. 2020;32(7):1189–94.
5. Vahia I, Jeste D, Reynolds C. Older Adults and theMental Health Effects of COVID-19. JAMA. 2020;324(22):2253–4.
6. Kretchy IA, Asiedu-Danso M, Kretchy JP. Medication management and adherence during the COVID-19 pandemic: Perspectives and experiences from low-and middle-income countries. Res Soc Adm Pharm. 2021;17(1):2023–6.
7. Rahman S, Singh K, Dhingra S, Charan J, Sharma P, Islam S, et al. The double burden of the COVID-19 pandemic and polypharmacy on geriatric population – public health implications. Ther Clin Risk Manag. 2020;16:1007–22.
8. Wicaksana AL, Hertanti NS, Ferdiana A, Pramono RB. Diabetes management and specific considerations for patients with diabetes during coronavirus diseases pandemic: A scoping review. Diabetes Metab Syndr Clin Res Rev. 2020;14(5):1109–20.
9. Potempski F, Bilimoria K. Polypharmacy in the age of covid-19: Medication management during a pandemic. Univ Toronto Med J. 2021;98(1):73–5.

10. United Nations. Policy Brief: The Impact of COVID-19 on older persons. United Nations Sustain Dev Gr. 2020;(5):1–16.

11. Cugmas M, Ferligoj A, Kogovšek T, Batagelj Z. The social support networks of elderly people in Slovenia during the Covid-19 pandemic. PLoS One. 2021;16(3 March):1–16.

12. McCook A. COVID-19: Stockpiling Refills May Strain the System - Infectious Disease Special Edition. COVID-19: stockpiling refills may strain the system. 2020 [cited 2022 Jan 16]. Available from: https://www.idse.net/Policy--Public-Health/Article/03-20/COVID-19-Stockpiling-Refills-May-Strain-the-System/57583

13. Altin Z. Elderly People in Covid-19 Outbreak. J Tepecik Educ Res Hosp. 2020;30:49–57.

14. Bambra C, Albani V, Franklin P. COVID-19 and the gender health paradox. Scand J Public Health. 2021;49(1):17–26.

15. Abedi V, Olulana O, Avula V, Chaudhary D, Khan A, Shahjouei S, et al. Racial, Economic, and Health Inequality and COVID-19 Infection in the United States. J Racial Ethn Heal Disparities. 2021;8(3):732–42.

16. Grey I, Arora T, Thomas J, Saneh A, Tomhe P, Abi-Habib R. The role of perceived social support on depression and sleep during the COVID-19 pandemic. Psychiatry Res.2020;293(September):113452.

17. Gumustakim RS, Ayhan Baser D. Multiple drug use in elderly in primary care: An example of rural field. Turkish Journal of Family Medicine.2019;23(1):2–8.

18. Bozan O, Atis SE, Cekmen B, Kocer MT, Koca Y, Karaaslan EB, et al. Clinical findings and prognosis of hospitalized elderly COVID-19 patients. Turkish Journal of Geriatrics. 2021;24(1):1-12.

19. Ramachandran P, Onukogu I, Ghanta S, Gajendran M, Perisetti A, Goyal H, et al. Gastrointestinal Symptoms and outcomes in hospitalized coronavirus disease 2019 patients. Dig Dis. 2020;38(5):373–9.

20. Banerjee D. 'Age and ageism in COVID-19': Elderly mental health-care vulnerabilities and needs. Asian J Psychiatr. 2020;51(January).

21. Ilgili O, Gokce Kutsal Y. Impact of COVID-19 among the elderly population. Turkish Journal of Geriatrics. 2020;23(4):419–23.

22. Yigitalp G. COVID-19 and elderly health. Ankara; 2021. p. 379–402.

23. Iloanusi S, Mgbere O, Essien EJ. Polypharmacy among COVID-19 patients: A systematic review. J Am Pharm Assoc. 2021;61(5):e14–25.

24. Khademi F, Moayedi S, Golitaleb M, karbalaie N. The COVID-19 pandemic and death anxiety in the elderly. Int J Ment Health Nurs. 2021;30(1):346–9.

25. Ekici E. Care management of elderly people during Covid 19 pandemic. Haliç University Health Science Journal. 2020;3(3):145–52.

26. Armitage R, Nellums LB. COVID-19 and the consequences of isolating the elderly. Lancet Public Heal. 2020;5(5):e256.

27. Boukhatem MN. Essential oils , and phytochemical extracts as potential therapies for Coronaviruses : Future perspectives. Plants. 2020;9(6):800.

28. Smith Jervelund S, Eikemo TA. The double burden of COVID-19. Scand J Public Health. 2021;49(1):1–4.

29. Baxter R, Jemberie WB, Li X, Naseer M, Pauelsen M, Shebehe J, et al. COVID-19: Opportunities for interdisciplinary research to improve care for older people in Sweden. Scand J Public Health. 2021;49(1):29–32.

30. Mazurek J, Biernat K, Kuciel N, Hap K, Sutkowska E. The use of medical and non-medical services by the elderly during the sars-cov-2 pandemic differs between general and specialist practice: A one-center study in Poland. Healthc. 2021;9(1).

Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci **August 2022; 8(3): 314-319**

RESEARCH ARTICLE **DOI:** 10.19127/mbsjohs.1082154

Could the SARS-CoV-2 Outbreak Cause an Increase in Rickettsia Infection? North Cyprus Observation

Meryem Guvenir[1](ID), Emrah Guler[2](ID), Kaya Suer[3](ID)

[1]Near East University, Vocational School of Health Services, Department of Medical and Clinical Microbiology, Nicosia, Cyprus
[2]Near East University, Faculty of Health Sciences, Department of Medical and Clinical Microbiology, Nicosia, Cyprus
[3]Near East University, Faculty of Medicine, Depatment of Infectious Diseases and Clinical Microbiology, Nicosia, Cyprus

Received: 03 March 2022, Accepted: 18 May 2022, Published online: 31 May 2022

Abstract

Objective: The aim of the study was to determine the prevalence rate of the Rickettsiae infection during the Turkish Republic of North Cyprus SARS-CoV-2 pandemic according to years.

Methods: This cross-sectional study was carried out during 2016 to 2020. Weil-Felix test is based on cross-reactions which occur between antibodies produced in acute rickettsial infections with antigens of OX (OX 19, OX 2, and OXK) strains of Proteus species. On a lam surface, a small 100 µL of the patient's serum is placed. A single drop of the desired antigen (OX19, OX2 ve OXK) is added, and the resulting suspension is mixed and then rotated for one minute. Visible agglutination is indicative of a positive result and corresponds roughly to a titer of 1:20. Statistical analysis of the data obtained was conducted with SPSS (Statistical Package for the Social Sciences) Demo Ver 22.0 (SPSS Inc., Chicago, IL, USA) program.

Results: Total patient number were 369 (Male: 192, 52%; Female: 177, 48%) and the mean age was 33.40±21.37. The number of patients who found as positive for any of the Rickettsiae infection (OX19, OX2 and OXK) were 15.4% in 2016; 21.1% in 2017; 22.9% in 2018 %; 23% in 2019 and 37.3% in 2020. It has been observed that OX19 and OX2 positivity has increased significantly over the years. It is seen that the Proteus OX19 positive cases in 2020 are significantly higher than in other years (p=0.026). It is found that the positive cases of OX2 positivity in 2020 are significantly higher than in other years (p=0.036). Additionaly, considering the distribution over the years, it was seen that Rickettsiae positive patients increased significantly between 2016 and 2020 (p=0.017). Additionaly, considering the distribution over the years, it was seen that Rickettsiae positive patients increased significantly between 2016 and 2020 (p=0.017).

Conclusion: Our hypothesis is the because of the SARS-CoV-2 pandemic due to the people staying at home the animal population such as rodents' population caused an increase. Therefore, the increase in zoonotic infections should not be ignored and it should not be forgotten that necessary precautions should be taken to prevent these infections from getting out of control.

Keywords: Rickettsiae, SARS-CoV-2, North Cyprus

Suggested Citation: Guvenir M, Guler E, Suer K. Could the SARS-CoV-2 Outbreak Cause an Increase in Rickettsia Infection? North Cyprus Observation. Mid Blac Sea Journal of Health Sci, 2022;8(2): 314-319.

Address for correspondence/reprints:
Meryem Guvenir

Telephone number: +90 (542) 850 06 43
E-mail: meryemguvenir@hotmail.com

INTRODUCTION

Rickettsiae are Gram negative obligate intracellular bacteria which include several zoonotic pathogens distributed in the worldwide (1). Rickettsiae genus consist of four group. Typus group Rickettsiae (TGR) include the *R. prowazekii* and the *R. typhi*. Except for the rickettsial diseases inluded the epidemic typhus (*R. prowazekii*), Rocky Mountain spotted fever caused (*R. rickettsii*), Mediterranean spotted fever caused (*R. conorii*), and murine typhus caused (*R. typhi*), at least 10 other rickettsial diseases have been described and attributed to Rickettsia species within the Spotted Fever Group (2,3).

The reservoir of the R. typhi infection are rats (*Rattus rattus* and *Rattus norvegicus*) and the vector is the oriental rat flea (*Xenopsylla cheopis*). The way of transmission is percutaneous inoculation of the microorganisms presentin flea feces (4). Its distribution is worldwide however in the southern areas of the USA, South America, Australia, Southeast Asia, and Southern Europe has been reported as endemic (5). *R. conorii* infection is transmitted to humans by the bite of the brown dog tick name as the *Rhipicephalus sanguineus* and endemic in some areas of Spain and other Mediterranean countries (6). So main transmission way of the TGR are the invasive rodents, specifcally the black rats (*Rattus rattus*), and the brown rats (*Rattus norvegicus*), serve as primary reservoirs. Humans are infected by the contamination of disrupted skin, respiratory tract, or conjunctivae with infected fea faeces (7).

Cyprus is a third largest country in the Eastern Mediterranean and located south of Turkey, west of Syria and Lebanon, North of Egypt, Israel and southeast of Greece. The North part of the Cyprus is consisting of approximately 375 000 population who are Turkish Cypriots (8). The aim of the study was to determine the prevalence rate of the Rickettsiae infection during the SARS-CoV-2 pandemic and compare the other years.

METHODS

Study Group

This cross-sectional study was carried out during 2016 to 2020. Samples were analyzed in a micobacteriology laboratory at Near East Hospital, in North Cyprus. All the suspected cases of Rickettsiae infection visiting the microbiology laboratory of the hospital were enrolled. Samples that were not suitable for transfer or not approved by the center expert were excluded from the study. The study were approval of the Near East University Hospital Ethics Committee (decision number: YDU/2021/94-1390)

Serology

Weil-Felixtest is a nonspecific agglutination test which detects anti-rickettsial antibodies in patient's serum. Weil-Felix test is based on cross-reactions which occur between antibodies produced in acute rickettsial infections with antigens of OX (OX 19 (Code: 524005A, Lorne Laboratory), OX 2 (Code: 522005A, Lorne Laboratory), and OXK (Code: 526005A, Lorne Laboratory)) strains of Proteus species. Typhus group rickettsiae (*Rickettsia prowazekii, R. typhi*) react with *P. vulgaris* OX19, and scrub typhus (*Orientia tsutsugamushi*) reacts with *P. mirabilis* OXK. The spotted fever group rickettsiae (*R. rickettsii, R. africae, R. japonica*, etc.) react with *P. vulgaris* OX2 and OX19, to varying degrees, depending on the species. On a solid surface, a small 100 µL of the patient's serum is placed. A single drop of the desired antigen is added, and the

resulting suspension is mixed and then rotated for one minute. Visible agglutination is indicative of a positive result and corresponds roughly to a titer of 1:20.

Statistical Analysis

Statistical analysis of the data obtained was conducted with SPSS (Statistical Package for the Social Sciences) Demo Ver 22.0 (SPSS Inc., Chicago, IL, USA) program. Person Chi-Square, Fisher's Exact test and Binary Logistic Regression Analysis were used to determine statistical significance and the significance was evaluated at $p < 0.05$.

RESULTS

According to our results between 2016-2020, total patient number were 369 (Male: 192, 52%; Female: 177, 48%) and the mean age was 33.40±21.37. The mean age of Rickettsiae positive patient (95/369, 25.7%) was 33.15±20.28. The number of OX19, OX2 and OXK positive patients were 2/52 (3.8%); 5/52 (9.6%) and 2/52 (3.8%), retrospectively in 2016. The number of OX19, OX2 and OXK positive patients were 1/76 (1.3%); 12/76 (15.8%) and 3/76 (3.9%), retrospectively in 2017. The number of OX19, OX2 and OXK positive patients were 1/70 (1.4%); 13/70 (18.6%) and 5/70 (7.1%), retrospectively in 2018. The number of OX19, OX2 and OXK positive patients were 2/61 (3.3%); 9/61 (14.8%) and 9/61 (14.8%), retrospectively in 2019. The number of OX19, OX2 and OXK positive patients were 3/59 (5.1%); 22/59 (37.3%) and 2/59 (3.4%), retrospectively in 2020.

The number of patients who found as positive for any of the Rickettsiae infection (OX19, OX2 and OXK) were 15.4% in 2016; 21.1% in 2017; 22.9% in 2018 %; 23% in 2019 and 37.3% in 2020.

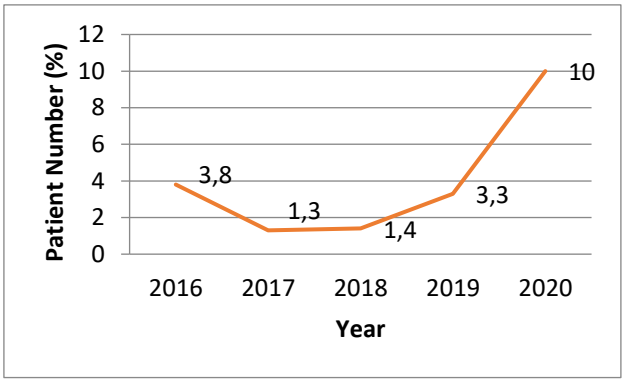

Figure 1. Distrubition of the OX19 positive patient number accrording to the years

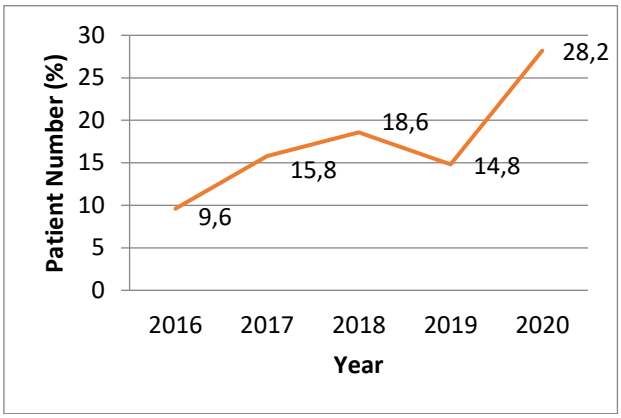

Figure 2. Distrubition of the OX2 positive patient number accrording to the years

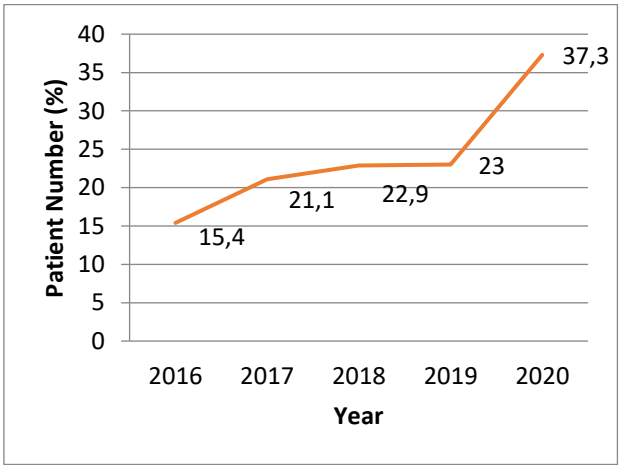

Figure 3. Distrubition of the Rickettsiae positive patient number accrording to the years

It is seen that the Proteus OX19 positive cases in 2020 are significantly higher than in other years ($p=0.026$) (Figure 1). It is found that the positive cases of OX2 positivity in 2020 are significantly higher than in other years ($p=0.036$) (Figure 2).

Additionaly, considering the distribution over the years, it was seen that Rickettsiae positive patients increased significantly between 2016 and 2020 (p=0.017) (Figure 3).

DISCUSSION

Murine typhus (endemic typhus) is a zoonotic infectious disease caused by *R. typhi* (*R. mooseri*), which is an obligate intracellular bacterium. The main syptoms of the disease is headache, rash, and fever (8). The life cycle of murine typhus inluded rats (*Rattus norvegicus* and *R. rattus*) as reservoirs, and their fleas and the main vector is the oriental rat flea *Xenopsylla cheopis* (9). Studies reported that three Rickettsiae spesies have been detected as *R. conorii*, *R. typhi* and *Rickettsia felis* in Southern Cyprus (10,11,12,13). However, enough information is not available on the presence and distribution of fleaborne rickettsiae in in Southern Cyprus. In the study of Christou C et. al, fleas collected from rats between 2000–2003 in 51 areas of all provinces of Southern Cyprus. They were studied with the molecular analysis to distinguish the prevalence and identification of fleaborne rickettsiae. They reported that *R. typhi* was found in 4% of the *Xenopsylla cheopis* and in 6.6% in the *Leptopsylla segnis*. This is the first report of *R. typhi* in *X. cheopis* and *L. segnis* from rats in Southern Cyprus. This study results indicated that the geographic distribution of fleas coexit with the geographic distribution of the pathogen they can harbor, which indicate the potential risk of flea-transmitted infections in Southern Cyprus (14).

Although we are not enough information about the Rickettsiae infections in North Cyprus, we are realized that the Rickettsiae infections has been increases during the SARS-CoV-2 pandemi in North Cyprus. Therefore, the aim of the study was to determine the prevalence rate of the Rickettsiae infection during the SARS-CoV-2 pandemic and compare the prevalence with other years. It is seen that the positive cases of OX2 positivity in 2020 are significantly higher than in other years (p=0.036). Additionaly, considering the distribution over the years, it was seen that Rickettsiae positive patients increased significantly between 2016 and 2020 (p=0.017).

One of the few studies that Economides P. reported that 44.6% of the human population were seropositive to *R. conorii* and 46.8% of the human population were seropositive to *R. typhi* in Southern Cyprus. Also, they indicated that *R. typhi* were isolated from humans with clinical symptoms of rickettsioses during the study (15).

Although there is no explanation about the increase of rodent prevalence from local governments in North Cyprus, patients who participated in our study during SARS-CoV-2 pandemic indicated that they lived in places and / or had contact with a high rodent population in their anamnesis. Bedoya-Perez et al indicated that after ‘lock dowm’ for SARS-CoV-2 pandemic, some local governments and public health authorities related the closures of restaurants and food-related venues to increased prevalence of rats (16). Also, Centers of Disease Control and Prevention was published the report about the Rodent Control during SARS-CoV-2 pandemic on 21 May 2020 (17). Although these study results support our hypothesis, this interaction might be increased the zoonotic infections such as Rickettsiae infections in North Cyprus

Study Limitation

The fact that the study was conducted retrospectively in a single center and the small number of cases are limiting the study.

CONCLUSION

To reduce human mobility in order to prevent transmission during the SARS-CoV-2 pandemic process, all countries were 'lock down'. It has been observed that there is an increase in animal populations as a result of the decrease in human mobility. Therefore, the increase in zoonotic infections should not be ignored and it should not be forgotten that necessary precautions should be taken to prevent these infections from getting out of control.

Ethics Committee Approval: The study was approved by the decision of the Near East University Clinical Research Ethics Committee (26.08.2021 and no: 2021/94).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: HK, Design: HK, MG Literature search: EG, MG, HK, Data Collection and Processing: MG, HK, EG Analysis or Interpretation: EG, Writing: EG, MG, HK

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

Financial Disclosure: The authors also decline any financial support neither from any pharmaceutical company, nor from a company that provides or produces medical instruments and materials.

REFERENCES

1. Raoult D, Roux V, Ndihokubwayo JB, Bise G, Baudon D, Martet G, et al. Jail fever (epidemic typhus) outbreak in Burundi. Emerg Infect Dis 1997;3:357-60
2. Merhej V, Raoult D. Rickettsial evolution in the light of comparative genomics. Biol Rev Camb Philos Soc .2011; 86: 379–405
3. Parola P, Paddock CD, Raoult D Tick-borne rickettsioses around the world: emerging diseases challenging old concepts. Clin Microbiol Rev 2005; 18: 719–756
4. Traub R, Wisseman CL, Azad AF. The ecology of murine typhus, a critical review. Trop Dis Bull 1978;75:237–317.
5. Whiteford SF, Taylor JP, Dumler JS. Clinical, laboratory, and epidemiologic features of murine typhus in 97 Texas children. Arch Pediatr Adolesc Med 2001;155:396–400.
6. Font-Creus B, Espejo Arenas E, Mun˜oz Espı´n T, Uriz Urzainqui S, Bella Cueto F, Segura Porta F, et al. Mediterranean boutonneuse fever. Study of 246 cases. Med Clin (Barc) 1991;96:121–5.
7. Parola P, Raoult D. Tropical rickettsioses. Clin Dermatol. 2006;24:191–200.
8. Azad AF. Epidemiology of murine typhus. Annu Rev Entemol 1990; 35:553-569.
9. Chaniotis B, Psarulaki A, Chaliotis G, Gozalo Garcia G, Gozadimos T, Tselentis Y. Transmission cyce of murine typhus in Greece. Ann Trop Med Parasitol 1994; 88:645-647.
10. Psaroulaki A, Antoniou M, Papaeustathiou A, Toumazos P, Loukaides F, Tselentis Y. First detection of *Rickettsia felis* in *Ctenocephalides felis* fleas parasitizing rats in Cyprus. Am J Trop Med Hyg 2006; 74: 120–122.
11. Koliou M, Psaroulaki A, Georgiou C, Ioannou I, Tselentis Y, Gikas A, Murine typhus in Cyprus: 21 paediatric cases. Eur J Clin Microbiol Infect Dis 2007; 26: 491–493.
12. Christou C, Psaroulaki A, Antoniou M, Toumazos P, Ioannou I, Mazeris A, et al. *Rickettsia typhi* and *Rickettsia felis* in *Xenopsylla cheopis* and *Leptopsylla*

segnis parasitizing rats in Cyprus. Am J Trop Med Hyg 2010; 83: 1301–1304.

13. Psaroulaki A, Antoniou M, Toumazos P, Mazeris A, Ioannou I, Chochlakis D, et al. Rats as indicators of the presence and dispersal of six zoonotic microbial agents in Cyprus, an island ecosystem: a seroepidemiological study. Trans R Soc Trop Med Hyg 2010;v104: 733–739
14. Christou C, Psaroulaki A, Antoniou M, Toumazos P, Ionnou I, Mazeris M, et al.. *Rikketsia typhi* and Rickettsia felix in Xenopsylla cheopis and Leptopsylla segnis Paraziting Rats in Cyprus. Am J Trop Med Hyg 2010; 83 (6):1301-1304.
15. Economides P. Control of zoonoses in Cyprus. Rev. Sci. Tech. Off. Int. Epiz. 2000; 19(3):725-734.
16. Bedoya-Perez MA, Ward MP, Loomes M, McGregor IS, Crowther M.S. The effect of COVID19 pandemic restrictions on an urban rodent population. Nature 2021;12957.
17. https://www.cdc.gov/coronavirus/2019-ncov/php/rodents.html

Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci **May 2022; 8(2): 320-331**

REVİEW **DOI:** 10.19127/mbsjohs.1071048

Endoscopic Sinus Surgery- Surgical Steps with Implications in Intraoperative Complications

Hakan Korkmaz[1](ID), Mukadder Korkmaz[2](ID)

[1]Ordu University, Faculty of Medicine, Department of Otorhinolaryngology Head and Neck Surgery, Ordu, Turkey

[2]Private Clinics, Otorhinolaryngology, Ordu, Turkey

Received: 10 February2022, Accepted: 14 April 2022, Published online: 31 May 2022

Abstract

Objective: Endoscopic sinus surgery is a worldwide performed operation which has gained acceptance as the primary treatment modality in paranasal sinus diseases. Any surgeon performing this surgery needs a valid treatment algorithm. Inappropriate surgical techniques may lead to failure and complications. Proximity of the surgical field to the critical structures poses difficulties to the surgeon. Too much removal of the normal structures and too little removal of the diseased tissues can have undesirable consequences. Although several techniques have been defined for each step, highlight ing critical points in a concise manner will be beneficial.

Methods: This review article aimed to enlight the complex paranasal sinus and relevant anatomy, define the intraoperative maneuvers to achieve a successful sinus surgery while avoiding surgeon-related complications. Books and journals were reviewed comprehensively. Classic techniques and contemporary aspects of the endoscopic sinus surgery were assembled.

Results: Paranasal sinus surgical anatomy and diseases show great variations. Endoscopic sinus surgery is performed in ameliorating paranasal sinus diseases. Improving the efficiency and safety of this surgery remains an important matter. There is a narrow border between suggested surgical steps and perilous complications. A thorough surgical anatomy knowledge and meticulous surgical methods needs to be defined.

Conclusion: Sinus surgeon must carefully evaluate the underlying disease process, apply a precise surgical method, avoid possible complications, and should take necessary measures in case of a complication. A systematic surgical technique is mandatory for success.

Keywords: endoscopic sinus surgery; optic nerve injury; internal carotid artery injury; cerebrospinal fluid leak; Draf classification

Suggested Citation: Korkmaz H, Korkmaz M. Endoscopic sinus surgery- surgical steps with implications in intraoperative complications . Mid Blac Sea Journal of Health Sci, 2022;8(2): 320-331.

E-mail: hakankorkmaz@hotmail.com

Address for correspondence/reprints:

Hakan Korkmaz
Telephone number: +90 (452) 225 23 42.

INTRODUCTION

Endoscopic sinus surgery (ESS) is a worldwide performed surgery. It is indicated for those patients with intractable chronic sinusitis or its complications, mucoceles, nasal poliposis, fungal diseases and neoplasms (1). There are studies aiming at identification of endotype and pathophysiology of the chronic sinusitis. These findings can lead to integrated treatment pathways of medical and surgical methods (2). Despite beneficial effects of medical therapy in nasal poliposis patients, combination of medical and surgical therapies in these patients have been found to be more efficacious with respect to general nasal symptoms (3).

It was reported that, ESS was not free of complications, even if the surgery was executed by an experienced surgeon. There was a direct relationship between the occurence of complications and the extend of the surgery, presence and the grade of the polyposis, and if it was performed as a revision surgery (4). These complications comprise a great source of litigation facing otolaryngologists (5). While the occurence of the minor complications is about 6 %, the risk of major complications varies between 0.5 to 1 % (4,6,7). A study analyzing the ESS complications in Japan evaluated 50734 patients and the incidences of cerebrospinal fluid leakage, orbital injury, bleeding requiring surgery and blood transfusion were 0.09%, 0.09%, 0.10% and 0.18% respectively, whatever the extent of surgery (8). The fear of causing complication causes many surgeons to perform incomplete surgeries, partial clearance of the diseased cells, with residual bony partitions. Incomplete removal of cells during ESS is an important reason for disease recurrence and poor outcome (9-11). Applying a precise surgical method will improve the success rate and help to avoid complications. In an attempt to lessen complications, frameless stereotaxic surgery has been developed. Nevertheless, image guidance cannot be a substitute for a competent knowledge of the anatomy and meticulous use of instruments (12).

The goal of this article is to elucidate the surgical steps of a comprehensive endoscopic sinus surgery which will improve the mucociliary function and paranasal sinus ventilation, while highlighting critical points to avoid complications and methods of handling complications. The aim is to establish a practicable and valid surgical technique, enhancing the ease and safety of the ESS.

A range of methods from minimally invasive surgery to comprehensive ESS have been described. The degree to which extend the surgery should be performed varies from patient to patient. Operative procedure should be tailored to the pathology of the patient.

Given the closeness of the surgical area to the intracranial structures, orbital cavity, internal carotid artery and other vascular structures, optic nerve, and considering their relevant risks, ESS must be accomplished with utmost care, anatomical knowledge, appropriate surgical techniques. To avoid intraoperative complications and postoperative morbidities, critical points must be recognized. In case of an unfortunate trauma, appropriate steps to correct it must be undertaken without any hesitation.

To accomplish appropriate surgery and avoid intraoperative complications, preoperative assesment and preparation carry indispensable value. General medical condition should be determined. Scrutinizing axial and coronal paranasal sinus computed

tomography (CT) scans helps to identify the extend of the disease and defines the areas of technical difficulty (1). Structure of the paranasal sinuses, anatomical variations, deficient areas of the revision cases should be evaluated. Position of the cribriform plate, anterior ethmoid artery, dimensions of the infundibulum, presence of Onodi cells should be carefully assessed.

ESS is a challenging surgery because of neighborhood to the intracranial and orbital structures. Although having a detailed anatomic knowledge is prerequisite, distorted structures because of intranasal pathology, altered anatomy of revision surgeries, intraoperative bleeding may be misleading. Image guided surgery (IGS) provides detailed topographic localization of the surgical instruments within 2 mm (13). IGS is valuable especially in risky areas such as frontal sinus, skull base, anterior ethmoid artery.

ESS procedures can be performed using cold instruments or microdebriders. Microdebriders are powered tools that permit tissue removal and suction functions simultaneously. Specifically designed blades give the opportunity of precise soft tissue cutting in difficult to reach areas, such as frontal recess.

All paranasal sinuses except frontal sinus can be operated on using 0 degree and 30-degree rigid endoscopes. Using 0-degree endoscope yields minimal distortion of the vision and the spatial orientation will be better. The position of the anatomic landmarks, including uncinate process, ethmoid bulla, maxillary sinus ostium and basal lamella should always be considered throughout the surgery. 70-degree endoscopes are helpful in acute angle areas, such as frontal recess.

METHODS

Surgical Technique:

Following the administration of oxymetazoline soaked cottonoids into both nasal cavities, vasoconstriction is obtained for endoscopic examination. After withdrawal of these cottonoids, nose is evaluated with a 0-degree 4 mm diameter endoscope. Topical anesthesia and additional vasoconstriction are achieved by using 1 % xylocaine with 1:100000 epinephrine injection into the lateral nasal wall, uncinate process and middle turbinate (1).

Middle turbinate is of utmost importance with respect to spatial orientation. Levin M et al concluded that middle turbinate is a significant landmark of the maxillary sinus ostium. Maxillary antrostomy through the inferior middle turbinate and 16.4mm posterior to its anterior border is secure in 98.5% of patients (14).

Uncinectomy: The first step of the endoscopic sinus surgery is uncinectomy, which is the excision of the uncinate process. Uncinectomy exposes the infundibulum. It is the key step in resolving pathologies affecting anterior sinus complexes (frontal, anterior ethmoid sinus and maxillary sinuses). The middle and lower posteroinferior parts of the uncinate process are resected while keeping the most upper part intact.

Medialization of the middle concha with Freer elevator displays the middle meatus and uncinate process. Several instruments can be used to excise the uncinate process, such as back-biters, through cutting forcepses, microdebrider or sickle knife. Initially, the uncinate process is palpated laterally using a ball-

tipped probe. It is applied to pull the uncinate process medially. Back-biter removes the uncinate process in a retrograde approach. Movable jaw of the backbiter is passed to the infundibulum and uncinate process is removed piece by piece. Remaining parts of the uncinate process can be trimmed with back-biter or through cutting forcepses. Care should be given not to harm anteriorly placed nasolacrimal duct. Any resistance should alert the physician since the uncinate process has a thin structure (15).

At times, microdebrider can be used to take out the uncinate process instead of back-biters. If the microdebrider blade is forced against the orbital wall, orbital damage may ensue.

Sickle knife is used to incise the anterior attachment of the uncinate process to the nasolacrimal duct. Incision starts at the upper part and and goes down and posteriorly along the sagittal plane. Alternatively, incision may be placed at the middle part, and can be extended up and down. Sharp edge of the freer elevator may be used instead of sickle knife. The depth of the incision more than 1 mm carries the risk of penetration of the lamina papyracea, especially when the maxillary sinus is hypoplastic and infundibulum is shallow. This trauma results in intraorbital bleeding or orbital fat exposure.

After a successful uncinectomy, maxillary sinus ostium can be visualized in most cases. When it is not clear, an angled sucker or a ball probe can be used to palpate the ostium. Usually, ostium lies at the level of the inferior edge of the middle turbinate. Minimal pressure should be applied in order to avoid entering the orbital cavity. For patients with limited disease, exposure of the natural ostium may be sufficient. Depending on the degree of the pathology, natural ostium may be enlarged from 1 cm up to a wide antrostomy (Figure 1). The level of the wide antrostomy may extend to the posterior antral wall and inferior turbinate. Maximum enlargement is preferred in pathologies requiring wide access to the sinus cavity, such as cystic fibrosis, antrochoanal polyp, foreign body, fungus ball. When widening the maxillary ostium, pulling mucosa roughly should be avoided since this maneuver denudes the underlying maxillary sinus bone. Loose pieces of mucosa around the ostium should be trimmed carefully.

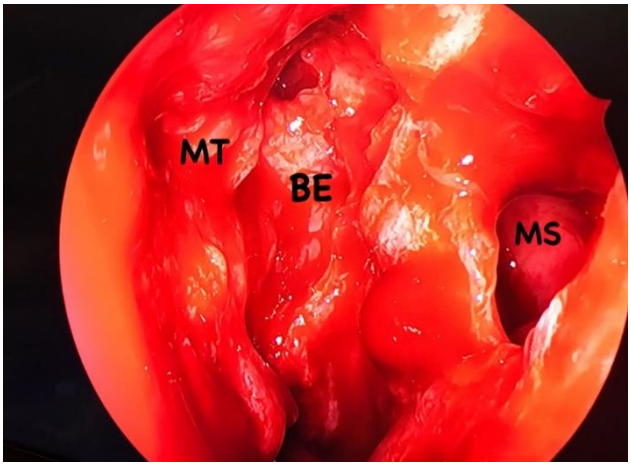

Figure 1. Left nasal cavity demonstrating middle meatus after removal of the nasal polyps and unsinate process.Maxillary sinüs ostium enlarged. MT:middle turbinate BE:bulla ethmoidalis MS: maxillary sinüs

Primary surgical preference is adenoidectomy in refractory sinusitis cases in children. However sometimes ESS in needed in this age group. Main objective is the dilation of the natural ostia. Balloon catheter sinuplasty is an effective method in children. Mostly maxillary ostium is dilated since frontal sinus is not fully developed in most pediatric patients (16).

Maxillary sinus ostium is mostly enlarged to ameliorate antral diseases. Also, this procedure exposes the roof of the maxillary sinus so the level of the orbital floor is identified for the rest of the procedure. It is used as anatomic landmark during

entry and opening the posterior ethmoid cells to avoid penetration of the skull base.

Because of long standing chronic sinus infections, identification of the maxillary sinus ostium may not be possible. In this case, a right- angled probe can be used to palpate posteriorly located fontanelle. This mucosa is punctured and widened creating an accessory ostium. It can be enlarged far enough forward to connect to natural ostium. Any accessory ostium should be connected to the natural ostium to prevent recirculation of the mucus back into the maxillary sinus.

Aggressive widening of the ostium anteriorly may harm anteriorly placed nasolacrimal duct, causing nasolacrimal duct stenosis or collection of the tears in the maxillary sinus. In most cases it remains asymptomatic and no therapy is necessary. If it results in drainage problems in the postoperative period, dacryocystorhinostomy is recommended.

When the maxillary sinusotomy is extended to within the 0.5 cm of the posterior wall, a branch of the sphenopalatine artery is encountered and it may need cautery.

During uncinectomy and exploration of the maxillary sinus ostium, if the lamina papyracea is entered and orbital fat is exposed, eyelid ecchymosis and edema may ensue in the early postoperative period. Orbital fat tissue should not be removed. Repositioning of any orbital fat tissue is not necessary. Usually, it heals without any intervention.

Lateralization of the middle turbinate postoperatively may cause recurrence of sinüs problems. Providing medialization and scar adhesion of the middle turbinate by decortication of the head of the turbinate and septal mucosa prevent such sequelas (17).

Anterior Ethmoidectomy: Following uncinectomy and opening maxillary sinus ostium, ethmoid bulla is opened.

The initial point of entry into the bulla ethmoidalis is the medial and inferior aspect. Upon feeling the sinus cavity with an instrument, removal advances superiorly and laterally. Anterior wall of the bulla ethmoidalis is removed disclosing the posterior basal lamella. Its lateral border is the lamina papyracea. It is better not to touch the anterior superior wall of the bulla ethmoidalis in order to keep it as a landmark to help localize the frontal recess and anterior ethmoid artery.

Posterior Ethmoidectomy: The posterior wall of the bulla ethmoidalis, which is called the basal (third) lamella, forms the anterior boundary of the posterior ethmoid cells. Posterior ethmoid cells are entered through the basal lamella (Figure 2). This part of the surgery is important since careless instrumentation may lead to inadvertant skull base injury. Both the location and the direction of the removal of the basal lamella are important. Working medially and inferiorly is safe generally. The axial limit of the opening the posterior ethmoids should be below the level of the orbital floor and sagittal plane should be medial to the medial wall of the maxillary sinus. When this space is opened, superior concha and anterior wall of the sphenoid sinus are exposed.

Lamina papyracea is a very thin structure and can be breached easily. Its integrity ought be controlled by Stankiewicz maneuver in suspicious cases: Under endoscopic observance of the test area, pressing the globe will move the orbital fat. Halting additional

tissue removal in this area will prevent any muscle or nerve damage.

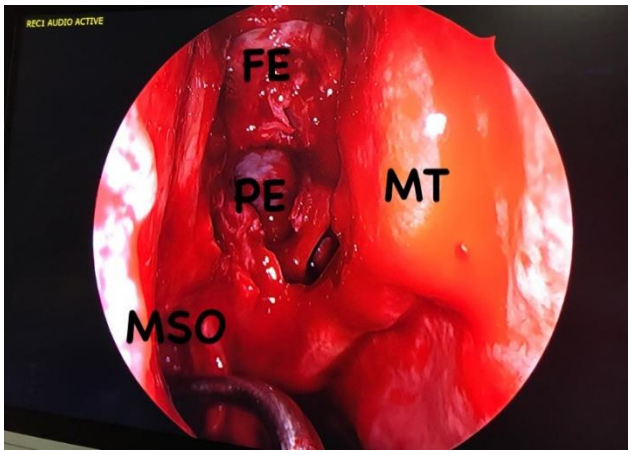

Figure 2. Right middle meatus following ethmoidectomy. MT:middle turbinate FE:fovea ethmoidalis PE: posterior ethmoidal cells MSO: maxillary sinüs ostium and suction device

Sphenoidotomy and sphenoidectomy: The sphenoid sinus ostium can be identified by either the transethmoid or transnasal approach. Entering the sphenoid sinus by way of the posterior ethmoid cells is risky. It is best to find the sphenoid sinus ostium medial to the middle turbinate. Sphenoid sinus ostium is 1 cm above the posterior choana, medial to the superior turbinate, just lateral to the septum. By following the choana superiorly with a ball point probe, sphenoid ostium can be identified. An instrument placed between the anterior nasal spine and the anterior wall of the sphenoid sinus at an angle of 30 degrees will measure 7 cm (18). When the anterior wall of the sphenoid sinus is thick because of hyperostosis, anterior wall can be drilled under the control of CT evaluation (Figure 3).

The transethmoid approach is preferred when concurrent disease occurs in the ethmoid sinus that requires treatment. Once the posterior ethmoid cell has been identified, dissection proceeds inferiorly and medially. Superior turbinate and meatus are exposed. Sometimes, removing posterioinferior end of the superior turbinate facilitates identification of the sphenoid sinus ostium. This removal exposes the sphenoid ostium, which is medial to the resection area. This maneuver should be limited. It is wise to avoid unnecessary superior turbinate resection since there resides olfactory epithelium.

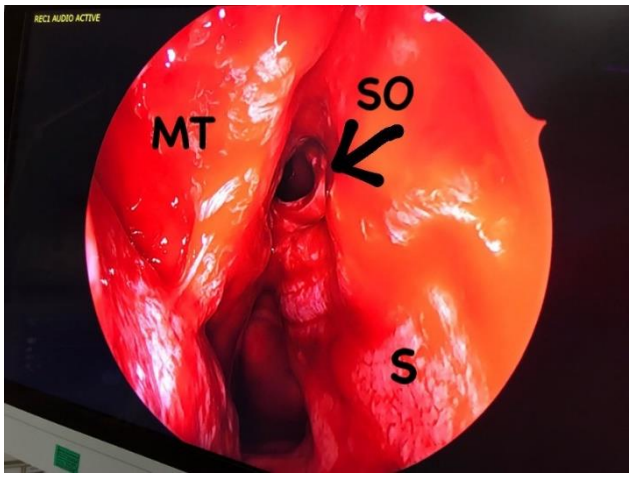

Figure 3. Enlarged right sphenoid sinüs ostium. MT:middle turbinate SO: sphenoid sinüs ostium S:septum

After the sphenoid sinus ostium is visualized, it can be enlarged. At the anterior surface, septal branch of the sphenopalatine artery runs horizontally inferior to the ostium. So, widening of the ostium inferiorly should be limited. If this artery bleeds, it can be safely cauterized. Anterior wall is removed superiorly until it is flush with the skull base. The roof of the sphenoid sinus represents the lowest point of the skull base.

Once the sphenoid sinus ostium is enlarged, the medial- inferior aspect of the posterior ethmoid cells can be punctured just lateral to the superior turbinate in order to join the sphenoid sinus and posterior ethmoid cells. This partition can be enlarged laterally up to the lateral wall of the sphenoid sinus.

Both the optic nerve and the internal carotid artery are situated along the posterolateral wall of the sphenoid sinus. At times, bone overlying these structures may be dehiscent. Mostly, sphenoid

sinuses are not symmetric and intersinus septum shows variable connections to surrounding structures. It is not uncommon that intersinus septum attaches to internal carotid artery making its manipulation dangerous (19). Medial and superior wall of the sinus leads to the sella turcica and pituitary gland in it. Superior wall of the sphenoid sinus is extremely thin. Manipulations within the sphenoid sinus deserves utmost care in order to avoid catastrophic complications.

Sometimes, sphenoethmoid (Onodi) cells extend laterally and superiorly to the sphenoid cells. These cells can be identified in the CT scan. Onodi cell may embrace or completely surround the optic nerve. The internal carotid artery may also bulge through posterolateral wall of this cell. Approaching to the sphenoid sinus through Onodi cell may damage the optic nerve and the internal carotid artery.

Injury of the internal carotid artery is the most dreaded complication of the ESS. Anomalies of the artery, aggressive manipulation of the lateral intersinus sphenoid septations or greater extend of surgery increase the likelihood of this trauma. This injury requires immediate tamponade of the sphenoid sinus and balloon occlusion of the artery. There is a high probability of neurologic sequelae and death.

Most injuries of the optic nerve occur in the presence of the Onodi cell. In the event of optic nerve injury, repair is not helpful and it results in irreversible blindness.

Total ethmoidectomy: Once the level of fovea ethmoidalis is established, posterior ethmoid dissection can be commenced from posterior to anterior, from known to unknown, up to the anterior ethmoid artery. The fovea ethmoidalis is followed anteriorly along the posterior ethmoids first and anterior ethmoids later. The width of the ethmoid cavity decreases from posterior to anterior. During dissection of both anterior and and posterior ethmoidal cells, the level of the fovea ethmoidalis (superior wall), lamina papyracea (lateral wall) and cribriform plate (medial wall) should be taken into consideration. The level of the fovea ethmoidalis is usually above the roof of the sphenoid sinus. Mostly, the angle of the surgical instruments is perpendicular to the skull base. Fovea ethmoidalis seems like a white plate of bone, while lamina papyracea has a yellow reflection. The junction of the fovea ethmoidalis and middle turbinate (lateral cribriform lamella) is especially vulnerable to injury. While the thickness of the ethmoid roof next to the lateral lamella is about 0.5 mm, thickness of the lateral lamella of the cribriform plate is about 0.05 mm (20). A deeper olfactory fossa (cribriform plate) relative to the fovea ethmoidalis increases the risk of lateral lamella injury with resultant cerebrospinal fluid (CSF) leak (21).

Ethmoid cells should be removed close to the skull base, trying to keep the mucosa intact. Each bony lamella should be checked carefully before removal. If the area behind the bony lamella is empty, it can be removed safely, preferably using through cutting instruments. Ethmoid cells medial to the lamina papyracea are removed.

Despite adequate precautions, cases of CSF leak will still be encountered. Repairing any CSF leak at the time of surgery avoids serious complications. First of all, extent of the injury should be evaluated. Neighbouring bone partitions and nasal mucosa are removed to facilitate contact of the graft with the skull

base. When the bony defect size is large, underlay bone or cartilage graft can be used to occlude the gap. The nasal side of the injury is closed with a variety of grafts, such as nasal or turbinate mucosa, temporalis fascia, fascia lata, temporalis muscle, abdominal fat, acellular dermal grafts, perichondrium. The graft is secured with gelfoam and nasal cavity is packed (22).

If the lamina papyracea is breached, medial rectus and superior oblique muscles may be injured. Immediate treatment of the laceration is recommended since late interventions are ineffective. Muscle must be repaired by an ophthalmologist through an external approach.

Frontal sinus surgery: If there is opacification of the frontal recess, it is best to perform anterior ethmoidectomy as the first step surgery and reserve frontal recess surgery if this fails. Anterior ethmoidectomy can be adequate to resolve the frontal recess pathology. In the case of osteoma, mucocele, fungal infection, frontal recess is operated on at the first step.

Computer assisted navigation system is valuable in ESS, especially in revision cases and advanced surgeries. Frontal recess approach is the most challenging part of the ESS. Navigation of the frontal sinus surgery reduces the disease process and improves the patient satisfaction (23).

Access into the frontal recess is technically demanding and potentially dangerous step of the ESS. Frontal recess surgery is susceptible to high failure rate, postoperative stenosis and major complications. Especially when the dimentions of the frontal recess is small, any attempt to open it is more risky. Manipulation of the frontal sinus is critical since the frontal sinus is close to the anterior cranial cavity, orbit and anterior ethmoid artery. Before commencing to the frontal sinus surgery, the neighborhood of this narrow space should be taken into account to avoid unwanted complications (24). Lateral lamella of the cribriform plate is very thin and easily injured with resultant cerebrospinal fluid leak, so pressure should not be applied medially. Again, when the agger nasi cells are absent or rudimentary, probing laterally may damage orbital cavity. Additionally, inadvertant trauma to the frontal recess mucosa may cause stenosis. The obscure location of the frontal resess and its close proximity to the eye and brain may dissuade the surgeon from performing appropriate surgery (25).

Insertion site of the anterior uncinate process should be considered from the CT scan. If uncinate process inserts to the lamina papyracea, frontal recess drains to the middle meatus. If uncinate process attaches to the skull base or middle turbinate, frontal recess opens to the infundibulum.

Switching to the 45 degrees endoscope gives better visualization at this level of the surgery. The anterior ethmoid artery usually lies posteroinferior to the frontal recess (Figure 4). It is mostly posterior to the supraorbital ethmoid cells but may be situated between supraorbital cells and frontal sinus. It runs along the roof of the ethmoid from the orbital cavity to the anterior cranial cavity. If there is a supraorbital cell, frontal sinus ostium will be more medially located.

Leading a ball probe gently lateral to the anterior middle turbinate reveals the frontal recess. Anterior wall of the ethmod bulla helps to define the frontal recess (Figure 5). This part of the ethmoid bulla is removed. This will reveal the suprabullar recess.

Agger nasi cells are opened anteroinferiorly with curettes. Bone fragments are removed. Removal of the agger nasi cells is safe since they are away from the eye and intracranial cavity (25).

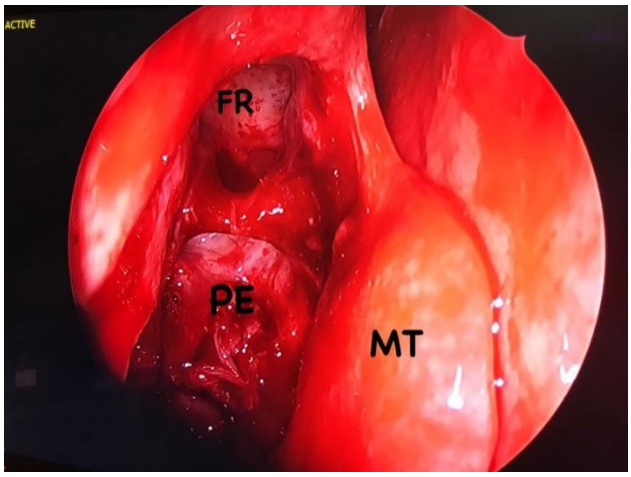

Figure 4. 45-degrees view of the frontal recess in the right nasal cavity. Note that anterior ethmoidal artery is located just posterior to the recess. MT:middle turbinate FR:frontal recess PE: posterior ethmoidal cell

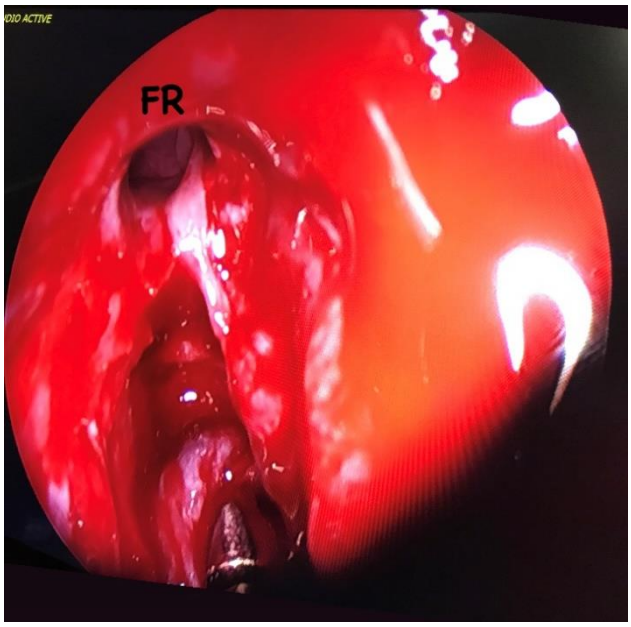

Figure 5. 45-degrees view of the frontal recess in the right nasal cavity of a different patient. Suction device is pointing the posterior ethmoidal cell. FR: frontal recess

Endoscopic light can be used to delineate the borders of the frontal sinus in case of frontal sinus obliteration surgery. Transillumination of the frontal recess area intranasally demonstrates the extension of the frontal sinus at the level of dark and bright zone intersection.

Additionally, frontal sinus transillumination can be used to assess the patency of the frontal recess. Intranasal application of the endoscopic light can be seen as brightness in the frontal area if the frontal sinus is patent. (26).

The Draf classification of the frontal recess surgery consists of 3 steps (27). In a Draf I surgery, after dissection of the anterior ethmoid cells, frontal sinus drainage pathway is palpated with a probe and its patency is confirmed. Any obstructive pathology inferior to the frontal sinus ostium is removed. Anterosuperior ethmoid cells and frontal cells are dissected from posterior to anterior, remaining anterolaterally. Care is taken to avoid stripping and removing surrounding mucosa. Bony fragments are removed taking care to keep the mucosa undisturbed. The Draf II and III are extended frontal sinusotomies. They are preferred when more conservative surgeries fail or in recalcitrant frontal sinus diseases. The extent of the Draf II surgery includes the cells removed in Draf I surgery and also obstructing structures extending to the frontal sinus ostium. Nasofrontal beak or frontal recess cells protruding into the frontal sinus are removed. In a Draf IIa surgery, the frontal sinus ostium is opened between the lamina papyracea and the middle turbinate. Draf IIb involves the opening of the frontal sinus ostium between the lamina papyracea and the nasal septum. First, Draf IIa procedure is performed and additionally anterior attachment of the middle turbinate to the skull base is removed. Draf IIb is indicated when the Draf IIa fail, especially if the frontal sinus ostium is narrow. The Draf III frontal sinusotomy, also known as

endoscopic modified Lothrop procedure, is bilateral Draf IIb procedure with the addition of removal of the part of the superior nasal septum and part of the inferior frontal intersinus septum creating one common recess. To form the common recess by this method, the size of the frontal recess should be adequate. The minimum anterior- posterior distance of the frontal recess should be 5-6 mm on the CT scan. The risk of CSF leak is 10 % with this technique (28).

The anterior ethmoid artery crosses the roof of the anterior ethmoid cells posterior to the frontal recess. Anterior and posterior ethmoid arteries are branches of the ophthalmic artery, passing from the orbital cavity to the nasal cavity. The anterior ethmoid artery travels anteromedially to the anterior cranial cavity. It may be at the level of skull base or may be placed inferiorly, tenting in bony mesenteries. Posterior ethmoid artery lies within the skull base anterior to the sphenoid sinus and it is difficult to identify. When the anterior ethmoid artery is severed, it may retract into the orbital cavity with resultant orbital hematoma. Ligation of this vessel is very difficult since it will retract into the orbit. A sudden onset of increased intraorbital pressure and proptosis occurs. If this high pressure is not relieved within 60 to 90 minutes, blindness may ensue (29). An ophthalmology consultation is necessary. Steroid and mannitol administration are helpful. Intraocular pressure greater than 40 mm Hg is an absolute indication for lateral canthotomy and cantholysis (22). If these are not sufficient, medial orbital decompression may be needed additionally. Bleeding of the posterior ethmoid artery is rarely encountered. It can be identified after posterior ethmoidectomy and sphenoidotomy, coursing anteroposteriorly. Bleeding can be controlled with bipolar electrocautery.

Avoidance of nose blowing after surgery is recommended as these attempts can cause subcutaneous or orbital emphysema. Intranasal packing can be considered if there is a bleeding tendency, overmobile middle turbinate, or in cases of simultaneous septoplasty surgery cases.

Postoperative care of the nasal cavity has considerable importance with respect to optimum healing. Irrigationation of the operative field using hypertonic or isotonic solutions and periodic debritment of clots, mucous plugs improve rapid healing and decrease any synechiae formation. Debritment can beging in the postoperative first or second weeks and performed several times as needed. Following surgery, irrigation of the nasal cavity by diluted baby shampoo was shown to reduce crusting and synechia and improved SNOT-22 scores (30).

REFERENCES

1. Clemente MP (2005) Combined microscopic and endoscopic technique (COMET surgery). In: Levine HL, Clemente MP (eds) Sinus surgery, endoscopic and microscopic approaches, Thieme, New York, pp 162-206.
2. Xu Z, Huang Y, Delemarre T, Cavaliere C, Zhang N, Bachert C. Advances in chronic rhinosinusitis in 2020 and 2021. J Allergy Clin Immunol. 2021 Dec 29:S0091-6749(21)02744-5. doi: 10.1016/j.jaci.2021.12.782. Epub ahead of print. PMID: 34973298.
3. Lourijsen ES, Reitsma S, Vleming M, Hannink G, Adriaensen GFJPM, Cornet ME, et al. Endoscopic sinus surgery with medical therapy versus medical therapy for chronic rhinosinusitis with nasal polyps: a multicentre, randomised, controlled trial. Lancet Respir Med. 2022;7:2213-2600(21)00457-4. doi:

10.1016/S2213-2600(21)00457-4. Epub ahead of print. PMID: 35012708.

4. Ribeiro RB, Reis CP, Castro SS, Ferreira JP, Sousa CA. Endoscopic sinus surgery: A safe procedure among the less experienced surgeons? Auris Nasus Larynx 2012;39:490-95.
5. Bolger W, Kennedy D. Complications of surgery of the paranasal sinuses. In: Eisele D, ed. Complications in Head and Neck Surgery. St. Louis: Mosby Yearbook, 1993:458-70.
6. May M, Levine HL, Mester SJ, Schaitkin B. Complications of endoscopic sinus surgery. Analysis of 2108 patients: incidence and prevention. Laryngoscope 1994;104:1080-3.
7. Kennedy DW, Shaman P, Han W, Selman H, Deems DA, Lanza DC. Complications of ethmoidectomy: a survey of fellows of the American Academy of Otolaryngology- Head and Neck Surgery. Otolaryng Head Neck Surg 1994;111:589-99.
8. Suzuki S, Yasunaga H, Matsui H, Fushimi K, Kondo K, Yamasoba T. Complication rates after functional endoscopic sinus surgery: analysis of 50,734 Japanese patients. Laryngoscope 2015;125:1785–91.
9. Okushi T, Mori E, Nakayama T, Asaka D, Matsuwaki Y, Ota K, et al. Impack of residual ethmoid cells on postoperative course after endoscopic sinus surgery for chronic rhinosinusitis. Auris Nasus Larynx 2012;39:484-489.
10. Bradley DT, Kountakis SE. The role of agger nasi air cells in patients requiring revision endoscopic frontal sinus surgery. Otolaryngol Head Neck Surg 2004;131:525-7.
11. Wormald PJ. The agger nasi cell: the key to understanding the anatomy of the frontal recess. Otolaryngol Head Neck Surg 2003;129:497-507.
12. Chu ST. Endoscopic sinus surgery under navigation system- Analysis report of 79 cases. J Chin Med Assoc 2006;69(11):529-533.
13. Labadie RF, Davis BM, Fitzpatrick JM. Image-guided surgery: what is the accuracy? Curr Opin Otolaryngol Head Neck Surg 2005;13(1):27–31.
14. Levin M, Chan TJ , Hua G, Sommer DD. The middle turbinate as an anatomical landmark for a safe maxillary antrostomy during endoscopic sinus surgery: A computed tomography study. Operative Techniques in Otolaryngology 32 (2021) e6–e11.
15. Simmon D, Jones N (2005) How? Operative procedures: A step-by-step safe and logical approach. In: Simmon D, Jones N (eds) Manuel of endoscopic sinus surgery and its extended applications, 1st edn. Thieme, Stuttgard, New York, pp: 50-105.
16. Rose AS, Thorp BD, Zanation AM, Ebert CS Jr. Chronic rhinosinusitis in children. Pediatr Clin North Am. 2013 Aug;60(4):979-91. doi: 10.1016/j.pcl.2013.04.001. Epub 2013 May 13. PMID: 23905832.
17. Brescia G, Contro G, Frasconi S, Marioni G. Middle turbinate handling during ESS. Our experience. Am J Otolaryngol. 2021 Jul-Aug;42(4):102980. doi: 10.1016/j.amjoto.2021.102980. Epub 2021 Feb 16. PMID: 33621766.
18. CasianoRR. A stepwise surgical technique using the medial orbital floor as the key landmark in performing endoscopic sinus surgery. Laryngoscope 2001;111:964-974.
19. Sareen D, Agarwal AK, Kaul JM, Sethi A. Study of sphenoid sinus anatomy in relation to endoscopic surgery. Int J Morphol 2005;23(3):261-266.
20. Kainz J, Stammberger H. Das Dach des vorderen Siebbeins: ein Locus minoris resistentia an der Schadelbasis. Laryngorhinootologie 1998;67:142-149.
21. Tewfik MA, Wormald PJ. Ten pearls for safe endoscopic sinus surgery. Otolaryngol Clin n Am 2010;43:933-944.
22. Welch KC, Palmer JN. Intraoperative emergencies during endoscopic sinus surgery: CSF leak and orbital hematoma. Otolaryngol Clin n Am 2008;41:581-596.

23. Galletti B, Gazia F, Freni F, Sireci F, Galletti F. Endoscopic sinus surgery with and without computer assisted navigation: A retrospective study. Auris Nasus Larynx. 2019 Aug;46(4):520-525. doi: 10.1016/j.anl.2018.11.004. Epub 2018 Dec 6. PMID: 30528105.

24. Huang BY, Lloyd KM, DelGaudio JM, Jablonowski E, Hudgins PA. Failed endoscopic sinus surgery: spectrum of CT findings in the frontal recess. Radiographics. 2009;29(1):177-95.

25. Friedman M, Landsberg R. Frontal sinus surgery: endoscopic technique. Operative Techniques in Otolaryngol- Head Neck Surg 2001;12(2):60-65.

26. Friedman M, Landsberg R, Tanyeri H. Intraoperative and postoperative assessment of frontal sinus patency by transillumination. Laryngoscope. 2000 Apr;110(4):683-4. doi: 10.1097/00005537-200004000-00027. PMID: 10764019.

27. Weber R, Draf W, Kratzsch B, Hosemann W, Schaefer SD. Modern concepts of frontal sinus surgery. Laryngoscope 2001;111(1):137-46.

28. Govindaraj S, Agbetova A, Becker S. Revision sinus surgery. Oral Maxillofacial Surg Clin N Am 2012;24:285-293.

29. Stankiewicz JA, Chow JM. Two faces of orbital hematoma in intranasal (endoscopic) sinus surgery. Otolaryngol- Head Neck Surg 1999;120:841-7.

30. Tulaci KG, Arslan E, Tulaci T, Yazici H. Comparison of effects of baby shampoo vs. saline irrigation on endoscopic sinus surgery outcomes and quality of life. Auris Nasus Larynx. 2021 Jun;48(3):408-414. doi: 10.1016/j.anl.2020.08.009. Epub 2020 Aug 26. PMID: 32859445

May, 2022 Referees Index In Our Journal Publications Process, Extend Our Thanks To Article Assessment Referees.	
Abdulkadir Ozgur	Yeni Yuzyıl University, Istanbul
Abdullah Alper Şahin	Ordu University, Ordu
Ali Beytur	Inonu University, Malatya
Ali Özdamar	Antalya Kepez State Hospital, Antalya
Ali Yilmaz	Ordu University, Ordu
Alper Cirakli	Ordu University, Ordu
Arzu Bulut	Bandırma Univesity, Bandırma
Aslı Metin Mahmutoğlu	Bozok University, Yozgat
Ayhan Tekiner	University of Health Sciences, Ankara
Ayse Arıkan	Near East University, Cyprus
Cemil Colak	Inonu University, Malatya
Deha Denizhan Keskin	Ordu University, Ordu
Eda Sahin	Giresun University, Giresun
Emine Ibici Akca	Amasya University, Amasya
Emre Gökcen	Bozok University, Yozgat
Erdal Uzun	Erciyes University, Kayseri
Gonca Gulbay	Ordu University, Ordu
Gulgez Neslihan Taskurt Hekim	Ondokuz Mayıs University, Samsun
Hatice Gul Oztas	Sutçü İmam University, Kahramanmaras
Hulya Ince	Private Medical Park Samsun
Ibrahim Keles	Afyon Kocatepe University, Afyon
Ilhan Gecit	Inonu University, Malatya
Kasım Ilter Ital	Abant Izzet Baysal Univesity, Bolu
Mehmet Çetin	Ömer Halisdemir University, Niğde
Muhammet Alibeyoğlu	University of Health Sciences, Ankara
Nilay Ildız	Erciyes University, Kayseri
Ozgur Yağan	Hitit Univesity, Çorum
Seda Eryılmaz	Ahievran University
Seda Keskin	Ordu University, Ordu
Sedat Sen	Ondokuz Mayıs University, Samsun
Songul Aktas	Karadeniz Tecnical University, Trabzon
Yasemin Kaya	Ordu University, Ordu
Yasemin Ustun	Ondokuz Mayıs University, Samsun
Yavuz Erdem	Health Practice and Research Center, Ankara
Yeliz Kasko Arici	Ordu University, Ordu
Yonca Coluk	Giresun University, Giresun