2023 VOL 6 ISSUE 3

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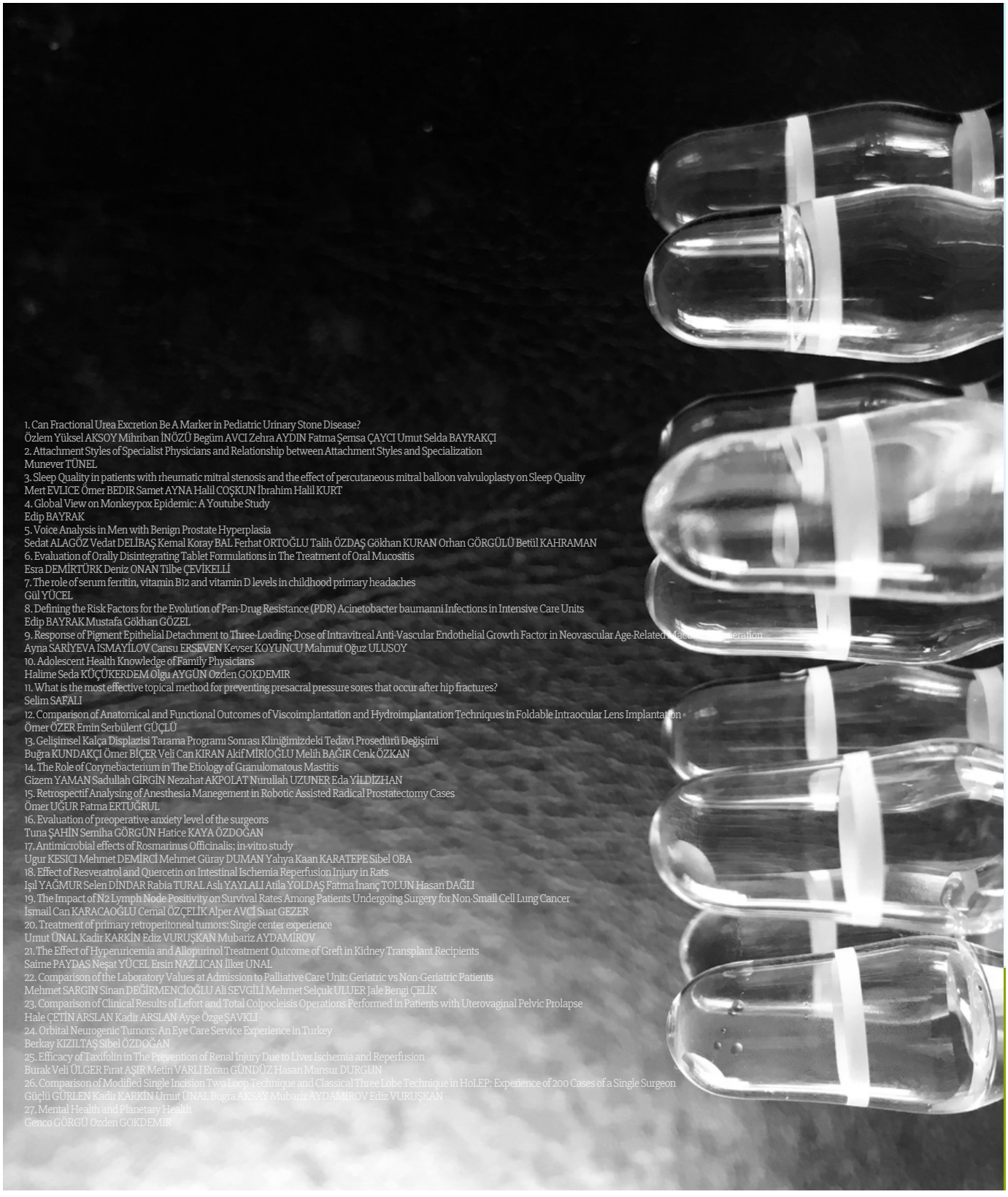

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ABSTRACTED & INDEXED

TRDizin
CrossRef
Index Copernicus Master Journal List
Scilit
Türk-Medline
BASE
Google Scholar
ASOS Indeks
Türkiye Atıf Dizini

AIM

The aim of the journal is to announce offering of national and international scientific environment and share high quality research studies, case studies and reviews conducted in the field of anesthesia, pain medicine, intensive care and surgical sciences both in Turkey and abroad; and to contribute to the development of scientific communication by establishing a continuous educational platform.

SCOPE

Çukurova Anestezi ve Cerrahi Bilimler Dergisi (J Cukurova Anesth Surg) is published online three times a year (April, August, December). Special or supplement series may also be published where necessary. Manuscripts submitted to the journal are evaluated by independent peer reviews according to double blind peer review system. Scientifically reviewed manuscripts can be freely accessed through the internet without financial, legal and technical barriers. These manuscripts can be read, downloaded, copied, distributed, printed, scanned, linked to full texts, indexed, transferred as data to the software and used for any legal purpose. Authors and copyright owners agree that all users have freeaccess.
All scientific papers sent to the Çukurova Anestezi ve Cerrahi Bilimler Dergisi should take into account the recommendations of the International Committee of Medical Journal Editors and the International Standards for Editors (ICJME) and Authors of the Committee on Publication Ethics(COPE).

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ETHICAL PRINCIPLES & PUBLICATION POLICY I

Scientific Responsibility

In terms of scientific publishing standards, the articles to be submitted should be prepared in accordance with the criteria of the International Medical Journal Editors Board (ICMJE), Publication Ethics Committee (COPE).
https://publicationethics.org/files/Full_set_of_flowcharts_Turkey_2017%20%281%29.pdf
http://www.icmje.org/recommendations/browse/roles-and-responsibilities/responsibilities-in-the-submission-and-peer-peview-process.html
• The articles to be submitted must comply with research and publication ethics. The responsibility of the articles belongs to their authors.
• Articles should not have been published anywhere before and / or should not be in the evaluation process for publication.
• In order for the evaluation process to begin, the articles must be submitted with the Copyright Transfer Form signed by all authors. For author ranking, the signature order in the Copyright Transfer Form is taken into consideration.
• Corresponding author bears the responsibility of the final version of the article on behalf of all authors.

Ethical Responsibility

• Compliance with the Helsinki Declaration Principles (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/) is sought in all studies involving the element of "Human". In such studies, the authors should state that they carried out the study in accordance with these principles in the MATERIAL AND METHODS section, and that they received approval from the ethics committees of their institutions and "informed consent" from the people who participated in the study.
• If the item "Animal" is used in the study, the authors should be informed in the MATERIAL AND METHODS section of the Guide for the Care and Use of Laboratory Animals (https://grants.nih.gov/grants/olaw/guide-for-the-care-and-use- of-laboratory-animals.pdf), they should state that they protect animal rights in their work and that they get approval from the ethics committees of their institutions.
• In case presentations, "informed consent" should be obtained from the patients.
• Ethics committee approval information should be stated in the MATERIAL and METHODS section, together with the name, approval date and number of the committee.
• If there is a direct-indirect commercial connection or financial support institution in the study, the authors; used commercial product, drug, company, etc. They should indicate to the editor on the presentation page that they have no commercial relationship with or what kind of relationship (consultant, other agreements) they have.
• Authors are responsible for reporting all personal and financial relationships related to the study. It must be clearly declared whether there is any conflict of interest associated with the application and / or evaluation of the article.
• The authors are responsible for the compliance of the articles with scientific and ethical rules.

1. Authors

Authors must comply with all authorship policies and conflict of interest statements detailed in Sections IIA and B of this document.

a. Predatory or Fake Journals

These are called predatory journals because of the rapidly increasing numbers of journals called 'scientific journals' but that publish all the posts for a fee without any screening for profit. It has become more important to maintain some standards in scientific journalism. For this reason, our journal follows the recommendations of organizations such as ICMJE, COPE and WAME and complies with the standards.

2. Journals

a. security

Manuscripts submitted to journals are privileged communications that are the private, confidential property of the author, and authors can be harmed by premature disclosure of any or all the details of a manuscript.
For this reason, editors should not share with anyone other than the authors and reviewers whether it has been handled and reviewed, its content and status in the review process, including the reviewers' critique and eventual fate. Requests from third parties to use reviews in manuscripts and legal proceedings should be politely refused, and editors should do their best not to provide such confidential material as subpoenas.
Editors should also make it clear that the reviewers must keep the manuscripts, related materials, and information they contain strictly confidential.
Reviewers and editorial staff should not publicly discuss the author's work, and reviewers should not endorse the ideas of the authors prior to publication. Reviewers should not keep the article for their personal use and should destroy the hard copies of the articles and delete the soft copies after submitting their reviews.
When an article is rejected, it is best practice for journals to delete copies from their editorial systems unless local regulations require retention.
Journals that maintain copies of rejected manuscripts should disclose this practice in the Authors' Notice.
When an article is published, journals should retain copies of the original submission, review, revision, and correspondence for at least three years, and possibly permanently, depending on local regulations, to answer future questions about the work.
Editors should not publish reviewers' comments without the permission of reviewers and authors. If journal policy will protect authors against the reviewer's identity and comments are not signed, that identity should not be disclosed to the author or others without the express written consent of the reviewers.
Confidentiality may need to be breached if fraud or alleged fraud is present, but editors notify authors or reviewers of their willingness to do so, and confidentiality should be honored otherwise.

b. Timing

Editors should do their best to ensure that manuscripts are processed in a timely manner with the resources available to them. If editors are going to publish an article, they should try to do it on time and planned delays should be negotiated with the authors. If a journal has no intention of continuing an article, editors should try to reject the article as soon as possible to allow the author to submit it to a different journal.

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ETHICAL PRINCIPLES & PUBLICATION POLICY II

c. Peer Review

Peer review is a critical evaluation of manuscripts submitted to journals by experts who are not usually part of the editorial staff. Peer review is an important extension of the scientific process, as impartial, independent, critical evaluation forms the core of all scientific work, including scientific research.

The true value of peer review is debated, but the process facilitates a fair hearing for an article among members of the scientific community. More practically, it helps editors decide which articles are appropriate for their journal. Peer review often helps authors and editors improve the quality of their reporting.

It is the editor's responsibility to ensure that reviewers have access to all material related to the review of the manuscript, including additional material for email-only, for selection of appropriate reviewers, and to ensure that reviewer reviews are appropriately evaluated and interpreted in context.

A peer-reviewed journal is not obligated to submit articles submitted for review and is not obligated to follow up on reviewers' suggestions, positive or negative. The editor of a journal is ultimately responsible for the selection of all content, and editorial decisions may be made aware of matters unrelated to the quality of a manuscript, such as journal relevance. An editor may reject any article at any time, including after it has been accepted when concerns about the integrity of the work arise.

Journals may differ in the number and types of articles they submit for review, the number and types of reviewers they seek for each article, whether the review process is open or blind, and other aspects of the review process. For this reason, and as a service to authors, journals should publish a description of the peer review process.

Journals should ultimately review their decision to accept or reject a paper and acknowledge the reviewers' contribution to their journals. Editors are encouraged to share reviewers' comments with reviewers of the same article so that reviewers can learn from each other during the review process.

As part of peer-review, editors are encouraged to review research protocols, statistical analysis plans if separate from the protocol, and/or contracts related to project-specific studies. Editors should encourage authors to make such documents public at the time of or after publication before accepting such work for publication. Some journals may require these documents to be publicly posted as a condition of their acceptance.

Log requirements for independent data analysis and availability of publicly available data were published during this revision; this reflects evolving views on the importance of data availability for pre- and post-publication peer review. Some journal editors currently request statistical analysis of trial data by an independent biostatistician before accepting studies for publication. Others encourage or request authors to share their data with others for review or reanalysis, while others indicate whether study data may be used by third parties for viewing and/or reanalysis. Each journal should establish and publish its own specific requirements for data analysis and registration in a place easily accessible to potential authors.

Some people believe that true scientific peer review only begins when a paper is published. In this regard, medical journals should have a mechanism for readers to submit comments, questions or criticisms on published articles, and authors should respond appropriately and cooperate with requests for journal data or request additional information regarding the paper. occurs after publication (see Chapter III).

d. Integrity

Editorial decisions should be based on the relevance of a manuscript to the journal and its contribution to the evidence for its originality, quality, and important questions. These decisions should not be influenced by business interests, personal relationships, or agendas, or by findings that are negative or credibly question accepted wisdom. In addition, authors should submit for publication or make it publicly available, and editors should not consider publication, exclude studies with findings that are not statistically significant or have inconclusive findings. Such studies may provide evidence that evidence pooled with other studies through meta-analysis can still help answer important questions, and public recording of such negative or inconclusive findings may prevent unintended duplication of effort or other researchers considering similar studies. can be valuable to Journals should clearly outline the appeals process and have a system in place to respond to appeals and complaints.

e. Journal Metrics

Journal impact factor is widely misused as a proxy for research and journal quality and as a measure of the benefits of research projects or individual researchers, including their eligibility for recruitment, promotion, hiring, awards, or research funding. The ICMJE recommends that journals reduce the emphasis on impact factor as a single measure, instead offering a set of articles and journal metrics related to their readers and authors.

3. Reviewers

Manuscripts submitted to journals are privileged communications that are the private, confidential property of the author, and authors may suffer from early disclosure.

Therefore, the reviewers should keep the articles and the information they contain strictly confidential. Reviewers should not publicly discuss the author's work and properly write down the authors' ideas before the article is published. Reviewers should not keep the article for their personal use and should destroy the copies of the articles after reviewing them.

Reviewers are expected to respond promptly to review requests and submit reviews within the agreed timeframe. Reviewers' comments should be constructive, honest, and polite.

Reviewers must declare conflicts of interest and withdraw themselves from peer review if there is a conflict.

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PLAGIARISM POLICY

The journal "Çukurova Anestezi ve Cerrahi Bilimler Dergisi" are committed to publishing only original material, i.e., material that has neither been published elsewhere, nor is under review elsewhere.
The journal "Çukurova Anestezi ve Cerrahi Bilimler Dergisi" uses software to detect instances of overlapping and similar text in submitted manuscripts: Manuscripts in which plagiarism or textual borrowings are found without reference to the original source are rejected by the editorial board for publication in the journal.

Plagiarism before publication

The journal "Çukurova Anestezi ve Cerrahi Bilimler Dergisi" will judge any case of plagiarism on its own merits. If plagiarism is detected, either by the editors, peer reviewers or editorial staff at any stage before publication of a manuscript - before or after acceptance, during editing or at page proof stage, we will alert the author(s), asking her or him to either rewrite the text or quote the text exactly and to cite the original source. If the plagiarism is extensive - that is, if at least 25% of the original submission is plagiarized - the article may be rejected and the author's institution/employer notified.

Policy of checking for plagiarism

The manuscripts in which plagiarism is detected are handled based on the extent of plagiarism present in the manuscript: if < 25% plagiarism – the manuscript is immediately sent back to the authors for content revision, and if > 25% plagiarism – the manuscript is rejected without editorial review. The authors are advised to revise the plagiarized parts of the manuscript and resubmit it as a fresh manuscript. The percentage of plagiarism is calculated by software and also assessed manually.

Plagiarism after publication

If plagiarism is detected after publication, the Journal will conduct an investigation. If plagiarism is found, the journal editorial office will contact the author's institute and funding agencies. The paper containing the plagiarism will be marked on each page of the PDF. Depending on the extent of the plagiarism, the paper may also be formally retracted.

Recommendations for avoiding plagiarism

Use quotation marks around words taken verbatim from a source Change no part of quotation within the context of the sentence Use single marks for a quotation within a quotation Use ellipses (a space and three periods) for a part of the quotation omitted. Use brackets around added words Limit the use of direct quotes
Attempt to paraphrase the information, or summarize the information derived from a variety of sources using own words.
Authors are responsible for obtaining copyright permission for reproducing illustrations, tables, figures taken from other authors and/or source. Permission must be placed at the foot of each figure.

Self-Plagiarism

Some authors have written several chapters for several different books that are changed only slightly. Each manuscript is copyrighted when published. Because the author no longer owns the rights to these words, one should not plagiarize them. Most editors and reviewers would argue that self-plagiarism is unethical. Thus, an author cannot copy one's own material for a new manuscript without permission of the copyright holder. Alternatives include using quotes around short phrases of own work and citing appropriate references.

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OPEN ACCESS POLICY

Çukurova Anestezi ve Cerrahi Bilimler Dergisi adheres to the Budapest Open Access Initiative and defines its Open Access policy according to the definition developed in the original BOAI: By "open access" to [peer-reviewed research literature], we mean its free availability on the public internet, permitting any users to read, download, copy, distribute, print, search, or link to the full texts of these articles, crawl them for indexing, pass them as data to software, or use them for any other lawful purpose, without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. The only constraint on reproduction and distribution, and the only role for copyright in this domain, should be to give authors control over the integrity of their work and the right to be properly acknowledged and cited.

1. On policy

1.1. Every institution of higher education should have a policy assuring that peer-reviewed versions of all future scholarly articles by faculty members are deposited in the institution's designated repository. (See recommendation 3.1 on institutional repositories.)

- Deposits should be made as early as possible, ideally at the time of acceptance, and no later than the date of formal publication.
- University policies should respect faculty freedom to submit new work to the journals of their choice.
- University policies should encourage but not require publication in OA journals, and should help faculty understand the difference between depositing in an OA repository and publishing in an OA journal.
- When possible, university policies should be adopted by faculty vote, should require immediate OA, and should welcome repository deposits even when not required (e.g. datasets, conference presentations, books or book chapters, work published before the policy's adoption, and so on).
- When publishers will not allow OA on the university's preferred terms, we recommend either of two courses. The policy may require dark or non-OA deposit in the institutional repository until permission for OA can be obtained. Or the policy may grant the institution a nonexclusive right to make future faculty research articles OA through the institutional repository (with or without the option for faculty to waive this grant of rights for any given publication).

1.2. Every institution of higher education offering advanced degrees should have a policy assuring that future theses and dissertations are deposited upon acceptance in the institution's OA repository. At the request of students who want to publish their work, or seek a patent on a patentable discovery, policies should grant reasonable delays rather than permanent exemptions.

1.3. Every research funding agency, public or private, should have a policy assuring that peer-reviewed versions of all future scholarly articles reporting funded research are deposited in a suitable repository and made OA as soon as practicable.

- Deposits should be made as early as possible, ideally at the time of acceptance, and no later than the date of formal publication.
- When publishers will not allow OA on the funder's terms, funder policies should require grantees to seek another publisher.
- If funder policies allow embargoes before new work becomes OA, the embargoes should not exceed six months. Policies should allow no embargoes at all for uncopyrightable work.
- Funders should treat publication costs as research costs, and should help grantees pay reasonable publication fees at fee-based OA journals.
- When possible, funder policies should require libre OA, preferably under a CC-BY license or equivalent.
- A repository is suitable for this purpose when it provides OA, supports interoperability with other repositories, and take steps toward long-term preservation. The funder's choice should be determined by ongoing research into questions such as which choice best fosters the deposit of covered articles, the utility of deposits, the convenience of funders and authors, and incentives for the further growth of OA.

1.4. All university and funder OA policies should require deposit in a suitable OA repository between the date of acceptance and the date of publication. The metadata should be deposited as soon as it is available and should be OA from the moment of deposit. The full-text should be made OA as soon as the repository has permission to make it OA.

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On the first page of the article file, only the author information and, if applicable, the related notes should be found on the first page of the article.
Article text should start from the second page.
The abstract should have a maximum length of 250 words. The Objective should include Materials and Methods, Results and Conclusion. Keywords with at least 3 (three) words should be written with a space between the abstract.
Research article format; Introduction, material and method, findings, discussion and conclusion
Case presentation format; Introduction, case report, history, tests, progress, treatment and outcome, discussion-literature review, recommendations
References
The authors themselves are responsible for the accuracy of the resources.
References should be written on a separate page and should be numbered according to the order of transition.
If the name is not given in the sentence, the source number should be given in superscript before the pointYear, volume, start and end pages should be gn in journal sources, but only the year should be stated in book sources.
If there are more than two consecutive sources, the first and last ones should be given a "-" sign:
References should contain the full surnames of the authors and the first letters of their names.
If the number of writers in the source is 3 or less, all authors should be mentioned. the source should be written.
Journal names should be shortened according to Pubmed.
Authors are responsible for the correctness of references and spelling.
Manuscripts and punctuation marks must comply with the following examples.
The source is a magazine; The author should be written in full capitalization, and the first name should be written as first letter and larger. Title of article. The journal is abbreviated to Index Medicus. Year: Volume: First page number-Last page number
If the source is a book; Name (s) of the surname of the author (s). The name of the book. What is the pressure? Publication Place: Printing House, Publication Year.
If a chapter from the book was used as a source;Name (s) of the surname of the chapter author (s). Section title. The name of the book. What is the pressure? (First name and last name (s) of ed and Eds. Editor (s): First page number-last page number of the section. Printing place, Publisher, Year of printing.
If the website is shown as source; The name of the Web site. (accessed date)
The source thesis is; First name of the author's surname. Title of the thesis (thesis). Name of the city, University name (if university), Year.
Tables:
1. Tables should be written on a separate page with a single line spacing.
2. Each table should have number and descriptive information above it.
3. If abbreviations are given in the table, these abbreviations can be defined as subtitles under the table and alphabetical order.
4. When previously printed or electronically published tables are used, written permission must be obtained from both the author and the printer and this must be sent to the editor of the journal by fax or mail.
5. Transverse and longitudinal lines should not be used in the table, only a straight line should be drawn at the top and bottom.
6. Tables should not be repeated in the text.
7. Tables should not be placed in writing.
8. Tables should be in the file to which each post is sent to a table.
Figure Graphic Pictures and Subtitles:
1. Subtitles should be written on a separate page with two lines spaced apart.
2. Numbered according to the order in the text and abbreviations in figures, graphics and pictures, abbreviations should be placed in the alphabetical order below the subtitle.
3. Tables, figures and graphics should not be placed in the writing.
4. Magnification ratio and staining technique should be explained in microscopic pictures.
5. When using previously printed or electronically published figures, graphics and illustrations, written permission must be obtained from both the author and the printer, and should be sent to the editor of the journal by fax or post.
6. Written permission must be obtained when using the images of the persons to be recognized.
7. The explanations of the figures should be written at the end of the file to which the manuscript is sent.
8. Table, figure and graphs should be mentioned in the text.
9. The pictures / photos should be colored, the details should be clearly visible and clear.
10. Figures, pictures / photos are separate. jpg file should be added to the system.
11. Image and photo files should not be less than 100 pixel / inch, 8 cm wide and 300dpi.

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STATISTICS

TIME STATISTICS, ACCEPTANCE-REJECTION STATISTICS 2022

	Number of Articles Calculated	Average Time (Day)
Article Submission - Withdraw:	3	13
Article Submission - Return:	8	58
Article Submission - First Editor Assignment:	75	4
First Editor Assignment - Acceptation Decision Statistic		
Peer review:	54	58
Non peer review:	0	0
First Editor Assignment - Rejection Decision Statistic		
Peer Review:	5	84
Non-Peer Review:	7	12
Article Submission - Acceptation Decision Statistic		
Peer Review:	54	62
Non-Peer Review:	0	0
Article Submission - Rejection Decision Statistic		
Peer Review:	5	8
Non-Peer Review:	7	13

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VOL 6 ISSUE 3

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Sait YEŞİLLİK
Sağlık Bilimleri Üniversitesi, Gülhane Eğitim Ve Araştırma Hastanesi, İç Hastalıkları Ana Bilim Dalı, Allerji Ve İmmunoloji Bilim Dalı
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Sema YÜKSEKDAĞ
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ÇUKUROVA
ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ

CONTENTS I

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CONTENTS II

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Can Fractional Urea Excretion Be a Marker in Pediatric Urinary Stone Disease?

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Abstract

Aim: In the setting of pediatric urolithiasis, it is important to determine the presence of any metabolic disorder to prevent new stone formation and to treat the existing stone. With this aim, the urinary excretions of electrolytes and uric acid are usually obtained. Fractional excretion of urea (FeU) has been demonstrated to be useful in the setting of acute renal injury. The objective of this study is to search the importance of FeU in pediatric stone disease and to compare FeU with other urine electrolyte excretions and uric acid excretion.

Methods: We retrospectively evaluated the laboratory and medical records of 41 pediatric urolithiasis patients whose FeU percentages were studied together with the etiologic work-up. Patients were divided into two groups as microlithiasis and macrolithiasis. Demographic and laboratory data as well as FeU were compared between the two groups.

Results: Twenty-four patients (59%) had stone size less than 3 mms, seventeen patients (41%) had stones larger than 5 mms. Among all patients 20 of them were boys, 21 of them were girls. M/F ratio was 13/11 in microlithiasis and 7/10 in macrolithiasis group. Mean age was 55.8 months in microlithiasis group, whereas 39 months in macrolithiasis group. Among 24 patients with microlithiasis, 20 patients had FeU greater than 35%, and 4 patient had FeU less than 35%. To differentiate microlithiasis from macrolithiasis the sensitivity and specificity of FeU≥35 is 83% and 6% respectively. For FeU<35%, sensitivity and specificity of the test to differentiate microlithiasis from macrolithiasis is 17% and 94% respectively (p>0.05).

Conclusions: Fractional excretion of urea is not affected from the size of the stone. However, urinary urea excretion is associated with urinary sodium and uric acid excretion. Further studies with larger groups and comparison of the urolithiasis patients with healthy children without urinary stones in the controlled studies will reveal the exact results.

Keywords: *Urea excretion, nephrolithiasis, children*

1. Introduction

Urinary stone disease has become an important problem in the pediatric group, the incidence of which has increased in recent years.[1,2] Turkey is an endemic place for urinary stones affecting 10-20% of the pediatric population.[2-4] Kidney stone formation is multifactorial and metabolic etiological investigation is needed to identify underlying causes such as hypercalciuria, hyperoxaluria, and hypocitraturia, hyperuricosuria and cystinuria etc. In addition, ethnic origin, genetic factors, dietary habits and urinary tract infections, and congenital anomalies of the kidney and urinary tract may be associated with kidney stone formation.[1-3] Identification of risk factors is important for determining treatment and prevention. The most common risk factors detected in urolithiasis patients in Turkey are metabolic abnormalities and anatomical problems.[2,5]

Hypercalciuria and hypocitraturia are the most common metabolic risk factors detected in patients with nephrolithiasis.[1] Normal uric acid and calcium excretion differ in different age groups.

Urea is a fat-soluble molecule that can pass through membranes by passive diffusion, freely filtered in the glomeruli, and reabsorbed in the proximal tubule and 50-60% of the filtered urea is excreted in the urine.[6,7]

Urea is also actively transported in the renal tubules. When per-

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fusion is decreased, urea reabsorption is increased, resulting in decreased urea excretion (usually <35%). If the patient has intrinsic renal failure due to tubular damage, urea reabsorption decreases and fractional excretion of urea (FeU) exceeds 50%.[6-8] However, many conditions such as sepsis, sex, aging, protein infusion, liver disease, and some drugs affect the FeU result by interfering with the active transport of urea.[6,9,10]

There are few studies that mention urea excretion in kidney stone patients. In our study, we wanted to document the relationship between the fractional excretion of urea and the urinary excretions of some other electrolytes, and the associations with the size of the stone.

2. Materials and methods

We evaluated the laboratory and medical records of 41 pediatric urolithiasis patients whose FeU percentages were studied together with other urinary excretions certain electrolytes for the etiologic work-up. The study was conducted in Ankara Bilkent City Hospital in 2019-2020. With the help of radiology records, patients were divided into two groups as microlithiasis and nephrolithiasis according to the size of the stone as less than 3 mms and greater than 5 mms. Demographic and laboratory data as well as FeU percentages were compared between the two groups.

Demographic data, age, serum urea, creatinine, sodium, potassium levels, FeNa, FeU, random urine calcium/creatinine ratio, random urine uric acid/creatinine ratio, tubular reabsorption of phosphorus (TRP), ultrasound results were recorded. Patients were further divided into four subgroups according to their fractional excretion results as FeNa<1%, FeNa≥1% and FeU<35%, FeU≥35%, and the patient numbers were compared, in order to calculate sensitivities and specificities of the tests, between microlithiasis and macrolithiasis groups. Newborns were excluded due to the immaturity of their renal tubular functions.

Statistical analyses were performed using IBM SPSS for Windows (SPSS version 17.0). Distribution of the data for normality was tested by the Shapiro-Wilk test. Student t test was performed for normally distributed data, and Mann-Whitney U test for non-normally distributed data. Frequencies and percentages were used as descriptive values in the categorical data. Arithmetical mean ± standard deviation was used for the normally distributed data, and median and interquartile range (IQR) were used for the non-normally distributed data. Chi square test was used for fractional excretion analysis. Sensitivities and specificities were calculated. Spearman Rank Correlation analysis and Kruskal-Wallis tests were used for the relations of the electrolyte excretions. Statistical significance was accepted as 0.05.

The study was approved by the Local Ethics Committee (Ankara City Hospital, Clinical Studies E2-21-329) and the study was conducted by the Declaration of Helsinki. All data were collected and checked by two researchers.

3. Results

The relevant data regarding the urinary stone patients having the etiological work-up, including random urine urea and creatinine as well as serum urea and creatinine at the same time to calculate the fractional excretion of urea, were obtained from the medical records of the hospital. Total 41 patients were found with available data. The data regarding 41 patients were evaluated. Twenty-four patients (59%) had stone size less than 3 mms, seventeen patients (41%) had stones larger than 5 mms. Mean serum urea, creatinine, sodium, potassium, phosphorus levels and FeNa, FeU and TRP percentages were similar between the two groups (p>0.05).

Table 1

Demographic and Laboratory Data of the Groups

	Microlithiasis (≤3mm)	Nephrolithiasis (≥5 mm)	P value
n	24	17	
m/f	13/11	7/10	0.41
Mean age (months)	55.8	39.0	0.07
Serum urea (mg/dL)	23.1	21.6	>0.05
Serum creatinine (mg/dL)	0.5	0.5	>0.05
Serum potassium (mmol/L)	4.3	4.3	>0.05
Serum sodium (mmol/L)	136.6	135.2	>0.05
FeU (%)	56.9	62.9	>0.05
TRP (%)	86.8	91.9	>0.05
Random urine uric acid/creatinine ratio	1.2	1.1	>0.05
Random urine calcium/creatinine ratio	0.3	0.4	>0.05
Urine urea (mg/dL)	1108.0	835.0	
Urine sodium (mmol/L)	80.0	81.0	>0.05
Urine potassium (mmol/L)	37.0	35.0	>0.05
Urine phosphorus (mg/dL)	34.0	17.0	
FeNa(%)	1.1	1.3	>0.05

FeU: Fractional Excretion of Urea, FeNa: Fractional Excretion of Sodium, TRP: Tubular reabsorption of Phosphate

Table 2
Fractional Urea and Sodium Excretion Between the Groups

		Microlithiasis (≤3mm), n	Nephrolithiasis (>5 mm), n	n(%)
FeU (%)	≥35	20	16	36(87.8)
	<35	4	1	5(12.2)
Total p=0.299		24	17	41(100)
FeNa (%)	≥1	7	3	10(37)
	<1	8	9	17(63)
Total p=0.247		15	12	27(100)

FeU: Fractional Excretion of Urea, FeNa: Fractional Excretion of Sodium

Among all patients 20 of them were boys, 21 of them were girls. Male/female (M/F) ratio was 13/11 in microlithiasis and 7/10 in macrolithiasis group. Microlithiasis was more prevalent in boys, however the difference is not significant (p=0.41). Mean age was 55.8 months in microlithiasis group, whereas 39 months in macrolithiasis group (p=0.07) (Table 1).

We divided the patients according to their FeU percentages as FeU<35% and FeU ≥35%, and compared the microlithiasis and macrolithiasis groups. Among 24 patients with microlithiasis, 20 patients had FeU greater than 35%, and 4 patient had FeU less than 35%. To differentiate microlithiasis from macrolithiasis the sensitivity and specificity of FeU≥35 is 83% and 6% respectively. For FeU<35%, sensitivity and specificity of the test to differentiate microlithiasis from macrolithiasis is 17% and 94% respectively (p>0.05). When we analyze FeNa, among the two groups, for FeNa<1%, sensitivity and specificity of the test to differentiate microlithiasis from macrolithiasis is 53% and 25% respectively. In addition, for FeNa ≥1% the sensitivity and the specificity of the test is 47% and 75% respectively (p>0.05) (Table 2).

The urinary calcium excretion of the patients (random urine calcium/creatinine ratios) are correlated with random urine uric acid/creatinine ratios in both microlithiasis and macrolithiasis groups (p=0.001). Random urine calcium/creatinine ratio also correlates with the tubular phosphorus reabsorption (p=0.023), as well as random urine uric acid excretion correlates with tubular phosphorus reabsorption (p=0.024).

Urine calcium excretion correlates with urine sodium excretions (p= 0.04), urine calcium excretion does not significantly correlate with urea excretion (p=0.08). Urea excretion significantly correlates with sodium and uric acid excretions (p= 0.001 and p=0.01 respectively).

4. Discussion

Kidney stones are a common nephrological problem in childhood. Diagnostic procedures and follow-up in children are different from adults and metabolic study is usually expected. In parts of the Near/Middle East and North Africa (Turkey, Saudi Arabia, Egypt and Pakistan) nephrolithiasis is an endemic disease affecting 10-20% of the population.[11]

In this study, we compared the urinary electrolytes and kidney function tests of patients with microlithiasis, which can be considered as a more benign condition, and patients with stones of 5 mm or larger. Consistent with the literature we did not find any difference. Most of the microlithiasis patients were male, although not statistically significant. Microlithiasis can be considered as a more benign condition according to many studies, patients can be followed without medical treatment if there is no metabolic and/or anatomical risk factor. Medical treatment should be reserved in cases with metabolic risk factors.[2]

In a large series, it was found that the rate of microlithiasis was higher in infants (40.6%) and 64.5% of patients with microlithiasis were infants.[2] However, in our patient group, the mean age was higher in the microlithiasis group, but the difference was not significant. This can be attributed to the design of our study.

In infants or young children, microliths are sometimes not thoroughly searched for due to the presence of transient echogenicity on ultrasound. Metabolic risk factors play an important role in kidney stone formation. Calcium excretion, oxalate and citrate excretion and uric acid excretion are important in the etiological work-up of kidney stones.[5]

Urea and ammonia are the main determinants in nitrogen metabolism. Urea is transported via specific transport proteins that play an important role in concentrating urine.[12] Urea excretion is mostly the result of glomerular filtration and less tubular reabsorption. A low urea excretion indicates increased tubular reabsorption.[13]

Renal ammonia metabolism requires intrarenal ammonia formation from glutamine. Changes in factors regulating renal ammonia metabolism may have significant effects on glutamine in addition to nitrogen balance. Clinical conditions associated with altered urine concentration ability or water homeostasis can cause changes in urea excretion and urea transporters.[14]

When we examined whether there was a difference between fractionated urea excretion and urinary sodium excretion in differentiating microlithiasis from larger stones, we could not find a significant difference. In the case of low urea excretion (<35%), the probability of the stone being microlithiasis was higher, but it was not statistically significant. At the same time, the probability of detecting microlithiasis was higher in cases where the fractional sodium excretion was above 1% (sensitivity: 47%, specificity: 75%).

Clinical conditions associated with altered ammonia excretion can have significant effects on nitrogen balance. In a study, 24-hour urinary urea excretion, calculated as a reflection of protein intake, was evaluated in a study evaluating 65 children with idiopathic hypercalciuria and 76 normocalciuric control children. Urinary urea excretion was higher in patients with idiopathic hypercalciuria compared to controls. Urinary urea excretion decreases significantly with age, body weight, and height increase.[14]

Calcium and uric acid excretion were correlated in both groups. Both random urinary calcium/creatinine and uric acid/creatinine

excretion rates are associated with tubular phosphorus reabsorption. Polito et al.[14] showed that calcium excretion increases significantly with increased sodium and urea excretion. A significant interaction between urinary sodium and urea excretion has been demonstrated in increased calciuria in patients with idiopathic hypercalciuria in their study.[14] In our study, we found a correlation between calcium excretion and sodium and uric acid excretion. Urea excretion was significantly associated with sodium and uric acid excretion, but the correlation with calcium excretion was not significant in our study. In another study, urea excretion was found to be significantly higher in hypercalciuria and hyperuricosuria patients when compared with the controls.[15]

In a different study, it is demonstrated that variations in urinary urea explained 11.4% of the overall variability of urinary calcium excretion, when the urinary sodium effect is added this association rises to 16%[16]. Children with hypercalciuria have a higher dietary protein intake than children with normocalciuria. The decrease in urea excretion with increasing age and body mass may reflect the relatively higher protein intake of young growing individuals. Salt and protein have a cumulative effect on increased calcium excretion. A significant positive correlation was found between the 24-hour urinary sodium creatinine ratio and the urinary calcium creatinine ratio.[16]

Urea excretion has also been studied by other researchers; 24-hour urea excretion has been shown to increase with both potassium and sodium supplementation.[17] Potassium supplementation causes a decrease in fractional calcium excretion, while sodium supplementation causes an increase in urinary calcium excretion.[17]

The limitations of this study are that it is retrospective and the sample size is small. Urea excretion is not routinely requested in the etiological examination of patients with urinary tract stones, therefore prospective studies with sufficient number of patients will elucidate its definite benefits.

5. Conclusions

Fractional urea excretion is not affected by the size of the stone. However, urinary urea excretion is associated with urinary sodium and uric acid excretion. In daily clinical practice, urea excretion may not be beneficial in the diagnostic work-up of kidney stone patients, but it may be associated with high urinary sodium (which may imply high sodium intake, a risk for stone formation) and high uric acid excretion. Further studies with larger groups and comparison of urolithiasis patients with healthy children without urinary stones in controlled studies will reveal definitive results.

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None.

Statement of ethics

This study was approved the approval of the Local Ethical Committee was obtained (Ankara City Hospital). (07/04/2021-E2-21-329)

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author contributions

OYA is the major contributor in writing the manuscript. OYA and USB are involved in the design and conception of the study. OYA, Mİ, ZA, BA, FSC, and USB were involved in the collection of the data and the clinical follow-up of the patients. All authors read and approved the final manuscript.

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Attachment Styles of Specialist Physicians and The Relationship between Attachment Styles and Specialization Field

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Abstract

Aim: The aim of this study is to evaluate the attachment styles of specialist physicians and to examine the differences in attachment styles according to their specialty and whether they are placed in their first preference in the medical specialty exam (TUS).

Methods: A total of 92 physicians were included in the study. Individual information collection forms and the Relationship Scales Questionnaire (RSQ) were administered to all participants. Participants were asked about their gender, their specialization field, and whether their current specialization field was their first choice in the Medical Specialization Exam (TUS). Specialization fields were divided into 4 groups: surgical specialties, internal medicine specialties, basic medical sciences, and family medicine specialization.

Results: Among all participants, 14.1% exhibited secure attachment, 57.6% displayed fearful attachment, 32.6% demonstrated preoccupied attachment, and 3.3% had dismissive attachment. There was no significant difference in attachment styles based on the participants' genders. There was no significant difference in attachment styles based on whether they entered their first choice in the Medical Specialization Exam (TUS). There was no significant difference in attachment styles based on the specialization fields in which the participants received their education.

Conclusions: Among expert physicians, anxious attachment was the most common attachment style. Although there was no statistically significant difference in attachment styles based on physicians' specialization fields, family medicine and internal medicine practitioners exhibited a higher rate of secure attachment compared to those in the basic medical and surgical sciences. Determination of other possible motivational factors as well as attachment styles could provide guidance and insight to the physician in this choice that will affect her/his whole life.

Keywords: *Attachment styles, medical education, specialization field*

1. Introduction

Attachment is defined as an emotional bond established between an infant and their caregiver during the early stages of life, characterized by a seeking of closeness with the caregiver, and marked by consistency and continuity.[1] According to attachment theorists, once established as secure or insecure during infancy, attachment tends to show minimal variation throughout life. The prior psychological experiences of individuals with their caregivers give rise to enduring cognitive models and caregiving maps that persist into adulthood.[2] An individual's sense of personal competence and positive self-worth relies on the development of secure attachment. Secure attachment fosters healthy emotional and social development while shielding an individual from stress-inducing conditions. Different attachment patterns assume various forms at different stages, influencing an individual's life experiences.[3]

Adult individuals are characterized by one of the four dominant relationship styles derived from attachment theory: secure attachment, fearful attachment, dismissive attachment, and preoccupied attachment. These relationship styles are learned ways of interacting that persist throughout life, especially during vulnerable periods. Individuals with a secure attachment style tend to evaluate themselves and

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others positively. They display more accepting and intimate behaviors because they perceive both themselves and others as valuable. Individuals with a fearful attachment style, on the other hand, tend to evaluate both themselves and others negatively. Despite desiring intimacy in their relationships, they avoid social situations and close relationships due to a lack of trust in others and a fear of rejection. Individuals with a preoccupied attachment style tend to view themselves as unworthy but perceive others in a positive light. In this attachment style, a person's self-worth is contingent on others accepting them, leading them to make excessive efforts to gain approval in their relationships. On the other hand, individuals with a dismissive attachment style see themselves as valuable and lovable but tend to evaluate others negatively. These individuals have an excessive sense of self-reliance but avoid close relationships because they don't trust others enough to engage with them.[4-5]

Attachment theory is employed to explore career orientation, decision-making processes, and more. Recently, it has also become a subject of research to understand the interpersonal aspects of medical care, psychotherapeutic relationships, and the patient-clinician relationship.[5-6-7] During and after medical education, numerous factors come into play in an individual's choice of specialization. Factors such as working hours, the prestige of the specialization, the duration of the specialization program, interest in research, inclination towards long-term relationships with patients, doctor-patient interactions, patient diversity, expected income, and a focus on public health can influence a person's choices in specialization[8]. An individual's attachment style can shape their inclination to engage in long-term relationships or otherwise mediate a person's choice of specialization. Some studies conducted on medical school students have shown that the longitudinal desire for patient care has a significant impact on their choice of primary care specialties.[6-9-10]

Learning about the attachment styles of physicians or patients can be useful as a way to better understand the dynamics of the patient-doctor relationship. While many studies have begun to explore the relationship between medical care and clinical treatment and patients' attachment styles, only a few have examined clinicians' attachment styles.[6-11]

Previous studies were conducted among medical school students, and we wanted to compare the results by evaluating the attachment styles of the specialist physicians who made their choices. In addition, we wanted to investigate whether there is a difference between specialist physicians who entered their first choice and those who did not.

In the literature, we could not find any study investigating the attachment styles of physicians who graduated from medical school, passed the Medical Specialization Examination (TUS), and worked as specialist physicians, and examined the relationship between the department and attachment styles. In this direction, we planned to conduct this research.

2. Materials and methods

Our study is a cross-sectional and descriptive study. All participants were administered an individual information collection form and the Relationship Scales Questionnaire (RSQ). Participants were asked about their gender, their specialization field, and whether their current specialization fields were their first choices in the Medical Specialization Exam (TUS). Specialization fields were categorized into four groups: surgical specialties, internal medicine specialties, basic medical sciences, and family medicine specialization.

In our study, the Relationship Scales Questionnaire consisting of 17 questions was used to determine the participants' attachment styles. This scale was validated and demonstrated reliability in Turkish by Sümer and Güngör (1999).[12] The scale is a 7-point scale ranging from 1 (Doesn't Describe Me at All) to 7 (Describes Me Completely). The 7th and 17th questions on the scale are reverse-coded, and the 5th question is both reverse-coded and forward-coded. The questions used for each attachment style are as follows:

- Secure Attachment: Questions 3, 7 (reverse-coded), 8, 10, 17 (reverse-coded).
- Fearful Attachment: Questions 1, 4, 9, 14.
- Preoccupied Attachment: Questions 5 (reverse-coded), 6, 11, 15.
- Dismissing Attachment: Questions 2, 5 (reverse-coded), 12, 13, 16.

Arithmetic means obtained from the questions that make up attachment styles were used to classify participants. Participants were assigned to the attachment style to which they had the highest score. In case of equal scores, participants were included in both attachment styles.

According to the power analysis conducted before the study, our sample size was determined as 61 participants with a 95% confidence interval and 90% power. Ninety-two specialist physicians participated in our study.

This study was approved by the Başkent University Medical and Health Sciences Research Ethics Committee on 16.02.2021 with the approval number E-94603339-604.01.02-11640 (Project no: KA21/57) and supported by the Başkent University Research Fund.

In our study, the statistical software package SPSS 19.0 was used. The frequencies of the obtained data were examined. Shapiro-Wilk test was applied to evaluate the normality distribution of the scale scores. Since the obtained values are $p<0,05$, a normal distribution was not provided. Therefore, non-parametric tests were applied. Mann Withney U and Kruskal Wallis tests were applied for 2-variable and 3-variable comparisons, respectively. A p value less than 0.05 was accepted as significant.

2.1. Sociodemographic Data Form:

This questionnaire was developed by the researchers for use in this study to determine the sociodemographic characteristics of the participants. Participants were asked about their gender, their specialization field, and whether their current specialization fields were their first choices in the Medical Specialization Exam (TUS).

2.2. Relationship Scales Questionnaire (RSQ):

Developed by Griffin and Bartholomew (1994). This scale was adapted into Turkish by Sümer and Güngör (1999). The Relationship Scales Questionnaire consists of 17 items and aims to measure four attachment styles. Participants were initially asked to rate how well each item described themselves on a 7-point scale (1=does not describe me at all, 7=completely describes me). The secure and dismissive attachment styles are measured with five items each, while the preoccupied and fearful attachment styles are measured with four items each. Participants are categorized into the attachment style group in which they scored the highest based on the scores obtained from the sub-scales. In the validity and reliability studies conducted by Sümer and Güngör on the Turkish adaptation of the scale, it was found that the Relationship Scales Questionnaire consists of four factors: secure, dismissive, fearful, and preoccupied. Additionally, the reliability coefficients for all dimensions of the scale were calculated between 54 and 61 using the test-retest method.[12]

3. Results

In our study, there were a total of 92 participants, consisting of 52 females and 40 males. Among the participants, 26.1% were from surgical specialties, 21.7% were from internal medicine, 23.9% were from basic medical sciences, and 28.3% were from family medicine. The number of participants who chose their specialization as their

first choice in the TUS exam was 54 (58.7%), while the number of those who did not choose it as their first choice was 38 (41.3%) (Table 1).

Among all participants, 14.1% had secure attachment, 57.6% had fearful attachment, 32.6% had preoccupied attachment, and 3.3% had dismissive attachment (Table 2). There was no significant difference regarding the participants' attachment styles based on their gender (Table 3).

Table 1

Personal information of our participants

		Number (n)	Percentage (%)
Gender	Male	52	56.5
	Female	40	43.5
Branch	Surgery	24	26.1
	Internal	20	21.7
	Basic medicine	22	23.9
	Family Medicine	26	28.3
Was it your first choice in TUS?	Yes	54	58.7
	No	38	41.3

Table 2

Attachment styles of participating physicians

	Number (n)	Percentage (%)
Secure attachment	13	14.1
Fearful attachment	53	57.6
Preoccupied attachment	30	32.6
Dismissive attachment	3	3.3

When we look at the attachment styles of the participants based on their fields of specialization, the rates of secure attachment were found to be 8.3% in surgical sciences, 25% in internal medicine, 19.2% in family medicine, and 4.5% in basic medicine (Table 4).

According to the results of the Kruskal Wallis test conducted to examine the relationship between participants' fields of specialization and attachment styles, there was no statistically significant difference regarding participants' attacment styles based on specialization field (Table 5).

There was no significant difference observed in terms of attacment style between participants who made their first choice in the Medical specialization exam (TUS) and those who did not (Table 6).

Table 3

Comparison of participants' attachment styles by gender

	Female			Male			Mann Whitney U	
	Number (n)	Percentage (%)	Mean Rank	Number (n)	Percentage (%)	Mean Rank	U	p
Secure attachment	6	11.5	47.69	7	17.5	44.95	978.00	.418
Fearful attachment	30	57.7	46.46	23	57.5	46.55	1042.00	.985
Preoccupied attachment	18	34.6	45.58	12	30	47.70	1088.00	.642

Table 4

Attachment styles of participants according to their specializations

		Secure attachment	Fearful attachment	Preoccupied attachment	Dismissive attachment
Surgery	No (n)	2	16	9	0
	Percentage (%)	8.3	66.7	37.5	0
Internal	No (n)	5	10	6	1
	Percentage (%)	25	50	30	5
Basıc	No (n)	1	13	7	2
	Percentage (%)	4.5	59.1	31.8	9.1
Family medicine	No (n)	5	14	8	0
	Percentage (%)	19.2	53.8	30.8	0

Table 5

The relationship between participants' specialty and attachment styles

	Surgery	Internal	Basıc medicine	Family medicine	Kruskal Wallis	
	Mean Rank	Mean Rank	Mean Rank	Mean Rank	H	p
Secure attachment	49.17	41.50	50.91	44.15	4.783	.188
Fearful attachment	42.33	50.00	45.82	48.23	1.432	.697
Preoccupied attachment	44.25	47.70	46.86	47.35	.365	.947
Dismissive attachment	48.00	45.70	43.82	48.00	4.201	.241

Table 6

The relationship between being the first choice in TUS and attachment styles

	Yes			No			Mann Whitney U	
	No(n)	Percentage (%)	Mean Rank	No(n)	Percentage (%)	Mean Rank	U	p
Secure attachment	8	14.8	46.19	5	13.2	46.95	1043.00	.823
Fearful attachment	29	53.7	48.30	24	63.2	43.95	929.00	.369
Preoccupied attachment	20	37	44.46	10	26.3	49.39	1136	.283
Dismissive attachment	1	1.9	47.15	2	5.3	45.58	1732.00	.367

4. Discussion

This is the first known study to evaluate the attachment styles of specialist physicians and to examine the difference between attachment styles, first choice in TUS, and specialty. According to our results, we found that specialist physicians most commonly had anxious attachment styles (%57.6 fearful, %32.6 preoccupied). Among the participants, %14.1 had secure attachment styles. The rate of dismissive attachment was quite low at %3.3. There was no significant difference in attachment styles between both female and male physicians according to gender. In a study conducted by Erözkan with university students, it was reported that male students had more secure attachment styles compared to female students, while female students tended to have more fearful attachment styles. Approximately 55% of the general population has secure attachment styles.[13] According to our results, the prevalence of attachment styles was different from those found in the general population.

The field of attachment theory can influence career orientation and decision-making.[5] We had hypothesized that individuals with a sense of personal competence, positive self-worth, and secure attachment are more likely to win their first choice in the TUS exam. According to our results, however, we did not find a significant relationship between the status of entering the first choice in TUS and attachment styles. In addition, when we evaluated the attachment styles of physicians specializing in surgical sciences, internal sciences, basic medicine and family medicine, there was no significant difference between departments and attachment styles.

In a previous study conducted with second year medical school students, the rate of secure attachment was found to be similar to the general population, and it was reported that those with secure attachment were more likely to choose primary care specialties[6]. Family medicine and internal medicine specialties, compared to basic medical sciences and surgical specialties, are more likely to involve frequent and extended interpersonal relationships. Therefore, it is assumed that the rates of secure attachment may be higher in these groups.[6] According to our results, although there was no statistically significant difference between branch selection and attachment styles, the secure attachment rate of family physicians and internal medicine physicians was higher. When evaluating the secure attachment rates among the four groups of physicians, it is noteworthy that the lowest rate was found in basic medical sciences This observation supports the assumption that specialties involving extended relationships with patients are more likely to demonstrate secure attachment style, since basic medical sciences specialty requires less interaction and shorter term relationships with patients.

There could be several reasons why we found a lower rate of secure attachment among our participants, which differs from other studies. Firstly, the relatively small sample size in our study could be one of the reasons. Secondly, adult attachment models change over time and can be especially unstable in high-risk and clinical populations.[14] Although the origins of adult attachment seem to stem from early caregiving experiences, it is believed that adults' outcomes are not entirely determined by them.[15-16] Thirdly, individuals can develop relationship-specific attachment styles that can adapt to different interpersonal experiences.[15] Our participants consisted of physicians who graduated from university and specialized in any branch. Many years of difficult working conditions and clinical experience may have influenced the attachment styles of physicians and may partly explain the difference in results. However, based on our study, we cannot distinguish whether the participants had insecure attachment styles from the beginning or whether these attachment styles developed as a reflection of practicing a demanding and exhausting profession for many years. We cannot adjust our results to the patient-physician relationship. These findings may reflect an individual's romantic or close interpersonal relationships. Furthermore, an individual's overall attachment orientation may only be applicable to specific individuals and relationships. For instance, an individual who exhibits an insecure attachment style in romantic relationships might develop a different attachment style in their professional life.[15-17] The attachment system has an important role in activating human capacities that promote survival. In adulthood, it is believed that insecure attachment patterns can have adaptive functions and may provide some advantages in a professional context. Anxious attachment is reported to facilitate being alert to possible dangers, rapidly responding to threat signals, and effectively taking action to diffuse a threat. In a study examining the behaviors of adult groups, it was observed that individuals with avoidance attachment escaped more quickly from a room filled with non-toxic smoke emanating from a malfunctioning computer, while individuals with high attachment anxiety noticed the smoke more quickly than other groups.[16-18]

We observed a high prevalence of anxious attachment in a profession that involves caregiving. Secure attachment enhances adults' tendency to provide care and increases their sensitivity to the needs of others. Individuals with fearful attachment, when combined with self-focused tendencies and concerns about being unable to reach out to others when needed, can interfere with sensitive caregiving. However, it is overly simplistic to suggest that secure attachment always supports effective caregiving or that insecure attachment necessarily leads to inadequate caregiving.[15-17] Research has shown that individuals with anxious attachment are also willing to engage in prosocial behaviors, including concern for the welfare of others, caregiving behaviors, and other community-oriented actions.[19]
Looking at the main specialty fields separately and assessing the relationship between the first choice in the TUS and attachment style is a strength of our study. The relatively small sample size is a limitation of our study. The use of a single assessment scale is another limitation. In addition, the lack of a assessment scale that evaluates the mental status of the participants an the lack of clinical interviews are among the limitations. The lack of statistically significant analyzes is also one of the limitations. Another limitation is not assessing the relationship between different attachment styles and specialization choice, neglecting to consider other important factors such as prestige, financial rewards, lifestyle, and intellectual challenge in

specialization choice.

5. Conclusions

According to our findings, the most common attachment style among physicians in any specialization was anxious attachment, and there was no significant relationship between the specialization field and attachment styles. However, although not statistically significant, the rate of secure attachment was higher among family physicians and internal medicine specialists compared to physicians in basic medical sciences and surgical specialties. Choosing the right field of specialization is of great importance in the future life of the physician, for her/his productivity, and the healthy maintenance of the patient-physician relationship. Determination of other possible motivational factors as well as attachment styles could provide guidance and insight to the physician in this choice that will affect her/his whole life. Further and more comprehensive studies on this subject may contribute to physicians in determining their professional life and future.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Başkent University Medical and Health Sciences Research Ethics Committee on 16.02.2021 with the approval number E-94603339-604.01.02-11640

Conflict of interest statement

Author declare that they have no financial conflict of interest with regard to the content of this report.

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Sleep quality in patients with rheumatic mitral stenosis and the effect of percutaneous mitral balloon valvuloplasty on sleep quality

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Abstract

Aim: Impaired sleep quality is common in patients with heart disease. However, data on the effects of mitral stenosis severity and percutaneous mitral balloon valvuloplasty on sleep quality are scarce.

Methods: 205 patients included in the study were divided into two groups as severe and non-severe (mild to moderate MS) rheumatic MS. 123 patients with mild to moderate MS and 82 patients with severe MS were analyzed. 82 patients with severe rheumatic MS who underwent percutaneous mitral balloon valvuloplasty were prospectively enrolled. Sleep quality was prospectively investigated immediately before and approximately six months after the percutaneous mitral balloon valvuloplasty procedure. The Pittsburgh Sleep Quality Index (PSQI) was used to evaluate sleep quality.

Results: The PSQI score was considerably higher in patients with severe MS compared to mild to moderate MS (3.7 ± 2.0 vs. 7.7 ± 2.9, p<0.001, respectively). A significant correlation was demonstrated between total PSQI scores and echocardiographic parameters [Left atrial diameter (r= 0.599, p=0.003), Mitral valve area (r= 0.837, p<0.001), Transmitral mean gradient (r=0.773, p<0.001), TR max velocity (r=0.593, p=0.004), Estimated PAP (r=0.530, p=0.01), TAPSE (r=-0.510, p=0.013)]. In addition, mitral valve area (QR=0.73; 95% CI: 0.54-0.92; p=0.011) and transmitral mean gradient (QR=1.78; 95% CI: 1.44-2.18; p <0.001) were found to be statistically significant in the multivariate regression analysis performed between echocardiographic parameters and total PSQI scores. Total PSQI scores at 6 months after the PMBV procedure were significantly lower than before the PMBV procedure (7.1 ± 2.7 vs. 3.9 ± 2.5; p < 0.001). There was an improvement in the PSQI score, a subjective measure of sleep quality.

Conclusions: A correlation was found between the PSQI score, which can subjectively assess sleep quality, and the severity of mitral valve stenosis. Sleep quality may deteriorate as the severity of mitral stenosis increases. An additional benefit of PMBV may be that it can ameliorate the underlying sleep disorder. Percutaneous mitral balloon valvuloplasty may be beneficial in improving sleep quality in adult patients with MS.

Keywords: *Rheumatic mitral stenosis; percutaneous mitral balloon valvuloplasty; Pittsburgh Sleep Quality Index; sleep quality*

1. Introduction

Mitral stenosis (MS) is characterized by the narrowing of the mitral valve orifice, which leads to obstruction of blood flow from the left atrium to the left ventricle. Mitral stenosis (MS) is a disease that limits the normal physical abilities of patients and is accepted as an important cause of hospitalization.[1] It cripples some of the patients eventually. The leading cause of MS globally is rheumatic heart disease, which continues to be prevalent in economically developing countries. It remains a major cause of morbidity and mortality. Mitral stenosis causes increased left atrial pressure. This pressure increase is transmitted to the pulmonary vessels, causing pulmonary hypertension. It may present with advanced mitral stenosis, signs of right heart failure, and pulmonary hypertension. Patients with MS often present with exertional dyspnea or increased fatigue mainly related to the severity of the stenosis.[2]

Severe MS is defined as a mitral valve area ≤1.5 cm^2. Symptomatic severe MS is also called Stage D MS. Patients with mitral valve area >1.5

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cm^2 are defined as moderate MS, and patients with mitral valve area >2.5 cm^2 are defined as mild MS.[2]

The main treatment for mitral stenosis was open heart surgery for many years. However, due to the development of an alternative minimally invasive procedure called PMBV, PMBV has now taken its place as a popular treatment for mitral stenosis.[3] Medications can treat MS symptoms, but they cannot cure the root cause of MS. For this reason, MS is considered a mechanical disease whose mortality can only be corrected by PMBV or mitral valve surgery .[1] PBMV is a safe and effective treatment modality for symptomatic severe MS (mitral valve area <1.5 cm^2), (Stage D) with appropriate valve morphology.[1,4]

Sleep, in which an average of one-third of human life is spent, is a cyclical, temporary, and functional state controlled by neurobiological processes.[5] Recent studies have also shown that sleep deprivation or poor quality sleep has a strong effect on the occurrence and prognosis of many important diseases, including cardiovascular diseases, cancer, depression, obesity, and immune system dysfunction.[6] One of the most important factors contributing to physical functionality, psychological well-being, and quality of life is good sleep quality. A good sleep can also play a protective role in terms of cardiovascular diseases that may develop later. Sleep quality is generally used to express a set of sleep measures such as total sleep time, sleep onset latency, sleep efficiency, wakefulness after sleep onset, and daytime sleepiness.[7,8] Sleep quality is affected by many variables such as diet, physical activity, genetics, environmental factors, and comorbidities.[7] The gold standard method for assessing sleep quality, duration, and structure is polysomnography (PSG). However, due to the cost and limited accessibility of PSG, questionnaires to assess sleep quality are often more easily implemented in larger populations.[9]

Data on the sleep quality of patients with MS are limited in the current literature. There is no data in the relevant literature on the sleep quality of a popular treatment option such as PMBV. The aim of this study was to evaluate the relationship between MS severity and sleep quality, as well as the effect of PMBV on sleep quality.

2. Materials and methods

2.1. Study design

In this study, patients with rheumatic MS who were examined Echocardiography Laboratory in Adana City Training and Research Hospital between January 2020 and February 2023 were evaluated. Patients with severe rheumatic MS and mild-to-moderate rheumatic MS who were eligible for PMBV were analyzed. Patients with atrial fibrillation or those scheduled for mitral valve surgery due to MS were excluded. In addition, patients with moderate to severe mitral valve regurgitation, moderate to severe aortic valve regurgitation, moderate to severe aortic valve stenosis, severe tricuspid valve regurgitation, and heart failure coinciding with mitral stenosis were excluded. Patients with significant asthma, chronic obstructive pulmonary disease, sleep apnea syndrome, restrictive lung disease, chest deformities, and extremely obese were also excluded. Patients with neurological and psychiatric problems that may affect sleep quality and those who use drugs and substances that may affect sleep quality were also excluded from the study. After excluding all these patients, two hundred and five patients included in the study were divided into two groups as severe and non-severe (mild to moderate MS) rheumatic MS. 123 patients with mild to moderate MS and 82 patients with severe MS were analyzed.

Transesophageal echocardiography was performed in all patients with severe MS among patients diagnosed with rheumatic MS by transthoracic echocardiography. Mitral valve structure, mitral valve area (measured planimetrically), transmitral valve gradient, left atrium parasternal long axis diameter, tricuspid valve regurgitation maximum velocity, inferior vena cava diameter and collapsibility, estimated systolic pulmonary artery pressure, tricuspid annular plane systolic excursion, right ventricle basal diameter, and right atrium major diameter were evaluated in transthoracic echocardiography. All measurements were calculated in accordance with the recommendations of the American Society of Echocardiography (ASE). MS severity was defined according to ASE recommendations.[10]

Sleep quality was prospectively studied in all patients with rheumatic MS, regardless of severity. Then, sleep quality was re-examined 6 months after the procedure in patients with severe rheumatic mitral stenosis who underwent PMBV procedure. The revised Turkish version of the Pittsburgh Sleep Quality Index questionnaire was used to assess sleep quality. The quantitative component of the study collected data from participants to determine self-rated sleep quality by completing a series of scales in this questionnaire. Causes that impair sleep quality before and after the procedure, such as depression, anxiety, another concomitant disease, a sedative drug used and discontinued, pain, etc. were excluded. This questionnaire was administered to all patients (two hundred and five) who participated in the study. Eighty-two patients who underwent the PMBV procedure were re-administered to the PSQI questionnaire in the 6th month after the procedure. A total of 287 surveys were conducted and 287 were actually recovered, resulting in a 100% recovery rate. After checking the validity and completeness of the questionnaire, it was found that the effectiveness and completeness of the questionnaire was 100%.

The Pittsburgh Sleep Quality Index (PSQI) is a questionnaire compiled mainly to evaluate the sleep quality of patients with sleep disorders and mental disorders.[7,8] Moreover, it is a suitable questionnaire for assessing the sleep quality of ordinary people. The survey consists of nine questions in total. The first four questions are fill-in-the-blank questions. The last fivequestions are multiple-choice questions. Also, the fifth question contains ten small questions. The eighteen self-assessment items consist of seven components: subjective sleep quality, sleep duration, sleep latency, sleep disturbance, habitual sleep efficiency, daytime dysfunction, and sleep medication use. Each of these components is scored on a scale from 0 to 3. The cumulative score of each component is the total PSQI score, and the total score ranges from 0 to 21 points. A high total score indicates poor sleep quality. The lower the score, the better the sleep quality.[7,8]

2.2. Ethical considerations

This study was approved by the Institutional Review Board of Adana City Training and Research Hospital. The principles of this study were in accordance with the Declaration of Helsinki, and detailed written informed consent was obtained from all participants.

2.3. Statistical Analysis

Analyzes were performed to test the hypothesis that sleep quality may be associated with stenosis severity in patients with rheumatic mitral valve stenosis and that PMBV treatment may improve sleep quality by reducing the severity of stenosis. All collected data were numerically coded. For statistical analysis, the SPSS 22.0 computer software package was entered, and the variable and recorded. Quantitative data were expressed as mean ± standard deviation. Qualitative data were compared between groups using the chi-square test. The independent student T-test was used to analyze the severity of mitral valve stenosis and sleep quality data. Paired T-test was used to analyze sleep quality data before and after the PMBV procedure. Correlation and regression analyzes were performed between total PSQI scores and some echocardiographic parameters before the PMBV procedure in all patients with mitral valve stenosis.

3. Results

The mean age of these patients was 48.9 ± 8.1 years, and 81 (65.9%) of these patients were women. The mean age of the patients with severe MS was 48.9 ± 8.1 years, and 81 (65.9%) of these patients were women. There were 82 patients with severe MS. The mean age of these patients was 46.9 ± 9.8 years, and 53 (64.6%) of these patients were women.

Baseline characteristics of all patients, such as age, gender, smoking, heart rate, blood pressure, and weight, are documented in Table 1. There was no statistically significant difference between the two groups in terms of many demographic, clinical, and laboratory parameters (Table 1). However, the PSQI score was considerably higher in the group with severe mitral valve stenosis and undergoing percutaneous mitral balloon valvuloplasty (severe MS) compared to the group with mild to moderate MS (3.7 ± 2.0 vs. 7.7 ± 2.9, p<0.001, respectively).

Table 1

Comparison of demographic, clinical, and laboratory data before PMBV procedure in patients with rheumatic mitral stenosis

Parameters	Mild to moderate MS (n:123)	Severe MS (n: 82)	p-value
Age, year	48.9 ± 8.1	46.9 ± 9.8	0.11
Sex, male, n (%)	81 (65.9%)	53 (64.6%)	0.85
Smoking, n (%)	43 (35%)	30 (36.6%)	0.81
BMI, kg/m2	27.1 ± 4.1	27.7 ± 3.8	0.42
Heart rate, bpm	82.9 ± 14.5	81.1 ± 11.1	0.5
Systolic blood pressure, mmHg	118.5 ± 17.6	118.9 ± 14.6	0.9
Diastolic blood pressure, mmHg	72.7 ±11.9	72.8 ± 10.6	0.95
C-reactive protein, mg/L	5.2 ±1.5	4.9 ± 1.3	0.74
Thyroid-stimulating hormone,mUI/L	4.1 ± 1.3	3.9 ± 1.6	0.78
Hemoglobin, gr/dL	13.1 ± 2.8	13.3 ± 2.7	0.71
Albumin, gr/dL	42 ± 3.7	39.8 ± 3.5	0.93
Total bilirubin, mg/dL	0.64 ± 0.44	0.65 ± 0.33	0.92
Alanine aminotransferaz, U/L	16.8 ± 7.4	18.2 ±8.6	0.39
Aspartat aminotransferaz, U/L	23.2 ±7.3	22.8 ±7.2	0.75
NT-proBNP, µg/L	246.2 ± 150.5	257.9 ±162.1	0.74
Total PSQI	3.7 ± 2.0	7.7 ± 2.9	<0.001

BMI: Body Mass Index; MS: mitral stenosis; NT-proBNP: N-Terminal Pro–Brain Natriuretic Peptide; PMBV: percutaneous mitral balloon valvuloplasty; PSQI: Pittsburgh Sleep Quality Index. * The difference was statistically significant (P < 0.05).

There were statistically significant differences in echocardiographic parameters (mitral valve area 2.19 ± 0.42 vs. 1.13 ± 0.23 cm^2, p <0.001; transmitral mean gradient 6.43 ± 2.07 vs. 15.02 ± 4.82 mmHg, p<0.001; estimated PAP 37.0 ± 9.1 vs. 49.5 ± 13.7 mmHg, p=0.001; right ventricular basal diameter 36.4 ± 3.5 vs. 38.8 ± 4.4 mm, p <0.001, respectively) between the two groups before PMBV procedure. A significant correlation was demonstrated between total PSQI scores and echocardiographic parameters [Left atrial diameter (r= 0.599, p=0.003*), Mitral valve area (r= 0.837, p<0.001*), Transmitral mean gradient (r=0.773, p<0.001*), TR max velocity (r=0.593, p=0.004), Estimated PAP (r=0.530, p=0.01*), TAPSE (r=-0.510, p=0.013*)] (Table 3).

A mitral valve area lower than 1.5cm^2 was associated with high total PSQI scores in patients with MS, with a sensitivity of 63 % and a specificity of 82 % (Cut-off value: 6.5; Area under the ROC curve=0.887; 95% CI 0.844–0.930; p<0.001). A transmitral mean gradient higher than 10 mmHg was associated with high total PSQI scores in patients with MS, with a sensitivity of 82 % and a specificity of 90 % (Cut-off value: 5.5; Area under the ROC curve=0.891; 95% CI 0.849–0.933; p<0.001).

In addition, mitral valve area (QR=0.73; 95% CI: 0.54-0.92; p=0.011) and transmitral mean gradient (QR=1.78; 95% CI: 1.44-2.18; p <0.001) were found to be statistically significant in the multivariate regression analysis performed between echocardiographic parameters and total PSQI scores (Table 3).

Total PSQI scores at 6 months after the PMBV procedure were statistically significantly lower than before the PMBV procedure (7.1 ± 2.7 vs. 3.9 ± 2.5 points, p < 0.001). There was an improvement in the PSQI score, a subjective measure of sleep quality.

4. Discussion

This study showed that patients with mitral valve stenosis had impaired sleep quality as assessed by the PSQI questionnaire in relation to the severity of valve stenosis. In patients who underwent PMBV for severe rheumatic mitral valve stenosis, a significant improvement in sleep quality was found beyond the 6th month after PMBV when compared to pre-PMBV procedure. The PSQI score was 3.7 ± 2.0 in patients with non-serious rheumatic mitral valve stenosis and 7.7 ± 2.9 in patients with severe rheumatic mitral valve stenosis. In patients with severe rheumatic mitral valve stenosis, the PSQI score was quite high (p < 0.001), in other words, the quality of sleep was severely impaired when compared to patients with non-serious rheumatic mitral valve stenosis.

In patients with severe rheumatic mitral valve stenosis, the PSQI score before PMBV was 7.1 ± 2.7, and the PSQI score beyond 6 months after PMBV was 3.9 ± 2.5. Beyond 6 months after PMBV, PSQI scores were statistically significantly decreased (p<0.001), namely, sleep quality improved compared to the pre-PMBV procedure.

Table 2

Comparison of echocardiographic data before PMBV procedure in patients with rheumatic mitral stenosis

Parameters	Mild to moderate MS	Severe MS	p-value
Left ventricular EF, %	59.9 ± 3.2	60.1 ± 2.9	0.62
Left atrial diameter, mm	44.2 ± 7.1	47.0 ± 7.5	0.036
Mitral valve area, cm2	2.19 ± 0.42	1.13 ± 0.23	<0.001
Transmitral mean gradient, mmHg	6.43 ± 2.07	15.02 ± 4.82	<0.001
Right ventricular diameter, mm	36.4 ± 3.5	38.8 ± 4.4	<0.001
Right atrial diameter, mm	41.3 ± 5.2	42.9 ± 5.6	0.051
TR degree			
• Mild, n (%)	84 (68.3)	37 (45)	0.026
• Moderate, n (%)	25 (20.7)	30 (37)	
• Severe, n (%)	14 (11)	15 (18)	
TR max velocity, m/s	2.72 ± 0.42	3.4 ± 0.67	<0.001
Estimated PAP, mmHg	37.0 ± 9.1	49.5 ± 13.7	0.001
TAPSE, mm	22.6 ± 2.5	22.2 ±2.3	0.34

EF: Ejection Fraction; MS: mitral stenosis; PAP: Pulmonary Artery Pressure; PMBV: percutaneous mitral balloon valvuloplasty; TAPSE: Tricuspid Annular Plane Systolic Excursion; TR: Tricuspid Valve Regurgitation * The difference was statistically significant (P < 0.05).

Table 3

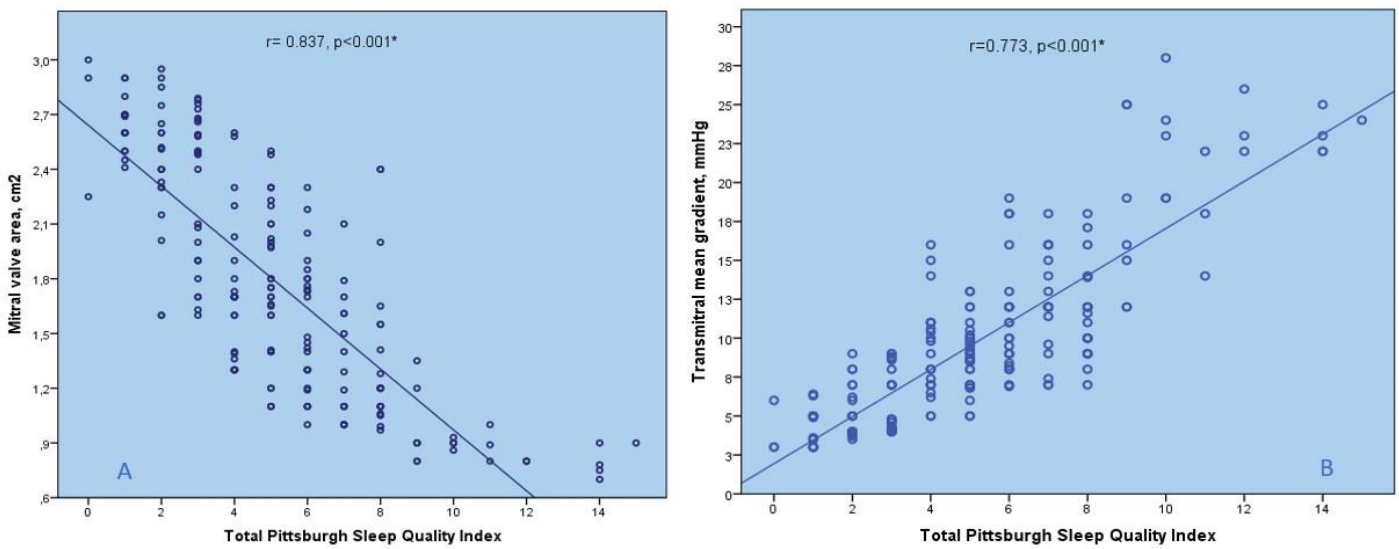
Univariate and multivariate analyses of echocardiographic parameters before PMBV procedure factors related to PSQI scores

	Univariate analysis		Multivariate analysis		
	r-value	p-value	QR	95% CI	p-value
Left ventricular EF	0.044	0.43	-		-
Left atrial diameter	0.599	0.003*	1.09	0.95-1.29	0.19
Mitral valve area	0.837	<0.001*	0.73	0.54-0.92	0.011*
Transmitral mean gradient	0.773	<0.001*	1.78	1.44-2.18	<0.001*
Right ventricular diameter	0.165	0.25	-		-
Right atrial diameter	0.358	0.066	-		-
TR max velocity	0.593	0.004	-		-
Estimated PAP	0.530	0.01*	1.58	0.92-2.35	0.19
TAPSE	-0.510	0.013*	1.05	0.96-1.15	0.42

EF: Ejection Fraction; PAP: Pulmonary Artery Pressure; PMBV: percutaneous mitral balloon valvuloplasty; PSQI: Pittsburgh Sleep Quality Index; TAPSE: Tricuspid Annular Plane Systolic Excursion; TR: Tricuspid Valve Regurgitation * The difference was statistically significant (P < 0.05).

Figure 1

Correlation graphs between mitral valve area, transmitral mean gradient and total PSQI before PMBV procedure in patients with rheumatic mitral stenosis. PMBV: percutaneous mitral balloon valvuloplasty; PSQI: Pittsburgh Sleep Quality Index. * The difference was statistically significant (p < 0.05).



In our study, a significant correlation was demonstrated between total PSQI scores and echocardiographic parameters such as left atrial diameter, mitral valve area, transmitral mean gradient, TRmax velocity, estimated PAP, and TAPSE (Table 3). In addition, multivariate regression analysis between total PSQI scores and some echocardiographic parameters showed that mitral valve area and transmitral mean gradient were statistically significant (Table 3).

These data may indicate that the increase in left atrial pressure load as a result of increased transmitral gradient and decreased mitral valve area and its reflection on the pulmonary veins and subsequently on the pulmonary capillary network may be associated with deterioration of sleep quality. In addition, due to the increased venous return at night, the right heart and pulmonary capillary volume load will increase somewhat, which may have an additional negative effect on sleep quality.

Sleep quality is significantly lower in patients with cardiovascular diseases compared to the general population. There are a few studies in the literature about a deterioration in sleep quality in patients with heart failure, coronary artery disease, and cardiac arrhythmia.[11-15]

Hajj J. and colleagues suggested that although there was no significant difference in sociodemographic and clinical characteristics in heart failure patients with NYHA class II and III symptoms, the increase in sleep quality disturbances in class III was likely due to clinical worsening in HF status. They found that the total PSQI score (6.72 versus 9.65) was lower in patients with NYHA class II heart failure compared with patients with NYHA class III heart failure. They explained that NYHA class II heart failure patients had better sleep quality compared to NYHA class III heart failure patients.[11]

Redeker NS. and colleagues showed that patients with heart failure had higher PSQI scores compared to the control group. They showed that sleep quality was worse in patients with heart failure. (7.17 ± 3.29 vs. 5.76 ± 3.03; p=0.017, respectively). Additionally, 67% of the patients with heart failure compared with 51% of to the

control group had poor global sleep quality (PSQI scores greater than 5).[12]

Kyoung Suk Lee, RN. and colleagues reported that 63% of patients had poor sleep quality. Those with poor sleep quality were 2.5 times more likely to have a shorter cardiac event-free survival (95% CI, 1.164-5.556) than those with good sleep quality after controlling for covariates. They found that impaired sleep quality in patients with heart failure was common and was associated with reduced cardiac event-free survival.[16]

Xiang Qian Lao and colleagues also stated that poor sleep quality is associated with the risk of coronary heart disease and may increase the risk of coronary heart disease in adults aged 40 and over. They also emphasized the importance of considering sleep quality when developing strategies to improve sleep for the prevention of cardiovascular diseases.[17]

Coşkun and colleagues found that poor sleep quality is common in patients with premature ventricular contractions, and sleep quality improved significantly after the radiofrequency catheter ablation procedure. They stated that poor sleep quality in patients with premature ventricular contractions is closely related to burden at nighttime.[15]

Rheumatic heart disease stands as the predominant worldwide cause of MS and continues to be a significant public health concern. There are almost no studies in the literature evaluating sleep quality in patients with MS.[18] In our study, we detected deterioration in sleep quality in patients with MS using the PSQI questionnaire. Furthermore, through this PSQI questionnaire, we found a statistically significant improvement in sleep quality after the PMBV procedure.

We showed that sleep quality deteriorates as the severity of stenosis increases in patients with mitral stenosis and that sleep quality may sometimes improve after PMBV. Questioning sleep-related parameters such as sleep quality may be considered in the clinical evaluation of patients with mitral stenosis.

4.1. Limitations

Because it is a small-scale, single-center study with limited follow-up, this study should be supported by studies with a larger population and longer follow-ups. Although atrial fibrillation was excluded from the study, undiagnosed paroxysmal atrial fibrillation could not be completely excluded from this study. In addition, the factors affecting sleep quality were not examined in detail in this study. Mitral valve replacement and PMBV procedure could not be compared due to the low number of patients undergoing mitral valve replacement due to severe MS and their demographic and echocardiographic differences from patients undergoing the PMBV procedure. Future studies are needed to examine sleep quality and sleep quality-related factors comparing mitral valve replacement and PMBV procedure in patients with MS, combining objective (polysomnography, etc.) and subjective (sleep-related questionnaires, etc.) sleep quality measures.

5. Conclusions

A correlation was found between the PSQI score, which can subjectively assess sleep quality, and the severity of mitral valve stenosis. Sleep quality may deteriorate as the severity of mitral stenosis increases. A decrease in the PSQI score was detected in the patients at 6 months after the PMBV procedure. In addition to its benefits, PMBV may increase sleep quality. The study needs to be supported by polysomnography, which can objectively assess sleep quality in a larger MS population.

Statement of ethics

This study was approved by the Institutional Review Board of Adana City Training and Research Hospital. The principles of this study were in accordance with the Declaration of Helsinki, and detailed written informed consent was obtained from all participants.

Conflict of interest statement

Author declare that they have no financial conflict of interest with regard to the content of this report.

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Global View on Monkeypox Epidemic: A Youtube Study

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Abstract

Aim: We aimed to evaluate the quality of the videos on Youtube about Monkeypox, the precision of the content, and the video features by using various tools.

Methods: Videos about Monkeypox were searched on YouTube™ (http://www.youtube.com) on 22/05/2022. After sorting by relevance for the search term "Monkeypox," the first 200 videos were recruited and saved as a file for later consideration. The browsing history was deleted before the search so that it would not be affected by previous searches. The Global Quality Scale (GQS) was used to evaluate the quality of the videos. A p value of <0.05 was considered statistically significant.

Results: Video topics were mainly about symptoms (68.4%), transmission (48.5%), definitions (39.7%), and prevention (33.8%), and as for the video sources; News agencies/ Tv sources (106) uploaded the most videos. While the GQS and Discern median values of the videos were 2 and 3, respectively, they were 2 and 3 for useful videos; and both 1 for misleading videos. Misleading videos had significantly and consistently lower GQS and Discern scores (1; p=0.001). Most of the videos were of USA (64) origin. While users upload the most useful and misleading videos from the USA, uploads were made from 17 different countries.

Conclusions: It is necessary to prefer useful videos for accessing medically accurate and quality information. Quality video sources such as Physicians and Scientific Journals should upload more videos to Youtube for users to access useful/quality information.

Keywords: *Monkeypox; Youtube™; videos; The Global Quality Scale; quality information.*

1. Introduction

Monkeypox disease is a zoonotic disease caused by the Monkeypox virus, a member of the Orthopoxvirus family. It is similar to smallpox, and patients are often misdiagnosed as chickenpox.[1] After an incubation period of 10-14 days; malaise, chills, fever, and reactive lymph nodes emerge. These are prodromal signs 1-3 days before the rashes appear. These may be accompanied by sore throat, cough, shortness of breath, back, and headache.[2] Macular rashes ashes characteristically start on the trunk and may spread to all body parts as they become more severe. The disease is contagious for one week after the rashes without PCR being positive.[2-3] Between the 2nd and 4th weeks, the lesions change the form of papules-vesicles-pustules[3], and healing occurs spontaneously if no secondary infections develop.

Pregnant women, children, and immunosuppressed individuals are more prone to secondary infections. Nevertheless, a chronic process should not be overlooked in major secondary infections such as eye infections, pneumonia, and encephalitis.[4] Monkeypox was usually present in Central and Western Africa, and so far caused sporadic infections. However, with its emergence as an outbreak outside the African continent on May 7, 2022, it became a source of concern that now affects the whole world. While not recovering from the effects of an ongoing COVID-19 pandemic, the world is facing great challenges, with thousands of monkeypox cases emerging globally.[5-6] Such health crises affect daily life, including changing daily routines and canceling important activities.[7]

Since more than 1 billion people worldwide use Youtube with its extensive and rich archive, Youtube has become a popular source of information about diseases and health services and an assistant in health-related decision-making processes.[4-8-9] A wide variety of users, including physicians and medical students, non-medical healthcare professionals, non-profit organizations, TV/media sources, and even commercial organizations, upload videos to YouTube. So, video uploaders are a very heterogeneous community; thus, the quality of information varies widely in all aspects, which can sometimes correlate with video features. The essential concern about

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YouTube from a public health perspective is that; it has a public video upload policy without a control mechanism.[9]

The monkeypox epidemic is a brand-new situation; with its emergence in the shadow of an ongoing pandemic, people are more in need of information. The Covid Pandemic has impaired people's sense of concern and reasoning.[8] Video sources may upload an incorrect or low-quality video about Monkeypox, and biased or inaccurate information can easily be spread. The possibility of spreading false information should be carefully considered and put on the agenda, mainly to prevent an unduly increase in public groups who are worried about the new health condition. Many studies are already evaluating YouTube content on various subjects, such as air pollution, syphilis, vesicoureteral reflux, and scoliosis.[4-9-10-11] Previous studies have evaluated whether information on YouTube offers an excellent educational or awareness-raising opportunity to the public, the accuracy of the content, whether it is biased or coherent, video quality, and its characteristics. Therefore, we aimed to evaluate the quality of the videos on Youtube about Monkeypox, the precision of the content, and the video features by using various tools.

2. Materials and methods

Videos about Monkeypox were searched on YouTube™ (http://www.youtube.com) on 22/05/2022. After sorting by relevance for the search term "Monkeypox," the first 200 videos were recruited and saved as a file for later consideration. The browsing history was deleted before the search so that it would not be affected by previous searches. Off-topic, non-English, duplicate videos were excluded from the study.

2.1.Video Parameters

The videos' upload date, duration, number of views, comments, and likes were recorded. Then, based on the total number of days the video has been on YouTube, comments per 1000 views and daily likes for each video were calculated and used in some comparisons. Finally, the total number of days was calculated based on the time from the video upload to the search date.

2.2. Video Content

Symptoms, transmission, definitions, prevention, causes, treatment, complications, and risk factors were examined.

2.3. Video Sources

Sources were classified as News agencies/TV, Independent users/blogs, Physicians, Organizations/Associations, Non-physician health personnel, and Scientific journals.

2.4. Auditing of Quality and Reliability

The Global Quality Scale (GQS) was used to evaluate the quality of the videos. This scale ranges from 1 to 5 points on the GQS tool designed by Bernard. A video score of 4 or 5 points is considered high quality, 3 points medium quality, and 1- or 2-points low quality. The modified DISCERN tool (DS) was used to score the reliability of the videos. In this scale, adapted by Singh, the distinctiveness score ranges from 0 to 5 points. A high score on this scale indicates high reliability. Each yes answer is given a point and consists of 5 questions.[12-14] (Table 1).

The information quality and reliability of the videos were independently evaluated by two medical doctors. In case of any disagreement between the referees, the opinion of the third researcher was sought.

2.5. Statistical Analysis

The data obtained in the study were statistically analyzed using SPSS version 15 software. Cohen's kappa coefficient was used for inter-rater agreement. The conformity of data to normal distribution was evaluated with the Kolmogorov-Smirnov test. The Shapiro Wilk (for non-normally distributed data) test was used to compare video parameters between quality groups. A p value of <0.05 was considered statistically significant.

3. Results

After applying the exclusion criteria (32 non-English, 22 repetitions, 10 off-topic videos), all the remaining 136 videos were evaluated. Kappa values for information quality and information reliability were found to be 0.74 and 0.78, respectively, in the evaluation of agreement between observers. Video topics were mainly about symptoms (68.4%), transmission (48.5%), definitions (39.7%), and prevention (33.8%), and as for the video sources; News agencies/ Tv sources (106) uploaded the most videos (Table 2 and 3). While the GQS and Discern median values of the videos were 2 and 3, respectively, they were 2 and 3 for useful videos; and both 1 for misleading videos. Misleading videos had significantly and consistently lower GQS and Discern scores (1; p=0.001). The vast majority (121) of the videos were categorized as misleading. Median video duration was 2.92 minutes; the number of days on YouTube was 2 days; the view count was 10215.50; views/number of days on YouTube was 4851; likes/1000 views were 12.87, and comments/1000 views were 12.37.

Table 1

Quality and reliability assessment tool

Global Quality Scale tool
1.Poor quality, poor flow, most information missing, not helpful for patients
2.Generally poor, some information given but of limited use to patients
3.Moderate quality, some important information is adequately discussed
4.Good quality good flow, most relevant information is covered, useful for patients
5.Excellent quality and excellent flow, very useful for patients
Modified DISCERN reliability tool
1.Are the aims clear and achieved?
2.Are reliable sources of information used?
3.Is the information presented balanced and unbiased?
4.Are additional sources of information listed for patient reference?
5.Are areas of uncertainty mentioned?

Table 2

Distribution of the video contents, n (%)

Video contents*	n	%
Symptom	93	68,4
Transmission	66	48,5
Definition	54	39,7
Prevention	46	33,8
Causes	36	26,5
Treatment	24	17,6
Complication	18	13,2
Risk factor	14	10,3
Diagnosis	6	4,4

*There is more than one topic, n: number, %: percentage

Table 3
GQS and Discern Analysis

	Total (n =136)	Useful (n=121)	Misleading (n=15)	p value
Variables				
Video duration (min)	2,92 (0,40-158,58)	2,90 (0,40-158,18)	2,97 (0,55-72,45)	0,326
Number of days on YouTube	2 (1-1689)	2 (1-1689)	2 (1-1658)	0,913
Views	10215,50 (212-1562051)	9438 (304-526249)	36302 (212-1562051)	0,023
Views/day	4851 (0,63-781025,5)	4302 (0,63-391563)	12100 (48,26-781025,5)	0,088
Likes/1000 views	12,87 (3,22-149,88)	12,58 (3,22-149,88)	35,81 (4,50-133,05)	0,007
Comments/1000 views	12,37 (0-79,80)	12,37 (0-79,80)	9,57 (0-37,61)	0,914
Quality and reliability scores				
GQS*	2 (1-5)	2 (1-5)	1 (1-2)	<0,001
DISCERN**	3 (0-5)	3 (1-5)	1 (0-1)	<0,001
Video source				
News agencies/TV	106	97	9	
Independent users/blog	15	9	6	
Physician	11	11	0	
Organization/association	2	2	0	
Non-physician health personal	1	1	0	
Scientific journal	1	1	0	
Country				
USA	64	57	7	
India	16	15	1	
Canada	12	9	3	
Australia	11	11	0	
England	9	8	1	
South Africa	4	3	1	
Nigeria	4	4	0	
Singapore	3	3	0	
Israel	3	3	0	
Turkey	2	1	1	
Philippines	2	2	0	
Others (Germany, China, France, Qatar, Norway, New Zealand)	6	5	1	

Data presented as number or median (minimum–maximum)
**DISCERN modified DISCERN score, GQS Global Quality Scale score

Video lengths (2.90 and 2.97, respectively p=0.326), number of days on YouTube (2 and 2, respectively p=0.913), and views/number of days on YouTube (4302 and 12100, respectively p=0.088) were not different according to the categories of useful and misleading. However, view counts (9438 and 36302, respectively, p=0.023) and likes/1000 views (12.58 and 35.81 p=0.007, respectively) differ statistically according to the useful and misleading categories (Table 3).

Sources, especially new agencies/TV uploading the most videos, uploaded useful videos at a high rate; physician/non-physician health personnel, organizations/associations, and scientific journals did not upload any misleading videos. Independent users/blog sources proportionally uploaded the most misleading videos. Most of the videos were of USA (64) origin. While users upload the most useful and misleading videos from the USA, uploads were made from 17 different countries. Most of the videos originated from the following 5 countries, mainly from the USA: USA (64), India (16), Canada (12), Australia (11), and England (9) (Table 3).

4. Discussions

In the 21st century, also called the age of technology, the internet has become available everywhere in the world. YouTube is one of the most preferred video platforms since it is free and appeals to large audiences in a short time. Moreover, during the pandemic and

endemic periods, deadly diseases that directly affect global health spread rapidly; an increase can be expected in the use of YouTube as a source of medical information to obtain information quickly and easily.

The presence of videos containing medical information does not mean that YouTube always provides high-quality information useful to society. In addition to quality/useful videos, there are also poor/misleading videos on the platform.

Poor quality/misleading videos on the Youtube platform during epidemic periods can create an environment of anxiety and panic due to the spread of false information in society and may cause undesirable results. For this reason, scanning and evaluating YouTube-based videos during the Monkeypox epidemic period will be socially beneficial.

Monkeypox-related videos included in our research were found to be highly beneficial (88.9%). News agencies/TV and Physician were the primary sources of useful videos. The main source of misleading videos was independent users/blogs.

According to the results of GQS and DISCERN regarding the quality and reliability of the videos, the average score of Useful videos was higher than the misleading videos. Some reviewed studies reported that 67% of videos regarding the COVID-19 pandemic, 70.3% of videos regarding the Zika virus, and 61.3% of videos regarding the H1N1 virus were beneficial.[15-17] Video studies which reported low benefit rates are also present in the literature .[18-19] The difference in the rates in the literature may be due to many variable factors. We interpret studies with a high benefit rate as focused on disease. Since our research also aimed at disease-focused screening, the video content was uploaded in higher numbers by competent people, and the benefit rate was higher.

The primary sources of useful videos in our research were News agencies/TV and Physicians, while the main proportional source of poor quality and misleading videos was independent users/blogs. When we look at the source countries, although the USA was high in the number of useful videos, it needed to be proportionally in the first place. We found that videos from Australia were 100% useful. While the main source of useful videos during the Zika virus pandemic is News agencies/TV, the source of low-quality videos has been identified as independent users[15]. In their study, Sahin et al. reported that independent people's videos were of low quality, similar to our results.[20] According to the studies in the literature and the current study results, the sources that upload the videos have crucial importance in the reliability of Youtube for medical purposes. As for Monkeypox, Physicians and News agencies/TV should be known as high-quality video sources. In our research, Scientific Journals uploaded a few high-quality and useful videos. Therefore, Scientific Journals as a source of videos should be supported in video uploading and should increase video production.

Our other major evaluation was on view counts and like/1000 views. Useful videos had significantly higher view counts as compared to misleading videos. However, for the number of likes per 1000 views, the number of likes of the misleading videos was significantly higher. Likewise, misleading/poor-quality videos were reported to have more views in video-based studies regarding the Zika virus and H1N1.[16-17] Although useful videos have a high number of views, it should be noted that misleading videos have a higher rate of likes; YouTube videos with a high number of likes on Monkeypox should be watched carefully.

4.1. Limitations

Studies that focus on YouTube videos may have limitations. Although three physicians evaluate the videos, the process may contain subjectivity. At the time of our study, 200 videos were recruited, and 136 videos were evaluated after exclusion criteria. Since Youtube is a dynamic platform, the number of videos, comments, and views may vary. Only English-language videos were scanned. Since a video search would be affected by past searches, to minimize it, the entire list of historical searches has been cleared before the investigation. Finally, our sample size can be counted as another limitation.

5. Conclusions

Although the number of useful and quality videos was high, misleading videos received higher likes. Therefore, it is necessary to prefer useful videos for accessing medically accurate and quality information. Thus it is crucial to select the appropriate video sources. Quality video sources such as Physicians and Scientific Journals should upload more videos to Youtube for users to access useful/quality information.

Statement of ethics

Ethics Committee approval was not required for this study as all videos were publicly available.

Conflict of interest statement

Author declare that they have no financial conflict of interest with regard to the content of this report.

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Voice Analysis in Men with Benign Prostate Hyperplasia

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Abstract

Aim: In this study, we aimed to determine the differences by performing voice analysis in men with benign prostatic hyperplasia (BPH) and discussing it with the literature

Methods: The study included 77 male patients who came to the urology outpatient clinic and were diagnosed with BPH and consult to us for voice analysis. Patients' ages, testosterone, prostate specific antigen (PSA) levels, prostate volumes (milliliters) were recorded. International prostate symptom scoring (IPSS) was applied to the patients. Mild, moderate, severe patients according to IPSS scoring; were classify as group 1, group 2, group 3, respectively. Voice Handicap Index-10 Turkish version (VHI-10) was realized to the patients and the results were saved.

Results: 77 male patients were accepted to the study. The average age was 60. The mean prostate volume of the patients was 41.1 ml. The IPSS score of the patients was 16 on average. The mean VHI-10 scores were 9.14. The mean PSA levels of the patients were 1.43; testosterone levels were 3.04. F0 Hz (mean pitch) values were 157.74; jitter % values mean 0.26; shimmer % values mean 2.42; The mean HNR dB values were 22.91.

Conclusions: Maybe it would be more logical to think that many local factors, hormones and growth factors are efficient in place of a testosterone.

Keywords: *Benign prostatic hyperplasia, voice, analysis, frequency*

1. Introduction

Benign prostatic hyperplasia (BPH), is a histological diagnostic characterized by the cellular proliferation components of prostate gland, resulting in gland enlargement. BPH can cause retention of urinary, renal function impairment, continuing infections of urinary tract, macroscopic hematuria, and bladder stones[1]. The degree of BPH, analized by the International Prostate Symptom Score (IPSS)[1]. In individuals with indications of urinary retention or kidney failure, ultrasonography (USG) can help estimate prostate gland and bladder size, as well as the severity of hydronephrosis (if present).[1] Prostate hypertrophy is dependent on the dihydrotestosterone (DHT). In the prostate, type II 5-alpha-reductase metabolizes circulating testosterone to DHT, which works better locally rather than systemically.

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DHT connect to androgen receptors in the nucleus, which may contribute to BPH.[2] PSA is a prostate gland-specific hormone and may increase in prostate cancer (CA) or BPH. It is commonly employed in prostate CA screening and follow-up, and it can have a high course in some BPH patients.[2]

Currently, voice examination in the clinic is done with objective methods such as acoustic analysis, videostroboscopy, and the evaluation of the clinician and the subjective evaluation of the patient. Among the many measurement methods, the most common one is the VHI (Voice Handicap Index) questionnaire developed by Jacobson et al. There is also a version of the test adapted to Turkish society, and its internal reliability is significant.[3-4] Testosterone becomes active in the prostate tissue, promoting hyperplasia and hypertrophy[2]. Testosterone also causes hyperplasia and hypertrophy of the vocal cords and surrounding tissue[5]. Jitter(%): It is the average of the absolute value of the difference of each period of the analyzed sound with the next period. It is the parameter that shows the change between periods. Jitter reflects the irregularity of the vocal cords and is also called frequency perturbation. Its normal value is below 1%.[6] Shimmer(%): It is obtained by dividing the average of the absolute value of the dif-

ference in intensity (amplitude) between each period and the following period by the average period intensity, and its normal value is below 3%.[6] Harmonic-to-Noise Ratio (HNR-dB): It is the ratio of the total energy of F0 and its multiples of harmonics to the noise energy.[6] Fundamental frequency (f0) (Hz): It is the number of opening-closing cycles that occur per second of sound folds. It reveals the thickness and thinness of the sound.[6] In our study, we aimed to examine the relationship between the degree of prostate obstruction and voice.

2. Materials and methods

The study comprised 77 male patients with benign prostatic hyperplasia (BPH) hospitalized at Adana City Hospital between January 1, 2021, and July 1, 2021. Urinary system ultrasonography was requested from the patients for prostate-specific antigen (PSA) level, testosterone level, prostate volume (in milliliters, ml), which are routine BPH examinations in Urology department. Testosterone (reference values 1.75-7.81 ng/mL), PSA (reference values 0-4 ng/mL) levels, and prostate volumes (ml) of the patients and their ages were recorded. International prostate symptom scoring (IPSS) was performed on the patients. According to the IPSS scoring, those with 0-7 points are grouped as mild (mild obstruction), those with 8-19 points as moderate (moderate obstruction), and those with 20-35 points as severe (severe obstruction). Mild, moderate, severe patients were categorized as group 1, group 2 and group 3, respectively. Voice Handicap Index-10 Turkish version (VHI-10) was realized to the patients and the results were saved.

Our study was approved by the Adana City Hospital Clinical Research Ethics Committee (Meeting Number: 80, Decision Number: 1404, Date: 06/05/2020). Written consent was obtained from the patient (or legal guardian) that her/his medical data can be published.

3. Results

The study involved 77 male patients. The ages of the patients ranged from 48 to 74, with an average of 60 years. There were 24 patients in Group 1, 26 patients in Group 2, and 27 patients in Group 3. The prostate volumes of the patients ranged from 27 ml to 62 ml, with an average of 41.1 ml. Patients' IPSS scores varied from 4 to 27, with a mean of 16. The patients' VHI-10 scores ranged from 0 to 21, with a mean of 9.14.

The PSA levels of the patients ranged from 0.2 to 3.1, with a mean of 1.43. Testosterone levels of the patients ranged between 1.78 and 5.32, and the mean was 3.04.

The patients' fundamental frequency F0 Hz (mean pitch) values ranged from 121.11 to 197.62, with a mean of 157.74. Jitter % (frequency perturbation jitter) values of the patients ranged from 0.22 to 0.34, and the mean was 0.26. The shimmer % (amplitude perturbation shimmer) values of the patients ranged between 1.82 and 3.44, with a mean of 2.42. The HNR dB values of the patients ranged from 20.37 to 24.81, and the mean was 22.91. The minimum, maximum, and average values are all presented in Table 1.

Among the three groups, there was a statistically significant difference in terms of prostate volume (p=0.001), Jitter % (p=0.001), Shimmer % (p<0.001), and HNR dB (p=0.002) variables.

For the prostate volume variable, the difference between Group 1 and Group 2 was statistically significant (p<0.001). Group 2 had a larger prostate volume than Group 1. For the jitter % variable, the difference between Group 2 and Group 3 was statistically significant (p<0.001). Jitter% was found to be higher in Group 2.

Table 1

Minimum and maximum values

Variables	Minimum	Maximum	Mean±SD
Age	48	74	60,08±8,76
Testosterone	1,78	5,32	3,04±1,12
PSA	0,2	3,10	1,43±0,95
Prostate Volume(ml)	27	62	41,1±9,62
VHI-10 Points	0	21	9,14±7,76
IPSS Score	4	27	16±7,52
Fundamental frequency F0 Hz(Mean Pitch)	121,11	197,62	157,74±25,95
Jitter % (frequency perturbation jitter)	0,22	0,34	0,26±0,05
Shimmer % (amplitude perturbation shimmer)	1,82	3,44	2,42±0,70
HNR dB	20,37	24,81	22,91±1,86

For the Shimmer% variable, the difference between Group 3 and Group 2 was statistically significant (p<0.001). The difference between Group 3 and Group 1 was statistically significant (p<0.001). Shimmer % value in Group 3 was statistically significantly lower than both other groups.

For the HNR dB variable, the difference between Group 1 and Group 2 was statistically significant (p=0.049). HNR dB values in group 1 were higher than the other groups. For the HNR dB variable, the difference between Group 2 and Group 3 was statistically significant (p=0.002). HNR dB values in Group 3 were higher than the other groups. The p values between the groups are shown in Table 2.

There was a weak negative linear correlation between PSA and fundamental frequency F0 Hz (Mean Pitch) (r=-0.312, p<0.01). There was a moderate positive linear correlation between PSA and jitter % (r=0.449, p<0.01) (The negative relationship represents an inverse relationship, that is, a relationship that decreases as one increases or increases as the other decreases, while a positive relationship represents a direct ratio, that is, a relationship that increases as one increases or decreases as the other decreases).

There was a strong positive linear correlation between prostate volume and jitter % (r=0.646, p<0.01). There was a weak negative linear correlation between prostate volume and HNR dB (r=-0.277, p<0.05).

There was a weak negative linear correlation between testosterone and fundamental frequency F0 Hz (Mean Pitch) (r=-0.246, p<0.05). There was a weak negative linear correlation between testosterone and jitter % (r=-0.339, p<0.01). There was a moderate linear correlation between testosterone and shimmer % (r=0.454, p<0.01). The p and r values are demonstrated in Table 3.

4. Discussions

Hormones are thought to have an effect on the voice function of the larynx.[7] Hormonal balance changes during adolescence, affecting body, provide one of the reasons for voice changes and form the source of hypotheses and studies regarding the effect of hormones.[8] Progesterone and testosterone ratios were high in Reinke's edema.

Table 2

Groups and p values

Variables	Groups			p values
	Group 1 [Q1:Q3] Median	Group 2 [Q1:Q3] Median	Group 3 [Q1:Q3] Median	
Age	[51.00:61.00] 56.00	[56.00:67.00] 61.00	[49.00:71.00] 64.00	0.310
Prostate Volume(ml)	[27.50:44.00] 34.00	[44.00:54.00] 44.00	[37.00:48.00] 42.00	0.001
PSA	[0.44:1.66] 0.48	[1.66:2.01] 1.66	[0.49:2.52] 1.64	0.071
Testosterone	[1.88:2.95] 2.72	[2.72:4.32] 2.95	[1.78:5.32] 2.88	0.353
Fundamental frequency F0 Hz(Mean Pitch)	[138.37:179.11] 149.48	[138.37:160.59] 160.59	[121.11:183.87] 183.87	0.864
Jitter % (frequency perturbation jitter)	[0.22:0.29] 0.23	[0.23:0.34] 0.34	[0.22:0.23] 0.23	0.001
Shimmer % (amplitude perturbation shimmer)	[1.90:3.07] 2.31	[1.93:3.44] 3.44	[1.82:1.93] 1.82	<0.001
HNR dB	[21.12:24.81] 23.32	[20.37:24.77] 20.37	[23.46:24.77] 23.46	0.002
VHI-10 Points	[3.50:16.00] 10.00	[0.00:21.00] 10.00	[0.00:18.00] 7.00	0.298

Table 3

p and r values

Variables	Fundamental frequency F0 Hz(Mean Pitch))	Jitter % (frequency perturbation jitter)	Shimmer % (amplitude perturbation shimmer)	HNR dB
PSA	-.312**	.449**	.151	-.005
Prostate Volume (ml)	.020	.646**	.055	-.277*
Testosterone	-.246*	-.339**	.454**	-.218

*P< 0.05 , ** P< 0.01, r<0.2 too weak, 0.2-0.4 weak, 0.4-0.6 moderate intensity, 0.6-0.8 high, 0.8> very high

These findings support the theory progesterone and testosterone hormones cause edema by affecting the larynx mucosa.[9] Nacci et al. hypothesized that in the larynx there are particular receptors for gender hormones. In a study, sample of vocal cords received from healthy people, cadavers and larynx cancer were research for the androgen, estrogen and progesterone receptors by immunohistochemically. However, while progesterone and mild estrogen receptors were found in cancerous samples, no receptors in other samples. According to this study, there is sex hormones no receptor in the larynx.[7] In our study, the effects of IPSS data, prostate volume, PSA and testosterone levels on voice in male BPH patients were examined. Among the 3 groups, we detected a statistically significant difference of prostate volume, Shimmer, Jitter and HNR dB variables in our study. When group 1 and group 2 were compared, it found that the prostate volume of group 2 was higher. When group 2 and group 3 were as per, jitter was found to be % higher in group 2. When the three groups were examined, it was observed that the group with the lowest average shimmer % value was group 3. As a result, as the prostate volume increased, the degree of obstruction and BPH also increased. Although PSA, testosterone, and prostate volume were not statistically strong in patients with a high BPH grade, a slope in the same direction was detected between them. While the shimmer and jitter values were advanced in group 2, which had the highest PSA and prostate volume, the HNR dB value was found to be lower. A negative weak linear relationship was seen between PSA and Testosterone with fundamental frequency F0 Hz (Mean Pitch). There was a negative weak linear relationship between prostate volume and HNR dB. While there was a weak negative linear relationship between testosterone and jitter %, we suggest that a positive moderate linear relationship between testosterone and shimmer %.

Pedersen et al. suggested that the fundamental frequency (f0) decreases in females at the transition to puberty, as in males, but decrease is less pronounced in females. The variety of downward in frequency related to the dissimilarity of testosterone or estrogen.[10] We suggest that a negative weak linear correlation was testosterone and F0 (Hz).

In order to better understand the effect of testosterone on the voice, it may be illuminating to examine the studies in which a female patient was given the hormone testosterone for any reason. Cler, reported that a transgender men treated testosterone therapy during one year, the f0 value fell into the normal range from female to male. In addition, it was found that the larynx structure of the patient showed changes (forward-sloping and longer larynx) seen in a male adolescent in the regular endoscopic examinations.[11] In another study, 10 female patients were given regular testosterone with a subcutaneous implant and voice analyzes were carried out at 3, 6, and 12 months. The results were evaluated and no significant changes were detected in the unbiased properties of the voice. In this study whereas, the testosterone dose is at the treatment dose level, not the advanced dosage used for transgender patients.[12] Bioavailable testosterone and DHEAS were seen to be related with less f0 in men.[13] In female-to-male transition subjects treated with testosterone, voice analysis showed that testosterone decreased f0. In another study, a significant decrease in mean pitch value was observed in the high-dose group, depending on dose and concentration, after the 24th week in women treated with testosterone.[14] Akcam et al., suggest that F0 value was between normal men and women in untreated Idiopathic Hypogonadotropic Hypogonadism (IHH) men. Those patients is treated with testosterone, the f0 value is close to that of a normal range. In other words, when testosterone

increases, the f0 value decreases.[15] In our study, the group with the highest testosterone average was group 2. We seen a negative weak linear correlation between testosterone and F0 Hz (Mean Pitch). While there was a negative weak linear relationship between testosterone and jitter %, we found a moderate positive relationship between testosterone and shimmer %. The highest Jitter % and shimmer % values were in group 2.

As far as the literature can be scanned, showed that studies on voice analysis in the field of otolaryngology are less than in other subjects.. By categorizing men with BPH according to testosterone, PSA and IPSS values, prostate volume measured by USG and performing voice analysis, we evaluate our article as different from previous literature and as the first. Studies on voice analysis in the literature have often been conducted on women with menstrual cycles, patients on hormone therapy, transgender people, or patients receiving treatment for acromegaly. [12-4,16-8]

The Voice Handicap Index is a 30-question personal feedback survey. It has 10 questions each of three subgroups: emotional, functional and physical. Each question is answered by the patient between 0-4 and the maximum score is 120. The score when increase, the greater the voice problem. This tool can supply adequate information to the physician.[4] Kılıç et al. They investigated the reliability and validity of the Turkish Voice Handicap Index and concluded that it is more suitable for use in clinics.[3] Our study found that the mean value of VHI-10 had the highest mean value with 10 points equally in group 1 and group 2. This score; 7 in group 3. Group 3 was the group with the highest IPSS score. This show that this group feels the voice problem not so much. This may have occurred as a result of the hormones and growth factors studied here.

In conclusion, although there is much debate about the effect of hormones on the voice, it is clear that nothing is clear. However, we currently believe that testosterone has a more pronounced effect on voice, in men. A combined thought that not only testosterone but other local and systemic hormonal factors are effective is more correct.

Statement of ethics

Adana City Hospital Clinical Research Ethics Committee (Meeting Number: 80, Decision Number: 1404, Date: 06/05/2020).

Conflict of interest statement

Author declare that they have no financial conflict of interest with regard to the content of this report.

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Evaluation of Orally Disintegrating Tablet Formulations in The Treatment of Oral Mucositis

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Abstract

Aim: Orally disintegrating tablets (ODT) are widely used dosage forms with high patient compliance, which preferred in the treatment of many diseases currently. In this study we aimed to develop an orally disintegrating tablet formulation can be preferred in the treatment of oral mucositis, which often occurs after chemotherapy during cancer treatment.

Methods: Lidocaine hydrochloride, which is a local anesthetic substance, was used as active pharmaceutical ingredient to obtain ODT formulation for the treatment of oral mucositis. ODTs were prepared by direct compression technique and crospovidone was used as super-dispersant

Results: The method developed for lidocaine determination was validated. Characterization of powder mixtures conducted; angle repose was found to be as 25.780°±0.810, flow time was 4.180±0.772 s, compressibility index was 9.591±0.774% and Hausner's ratio was calculated as 1.106±0.014. The uniformity of weight and content for the ODT formulation was 493.705±3.583 g, 78.890±2.546 mg, respectively. The tablets had a diameter of 12.031 ±0.015 mm while thickness was 4.420 ±0.021 mm. The hardness was calculated as 28.701±1.123 N, while percent friability value was 0.760%. Disintegration time of the tablets were 31.551±0.354 s, and approximately 90% of the prepared formulation dissolved in around 20 minutes according to dissolution testing.

Conclusions: The prepared formulation was evaluated through powder and tablet controls; it was found to comply with the limits specified in the European Pharmacopoeia. The developed ODT formulation for the treatment of oral mucositis, is planned to be evaluated through in vivo tests to complete the assessment of the formulation.

Keywords: *Orally disintegrating tablets, Evaluation methods, Lidocaine hydrochloride*

1. Introduction

When taken orally, the tablets disintegrate rapidly before swallowing. ODT is defined in the European Pharmacopoeia as "uncoated tablets which are placed in the mouth and quickly disintegrate before swallowing". The U.S. Food and Drug Administration defines ODT formulations as solid drugs containing active ingredients that disintegrate quickly, usually within a few seconds inside the mouth. These dosage forms are also called as fast-dissolving, orodispersible tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapimelt saccording to different sources[1].

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ODTs should be swallowed quickly without the need for water and should not leave any residue in the mouth. ODTs should be prepared in a way that leaves a pleasant aftertaste, especially for bitter-tasting active substances.

They must be durable for use during and after production. In addition, it should not be sensitive to environmental factors such as humidity and temperature. ODTs must be manufacturable by standard production and packaging methods and the cost of production must be low. In addition to these properties, ODTs are expected to be bioequivalent to conventional market preparations where drug absorption occurs in the post-gastric route. Depending on the physicochemical properties of the active substance contained in ODTs, the drug is absorbed at different levels along the pregastric tract. This may have an impact on the pharmacokinetic profile and bioavailability of ODT. Differences in the pharmacokinetic profile of ODTs due to high drug levels in the blood and systemic exposure are a result of the lack of first-pass effect of ODTs due to pregastric absorption. This has an impact on the safety and efficacy of ODTs[2-3].

In addition, the solubility of the active ingredient in the ODT formulation is highly effective in the disintegration time of the tablets, depending on the particle size. The aim in the development of ODT is that the drug has a systemic effect rather than a local effect. For this reason, active substances with systemic effects are used. In addition, some of the active ingredient is absorbed in the mouth, as the tablet is disintegrated by the salivary fluid. Therefore, it is very important that the active ingredient used for formulation is in non-ionized form. Choosing the appropriate dispersing agent and water-soluble excipients is very important in the creation of ODTs. This improves the porous structure of the tablet and allows rapid absorption of water into the tablet matrix. As a result, it allows the tablets to disintegrate quickly.

ODT tablets contain excipients such as superdispersant, diluent, lubricant, permeability enhancer, sweetener and aromatizer. In the selection of these excipients, rapid dispersion, not adversely affecting the validity of other excipients and the stability of the finished product, and a melting point between 30 and 35 degrees Celsius are taken into account. The pleasant taste in the mouth of ODT formulations is an important factor that makes the patient more responsive to using the drug. The properties and proportions of the excipients in the composition of the formulation affect the taste of the tablets in the mouth. The excipients used in the formation of ODT should hide the bad taste of the drug, leave a smooth and pleasant taste without leaving any residue in the mouth, and should not be affected by factors such as humidity and temperature[4]. Dispersants, taste masking polymers, diluents, lubricants, sweeteners, aromatizers, preservatives, binders and flocculating agents are frequently used in ADT formulations[5-7]. Superdispersants are excipients that change the disintegration time and dissolution of the tablet with high dispersion efficiency at low concentrations. When used in high doses, superdispersants can affect the mouthfeel, hardness and friability of the tablet. To be a good superdispersant, tablets require rapid dispensing, a pleasant mouthfeel, small particle size and high fluidity. In addition, it should be of a quality to increase the flow properties of the powder mixture[8].

Lidocaine hydrochloride, which is one of the local anesthetics with average potency and duration of action, has a 1% solution in 0.9% sodium chloride at a pH of 6.5–7 and is freely soluble in water. It can be described as a reliable agent. Prepared solutions should be stored away from light. It does not harm the tissues even at 8% concentration. It is three times more potent and 1.5 times more toxic than procaine. 0.5%, 1%, 1.5% and 2% solutions are available for peripheral nerve blocks and peridural block applications. In spinal anesthesia applications lasting 30-60 minutes, 7.5% glucose and 5% lidocaine solution can also be used[9-10]. Various damages occur in the mouth and pharynx of cancer patients due to chemotherapy treatment. This is called oral mucositis. Hoarseness and sore throat are also among the main symptoms[11]. The incidence of oral mucositis is 85-95% in patients receiving high-dose chemotherapy for hematopoietic stem cell transplantation, and 98% in patients with head and neck cancer who receive chemotherapy together with radiation. Oral mucositis, a four-phase process recommended by the World Health Organization, is classified into the initial inflammatory or vascular phase (Stage I), epithelial phase (Stage II), ulcerative or bacteriological phase (Stage III), and healing phase (Stage IV)[12]. It occurs one week after chemotherapy and usually resolves after 21 days. However, during periods of mucositis, dehydration, malnutrition, anorexia, cachexia, and daily life functions and nutrition of the patients are adversely affected. This causes pain, difficulty chewing, swallowing, and slurred speech. The use of opioid analgesics due to pain and the transition to total parenteral nutrition due to nutritional problems are due to mucositis. In addition, oral mucositis causes infections, which increases the spread of opportunistic infections, increases sepsis deaths and hospital stays, increasing the cost of treatment. In addition, this may result in skipping or reducing the dose of therapy administered to the patient until the mucositis resolves. The above-mentioned adverse effects of mucositis significantly reduce the quality of life of patients, while at the same time causing problems in responding to treatment and the development of life-threatening conditions. A gel, ointment, or ODT is applied for this side effect or other oral mucositis issues.

In this study, it was aimed to develop ODT formulations containing lidocaine hydrochloride as a model drug and to evaluate them with in vitro characterization tests.

2. Materials and methods

2.1. Determination of Lidocaine Hydrochloride

The chromatographic conditions of the high pressure liquid chromatography (HPLC) method to be used for the determination of lidocaine hydrochloride are shown in Table 1. In order to obtain the calibration line of lidocaine hydrochloride, a stock solution of 100 µg/mL concentration was prepared in a mixture of Water:Acetonitrile (50:50, v/v), which is the mobile phase in the quantification method. Based on this solution, standard solutions were prepared at eight different concentrations (5-40 µg/mL), 6 for each concentration, with appropriate dilutions. After quantification, the regression analysis with concentration versus peak areas data yielded the calibration line and the correct equation to be used in other analyses. The validity of the analytical method was demonstrated by evaluating the parameters of linearity, accuracy, precision, limit of detectability/observability (LOD), and limit of detectability (LOQ).

Table 1

The HPLC chromatographic conditions used for the determination of the active ingredient

Device	Shimadzu, LC-2030C Prominence
Stationary phase	VP-ODS C-18 column
Mobile phase	Water:Acetonitrile (50:50, w/w), pH 2.5
Temperature conditions	40 ± 2 °C
Flow rate	1 mL/min
Injection volume	20 µL
Monitoring wavelength	240 nm

Table 2

Prepared ODT formulation unit formula

Composition	mg/tablet
Lidocaine hydrochloride	80
Avicel pH 1*2	150
Mannitol	150
Crospovidone	50
PVP K30	60
Aerosil	5
Talc	5
Total amount	500

2.2. ODT Formulation and Preparation Method

ODT formulation is given in Table 2. Direct compression method was preferred for the preparation of the tablet formulation. For this purpose, all formulation content (Lidocaine HCl, Avicel PH 102, mannitol, crospovidone, PVP-K30) except the lubricants (Aerosil and talc) were weighed and mixed homogenously. Aerosil and talc were finally added to the mixture and mixed for another 5 min. and tablets were pressed with a single punch tablet machine.

2.3. Evaluation of Powder Properties Before Compression

In order to evaluate the powder properties of the prepared ODT formulation powder mixture, the angle of repose, flow time, compressibility index and Hausner's ratio values were calculated and evaluated according to the European Pharmacopoeia[13].

2.4. Evaluation of ODT Controls

The parameters of weight and content uniformity, diameter, thickness, hardness, disintegration time, dissolution tests were evaluated on the ODT formulation prepared using the direct compression method.

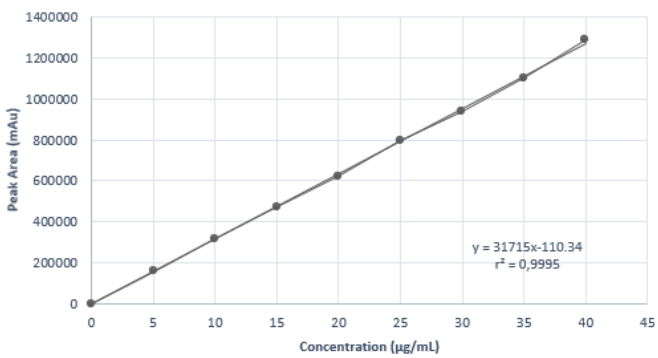
2.5. Results and Discussion

2.5.1. Determination of Lidocaine Hydrochloride

The resulting calibration line and equation are shown in Figure 1. The validity of the analytical method was proved by evaluating the linearity (R:0.9995), accuracy (% Relative error <2%), precision (Coefficient of variation <2%), Limit of Detectability (LOD) (0.440 µg/mL) and Limit of Determinability (LOQ) (1.280 µg/mL) parameters.

Figure 1

Lidocaine HCl calibration curve and equation



2.5.2. Results of Powder Properties Before Compression

Powder properties were carried out to determine the flow properties of the powder mixture prepared for lidocaine HCl ODT formulation. The results of the powder properties for lidocaine HCl ODT formulation are shown in Table 3.

Table 3

Results of powder control tests for lidocaine HCl ODT formulation

Powder Controls	Results (X±SD)
Flow time (s, n=10)	4.180±0.772
Angle of repose (n=10; °)	25.780±0.810
Compressibility index (n=6; %)	9.591±0.774
Hausner ratio (n=6)	1.106±0.014

X=Average; SD=Standart deviation

2.5.3. Results of ODT Controls

An example digital photograph of ODT containing lidocaine HCl is given in Figure 2. In vitro control findings of the prepared ODT formulation are given in Table 4. The dissolution test on lidocaine HCl ODT formulation was performed in pH 6.8 phosphate buffer medium (n=6) and the dissolution test profiles are shown in Figure 3.

Figure 2

Lidocaine HCl-containing ODT formulation digital photograph

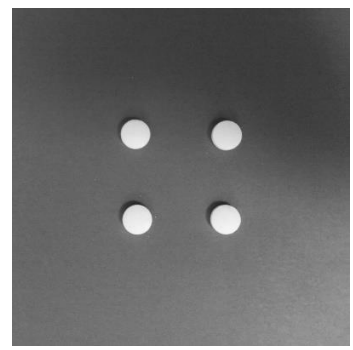
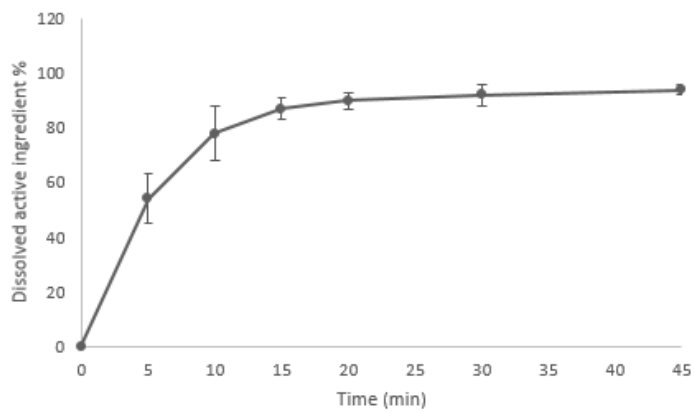


Figure 3

Lidocaine HCl ODT formulation dissolution profile



3. Results

Direct compression is faster, simpler and easier compared to other techniques used in the preparation of tablets, such as wet and dry granulation. For direct compression, the compressibility and flow properties of the powder mixture must be suitable. Poor powder flow properties are an important parameter that deteriorates the quality characteristics of the prepared tablet, including content uniformity. Therefore, before the ODT formulation was prepared, necessary controls were first performed on the powder mixture prepared for the formulation. These checks reveal the powder flow properties and allow for a preliminary assessment prior to tablet pressing[14]. Angle repose, flow time, compressibility index and Hausner's ratio values were calculated on the powder mixture forming the ODT formulation and evaluated according to the European Pharmacopoeia. When the findings obtained were evaluated (Table 3); angle repose was found to be 25.780°±0.810, flow time 4.180±0.772

s, compressibility index 9.591±0.774% and Hausner's ratio 1.106±0.014. According to the European Pharmacopoeia when the angle repose degree is within the range of 25-30°, the powder mixture is described as exhibiting ''excellent flow''; additionally the compressibility index and Hausner's ratio are defined as 1-10% and 1-1.1115, respectively, for a powder mixture to be categorized as demonstrating "excellent flow" [15-16]. Furthermore, a repeatable flow time of less than 10 s was achieved and all these findings were found compatible within the limits specified in the European Pharmacopoeia[16].

In order to develope ODT formulation in vitro experiments have been performed. These tests included content and weight uniformity, diameter, thickness, hardness, disintegration time and dissolution tests. The results obtained (Table 4) indicated that the uniformity of weight for the ODT formulation was 493.705 (±3.583 g) and the calculated % deviation value did not exceed the 5% limit[17]. The uniformity of content for the prepared tablet (Table 4) was determined as 78.890 mg (+2.546 mg)[18]. For the prepared formulation, the tablets had a diameter of 12.031 ±0.015 mm and a thickness of 4.420 ±0.021 mm (Table 4).

Table 4

In vitro control findings for lidocaine HCl ODT formulation

Disintegration time (s, n=6)	31.551±0.354
Uniformity of weight (mg, n=20)	493.705±3.583
Uniformity of content (mg, n=6)	78.890±2.546
Friability (%)	0.760
Hardness (N, n=10)	28.701±1.123
Diameter (mm, n=20)	12.031±0.015
Thickness (mm, n=20)	4.420±0.021

When the results were examined in terms of SS data it was shown that the diameter and thickness were found to be appropriate. Even though the diameter and thickness of the tablets are not registered in the pharmacopoeia, keeping the size of the prepared tablets consistent is important[19]. Furthermore, the hardness of the formulation prepared by direct compression method, reached approximately 28.701 ± 1.123 N. For ODTs, it is recommended that the hardness should be below 50 N to allow for faster disintegration in the mouth. Prepared formulation had shown compatible results within the literature in terms of hardness. Friability is defined as measurement of the mechanical strength of a tablet. High values of friability is undesirable condition as it may lead to the tablet not maintaining its integrity during transportation, packaging, or handling[1]. For the prepared ODT formulation, the % friability value was calculated as 0.760 (Table 4). The friability test results for the tablets were evaluated according to the European Pharmacopoeia (<1%) and were found compatible with pharmacopeial limits[20]. It has been reported in the European Pharmacopoeia that orally dispersible tablets should "disintegrate in less than 3 minutes". Disintegration time was determined as 31.550±0.354 s (Table 4). The disintegration time of the formulation is within the appropriate limits specified by the European Pharmacopoeia[21]. In vitro dissolution testing is low cost and fast experiment widely used in drug development studies to demonstrate drug quality and predict in vivo performance[22-23]. According to dissolution results, approximately 90% of the prepared formulation dissolved in around 20 minutes. Sink conditions were ensured in dissolution studies.

The ODT formulation containing lidocaine hydrochloride was prepared using the direct compression method with the use of crospovidone as superdispersant. When the prepared formulation was evaluated through powder and tablet controls, it was found to comply with the limits specified in the European Pharmacopoeia. The developed formulation, which is considered an important and effective step providing the advantages of ODT tablets in the treatment of oral mucositis, is planned to be evaluated through in vivo tests to complete the assessment of the formulation. This formulation preparation represents a significant milestone in offering an alternative product to the formulations in the Turkish Pharmaceutical Market.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Çukurova University Medical Ethics Committee with the decision no. 80-31 dated 31.08.2018.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author contributions

Study design: ED, DO, TÇ; Materials: ED, DO, TÇ; Data analysis and evaluation: ED, DO, TÇ; Literature search: ED, DO, TÇ; Manuscript writing: ED, DO, TÇ; Data interpretation and compilation: ED, DO, TÇ.

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The Role of Serum Ferritin, Vitamin B12 and Vitamin D Levels in Childhood Primary Headaches

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Abstract

Aim: In this study, it was aimed to investigate the relationship between headache components and serum ferritin, vitamin B12 and vitamin D levels in pediatric patients with migraine and tension-type headache (TTH).

Methods: The data of patients aged 7-17 years who applied to the outpatient pediatric neurology clinic with a complaint of headache and were diagnosed with migraine and TTH based on the International Classification of Headache Disorder (ICHD)-3 beta criteria were evaluated retrospectively.

Results: The mean age of the patients was 13.80 ± 3.89 years in the migraine group and 14.10± 4.17 years in the TTH group. In the migraine group, the duration of the attack was longer and the pain intensity was higher. Unilateral headache, throbbing character, nausea, vomiting, discomfort from light and sound were statistically significantly higher in the migraine group. In patients with migraine, low vitamin D and low ferritin levels were associated with a prolongation of the disease duration and an increase in the frequency of attacks. A decrease in serum iron level was associated with an increase in pain severity and a decrease in vitamin D levels was associated with an increase in attack duration. It was observed that there was an increase in the frequency of attacks with a decrease in serum ferritin levels in the TTH group. No statistically significant correlation was found between headache characteristics and vitamin B12.

Conclusions: Our study shows the necessity of routine evaluation of vitamin D and ferritin levels in childhood primary headaches.

Keywords: *Migraine, Tension-type headache, iron deficiency anemia, vitamin D, vitamin B12*

1. Introduction

Headache is among the most common reasons for referral to pediatric neurology outpatient clinics. In recent years, the frequency of childhood migraine and recurrent headache has increased due to undesirable changes in children's lifestyles.[1] The frequency of headaches in childhood ranges from 26.6% to 93.3%.[2,3] The majority of headaches in children are primary headaches, including migraine and tension-type headaches (TTH)[1]. The etiology of headache can usually be revealed with a detailed history and a careful neurological examination. It is the most important point that the clinician should not miss the secondary headaches that require urgent treatment in a patient with headache. Detailed history and neurological examination play an important role in excluding secondary causes, classifying headaches and relieving families concerns.[4] Neuroimaging techniques should be used in differential diagnosis when necessary to exclude secondary causes. An accurate definition and classification of the headache symptom is an important factor influencing patient management. Neuroimaging techniques should be used in differential diagnosis when necessary to exclude secondary causes. An accurate definition and classification of the headache symptom is an important factor influencing patient management. The International Classification of Headache Disorder (ICHD-3 beta version) has been proposed to support and prove this common neurological problem.[5] Chronic headaches prevent school attendance, cause loss of daily activities, insufficient participation in regular activities, loss of productivity and significant deterioration in quality of life.[4]

In this study, we aimed to compare the headache components and scores, including the number of attacks, duration of attacks, frequency, severity and accompanying symptoms, between the two groups, and to reveal their effects on daily life in pediatric patients with migraine and TTH. At the same time, it was aimed to investigate the relationship between headache characteristics and serum ferritin, vitamin B12 and vitamin D levels.

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2. Materials and methods

This single-center, cross-sectional, clinical-based and retrospective study was conducted on patients who applied to the outpatient neurology outpatient clinic with headache complaints between January 2021 and January 2023 and were diagnosed with migraine and TTH based on the "International Classification of Headache Disorder (ICHD-3 beta)" criteria was included in the study. Patients with secondary headaches who could not be classified according to the criteria were not included in the study[5]. As the control group, 100 healthy children aged 7-17 years, who applied to the pediatric health and diseases polyclinics for routine control, did not have acute and chronic diseases and did not use drugs, and whose demographic characteristics were similar to the patient group, were included. Although there is no standard approach in the evaluation of patients who apply to pediatric neurology outpatient clinics with the complaint of outpatient headache, a detailed history is taken from all patients and a detailed neurological examination including blood pressure measurement and ophthalmological examination is performed. All these data are recorded in the electronic hospital database by the pediatric neurologist at each control. Demographic characteristics such as age, gender, neurological examinations, headache characteristics, laboratory findings (hematological parameters, routine biochemistry, serum ferritin, vitamin B12 and vitamin D), neuroimaging results, if any, were recorded. Patients who were diagnosed with migraine and TTH and kept a complete headache diary for the last 3 months were included in the study in the order of admission to the hospital, without any other selection. In the headache diary; days of headache, duration of pain, severity of pain (out of 10), accompanying nausea-vomiting during pain, being disturbed by light and/or sound, pain, taking painkillers, not being able to go to school, having to return home from school, not being able to study at home or whether it caused the inability to attend a social event. These diaries were kept by the patients with parental control. Pediatric Migraine Disability Assessment (PedMIDAS) scores of each patient were calculated with the help of diaries[6]. Today, the determination of the effects of headache, the decision of prophylaxis, the follow-up of the chronicity process is done with the PedMIDAS scoring system. While evaluating the PedMİDAS scale; Those with a score of 1-10 were classified as none, between 11-30 as mild, 31-50 as moderate, and above 50 as severe[6]. Written informed consent was obtained from the patients and parents participating in the study. Medical Ethics Committee approval was obtained for the study protocol and the study was conducted within the scope of the Declaration of Helsinki (Number. 2023/4904)

2.1. Statistical analyses

The variables used in the study were summarized with mean, standard deviation, median, minimum and maximum values, frequency and percentage according to measurement levels. The assumption of normal distribution for numerical variables was examined using the Shapiro-Wilk test. The comparison of continuous variables that did not conform to normal distribution between more than two groups was compared with the Kruskal-Wallis H test and then with the Dunn test as a Post Hoc test. Comparisons of continuous variables that did not fit normal distribution between two independent groups were compared with the Mann Whitney U test. Pearson chi-square and Fisher's Exact tests were used for categorical variables. Spearman rho correlation coefficient was used to determine the relationship between two independent variables with continuous measurement values that did not conform to the normal distribution. $p \leq 0.05$ was accepted as statistical significance level. IBM SPSS Statistics 22 program was used in the analysis.

3. Results

A total of 264 patients (100 migraine, 64 TTH and 100 controls), 169 (64%) girls, aged 7-17 years, were included in the study. There was no difference between migraine, TTH and control patients in terms of age and gender. The demographic characteristics of the patients and their comparison between the three groups are summarized in Table 1.

Table 1

Demographic and clinical information of the patients

		Migraine (n=100)	TTH (n= 64)	Control (n=100)	P
Age /year (Mean±SD)		13.80 ±3.89 (7.16-17.00)	14.10±4.17 (7.35-17.00)	13.60±3.21 (8.31-17.00)	0.868
Gender	F (%)	64 (%64.00)	42 (%65.60)	63 (%63.00)	0.782
	M(%)	36 (%36.00)	22 (%34.40)	37 (%37.00)	
Disease duration month median (min-max)		26 (6-82)	18 (8-61)	—	0.038

TTH, Tension-type headache; SD, standard deviation

Table 2

Comparison of headache characteristics in migraine and TTH groups

	Migraine (n, %)	TTH (n, %)	P
Headache attack frequency			
• 1-3 times a month	16 (%16.00)	8 (%12.50)	
• 1 time per week	14 (%14.00)	8 (%12.50)	
• 2-3 times a week	45 (%45.00)	31 (%48.43)	0.734
• 4 times a week	25 (%25.00)	17 (%26.56)	
Headache attack duration			
• 0.5-1 hour	22 (%22.00)	22 (%34.37)	
• 1-3 hours	42 (%42.00)	36 (%56.25)	
• 4-24 hours	31 (%31.00)	6 (%9.37)	0.032
• 24-72 hours	5 (%5.00)	0 (%0.00)	
Shape of the headache			
• Pulsating	65 (%65.00)	4 (% 6.25)	
• Printmaker	15 (%15.00)	50 (%78.12)	<0.001
• Both of them	20 (%20.00)	10 (%15.62)	
Headache severity			
• Mild	1 (%1.00)	0 (%0.00)	
• Middle	34 (%34.00)	40 (%62.50)	0.022
• Severe	65 (%65.00)	24 (%37.50)	
Headache localization			
• One sided	64 (%64.00)	21 (%32.81)	
• Bilateral	27 (%27.00)	34 (%53.12)	0.044
• Uncertain	9 (%9.00)	9 (%14.06)	

TTH, Tension-type headache

When the subgroups of migraine patients were evaluated according to ICHD-3 beta classification; 80 (80%) patients were diagnosed as migraine without aura, 11 (10%) migraine with aura, 9 (9%) chronic migraine. When patients with migraine are evaluated in terms of visual, auditory and sensory auras; Auras were detected in 14 patients (14%), color vision in 6 patients (6%), linear shapes in 17 patients (17%), numbness in the arms and legs in 10 patients

(10%). Migraine history in the family (mother, father, sibling, first degree relatives) was found in 49 (49%) migraine group and 16 (25%) in TTH group (p=0.001). When we look at the headache characteristics of the patients; There was no statistically significant difference between the groups in terms of attack frequency. In the group of patients diagnosed with migraine, the duration of attacks was statistically significantly longer and the severity of headache was higher (p=0.032; p=0.022, respectively). Unilateral, throbbing, nausea, vomiting, and discomfort from light and sound were statistically significantly higher in the migraine group (respectively-p=0.044; p <0.001; p < 0.001; p=0.003; p <0.001; p=0.047). Triggering/increasing pain with both physical and mental activity was significantly higher in the migraine group (p=0.006; 0.086, respectively). In addition, the increase in pain with hunger, insomnia, cold weather and smoking environment was significantly higher in this group (p=0.087; p= 0.008; p=0.006; p=0.035). The comparison of headache characteristics between the two groups is summarized in Tables 2 and Table 3.

When patients were asked to determine the severity of pain according to Visual Analogue Scoring (out of 10), it was significantly higher in the migraine group (p=0.038). There was no statistical significance between the two groups in terms of the pedMIDAS score used to show the severity of pain (p=0.138) (Table 4). In the migraine patient group, a positive and significant relationship was found between prolongation of the disease duration and an increase in the frequency of attacks and an increase in the duration of attacks (p=0.032; p=0.013, respectively). There was no statistically significant difference in hematological parameters, iron, ferritin, vitamin B12 and vitamin D levels between the three groups (p> 0.05) (Table 5). The relationship between headache characteristics and laboratory parameters was also evaluated in the study. It was found that low vitamin D and ferritin levels in patients with migraine were significantly associated with longer disease duration (p= 0.032; p=0.004, respectively). The frequency of migraine headache attacks was increased in children with iron deficiency anemia (IDA) and vitamin D deficiency (p= 0.004; p=0.003, respectively). At the same time, a decrease in serum iron was associated with an increase in headache severity (p= 0.001) and a decrease in vitamin D levels with an increase in attack duration (p= 0.042). No statistically significant correlation was found between headache characteristics and vitamin B12. No statistically significant correlation was found between the Visual Analogue Scale (VAS) values, in which the severity of headache was measured, and the pedMIDAS score and laboratory parameters. There was no statistically significant relationship between disease duration, attack frequency, headache severity and attack duration in the patient group with TTH. A correlation was observed between a decrease in serum ferritin level and an increase in the frequency of attacks (p= 0.026). No statistically significant correlation was found between headache characteristics and other laboratory parameters in children with TTH.In migraine patients, 52% of cranial magnetic resonance imaging (MRI) were normal and 48% of them had benign changes. In TTH patients, 33 (51.5%) of the cranial MRIs were normal and 31 (48.4%) had benign changes.

Table 3

Comparison of headache accompanying symptoms in migraine and TTH groups

	Migraine (n, %)	TTH (n, %)	P
Symptoms accompanying headache			
• Photophobia	80 (%80.00)	28 (%43.75)	< 0.001
• Phonophobia	91 (%91.00)	47 (%73.43)	0.047
• Discomfort with odor	40 (%40.00)	15 (%23.44)	0.126
• Nausea	65 (%65.00)	0 (%0.00)	< 0.001
• Vomiting	27 (%27.00)	0 (%0.00)	0.003
• Dizziness	63 (%63.00)	31(%48.44)	0.074
• Tears in the eyes	42 (%42.00)	17 (%26.56)	0.127
• Stomachache	26 (%26.00)	15 (%23.44)	0.936
Causes of headache			
• Physical fatigue	42 (%42.00)	9 (%14.06)	0.006
• Mental work	56 (%56.00)	23 (%35.93)	0.086
• Extreme excitement	17 (%17.00)	10 (%15.62)	0.862
• Stress	76 (%76.00)	47 (%73.43)	0.538
• Hunger	65 (%65.00)	28 (%43.75)	0.087
• Thirst	34 (%34.00)	13 (%20.31)	0.151
• Insomnia	80 (%80.00)	29 (%45.31)	0.008
• Going to school	37(%37.00)	18 (%28.12)	0.621
• Watching television	31 (%31.00)	14 (%21.87)	0.391
• Using a computer	37 (%37.00)	20 (%31.25)	0.623
• Cold weather	45 (%45.00)	10 (%15.62)	0.006
• Hot weather	32 (%32.00)	16 (%25.00)	0.812
• Smoking environment	30 (%30.00)	6 (%9.37)	0.035
Causes of headache relief			
• To relax	80 (%80.00)	43 (%67.18)	0.367
• Cold application	7 (%7.00)	6 (%9.37)	0.728
• Eating	27 (%27.00)	15 (%23.43)	0.855
• Vomiting	14 (%14.00)	0 (%0.00)	0.074
• Medication intake	56 (%56.00)	33 (%51.56)	0.631

TTH, Tension-type headache

Table 4

Comparison of VAS and PedMIDAS Scores in migraine and TTH patient groups

	Migraine Median (min-max)	TTH Median (min-max)	P
Visual Analoque Scoring	8.00 (4-10)	7.00 (4-10)	0.038
Pediatric Migraine Disability Assesment	19.00 (0-155)	15.00 (0-77)	0.138
Rating according to the PedMIDAS scale			
• Very little-none	25 (%25.00)	18 (%28.10)	0.342
• Mild	47 (%47.00)	35 (%54.70)	
• Middle	13 (%13.00)	9 (%14.10)	
• Severe	15 (%15.00)	2 (%3.10)	

TTH, Tension-type headache, PedMIDAS, Pediatric Migraine Disability Assesment

Table 5

Comparison of laboratory parameters in migraine, TTH and control patient groups

	Migraine n=100	TTH n=64	Control n=100	P
Hb (g/dl)	13.70±1.35 (11.20-16.60)	13.81±1.40 (10.90-16.60)	13.80 ±1.38 (8.60-17.80)	0.931
MCV (fl)	84.65 ±2.74 (60.90-96.40)	83.80±2.80 (74.70-91.80)	83.50 ±3.52 (64.20-96.30)	0.405
Serum iron (ug/dl)	69.50 ±22.10 (3.00-165.00)	64.00±20.32 (12.00-135.00)	58.50±20.80 (6.00-168.00)	0.091
Ferritin (ng/ml)	25.60±16.38 (5.70-247.40)	23.45 ±12.44 (3.90-96.40)	25.90±14.51 (3.90-161.80)	0.792
Vitamin B12 (pg/ml)	278.50±105.34 (135.00-748.00)	283.50 ±95.54 (147.00-419.00)	278.00 ±124.50 (131.00-907.00)	0.428
Vitamin D (ng/ml)	17.40 ±18.56 (3.30-123.00)	13.85±5.64 (1.10-56.00)	18.30±9.28 (1.00-89.00)	0.629

Hb, Hemoglobine; MCV, Mean Corpusculer Volume; TTH, Tension-type headache

4. Discussions

This study shows that low vitamin D and serum ferritin levels are associated with longer disease duration and increased frequency of attacks in childhood migraine patients. While a decrease in serum iron level was associated with higher headache severity, a decrease in vitamin D level was associated with increased attack duration. It was found that low ferritin level was associated with increased attack frequency in children with TTH diagnosis.

In previous studies investigating migraine and vitamin D deficiency, it was reported that migraine attacks increase in cold seasons and high latitudes, and the increase in the frequency of attacks may be due to low vitamin D.[7,8] A negative correlation was shown between vitamin D level and the frequency of headache attacks. In a study evaluating 300 children with migraine, it was reported that vitamin D deficiency was common in children and the prevalence of recurrent headache was higher in the vitamin D deficiency group than in the control group.[9] Vitamin D levels were found to be low in children with primary headache, both migraine with and without aura, and children with TTH.[10] In a study conducted in our country, the vitamin D level was found to be lower in the migraine patient group than in the TTH group.[11] On the contrary, several studies reported that no relationship was found between vitamin D level and migraine attack frequency, duration and severity.[12,13] In our study, vitamin D deficiency was detected in migraine, TTH and healthy control group. This result supports that vitamin D deficiency is a common health problem in our society. When evaluated in terms of headache characteristics, a decrease in vitamin D levels in patients with migraine was found to be associated with a prolongation of the disease duration and an increase in the frequency of attacks. No relationship was found between headache characteristics and vitamin D levels in children with TTH.

Previous studies investigating migraine and IDA reported that IDA was common in patients with menstrual migraine, and the severity and duration of headache increased in this group[14]. In a study conducted in children with IDA accompanying migraine, it was found that the frequency of headache attacks and pain severity were higher, and the pedMIDAS score was higher than those without anemia[15]. This study reported that when migraine children with anemia were re-evaluated after three months of iron treatment, the frequency, severity and duration of headache attacks decreased, and the pedMIDAS score also decreased[15]. A similar study supported that IDA was more common in children with migraine than the control group, and that low levels of hemoglobin, iron, and ferritin had an effect on the frequency, severity and duration of headache attacks.[16] While the increase in the frequency of pain in the TTH patient group was related to the decrease in serum ferritin and hemoglobin, it was shown that it did not affect the severity and duration of headache.[17] In another study, it was reported that the ferritin level was found to be significantly lower during an attack than during the attack-free period, but this situation was not associated with the frequency of headache.[18] In our study, it was shown that the decrease in ferritin level in patients with migraine was associated with the duration of the disease and an increase in the frequency of attacks. While the decrease in ferritin level was associated with the prolongation of the disease duration in the TTH patient group, it was not found to be associated with the severity of headache and the duration of the attack.

There are differences between studies examining the relationship between migraine and vitamin B12 or homocysteine levels in the literature. In a population-based study, it was stated that low vitamin B12 and high homocysteine levels were found in children with recurrent headaches.[19] In another study, although homocysteine levels were increased in children with migraine compared to healthy children, vitamin B12 levels were found to be similar.[20] A few studies reported that the mean homocysteine level in patients with migraine was higher than the general population, however, the vitamin B12 level was within normal limits. When these patients were re-evaluated six months after B12 and folic acid supplementation, they reported that the frequency of migraine attacks and the severity of pain decreased with a decrease in homocysteine levels.[21,22] In our study, no statistically significant difference was found between the migraine, TTH and healthy control groups in terms of vitamin B12 levels. One of the limiting factors of our study is that homocysteine, which is an indicator of functional vitamin B12 deficiency, and serum and urine methylmalonic acid levels were not measured in our study.

5. Conclusions

Recurrent headaches in children constitute an important patient burden for pediatric and pediatric neurology outpatient clinics. A detailed history and careful general and neurological examination can be diagnosed in the majority of patients. Iron deficiency anemia, vitamin D and vitamin B12 deficiency should be routinely screened and treated in these patients.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Inönü University Faculty of Medicine Ethics Committee with the decision no. 2023/4904.

Conflict of interest statement

Author declare that they have no financial conflict of interest with regard to the content of this report.

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Concept/Design, Data acquisition, Data analysis and interpretation, Drafting manuscript, Critical revision of manuscript and Final approval and accountability: GY.

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Defining the Risk Factors for the Evolution of Pan-Drug Resistance (PDR) Acinetobacter Baumanni Infections in Intensive Care Units

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Abstract

Aim: Acinetobacter baumannii is one important nosocomial pathogens. Acinetobacter infections causes long in hospital stay, mortality and morbidity. The aim of this study is to define the risk factors of PDR A. baumannii caused health care related (HCR) infections.

Methods: In the study of Cumhuriyet University Hospital between 01.01.201231.12.2013 is a case-control study was performed retrospectively. 49 PDR A. baumannii caused ventilator associated pneumonia and bacteremia, 71 other bacteria caused ventilator associated pneumonia and bacteremia patients were involved in this study. The PDR A. baumannii infection observed cases and the cases irrelevant to PDR A. baumannii infections are compared in terms of risk factors.

Results: As a result of the Univariate Analysis, it was found that DM, traumas, CCI>4, steroid use, hospitalization history in the last 3 months, and antibiotic use in the last 3 months were statistically and significantly higher in the PDR A. baumannii Group. Multivariate analysis was used to determine the risk factors with a p value of 0.1 and below by univariate analysis. In this respect, traumas (OR=93.32, p=0.011), steroid use (OR=21.09, p<0.001) and antibiotic use in the last 3 months. (OR=26.97, p=0.001) were determined as independent risk factors in the development of PDR A. baumannii VAP and bloodstream infection.

Conclusions: All risk factors for health care related PDR. Acinetobacter infections were modifiable. The control of these factors may decrease the ratio of PDR A. baumannii. In case of detection of PDR A. baumannii infection in hospitals, control measures should be applicated, hospital staff should be educated and inappropriate antibiotic use should be prohibited.

Keywords: *PDR. Acinetobacter baumannii. risk factors. control precautions*

1. Introduction

Due to its improved environmental resistance, Acinetobacter baumannii, a non-fermentative Gram-negative coccobacillus, has gained more notoriety as a pathogen in healthcare settings.[1] A.baumannii is thought to make up 4%–7% of ventilator-associated pneumonia(VAP) and 1%–2% of nosocomial bloodstream infections.[2-5] According to epidemiological research, the death rates of infections caused by A. baumannii range from 7.8% to 23% outside of intensive care units (ICUs) and from 10% to 43% in ICUs, which has greatly raised the infirmary's expenses.[6] According to studies, there are clear patterns in the distribution of departments where pan-resistant Acinetobacter baumannii infections occur, with ICUs having one of the highest infection rates.[7-8] For instance, ICU patients have undergone more invasive procedures in addition to being severely ill. The vast majority of patients have also taken a combination of a lot of different broad-spectrum antibiotics, which weakens their body's defenses and makes it easier for them to contract hospital infections. The current strain of pan-resistant Acinetobacter baumannii can result in infections of the blood, urinary tract, central nervous system, lungs and abdomen. Pulmonary infection is one of the most prevalent.[9-10]

According to some studies, the host's health, prior antimicrobial drug exposure (especially broad-spectrum antibiotics), prior colonization with A baumannii, increased Pitt bacteremia score, being in the intensive care unit, and recent invasive procedures are risk factors associated with the acquisition of pan drug resistant (PDR) in A

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baumannii bacteremia.[11-13] Old age, neutropenia, malignancy, surgery prior to bacteremia, post-transplantation, severity of illness as determined by Pitt bacteremia score or Acute Physiology and Chronic Health Evaluation II score, ICU stay, having a lower level of albumin, respiratory tract as the origin of bacteremia, and inappropriate initial antimicrobial therapy are risk factors of mortality of A. baumannii bacteremia that have been reported in various parts of the world in recent years.[14-16]

All patients who were treated in intensive care units and who developed VAP and bloodstream infections, which are the most common PDR Acinetobacter infections, were included in this study. Two groups were formed as infections caused by PDR A. baumannii and infections caused by other bacterial agents, and it was aimed to determine the risk factors for VAP and bloodstream infection caused by PDR A.baumanni.

2. Materials and methods

2.1. Objective

The patients who were treated in ICUs , had high mortality and developed the most common PDR (Pan Drug Resistance) Acinetobacter infections VAP (Ventilator Associated Pneumonia) and bloodstream infections were included in the present study, and the risk factors for the development of PDR A. baumannii infection were aimed to be determined.

2.2. Patient Population

Cumhuriyet University Medical Faculty Hospital is a tertiary healthcare institution that serves in all branches with a bed capacity of 1150. Anesthesia ICU provides intensive care service with a bed capacity of 25. Patients receiving inpatient treatment at Cumhuriyet University Practice and Research Hospital are followed by the Infection Control Committee with the Active Surveillance Method. Daily surveillance continues until the patients are discharged from the Intensive Care Unit or until mortality, and patient information is recorded in the surveillance follow-up form. The names-surnames, ages, genders, hospitalization dates, hospitalization departments, clinical diagnoses, underlying diseases, risk factors, operations, interventions, hospital infection diagnoses, antibiotics used, reproducing agents, and susceptibility to antibiotics of patients are recorded in the surveillance follow-up form.

2.3. Definitions

The definitions of hospital-acquired infections were made according to CDC (Centers for Disease Control and Prevention) criteria in the present study (56). Among the patients who were hospitalized and who developed nosocomial infections (VAP and bloodstream infections) during the study period, the cases with PDR Acinetobacter Infection were included as the Case Group, and infections with other bacteria than PDR Acinetobacter were included as the Control Group.

2.4. Data Collection and Microbiological Analysis:

The patient files were examined from the registry system in the Cumhuriyet University Practice and Research Hospital Infection Control Committee Surveillance System, Hospital Automation System, and patient archive files. In this respect, the clinical and microbiological data of the patients who were hospitalized in the Anesthesia ICU between 01/01/2012 and 31/12/2013 in lower respiratory tract samples (deep tracheal aspirate and endotracheal aspirate) and blood cultures with VAP and bloodstream infections caused by other bacteria than A. baumannii were evaluated retrospectively. Patients were followed up with visits by an infectious diseases specialist. Adult patients who were over 18 years of age were included in the study. Healthcare and ventilator-associated pneumonia and bloodstream infection caused by A. baumannii and non-A. baumannii bacteria were evaluated in each patient. In cases with more than one infection episode, those with one single episode were included in the study. Patient information was recorded in the form obtained by scanning previous literature. The patients' names-surnames, ages, genders, dates of follow-ups, hospitalizations, history of hospitalization in the last 3 months, Glasgow Come Score, APACHE 2 (Acute Physiology And Chronic Health Evaluation) scores, SOFA (Sequential Organ Failure Assessment) Scores, and CCI (Carlson Comorbidity Index scores), underlying diseases, invasive procedures, antibiotic use in the last 3 months, the day of infection, the sites of infections and reproduction sites of bacteria, laboratory values, radiological imaging results, initial treatments, mortality status, and antibiotic susceptibility were included in the form.

The cases with PDR Acinetobacter infection and infections with non-Acinetobacter bacteria were compared in terms of risk factors. Lower respiratory tract samples were diluted 1/10 and inoculated at Columbia Agar 5% sheep-blood (Salubris) and Eosin Methylene Blue (EMB) Agar (Salubris) media with 0.01 ml diameter sterile cells and incubated at 35.5-37.5oC for 24-48 hours. The colonies >10 over 6 on Columbia Agar and EMB Agar Media were considered significant and were taken to Phoenix NMIC ID/82 Panels (Mc Farland 0.5) within the framework of the manufacturer's operating instructions and in line with the Clinical and Laboratory Standards Institute (CLSI) recommendations. The identifications were then made with the BD Phoenix 100 (BD Diagnostic Instrument Systems USA) and antimicrobial susceptibilities were determined. Blood cultures were evaluated with the BACTEC 9120 Automated System (BD Diagnostic Instrument Systems USA). Control passage was performed for those who did not have a growth signal for 5 days. The samples with a growth signal were added to Columbia Agar 5% sheep blood (Salubris) and Eosin Methylene Blue (EMB) Agar (Salubris) Media and were incubated for 24-48 hours at 35.5-37.5°C. Growing samples were taken to Phoenix NMIC ID/82 Panels (Mc Farland 0.5) within the framework of the manufacturer's instructions and in line with the Clinical and Laboratory Standards Institute (CLSI) recommendations. The identification was then made with the BD Phoenix 100 (BD Diagnostic Instrument Systems USA) and antimicrobial susceptibility was determined. The data reported with these definitions were obtained from the Registry System of the Cumhuriyet University Practice and Research Hospital Infection Control Committee Surveillance System.

2.5. Statistical Analysis:

The data obtained in the present study were loaded into the SPSS 14.0 (Statistical Package for Social Sciences) program, and the significance test of the difference between two means in independent groups and the Chi-Square Test was used in the evaluation of the data. In cases where the assumptions about the Fisher Exact Chi-Square Test could not be fulfilled, the Fisher Exact Chi-Square Test was used to calculate the Chi-Square Value with the Monto Carlo Method. Multivariate Logistic Regression Analysis was used to determine the risk factors and the error level was taken as 0.05.

3. Results

The mean age of the patients who were included in the study was found to be 69.8±SD15.0 years and no significant differences were detected between the groups in terms of age and gender.

The most frequent hospitalization diagnoses of the cases were infection and respiratory failure. Trauma, Systemic Vascular Disease (SVD), Acute Kidney Injury (AKI), surgery, and immunosuppressive treatment were other less frequent diagnoses.

At least one underlying disease that might affect mortality and morbidity was detected in 99 of the patients in the Study Group. The most common diseases were Diabetes Mellitus (DM), Chronic Obstructive Pulmonary Disease (COPD), and Hypertension (HT). In the

PDR A. baumannii VAP and bacteremia group, 22 (50%) of the patients had DM, and 19 (26.8%) of the patients in the control group had DM. The frequency of DM was found to be statistically and significantly higher in the PDR A. baumannii Group (p=0.013). Similarly, when the groups were evaluated in terms of traumas, the frequency of traumas was found to be statistically higher in the group in which PDR A. baumannii was the causative agent (p=0.011).

The Carlson Comorbidity Score (CCI) rate was found to be ≤4 in 52 (46%) in the patients in the Study Group, and the CCI rate was 4> in 61 patients (54%). The CCI score was ≤ 4 in 14 (33.3%) in the PDR A. baumannii VIP and Bacteremia Group, and 28 (66.7%) of them had scores above 4. In the control group, 38 (53.5%) of the patients had a CCI score of 4 or lower, and 33 (46.5%) had a CCI score above 4. A statistically significant CCI score greater than 4 was detected in the PDR A. baumannii Group as the risk factor (p=0.037).

Steroid use at a dose that would cause immunosuppression was detected in 35 (31%) of the patients in the Study Group and steroid use was not detected in 78 (69%) patients. In the PDR A. baumannii VAP and Bacteremia Group, 26 (61.9%) patients had steroid use, and 16 (38.1%) did not use steroids. In the control group, 9 (12.7%) patients were using steroids and 62 (87.3%) were not using. When the groups were evaluated based on the statistical analysis, steroid use was found to be higher in the group in which PDR A. baumannii was the causative agent (p<0.001).

No significant differences were detected in the comparison of the Study and Control Group patients in terms of invasive interventions.

Significant differences were detected between the groups in terms of hospitalization in the last 3 months, antibiotic use in the last 3 months, and infection occurring 30 days after hospitalization.

As a result of the Univariate Analysis, it was found that DM, traumas, CCI>4, steroid use, hospitalization history in the last 3 months, and antibiotic use in the last 3 months were statistically and significantly higher in the PDR A. baumannii Group.

Multivariate analysis was used to determine the risk factors with a p value of 0.1 and below by univariate analysis. In this respect, traumas (OR=93.32, p=0.011), steroid use (OR=21.09, p<0.001) and antibiotic use in the last 3 months (OR=26.97, p=0.001) were determined as independent risk factors in the development of PDR A. baumannii VAP and bloodstream infection.

Antibiotic use in the last 3 months (Ampicillin-Sulbactam, 2nd and 3rd-generation Cephalosporin, Quinolone, Piperacillin-Tazobactam, Carbapenem, or Glycopeptide) was found to be statistically and significantly higher when the groups were compared.

As a result of the comparisons of the clinical and laboratory results between the groups, no significant differences were detected between the clinical and laboratory results.

Table 1

Significant findings as a result of the comparison of the demographic and clinical characteristics of the study and control group patients

Variables	PDR A. baumannii VAP and bacteremia N:42(%)	Control group VAP ve bacteremia N:71(%)	Total patients N:113(%)	P value
Comorbid Diseases				
•Diabetes mellitus	21(50)	19(26.8)	40(35.4)	0.013
•COPD	29(69)	39(54.9)	68(60.2)	0.138
•Hypertension	26(61.9)	46(64.8)	72(63.7)	0.758
•Trauma	5(11.9)	1(1.4)	6(5.3)	0.026
CCI				
•≤4	14(33.3)	38(53.5)	52(46)	0.037
•>4	28(66.7)	33(46.5)	61(54)	
History of hospitalization in the last 3 months				
•Yes	27(64.3)	22(31)	49(43.4)	0.001
•No	15(35.7)	49(60)	64(56.6)	
Day of hospitalization for infection				
•≤30 day	23(54.8)	58(81.7)	58(81.7)	0.004
•>30 day	19(45.2)	13(18.3)	13(18.3)	
Use of antibiotics in the last 3 months	39(92.9)	32(45.1)	71(62.8)	0.001
Steroid use				
•Yes	26(61.9)	9(12.7)	35(31)	0,001
•No	16(38.1)	62(87.3)	78(69	

Table 2

Independent risk factors for the development of PDR A. baumannii VAP and Bloodstream infections (multivariate logistic regression analysis)

Variable	Coefficent	SE	P value	Odds ratio	%95 CI
Trauma	4.54	1.79	0.011	93.32	(2.8-3110.4)
Steroid use	3.05	0.73	<0.0001	21.09	(5.09-87.44)
Use of antibiotics in the last 3 months	3.29	0.99	0.001	26.97	(3.82-190.4)
Constant	-14.22	4.48	0.002	0.000	

SE,standart error ; CI(confidence interval)

Table 3

Comparison of antibiotic use in study and control group patients

Variables	PDR A.baumannii VAP and bacteremia N:42(%)	Control group VAP and bacteremia N:71(%)	Total patients N:113(%)	P value
Antibiotic used				
Ampicillin sulbactam	28(66.7)	17(23.9)	45(39.8)	0.001
Cephalosporins	17(40.5)	10(14.1)	27(23.9)	0.001
Aminoglycosides	3(7.1)	3(4.2)	6(5.3)	0.669
Qinolones	9(21.4)	2(2.8)	11(9.7)	0.002
Piperacillin tazobactam	23(54.8)	6(8.5)	29(25.7)	0.001
Carbapenems	13(31)	4(5.6)	17(15)	0.001
Glycopeptides	10(23.8)	2(2.8)	12(10.6)	0.001
Linezolid	2(4.8)	-	2(1.8)	0.136
Colistin	-	-	-	-
Metronidazole	3(7.1)	1(1.4)	4(3.5)	0.144

4. Discussions

Patients hospitalized in ICUs have a higher risk of NI because of complex problems such as low immune status, comorbid diseases (e.g., cancer, burns, diabetes), and invasive device applications that disrupt body integrity.[17] Studies have been conducted for many years to evaluate the risk factors and their effects on mortality in

infections caused by *A. baumannii* and different results were reported. The present study examined the effects of bacteremia and pneumonia caused by *A. baumannii* on risk factors and mortality with univariate and multivariate analyses and the independent risk factors.

Comorbid diseases prolong the length of stay in hospitals and intensive care units and increase the frequency of invasive interventions. In a previous study, Diabetes Mellitus was found to be a risk factor in the formation of infection with *A. baumannii* in terms of underlying diseases.[18] Similarly, in the present study, PDR (Pan Drug Resistance) *A. baumannii* was found to be a Diabetes Mellitus risk factor in the VAP (Ventilator-Associated Pneumonia) and Bacteremia Group.

The relationship between traumatic events and the development of Nosocomial Infections is associated with increasing injury severity scores of the patients.[19] It is also considered that trauma results in neutrophil dysfunction, which leads to decreased immune response and Nosocomial Infections.[20] In the study conducted by Bergogne-Berezin et al., trauma was identified as a risk factor for infection with *A. baumannii*.[21] In the present study, traumas were evaluated in the group of underlying diseases, and similarly, PDR *A. baumannii* was identified as a risk factor in the VAP and Bacteremia Group.

The CCI score is calculated based on the underlying diseases and age. Various risk factors are frequently investigated in Nosocomial Infections caused by *Acinetobacter baumannii*. Age, gender, length of hospital stay, length of stay in the Intensive Care Unit, co-morbidities, invasive interventions, and antibiotics given to patients were identified as risk factors in previous studies.[22-23-24] In the present study, CCI (Carlson Comorbidity Score) was determined as a risk factor in the occurrence of PDR *A. baumannii* infection.

It is now known that secondary infections can occur in patients who use steroids. In the study that increased the risk of infection with *A. baumannii* in patients using ≥1 mg/kg/day steroids, the patients were exposed to steroids according to their underlying diseases.[18] Similarly, PDR *A. baumannii* infection was found to be a risk factor in patients using steroids in the present study.

Exposure to colonization and interventional procedures increases in patients who are hospitalized in the last 3 months. For this reason, hospitalization in the last 3 months was found to be an important risk factor for PDR *A. baumannii* infection in a previous study.[25] In the present study, the history of previous hospitalization was found as a risk factor.

Antibiotic use was previously recognized as a risk factor for multidrug-resistant gram-negative infections.[26] Previous studies reported that frequent use of Carbapenem, third-generation Cephalosporins, Quinolones, and Aminoglycosides are risk factors for Acinetobacter colonization infection.[27-28-29] Ampicillin Sulbactam, 2nd and 3rd-generation Cephalosporins, Quinolones, Piperacillin Tazobactam, Carbapenem, and Glycopeptide Antibiotics were identified as risk factors in the present study, similar to other studies.

In the statistical analysis made to compare the day of hospitalization in the formation of infection, the infection occurred after 30 days in the group with PDR *A. baumannii* infection and was determined as a risk factor. The emergence of nosocomial antibiotic-resistant pathogens increases with each day of hospitalization. The longer the hospital stay, the longer the contact with contaminated floors and equipment. In their study, Tunay et al. reported that the duration of hospital stay was determined as a risk factor for the formation of PDR *A. baumannii*.[29]

A. baumannii strains have become resistant to many antimicrobial agents, especially in recent years, which has caused a limited number of antimicrobial agents to remain against Acinetobacter infections.[30]

Univariate analysis was used in the present study to determine the risk factors with a ***p***-value of 0.1 and below to determine the independent risk factors, and multivariate analysis was used for this purpose. Traumas, steroid, and antibiotic use in the last 3 months were determined as independent risk factors for the development of PDR *Acinetobacter baumannii* VAP and bloodstream infections.

In recent studies, conditions such as underlying diseases, antibiotic use, and invasive procedures continue to be risk factors for Acinetobacter baumannii.[31-32]

5. Conclusions

In conclusion, when the results obtained in the present study were evaluated, VAP and bacteremia are frequently detected in wards such as ICUs with many underlying diseases and where more than one invasive intervention is applied. This shows that infection control procedures must be applied strictly in these wards and units. We think that it is important, especially in terms of ensuring the continuity of infection control training for the staff working in these units, reducing the transmission of bacteria between patients, between staff and patients, between equipment and patients, and between staff and between units. The importance of antibiotic use in these patients with multiple comorbidities and invasive procedures has been shown once again.

It is important to have information on the risk factors in the development of infection with *Acinetobacter baumannii* and to follow these patients closely in terms of early detection.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Cumhuriyet University Faculty of Medicine Ethics Committee.
https://tez.yok.gov.tr/UlusalTezMerkezi/tezDetay.jsp?id=veDPLuExfG-pX23kTNj-9Q&no=SkmQOaBcD2WcW8e5my-XUg
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Response of Pigment Epithelial Detachment to Three-Loading-Dose of Intravitreal Anti-Vascular Endothelial Growth Factor in Neovascular Age-Related Macular Degeneration

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Abstract

Aim: Response of pigment epithelial detachment (PED) to three loading dose of intravitreal bevacizumab (IVB) treatment in neovascular age-related macular degeneration (nAMD) cases.

Methods: Optical coherence tomography (OCT) findings (PED height (µm), diameter(µm) and area (mm²), central macular thickness (CMT), central choroidal thickness (CCT), intraretinal fluid (IRF), subretinal fluid (SRF), and morphological features of macular neovascularization (MNV) in optical coherence tomography angiography (OCTA) before and after three loading doses of IVB were examined and compared.

Results: Forty-two eyes of 42 naive nAMD patients with PED were included. Fifteen patients had serous and 27 patients had fibrovascular PED. After three loading doses, best corrected visual acuity (BCVA) (in Snellen chart) increased from 0.22±0.19 to 0.29±0.22 (p<0.001). The mean PED height, width and area decreased (323.46±189.80 µm,274.79±199.80 µm, p=0.007; 1639.87±1037.44 µm, 1599.01±993.88 µm, p=0.138; 2.90±2.76 mm², 2.24±2.38 mm², p=0.038 respectively). CMT decreased from 500.34±286.62 µm to 366.14±238.10 µm, CCT decreased from 251.55±74.44 µm to 197.09±50.36 (p<0.001 for both). IRF or SRF were significantly regressed (p=0.008 and p=0.032). Branching decreased from 23.8% of patients to 11.9% (p=0.044), loops completely regressed (p<0.001), hypointense halo decreased from 7.1% of patients to 4.6% (p=0.323), open circuit pattern decreased from 23.8% to 4.6% (p<0.001). Seafan and medusa NV were present in 2.3% and 4.6% of patients, however did not differ. The pruned tree NV increased from 11.9% to 33.3% (p<0.001). Closed circuit pattern increased from 33.3% to 38% (p=0.083).

Conclusions: After three loading doses of IVB, PED height and area were significantly reduced and also 21.4% of PED completely regressed and 52.3% of PED decreased. MNV with PED, particularly brancing, loops had regressed, and most of the pruned tree NVs were increased and some of the open circuit pattern were converted to closed circuit pattern. In conclusion, 3 loading doses IVB decreased the size a half of PEDs and changed feature of MNVs with PED.

Keywords: *Pigment epithelial detachment, neovascular age-related macular degeneration, optical coherence tomography, optical coherence tomography angiography*

1. Introduction

Pigment epithelial detachment (PED) is the separation of the retinal pigment epithelium (RPE) from Bruch's membrane. It is often seen with choroidal diseases like neovascular age-related macular degeneration (nAMD) (most common), central serous chorioretinopathy, choroidal tumors.[1] The pathogenesis of PED within nAMD is thought to be vascular endothelial growth factor (VEGF)-associated fluid from the choroidal neovascular membrane (CNV) between Bruch's membrane and the RPE.[2]

The most current treatment of nAMD is intravitreal anti-VEGF agents. Bevacizumab (Avastin, Genentech, South San Francisco, CA, USA), one of an anti-VEGF agent, a recombinant full-length human-

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ized monoclonal antibodies against all isoforms of VEGF was originally developed to treat systemic cancers (lungt, gastrointestinal tract).[3,4] It has been effective in treating AMD and in a variety of types of choroidal vascular abnormalities treatments.[5,6]
Optical coherence tomography (OCT) is of particular importance in evaluating the effects of anti-VEGF treatments. It is suitable for identifying intra- and subretinal edema as well as identifying PED and its changes over time after treatment. However, analysis and measurement of the dimensions of a PED is still not possible in an objective, observer-independent manner.

Optical coherence tomography angiography (OCTA) is a new, noninvasive imaging modality that demonstrates the morphology of macular neovascularization (MNV) in nAMD. OCTA can produce fast, reproducible, high-resolution and three-dimensional images of MNV. Since fluorescein has no masking effect in angiography (FA), it can show the neovascular network more clearly and can provide qualitative and quantitative information about MNV.[7,8]

PED can be found in 63% to 80% of eyes with nAMD.[9,10] The presence of PED in nAMD often indicates poor visual prognosis, persistent fluid, and complications such as RPE rupture.[11,12] Nowadays, anti-VEGFs are administered at various intervals and in different regimens. Intravitreal bevacizumab (IVB) monotherapy for ten eyes with refractory PED in AMD found limited effect, because all PEDs remain the same, although leakage from CNV resolved.[13] In a study, the 12-month follow-up of groups with PED treated with ranibizumab and aflibercept were compared, and they reported that maximum visual acuity improvement, PED height and radius reduction were observed in the first 3 months in both groups.[14] Although it is off-label for nAMD, IVB is used quite frequently in our country and in the world due to cost effectiveness. To our knowledge, the number of studies investigating the effect of three loading doses of IVB on PED with nAMD is quite limited. Therefore, we wanted to examine the response of three loading doses of IVB in patients with PED in nAMD using OCT and OCTA.

2. Materials and methods

This retrospective study was conducted in Department of Ophthalmology of Bursa Yuksek Ihtisas Training and Research Hospital and evaluated, naive nAMD patients with PED initially treated with three loading doses IVB therapy. Forty two eyes of 42 patients were included in the present study. Ethics committee approval (number: 2011-KAEK-25 2023/08-06) was obtained from Bursa Yuksek Ihtisas Training and Research Hospital Local Ethics Committee. The study adhered to the tenets of the Declaration of Helsinki.
Patients with previous treatment except loading doses of IVB (other anti-VEGF treatments, photodynamic therapy, laser photocoagulation), nAMD patients without PED, PEDs of different origins (central serous choroidopathy etc.), patients with concurrent diabetic retinopathy and uncontrolled hypertension were excluded from the study.

Demographic characteristics, best-corrected visual acuity (BCVA) with a Snellen chart, intraocular pressure, spherical equivalent, slit lamp examination and funduscopy, fluorescein angiography (FA), OCT and OCTA data were recorded.

2.1. Optical Coherence Tomography and Optical Coherence Tomography Angiography

Spectral domain OCT (SD-OCT) and OCTA were performed using the same device (RTVue XR AVANTI, Optovue, Inc., Fremont, CA, USA) (wavelength= 840 nm, 70,000 A-scans/s and 5µm axial resolution). Motion correction technology system (Optovue, INC.) minimizes defects caused by saccadic or involuntary movement. Central macular 6×6 mm scans were taken with OCTA which volume contains 304 B-scans has equally spaced on the X-axis and Y-axis. OCTA images with a quality score of 6 and above were evaluated by a clinician (A.S.I).

PEDs are structural splitting within the inner aspect of Bruch's membrane separating the retinal pigment epithelium (RPE) from the remaining Bruch's membrane. PED height was measured between the inner border of Bruch's membrane and the external border of the RPE and PED width was assessed by measuring maximum distance horizontal diameter by manually. PED area was calculated with ImageJ software (National Institutes of Health Bethesda, Maryland, USA). Central macular thickness (CMT) was taken central-1mm macular thickness and central choroidal thickness (CCT) was assessed measuring subfoveal region and the perpendicular distance from the outer layer of the retina pigment epithelium (RPE) to the inner surface of the sclera by using the software bundled manually. IRF, including fluid intraretinal area between the inner limiting membrane (ILM) and the elipsoid zone, SRF, subretinal fluid extending from the elipsoid zone and RPE layer.

The morphological features of each MNV were evaluated with OCTA by performing 6×6mm scan over the macular region. The morphological appearance of CNVs was evaluated qualitatively, similar to previous studies [15-18] : 1. Presence of small vessels (branching), 2. Internal anastomoses between small vessels (loops), 3. Peripheral integration between tiny branching vessels (peripheral arcade) 4. The hypointense area is considered the zone of choriocapillaris alteration (hypointense halo). 5. Vessels branching from the center in all directions (medusa) 6. More than 90% of the membrane spreading from one side of the lesion (sea fan) 7. A network of vessels with densely interconnected anastomosis but no visible main body (glomeruli) 8. Long dilated fibrous straight vessels with membranes (pruned vascular tree pattern) 9. Presence of an anastomotic vessel limiting the outer border of the vascular lesion in more than 50% of the entire CNV margin (closed-circuit pattern) 10. Includes anatomic vessels for less than 50% (open circuit pattern). Small MNVs could not be placed in a clear pattern category.

2.2. Statistical analysis

Statistical analyses were performed using the SPSS software version 22 (IBM Corp., Armonk, NY, USA). Variables were examined using the Shapiro-Wilk's test to determine distribution. Continuous data are presented as the mean ± standard deviation. Categorical characteristics are presented as numbers (%). OCT and OCTA findings after three loading doses were compared with a paired samples T-test. $p<0.05$ was considered statistically significant.

3. Results

3.1. Demographic Characteristics of Patients

Forty two eyes of 42 patients were included in the study. The mean age of the patients was 71.08±7.41 (58-82) years. Half of the participants were female. 28.5 % of patients had vascular disease (hypertension, diabetes, cardiac diseas etc.). The mean spherical equivalent was 0.26±0.77 (-4-(+4)) diopter. The initial mean best-corrected visual acuity (BCVA) was 0.22±0.19 (0.001-0.7) in Snellen. 64.2% of PEDs were fibrovascular type. The baseline characteristics of the patients before the injection were given in Table 1.

3.2. Changes in Best Corrected Visual Acuity (BCVA) and Findings of Spectral Domain Optical Coherence Tomography (SD-OCT)

Changes in BCVA and SD-OCT findings after three loading doses were given in Table 2. BCVA (in Snellen chart) increased from 0.22±0.19 to 0.29±0.22 ($p<0.001$). The mean PED height, width and area decreased (323.46±189.80 µm,274.79±199.80 µm, $p=0.007$; 1639.87±1037.44 µm, 1599.01±993.88 µm, $p=0.138$; 2.90±2.76 mm^2, 2.24±2.38 mm^2, $p=0.038$ respectively). CMT decreased from

Table 1

Demographic Characteristics and Baseline Values

	n= 42 eyes with PED
Age (years)	71.08±7.41 (58-82)
Gender (F/M)	21/21
Vascular disease (yes/no) (n) (%)	12 (28.5%)
Laterality (R/L)	21/21
Intraocular pressure (mmHg)	15.07±3.89 (8-22)
Lens condition (phakic/pseudophakic)	23/19
Spherical equivalent (diopter)	0.26±0.77 (-4-(+4))
Initial BCVA (Snellen)	0.22±0.19 (0.001-0.7)
Serous/Fibrovascular PED	15(35.7%) /27(64.3%)

BCVA, best corrected visual acuity; PED, pigment epithelial detachment; Mean±SD, n (%)

Table 2

Changes in Best Corrected Visual Acuity (BCVA) and Spectral Domain Optical Coherence Tomography (OCT) Findings After Three Loading Doses

	Pre-injections	Post-injections	p-value
BCVA (Snellen)	0.22±0.19	0.29±0.22	0.001
CMT (µm)	500.34±286.62	366.14±238.10	<0.001
CCT (µm)	251.55±74.44	197.09±50.36	<0.001
IRF (yes/no) (%)	4 (9.5%)	1 (2.3%)	0.008
SRS (yes/no) (%)	17 (40.7%)	9 (21.4%)	0.032
IRS+SRS (yes/no) (%)	13 (30.9%)	10 (23.8%)	0.631
PED			
-height (µm)	323.46±189.80	274.79±199.80	0.007
-width (µm)	1639.87±1037.44	1599.01±993.88	0.138
-area mm2	2.90±2.76	2.24±2.38	0.038

BCVA, best corrected visual acuity; CMT, central macular thickness; CCT, central choroidal thickness; IRF, intraretinal fluid; SRF, subretinal fluid; PED, pigment epithelial detachment. Paired Samples T-test, Mean±SD, p <0.05

Table 3

Changes in Morphological Features of Macular Neovascularization (MNV) in Optical Coherence Tomography Angiography (OCTA) After Three Loading Doses

n (%)	Pre-injections	Post-injections	p-value
Branching	10 (23.8%)	5 (11.9%)	0.044
Loops	5 (11.9%)	0	<0.001
Hypointense halo	3 (7.1%)	2(4.6)	0.323
Peripheral arcade	2(4.6%)	0	0.044
Seafan	1 (2.3%)	1 (2.3%)	1
Medusa	2 (4.6%)	2 (4.6%)	1
Glomeruli	2 (4.6%)	1 (2.3%)	0.423
Prunedvascular tree	5(11.9%)	12 (33.3%)	<0.001
Open circuit pattern	10 (23.8%)	2 (4.6%)	<0.001
Closed circuit pattern	14 (33.3%)	18 (38%)	0.083

n, (%) , p <0.05

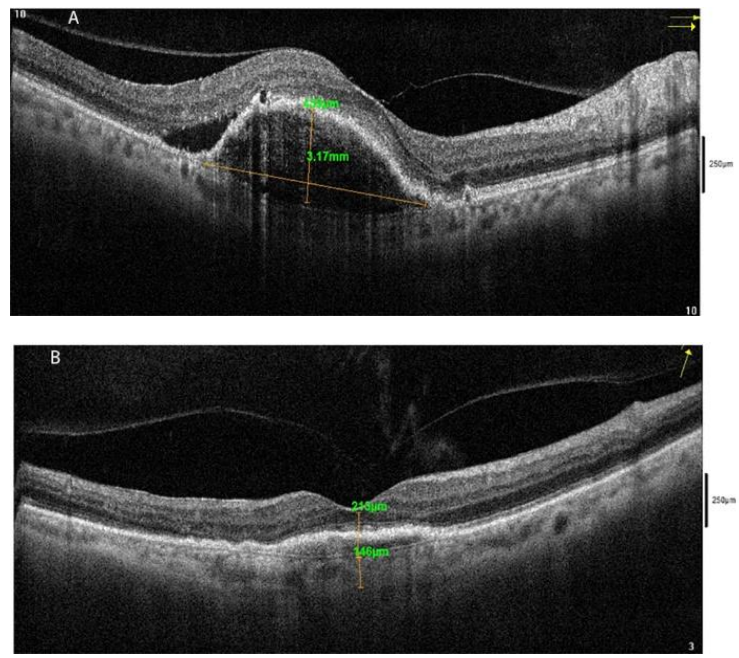
500.34±286.62 µm to 366.14±238.10 µm, CCT decreased from 251.55±74.44 µm to 197.09±50.36 (p<0.001 for both). IRF or SRF were significantly regressed (p=0.008 and p=0.032). The proportion of eyes with both IRF and SRF decreased from 30.9% to 23.8% (p=0.631). After treatment, PED resolved completely in 9 eyes (21.4%) and PED decreased in 22 eyes (52%3).

3.3. Changes in Morphological Features of Macular Neovascularization (MNV) in Optical Coherence Tomography Angiography (OCTA)

Changes in morphological features of MNV in OCTA were given in Table 3. After three doses of IVB, branching decreased from 23.8% (n=10) of patients to 11.9% (n=5) (p=0.044), loops (n=5) completely regressed (p<0.001), hypointense halo decreased from 7.1% (n=3) of patients to 4.6% (n=2) (p=0.323), open circuit pattern decreased from 23.8% (n=10) to 4.6% (n=2) (p<0.001). Seafan and medusa NV were present in 2.3% (n=1) and 4.6% (n=2) of patients, however did not differ. The pruned tree NV increased from 11.9% (n=5) to 33.3% (n=12) (p<0.001). Closed circuit pattern increased from 33.3% (n=14) to 38% (n=18) (p=0.083).

Figure 1

A) Measurement of pigment epithelial detachment (PED) height and width at optical coherence tomography (OCT)
B) Measurement of central macular thickness (CMT) and central choroidal thickness (CCT) after three loading doses of intravitreal bevacizumab in the same patient



4. Discussions

Worsening of visual acuity during the natural course emphasizes the clinical implication of PED. Approximately 50% of patients with newly diagnosed untreated PED experienced a loss of more than 15 letters during observation period of 1 year.[19] However, there is no consensus on the therapeutic effect or even the need for active treatment for PED.

Shima et al.[20] reported that after combined photodynamic therapy (PDT) and IVB, and followed 1-year, PED resolved in 12 eyes (55%) and decreased in ten eyes (45%), however Axer-Siegel R et al.[21] found that eyes with AMD with severe PED due to BCVA more than 56% worsened and had a low percentage eyes with anatomical success after PDT. Bolz et al.[22] successfully treated nine eyes with AMD with three systemic bevacizumab treatments in 2 weeks intervals; BCVA recovered and height of PED decreased significantly at 3 months but regression of PED was slower than regression of

intra- or subretinal oedema. Abi-Ayad N et al.[23] reported that sytemic bevacizumab therapy appears to be safe and effective in the treatment of retinal angiomatous proliferation (RAP) associated with PED during this short follow-up period of 3 months. They observed improvement of in BCVA and total regression on PED in OCT.

Intravitreal anti-VEGFs are still the most commonly used agents in nAMDs with PED. In a study, the 12-month follow-up of groups with PED treated with ranibizumab and aflibercept were compared, and they reported that final visual acuity and parameters of PED were better in aflibercept group.[14] Post Hoc analysis from the HABOR Trial, after a single ranibizumab injection, 35.5% of PEDs were flattened, 17.3% of them were flattened at 2 months, in other words, almost half of the PEDs were flattened after the 2nd injection, but this flattening was not reflected in visual acuity.[24] Twenty eight naive eyes with PED and sub- or juxtafoveal occult CNV as a result of nAMD and additional IRF and/or SRF were treated with IVB. During follow up time (37.9±18.3 weeks), mean PED height decreases in 50% of patients.[25] In another study, after 12 months of ranibizumab or aflibercept (with first three monthly loading doses) treatment, the mean PED height decreased from 453±261 µm at baseline to 230±142, the proportion of complete PED resolution after treatment was 19.3% (39 eyes).[26] Similarly, in present study, after three loading doses of IVB, 21.4% of PED completely regressed and 52.3% of PED decreased. The mean PED height (from 323.46±189.80 µm to 274.79±199.80 µm), width (from 1639.87±1037.44 µm to 1599.01±993.88 µm) and area (from 2.90±2.76 mm^2 to 2.24±2.38 mm^2) decreased.

Particularly, fibrovascular PED in AMD is associated with type 1 CNV, which can be visualized by FA and SD-OCT.[2] OCTA was found to have a sensitivity of 76%, specificity of 61%, positive predictive value of 83%, and negative predictive value of 50% for detecting vascularized PEDs. False positive cases in non-vascularized PED caused by projection or flow artifacts from the reflective material. False-negative cases were seen in eyes with minimal exudation on structural OCT, and also those showing retinal pigment epithelial tears [27]. In this study, we examined MNVs which shape were able to categorize (like branching, loops, hypointense halo etc.) in OCTA. In this study, although 64.3 % (n=27) eyes had fibrovascular PED, only 30.9% (n= 13) had MNV that could be categorized. After three loading doses, branching decreased from 23.8% of patients to 11.9%, loops completely regressed, hypointense halo decreased from 7.1% of patients to 4.6%, open circuit pattern decreased from 23.8% to 4.6%. Seafan and medusa NV were present in 2.3% and 4.6% of patients, however did not differ. The pruned tree NV increased from 11.9% to 33.3%. Closed circuit pattern increased from 33.3% to 38%. Three loading doses of IVB were found to alter the shape of MNVs associated with PED.

Limitations of this study; retrospective pattern, small simple size, single anti-VEGF (bevacizumab), short treatment period (three loading dose).

5. Conclusions

After three loading doses of IVB, PED height and area were significantly reduced and also 21.4% of PED completely regressed and 52.3% of PED decreased. Macular NV with PED, particularly brancing, loops had regressed, and most of the pruned tree formations were increased and some of the open circuit pattern were converted to closed circuit pattern. As a result, three loading doses IVB decreased the size of PEDs and changed morfological feature of MNVs with PED.

Statement of ethics

Ethics committee approval (number: 2011-KAEK-25 2023/08-06) was obtained from Bursa Yuksek Ihtisas Training and Research Hospital Local Ethics Committee.

Conflict of interest statement

Author declare that they have no financial conflict of interest with regard to the content of this report.

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Adolescent Health Knowledge of Family Physicians

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Abstract

Aim: There are specific life periods when physicians are more cautious with their patients. However, health needs are often disregarded throughout the adolescent era, even though it is a time when fast changes occur in many facets of life, including physical, psychological, cognitive, and social development. This study aimed to improve adolescent health by measuring the degree of knowledge of family physicians (FPs) on adolescent health services.

Methods: This was a descriptive-cross-sectional design study. A questionnaire was given to 2200 FPs by e-mail, and 344 accepted to participate. Two hundred fifteen (62.5%) of the FPs who participated in the survey, had encountered adolescent patients. The questionnaire had a 13% response rate.

Results: Women made up 56.4% of the participants (n=194), and the average age of the participants was 38.77 years (SD: 10.08) (min: 25, max: 80). A statistical correlation was found between having children and the belief that questions should be directed towards obtaining one-word answers from the target in the adolescent age group ($p<0.05$).

Conclusions: The active training of all family physicians in adolescent health can positively enhance the quality of healthcare services provided, primarily supported by the evidence of post-graduate education's beneficial impacts on knowledge and attitudes.

Keywords: *Primary care; adolescent health; family physician.*

1. Introduction

Physicians behave cautiously in their regular procedures during specific life periods. These distinct eras include childhood, characterized by rapid growth and development; old age, associated with frailty; and pregnancy, with particular demands. However, health needs are often disregarded throughout the adolescent era, even though it is a time when fast changes occur in many facets of life, including physical, psychological, cognitive, and social development.

The adolescent period is defined as the period between childhood and adulthood during which physical and sexual maturation, social and economic independence, identity development, the acquisition of necessary skills for adult relationships and roles, and the capacity for reasoning skills all occur. The World Health Organization (WHO) defines *adolescence* as the period between the ages of 10 and 19 years.[1]

Accidents, sexually transmitted diseases, and substance misuse are more common among adolescents than in general society. Although adolescence is not a very long period, it is split into distinct phases based on the extent of the changes that occur as early adolescence (ages 10-15 years), middle adolescence (ages 14-17 years), and late adolescence (ages 16-19 years). These periods have different features on the growth of the body, cognition, peer group and family relations, and sexuality. Youth is defined as the time between the ages of 15 and 24 years, and "young people" covers the age range of 10-24 years.[2]

Because adolescent health is a profession with few trained physicians in our country, family physicians (FPs) and pediatricians still provide health care for this age group. In their daily practice, FPs frequently encounter teenagers registered in their population for various reasons.[3,4] Family medicine, which approaches health holistically and provides health services, plays a role in all areas of health care, including treatment, screening, preventive health services, and health counseling. They attend sessions with their patients regarding disease treatment and health promotion and protection. School health examinations, regularly used in family health clinics, encompass the adolescent years and establish the framework for the minimum service to be offered to adolescents.[5] Psychosocial interviews with adolescents were attempted to be

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standardized in a "booklet of infant-child-adolescent follow-up protocols' developed for FPs, with the inventory abbreviated as "HEEADSSS". The acronym can be explained as Home, Education/Employment, Eating, Activities, Drugs, Sexuality, Suicide/depression, and Safety. Recently, researchers have expressed opinions advocating the inclusion of internet addiction in this evaluation form.[6] FPs are uniquely positioned to discuss risks and offer strategies to assist teens in avoiding unwanted pregnancies, sexually transmitted infections, unintentional accidents, depression, suicide, and other issues.[7] Compared with the short-term and more disease-focused presentations made by adolescents in the hospital setting, the chances of having interviews with FPs in which a trusting environment is built are relatively high.

Each age group's psychological features differ in addition to their growth and development characteristics. Prioritizing these distinctions in communication with the adolescent age group has various elements that should be examined. As a result, conducting interviews with adolescents necessitates a thorough understanding of this age group's features and the application of proper interview strategies.[7,8]

Notwithstanding access to health services, major health problems, risky behaviors, and poor health habits persist among adolescents [7]. Not benefiting from health services adequately has been associated with issues such as adolescents' inability to act independently throughout the medical system, concerns about trust and privacy, long waiting times in healthcare institutions, and fear of being seen by others.[9]

According to data from the Turkish Statistical Institute (TUIK), the teenage population accounted for 15% of the overall population in 2017; there has been no significant change in this ratio in recent years. The leading cause of mortality in the adolescent age group was "external injuries and deaths related to poisoning," according to a study that used TUIK data. Transportation accidents, accidental falls, accidental poisoning, suicide, willful self-harm, and murder-assault are among the five causes of mortality.[10] According to TUIK data, the overall suicide rate for all age groups was 3.94 per 100,000 in 2018, falling to 3.88 per 100,000 in 2019.[11] Suicidal thoughts were detected in 60-70% of teenagers with depression in one study, with suicide attempts recorded in 13-39% of them.[12]

In the United States of America (USA), 95% of 13-17-year-old adolescents reported having smartphone access, and nearly 50% reported regular smartphone use. The same study reported that adolescents' use of computers for 3 hours or more per day in tasks unrelated to school nearly doubled from 2007 to 2017, at a rate of 43%.[6]

According to a WHO report, it was estimated that 1 in 7 (14%) 10-19 year-olds globally experience mental health conditions, yet these remain primarily unrecognized and untreated.[13] In studies, depression and anxiety in adolescents have a variety of negative consequences, including lower education levels, dropping out of school, strained social relationships, and an increased risk of substance abuse, mental health problems, and suicide.[14] Some reviews and meta-analyses demonstrate a connection between adolescent social media use and depression.[15161718]

This study aimed to enhance adolescent health by measuring the degree of knowledge of FPs on adolescent health services and generating projects for the missing areas in the future.

2. Materials and methods

2.1. Study Design:

The study was descriptive cross-sectional research. The target population consisted of registered members (n=2200) of the Family Medicine Association, which holds a nationwide membership. The survey explored family physicians' knowledge and attitudes toward adolescent health.

2.2. Sampling Method:

A questionnaire was distributed to 2200 participants via e-mail and Family Medicine Association communication channels. The sample size was determined based on a 95% confidence level, a 5% error margin, and an assumed population proportion of 50%. The goal was to reach a minimum of 328 respondents from this pool of 2200 FPs.

2.3. Survey Instrument:

Given the absence of validated scales in the field during the study period, a comprehensive literature review was conducted, leading to the creation of the survey instrument. The questionnaire comprised a demographic information section and a segment containing 19 Likert-type questions. The demographic section encompassed questions about physicians' parental status, years of professional experience, post-graduate education in adolescent health, and frequency of interactions with adolescent patients. The Likert-type question segment assessed family physicians' perceptions and attitudes towards various aspects of adolescent health, including risk behaviors, health screenings, communication, sexuality, family relationships, substance/alcohol use, nutrition, exercise, and mental well-being assessment.

Data Collection: The survey, in the form of a Google Forms questionnaire, was disseminated through a series of announcements between January 5, 2021, and April 30, 2022

2.4. Data Analysis:

Statistical data analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows 25.0 package application. Percentage values were used to interpret frequency, one of the descriptive statistics for the information obtained. We used the Chi-square test to ascertain the relationship between two categorical variables. In the study, $p<0.05$ was accepted as the level of statistical significance, and data were evaluated using this level of significance.

The study received approval from the Ethics Committee of İzmir Ekonomi University (Decision date: 21.12.2021, Number: B.30.2.IEÜSB.0.05.05-20-147).

3. Results

There were 344 participants accepted to participate and answered the questionnaire. The questionnaire had a 15,63% response rate.

Women comprised 56.4% of the participants (n=194); one individual did not state their sex. The average age of the participants was 38.77 (min: 25, max: 80, SD: 10.08) years. The participants' rate of having children was 61.9% (n=213). The average occupational work years was 17.22 among the 214 physicians who responded (min: 1 max: 40 SD: 9.10). Table 1 shows the descriptive data.

Two hundred fifteen (62.5%) of the FPs who participated in the survey said they had encountered adolescent patients, and 129 (37.5%) said they had not. Of those who met adolescent patients, 75.8% said they met at least one adolescent patient daily (n=163).

Living conditions affected the perspective of "wellness." For example, FPs living in city centers (77%) thought they should undergo follow-up measurements periodically, although the adolescents were at healthy ages. FPs living in the villages/suburbs thought communicating with adolescents was more demanding than with other patient groups.

Table 2 provides detailed information on the participants' opinions on the hypotheses related to their knowledge of and attitudes toward adolescent health by sex, age, and place of residence.

When the sex-related responses to the propositions were examined, female FPs agreed with the following propositions more

than male FPs: "Physical activity and nutritional status are among the situations that should be questioned in interviews," "There is no need to recommend a special physical activity to adolescents since they are already in an active age period," "It is necessary to question their eating habits," and "Questions in adolescent interviews are open-ended and non-judgmental sentences ($p<0.05$).

The participants were divided into three age groups for age evaluation: 25-34 years, 35-44 years, and over 45 years. It is harder for some patient groups to develop a relationship with their physician, and it is inappropriate to inquire about technology addiction during interviews. Female FPs aged 25-44 agreed with these propositions more than male FPs, statistically significant. It was an exciting finding that older FPs thought that younger adolescents' risky behavior was less regarding "talking about suicidal thoughts." FPs aged over 45 years reported that talking about suicidal thoughts would be a reason that suicide attempts could occur more quickly.

Income was found to be statistically associated with the statement, "Family relationships are important in the evaluation of people in this period" ($p<0.05$). Interestingly, the low-income group of FPs thought more about how important family relations were.

There is a statistical correlation between having children and the idea that "questions should be asked with one-word answers to the target to get answers in the adolescent age group" ($p<0.05$). It was seen that 30.2% of those without children and 28.8% of those with children strongly agreed with this statement.

Table 1

Participants' Distribution Based on General Characteristics

Characteristics		n	%
Age ($\bar{X}$: 38,77; SS: 10,08) (min:25, max:80)	25-34	147	42,7
	35-44	95	27,6
	45 and more	102	29,7
Sex	Female	194	56,4
	Male	150	43,6
Income	Good	117	34,0
	Mediım	197	57,3
	Bad	30	8,7
Settlement	Urban	298	86,6
	Rural	46	13,4
Having child/children	Yes	215	62,5
	No	129	37,5
The number of children*	1	90	42,3
	2	104	48,8
	3	15	7,0
	4	4	1,9
Working duration in profession (year)*	($\bar{X}$: 17,22; SS: 9,10) (min:1, max:40, n:214)		
Status of education in post-graduate adolescent health *	Yes	76	35,3
	No	139	64,7
How frequently do adolescent apply to your outpatient clinic? *	Every day, at least one patient	163	75,8
	Every week, at least one patient	32	14,9
	Every month, at least one patient	9	4,2
	Monthly, fewer than one patient	11	5,1
Adolescent age is defined correctly *	Doğru	43	20,0
	Hatalı	172	80,0

*n<344

Table 2

Distribution of Participants' Opinions on Propositions Regarding Knowledge and Attitudes Towards Adolescent Health by Sex, Age, and Place of Residence

		Sex		Age			Place of Residence	
		Female	Male	25-34	35-44	45+	City	District
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Adolescents are more prone to risky behaviors	I do not agree at all	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)	0 (0.0)
	Disagree	21 (10.8)	16 (10.7)	10 (6.8)	12 (12.6)	15 (14.7)	29 (9.7)	8 (17.4)
	Undecided	6 (3.1)	6 (4.0)	3 (2.0)	7 (7.4)	2 (2.0)	12 (4.0)	0 (0.0)

	I quite agree	101 (52.1)	79 (52.7)	91 (61.9)	45 (47.4)	44 (43.1)	158 (53.0)	22 (47.8)
	Totally agree	66 (34.0)	48 (32.0)	43 (29.3)	31 (32.6)	40 (39.2)	98 (32.9)	16 (34.8)
	Test and p Values	χ2=1.605, p=0.900		χ2=17.316, p=0.014*			χ2=4.401, p=0.366	
Discussing sexually transmitted diseases with adolescents can have negative consequences	I do not agree at all	112 (57.7)	75 (50.0)	71 (48.3)	56 (58.9)	60 (58.8)	166 (55.7)	21 (45.7)
	Disagree	50 (25.8)	42 (28.0)	43 (29.3)	26 (27.4)	23 (22.5)	80 (26.8)	12 (26.1)
	Undecided	23 (11.9)	20 (13.3)	21 (14.3)	10 (10.5)	12 (11.8)	35 (11.7)	8 (17.4)
	I quite agree	7 (3.6)	9 (6.0)	7 (4.8)	3 (3.2)	6 (5.9)	13 (4.4)	3 (6.5)
	Totally agree	2 (1.0)	4 (2.7)	5 (3.4)	0 (0.0)	1 (1.0)	4 (1.3)	2 (4.3)
	Test and p Values	χ2=3.573, p=0.472		χ2=7.702, p=0.453			χ2=4.845, p=0.263	
Physical activity and nutritional status are among the conditions that should be questioned in interviews	I do not agree at all	2 (1.0)	4 (2.7)	1 (0.7)	2 (2.1)	3 (2.9)	5 (1.7)	1 (2.2)
	Disagree	8 (4.1)	6 (4.0)	6 (4.1)	6 (6.3)	2 (2.0)	13 (4.4)	1 (2.2)
	Undecided	2 (1.0)	2 (1.3)	2 (1.4)	1 (1.1)	1 (1.0)	4 (1.3)	0 (0.0)
	I quite agree	41 (21.1)	51 (34.0)	44 (29.9)	25 (26.3)	23 (22.5)	76 (25.5)	16 (34.8)
	Totally agree	141 (72.7)	87 (58.0)	94 (63.9)	61 (64.2)	73 (71.6)	200 (67.1)	28 (60.9)
	Test and p Values	χ2=9.462, p=0.039*		χ2=6.423, p=0.595			χ2=2.223, p=0.638	
To get answers to questions in the adolescent age group, targeted questions with one-word answers should be asked	I do not agree at all	38 (19.6)	30 (20.0)	27 (18.4)	20 (21.1)	21 (20.6)	54 (18.1)	14 (30.4)
	Disagree	42 (21.6)	36 (24.0)	36 (24.5)	26 (27.4)	16 (15.7)	68 (22.8)	10 (21.7)
	Undecided	46 (23.7)	27 (18.0)	38 (25.9)	15 (15.8)	20 (19.6)	68 (22.8)	5 (10.9)
	I quite agree	44 (22.7)	38 (25.3)	29 (19.7)	24 (25.3)	29 (28.4)	70 (23.5)	12 (26.1)
	Totally agree	24 (12.4)	19 (12.7)	17 (11.6)	10 (10.5)	16 (15.7)	38 (12.8)	5 (10.9)
	Test and p Values	X2=1.769, p=0.781		χ2=9.777, p=0.281			χ2=5.896, p=0.201	
There are no regular check-ups that need to be done because there is a period of life when people are healthy	I do not agree at all	146 (75.3)	111(74.0)	108 (73.5)	73 (76.8)	76 (74.5)	230 (77.2)	27 (58.7)
	Disagree	35 (18.0)	25 (16.7)	27 (18.4)	19 (20.0)	14 (13.7)	49 (16.4)	11 (23.9)
	Undecided	3 (1.5)	6 (4.0)	2 (1.4)	0 (0.0)	7 (6.9)	7 (2.3)	2 (4.3)
	I quite agree	3 (1.5)	7 (4.7)	6 (4.1)	1 (1.1)	3 (2.9)	6 (2.0)	4 (8.7)
	Totally agree	7 (3.6)	1 (0.7)	4 (2.7)	2 (2.1)	2 (2.0)	6 (2.0)	2 (4.3)
	Test and p Values	χ2=7.758, p=0.095		χ2=11.814, p=0.132			χ2=10.670, p=0.019*	
Family relationships are important in the evaluation of people in this period	I do not agree at all	1 (0.5)	3 (2.0)	1 (0.7)	1 (1.1)	2 (2.0)	4 (1.3)	0 (0.0)
	Disagree	4 (2.1)	6 (4.0)	5 (3.4)	3 (3.2)	2 (2.0)	8 (2.7)	2 (4.3)
	Undecided	5 (2.6)	2 (1.3)	2 (1.4)	4 (4.2)	1 (1.0)	7 (2.3)	0 (0.0)
	I quite agree	41 (21.1)	46 (30.7)	40 (27.2)	19 (20.0)	28 (27.5)	72 (24.2)	15 (32.6)
	Totally agree	143 (73.7)	93 (62.0)	99 (67.3)	68 (71.6)	69 (67.6)	207 (69.5)	29 (63.0)
	Test and p Values	χ2=7.925, p=0.079		χ2=5.811, p=0.675			χ2=2.647, p=0.550	
Difficulties experienced by adolescents in their educational life should be questioned in patient interviews	I do not agree at all	2(1.0)	6 (4.0)	3 (2.0)	2 (2.1)	3 (2.9)	7 (2.3)	1 (2.2)
	Disagree	8 (4.1)	8 (5.3)	6 (4.1)	5 (5.3)	5 (4.9)	14 (4.7)	2 (4.3)
	Undecided	18 (9.3)	9 (6.0)	11 (7.5)	9 (9.5)	7 (6.9)	24 (8.1)	3 (6.5)
	I quite agree	57 (29.4)	51 (34.0)	49 (33.3)	30 (31.6)	29 (28.4)	89 (29.9)	19 (41.3)
	Totally agree	109 (56.2)	76 (50.7)	78 (53.1)	49 (51.6)	58 (56.9)	164 (55.0)	21 (45.7)
	Test and p Values	χ2=5.685, p=0.226		χ2=1.972, p=0.988			χ2=2.485, p=0.635	
Questioning about substance abuse and smoking may encourage these behaviors	I do not agree at all	116 (59.8)	81 (54.0)	77 (52.4)	56 (58.9	64 (62.7)	173 (58.1)	24 (52.2)
	Disagree	46 (23.7)	40 (26.7)	39 (26.5)	28 (29.5)	19 (18.6)	78 (26.2)	8 (17.4)
	Undecided	18 (9.3)	12 (8.0)	19 (12.9)	5 (5.3)	6 (5.9)	23 (7.7)	7 (15.2)
	I quite agree	6 (3.1)	11 (7.3)	6 (4.1)	5 (5.3)	6 (5.9)	14 (4.7)	3 (6.5)
	Totally agree	8 (4.1)	6 (4.0)	6 (4.1)	1 (1.1)	7 (6.9)	10 (3.4)	4 (8.7)
	Test and p Values	χ2=4.031, p=0.405		χ2=13.155, p=0.099			χ2=7.225, p=0.101	
Mood assessments of adolescents should be done routinely during interviews	I do not agree at all	2 (1.0)	5 (3.3)	2 (1.4)	3 (3.2)	2 (2.0)	7 (2.3)	0 (0.0)
	Disagree	8 (4.1)	7 (4.7)	6 (4.1)	3 (3.2)	6 (5.9)	12 (4.0)	3 (6.5)
	Undecided	14 (7.2)	14 (9.3)	15 (10.2)	9 (9.5)	4 (3.9)	21 (7.0)	7 (15.2)
	I quite agree	49 (25.3)	45 (30.0)	40 (27.2)	29 (30.5)	25 (24.5)	79 (26.5)	15 (32.6)
	Totally agree	121 (62.4)	79 (52.7)	84 (57.1)	51 (53.7)	65 (63.7)	179 (60.1)	21 (45.7)
	Test and p Values	χ2=4.793, p=0.311		χ2=6.883, p=0.548			χ2=6.471, p=0.137	
Questioning suspected adolescents about suicidal thoughts	I do not agree at all	98 (50.5)	63 (42.0)	68 (46.3)	44 (46.3)	49 (48.0)	144 (48.3)	17 (37.0)
	Disagree	43 (22.2)	37 (24.7)	37 (25.2)	29 (30.5)	14 (13.7)	66 (22.1)	14 (30.4)
	Undecided	33 (17.0)	21 (14.0)	21 (14.3)	13 (13.7)	(19.6)	47 (15.8)	7 (15.2)

facilitates the emergence of this behavior	I quite agree	12 (6.2)	15 (10.0)	14 (9.5)	6 (6.3)	(6.9)	25 (8.4)	2 (4.3)
	Totally agree	8 (4.1)	14 (9.3)	7 (4.8)	3 (3.2)	(11.8)	16 (5.4)	6 (13.0)
	Test and p Values	χ2=7.185, p=0.126		χ2=15.552, p=0.049*			χ2=6.351, p=0.163	
There is no need to recommend a special physical activity for adolescents as it is an active age period	I do not agree at all	153 (78.9)	91 (60.7	101 (68.7)	71 (74.7)	72 (70.6)	214 (71.8)	30 (65.2)
	Disagree	28 (14.4)	40 (26.7	36 (24).5	19 (20.0)	13 (12.7)	57 (19.1)	11 (23.9)
	Undecided	2 (1.0)	8 (5.3)	4 (2.7)	2 (2.1)	4 (3.9)	9 (3.0)	1 (2.2)
	I quite agree	7 (3.6)	5 (3.3)	5 (3.4)	1 (1.1)	6 (5.9)	8 (2.7)	4 (8.7)
	Totally agree	4 (2.1)	6 (4.0)	1 (0.7)	2 (2.1)	7 (6.9)	10 (3.4)	0 (0.0)
	Test and p Values	χ2=16.853, p=0.001*		χ2=15.513, p=0.036*			χ2=5.511, p=0.187	
It is necessary to question eating habits	I do not agree at all	3 (1.5)	4 (2.7)	1 (0.7)	4 (4.2)	2 (2.0)	7 (2.3)	0 (0.0)
	Disagree	8 (4.1)	4 (42.7)	8 (5.4)	2 (2.1)	2 (2.0)	11 (3.7)	1 (2.2)
	Undecided	2 (1.0)	8 (5.3)	3 (2.0)	5 (5.3)	2 (2.0)	9 (3.0)	1 (2.2)
	I quite agree	36 (18.6)	39 (26.0)	39 (26.5)	19 (20.0)	17 (16.7)	64 (21.5)	11 (23.9)
	Totally agree	145 (74.7)	95 (63.3)	96 (65.3)	65 (68.4)	79 (77.5)	207 (69.5)	33 (71.7)
	Test and p Values	χ2=9.995, p=0.035*		χ2=11.969, p=0.126			χ2=0.697, p=0.965	
In adolescent interviews, questions should be open-ended and non-judgmental	I do not agree at all	2 (1.0)	4 (2.7)	3 (2.0)	1 (1.19	2 (2.0)	6 (2.0)	0 (0.0)
	Disagree	4 (2.1)	11 (7.3)	9 (6.1)	4 (4.2)	2 (2.0)	13 (4.4)	2 (4.3)
	Undecided	0 (0.0)	4 (2.7)	3 (2.0)	0 (0.0)	1 (1.0)	2 (0.7)	2 (4.3)
	I quite agree	32 (16.5)	32 (21.3)	31 (21.1)	19 (20.0)	14 (13.7)	54 (18.1)	10 (21.7)
	Totally agree	156 (80.4)	99 (66.0)	101 (68.7)	71 (74.7)	83 (81.4)	223 (74.8)	32 (69.6)
	Test and p Values	χ2=14.808, p=0.003*		χ2=7.622, p=0.443			χ2=4.814, p=0.246	
Skin problems are a common condition	I do not agree at all	1 (0.5)	5 (3.3)	2 (1.4)	0 (0.0)	4 (3.9)	5 (1.7)	1 (2.2)
	Disagree	6 (3.1)	5 (3.3)	6 (4.1)	4 (4.2)	1 (1.0)	9 (3.0)	2 (4.3)
	Undecided	5 (2.6)	8 (5.3)	4 (2.7)	5 (5.3)	4 (3.9)	13 (4.4)	0 (0.0)
	I quite agree	57 (29.4)	54 (36.0)	45 (30.6)	35 (36.8)	31 (30.4)	93 (31.2)	18 (39.1)
	Totally agree	125 (64.4)	78 (52.0)	90 (61.2)	51 (53.7)	62 (60.8)	178 (59.7)	25 (54.3)
	Test and p Values	χ2=8.756, p=0.061		χ2=8.729, p=0.345			χ2=3.459, p=0.428	
Establishing a patient-physician relationship with adolescents is more difficult than with other patient groups	I do not agree at all	19 (9.8)	12 (8.0)	8 (5.4)	4 (4.2)	19 (18.6)	28 (9.4)	3 (6.5)
	Disagree	29 (14.9)	34 (22.7)	26 (17.7)	21 (22.1)	16 (15.7)	61 (20.5)	2 (4.3)
	Undecided	34 (17.5)	16 (10.7)	21 (14.3)	16 (16.8)	13 (12.7)	39 (13.1)	11 (23.9)
	I quite agree	70 (36.1)	58 (38.7)	53 (36.1)	53 (36.8)	40 (39.2)	106 (35.6)	22 (47.8)
	Totally agree	42 (21.6)	30 (20.0)	39 (26.5)	19 (20.0)	14 (13.7)	64 (21.5)	8 (17.4)
	Test and p Values	χ2=6.054, p=0.197		χ2=21.653, p=0.006*			χ2=11.835, p=0.016*	
Technology addiction is a topic that should not be questioned in interviews	I do not agree at all	106 (54.6)	68 (45.3)	79 (53.7)	50 (52.6)	45 (44.1)	153 (51.3)	21 (45.7)
	Disagree	20 (10.3)	25 (16.7)	18 (12.2)	14 (14.7)	13 (12.7)	37 (12.4)	8 (17.4)
	Undecided	9 (4.6)	6 (4.0)	8 (5.4)	5 (5.3)	2 (2.0)	13 (4.4)	2 (4.3)
	I quite agree	23 (11.9)	21 (14.0)	22 (15.0)	12 (12.6)	10 (9.8)	39 (13.1)	5 (10.9)
	Totally agree	36 (18.6)	30 (20.0)	20 (13.6)	14 (14.7)	32 (31.4)	56 (18.8)	10 (21.7)
	Test and p Values	χ2=4.537, p=0.341		χ2=15.936, p=0.043*			χ2=1.559, p=0.817	
Test anxiety is a point to be included in the interviews	I do not agree at all	3 (1.5)	3 (2.0)	1 (0.7)	2 (2.1)	3 (2.9)	6 (2.0)	0 (0.0
	Disagree	8 (4.1)	8 (5.3)	7 (4.8)	7 (7.4)	2 (2.0)	15 (5.0)	1 (2.2
	Undecided	12 (6.2)	8 (5.3)	9 (6.1)	7 (7.4)	4 (3.9)	16 (5.4)	4 (8.7
	I quite agree	50 (25.8)	47 (31.3)	48 (32.7)	25 (26.3)	24 (23.5)	81 (27.2)	16 (34.8
	Totally agree	121 (62.4)	84 (56.0)	82 (55.8)	54 (56.8)	69 (67.6)	180 (60.4)	25 (54.3
	Test and p Values	χ2=1.975, p=0.755		χ2=9.592, p=0.274			χ2=2.747, p=0.586	
Since the growth and development process is very rapid, it is not necessary to monitor height and weight during this period	I do not agree at all	130 (67.0)	105 (70.0)	93 (63.3)	69 (72.6)	73 (71.6)	207 (69.5)	28 (60.9)
	Disagree	26 (13.4)	28 (18.7)	30 (20.4)	12 (12.6)	12 (11.8)	49 (16.4)	5 (10.9)
	Undecided	13 (6.7)	3 (2.0)	7 (4.8)	6 (6.3)	3 (2.9)	15 (5.0)	1 (2.2)
	I quite agree	9 (4.6)	7 (4.7)	11 (7.5)	0 (0.0)	5 (4.9)	12 (4.0)	4 (8.7)
	Totally agree	16 (8.2)	7 (4.7)	6 (4.1)	8 (8.4)	9 (8.8)	15 (5.0)	8 (17.4)
	Test and p Values	χ2=7.246, p=0.124		χ2=16.684, p=0.029*			χ2=10.810, p=0.020*	
Counseling on contraceptive methods is an appropriate health service for this age group	I do not agree at all	8 (4.1)	15 (10.0)	7 (4.8)	9 (9.5)	7 (6.9)	6.0	10.9
	Disagree	15 (7.7)	18 (12.0)	20 (13.6)	7 (7.4)	6 (5.9)	9.4	10.9
	Undecided	38 (19.6)	22 (14.7)	36 (24.5)	12 (12.6)	12 (11.8)	17.1	19.6
	I quite agree	53 (27.3)	41 (27.3)	38 (25.9)	29 (30.5)	27 (26.5)	27.2	28.3
	Totally agree	80 (41.2)	54 (36.0)	46 (31.3)	38 (40.0)	50 (49.0)	40.3	30.4
	Test and p Values	χ2=7.745, p=0.101		χ2=19.071, p=0.014*			χ2=3.007, p=0.552	

*p<0.05

4. Discussions

In our study, 344 individuals responded to 19 5-item Likert-type questions that probed FPs' knowledge and attitudes toward adolescent health. FPs, who are the 'gatekeepers' of healthcare for all age groups, must be aware of the needs and peculiarities of each age group in their daily practice.[19]

The group of FPs who had children thought that "target-aimed and/or not open clause questions were more efficient" than the group of FPs who did not have children. This finding needs to be studied further to reveal the root reason for to search sex differences among different professions and dominant cultures. We did not assess whether the FPs' child/children were adolescents; it could be another research question.

Female physicians' knowledge about physical activity, eating habits, asking open-ended questions, and being non-judgemental was significantly better than in the male FPs, and it was interesting that there were no statements that were assessed as "favorable/appropriate" about adolescent health among male FPs. [20]

FPs aged 25-34 years were more aware of counseling for risky behaviors among adolescents. The root reasons for this finding could be evaluated by qualitative studies.[21,22] The 35-44-year-old group reported that a physical activity plan was needed for adolescents more than the other groups. This age group also thought weight and height follow-ups should be performed more than the other FP groups. Follow-up for adolescents and other individuals is essential according to family medicine discipline [232425]. From the lifestyle medicine perspective, these data could be used to improve the community's health.[26,27]

Interestingly, the opinion "addiction to technology should be asked" was the lowest in the group aged 45 years and over; this decreased with age among the FPs. These kinds of addiction may not be well known by the physicians in this group.[28,29] This topic could be added to lifelong learning and continuing medical education. [30,31,32]

As the age of the FPs increased, they thought communication with adolescents was difficult. From patient-centeredness as a core value of family medicine, communication skills, and motivational interview techniques are needed 35 to reach that target group.

The statement, "Contraception methods should be a part of counseling for adolescents," was more acceptable among older FPs; acceptance rates increased as the ages increased.[33,34,35] This was also an exciting finding.

Interestingly, the low-income group of FPs thought more that family relations were essential. Living conditions also affect the perspective about "wellness." For example, although the adolescents were at healthy ages, the FPs who lived in city centers (77%) thought they should undergo follow-up measurements periodically. FPs living in villages/suburbs thought communicating with adolescents was more challenging than with other patient groups.

In our study, female FPs were statistically significantly more likely than male FPs to question their patients' eating habits, mobility, and physical activity. Numerous socioeconomic and behavioral traits in the pediatric population have been found to indicate that older, female, non-English speaking, urban children, as well as those with lower socioeconomic status (SES) and neighborhood social capital, have lower levels of physical activity.[36] Accordingly, for the wellness of the population, this topic is crucial. Stanford et al. reported that "compared with those who did not meet the guidelines or were overweight or obese, physicians and medical students with a normal BMI and who met the moderate and vigorous USDHHS guidelines were more likely to feel comfortable advising their patients about physical activity.[37] Lifestyle medicine (e.g., physical activity, healthy diet, stress management) could help patients and FPs.

According to studies, adolescents are frequently affected by sexually transmitted diseases (STDs), and their awareness of STDs is insufficient.[19,35] Adolescents disproportionately affected by the disease continue to be at risk for sexually transmitted infections (STIs), a significant cause of morbidity. Many infections in this at-risk population are asymptomatic but still carry a high risk of long-term consequences.[38] In our study, 35% of FPs said that discussing STDs with adolescents would have a negative impact. This percentage was statistically significantly higher among FPs who had not received training on adolescent health. Adolescent STIs are a particular concern for primary care providers. To lower the prevalence, complications, and transmission of STIs in the adolescent population, primary care providers must improve adherence to their recommendations for screening, treatment, and immunization.[38] Physical fitness, nutrition, and growth were the three most significant concerns in research on teenage healthcare objectives from the viewpoints of youth (13-18 years). Although 70% and 66% of respondents reported that they wanted to discuss STDs and contraception difficulties, respectively, these topics were only discussed 18% and 22% of the time.[39] From this perspective, it may be easier for FPs to proceed through interviews, beginning with topics that adolescents are most interested in and progressing to specific topics that are thought to be more challenging to discuss (e.g., STDs, depression, alcohol-substance use) after a healthy communication has been established.

Ozkul et al. published that FPs evaluated that adolescents over 15 years were at higher risk than those younger. Those risks included smoking, having an accident, fighting, and substance use. They stated that follow-ups should also contain height-weight measurements, weight change, blood pressure measurements, and question exercise.[40] In our study, FPs stated that the topics that needed to be discussed with adolescents the most were those related to physical activity and nutrition, family relationships, exam anxiety, and skin issues.[40] Jones et al. stated that, in a survey of 104 parents, 87% were interested in a parenting program in primary care. From the parents' perspective, it was deemed highly important to seek help on communication (65%) and conflict management (50%) from the list of parenting difficulties. However, it was focused mainly on sexuality (77%), mental health (75%), alcohol (50%) and drugs (74%). The parents/caregivers were looking for advice. The study by Jones et al. discovered that parents recognized several rewarding and challenging aspects of raising adolescents and were willing to seek help on various parenting issues through primary care settings.[41]

A sedentary lifestyle, poor diet, smoking, and risky drinking are four interrelated health risk behaviors that are thought to have origins in childhood and adolescence in the USA. These dangers are linked to the leading causes of disease, disability, the cost of medical care, and early death.[42,43] Most residents believed that adolescent preventive and clinical services were covered by their field in a study on the attitudes and education of pediatrics, family medicine, and obstetrics-gynecology (Ob-Gyn) residents about adolescent health that was conducted in the USA. To refer youths to drug abuse treatment programs and address physical and sexual abuse, assistants from all three fields needed more training and experience in mental health issues48. Additionally, pediatric residents reported a lack of training and experience in sexual health services. In contrast, Ob-Gyn residents reported a lack of training and experience in preventive counseling and general health services.[44]

4.1. Limitations of the Study:

Due to the lack of an existing valid and reliable scale in the literature to assess physicians' knowledge and attitudes towards

Adolescent Health, the questions were developed by researchers through a literature review.
Although the participating physicians were from various regions across the country, the information regarding the specific provinces where the participants practiced was not collected, which resulted in the inability to stratify the data.
In the Discussion section, while highlighting the gaps in these areas due to the limited availability of similar studies for comparison, the discussion of findings is constrained by the need for more comparable literature.

5. Conclusions

Community health is improved by raising the level of expertise in adolescent health among FPs, who offer services to all age groups of society without distinction regarding disease and ongoing health. The training of all FPs about adolescent health can positively contribute to the quality of the healthcare services offered, mainly because it has been determined that post-graduate education positively affects knowledge and attitudes.
Our country has limited studies on adolescent health because it is a new field of specialization. FPs, who constitute the entry point of the health system, should increase their knowledge in this field.

Statement of ethics

The study received approval from the Ethics Committee of İzmir Ekonomi University (Decision date: 21.12.2021, Number: B.30.2.IEÜSB.0.05.05-20-147).

Conflict of interest statement

Author declare that they have no financial conflict of interest with regard to the content of this report.

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What is the most effective topical method for preventing presacral pressure sores that occur after hip fractures?

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Abstract

Aim: To investigate the effectiveness of topical agents in preventing pressure ulcers in patients with hip fractures. Patients with hip fractures often remain immobile in the preoperative preparation period due to pain, lie in the supine position, and have to use diapers to meet their toilet needs. In patients using diapers, incontinence-related dermatitis is observed, which is a fundamental cause of pressure ulcer formation. The comparison of local topical treatment alternatives that can be applied before surgical treatment has not yet been done in the literature.

Methods: A total of 114 patient images and data operated for hip fractures between 2020-2022 were retrospectively examined in our clinic. The aim was to find the most effective method for this important problem by comparing three different materials used in topical treatment and the control group.

Results: When comparing the groups, the most effective method was found to be washing the wound with isotonic solution, followed by the application of a barrier cream clothes and a barrier spray to protect against destructive fluids such as feces and urine. In terms of patient outcomes and satisfaction, the spray was better tolerated than the cream.

Conclusions: This study is the first and only study in the literature focused on the topical treatment of pressure ulcers that occur after hip fractures. Pressure ulcers are frequently seen in hip fractures, and the most effective method for preventing their formation and maceration is topical barrier creams and sprays.

Keywords: *Pressure sore, Hip fracture, Local treatment, incontinence-related dermatitis*

1. Introduction

Pressure ulcers are wounds that develop in areas of the body where tissues are subjected to prolonged pressure, particularly in regions with bony prominences. These wounds almost always involve ischemic tissue loss. The term "decubitus ulcer" is derived from the Latin word "de cumbare," meaning "to lie down." However, since pressure is the most significant factor contributing to the development of these wounds, the term "pressure ulcer" is now considered a more accurate and appropriate name.[1] Determining the exact incidence of pressure ulcers can be challenging. It has been reported that pressure ulcers occur in approximately 15% of cases following orthopedic injuries.

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The frequency of pressure ulcer development is particularly high in patients with hip fractures. This situation is actively addressed with good patient care, advanced rehabilitation, and additional treatments aimed at prevention and management.[2,3]

The most significant factor in the development of pressure ulcers is pressure itself. Compression of soft tissues under pressure leads to ischemia, and if the pressure is not relieved, it can result in necrosis and ulceration. Additional extrinsic factors that contribute to the development of pressure ulcers in patients with hip fractures prior to surgery include immobility due to pain, moisture from the use of diapers due to difficulty in reaching the toilet, infections, friction, and shear forces during patient transfers. Intrinsic factors such as the patient's overall health, malnutrition, advanced age, diabetes, and edema also reduce the resilience of the area, making it more susceptible to the development of pressure ulcers.[1,4]

In his 1930 microinjection study, Landis determined the blood pressure in pre-capillary arterioles to be 32 mm Hg. According to this finding, when tissue pressure exceeds this value, it will obstruct blood flow to the capillary bed, leading to tissue ischemia. The areas most exposed to pressure are the soft tissues located over bony

prominences. In 1965, Lind calculated the pressures to which the body is exposed in various positions. In a supine position, pressure on the sacrum, buttocks, and heels ranges from 40-60 mm Hg, whereas when sitting, there is a pressure of 75-100 mm Hg over the ischial tuberosities. In the development of pressure ulcers, both the intensity and duration of pressure are crucial factors to consider.[1,5] Kosiak's study from 1959, conducted on dogs, revealed that exposure to low-intensity pressure for a prolonged duration of 2 hours at 70 mmHg or brief exposure to high-intensity pressure can lead to tissue damage similar to pressure ulcer formation. Even if the pressure is brief, its removal significantly enhances the tissue's resistance. Different tissues are affected by pressure at varying rates. This is due to differences in tissue sensitivity to pressure and how pressure is distributed at different tissue depths. Measurements of tissue internal pressure indicate that pressure affects a broader area in deep tissues adjacent to the bone and a narrower region on the surface.

As a result, in pressure ulcers that develop in a cone shape expanding towards deeper layers, the skin ulcer on the surface is typically like the tip of the iceberg, while the main damage occurs deeper within the tissues. This pattern often results in more extensive and earlier necrosis in deeper, less ischemia-tolerant muscle tissues, while the superficial skin is less affected.[3]

Urinary incontinence is a common issue leading to patients remaining wet. It can cause both maceration of the skin and increase the risk of ulcer formation in pressure-prone tissues. Friction, in a similar manner, disrupts the integrity of the skin and accelerates the development of pressure ulcers. At one point, shear forces, which were believed to be one of the major causes of pressure ulcers, were thought to occur when the patient was pulled up in bed or slid down while in a seated position. It was believed that this led to the tearing of perforating vessels from muscle to skin and disrupted skin perfusion. However, Dinsdale has proposed that this mechanism is not valid and that direct mechanical effects on the epidermis are responsible for ulcer development.[1]

One of the factors that facilitate the development of pressure ulcers is infection. In 1942, Groth demonstrated that in the presence of bacteremia, bacteria settle in areas under pressure, leading to local infection. Furthermore, it has been reported that when pressure is applied to contaminated wounds, bacteria multiply 100 times faster. Pressure ulcers almost always accompany bacterial infection. This is due to impaired lymphatic flow, ischemia, and immune system abnormalities.[5,6]

In patients with hip fractures, particularly in the early stages, there is a widespread development of tissue edema, especially in the fractured area. One of the reasons for this is the impairment of lymphatic flow due to decreased muscle function. Additionally, inflammatory mediators released due to pressure also contribute to edema. Increased edema raises interstitial pressure. When external pressure is added to this, capillary blood flow stops, and an ischemic process begins. Moreover, edema reduces the formation of sebum, which is an important substance in maintaining skin integrity.

In addition to these factors, the presence of pathologies that affect wound healing, such as the patient's overall health being compromised, the development of negative nitrogen balance, advanced age, diabetes, or connective tissue diseases, also makes the development of pressure ulcers more likely.[7]

1.1. Patogenesis

Although pressure ulcers are often considered chronic lesions, they have an acute onset period. During the acute phase, the skin exposed to pressure develops redness, followed by induration, blister formation, cyanosis, and tissue necrosis. In the acute phase, taking measures to eliminate pressure can prevent ulcer development. During the induration stage, the lesions can be mistaken for local abscess formation. Making an incision for drainage purposes can lead to infection and facilitate ulcer formation.[8]

In the chronic phase, pressure ulcers exhibit profound damage involving the skin, subcutaneous tissue, fat, fascia, and muscle. Longstanding ulcers are often characterized by recurring cycles of healing and ulceration attacks. Sometimes, pressure ulcers may have a thin, shiny epithelium covering. A wide, scarred area surrounds the lesion. In deep and extensive ulcers, epithelial progression halts, and the wound edges thicken, curling inward. The ulcer bed is usually covered with a pale granulation tissue with purulent characteristics due to bacterial invasion and tissue breakdown, often accompanied by a foul odor. In extensive ulcers, continuous drainage can lead to protein loss and anemia. Staphylococci, streptococci, Pseudomonas aeruginosa, E. coli, Proteus mirabilis, and combinations of these are frequently identified in wound cultures. Systemic antibiotic treatments are often ineffective due to the extensive scar tissue surrounding the lesion.

Pressure ulcers can be categorized into two groups based on their development. In the type associated with factors like friction, moisture, shear forces, or incontinence-related dermatitis, the lesion starts on the skin and progresses deeper into the tissues if not addressed. In the type developed due to pressure, you may observe skin redness or a small ulceration on the skin, but deep tissues exhibit a large cone-shaped damage. These differences in development patterns complicate the staging of pressure ulcers. However, staging can still be useful for standardized diagnosis.

2. Materials and methods

The study was conducted between 2020 and 2022, focusing on patients treated for hip fractures. After obtaining local ethics committee approval(2023-430), retrospective photographic data and file reviews were completed in 2023. Patients with Stage 1, 2, 3 wounds according to the wound classification and those with no wound formation were included in the study. Patients with Stage 4 wounds requiring surgery were not included. The effects of various products used in local treatment were compared.

The Anova test conducted among the groups revealed no significant demographic differences. And also used independent samples T-test for comparing results.

Patients with systemic diseases were excluded from the study, including those with malnutrition, anemia, liver failure, kidney failure, organ transplant recipients, rheumatoid diseases, patients undergoing chemotherapy, and uncontrolled diabetes patients. Morbidly obese patients, those who had pilonidal sinus or sacrum surgery, received negative-pressure wound therapy (WAC), and were unable to mobilize with full weight-bearing during the postoperative period were also excluded from the study.

The patients' wound sizes and characteristics were compared. The condition of the wounds on the 1st and 21st day of the 3-week treatment period was assessed. The same treatment protocols were applied in each group, with only the topical products used being different. Patients were provided with a high-protein diet, and albumin levels were monitored. Low-fiber diets were given to reduce stool contamination due to liquid stool caused by high-fiber diets. Frequent position changes were implemented in 30-minute intervals (not applied in the preoperative period due to hip pain). All patients were placed on an air mattress.

Patients aged 65 and above who had hip fractures and were treated for presacral pressure ulcers were retrospectively reviewed. The study included patients who had undergone partial hip arthroplasty surgery due to hip fracture during the postoperative period and were allowed to mobilize with full weight-bearing. They were all treated in the same clinic by the same team and received the same treatment protocol for presacral pressure ulcers during their hospitalization.

Table 1

Demographics of the patients

	Group1	Group 2	Group 3	Group 4
Number of patients	34	25	28	27
Average age	67.5	70.2	74.5	72
Number of diabetic patients	24	19	21	20
Intertrochanteric fractures	19	18	18	20
Femoral neck fractures	9	8	10	7
Preoperative length of stay	3,9	3,8	4,1	4
Postoperative length of stay	5,7	5,5	5,4	6
Presacral wound classification average	1,79	1,8	1,75	1,82
Patient satisfaction score	55	61	75	71
Number of patients using diapers	28	26	28	27
Number of patients using urinery catheters	28	26	28	27
Use of antibiotics due to infection	25	20	14	16
Right hip	15	13	13	14
Left hip	19	12	15	13

Only different product types used in patients were compared. Patient variables and demographic characteristics were recorded.

Patients were divided into four groups, and the groups and their demographic characteristics are listed in Table 1.

Group 1 (Control Group):

In this group, wound dressings were applied twice daily. During each dressing change, wound exudate was wiped with a sterile gauze, and then the wound was rinsed with 20 cc of isotonic solution. Subsequently, the wound was covered with a sterile gauze. For patients without incontinence issues and without wound formation, the perineal area was cleaned twice a day using classic warm water and cotton.

Group 2:

In this group, wound dressings were applied twice daily. During each dressing change, wound exudate was wiped with a sterile gauze, and then the wound was rinsed with 20 cc of isotonic solution. Afterward, the area immediately around the wound was wiped with a Med-Cover barrier cream clothes (% 3 dimethicone, Medoffice Health, Izmir , Turkey), and then the wound was covered with a sterile gauze. For patients without incontinence issues and without wound formation, the per- ineal area was treated with a Med-Cover Barrier Cream clothes twice daily.

Table 2

Staging System for Pressure Ulcers Recommended by the National Pressure Ulcer Advisory Panel

Stage 1: Characterized by persistent erythema that does not blanch when pressed. The epidermis is intact.
Stage 2: Characterized by partial-thickness skin loss with the presence of abrasion, vesicle, or a shallow crater, involving the epidermis and/or dermis.
Stage 3: Characterized by full-thickness skin loss extending down to the underlying fascia, but not involving the fascia itself.
Stage 4: Characterized by extensive tissue loss, tissue necrosis, or damage to muscles, bone, or supporting structures, involving full-thickness skin loss that is contiguous with body cavities.

These descriptions outline the stages of pressure ulcers as recommended by the National Pressure Ulcer Advisory Panel.

Group 3:

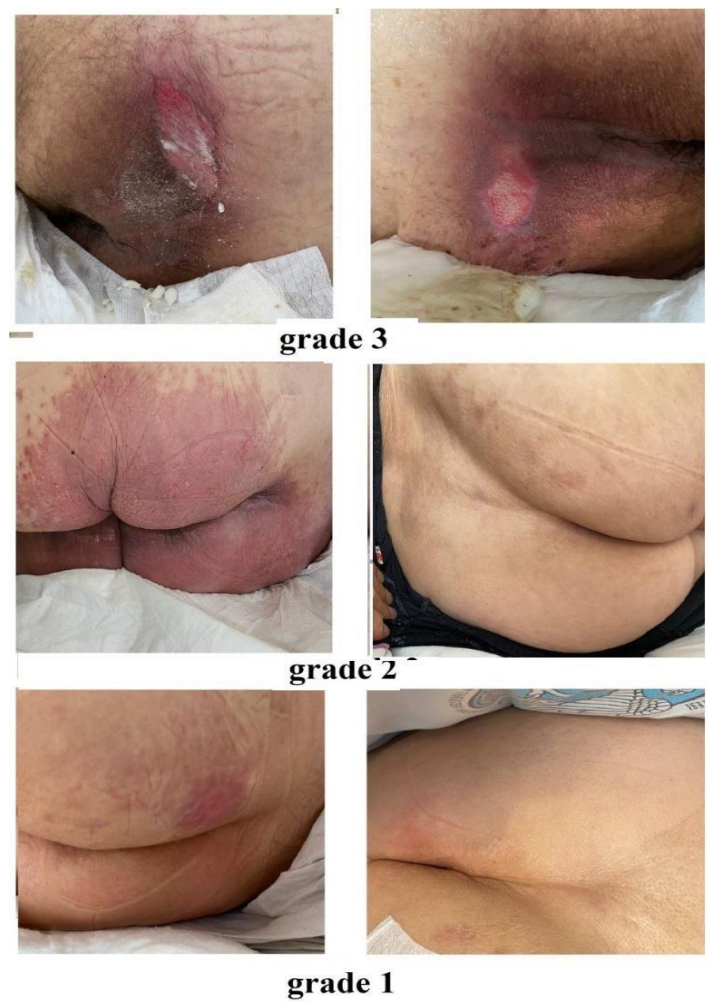
In this group, wound dressings were applied twice daily. During each dressing change, wound exudate was wiped with a sterile gauze, and then the wound was rinsed with 20 cc of isotonic solution. After that, the area immediately around the wound was wiped with a Med-Cover barrier cream clothes(% 3 dimethicone), and then Med-Cover barrier film spray (%100 silicone, Medoffice Health, Izmir, Turkey) was applied with 4 puffs around the microenvironment of the wound. The wound was then covered with a sterile gauze. For patients without incontinence issues and without wound formation, the perineal area was treated with a Med-Cover Barrier Cream clothes, followed by the applica- tion of Med-Cover Barrier Film Spray with 4 puffs, twice a day.

Group 4:

In this group, wound dressings were applied twice daily. During each dressing change, wound exudate was wiped with a sterile gauze, and then the wound was rinsed with 20 cc of isotonic solution. After that, the area immediately around the wound was wiped with a Med-Cover barrier cream clothes (% 3 dimethicone), and then a thin layer of Med-Cover barrier cream (% 3 dimethicone+%5 natural beeswax, Medoffice Health, Izmir , Turkey), was applied to the microenvironment of the wound.

Figure 1

Comparative images of patients from all three grades were provided on the 1st and 21st days in the study



The wound was then covered with a sterile gauze. For patients without incontinence issues and without wound formation, the perineal area was treated with a Med-Cover Barrier Cream clothes, followed by the application of a thin layer of Med-Cover Barrier Cream, twice a day.

In the case of presacral pressure ulcers, Baticon, which slows down wound healing, was not used in any of the groups.

Presacral pressure ulcer treatment was initiated as soon as the patient arrived at the clinic after recording necessary forms and details. The treatment continued in the postoperative period. Catheters were inserted for all patients on the 2nd postoperative day. Patients who required catheter monitoring during treatment and had to use adult diapers due to fecal incontinence were included in the study. When the patient was discharged, their caregiver was also instructed to continue treatment at home.

During weekly follow-up appointments, wound monitoring, wound classification, size, exudate status, infection status, and incontinence-related dermatitis were assessed. The response to treatment was evaluated by comparing the wound classification on the 21st day with the initial classification. Staging is essential for standardized diagnosis and treatment monitoring in pressure ulcers. For this purpose, a staging system recommended by the National Pressure Ulcer Advisory Panel is commonly used (see Table 2).[3] The images of patients from all three classes, categorized according to the ulcer classification used in the study, are presented in Figure 1.

All patients were able to mobilize with full weight-bearing during the postoperative period. Patients who were unable to mobilize were excluded from the study as prolonged immobility would affect the pressure duration. All patients received the same walking protocol, exercises, and rehabilitation procedures, and were taught and ensured to follow them. Patients who showed non-compliance with treatment and did not attend regular follow-up appointments were not included in the study.

3. Results

In the study, there were 34 patients in the control group (Group 1), 25 patients in Group 2, 28 patients in Group 3, and 27 patients in Group 4. In Group 1 (control group), the average wound classification at the time of hospital admission was 2.3, while it was 2.2 in Group 2, 2.5 in Group 3, and 2 in Group 4.

The average ages were 67.5 in Group 1, 70.2 in Group 2, 74.5 in Group 3, and 72 in Group 4. The comparison of groups was evaluated using Anova test and no statistically significant differences were found. During the 21-day treatment period, the fastest improvement was observed in Group 3. (Table3) The wound classification decreased from 2.5 at the initial presentation to 1.5, indicating the most effective treatment. It can be said that the spray applied in this group effectively created a barrier to protect the wound from the destructive effects of urine and feces and provided greater resistance against friction. The application, which involved the use of isotonic solution during and subsequent to the application, followed by the application of Med-Cover barrier cream clothes to remove and neutralize toxic and destructive effects of urine and feces from the skin, and then protecting it with the barrier created by the spray, emerged as the most effective method. This method, in comparison to the cream used in Group 4, does not involve a painful process such as manually applying the cream around the open wound, making it easier for patients to tolerate. The fact that the highest satisfaction score for the application method was given in this group also supports this.

This indicates that patients found it easier to tolerate using the spray rather than applying cream around the open wound. In all three groups, it was observed that the method significantly prevented maceration compared to the control group and also significantly prevented incontinence-related dermatitis in areas without wounds. Statistically significant improvement was observed in group 3 and group 4 in the comparison of group satisfaction survey results and wound sizes. The sentence describes the use of an dependent sample T-test to compare four independent variables and finding a significant difference among the groups based on the test results. To determine which specific groups have differences, a post hoc analysis using the Scheffe test was conducted, and it revealed that there is a significant difference in favor of Group 3 when comparing Group 3 and Group 4.

Table 3

Comparison of the results of groups based on wound classification at 1st and 21st days

	Group1	Group2	Group3	Group4
Average patient satisfaction score	55	61	75	71
Wound classification at the time of admission	2,3	2,2	2,5	2
Wound classification after treatment	2	1,8	1,5	1,5
p	0.09	0.07	0.02	0.038

4. Discussions

Pressure ulcers are extremely challenging to treat once they have developed. Recurrence rates of up to 95% have been reported in wounds closed using surgical methods. Therefore, the most effective treatment is the recognition of at-risk patients and the prevention of pressure ulcer formation. Treatment can be broadly categorized into systemic and local approaches. Systemic treatment includes protecting patients from developing wounds, correcting their nutritional status, treating anemia, and preventing incontinence-related dermatitis. Local treatment can be further divided into conservative and surgical methods. These patients should be evaluated as a whole, and treatment should be tailored accordingly; otherwise, local treatments may prove inadequate in the absence of systemic interventions.[3,4,7,8]

After the initial assessment of the patient, preventive measures should be taken to avoid pressure. Subsequently, the nutritional status of the patient should be evaluated. Patients with losses resulting from ulcer surfaces often suffer from malnutrition and negative nitrogen balance. Therefore, a high-calorie, high-protein, and vitamin-rich diet should be initiated for these patients. To support normal wound healing, serum albumin levels should be at least 2 g/100 ml. Essential nutrients for normal wound healing, such as vitamins A and C, calcium for epithelization and fibroblast function, and iron and copper for collagen metabolism, should be included in the diet. Low-fiber foods are preferred to avoid fecal contamination, which is a significant issue in the treatment of pressure ulcers.[9]

If a patient cannot consume sufficient nutrients orally, they may be given nutrition through a feeding tube, gastric diet, or ready-made formulas. In cases where enteral nutrition is insufficient or not possible, parenteral hyperalimentation should be applied. In this case, potential issues related to catheters should be kept in mind, and the patient should be closely monitored.[3,5,9]

To ensure adequate tissue oxygenation, it is essential to maintain high hemoglobin levels. For this purpose, dietary supplements that promote blood production, such as those containing liver, should be considered, and iron preparations should be administered.

In the presence of bacteremia, bacteria localized in ischemic tissues under pressure can lead to the development of localized infection. Systemic infections should be treated with appropriate antibiotics,

and care should be taken to clean urinary catheters and change them frequently, with residual urine being emptied.[6]

Pressure sores can also become infected through direct contamination, aside from the endogenous route. To prevent fecal contamination, a low-residue diet should be provided, and when changing the patient's diapers, barrier cream (effective) products should be preferred. In advanced ulcers, the temporary or permanent creation of a colostomy may also be considered.

The fundamental principle in both the prevention and treatment of pressure ulcers is to minimize the pressure exerted on weight-bearing areas and avoid prolonged pressure. The position of bedridden patients should be changed every 2 hours, and a prone sleeping position is preferred during sleep. The goal is to evenly distribute the patient's weight, ideally allowing no area of the body to experience pressure exceeding 32 mm Hg. In pursuit of this goal, the use of air mattresses is a common practice.[10,11,12]

The local treatment of pressure ulcers includes both conservative wound care and local surgical procedures. When faced with a pressure ulcer, the initial step is to evaluate the wound. In cases where surgery is not considered, the treatment plan should be based on the wound classification. The objectives include protecting the wound from friction and shearing forces, ensuring pressure distribution, providing adequate ventilation, safeguarding against local destructive substances like urine and feces, and preventing infection.[11,12]

Small and superficial ulcers can heal through pressure relief and proper wound care, with granulation tissue growing from below and eventually being covered by epithelium from the periphery. However, in wounds that heal in this way, the protective barrier is often not strong enough, leading to a higher risk of recurrence.

In topical wound care, the goal is to maintain moisture in the wound, mechanically remove debris that develops in the wound, and reduce local infection with bactericidal effects. Solutions commonly used for wound dressing purposes include bactericidal solutions such as saline, povidone-iodine, hydrogen peroxide, acetic acid, and sodium hypochlorite (Dakin's solution). Bactericidal solutions can help reduce infection, but they can also lead to tissue toxicity, which makes their use controversial. Although it has been suggested that 1:1000 diluted povidone-iodine and 1:100 Dakin's solution can exhibit bactericidal effects without causing tissue toxicity, it is not appropriate to use them in cases where there is no active wound infection. Hydrogen peroxide and acetic acid, even when diluted, can still cause tissue toxicity.

In topical wound care, the goal is to maintain moisture in the wound, mechanically remove debris that develops in the wound, and reduce local infection with bactericidal effects. Solutions commonly used for wound dressing purposes include bactericidal solutions such as saline, povidone-iodine, hydrogen peroxide, acetic acid, and sodium hypochlorite (Dakin's solution). Bactericidal solutions can help reduce infection, but they can also lead to tissue toxicity, which makes their use controversial. Although it has been suggested that 1:1000 diluted povidone-iodine and 1:100 Dakin's solution can exhibit bactericidal effects without causing tissue toxicity, it is not appropriate to use them in cases where there is no active wound infection. Hydrogen peroxide and acetic acid, even when diluted, can still cause tissue toxicity. Although saline does not have bactericidal effects, it is the preferred solution because it does not cause tissue toxicity and creates a physiological environment that supports normal wound healing processes.

For a dressing to be effective, gauze should fill the entire cavity, and it should be changed every 6-8 hours. This helps remove tissues that provide a breeding ground for bacteria from the wound. The bactericidal properties of the dressing are more dependent on mechanical action than the solution used. Deep cavitated wounds should be irrigated at least once a day for mechanical cleansing. These traditional dressing methods, while providing rapid improvement in the wound, can be time-consuming and require the involvement of numerous healthcare professionals.

Appropriate wound care, pressure relief, barrier-effective applications, and addressing nutritional status can lead to the rapid healing of many superficial ulcers. In the case of deep wounds, only long-term dressings can promote healing. The rapid development of wound dressing materials and the high morbidity, cost, and subsequent high recurrence rates associated with surgical interventions have directed healthcare professionals toward conservative treatment as much as possible.

In orthopedic treatment, orthopedic surgeons often focus on the fracture, but additional pathologies are frequently observed in elderly patients. A comprehensive approach should be taken to prevent potential additional morbidities in the patient. In clinical practice, pressure ulcers occurring after hip fractures can significantly impact the patient's course of recovery and even their survival, especially in elderly patients with multiple comorbidities, and they can lead to life-threatening situations.[13] They also significantly increase treatment costs and hospitalization durations. It is clear that the most crucial aspect of these wounds is prevention. In the prevention of wounds, the foremost step is the awareness of orthopedists regarding the potential development of presacral pressure ulcers in every patient with a hip fracture. In this study, we compared three commonly used medical products, and we found that after cleansing the area with isotonic solution, the use of Med-Cover Barrier Cream clothes followed by Med-Cover Barrier Film Spray to protect the region under pressure, at least from enzymatic damage caused by bodily fluids and medical adhesives, significantly reduces the risk of pressure ulcer formation. It has been observed that when Med-Cover Barrier Effective products are applied to the wound area, they have a preventive effect on friction and the formation of incontinence-associated dermatitis.

In cases of presacral pressure ulcers that occur after a hip fracture, the situation is somewhat complicated. Hip fractures primarily affect an elderly patient population, often secondary to osteoporosis. Managing these patients systemically is of utmost importance. Furthermore, considering that these patients have undergone surgery for their hip fractures, treatment becomes even more complex and challenging. Patients with hip fractures are prone to systemic bleeding, either from the fracture site or intraoperative bleeding, both of which can lead to a decrease in hemoglobin levels. Hemoglobin deficiency reduces tissue oxygenation. These patients are often immobile during the preoperative preparation and postoperative recovery periods, which leads to an increased risk of pressure and pressure-related complications. Additionally, during this period, they may be unable to attend to their toileting needs, necessitating the use of adult diapers and catheters. The use of adult diapers reduces tissue ventilation, increases moisture levels, and raises friction forces. Moreover, skin irritation occurs following contact with feces and urine, which accelerates pressure ulcer formation[14].

In our study, there were no significant differences between the groups we compared in terms of systemic and positional changes. However, the results of patients who used different local topical products were compared.[15] The literature shows varying outcomes regarding the effects of local products, which can be attributed to the need for a multifactorial treatment approach and the presence of highly variable patients. We believe that the differences in results reported in the literature can be attributed to insufficient exclusion criteria and the difficulty in standardizing patients. Our study is unique in that it is the only one comparing three different topical products.

5. Conclusions

Pressure ulcers in hip fracture patients are frequently observed, and the most effective method for preventing their formation and maceration is the application of a barrier cream clothes and a barrier spray after washing with isotonic solution. This study was con- ducted with a limited number of patients who had 1st, 2nd, and 3rd- degree ulcers and observed incontinence. In the future, conducting studies with a larger number of patients will shed further light on the literature.

Statement of ethics

The study received approval from the Ethics Committee of Selçuk University (Decision date: 2023, Number: 430).

Conflict of interest statement

Author declare that they have no financial conflict of interest with regard to the content of this report.

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Comparison of Anatomical and Functional Outcomes of Viscoimplantation and Hydroimplantation Techniques in Foldable Intraocular Lens Implantation

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Abstract

Aim: The aim of this study was to compare the anatomical and functional results of viscoimplantation and hydroimplantation techniques in monofocal foldable intraocular lens implantation.

Methods: The study included 387 patients older than 50 years who underwent surgery for senile cataract. They were divided into two subgroups as hydroimplantation (group 1) and viscoimplantation (group 2).

Results: The mean implantation time was 397.5±44.3 s in group 1 and 580±105.1 s in group 2. During the follow-up period (12 months), 4 (2.1%) patients in group 1 and 28 (14.6%) patients in group 2 developed posterior capsular opacification. The implantation time was shorter and the rate of posterior capsular opacification was lower in group 1 compared to group 2 ($p<0.001$). Intraocular pressure measurements were 16.5±2.87 mmHg in group 1 and 20.3±2.9 mmHg in group 2 at the first hour after surgery. At the twenty-fourth hour, the mean intraocular pressure was 14.1±1.3 mmHg in group 1 and 17.5±1.8 mmHg in group 2. This difference between the groups was statistically significant ($p=0.011$ and $p<0.001$, respectively).

Conclusions: In the hydroimplantation technique, the changes in anterior segment parameters between the preoperative and postoperative period are very small. It causes less intraocular pressure elevation. Therefore, hydroimplantation is a cost-effective, safe and effective method for monofocal foldable intraocular lens implantation in uncomplicated cataract surgeries

Keywords: *Cataract, Hydroimplantation, Intraocular Lens, Viscoimplantation*

1. Introduction

Small incision cataract surgery is the preferred method of cataract surgery by most surgeons. Ophthalmic viscoelastic materials (OVDs) have numerous advantages during small incision cataract surgery. OVDs protect the corneal endothelium against fluid turbulence, free oxygen radicals released during ultrasonic fragmentation, contact with surgical instruments, air bubbles and lens fragmentation[1,2]. In addition, it facilitates the surgical procedure, reduces the risk of secondary damage to delicate intraocular tissues, and creates and stabilizes the anterior chamber[3]. These positive aspects may vary according to the physical, chemical and rheologic properties of OVDs[4].

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An ideal OVD should be easily injected into the eye, contribute to the formation and maintenance of the anterior chamber, trap air bubbles, not increase intraocular pressure (IOP) and be easily cleaned at the end of the operation[5,6].

An important disadvantage of OVDs is the increase in IOP, especially in the early period after cataract surgery due to the length of stay in the eye. Molecules that cannot be completely cleared after surgery mechanically occlude the trabecular meshwork, preventing the outflow of aqueous humor and causing IOP increases within 24 hours after surgery, which has become a concern especially for glaucoma patients[7-10]. In addition, viscoelastic materials, especially behind the intraocular lens, cause early development of posterior capsular opacification (PCO) and the need for a higher Neodymium-doped Yttrium Aluminum Garnet (Nd:YAG) laser[11].

Therefore, OVDs should be completely removed at the end of the operation to avoid these complications. It is a more rational approach to use OVDs in a limited way to reduce these disadvantages. In this context, some cataract surgeons have preferred the hydroimplantation technique for intraocular lens implantation (without OVDs).

Tak was the first to describe the hydroimplantation technique[12]. In this technique, intraocular lens implantation is performed under continuous balanced salt solution irrigation without OVDs. Many studies have reported the safety of the hydroimplantation technique

in the literature[13-15].The aim of our study was to compare the anatomical and functional results of viscoimplantation and hydroimplantation techniques in foldable intraocular lens implantation.

2. Materials and methods

This retrospective, cross-sectional study included 387 patients older than 50 years who underwent surgery for senile cataract between January 2020 and July 2021 at our clinic. Patients with Marfan syndrome, lens ectopia, homocystinuria, history of trauma, history of previous ophthalmic surgery, pseudoexfoliation, uveitis, glaucoma, corneal haze, corneal astigmatism greater than 1.25 diopters (D) and axial length greater than 25 mm were excluded.

Patients who underwent cataract surgery with phacoemulsification with a 2.8 mm clear corneal incision under topical anesthesia were included in the study. In all patients, 3% sodium hyaluronate was used to form the anterior chamber during cataract surgery. Patients were divided into two subgroups. These were those who used balanced salt solution (hydroimplantation) for monofocal foldable intraocular lens (hydrophobic, acrylic) implantation (following removal of cortical material in the final stage of the operation (group 1) and those who used ophthalmic viscoelastic material (group 2). Both techniques were used by two surgeons (ESG, ÖÖ). After monofocal foldable intraocular lens implantation with ophthalmic viscoelastic material, the remaining viscoelastic material in the eye was attempted to be removed both from the front of the foldable intraocular lens and from the space between the intraocular lens and the posterior capsule using irrigation and aspiration (I/A) probes. No intraoperative posterior capsule rupture was observed in any patient. Both surgeons have experience of more than a thousand cataract surgeries. Moxidexa 5 mg/1 mg sterile ophthalmic solution (5.45 mg moxifloxacin and 1.1 mg dexamethasone sodium phosphate, Abdi Ibrahim, Istanbul, Turkey) was used every 4 hours for two weeks after surgery.

Age, gender and laterality to be operated on were recorded in all patients. Anatomical measurements of all patients were performed with Eyestar 900 (HAAG-STREIT AG, Koeniz, Switzerland) before and one month after surgery. SRK/T and Barrett Universal II formula were used for intraocular lens power calculation. Surgical time was calculated from the time the clear corneal incision was made to the time the corneal incisions were closed and implantation time was calculated from the time the cortical material was completely removed to the time the corneal incisions were closed. Anatomic lens position (ALP), a marker of effective lens position, was defined as the total distance between the corneal epithelium and the anterior surface of the lens.

In the postoperative period, best-corrected visual acuity (logMAR), intraocular pressure measurements with Goldmann applanation tonometry (preoperatively and at the 1st hour, 4th hour and 24th hour after surgery) and complete ophthalmologic examination were performed. Patients were followed up for at least 12 months for intraoperative and postoperative complications. Posterior capsular opacification (PCO) was subjectively evaluated by retro-illumination on slit-lamp examination. When Elschnig's pearls or fibrosis was seen in the posterior capsule, the patient was considered to have developed PCO.

The necessary permissions were obtained from Local Ethics Committee before this study (07/12/2022 - 2022/807). The principles of the Declaration of Helsinki were followed throughout the study. Written informed consent was obtained from all participants.

Statistical analysis was performed using IBM SPSS Statistics 28.0.1.0 (Armonk, NY, USA). Shapiro-Wilk test was used for the conformity of the data to normal distribution. Numerical data were expressed as mean and standard deviation. Student t test was used for comparison in independent groups in two groups, and ANOVA test was used if the number of groups was more than two. Categorical data are shown with number (percentage-%). Chi-square test was used to compare categorical data. Statistical significance was accepted when $p<0.05$.

3. Results

Of the patients included in the study, 195 (50.4%) underwent hydroimplantation (group 1) and 192 (49.6%) underwent viscoimplantation (group 2). Of the operated eyes, 194 (50.1%) were right and 193 (49.9%) were left. Of the patients, 188 (48.6%) were male and 199 (51.4%) were female. The mean age of patients in group 1 was 64.7±5.8 years, while the mean age of patients in group 2 was 63.4±5.1 years. Demographic characteristics were similar between the patient groups ($p>0.05$, for all) (Table 1).

Table 1

Demographic characteristics of the patients

	Group 1	Group 2	p
N	195	192	
Age (year)	64.7±5.8	63.4±5.1	0.227
Right (n,%)	96 (49.2%)	98 (51%)	0.721
Left (n,%)	99 (50.8%)	94 (49%)	
Male (n,%)	92 (47.2%)	96 (50%)	0.579
Female (n,%)	103 (52.8%)	96 (50%)	

Table 2

Patients' preoperative anatomical measurements and calculated IOL power

	Group 1	Group 2	p
N	195	192	
Axial Length (mm)	23.34±1.2	23.24±1.3	0.626
Anterior Chamber Depth (mm)	3.19±0.46	3.22±0.6	0.693
Central Corneal Thickness (µm)	537.8±36.2	529.7±43.1	0.157
White to white distance (mm)	11.92 ± 0.72	11.91 ± 0.56	0.842
SRK/T (D)	21.5±1.8	21.4±1.8	0.737
Barrett Universal II (D)	21.5 ± 1.8	21.3 ± 1.9	0.811

Table 3

Patients' preoperative anatomical measurements and calculated IOL power

	Group 1	Group 2	p
N	195	192	
Postoperative Anterior Chamber Depth (mm)	3.38±0.7	3.54±0.72	0.021
Postoperative Central Corneal Thickness (µm)	554±45.1	554.4±46	0.977
Anatomical Lens Position (mm)	3.93±0.84	4.09±0.92	0.236
Spherical Equivalent (D)	- 0.35±0.16	- 0.43±0.23	0.881

Table 4

Duration of surgery and complication data of the patients

	Group 1	Group 2	p
N	195	192	
Duration of implantation (s)	397.5±44.3	580±105.1	< 0.001
Total duration of surgery (min)	23.4 ± 2.14	27.6 ± 3.22	< 0.001
Intraocular pressure – Preoperative (mmHg)	15.7 ± 2.6	15.8 ± 2.9	0.377
Intraocular pressure - First hour (mmHg)	16.5±2.87	20.3±2.9	0.011
Intraocular pressure - Fourth hour (mmHg)	19.2±2.1	22.4±4.6	0.042
Intraocular pressure - 24th hour (mmHg)	14.1±1.3	17.5±1.8	< 0.001
Posterior capsular opacification	4 (2.1%)	28 (14.6%)	< 0.001

In the preoperative anatomical measurements of the patients, the mean axial length was 23.34±1.2 mm in group 1 and 23.24±1.3 mm in group 2. Mean anterior chamber depth was 3.19±0.46 mm in group 1 and 3.22±0.6 mm in group 2. Mean central corneal thickness was 537.8±36.2 µm in group 1 and 529.7±43.1 µm in group 2. The mean intraocular lens power calculated according to the Barrett Universal II formula was 21.5±1.8 diopters (D) in group 1 and 21.4±1.8 D in group 2. Anatomical measurements of the groups were similar (p>0.05, for all). (Table 2)

In the postoperative anatomical measurements of the patients, the mean anterior chamber depth was 3.38±0.7 mm in group 1 and 3.54±0.72 mm in group 2. Mean central corneal thickness was 554±45.1 µm in group 1 and 554.4±46 µm in group 2. Mean anatomical lens position was 3.93±0.84 mm in group 1 and 4.09±0.92 mm in group 2. Patients in group 1 had less anterior chamber depth than patients in group 2 (p=0.021). Refractive errors (spherical equivalan) were mean (-) 0.35±0.16 D in group 1 and mean (-) 0.43±0.23 D in group 2. (Table 3)

In the surgical data, the mean implantation time was 397.5±44.3 s in group 1 and 580±105.1 s in group 2. During the follow-up period (12 months), 4 patients (2.1%) in group 1 and 28 patients (14.6%) in group 2 developed posterior capsular opacification. The implantation time was shorter in group 1 than in group 2 (p<0.001) and the rate of posterior capsular opacification was lower (p<0.001) (Table 4).

Intraocular pressure measurements at the first hour after surgery averaged 16.5±2.87 mmHg in group 1 and 20.3±2.9 mmHg in group 2. At the fourth hour after surgery, the mean intraocular pressure was 19.2±2.1 mmHg in group 1 and 22.4±4.6 mmHg in group 2. At the twenty-fourth hour, the mean value was 14.1±1.3 mmHg in group 1 and 17.5±1.8 mmHg in group 2. This difference between the groups was statistically significant (p=0.011, p=0.042 and p<0.001, respectively).

4. Discussion

Each technique and stage of cataract surgery has different goals and complications. Some of these are technique-specific, while others depend on the ancillary medical supplies used. While ophthalmic viscoelastics are beneficial to the surgeon during surgery in all types of cataract surgery, they also bring certain risks in the postoperative period.

In a study conducted by Wright et al. on 46 patients, the visual results of small incision cataract surgery without the use of viscoelastic materials were quite satisfactory. However, it was emphasized that the use of viscoelastic can be used to protect the corneal endothelium[16]. Studeny et al. compared the results of standard viscoimplantation and hydroimplantation techniques. It was reported that both techniques were similar in terms of endothelial cell loss, postoperative IOP changes and complications[13].

In another study in the literature, Oğurel et al. found that hydroimplantation applied to patients with pseudoexfoliation had no adverse effect on postoperative central corneal thickness, IOP and corneal endothelial cell count compared to viscoimplantation. They also showed that IOP value 24 hours after surgery was lower in the hydroimplantation group[14].

In our study, intraocular pressure values measured at the first, fourth and twenty-fourth hours after surgery in patients who underwent hydroimplantation were found to be lower than those in the viscoimplantation group. In addition, postoperative central corneal thickness was similar between the two groups. In both techniques, no posterior capsule rupture was observed at the time of surgery. Therefore, hydroimplantation technique is an effective and safe technique. However, this technique is not recommended in eyes with posterior capsule rupture, floppy iris syndrome, irregular anterior capsulorhexis or tear. This technique should be avoided if the implanted intraocular lens is an abrupt opening or if the surgeon is not experienced enough. In accordance with the literature findings, lower intraocular pressure values were obtained in the postoperative period. The fact that it does not cause high intraocular pressure values and does not require additional cost makes this technique prominent.

Özateş et al. reported that patients who underwent hydroimplantation technique had lower refraction in the postoperative period compared to patients who underwent

viscoimplantation[15]. According to our findings, the mean postoperative refractive errors were lower in the hydroimplantation group. This may be because the anatomical lens position values were lower in the hydroimplantation group than in the viscoimplantation group. This may be due to the fact that the intraocular lens power calculated in the preoperative period was based on the estimation of the effective lens position and the patients in the hydroimplantation group were actually closer to this value.

In a study conducted by Chen et al., concluded that the hydroimplantation technique shortens the surgical time, reduces the cost of the operation and eliminates the danger of IOP elevation due to OVD[18].

Another advantage of this technique is that it can shorten the total surgical time. In a study published by Özcura and Çevik, the mean surgical time of patients who underwent hydroimplantation was significantly shorter than that of the viscoimplantation group (953.8 vs 1072.3 seconds, respectively, $p<0.001$)[17]. Oğurel et al. reported that the total surgical time was shortened by approximately three minutes[14]. In our results, the total surgical time was shortened by an average of 4.2 minutes in accordance with the literature.

This study has some limitations. The first one is that only monofocal intraocular lens implantation was performed. Other limitations include the relatively small number of patients, not including patient subgroups with different axial lengths, and not measuring intraocular pressure changes during implantation. Another limitation is that the endothelial count was not evaluated before and after surgery.

In the hydroimplantation technique, the changes in anterior segment parameters between the preoperative and postoperative period are very small. It causes less intraocular pressure elevation. Therefore, hydroimplantation is a cost-effective, safe and effective method for monofocal foldable intraocular lens implantation in uncomplicated cataract surgeries.

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None.

Statement of ethics

This study was approved The approval of the Local Ethical Committee was obtained (Mersin City Hospital). (2022-807)

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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The Impact of The National Screening Program for Developmental Dysplasia of The Hip on Radical Surgical Procedures

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Abstract

Aim: Developmental dysplasia of the hip (DDH) encompasses a broad pathological spectrum from mild acetabular dysplasia to complete hip dislocation and can be treated with simple and non-invasive methods with early diagnosis. In contrast, major surgical interventions may be required in those with late diagnosis, and most heal with sequelae. This study aimed to investigate the effects of the national developmental dysplasia of the hip (DDH) screening program initiated in 2013 on the developmental dysplasia treatment approaches and the number of surgical treatments in Balcalı Hospital of Cukurova University Medical Faculty.

Methods: All patients operated on for DDH in our clinic from 2007 to 2021 were retrospectively reviewed from records, and the number of closed reductions, open reductions, and pelvic osteotomies performed before and after the screening program were analyzed.

Results: Between 2007-2021, 255 surgical and 125 non-surgical procedures were performed under anesthesia in DDH patients. With the national hip screening program, the rate of closed reduction and spica casting increased from 14,8% to 46,3%. The rate of open reduction also increased from 24,1% to 29,4% in this period, and the rate of major surgical procedures with pelvic osteotomy decreased significantly from 61,1% to 24,3%.

Conclusions: In this study, it was observed that after the initiation of the screening program for DDH, major surgical interventions involving pelvic osteotomies were significantly reduced in our clinic, while the rate of closed reduction increased.

Keywords: *Developmental dysplasia of the hip, Screening program, Pelvic osteotomy*

1. Introduction

Developmental dysplasia of the hip (DDH) includes the spectrum of idiopathic abnormal hip developmental disorders with mild acetabular dysplasia, subluxation, or hip dislocation due to capsular laxity and mechanical instability in the growing and developing hip joint [1]. Hip pathologies secondary to neurological, neuromuscular, and syndromic diseases are excluded from this group and are called teratogenic hip dislocation[2]. While in the past years, the term congenital hip dislocation was used, which did not define the developmental aspect of this disorder, today the definition of developmental dysplasia of the hip, which is more descriptive of the disease, is used. Changing the definition of congenital to developmental increases physicians' legal liabilities [3].

While dislocated and subluxated hips can be diagnosed clinically at early stages, the clinical diagnosis of dysplastic hips is comparatively more challenging. Mild dysplasia may never occur or become clinically evident until adulthood, while severe dysplasia is more likely to occur clinically in late infancy or early childhood[4].

Developmental dysplasia of the hip has a multifactorial etiology. There are well-defined risk factors for DDH. These include female gender, being the firstborn, breech presentation, and positive family history [5]. In addition, the traditional method of newborn swaddling in Turkey and eastern societies increases the risk of DDH[6,7].

Developmental dysplasia of the hip can be diagnosed by clinical examination, hip ultrasonography, or an x-ray taken after the 4th month. There is no international consensus on the screening programs for the early diagnosis of DDH. In countries such as the USA and Canada, screening begins with an examination, and ultrasound

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is performed in clinically high-risk groups. On the other hand, universal screening is performed in many European countries[8–11]. While universal ultrasonography screening has disadvantages such as false positivity, overtreatment and cost, some cases can be missed in selective screening[12]. Studies on DDH early diagnosis and treatment programs in Turkey were initiated in 2010 in cooperation with the Ministry of Health and the Turkish Pediatric Association, and family physicians were trained. With the participation of the Turkish Society of Radiology Executive Committee in 2013, it was updated throughout the country and started to be actively implemented. As part of the national screening program, all infants undergo a hip dislocation examination during the neonatal period (3-4 weeks). Infants with positive findings or risk factors are referred to orthopedic and radiology clinics for further evaluation. Hip ultrasound is performed in the first 3-6 weeks of life for infants in this group. The goal is to evaluate infants and provide prompt and appropriate treatment when needed, while minimizing the need for surgery and potential complications associated with hip dislocation[13].

There is a well-known relationship between residual dysplasia and the age at reduction. When patients are diagnosed within the first six months, treatment consists of using a Pavlik harness. For those aged between 6-18 months, closed reduction and spica casting are performed under general anesthesia, whereas in later stages, open reduction and pelvic osteotomies are the preferred methods. If the diagnosis is delayed, the success rate decreases, and it may cause severe long-term health problems, such as early-onset degenerative arthritis. This disease, which is an important cause of disability in the period from childhood to adulthood, is also the cause of 9% of all primary hip replacements and up to 29% of people with this disease under the age of 60 have primary total hip replacement[7,14,15].

This study aims to investigate the effect of the Turkish National Hip Screening Program on the procedures performed for DDH in our clinic and to show the decrease in the rate of radical surgical procedures with early diagnosis.

2. Materials and methods

This retrospective study was conducted between June 2007 and June 2021 at the Department of Orthopedics and Traumatology, Faculty of Medicine, in Çukurova University Balcalı Hospital. Ethics committee approval was obtained from the non-interventional clinical research ethics committee of Çukurova University Faculty of Medicine with decision number 121 and number 54 dated April 8, 2022. Patients who underwent anesthesia for the treatment of developmental dysplasia of the hip were identified through the surgery records. Patients who had been treated with a Pavlik harness were excluded from the study due to insufficient outpatient records. Records before 2007 were also excluded due to inadequate surgical documentation. Patients who had undergone surgery for teratogenic hip dislocation, such as arthrogryposis multiplex congenita and meningomyelocele, were also excluded from the study.

As a result, 380 patients were included in the study. The patients were divided into three groups pelvic osteotomy, open reduction, and closed reduction. The pelvic osteotomy group included Salter osteotomy, Pemberton osteotomy, Steel osteotomy, and Dega osteotomy. Radical reduction including femoral shortening osteotomy was performed when necessary in the patient who underwent pelvic osteotomy. An anterior approach was performed in all patients in the open reduction group. Percutaneous adductor tenotomy was performed in the closed reduction group if necessary. Arthrography was not applied. A hundred and twenty-seven patients had bilateral DDH. In cases where patients underwent different procedures on both hips, the patient was included in the group that underwent the more extensive surgery. Additionally, patients were categorized based on the year of their surgery.

Although there are some exceptions, infants with DDH are typically treated with the Pavlik harness up to six months of age, followed by closed reduction from six to twelve months, open reduction from twelve to eighteen months, and pelvic osteotomies from 18 months onwards. Following all surgical procedures, hip spica casting is administered to patients under fluoroscopy.

The national DDH screening program in Turkey mandates clinical examinations for all newborns, with selective sonography performed only on those with risk factors. Risk factors for prenatal sonography include family history (first and second-degree relatives), first-born female, multiple pregnancies, amniotic fluid anomalies, breech presentation, congenital foot deformities, plagiocephaly, scoliosis, pelvic tilt, limited hip abduction, congenital torticollis, and swaddling. If there are no risk factors, newborns are examined by primary care physicians at the 6th week of birth. In case of hip instability or any positive risk factor in this examination, babies are referred to the radiology department for ultrasonographic examination.

2.1. Statistical Analysis:

Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation. Chi-square test was used to compare categorical variables between the groups. All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package. The statistical level of significance for all tests was considered to be 0.05. SPSS referance: IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0 Armonk, NY: IBM Corp.

3. Results

Of the 380 patients included in the study, 127 (33.4%) had bilateral and 255 (66.6%) had unilateral DDH. The number of female patients was 305 (80%) and male patients was 75(20%). 255 (%67) patients underwent surgical treatment, of which 152 (%40) were pelvic osteotomy and 103 (%27) were open reduction. Of the 152 pelvic osteotomies, 47 were Salter, 25 were Pemberton, 5 were Dega, 68 were radical, and 7 were Steel. Closed reduction was performed in 125 (%33) patients (Table 1).

Table 1

Distribution of closed reduction, open reduction and radical surgical procedures by years

	CR	OR	Salter	Pemberton	Dega	Radical	Steel
2007		1	16			10	
2008	2	5	6			10	
2009	3	4	4			7	
2010	1	5	7			4	
2011	4	7	5	3		3	
2012	2	8	2	3	1	2	1
2013	12	9		9	2	4	
2014	12	10		8		10	
2015	18	9	2	2		4	4
2016	9	16				1	1
2017	14	6	2			1	1
2018	8	11	3			6	
2019	15	6				4	
2020	15	2			1	1	
2021	10	4			1	1	
	125	103	47	25	5	68	7

**CR: closed reduction, **OR: open reduction*

Table 2

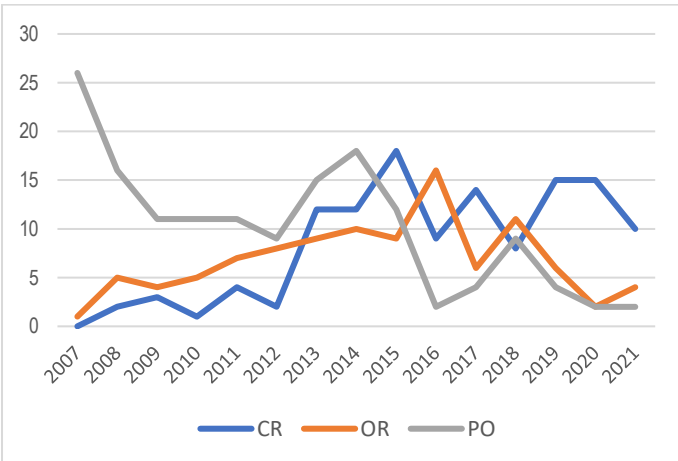
Crosstabulation of procedures by year

			Years		Total
			2007-2013	2014-2021	
Procedures	CR	Count	24a	101b	125
		% within procedures	19,2%	80,8%	100,0%
		% within years	14,8%	46,3%	32,9%
	OR	Count	39a	64a	103
		% within procedures	37,9%	62,1%	100,0%
		% within years	24,1%	29,4%	27,1%
	PO	Count	99a	53b	152
		% within procedures	65,1%	34,9%	100,0%
		% within years	61,1%	24,3%	40,0%
Total		Count	162	218	380
		% within procedures	42,6%	57,4%	100,0%
		% within years	100,0%	100,0%	100,0%

*Each subscript letter denotes a subset of years categories whose column proportions do not differ significantly from each other at the ,05 level. *CR: closed reduction, **OR: open reduction, ***PO: pelvic osteotomies*

Figure 1

Change of procedures over the years



**CR: closed reduction, **OR: open reduction, ***PO: pelvic osteotomies*

Between the years 2007-2013 (before screening): 24 closed reductions, 39 open reductions, and 99 pelvic osteotomies were performed. Between the years 2014-2021 (after screening): 101 closed reduction, 64 open reduction, and 53 pelvic osteotomy were performed (Figure 1). Closed reduction and open reduction rates increased significantly from 14.8% to 46.3% and from 24.1% to 29.4%, respectively. Pelvic osteotomy rate decreased significantly from 61.1% to 24.3%. While closed reduction was 19.2% of all procedures in the years before 2014, this rate increased significantly to 80.8% after 2013. On the contrary, while patients who underwent pelvic osteotomy were 65.1% of all patients before 2014, this rate decreased significantly to 34.9% after 2013 (Table 2).

4. Discussions

Considering the successful outcomes observed in our clinical practice and the decrease in major surgical interventions, it is necessary to accept the effect and success of the Turkish National DDH Screening Program in our region and clinic.

Early diagnosis provides easier treatment options to achieve and maintain reduction, increases the potential for acetabular and femoral remodeling, and reduces the risk of complications and treatment costs. Delayed diagnosis reduces treatment success, increases treatment costs and can cause long-term disability [2,16,17].

Screening for DDH is controversial. There are no internationally agreed guidelines or standards. Universal screening, which is the USG screening of all newborns, or selective screening, which is the examination and screening in the presence of risk factors, can be performed. In Austria and Germany, there is a universal sonographic hip joint screening program for newborns [18–20]. In Norway and France, there are universal clinical and selective sonographic hip screening programs[10,11]. In the USA it has been advocated that breech presentation and family history in females and breech presentation in males may be selectively screened[21]. There is no international consensus on which method should be preferred in terms of efficiency and cost. Studies comparing universal and selective ultrasound have found no significant difference in the criteria for subluxation - dislocation or acetabular dysplasia - degenerative changes. [11,22].

Universal clinical and selective ultrasound screening for DDH in Turkey started in 2010 with the training of family physicians and regional practices and was updated and implemented nationwide in 2013. Due to the developmental nature of the disease, neglect or delay in diagnosis creates medicolegal problems for the physician who screens and refers according to risk factors. We believe that these medico-legal issues point family physicians to the universal ultrasound screening program in Turkey. Ultrasound screening is crucial for the diagnosis of DDH although there is still disagreement about who should undergo ultrasound screening and when because the disease is not easy to diagnose in the early stages. If diagnosed early, it is easier to treat, cheaper, and less invasive, and critical hip disorders can be prevented[23].

Breech presentation, oligohydramnios, family history, firstborn, female sex and primiparity were confirmed as risk factors for DDH. It has been reported that women are 2-7 times more likely to have DDH compared to men[5,24]. Furthermore, it has been reported that up to 75% of DDH patients are women[25] . Consistent with the literature in our study, 80% of the patients were female. Estrogen in the maternal and fetal circulation causes ligament laxity and increases the risk of DDH in females. At the same time, the higher number of estrogen receptors in DDH patients compared to controls supports the role of hormones in the development of DDH[26].

In the first months after birth, a concentrically reduced femoral head in the acetabulum is usually sufficient for acetabular development. As the infant grows older, the potential for normal development of the dysplastic acetabulum decreases, and the prevalence of acetabular dysplasia increases with age at hip reduction [27]. Up to 19% residual dysplasia may occur even in patients successfully treated with a Pavlik harness[28]. In infants diagnosed with DDH after 6 months of age, or who have failed Pavlik harness treatment for hip reduction, the next step in the treatment algorithm is closed reduction and hip spica casting. In patients treated with closed or open reduction, residuel dysplasia rate increases by 22% to 33%, respectively, and this rate increases significantly in pelvic osteotomies[29,30]. While only 7% of the procedures performed in our clinic before 2010 were closed reduction and spica casting, this rate increased to

40% after the screening program. The rate of pelvic osteotomies decreased from 75% to 30% during this period.

In patients with persistent acetabular dysplasia, pelvic and femoral osteotomies may be indicated to provide normal development of the acetabulum and prevent or minimize the risk of adult coxarthrosis. Although the timing of osteotomy is not accurately defined, the variation in age and acetabular index may help us predict the development of acetabular dysplasia in adulthood. Femoral osteotomies are designed to reorient the femoral head by increasing derotation and varus to stabilize and stimulate acetabular development. Furthermore, experimental studies have shown that these procedures also increase acetabular volume[31,32]. Pelvic osteotomies are designed to increase femoral head coverage in the acetabulum, maintain concentric reduction, and reduce the risk of developing degenerative hip arthritis. But this risk cannot be eliminated. Thomas et al. reported that 23.8% of patients treated with Salter's osteotomy required total hip arthroplasty (THA) 40 years after acetabuloplasty [33]. Similarly, Steppacher et al. stated that after 20 years of follow-up of patients with pelvic osteotomy, 38% of patients needed THA[34]. In our study, the rate of pelvic osteotomy among procedures performed for DDH decreased from 75% to 30%.

The requirement of surgical intervention for DDH in Germany has decreased from 1 per 1000 live births to 0.26 per 1000 live births since the start of the national screening program[20]. In Austria, the benefit of the universal screening program was associated with a lower rate of surgical interventions for DDH[19]. 5-year surveillance data in Germany reported that about 0.14 (55%) of 0.26 surgical procedures per 1000 live births were for cases diagnosed early by the ultrasound screening programme.[20] This group may represent some patients who would not benefit from early conservative treatment.

There were some limitations in our study. Data on patients treated with Pavlik harness were absent. In addition, we did not have national data. Data were limited to the patient population in the Eastern Mediterranean region of Turkey. We did not evaluate the long-term outcomes and dysplasia rates of the procedures. Our aim in the study was not to compare screening programs but to evaluate the effect on surgical procedures.

5. Conclusions

In our study, although there was no significant decrease in the number of procedures performed in the operating room after the selective screening program, there was a significant decrease in the number and rate of pelvic osteotomies. The significant achievement of the national screening program is the earlier diagnosis of patients and the reduction in the rate of major surgical procedures.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Cukurova University Faculty of Medicine Ethics Committee. (2022-121-54)

Conflict of interest statement

Author declare that they have no financial conflict of interest with regard to the content of this report.

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Author contributions

Concept/Design, Data acquisition, Data analysis and interpretation, Drafting manuscript, Critical revision of manuscript and Final approval and accountability: BK, ÖSB, VCK, AM, MB, CÖ

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The Role of Corynebacterium in The Etiology of Granulomatous Mastitis

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Abstract

Aim: Granulomatous mastitis (GM) is a rare, benign, chronic inflammatory illness of the breast. It is characterized by necrotizing granulomatous lobulitis of the breast that clinically mimics breast cancer. In this study, we aimed to examine the existence of Corynebacterium strains thought to be covered in the etiology of idiopathic granulomatous mastitis.

Methods: We retrospectively analyzed the results of 201 breast tru-cut biopsies carried out for diagnostic purposes in the Department of General Surgery. The tissue samples of 41 patients with histopathologically diagnosed GM were examined by Gram staining. The existence of Corynebacterium kinds was investigated microscopically by adding appropriate medium.

Results: The mean age of 41 female patients with GM was 35.7 years and the age range was 20-58 years. Corynebacterium amycolatum was defined as the causative microorganism after microbiologic examination of the tissue sample of only one patient (2.4%).

Conclusions: We consider that Corynebacterium is not the etiologic agent of GM. Additionally studies with large case series are needed to explain the etiology.

Keywords: *Mastitis, Corynebacterium, Granulomatous mastitis.*

1. Introduction

Granulomatous mastitis (GM) is a rare chronic inflammatory illness of the breast first defined by Kessler and Wolloch in 1972[1]. It is characterized by necrotizing granulomatous lobulitis of the breast that clinically mimics breast cancer. Kessler and Wolloch thought that the local immune response against secretions extravasated from the lobules played a role in the pathogenesis because most patients diagnosed with GM were in the lactation period at the onset of symptoms or had given birth before[2]. Infectious agents such as tuberculosis, histoplasmosis, corynebacterium, and Wegener's granulomatosis, sarcoidosis and diabetes mellitus (DM) have been recommended to play a role in the etiology[3].

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Microbiologic diagnosis of corynebacterium lipophilic kinds, which are considered to play a role in the etiology of GM, is difficult due to their long incubation period and difficult isolation from breast tissue samples. Since most antimicrobial agents are hydrophilic, the treatment of GM caused by corynebacterium is difficult, and these patients usually undergo multiple surgical procedures and have a history of repeated antibiotic use over months to years[4].
The aim of this study was to determine the kinds of microorganisms isolated from GM patients, to examine the effectiveness of antibiotherapy on infection control, and to investigate whether surgical intervention was required.

2. Materials and methods

This study was confirmed by Dicle University Ethics Committee (07/01/2021-158). In this research, the consequence of 201 breast tru-cut biopsy materials analyzed in order to diagnostic aims in the outpatient clinic of the Department of General Surgery between December 2018 and September 2020 were retrospectively analyzed. The records of 41 patients with histopathologically diagnosed granulomatous mastitis whose contact data were obtained were resolved in detail.

Clinical findings such as mean age, age range, place of residence (urban/rural), symptoms, duration of symptoms, affected breast, total breastfeeding duration, number of live births, breastfeeding history, pregnancy and lactation status at presentation, story of trauma, oral contraceptive use (OCS), smoking and alcohol use, comorbidities (hypertension, diabetes mellitus, cerebrovascular disease), and treatment modality were investigated. In addition, tuberculosis vaccination, previous story of tuberculosis, family story of tuberculosis and ultrasonographic findings were evaluated in detail.

Examination of Breast Tissue Samples in Microbiology Laboratory

No new investigational biopsies were taken from any patient for the study. The tru-cut biopsy tissue samples were sent to the microbiology laboratory in anaerobic transport container. The tissue pieces were placed in a sterile mortar and first dissected with a sterile scalpel. The sample was then crushed by adding approximately 1 ml of liquid medium. Homogenized samples were processed for aerobic and anaerobic culture. Sections prepared from the specimens were examined by Gram staining. In the microscopic examination, the staining characteristics of the microorganisms present, their shape and the number of microorganisms present, the presence and density of leukocytes were noted. Antibiotic susceptibility tests were performed for Corynebacterium species that were predominantly grown in pure culture with numerous leukocytes and bacteria in the microscope image.

Disk diffusion method was used for antibiogram. Antibiogram conclusions were interpreted in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations for the year in which the strain was isolated.

3. Results

Demographic characteristics and clinical findings of 41 patients who were retrospectively analyzed in our study are summarized in Table 1. It was observed that the average time between the onset of the patients' complaints and their presentation to the hospital was 65. 3 days. The birth rates of the patients and the percentage of the number of children they had are shown in Table 2. All patients who gave birth had a history of breastfeeding and all reported breastfeeding from both breasts for the same duration. No patient was pregnant or lactating at the time of admission to the hospital.

Two of the patients (4.9%) stated that they had received trauma to the diseased breast in the past. Oral contraceptive use was present in 9 patients, while 16 patients (39%) had a story of smoking. None of the patients had a story of alcohol use. The treatment received by 22 of the patients for the symptoms of the disease is shown in detail in Table 2. It was also detected that all patients had received tuberculosis vaccine (BCG) according to the national vaccination program, 1 patient (2.4%) had a story of previous tuberculosis and 3 patients (7.3%) had a family story of tuberculosis.

Ultrasonographic findings showed that the most common finding was abscess (48. 8%) followed by irregular hypoechoic lesion with multiple tubular extensions (41. 4%). Other findings included edema and thickening of the skin (36.6%), fistulization of the skin (29.3%), benign lymphadenopathy in the axilla on the same side (14.6%), ductal dilatation (14.6%), and heterogeneous fatty tissue with increased echogenicity (9.7%). The size of the lesions measured on USG ranged from 5 mm to 4.5 cm.

Tru-cut biopsy specimens of all patients were processed in the microbiology laboratory for aerobic and anaerobic culture by adding appropriate media. Microbiologic investigation of the tissue sample of one patient (2.4%) identified Corynebacterium amycolatum as the causative microorganism. The disk diffusion test for Corynebacterium amycolatum showed that this patient was resistant to Penicillin G, Ciprofloxacin and Rifampicin.

Cefuroxime 500 mg 2x1 orally for 14 days was administered to 38 patients who presented with signs of inflammation in the breast. Surgical drainage was performed in 2 patients with abscess, 1 patient did not receive any treatment. Following the pathology results as idiopathic granulomatous mastitis, 1 patient (2.4%) underwent mass excision, 35 patients (85.4%) were started on steroid treatment, 1 patient (2.4%) with Corynebacterium amycolatum growth in tissue samples was treated with moxifloxacin 400 mg/day 1x1, and 4 patients (9.8%) did not receive any additional treatment. After 14 days of antibiotic treatment, 2 of 4 patients (4.9%) who were not given additional treatment developed recurrence during follow-up. One of the patients developed recurrence 5 months after response to the first treatment and the other patient developed recurrence 4 months later. Two patients with recurrence were also treated with steroids.

Table 1

Demographic characteristics and clinical findings of the patients

Total number of patients	41
Mean age of the patients	35.7
Age range	20-58 years
Age distribution	(40^+) 29.3 %
	(40^-) 70.7 %
Patients' place of residence	Urban 73.2 %
	Rural 26.8 %
Symptoms	Rash 73.1 %
	Swelling 60.9 %
	Pain 48.7 %
	Discharge 41.4 %
Site of involvement in the breast	Right Breast 43.9 %
	Left Breast 56.1 %
	Bilateral 0%

Table 2

Birth rates, number of children (%), comorbidities and treatment status of the patients.

Birth rates	Never given birth before (17.1 %)
	Gave birth before (82.9 %)
Number of births	1 birth: 8 patients
	2 births: 7 patients
	3 births: 11 patients
	4 births: 6 patients
	5 births: 2 patients
Comorbidities	Hypertension: 5 patients
	Diabetes mellitus: 4patients
	Cerebrovascular disease: 1 patient
Treatment Modality	Antibiotics: 13 patients
	Antibiotics+corticosteroids: 6 patients
	Antibiotics + corticosteroids + surgical excision: 1 patient
	No treatment: 2 patients

4. Discussion

Idiopathic granulomatous mastitis (IGM) is a benign inflammatory disease of the breast whose etiology is not fully understood, whose true incidence is unknown and which may clinically mimic breast cancer[5]. Some authors consider autoimmunity, infection, trauma, trauma, OCS use, ethnicity and lactation in the etiology. The fact that women diagnosed with IGM are frequently under 50 years of age and are diagnosed within 5 years of their last pregnancy suggests that childbirth and breastfeeding are involved in its etiology.

In the study by Al-Khaffaf et al. the mean age of 18 patients diagnosed with IGM was 36 years and more than half of them had a story of delivery within 5 years[6]. Shin et al. reported in their study that the mean age of 34 patients diagnosed with IGM was 37 years, 32 of these patients were in reproductive age, and the mean duration from the last birth to the time of diagnosis was 38 months[7]. Bani-Hani et al. reported that the mean age of 24 patients diagnosed with IGM was 34.3 years and 4 of 22 patients with a story of delivery had active pregnancy at the time of diagnosis[8]. In our study, the mean age of the patients was 35.7 years, 34 patients (82.9%) had a story of delivery and 7 patients (17.1%) were nulliparous. All patients with a story of delivery had a story of lactation. None of the patients were pregnant or lactating at the time of diagnosis.

The fact that most of the patients diagnosed with IGM had a story of childbirth and lactation does not make it possible to explain the etiology only with pregnancy and lactation, considering that the disease is observed in a wide range of ages including 11-83 years[8]. Although it has been reported in the literature that some patients diagnosed with IGM used OCS, no relation was found between OCS use and IGM[5]. In the study by Shin et al. 5 out of 34 patients (14.7%) used OCS[7], in the study by Barreto et al. 15 out of 90 patients (17.2%) (73), and in the study by Girgin et al. 9 out of 49 patients (18.4%) had a story of OCS use (9). In our study, 9 patients (21.9%) had a story of OCS use.

In studies, smoking has been considered to be a factor in the etiology of IGM. It was reported that 8 of 49 patients (16.3%) in Girgin et al.'s study[9], 4 of 8 patients (50%) in Özel et al.'s study[10], and 7 of 75 patients (9.33%) in Jieqing Li's study[11] had a story of smoking. In our study, 16 of 41 patients (39%) had a story of smoking.

Autoimmunity, local trauma, sarcoidosis, diabetes mellitus have been observed as triggering factors in the etiology of IGM. Girgin et al. 49 patients did not report a story of local trauma, DM, autoimmune disease[9]. In a study conducted by Özşen et al. on 90 patients, it was reported that sarcoidosis was diagnosed in 1 patient[12]. In our study, 4 patients had a story of DM and 2 patients had a story of local trauma to the diseased breast in the past.

Tuberculous mastitis is a rare clinical entity that frequently affects African and Indian women. It may be a part of systemic tuberculosis or may present as isolated mastitis. Agarwal et al. reported that tuberculosis was responsible for the etiology in 4 out of 10 patients diagnosed with GM[13]. Tuberculosis was found in 9 out of 34 patients in the study by Shin et al.[7], 1 out of 90 patients in the study by Özşen et al.[12], 27 out of 33 patients in the study by Chandanwale et al.[14], and tuberculosis was not detected in any patient in the studies by Prasad et al.[15], which included 73 patients, and Girgin et al.[9], which included 49 patients. In our study, 1 patient (2.4%) had a history of previous tuberculosis. In our study, PPD test after histopathologic diagnosis and ARB results in sputum for 3 consecutive days were negative in all patients.

A review of the literature reveals that large case series of GM have been reported from the Middle East, Mediterranean countries, Asia and the Americas. The high prevalence of GM among women of Asian, Hispanic and Arab origin has led to a debate about ethnicity[16]. In the study published by Al-Khaffaf et al. in 2008, it was reported that 10 (56%) of 18 patients diagnosed with IGM were Caucasian, 5 (28%) were Asian, 2 (11%) were Afro-Caribbean and 1 (5.5%) was of Central Asian origin[6]. In a study conducted by Gautier et al. in 2013, it was reported that 5 of 11 patients were of Canadian, 2 of Latin American, 2 of Arab and 1 of Russian origin[5]. In our study, all patients lived in the Southeastern Anatolia Region, 30 patients (73.2%) lived in urban areas and 11 patients (26.8%) lived in rural areas.

The normal endogenous bacterial flora of the breast is similar to that of the skin. Coagulase-negative Streptococci, Propiniobacterium species and Corynebacterium species are the dominant microorganisms[17]. Since Corynebacterium species are a member of the normal skin flora, their isolation in cultures of breast tissue samples of patients diagnosed with GM is considered contamination[18]. Taylor et al. reported a striking association between GM and Corynebacterium. In a study of 34 patients with GM, he described a histologic type that included granulomatous and neutrophilic inflammation surrounding a central lipid/cystic area. Gram positive bacilli were detected in these cystic cavities. It was reported that Corynebacterium species were isolated from 52 of 116 tissue samples obtained from these 34 patients with an average of 3.44 tissue samples. When compared with the control group, a significant difference was found[19].

Funke et al. in their study in 1997, argued that in order to associate Corynebacterium species with a disease, Corynebacterium should be observed in a tissue sample taken under sterile conditions. They also suggested that polymorphonuclear leukocyte reaction and gram-positive bacilli should be present to consider infection due to Corynebacterium[20].

In the study of Dobinson et al., C. kroppenstedtii was isolated most frequently with 10 patients and C. tuberculostearicum was isolated second frequently with 4 patients[4]. In a study conducted by Shoyele et al. on 7 patients, C. amycolatum was isolated in the tissue sample of one patient[18]. In the study by Troxell et al. Corynebacterium was isolated in 3 of 35 patients with a diagnosis of GM[21]. In the study by Taylor et al. C. kroppenstedtii was isolated in 13, C. tuberculostearicum in 10 and C. amycolatum in 2 of 28 patients diagnosed with GM[19]. Kıvılcım et al. reported that no bacterial DNA belonging to any normal skin flora including Corynebacterium was detected in tissue samples in a study conducted on 51 patients[20].

Paviour et al. reported that Corynebacterium was isolated in 24 patients and C. kroppenstedtii, C. tuberculostearicum and C. amycolatum strains were isolated in 13, 3 and 3 of these patients, respectively. They stated that most of the patients received antibiotherapy with more than one surgical procedure. In this study, 1 patient in whom both C. kroppenstedtii and C. amycolatum were isolated from tissue samples was treated with intravenous penicillin for 3 weeks. Subsequently, doxycycline 100mg orally with high fat solubility was administered as there was no response to treatment. After doxycycline treatment, surgical intervention was not needed in this patient[22].

In a case report of breast abscess with fistula formation, Butta et al. performed abscess drainage and fistula excision, continued the treatment with amoxicillin+clavulanic acid 1000mg (875/125mg) and doxycycline 200 mg for 7 days upon isolation of C. amycolatum in the tissue sample and reported that the patient responded fully to the treatment and recovered completely[23].

In our study to investigate the role of Corynebacterium strains in the etiology of granulomatous mastitis, tissue samples obtained from 41 patients were examined microscopically in terms of the number of microorganisms, staining characteristics and shapes of the existing microorganisms, and C. amycolatum was isolated from only 1 patient (2.4%). According to the disk diffusion test result for antibiogram, moxifloxacin 400mg/day treatment was given to this patient and a successful treatment was provided. After initial cefuroxime treatment, 2 of 4 patients who were not given any other treatment had recurrence and were treated with steroids. When the last treatment in which the patients in our study showed improvement is analyzed; cure was achieved with steroid treatment in 90.3% of the patients.

In our study, we investigated tissue culture samples for many microorganisms, especially Corynebacterium strains. At the end of the study, we observed that C. amycolatum was isolated from the tissue

samples of only one patient and most of the patients were cured with steroid treatment.

5. Conclusions

Corynebacterium, which has been considered as a contamination in the past, but is thought to be the causative agent of granulomatous mastitis etiology by various studies, was isolated from the tissue culture of only one of the 41 patients in our study. Failure to demonstrate the presence of Corynebacterium in the studies performed with molecular methods has led us away from the thesis that Corynebacterium is the causative agent in the etiology of GM. The etiology of idiopathic granulomatous mastitis is still unclear and further studies with large case series are needed.

Statement of ethics

The study was approved by the Ethics Committee of Dicle University Ethics Committee (07/01/2021-158)

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Retrospective Analyzing of Anesthesia Managements in Robotic Assisted Radical Prostatectomy Cases

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Abstract

Aim: In our study, we aimed to investigate anesthesia management, hemodynamic changes and complications that may occur due to steep trendelenburg, pneumoperitoneum and surgery in RARP patients operated in Akdeniz University School of Medicine, and to evaluate our initial results.

Methods: Patients who underwent RARP operation with the diagnosis of prostate adenocarcinoma by the Urology Clinic at Akdeniz University School of Medicine between January 2015 and February 2018 were evaluated retrospectively. Patient's demographic data, intraoperative hemodynamic and respiratory data, postoperative transfer sites, extubation times, post-extubation blood gas values, complications and discharge times were recorded. Obtained data were analyzed with IBM SPSS® 23.0 program.

Results: We found that mean age of the 131 patients included study was 62 years, and mean BMI was 27,6 kg/m^2. Also we found that 47 of patients were ASA-I, 69 of patients were ASA-II and 15 of patients were ASA-III. After general evaluation, it was seen that HR, SBP, DBP and MAP decreased significantly in intraoperative period in all patients. There was also a significant decrease in pH and increase in pCO_2 in patients due to pneumoperitoneum. In our study, we found that the most common postoperative complication was nausea and vomiting, and the second common was anastomotic leakage. However, none of our patients had a permanent complication.

Conclusions: In order to manage anesthesia in RARP, it is necessary to know the physiologic effects of trendelenburg position and pneumoperitoneum on the systems and physiological changes in old age.

Keywords: *Anesthesia, Robotic surgery, Prostatectomy*

1. Introduction

With the integration of advancements in technology into the field of medicine, diagnostic and treatment methods continue to evolve. Today, robotic-assisted surgical applications can be adapted to almost all surgical procedures. Among these, robotic-assisted radical prostatectomy (RARP) is the most frequently performed. RARP provides various advantages, such as facilitating micro-anastomosis in tight spaces through the movement capabilities of robotic arms, less bleeding, providing a more comfortable working area for the surgeon, along with other benefits offered by laparoscopic methods[1,2]. However, there are main disadvantages like the necessary steep Trendelenburg position, the implementation of pneumoperitoneum, and the long duration of surgery. Specifically, the deep Trendelenburg position and the added pneumoperitoneum have numerous physiological effects (on the cardiovascular system, respiratory system, central and peripheral nervous system, endocrine system, urinary system). In addition, the patient group on which RARP is applied generally consists of elderly patients with additional diseases. Considering all these effects, anesthesia management of RARP is quite a challenging process[3]. In this study, we aimed to analyze our anesthesia practices in RARP cases operated by the Urology Clinic at the Akdeniz University Faculty of Medicine Hospital, focusing on patient positioning, pneumoperitoneum, potential hemodynamic changes, and complications related to surgery, and to evaluate our preliminary results. Accordingly, we aimed to review the issues that should be considered during our anesthesia applications in RARP surgeries at our clinic.

2. Materials and methods

In this study, patients who underwent robotic-assisted radical prostatectomy (RARP) for the diagnosis of prostate adenocarcinoma at the Akdeniz University Faculty of Medicine between January 2015 and February 2018 were evaluated retrospectively. All patients were informed by the surgical and anesthesia teams before the operation, and necessary surgical and anesthesia consents were obtained. Following the acquisition of necessary permissions from

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the chief physician to examine hospital records and the ethical committee approval no. 156 dated 01.03.2017, data collection began. Patients' preoperative and postoperative examination records and laboratory data were accessed using the MIA-MED® program, which is the data database of Akdeniz University Hospital; intraoperative data were obtained by examining anesthesia monitoring forms for the operation. Also, records of the Anesthesia Intensive Care Unit (ICU) and Post-Anesthesia Care Unit (PACU) of Akdeniz University Hospital were reviewed for the data related to the patients' extubation.

In the preoperative evaluation, demographic data (age, weight, height, BMI), ASA classification, and presence of comorbid diseases (coronary artery disease, COPD/Asthma, hypertension, diabetes, others) were included.

In the intraoperative evaluation, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), peripheral oxygen saturation (SpO_2), and End-tidal carbon dioxide ($EtCO_2$) values were recorded hourly from the time of the patient's intubation until the patient was removed from the operating room, using anesthesia monitoring forms (Dräger Infinity® Delta). Arterial blood gas data (pH, pO_2, pCO_2, lactate) were recorded immediately after arterial catheterization, hourly for the next two hours, and then every two hours. Arterial blood gas measurements were made with the Siemens Rapidlab® 1200 device available in our hospital. The amounts of crystalloid and colloid given to the patient during the intraoperative process, the amount of blood transfusion if performed, anesthesia time, and operation time were also recorded. The operation time was considered as the time from the initial skin incision to the moment when the robotic system was separated from the patient, and all skin incisions were sutured. The anesthesia time was considered as the time from the beginning of the induction of anesthesia until the patient was removed from the operating room. Since all evaluated patients were transferred to the intensive care unit or post-anesthesia care unit, extubation was not considered the end of anesthesia.

During anesthesia induction, 1mg/kg lidocaine, 5-7 mg/kg sodium thiopental, 2-10 mcg/kg fentanyl and 0.6 mg/kg rocuronium are administered. After intubation, invasive arterial monitoring and other monitoring procedures are performed if necessary. Immediately after induction, 10 mg metoclopramide and 50 mg ranitidine are administered. For anesthesia maintenance, sevoflurane is administered at a concentration of 1-2%, and remifentanil is administered as an analgesic at a dose of 0.5-2 mcg/kg/min. Muscle relaxant infusion is not administered. Gastric emptying is provided to all patients by inserting a nasogastric tube without positioning after induction.

According to the operation protocol, the patients were fixed in a supine position, with arms adducted on both sides and legs lateralized at approximately 45 degrees. The patient was given a 35-40 degree Trendelenburg position; Protective measures have been taken against nerve and organ damage. Pneumoperitoneum is created by insufflation of CO2 to an intra-abdominal pressure of approximately 12±3 mmHg.

Mechanical ventilation was provided with a Dräger Primus® anesthesia workstation. Patients are routinely ventilated in VCV mode, 50% air - 50% oxygen mixture, 3 l/min fresh gas flow, 8 ml/kg tidal volume, 12 respiratory rate, 5 cmH2O PEEP pressure, 1:2 inspiration:expiration (I:E) ratio and with a maximum peak pressure of 40 cmH2O. Ventilation settings were changed to keep EtCO2 30-40 mmHg throughout the operation.

Regarding to postoperative data, the location where the patient was transferred after the operation (ICU or PACU), the time of extubation after transfer, arterial blood gas data (pH, pO_2, pCO_2, lactate) taken one hour after extubation, any postoperative complications developed (nausea-vomiting, peripheral nerve damage, vision loss, subcutaneous emphysema, compartment syndrome, infection, anastomotic leak, etc.), and discharge times were noted.

2.1. Statistical Analysis:

For statistical analysis, the descriptive statistics of the data used mean, standard deviation, minimum, maximum, median, frequency, and ratio values. Significance tests used include Student's T test for the analysis of quantitative data, Paired samples T test for the analysis of repeated measures, and the Mann Whitney U test and Wilcoxon Matched-Pairs test for the evaluation of categorical data. Analyses were conducted using the IBM SPSS® 23.0 program. A $p<0.05$ value was considered statistically significant.

3. Results

The study included 131 patients with an average age of 62.9±6.5 years, average body weight of 83.2±10.3 kg, average height of 1.73±0.05 meters, and average Body Mass Index (BMI) of 27.7±3.2 kg/m^2. The average duration of anesthesia was found to be 322.1±73.1 minutes and surgical time was 270.7±69.4 minutes (Table 1).

HR, SBP, DBP, MAP, $EtCO_2$, and SpO_2 values were obtained for the patients at the time of pre-induction of anesthesia (0^{th} hour) and each hour intraoperatively until the end of the operation. To statistically evaluate the changes in the obtained data, 0^{th} hour data were compared separately with data from 1^{st}, 2^{nd}, 3^{rd}, 4^{th}, 5^{th}, and 6^{th} hours (Table 2).

At the same time, arterial blood gas (ABG) data (pH, pO_2, pCO_2, and lactate) were obtained during the intraoperative period of the patients. Again, ABG data were compared to the 0^{th} hour at 1^{st}, 2^{nd}, 4^{th}, and 6^{th} hours respectively (Table 3).

Table 1

Demographic data of the patients

Age	62.9±6.5
Weight (kg)	83.2±10.3
Height (m)	1.73±0.05
BMI (kg/m^2)	27.7±3.2
Anesthesia Duration (min)	322.1±73.1
Surgical Duration (min)	270.7±69.4
Comorbidities (n:85)	Hypertension (61.2%)
	Diabetes Mellitus (32.9%)
	Coronary Artery Disease (23.5%)
	Asthma/COPD (10.6%)
	Other (15.3%)
American Society of Anesthesiologist (ASA) Classification	ASA I (35.9%)
	ASA II (52.6%)
	ASA III (11.5%)

COPD: Chronic obstructive pulmonary disease

Various data evaluated during the intraoperative and postoperative periods of the patients are provided in Table 4. It was found that none of the patients included in the study developed respiratory insufficiency ($pO_2<60$ mmHg or $pCO_2>50$ mmHg) after extubation. It was also found that none of the patients had postoperative peripheral nerve damage, vision loss or compartment syndrome, which could potentially occur due to RARP, until discharge.

The average day of hospital discharge postoperatively for the patients was found to be 5.9±2.6 days. However, there are prolonged hospital stays of 23 days for one patient due to a postoperative infection, and 15 and 20 days for two patients due to postoperative anastomotic leakage. Therefore, these patients were removed, and the average day of discharge was recalculated and found to be 5.6±1.6 days.

Table 2

Hemodynamic and respiratory data and intraoperative changes

	SBP	p value¶	DBP	p value¶	MAP	p value¶
0th hour	144.7±19.9		90.2±13.4		108.2±14.7	
1st hour	120.0±16.0	*0.000*	73.8±10.4	*0,000*	89.3±11.5	*0.000*
2nd hour	121.1±11.3	*0.000*	75.5±9.2	*0,000*	90.7±9.2	*0.000*
3rd hour	123.8±12.0	*0.000*	76.7±10.7	*0,000*	92.4±10.3	*0.000*
4th hour	124.5±12.1	*0.000*	77.5±10.5	*0,000*	93.1±9.4	*0.000*
5th hour	120.8±11.9	*0.000*	76.6±9.3	*0,000*	91.3±9.4	*0.000*
6th hour	119.3±11.1	*0.000*	76.1±8.9	*0,000*	90.4±8.8	*0.000*
	HR	p value¶	SpO_2	p value¶	$EtCO_2$	p value¶
0th hour	77.9±12.8		99.08±1.05		30.88±3.15	
1st hour	70.9±10.0	*0.000*	99.06±1.03	0.719	31.70±3.15	*0.001*
2nd hour	69.4±9.9	*0.000*	99.08±1.20	1.000	32.16±2.95	*0.000*
3rd hour	69.8±9.9	*0.000*	99.19±1.03	0.204	31.83±3.23	*0.002*
4th hour	70.3±10.3	*0.000*	99.24±0.95	*0.044*	31.52±3.20	0.064
5th hour	69.9±9.5	*0.000*	99.29±1.04	*0.013*	30.93±3.17	0.303
6th hour	70.0±10.3	*0.001*	99.36±0.94	*0.021*	29.90±3.12	0.185

* p<0.05, ¶ Compared to basal value

Table 3

ABG parameters and intraoperative changes

	pH	p¶	pO_2	p¶	pCO_2	p¶	Lactate	p¶
0th hour	7.45±0.03		181.5±69.6		33.1±3.6		1.24±0.43	
1st hour	7.43±0.05	*0.000*	161.9±55.5	*0.000*	36.5±4.9	*0.001*	1.22±0.40	0.363
2nd hour	7.39±0.05	*0.000*	167.8±47.9	*0.020*	37.1±4.9	*0.000*	1.24±0.44	0.981
4th hour	7.38±0.05	*0.000*	169.5±50.5	0.069	36.7±5.5	*0.000*	1.24±0.51	0.864
6th hour	7.39±0.06	*0.000*	172.1±41.3	0.506	35.1±5.3	0.118	1.35±0.61	0.172

* p<0.05, ¶ Compared to basal value

Table 4

Intraoperative and postoperative data

Av. Intraoperative Fluids Administered (ml)	•Balanced Crystalloid (3419±776.6) •Colloid [Gelatin Polysuccinate] (600±210.8)		
Amount of Blood Transfusion (n:1)			2 Units
Effect of Learning Process	Patient no 1-66	Patient no 67-131	p Value
Anesthesia Dur. (min)	364.4±73.6	279.1±40.4	***0.000****
Surgical Dur. (min)	311.8±68.3	229±39.4	***0.000****
Postoperative Condition	Post-Anesthesia Care Unit (n:110) Intensive Care Unit (n:21)		
Av. Extubation Time (min)			104.7±38.4
Complications	•Nausea-Vomiting (8.4%) •Anastomotic Leakage (2.3%) •Subcutaneous Emphysema (2.3%)		

* p<0.05

4. Discussions

The number of cases undergoing RARP is increasing every day due to its superiority over open prostatectomy[4,5]. The deep Trendelenburg position and pneumoperitoneum necessary for RARP to be performed have various effects on organ systems and hemodynamic systems[2,3,6,7]. In our study, we found a statistically significant decrease in HR, SBP, DBP, and MAP parameters at all intraoperative hours compared to the basal value in the comparison we made to see the hemodynamic effects of the deep Trendelenburg position and pneumoperitoneum. Two studies investigating the cardiac and respiratory effects of RARP operations found that MAP increased when Trendelenburg and pneumoperitoneum started, but began to decrease over time and significantly dropped below the basal MAP value[7,8]. Danic et al.[9] found a statistically significant decrease in HR and MAP after Trendelenburg and pneumoperitoneum in their retrospective study of 1500 cases related to anesthesia management in RARP operations. MAP generally increases with the start of Trendelenburg and pneumoperitoneum, but decreases over time and can drop below the basal value at the end of surgery. In our study, unlike other studies, we believe that the likely reason for MAP values being lower than the basal value at all compared time intervals is that while other studies, being prospective, divided the time intervals into moments like before Trendelenburg, the moment of Trendelenburg, 5 minutes after Trendelenburg, 15 minutes later, 60 minutes later, our study was retrospective, so we were not able to access these time intervals. Therefore, we compared the preoperative value with the intraoperative 1st hour, 2nd hour, 3rd hour, and so on. In our study, to observe the effects of the deep Trendelenburg position and pneumoperitoneum on the respiratory system and gas exchange, no statistically significant difference was found between the patients' basal SpO_2 values and the 1st hour, 2nd hour, and 3rd hour SpO_2 values. However, the SpO_2 values at the 4th, 5th, and 6th hours were found to be statistically significantly higher than the basal SpO_2 value. Despite these statistically significant SpO_2 elevations, there has been no change in amounts that have clinical importance. Lebowitz et al.[10] found no statistically significant difference between the SpO_2 values at preoperative and during the start and continuation of Trendelenburg in their study to examine gas exchange in RARP operations. Similarly, Bozkırlı et al.[11] also found no statistically significant difference between SpO_2 values. When $EtCO_2$ values were compared in our study, the 1st, 2nd, and 3rd hour intraoperative $EtCO_2$ values were statistically significantly higher than the basal $EtCO_2$ value, while no statistically significant difference was found between the 4th, 5th, and 6th hour $EtCO_2$ values and the basal $EtCO_2$ value. Kadono et al.[7] showed that $EtCO_2$ values statistically increased with the addition of pneumoperitoneum and the Trendelenburg position and returned to basal values with desulfation, and

they also found no correlation between the degree of Trendelenburg and $EtCO_2$ values. Lestar et al.[12], in a study examining the effects of the Trendelenburg position in RARP cases, found that $EtCO_2$ values were statistically significantly higher than the basal value from the beginning of pneumoperitoneum to the end of the operation, despite the absence of acid-base anomaly and stable pCO_2 values. In our study, similar to $EtCO_2$ values, patients' 1st, 2nd, and 4th hour intraoperative pCO_2 values were found to be statistically significantly higher than the basal pCO_2 value. The 6th hour pCO_2 value was higher than the basal pCO_2 value, but no statistically significant elevation was found. As expected, with the increase in pCO_2 values, the patient's intraoperative pH values at all hours were found to be statistically significantly lower than the basal pH value. In addition, it was also seen that no patient developed a serious acid-base balance disorder. Only the decrease in pO_2 values at the 1st and 2nd hours intraoperatively were found to be statistically significant. Lebowitz et al.[10], in a study to examine gas exchange in RARP operations, reported that with pneumoperitoneum and the Trendelenburg position, pO_2 values significantly decreased, pCO_2 values significantly increased, and the decrease in pO_2 value could be due to ventilation/perfusion mismatch and possibly interstitial pulmonary edema. They also reported that none of their patients developed hypoxemia or clinically/radiologically evident atelectasis. In our study, we found that an average of 3419±776.6 ml of crystalloid fluid was given to patients during the intraoperative period. Piegelar et al.[13], in a study examining the outcomes of fluid management in patients undergoing RARP surgery, reported similar results to ours, stating they used an average of 3600 ml of fluid intraoperatively. They also found that the risk of anastomotic leakage increased as the amount of fluid used increased, and that the amount of bleeding was independent of the type of crystalloid or colloid used. Ono et al.[14], in an observational study of patients undergoing RARP surgery, reported that an average of 2750 ml of fluid was given during the intraoperative period. Ozgen et al.[15], in a study conducted on patients undergoing RARP procedure, similarly to our study, found that there was no statistically significant change in lactate at any time during surgery. Oksar et al.[16], in a prospective study on RARP patients, divided their patients into two groups as pH<7.35 and pH>7.35 and found no significant change in terms of lactate between the two groups. Similarly, in our study, in parallel with the findings in the literature, it was found that there was no significant lactate elevation at any time period.

When we divided the patients included in our study into two groups considering surgical experience, we found that in the initial surgeries where experience was low, both anesthesia time and surgical duration were statistically significantly longer. In three separate studies related to the learning process in RARP procedure conducted by Raman, Ou, Pouget et al.[17-19], it was observed that as the surgeon's experience increased, the operation time significantly shortened. The most important factor affecting surgical time is the surgeon's experience.[6] These times may vary depending on the experience of the operation team.[13,14,20] In the postoperative period, only 16 of our patients (12.2%) developed complications related to anesthesia or surgery. The most common complications were nausea - vomiting, followed by vesicoureteral anastomotic leakage and subcutaneous emphysema. Danic et al.[9], in their study on patients who underwent RARP operation, reported that the most common postoperative complications were nausea-vomiting and abdominal distention. Piegelar et al.[13] found postoperative nausea - vomiting at a low incidence (1.1%) after the RARP procedure. In addition, Raman et al.[17], in their study on patients undergoing RARP operation, reported that complications developed in 4 patients, which were ileus, small bowel obstruction, and ureteral stricture. In our study, we observed that our patients were discharged on average 5.6±1.6 days postoperatively. In most of the literature, the average discharge day after RARP is seen to be between 1-2. [9,17,21,22] In contrast, Pradere et al.[13] found the average discharge day after RARP to be 3.9 days; Piegelar, Mortevazi et al.[20,23] found the average discharge day after RARP to be 8 days. There seems to be significant differences between centers in terms of discharge days. This difference is thought to be due to being discharged with or after the removal of the Foley catheter. It was observed that all the patients in our study were discharged after the Foley catheter was removed.

5. Conclusions

As seen in our study, RARP procedures are usually performed in older patients and in those with comorbidities. Our study showed that in anesthesia management of patients undergoing RARP, it is necessary to know and carefully manage the physiological effects of the steep Trendelenburg position and pneumoperitoneum on organ systems. Prospective studies are needed to identify the hemodynamic, respiratory or other physiological changes that may be encountered in the anesthesia management of robotic surgical procedures and to identify potential complications.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Akdeniz University Faculty of Medicine Ethics Committee. (2018--70904504) Thesis number: 539125-2018
https://tez.yok.gov.tr/UlusalTezMerkezi/TezGoster?key=as2oTjW5jfr9IKSvmCdJYm_Cb6RsDR9xPYsQINfEaAvvg6vJmgwj2B5gVOlU_sNR

Conflict of interest statement

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Evaluation of preoperative anxiety level of the surgeons

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Abstract

Aim: Preoperative anxiety is a common state experienced by the patients undergoing surgical procedures. Preoperative anxiety can occur not only in patients but also in surgeons. The aim of this study was to evaluate the preoperative anxiety level of the surgeons.

Methods: The study included 100 surgeons, aged 26-64 years. Before attending the first elective operation of the day, the surgeons were asked to fill the State-Trait Anxiety Inventory (STAI) and salivary cortisol sample was taken from them preoperatively. The surgeons also filled the evaluation form that includes information about their surgical department, academic superscription, years of clinical experience in medical sciences, years of clinical experience in relevant department, and the name and the group of the surgery.

Results: One hundred surgeons comprised of 46 assistant doctor, 34 specialists, 15 associate professor, 3 professor and 2 doctor lecturers were participated in the study. The mean STAI-1 score were 39.5 ± 11.2 and the mean STAI-2 were 40.4 ± 8.7. The mean salivary cortisol levels were 12.0 ± 8.1 nmol/l. There was no statistically significant difference between genders, surgical departments, academic superscriptions, years of medical and surgical experiences and surgical procedure groups in terms of STAI-1scores, STAI -2 scores and salivary cortisol levels (p>0.05)

Conclusions: Based on STAI-1 scores, STAI-2 scores and salivary cortisol levels, the preoperative anxiety level of the surgeons did not differ by gender, surgical department, academic superscription, years of medical and surgical experiences and surgical procedure groups.

Keywords: *Anxiety, Cortisol, Preoperative, Surgeon*

1. Introduction

Preoperative anxiety is reported to be present in up to 80% of patients[1]. Safe and qualified patient outcomes are directly related with good performance in the operating room. Surgery is a stressful event not only experienced by patients but also by the surgeons. The stressors that surgeons are exposed to during surgery may be related to technical or equipment problems, teamwork problems, distractions, poor time management, patient related factors and personal factors[2–4]. Anxiety of the patients prior to surgery has been well-studied. However, there are limited data in the literature about preoperative anxiety of the surgeons. In a study conducted in the United Kingdom, it was determined that surgical performance anxiety was very common, and it was associated with worse psychological wellbeing among surgeons[5]. Anxiety consists of physiological, cognitive and behavioral components[6]. Anxiety-related moderate physiological arousal can positively affect performance through increased motivation, attention, and motor skills[7]. On the other hand, performance anxiety can affect cognitive processes such as attentional control, self-focus, and worry. Performance anxiety is experienced not only among surgeons but also in musicians and athletes who are exhibiting skill performance. Surgeons can develop adaptive pre-performance rituals or coping strategies as behavioral responses to performance anxiety like musicians or athletes do[8]. In a study ritual such as a singer listening to the same playlist of songs before every show or a tennis star bouncing a tennis ball a certain number of times before serving are shown to improve performance by reducing anxiety[9]. The coping strategies used by surgeons can be summarized as: early recognition of risks, stop and stand back, control of self and control of the situation[2]. Although pre-performance rituals and coping strategies are useful in reducing anxiety, in some cases a surgeon's over-dependence on certain rituals may have detrimental effects in the longer term[8]. Spielberger's State-

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Trait Anxiety Inventory (STAI) has been a validated tool for examination of preoperative anxiety[10]. Cortisol is a stress hormone secreted from the adrenal cortex. Salivary cortisol levels accurately reflect free and active cortisol blood levels[11]. The assessment of salivary cortisol is used in studies for evaluating preoperative anxiety[12,13]. In this study the first question was 'Does the surgeons have preoperative anxiety like the patients have?'. The other questions were whether this preoperative anxiety was related with gender, surgical department, academic superscription, years of medical and surgical experiences and surgical procedure groups. Our aim in this study was to evaluate the preoperative anxiety level of the surgeons by using STAI scale and determining the salivary cortisol levels.

2. Materials and methods

The study was approved by the Ethics Committee of Adana City Training and Research Hospital (approval no.746 on March 11, 2020) and registered at ClinicalTrials.gov. One hundred surgeons aged 26-64 years were enrolled in this study. Surgeons were consisted of those performing operations in general surgery, obstetrics and gynecology, pediatric surgery, urology, orthopaedic surgery, ophthalmology, otorhinolaryngology, plastic and reconstructive surgery, gynecologic oncology, surgical oncology, cardiovascular surgery and neurosurgery. Their academic superscriptions were specialist, assistant doctor, doctor lecturer, associate professor, and professors. The study was conducted between November 2020 and December 2021. Surgeons, who would perform the first elective operation of the day and accepted to participate, were included into the study. Surgeons who were non volunteers and who had a history of anxiolytic, antidepressant drug usage were excluded. While the first elective patients of the day were admitted to the operating rooms and were being prepared by the anesthesiology team, informed consents were obtained from the surgeons. Salivary cortisol samples were taken from them, and they were asked to fill the evaluation form, STAI-1 (state anxiety section) form and STAI-2 (trait anxiety section) form. Participants in the study were selected among surgeons who had not eaten, drank anything other than water, or smoked 1 hour before saliva collection to eliminate the risk of affecting their cortisol levels. During saliva collection, surgeons were given a small amount of cotton and were asked to chew the cotton and place it in a sterile tube. As soon as the salivary cortisol samples were taken, the samples were numbered and delivered to the central laboratory by transportation, keeping the identity of the surgeons confidential. Salivary cortisol levels were measured with competitive immunoenzymatic colorimetric method, by using cortisol kits (DiaMetra Cortisol Salivary kits), Next Level Alisei (Italy) device. Each surgeon started the operation in 15 minutes after giving samples for salivary cortisol and filling the study forms. There are so many issues which affect to the anxiety such as hunger state, to be on duty the night before. Optimizing these conditions are very difficult. STAI and salivary cortisol levels were used as the subjective and objective measurements of preoperative anxiety in our study. STAI is a questionnaire consisted of two separate subsections of 20 items which measures state and trait anxiety. State anxiety is described as the degree of anxiety at a particular time and in a particular situation. The degree of anxiety in individual experiences in general is described as Trait anxiety[10]. The scores of STAI -1 and STAI-2 differs between 20 and 80. A STAI score of 20-37 is defined as no anxiety or low anxiety, a score of 38-44 is defined as moderate anxiety, a score exceeding 45 is defined as high anxiety by Spielberger[14]. The evaluation form consisted of the following information: age, gender of the surgeon, surgical department, academic superscription, years of clinical experience in medical sciences, years of clinical experience in relevant department, and the name and group of the surgery which was going to be performed.

2.1. Statistical analysis

A priori power analysis was made with statistical package program G*Power 3.1.9.7 (Franz Faul, Universitat Kiel, Germany); an effect size (0.35) was chosen between the medium (0.25) and large (0.4) effect sizes that Cohen standardized for ANOVA. The minimum sample size was found to be 93, with the number of groups being 3, the desired power being 85%, the effect size being (f)=0.35 and α =0.05. For those who may be excluded from the study for various reasons during the study, the sample size was increased by approximately 10% to 100. The study was conducted in a training and research hospital. Because of the diversity in terms of surgical departments, age, gender and academic superscriptions, we have determined a reasonably large size effect.

The IBM SPSS Statistics Version 25.0 statistical software package was used to perform the statistical analysis. Descriptive statistical methods (frequency, percentage, mean, standard deviation, minimum-maximum) were used to evaluate the study data. Conformity of data to normal distribution were analyzed using Kolmogorov-Smirnov, skewness-kurtosis, and graphical methods (histogram, Q-Q Plot, Stem and Leaf, Boxplot). In the evaluation of normally distributed quantitative data; Independent Samples t-test (T Test in independent groups) or One- Way Anova Test was used. Tukey HSD test was used to find the differences in cases where there is difference in multiple comparisons. Relationships between variables were evaluated with Pearson Correlation Test. A level of α= 0.05 was set to determine statistical significance.

3. Results

One hundred surgeons (19 Female, 81 Male), with an average age of 38 years were participated in the study. They comprised of 46 assistant doctor, 34 specialist, 15 associate professor, 3 professor and 2 doctor lecturers. Years of medical and surgical experiences were classified as <10 years, 10-19 years and ≥20 years. Demographic characteristics of the surgeons are shown in Table 1.

Table 1

Demographic characteristics of the surgeons

		n Mean ± SD	% Median(Min-Max)
Gender(F/M) *	F	19	19.0
	M	81	81.0
Age(years) **		38.0 ± 9.2	38.0 (26.0 – 64.0)
Academic superscriptions*	assistant doctor	46	46.0
	specialist	34	34.0
	doctor lecturer	2	2.0
	associate professor	15	15.0
	professor	3	3.0
Years of medical experience**		13.4 ± 9.2	13.0 (1.0 – 41.0)
	<10 years	42	42
	10-19 years	30	30
	≥20 years	28	28
Years of surgical experience**		9.8 ± 8.0	9.0 (0.0 – 37.0)
	<10 years	51	51.0
	10-19 years	33	33.0
	≥20 years	16	16.0

**: n / %, **: mean ± SD / median(min-max), F:Female M:Male*

Surgical procedure groups consist of Group A1: Specific surgeries and interventions. (eg, Liver transplantation), Group A2: Specific surgeries and interventions (eg, Radical prostatectomy, Bentall procedure), Group A3: Specific surgeries and interventions (eg, Cerebral aneurysm, debulking surgery), Group B: Special surgeries and interventions (eg, Histerectomy, total laryngectomy), Group C: Major surgeries and interventions. (eg, Tonsillectomy, dacryocystorhinostomy), Group D: Moderate surgeries and interventions (eg, Polypectomy uterus, histerescopy), Group E: Minor surgeries and interventions (eg, Curetage uterus, sphincterotomy). The numerical distribution of the surgeons according to their department and the number of surgeries according to surgical procedure groups are given in Table 2. The mean STAI-1 score were 39.5 ± 11.2 and the mean STAI-2 were 40.4 ± 8.7 in our study, which would correspond to a level of moderate anxiety. When we analyzed these values as a category, we would see that 48 % of the surgeons presented low anxiety, 22 % of the surgeons presented moderate anxiety, 30 % of the surgeons presented high anxiety for STAI-1. And 43 % of the surgeons presented low anxiety, 27 % of the surgeons presented moderate anxiety, 30 % of the surgeons presented high anxiety for STAI-2. The laboratory reference range of morning cortisol was 0.0-19.2 in our study. We determined that the mean salivary cortisol levels were 12.0 ± 8.1 nmol/l. The median salivary cortisol levels were 10.4 (1.3 – 48.6). There was no statistically significant difference between genders, surgical departments, academic superscriptions, years of medical and surgical experiences and surgical procedure groups in terms of STAI-1scores, STAI -2 scores and salivary cortisol levels as shown in Table 3 (p>0.05). The relationship between salivary cortisol levels and scores of STAI-1 and STAI-2 were also examined in the study. It was found that the relations between STAI-1 and STAI-2 scores were not statistically significant (p>0.05) as shown in Table 4.

Table 2

Surgical departments of the surgeons and groups of the surgeries

		n	%
Surgical department	Neurosurgery	12	12.0
	Pediatric surgery	7	7.0
	General surgery	11	11.0
	Surgical oncology	3	3.0
	Ophthalmology	6	6.0
	Obstetrics and gynecology	11	11.0
	Otorhinolaryngology	10	10.0
	Cardiovascular surgery	11	11.0
	Orthopedic surgery	10	10.0
	Urology	11	11.0
	Plastic and reconstructive surgery	3	3.0
Group of the surgery	A2	4	4.0
	A3	49	49.0
	B	32	32.0
	C	13	13.0
	D	2	2.0

Table 3

Comparison of STAI scores and salivary cortisol levels by gender, surgical department, academic superscriptions, years of medical and surgical experiences and surgery groups

			Score of STAI-1	Score of STAI-2	Salivary cortisol level
Gender	Female (n=19)		41.5 ± 10.6	42.0 ± 7.0	12.1 ± 6.5
	Male (n=81)		39.1 ± 11.4	40.0 ± 9.1	11.9 ± 8.5
		p*	0.408	0.364	0.942
Surgical department	Neurosurgery(n=12)		45.8 ± 11.3	42.8 ± 8.3	10.1 ± 5.2
	Pediatric surgery (n=7)		40.4 ± 10.2	38.9 ± 9.4	16.7 ± 7.5
	General surgery (n=11)		32.6 ± 8.5	39.1 ± 5.0	11.0 ± 9.7
	Surgical oncology (n=3)		34.0 ± 12.5	38.3 ± 9.3	7.4 ± 5.3
	Ophthalmology(n=6)		39.7 ± 11.6	40.7 ± 12.8	19.6 ± 13.1
	Obstetrics and gynecology(n=11)		39.5 ± 11.0	42.7 ± 10.5	8.8 ± 4.8
	Gynecologic oncology(n=5)		41.4 ± 9.7	44.4 ± 11.7	15.9 ± 10.8
	Otorhinolaryngology(n=10)		45.4 ± 12.9	43.0 ± 6.0	12.8 ± 4.8
	Cardiovascular surgery(n=11)		36.4 ± 9.2	38.8 ± 9.6	8.5 ± 4.4
	Orthopaedic surgery(n=10)		35.9 ± 9.3	35.9 ± 6.7	13.7 ± 12.7
	Urology(n=11)		43.3 ± 14.1	41.1 ± 9.8	12.2 ± 6.8
	Plastic and reconstructive surgery(n=3)		31.0 ± 4.0	33.7 ± 3.1	9.5 ± 5.1
		p**	0.120	0.619	0.168
Academic superscriptions	Assistant doctor(n=46)		40.2 ± 11.9	41.3 ± 8.3	11.8 ± 9.5
	Specialist (n=34)		38.9 ± 10.9	39.5 ± 9.3	12.8 ± 7.1
	Doctor lecturer(n=2)		35.0 ± 8.5	28.0 ± 4.2	9.1 ± 2.1
	Associate professor(n=15)		39.3 ± 12.1	39.8 ± 8.3	11.6 ± 7.3
	Professor(n=3)		41.0 ± 4.6	47.0 ± 4.6	9.0 ± 4.5
		p**	0.962	0.149	0.913
Years of medical experience	<10 years(n=42)		40.2 ± 12.0	40.9 ± 7.8	11.9 ± 9.6
	10-19 years(n=30)		36.4 ± 10.1	37.7 ± 8.8	12.5 ± 8.0
	≥20 years(n=28)		41.9 ± 10.9	42.5 ± 9.4	11.6 ± 5.8
		p**	0.159	0.096	0.907
Years of surgical experience	<10 years(n=51)		38.8 ± 11.6	40.1 ± 7.8	12.2 ± 9.8
	10-19 years(n=33)		38.9 ± 11.2	39.3 ± 8.9	11.7 ± 6.5
	≥20 years(n=16)		43.2 ± 10.2	43.4 ± 10.8	11.8 ± 4.9
		p**	0.371	0.299	0.972
Group of the surgery	A2(n=4)		34.8 ± 6.0	36.8 ± 4.3	5.2 ± 4.1
	A3(n=49)		39.1±10.6	40.5 ± 8.8	11.8 ± 8.5
	B(n=32)		40.5 ± 12.2	40.7 ± 8.9	12.8 ± 8.4
	C(n=13)		38.7 ± 11.3	40.0 ± 9.8	13.2 ± 7.0
	D(n=2)		49.5 ± 23.3	41.5 ± 9.2	8.9 ± 0.6
		p**	0.622	0.942	0.454

Table 4

The relationship between salivary cortisol levels and scores of STAI- 1, STAI-2

	Salivary cortisol level	
	r	P*
Score of STAI-1	-0.122	0.227
Score of STAI-2	-0.081	0.420

** Pearson Correlation Test*

4. Discussion

In this study, we evaluated the preoperative anxiety level of the surgeons. We determined that gender, surgical department, academic superscription, years of medical and surgical experiences of the surgeons and surgical procedure groups had no significant effect on STAI-1 scores, STAI -2 scores and salivary cortisol levels. Anxiety is an unpleasant sensation experienced in patients awaiting surgery. In the development of preoperative anxiety, the main fact is the fear of unknown. Fear from postoperative outcomes, complications, pain, death and worries about family members, worries about being consciousness during the operation are the factors leading to anxiety[15,16]. Patients experience preoperative anxiety. But what about surgeons? Do they have anxiety too? Surgery is a stressful process and increased stress can impair operative performance and have a negative impact on the patient safety and outcomes[2]. Jones et al. evaluated surgeon's stress with six colorectal surgeons in anterior resection procedures using heart rate variability (HRV) measurements and STAI scores[17]. They reported that significantly increased levels of stress were measured with HRV in correlation with STAI scores. Erestam et al. conducted an experimental simulation study with volunteer surgeons. They evaluated the stress during simulated operations with stressors. A sugar containing drink was given in the intraoperative period and was considered as intervention from the stressors. Changes in salivary cortisol, heart rate, STAI scores were evaluated. They reported that intraoperative pause did not reduced stress in surgeons measured with salivary cortisol, heart rate or STAI scores[18]. Marrelli et al. evaluated the stress among oral surgeons using salivary cortisol, salivary immunoglobulin A, heart rate and systolic blood pressure values. They randomly grouped the surgeons according to their experience level as: senior (more than 10 years of experience), expert (5-10 years of experience) and junior (less than 5 years of experience). They also grouped the operations as: easy, intermediate or complex according to technical difficulty. They reported that oral surgeons are exposed to stress related pathologies independently of experience and sex. They also reported that the stress management ability was higher in senior surgeons than the other less experienced surgeons independently of the difficulty of the operations[19]. Stress and anxiety are interrelated conditions. Various emotional and environmental stressful situations can precipitate anxiety disorders. In addition, anxiety can sometimes appear as a psychophysiological signal of stress[20]. While the stress of the surgeons is well examined in the literature, few studies exist about surgeon's anxiety. Miller et al. evaluated performance anxiety and wellbeing of the surgeons. The demographic data of the surgeons that they reported was similarly to our demographic data findings. They reported that mean participant age was 41.2 years, mean surgical experience was 15.3 years. Among participants, 62.7% of participants were male, 36.9% were female and 0.4% preferred not to say. They reported that a total of 87% of the surgeons experienced surgical performance anxiety, a total of 65% of the surgeons reported that performance anxiety negatively impacted their surgical performance and 96% of the surgeons felt that surgical performance anxiety impacted surgeons' wellbeing[5]. In our study the anxiety that the surgeons presented were stated as low, moderate and high anxiety according to Spielberger and were not as high as the anxiety percentage experienced by the surgeons in Miller's study. Kilavuz et al. conducted a survey administered to otorhinolaryngologists and investigated their anxiety levels during and after pediatric adenotonsillectomy procedures. They reported a significant increase in surgeon's anxiety in the postoperative period. They reported that anxiety levels of the surgeons were significantly negatively correlated with their years of experiences[21]. In our study, there was no significant difference in terms of experience and preoperative anxiety levels of the surgeons. Anxiety is a psychological and physiological condition. In general, anxiety is observed in all periods of life in women and in adult ages of men with a reduction after the age of 50[22]. In their study Norton et al. reported that women exhibit the cognitive and somatic symptoms of anxiety more severely than men[23]. Studies have shown that there was a gender difference in preoperative anxiety levels of the patients measured by STAI scores. Female patients were found to be more anxious than men[24–26]. In our study, however, there was no significant difference between male and female surgeons in this regard. The results expected from this study could have been different, for example, the preoperative anxiety level in female surgeons might have been higher than in men, it might have been lower in senior surgeons than in junior surgeons, it might have been higher in surgeons performing specific or major surgeries than surgeons performing minor surgeries. But our results showed that there was no statistically significant difference. This should not mean that the study did not contribute to the literature. Because not being able to find a statistically significant difference is actually a consequence itself. One of the limitations of this study was that the study was conducted in a single center. Another limitation of this study was that the academic superscriptions, genders, and surgical departments were not numerically equal distributed. There were only 2 doctor lecturers and 3 professors. The numbers of female surgeons participated in the surgery was approximately one quarter of the male surgeons. The numbers of the surgeons in surgical departments varied. Because STAI was used, response bias exists. The self-report nature of the STAI introduces the potential for response bias. Some surgeons may provide socially desirable answers, leading to underestimation or overestimation of their anxiety levels.

5. Conclusions

In conclusion, based on STAI-1 scores, STAI-2 scores and salivary cortisol levels, the preoperative anxiety level of the surgeons did not differ by gender, surgical department, academic superscription, years of medical and surgical experiences and surgical procedure groups. We think that our study, which is rare in the literature, is important in terms of guiding future studies. Further studies are needed to evaluate the preoperative anxiety including more surgeons with equally distributions.

Statement of ethics

The study was approved by the Ethics Committee of Adana City Training and Research Hospital (approval no.746 on March 11, 2020) and registered at ClinicalTrials.gov.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author contributions

-Conception or design of the work: Ş.T., G.S., Ö.HK.
-Data collection: Ş.T., G.S.
-Data analysis and interpretation: Ş.T., G.S., Ö.HK.
-Drafting the article: Ş.T., Ö.HK.
-Critical revision of the article: Ş.T., G.S., Ö.HK.
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Antimicrobial Effects of Rosmarinus Officinalis; in-vitro Study

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Abstract

Aim: The plant Rosmarinus officinalis (RO) is a member of the Lamiaceae family and is more commonly known as rosemary. This study's primary objective is to compare the antimicrobial effect of RO extract at different concentrations on various microorganisms.

Methods: Strains of S. aureus ATCC 29213, K. pneumoniae ATCC 13883, and E. coli ATCC 25922 obtained from the national reference center were inoculated into liquid Müller Hinton broth (Oxoid, UK) and incubated at 37 °C' for 24 hours. To assess the antimicrobial efficacy of the RO extract, dilutions of 0.0625%, 0.125%, 0.25%, 0.5%, 1%, 2%, 3%, and 4% were prepared.

Results: The MIC value for RO extract was 2% for S. aureus ATCC 29213 and K. pneumoniae ATCC 13883 and 3% for E. coli ATCC 25283. A statistically significant difference was found between the three groups, including 0.0625% and 2% of RO, in terms of the growth rates of microorganisms ($p<0.001$). There was no statistically significant difference between the concentrations of 3% and 4% ($p=1.00$).

Conclusions: The antimicrobial effect potential of RO has been demonstrated in the literature and in-vitro in this study. In addition, we believe it can be used as a prophylactic or as an alternative to antimicrobial agents in the topical or systemic treatment of SSIs due to its various effects, topical, oral, and systemic use, and low cost. Thus, it is anticipated that the costs of treatment will be reduced. To determine the efficacious dose and implement it in clinical practice, experimental and clinical studies are necessary.

Keywords: *S. aureus ATCC 29213, K. pneumoniae ATCC 13883, E. coli ATCC 25922, Rosmarinus officinalis, surgical site infection, antimicrobial.*

1. Introduction

The plant *Rosmarinus officinalis* (*RO*) is a member of the Lamiaceae family and is more commonly known as rosemary[1]. RO is a herbal product used for years in food and cosmetic/pharmaceutical applications[2,3]. Numerous studies have been published in the literature that demonstrate antioxidant, anti-inflammatory, anti-ulcer, cardiovasculoprotective, neuroprotective, hepatoprotective, antineoplastic, and antimicrobial effects[3-6]. Although *RO* extract contains many biomolecules, the specific effects of these biomolecules have rarely been demonstrated due to their synergistic effects[7]. According to scientific studies, the 1,8-cineole molecule has a bacteriostatic effect[8,9]. Surgical infections are usually polymicrobial. Therefore, microbial synergy may increase the net pathogenic effect and the severity of infection. The most commonly isolated microorganisms in surgical infections are *E. coli*, *Staphylococcus aureus*, *Klebsiella spp.*, *Pseudomonas aeruginosa, Bacteroides fragilis*, and *Peptostreptococcus spp.*[10]. Since it was predicted that it could be used in the prevention of surgical infections due to its antimicrobial effect potential and low cost, it was planned to investigate the effect of RO on the most frequently isolated microorganisms in surgical site infections in this study. This study investigated the effects of *RO*

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extract on the three most frequently isolated bacterial agents in surgical infections.

This study's primary objective is to compare the antimicrobial effect of *RO* extract at different concentrations on various microorganisms.

2. Materials and methods

Strains of *S. aureus ATCC 29213*, *K. pneumoniae ATCC 13883*, and *E. coli ATCC 25922* obtained from the national reference center were inoculated into liquid Müller Hinton broth (Oxoid, UK) and incubated at 37 °C' for 24 hours.

To assess the antimicrobial efficacy of the *RO* extract, dilutions of 0.0625%, 0.125%, 0.25%, 0.5%, 1%, 2%, 3%, and 4% were prepared (*RO* doses mg/dL). A 0.5 McFarland turbidity standard suspension (final measurement concentration of 1.5x108 CFU/mL) and 10 µl were added to the wells for each strain. Each procedure underwent three repetitions. Microwell plates were incubated for 24 hours on a microplate incubator shaker at 37°C. After incubation, the wells were measured with an Epoch spectrophotometer (BioTek Inst. Inc., Vermont, USA) at a wavelength of 600 nm (OD600). Wells containing neither antimicrobials nor plant extracts were growth controls, while wells containing only Mueller-Hinton broth were negative controls. The percentage of viable cells for growth control was normalized to 100%[11].

Broth microdilution method with Mueller Hinton broth (Oxoid, UK) using 96-well microplates in accordance with CLSI guidelines to determine minimum inhibitory concentration (MIC) values against *S. aureus ATCC 29213*, *K. pneumoniae ATCC1 3883*, and *E. coli ATCC 25922.* was used. To ascertain the minimal bactericidal concentration (MBC), 10 µl samples from each well that did not exhibit visible growth (viability) after 24 hours were seeded on Mueller-Hinton agar and examined for viable organisms. After 24 hours, it was incubated at 37°C to observe any colony growth[12].

Microorganisms used in the study were divided into three groups. Groups;

Group 1: *S. Aureus ATCC 29213*

Group 2: *E. Coli ATCC 25922*

Group 3: *K. Pneumoniae ATCC 13883*

2.1. Preparation of Rosmarinus officinalis extract: *RO* extract was prepared by the methodology described by Roohbakhsh et al. in their study[13]. Above ground parts of *RO* were obtained from Yalova Atatürk Horticultural Center. The shade-dried and powdered aerial portions of *RO* (150 g) were extracted at room temperature with a 70% hydroethanol solution. The selected solvent-plant ratio was 1:10. Using a rotary evaporator; the solution was filtered and concentrated under reduced pressure at 38-40 °C to produce an extract. The extract was then completely dried using a lyophilizer. Concentrations of 2% and 4% were obtained by diluting with isotonic.

2.2. Statistical analysis: Descriptive statistics were used to identify continuous variables. Mean+standard deviation values were given for parameters suitable for normal distribution, and median (minimum-maximum) values were given for parameters unsuitable for normal distribution. The conformity of continuous variables to the normal distribution was examined using the Shapiro-Wilks test. The Kruskal-Wallis test was used to analyze the difference between more than two independent group continuous variables that did not conform to the normal distribution. Significant results were analyzed with the double Post Hoc comparison Bonferroni corrected Mann Whitney U test. The statistical significance level was determined as 0.05. MedCalc Statistical Software version 12.77 was used for analyses.

3. Results

The MIC value for *RO* extract was 2% for *S. aureus ATCC 29213* and *K. pneumoniae ATCC 13883* and 3% for *E. coli ATCC 25283*. When the MBC value was examined, no MBC values were found in the examined range. The MIC values and dose-response curve are displayed in Table 1 and Graphic 1, respectively.

A statistically significant difference was found between the three groups, including 0.0625% and 2% of *RO,* in terms of the growth rates of microorganisms (**p<0.001**). There was no statistically significant difference between the concentrations of 3% and 4% (p=1.00). Table 2 displays the growth rates of microorganisms in each of the three groups, while Table 3 provides pairwise comparisons between the groups.

Figure 1

The dose-response curve for *Rosmarinus officinalis* extracts (%) against S. *aureus*, *E. Coli*, and *K. pneumoniae* after 24 h.

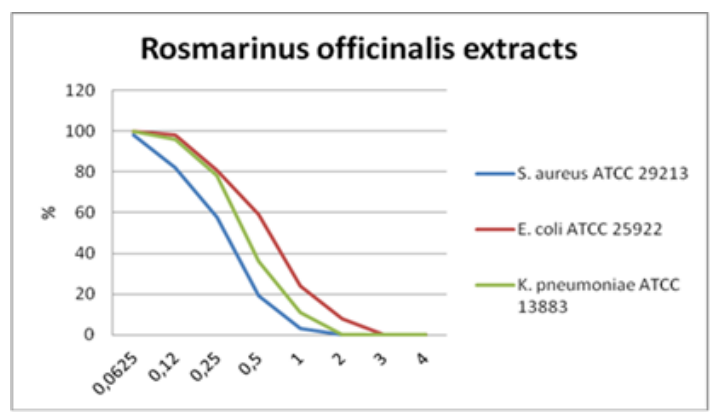

Table 1

MIC values of *Rosmarinus officinalis*

RO (%)	0.0625	0.12	0.25	0.5	1	2	3	4
Group 1	+	+	+	+	+	-*	-	-
Group 2	+	+	+	+	+	+	-*	-
Group 3	+	+	+	+	+	-*	-	-

*: MIC values, RO: Rosmarinus officinalis extracts

Group 1: S. Aureus ATCC 29213, Group 2: E. Coli ATCC 25922, Group 3: K. Pneumoniae ATCC 13883

Table 2

Reproduction percentages between groups

	0.0625	0.120	0.250	0.500	1.000	2.000	3.000	4.000
Group 1 (n=10)								
Mean+Sd	97.6±1.6	81.6±4.4	58.2±4.9	19.1±3.9	2.8±1.5	0±0	0±0	0±0
Med (min-max)	98 (94-99)	82 (76-88)	59 (50-5)	18.5 (14-26)	2.5 (1-5)	0 (0-0)	0 (0-0)	0 (0-0)
Group 2 (n=10)								
Mean+Sd	99.5±0.7	97.6±2.2	80.6±3.6	58.3±4.2	23.8±5.7	8.4±2.2	0±0	0±0
Med (min-max)	100 (98-100)	97.5 (94-100)	81.5 (76-85)	58.5 (51-65)	21.5 (17-34)	8.5 (5-12)	0 (0-0)	0 (0-0)
Group 3 (n=10)								
Mean+Sd	99.6±0.5	95.7±3.9	78.2±7.5	36.4±3.3	10.9±3.2	0±0	0±0	0±0
Med (min-max)	100 (99-100)	96.5 (85-99)	80.5 (60-85)	36 (31-42)	10.5 (7-18)	0 (0-0)	0 (0-0)	0 (0-0)
p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	1.00	1.00

Group 1: S. Aureus ATCC 29213, Group 2: E. Coli ATCC 25922, Group 3: K. Pneumoniae ATCC 13883
Sd: Standard deviation, Med: Median

Table 3

Pairwise Post Hoc comparisons between groups

Group	0.0625	0.120	0.250	0.500	1.000	2.000
1-2	0.003	<0.001	<0.001	<0.001	<0.001	<0.001
1-3	0.001	0.003	0.002	0.033	0.031	1.00
2-3	1.000	1.000	1.00	0.033	0.038	<0.001

Group 1: S. Aureus ATCC 29213, Group 2: E. Coli ATCC 25922, Group 3: K. Pneumoniae ATCC 13883

4. Discussion

Surgical site infection (SSI) is an important health problem that increases morbidity, mortality, and treatment costs[14]. It has been reported that the incidence of SSI in surgical patients is between 2% and 5%[15]. It is the most prevalent and expensive of all hospital-acquired infections and accounts for twenty percent[16]. Microorganisms in the cutaneous flora are frequently isolated in SSIs, and antimicrobial agents cefazolin, cefuroxime, cefoxitin, cefotetan, ertapenem, and vancomycin are frequently used for prophylaxis in many kinds of surgical applications[17]. SSIs have numerous intrinsic and extrinsic risk factors. Few of these risk factors are within the control of the surgeon. SSI prevention strategies are multimodal. A high level of adherence to these prevention strategies is crucial for success. As SSIs are the most prevalent and expensive hospital-acquired infections, preventing and reducing treatment costs is crucial. It is stated in the literature that 60% of SSIs can be prevented through the use of evidence-based measures[15]. Precautions are, therefore, the most essential and cost-effective method. Superficial SSIs that cannot be prevented can be treated topically, whereas deeper infections require debridement and antimicrobial treatment[18]. The use of topical and local antibiotics will continue to evolve in the context of SSIs[15]. For this reason, it is thought that *RO*, which has the potential for antimicrobial effects and has a very low cost, may be promising in treating SSIs. The clinical and experimental studies literature reveals that *RO* can be administered topically, orally, and systemically (intraperitoneally)[1,13,19]. For this reason, it can be predicted that the cost and efficacy of treatment will increase if it is used alone or as a supplement to conventional antibiotic therapy for both superficial and deep-seated SSI. In our study, *RO* was found to be antimicrobial against SSI-common pathogens such as *S. aureus, K. pneumoniae*, and *E. coli*. Among these three microorganisms, it was observed that the highest antimicrobial effect at different concentrations was against *S. aureus, K. Pneumoniae*, and *E. coli*, respectively. Bowbe et al.[8] reported that the MIC value of *RO* against *S. aureus* was 0.7 mg/mL. In our study, the minimum inhibitory concentration (MIC) against S. aureus was determined to be 20 mg/mL (2% concentration). It was hypothesized that the difference was due to using different strains in the studies. This significant dose difference in MICs indicates that resistant strains may require high concentrations for antimicrobial efficacy. According to Dhouibi et al.[20], *RO* has antimicrobial activity against diverse microorganisms. Although MIC values were not given in this study, it was reported that the antimicrobial activity against *S. aureus* was higher than that against *E. coli* when inhibition zone diameters were considered. In line with the results of this study, we discovered that the antimicrobial activity against *S. aureus* was greater than that against *E. coli*. According to Luca et al.[3], the MIC of *RO* against Methicillin-resistant *S. aureus* (*MRSA*) is 62.5 mg/mL. Based on these findings, the antimicrobial effective dose of *RO* varies with the virulence of microorganisms, and further research is required to determine the optimal effective dose. According to Ielciu et al.[21], the MIC value of *RO* was greater for *E. coli* than for *S. aureus.* In accordance with our findings, this study demonstrates that the antimicrobial effect potential of *RO* against *S. aureus* is greater than that against *E. coli*. In addition, Ielciu et al.[21] reported that even though the diameter of the *MRSA* inhibition zone was less than that of Methicillin-resistant *S. aureus* (*MSSA*), there was no difference in MIC values. This study's findings also disclose the need for more certainty regarding the optimal dose.

5. Conclusions

SSI increases morbidity, mortality, and treatment costs significantly. Consequently, prevention and treatment are crucial. A significant proportion of SSIs can be prevented with evidence-based

measures. However, topical use in superficial cases and debridement and systemic antibiotheraphy in deep SSI cases are required to treat unpreventable SSI. In this instance, the use of antimicrobial agents significantly increases treatment costs. In terms of SSIs, the application of topical and local antibiotics will continue to evolve. The antimicrobial effect potential of *RO* has been demonstrated in the literature and in-vitro in this study. In addition, we believe it can be used as a prophylactic or as an alternative to antimicrobial agents in the topical or systemic treatment of SSIs due to its various effects, topical, oral, and systemic use, and low cost. Thus, it is anticipated that the costs of treatment will be reduced. To determine the efficacious dose and implement it in clinical practice, experimental and clinical studies are necessary.

Statement of ethics

This study is an in vitro study and ethics committee approval is not required. Informed consent is not required for IVD studies involving samples that are non-identifiable (i.e., are labeled with identifiers or accompanied by the patient's non identifiable clinical information), as well as for studies in which the samples are not identifiable but are coded.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Effect of Resveratrol and Quercetin on Intestinal Ischemia Reperfusion Injury in Rats

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Abstract

Aim: Intestinal ischemia reperfusion (I/R) injury is an emergency condition with a high mortality rate and early diagnosis is very difficult. In this study, we aimed to examine the biochemical and histopathological effects of resveratrol and quercetin on intestinal I/R injury model.

Methods: In our study, 56 male Sprague-Dawley rats weighing 250-300 g were randomly divided into 7 groups consisting of 8 rats. Groups were control group (group 1), saline group (group 2), ethanol group (group 3), resveratrol group (group 4) (30mg/kg), quercetin group (group 5) (30mg/kg), resveratrol+quercetin group A (group 6) (15 mg/kg+15 mg/kg), resveratrol+quercetin group B (group 7) (30 mg/kg+30 mg/kg). At the end of the experiment rats intestinal tissues were divided into 2 parts for biochemical and histopathological examination. Total oxidant level (TOS), total antioxidant level (TAS), total thiol [(-SH)+(-S-S-)] (TT), native thiol [-SH] (NT), and protein content levels were measured spectrophotometrically, oxidative stress index (OSI) and disulfide [-S-S-] levels were calculated.

Results: A statistically significant difference was found between the groups in terms of TOS, OSI, TT, NT and disulfide levels ($p < 0.05$). No statistically significant difference was observed between the groups in terms of TAS levels ($p > 0.05$). A significant improvement in histopathological scoring was observed in all treatment groups compared to saline and ethanol groups ($p < 0.05$).

Conclusions: Resveratrol and quercetin have protective effects in reducing oxidative stress in intestinal I/R damage.

Keywords: *Ischemia-reperfusion, resveratrol, quercetin, intestinal tissue damage*

1. Introduction

Mortality rates due to acute intestinal I/R injury have decreased in recent years but they still remain at high levels. 26% of these patients who are hospitalized live less than 1 year (1). Although the relevant mechanisms have not been fully elucidated, studies show that free radical attack originating from toxic oxygen metabolites is effective in the pathophysiology of intestinal I/R injury[1-3].

Increased blood flow in I/R injury causes an increase in tissue oxygenation and thus the production of reactive oxygen species (ROS) such as superoxide radical ($O_2^{\bullet-}$), peroxynitrite ($ONOO^-$), hydrogen peroxide (H_2O_2) and hydroxyl radical ($OH^\bullet$) (4). While low ROS levels are effective in ischemic preconditioning, excessive elevation of ROS plays a role in the deterioration of the antioxidant system, mitochondrial membrane permeability, protein structure, lipid oxidation and deoxyribonucleic acid (DNA) damage. Thus, it causes an increase in cell membrane permeability and apapoptosis[4,5].

TOS is used as a cumulative indicator of oxidative stress in the body. TAS is used as a marker showing the amount of antioxidants produced in the body against oxidative stress[6]. The TOS/TAS ratio gives the OSI and is a parameter that shows whether the balance between antioxidants and oxidants increases on the oxidant side or on the antioxidant side[2,3,6,7].OSI index value of 1 indicates a healthy balance,

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while a value greater than 1 indicates an increase in oxidative stress or a decrease in the amount of antioxidants[6].

Thiols are molecules containing sulfhydryl (-SH) group and are effective in preventing the occurrence of oxidative stress. While thiols reduce oxidant substances, they themselves oxidize and turn into disulfide. Native thiol, dynamic disulfide and total thiol are among the parameters used in thiol disulfide balance measurement. NT shows antioxidant activity, and disulfide dynamic shows oxidant activity[8].

Antioxidants are used to prevent local or systemic effects caused by I/R injury. Studies have shown that both resveratrol and quercetin have high antioxidant capacity[9,10].

Resveratrol is a natural polyphenolic compound found mainly in peanuts, grapes, mulberries and red wine. With its antioxidant effect, it reduces the pathological progression in many diseases[11-13]. It is also stated that resveratrol has a protective effect on I/R damage[11]. Resveratrol has antioxidant activity by scavenging $OH^{\cdot}$ and $O_2^{\bullet-}$ and inhibiting lipid peroxidation caused by $OH^{\cdot}$ radical[9,10]. It is effective against oxidative stress by chelating copper (II) and phagocytizing free oxygen radicals[13].

Quercetin is a flavone derivative polyphenol found in many vegetables and fruits such as tea, apples, onions, strawberries and red grapes[4,5,14]. Its antioxidant activity is quite strong compared to other flavonoids[15]. It has the ability to scavenge free radicals via the Fenton reaction by chelating transition metals such as Fe^{2+} and Cu^{+} ions[5,11,16].

The protective properties of resveratrol and quercetin against intestinal I/R injury have not been adequately studied to date. The aim of this study is to investigate whether resveratrol and quercetin have anti-oxidant effects and histopathologically protective effects on intestinal tissue in I/R injuries.

2. Materials and methods

Ethics committee approval of this study was obtained by Kahramanmaraş Sütçü İmam University Experimental Animals Ethics Committee with the decision dated 26.12.2018 (Decision No: 02).

The study was carried out in Kahramanmaraş Sütçü İmam University Experimental Animals Laboratory. In all animal procedures used, care was taken to strictly comply with the "European Convention on Animal Care and the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals".

2.1. Subjects

In the study, 56 Sprague Dawley type male rats weighing between 250-300 grams were used. The groups were randomly divided into 7 groups of 8 rats in each group; control group, saline group, ethanol group, resveratrol (30 mg/kg) group, quercetin (30 mg/kg) group, resveratrol+quercetin group (A) (15 mg/kg+15 mg/kg), resveratrol+quercetin group (B) (30 mg/kg) kg+30 mg/kg). All rats were fed standard laboratory chow until the day of the experiment and were weighed before the experiment. Before the study, the rats were allowed to drink water but were fasted for 12 hours before the experiment. Surgery was performed in all rats under intraperitoneal ketamine (40 mg/kg) and xylasine (50 mg/kg) anesthesia. The rats were allowed to breathe spontaneously throughout the experiment.

2.2. Design of experimental groups:

Following ketamine anesthesia, median laparotomy was performed in all groups, and the superior mesenteric artery (SMA) was reached by entering the abdominal cavity.

Then, intestinal tissue samples were taken from the control group (n=8).

In other groups, 60 minutes ischemia damage is created and intraperitoneally; was given 0.3 ml of saline to the saline group; 5% ethyl alcohol (0.3 ml) to the ethanol group; resveratrol at a dose of 30 mg/kg dissolved in 5% alcohol to the resveratrol group[17]; to the quercetin group, quercetin at a dose of 30 mg/kg dissolved in 0.3 ml of saline[18]; resveratrol+quercetin group (A) (15 mg/kg + 15 mg/kg) intraperitoneally at a dose of 15 mg/kg of resveratrol dissolved in 5% alcohol and 15 mg/kg of quercetin dissolved in 0.3 ml of saline; 30 mg/kg resveratrol dissolved in 5% alcohol and 30 mg/kg quercetin dissolved in 0.3 ml saline to resveratrol+quercetin group (B) (30 mg/kg + 30 mg/kg). Afterwards, 60 minutes of reperfusion was applied to these groups and intestinal tissue samples were taken.

2.3. Conducting the Experiment and Taking Samples:

The rats were anesthetized by the intraperitoneal (IP) route. After shaving the abdominal skin of the rats, it was cleaned with an antiseptic solution and then laparotomy was performed with a midline incision. After entering the abdominal cavity, reaching the small intestines and temporarily removing the small intestines, the SMA was reached and the artery was carefully dissected and isolated from the surrounding tissues. The blood flow was stopped by placing an atraumatic microvascular clamp on the SMA, and then 60 minutes of ischemia and then 60 minutes of reperfusion were applied, and the ileum segment of approximately 2 cm, 15 cm proximal to the ileocecal valve was resected and tissue samples were taken[19]. All rats were sacrificed after the procedure. Tissue samples taken were divided into two and one part of each was stored at –80 °C for biochemical analysis. The other part of the samples was placed in 10% formaldehyde and used for histopathological examination. In our study, one rat in the quercetin group died during the experiment.

2.4. Biochemical Analysis:

Tissue samples reserved for biochemical studies were left to melt at +4 ˚C on the working day. Before the analysis, the tissues were weighed and homogenized on ice with 0.15 molar KCl at a ratio of 1/10 (Ultra turrax, 60 sec at 13500 rpm). Then, the supernatants were separated by centrifugation at 4000 rpm at + 4˚C for 20 minutes. TOS, TAS, TT, NT and protein levels were analyzed by spectrophotometric method (Shimadzu UV-1800).

2.5. Total oxidant/antioxidant level (TOS/TAS) and oxidative stress index (OSI):

Spectrophotometric analyzes were performed in Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Medical Biochemistry Research Laboratory.

TOS (Rel Assay) and TAS (Rel Assay) levels were analyzed spectrophotometrically, adhering to the commercial kit content. The results obtained as a result of TOS analysis were calculated as μmol H_2O_2 Eq/L and given as umol/L/mg protein, the results obtained as a result of TAS analysis were calculated as μmol Trolox Eq/L and given as mmol/L/mg protein.

OSI is the percentage degree of the ratio of TOS to TAS. In the calculation of OSI, the unit of TOS and TAS value is equal to μmol.

2.6. Total thiol-native thiol and thiol / disulfide balance:

TT (Rell Assay, Product Code: 0178) and NT (Rell Assay, Product Code: RL0185) levels were analyzed spectrophotometrically, adhering to the commercial kit content. The amount of dynamic disulfide bonds was obtained by calculating half of the difference between the TT and NT groups (μmol/L) .

2.7. Protein analyzes:

Protein analyzes were performed using the Lowry[20] method and the results were given in proportion to protein values.

2.8. Histopathological Analyzes:

At the end of the experiments, the jejunums of the sacrified rats were placed in 10% buffered formol and then routinely followed up with tissue. Then, 4.5 μm sections were taken and stained with hematoxylin-eosin dye, and then the groups were evaluated by a histologist

under the light microscope (Olympus BX41). Used in the histopathological evaluation of intestinal I/R injury, Chiu et al.[21] is a scoring system in which intestinal I/R damage and the effect of antioxidant agents used against it can be evaluated[16,21].

2.9. Statistical Analysis:

2.9.1. For biochemical analysis:

SPSS 21.0 (SPSS Inc. Chicago, USA) program was used for statistical analysis of research data. In the descriptive statistics part, continuous variables are presented with mean±standard deviation (mean±SD). Mann-Whitney U test was used for comparison analyzes between two independent groups and Kruskal Wallis test was used for comparison analysis between three groups. Statistical significance level was accepted as $p<0.05$.

2.9.2. For histopathological analysis:

Data were collected using SPSS 17 software (SPSS® version 17.0; SPSS, Chicago, IL, USA). Numerical variables are presented as mean±SD. The groups were compared using the ANOVA test, and within-group evaluations were made using the Tucey HSD method. Statistical significance level was accepted as $p<0.05$.

3. Results

3.1. Biochemical Findings:

In our current study, a statistically significant difference was observed between the groups in terms of TOS, OSI, TT, NT and disulfide values ($p<0.05$). There was no significant difference between the groups in terms of TAS (mmol/L/mg protein) values ($p=0.518$) (Table 1).

3.2. Histopathological Findings:

In the histopathological examination, intestinal appearance was normal in the control group (Figure 1). In the saline and ethanol groups, intestinal appearance compatible with Stage 3 and 4 was observed in Chiu scoring. Histopathology consistent with Stage 1 was observed in the quercetin and resveratrol groups. While there was no significant difference between resveratrol and quercetin group (A) (15 mg/kg+15 mg/kg), resveratrol and quercetin group (B) (30 mg/kg+30 mg/kg) groups, histopathology compatible with Stage 0 and 1 was observed. It has been shown statistically that quercetin, resveratrol and their combined low and high doses have a protective effect on the intestine (Table 2).

Table 1

TOS, TAS, OSI, TT, NT, disulfide levels of the groups (mean±SD.)

	Control (Group 1) (n=8)	Salin (Group 2) (n=8)	Ethanol (Group 3) (n=8)	Resveratrol (Group 4) (n=8)	Quercetin (Group 5) (n=7)	R+Q (A) (Group 6) (n=8)	R+Q (B) (Group 7) (n=8)	p1
TOS umol / L / mg Protein	0,11±0,01	0,22±0,05a	0,24±0,06a	0,15±0,03abc	0,14±0,02abc	0,15±0,01abc	0,14±0,03abc	< 0,001
TAS mmol /L/ mg Protein	0,03±0,01	0,03±0,00	0,03±0,00	0,03±0,00	0,03±0,00	0,03±0,00	0,03±0,00	0,518
OSI	0,31±0,05	0,77±0,23a	0,81±0,20a	0,51±0,06abc	0,44±0,05abcd	0,47±0,05abc	0,42±0,08abcd	< 0,001
TT [(-SH)+(-S-S-)] / Protein	5,78±0,76	3,4±0,21a	3,52±0,42a	3,91±0,61a	4,46±0,36abc	4,27±0,65abc	4,76±0,68abcd	< 0,001
NT (-SH) / Protein	5,27±0,68	2,51±0,18a	2,69±0,41a	3,15±0,58ab	3,72±0,43abcd	3,56±0,66abc	4,12±0,69abcd	< 0,001
Disulfide (-S-S-)	0,26±0,14	0,45±0,07a	0,41±0,12a	0,38±0,06b	0,37±0,11	0,35±0,06b	0,32±0,08b	0,016

Notes: p1 Kruskal Wallis test. aCompared to Group 1, bCompared to Group 2, cCompared to Group 3, dCompared to Group 4 (Mann-Whitney U test). R+Q: resveratrol + quercetin. TOS: Total oxidant level, TAS: total antioxidant level, OSI: oxidative stress index, TT: total thiol, NT: native thiol.

Figure 1

Intestine view of the groups

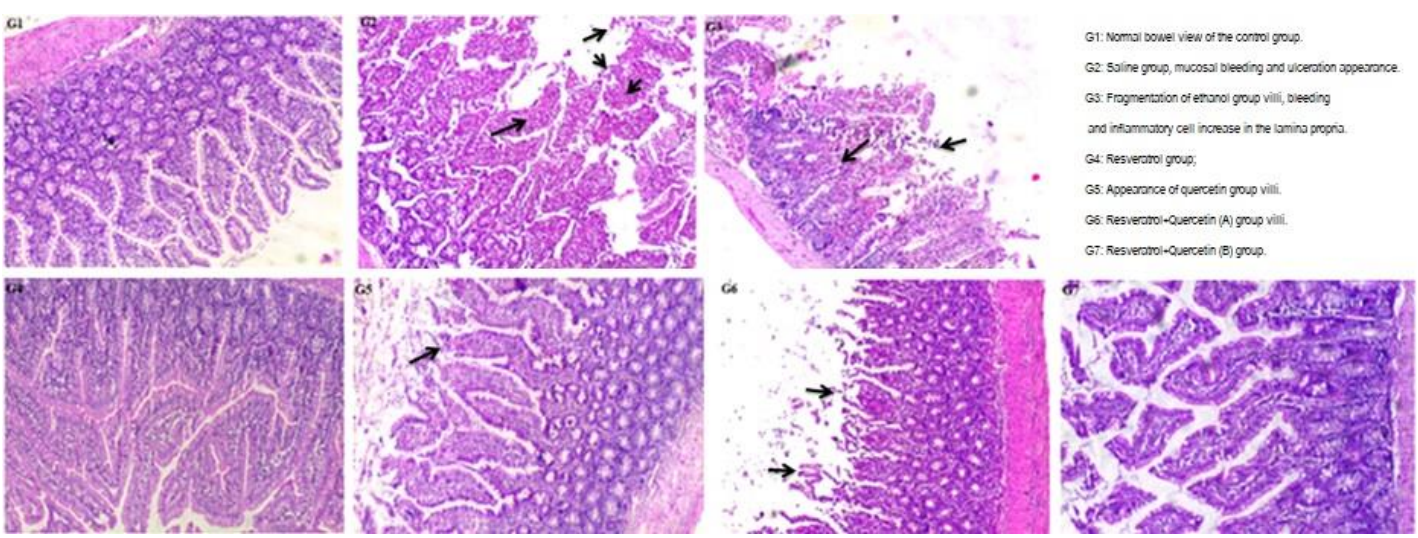

Table 2

Histopathological data of the groups (mean±SD)

	Control (Group 1) (n=8)	Salin (Group 2) (n=8)	Ethanol (Group 3) (n=8)	Resveratrol (Group 4) (n=8)	Quercetin (Group 5) (n=7)	R+Q (A) (Group 6) (n=8)	R+Q (B) (Group 7) (n=8)	p2
Chiu Score	0.62±0.44	4.12±0.83	4.25±0.70	2.87±0.83*	2.75±0.70*	3.50±0.92	2.75±0.70*	< 0,001

*Compared to Group 3 (p2: One Way ANOVA (with Tukey HSD)). R+Q: resveratrol + quercetin.

4. Discussion

One of the most life-threatening conditions in clinical practice worldwide is ischemic bowel disease. The most important approach to salvage intestinal tissue in ischemia is to restore blood flow as soon as possible. However, restoration of blood flow causes a more serious complication such as intestinal I/R injury[1]. After ischemia, reperfusion causes molecular oxygen to enter the tissue, causing rapid production of ROS and serious cellular damage[2,3,7].

In the study of Yazıcı et al.[6], serum OSI levels 2 hours after induction of mesenteric ischemia were found to be significantly higher compared to the control group. However, OSI levels after 6 hours decreased compared to OSI levels after 2 hours. The increase in OSI and TOS values at the 2nd hour was attributed to the changes experienced with oxidative stress. It has been stated that the decrease in these parameters at the 6th hour of ischemia may be due to the opening of the collateral circulation and the activation of systemic antioxidant mechanisms in prolonged ischemia[6]. In the study of Tanyeli et al.[2], it was observed that intestinal tissue TAS levels decreased significantly and TOS and OSI levels increased significantly in the rat group with mesenteric ischemia-reperfusion injury compared to the sham group. It has been seen in many studies that resveratrol has beneficial effects against intestinal I/R damage[14,22-25]. In the study of Yıldız et al.[12], they found that TAS was significantly higher, TOS and OSI were significantly lower in the intestinal tissue in the resveratrol treatment group compared to the control group in intestinal I/R damage. In the study of Tóth et al.[14], it was observed that quercetin reduced the mucosal damage caused by intestinal IR damage in rats. In the study of Bahadır et al.[4], the effects of quercetin on hepatic I/R damage were investigated, and TAS, TOS and OSI values in the sham group were found to be significantly lower than the control and quercetin applied study groups; the mean TAS, TOS and OSI values of the control group were found to be higher than those of the quercetin applied group, but no statistical difference was observed. In this case, it was stated that quercetin may be effective in reducing pro-oxidant production rather than increasing antioxidant capacity. In our current study, we aimed to investigate the effect of naturally occurring antioxidant compounds called polyphenols, resveratrol and quercetin, on I/R damage. For this, we measured the TAS and TOS values in the intestinal tissue and calculated the OSI values to see if there was a difference between the groups. A significant increase was observed in TOS and OSI levels in all other groups when compared to the control group. It is thought that TOS levels increase due to I/R injury in these groups. When compared with saline and ethanol groups, a significant decrease was observed in TOS and OSI levels in all other groups treated with resveratrol and/or quercetin. The significant decrease in OSI values in the quercetin and resveratrol+quercetin (B) applied groups compared to the resveratrol group suggests that quercetin is more effective in preventing oxidative stress than resveratrol. There was no difference between the groups in terms of TAS levels. This may be due to the time of administration of resveratrol and quercetin or the duration of I/R injury, or, as Bahadır et al.[4] said, resveratrol and quercetin may have been effective in reducing pro-oxidant production rather than increasing antioxidant capacity. Or, the measurement of oxidant and antioxidant levels alone may not be sufficient to clearly reveal most of the oxidative stress state[2]. There was no difference between the groups with the dose increase of antioxidants.

Thiols are organic compounds containing -SH group and play a critical role in preventing oxidative stress in cells. The first target in proteins for ROS is amino acids containing the -SH group. -SH groups are oxidized by ROS and -SH groups of two thiol groups combine to form a dynamic, redox sensitive covalent bond, a reversible disulfide bond[26-29]. With the increase in oxidative stress, the consumption of thiols for detoxification also increases[29]. Thus, while the native thiol decreases, the amount of disulfide increases[26]. Disulfide bonds formed by the oxidation of thiols can be reduced to thiol groups with the effect of antioxidants, thus maintaining thiol/disulfide homeostasis[27]. Thiol/disulfide homeostasis plays an important role in regulation of protein function, stabilization of protein structure, protection of cysteine residues of proteins against irreversible oxidation, cellular signal transduction, chaperone function, regulation of enzymatic activity, transcription factors, and apoptosis[27,28]. In normal healthy individuals, more than 50% of the physiological serum antioxidant capacity consists of thiols[29]. In the study of Yıldırım et al.[29], serum thiol values decreased from the first hour of acute mesenteric ischemia; at 3. and 6. hours, serum total thiol and native thiol values decreased significantly in mesenteric ischemia groups compared to control and sham groups, while serum disulfide values increased significantly. In the study conducted by Özçakır et al.[30], although no statistically significant difference was found in the plasma of rats exposed to intestinal ischemia for 60 and 180 minutes in terms of TT, NT and disulfide levels compared to the control group; TT and NT levels decreased and disulfide values increased at the 3. hour. In the study of Olas et al.[31], resveratrol was found to reduce the thiol-reducing effect of platinum compounds in platelets. In our study, there was improvement in the treatment groups in terms of TT and NT, but it did not approach the baseline value. Thus, we can say that resveratrol and quercetin may have a protective effect by reducing disulfide levels.

In intestinal I/R injury, the release of ROS and proteolytic enzymes cause an acute inflammatory response that increases ischemic damage and neutrophil infiltration, lipid peroxidation, apoptosis and necrosis[32]. It has been shown that reperfusion after occlusion of SMA can cause apoptosis in rat intestinal tissue[33]. Pergel et al.[34] and Tas et al.[32] showed that antiapoptotic treatment can be effective in preventing intestinal I/R damage. In the study of Yıldız et al.[12], it was observed that histological tissue damage in intestinal I/R injury was milder in the resveratrol treatment group compared to the control group. In the study of Bahadır et al.[4], no significant difference was found between the control and quercetin applied study groups in terms of necrosis and apoptosis in hepatic I/R injury. In the study of Curgali et al.[35], protective quercetin application before

jejunal I/R induction stimulated faster restoration of the jejunal mucosa. Yıldız et al.[16], after intestinal I/R application, it was observed that the most histopathological damage was in the I/R group among the sham group, quercetin+I/R and I/R groups. Histological damage was significantly reduced in the quercetin group compared to the I/R group. In our current study, when the groups were evaluated in terms of Chiu score, the highest scores were in the rats in group 2 and group 3, and there was no significant difference between the results of these two groups (p=0.975); however, there was a significant difference between group 3 and group 4 (p=0.021), between group 3 with group 5 and group 7 (p=0.008). When the treatment groups were evaluated within themselves, it was seen that the lowest scores were in the rats in group 5 and group 7, but there was no statistical difference within the treatment groups (p>0.05).

5. Conclusions

In the light of the biochemical and histopathological data we have obtained that resveratrol and quercetin have a protective effect on I/R damaged intestinal tissues. However, detailed studies are required to elucidate the mechanism of this effect and its relationship with thiols.

Statement of ethics

The study was approved by the Kahramanmaraş Sütçü İmam University Experimental Animals Ethics Committee with the decision dated 26.12.2018 (Decision No: 02).

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author contributions

Study conception and design: Fatma İnanç Tolun, Işıl Yağmur, Selen Dindar; acquisition of data: Selen Dindar, Atilla Yoldaş; analysis and interpretation of data: Fatma İnanç Tolun, Hasan Dağlı, Aslı Yaylalı, Rabia Tural; drafting of manuscript: Rabia Tural, Işıl Yağmur; critical revision: Fatma İnanç Tolun, Işıl Yağmur, Rabia Tural.

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The Impact of N2 Lymph Node Positivity on Survival Rates Among Patients Undergoing Surgery for Non-Small Cell Lung Cancer

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Abstract

Aim: Our study aims to identify patients diagnosed with non-small cell lung cancer who have undergone lung resection and have ipsilateral mediastinal metastatic lymph nodes (N2). We intend to categorize them into surprise N2 and potentially resectable N2 groups based on clinical approach and investigate the impact of these groups on survival outcomes.

Methods: Between January 2011 and December 2017, a retrospective cohort study was conducted on 953 patients who underwent lung resection for non-small cell lung cancer (NSCLC) at our hospital. Patients were categorized into three groups: patients without initial clinical N2 involvement but with postoperative pathological N2 involvement (group 1), patients with initial clinical N2 involvement who underwent immediate surgery (group 2), and patients with initial clinical N2 involvement who demonstrated stable pathological N2 involvement or partial regression after receiving neoadjuvant chemotherapy or chemoradiotherapy and subsequently underwent surgery (group 3).

Results: A total of 71 patients (7.45% of the cohort) with postoperative pN2 were included in this study. Among these 71 patients, 41 (57.74%) did not have initial cN2 involvement and were categorized as postoperative pN2 (group 1). Twenty patients (28.16%) with a single cN2 were considered as carefully selected patients and underwent surgery (group 2). Ten patients (14.08%) were selected patients who received neoadjuvant treatment and subsequently had a single N2 involvement, and they underwent anatomical resection (group 3). Statistical analysis revealed no significant differences in survival between the three groups (p=0.882).

Conclusions: No consensus currently exists regarding the role of surgery in the management of patients with NSCLC and mediastinal lymph node metastases. Existing evidence suggests that studies encompassing larger patient cohorts are necessary to comprehensively investigate the subgroups of patients with N2 disease.

Keywords: *Non-small cell lung cancer, N2, mediastinal lymph node, surprise N2, skip N2*

1. Introduction

Cancer remains a significant global and national public health concern, ranking second after cardiovascular diseases as the leading cause of death [1, 2]. Lung cancer, specifically, accounts for approximately 12.9% of all cancer cases, with an estimated 1.8 million new cases reported annually[3]. Unfortunately, only a small percentage (15-20%) of Non-Small Cell Lung Cancer (NSCLC) patients are diagnosed at an early stage (Stage IA, IB, IIA, IIB) and qualify for surgical intervention, while a larger proportion (30%) present with locally advanced disease (Stage 3A and 3B)[3]. In Turkey, the distribution of lung cancer cases is as follows: 18% present with localized disease, 30% with regional spread, and 52% with distant metastasis[4]. When considering clinical staging, the 5-year survival rates for NSCLC patients were reported as follows: 82% for Stage IA, 66% for Stage IB, 52% for Stage IIA, 47% for Stage IIB, 47% for Stage IIIA, 36% for Stage IIIB, and 19% for Stage IV[5]. Lung cancer treatment options include surgical treatment, chemotherapy, radiotherapy and immunotherapy. Despite advances in chemotherapy and radiotherapy, the best treatment option in early-stage lung cancer is still surgical treatment[6].

In numerous studies examining Non-Small Cell Lung Cancer (NSCLC), it has been consistently identified that N2 positivity represents a significant negative prognostic factor[7, 8, 9]. Consequently, one of the primary strategies for improving survival rates in NSCLC is to employ the most suitable treatment for mediastinal lymph node metastasis. Among physicians specializing in lung cancer treatment,

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the management of N2 positivity remains a topic of considerable debate and controversy.

In cases of locally advanced lung cancer with ipsilateral mediastinal metastatic lymph nodes, the current recommended treatment approach involves definitive chemotherapy (CT) or concurrent chemoradiotherapy (CRT). However, there is limited research available on the role of surgery in stage 3 patients with positive N2 lymph nodes.

In our study, we conducted a comparative evaluation of survival outcomes and prognostic factors within two distinct groups of NSCLC patients who underwent anatomical resection. The first group consisted of "surprise N2" cases, where no metastatic N2 disease was initially detected during the preoperative evaluation, but metastasis was later identified during postoperative pathologic evaluation. The second group comprised "probable resectable N2" cases, characterized by the presence of metastatic N2 disease detected during the preoperative evaluation.

2. Materials and methods

2.1 Patient Selection:

This retrospective study reviewed patients who were admitted to the Çukurova University Department of Thoracic Surgery between January 2011 and December 2017. The inclusion criteria were patients who underwent anatomical lung resection and mediastinal lymph node dissection for non-small cell lung cancer (NSCLC) and were found to have N2 lymph node metastasis (pN2) during postoperative pathologic evaluation. However, patients who were clinically diagnosed with N2 lymph node metastasis in preoperative evaluation (cN2), showed complete regression in clinical and radiologic evaluation after neoadjuvant treatment, or had no N2 lymph node metastasis in postoperative pathologic evaluation (N0) were excluded from the study.

2.2 Study Design:

We divided the patients into three groups: patients who did not have cN2 but had pN2 postoperatively (group 1), patients who had cN2 and were primarily operated (group 2), and patients who had cN2 and had stable pN2 or partial regression after neoadjuvant CT or CRT treatment and underwent surgery (group 3).

The study involved examining the data and archive files of the patients. Through this analysis, several factors were determined, including the demographic characteristics of the patients, histological type and location of the tumor, date of diagnosis, invasive mediastinal intervention, clinical and pathological TNM stages according to the 8th TNM staging system, treatment applied, and overall survival values.

2.3. Statistical Analysis:

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences Version 22.0; SPSS Inc. Chicago, IL, USA) software. Descriptive statistics were utilized to present the variables: parametric data were expressed as mean ± standard error, categorical data as frequency and percentage, and survival levels as median. To explore the relationship between parametric data and categori¬cal variables, independent t-test and one-way analysis of variance (ANOVA) tests were employed. Chi-square Fisher's Exact test was used to examine the relationship between categorical variables. The log-rank analysis was employed to assess the impact of various parameters on survival. Parameters with p-values of ≤0.10 in the log-rank analyses were included in the multivariate analyses. Model fit and the assumption of proportionality of periodic risk were evaluated using residual analyses, including Schoenfeld and Martingale methods. Any p-value below 5% was considered statistically significant, indicating a type 1 error level.

3. Results

Between January 2011 and December 2017, a retrospective review was conducted on 953 patients who underwent lung resection for NSCLC at our hospital. The study included 71 patients (7.45%) with postoperative pN2. Of these patients, the mean age was 58.83±1.07 years, with 63 (88.73%) being male and 8 (11.27%) being female. The most common histopathologic diagnosis was adenocarcinoma (n=36, 50.70%), followed by squamous cell carcinoma (n=28, 39.43%), pleomorphic carcinoma (n=3, 4.22%), adenosquamous carcinoma (n=1, 1.40%), large cell carcinoma (n=1, 1.40%), carcinosarcoma (n=1, 1.40%), and combined large cell - squamous cell carcinoma (n=1, 1.40%). In terms of tumor localization, 24 (33.80%) were located in the right upper lobe, 22 (30.98%) in the left upper lobe, 14 (19.71%) in the right lower lobe, 7 (9.85%) in the left lower lobe, 2 (2.81%) in the right middle lobe, 1 (1.40%) in the right hilar, and 1 (1.40%) in the left hilar.

3.1. Evaluation of groups

Forty-one (57.74%) of 71 patients in our study had no cN2 and were evaluated as pN2 postoperatively (group 1). Twenty (28.16%) patients with a single cN2 were evaluated as selected patients in good condition and underwent surgery (group 2). 10 (14.08%) patients were selected patients who received neoadjuvant treatment and then had a single N2 and anatomical resection was performed (Group 3).

3.1.1 Group 1 - "Surprise N2" (n=41)

In this group, 35 patients (85.36%) were male, while 6 patients (14.64%) were female, with a mean age of 59.07±1.32 years. Histopathologic evaluation revealed that 19 cases (46.34%) were diagnosed as adenocarcinoma, 18 cases (43.90%) as squamous cell carcinoma, and 4 cases (9.75%) as other types. The localization of the masses was as follows: 16 cases (39.02%) in the right upper lobe (RUL), 10 cases (24.39%) in the right lower lobe (RLL), 10 cases (24.39%) in the left upper lobe (LUL), 3 cases (7.31%) in the left lower lobe (LLL), 1 case in the right central region, and 1 case in the left central region. Among the 41 patients, 34 (82.93%) underwent lobectomy, while 7 (17.07%) underwent pneumonectomy. Single-station pathologic N2 lymph node involvement was detected in 34 (82.91%) cases, while multiple pathologic N2 lymph node involvement was observed in 7 (17.07%) cases. The postoperative pathologic evaluation showed N2 lymph node metastasis in 42 (22.70%) out of 185 lymph nodes examined. The most common metastases to N2 lymph node stations were observed in station 4 (n=15, 35.71%) and station 7 (n=11, 26.19%). Skip N2 lymph node metastasis was present in 22 (53.65%) patients. Among the patients, 22 (53.7%) were classified as Stage 3A, while 19 (46.3%) were classified as Stage 3B. Lymphovascular invasion was detected in 31 (75.70%) patients, while visceral pleural invasion was observed in 2 (4.87%) patients. The median survival of the patients was 33.53 months (95% CI 20.136-46.930), and 26 (63.41%) of the patients had deceased during the study period (Table 1, 2).

3.1.2. Group 2 - Known N2 "selected patients" (n=20)

In this group, there were 18 (90%) male and 2 (10%) female patients with a mean age of 58.25±2.31 years. The median survival was calculated as 22.70 months (min: 1, max: 92). In this group, adenocarcinoma (n=9, 45%) and squamous cell carcinoma (n=8, 40%) were the most common tumor types observed.

Table 1
Descriptive statistics of variables

		Group 1 (n=41)	Group 2 (n=20)	Group 3 (n=10)	Total (n=71)	p
Age (mean ± SE)		59.07±1.32	58.25±2.31	59 ±3.07	58.83±1.07	0.946
Gender	•Male n(%)	35, 85.36%	18(90%)	10(100%)	63 (88.73%)	0.592
	•Female n(%)	6, 14.64%	2 (10%)	0(0%)	8(11.27%)	
Histopathology n(%)	•Adenocarsinoma	19(46.34%)	9 (45%)	8(80%)	36(50.70%)	0.390
	•squamous cell carcinoma	18(43.90%)	8(40%)	2 (20%)	28(39.43%)	
	•Others	4(9.75%)	3(15%)	0(0%)	7(9.85%)	
Tumor size (cm)		5.017(±0.351)	5.015(±0.389)	4.010(±0.571)	4.66(±0.344)	0.369
Localization of tumour n(%)	•RUL	16 (39.02%)	4(20%)	4(40%)	24(33.80%)	0.533
	•RML	0 (0%)	1(5%)	1(10%)	2 (2.81%)	
	•RLL	10 (24.39%)	4(20%)	0(0%)	14 (19.71%)	
	•LUL	10 (24.39%)	8(40%)	4(40%)	22 (30.98%)	
	•LLL	3 (7.31%)	3(15%)	1(10%)	7 (9.85%)	
	•Right hilar	1 (2.43%)	0	0(0%)	1(1.40%)	
	•Left hilar	1 (2.43%)	0	0(0%)	1(1.40%)	
Operation n(%)	•Lobectomy	34 (82.93%)	17(85%)	7 (70%)	58(81.69)	0.569
	•Pneumonectomy	7(17.07%)	3(15%)	3(30%)	13(18.30%)	
Lymph node: N2 met./ total(%)		42/185(22.20%)	28/70(40%)	14/92(15.21%)	84/347(24.20)	0.001
N2 lymph node metastasis n(%)	•single station	34(82.91%)	14(70%)	7(70%)	55(77.46%)	0.433*
	•multiple station	7(17.07%)	6(30%)	3(30%)	16(22.53%)	
Pathologic Stage	•3A	22(53.7%)	9(45.0%)	7(70.0%)	38(53.52%)	0.444
	•3B	19(46.3%)	11(55.5%)	3(30.0%)	33(46.47%)	
Skip N2 metastasis n(%)		22(53.65%)	6(30%)	6(60%)	34(47.88%)	0.157
Lymphovascular invasion n(%)		31(75.70%)	18(90%)	9(%90)	58(81.69%)	0.176
Visceral pleura invasion n(%)		2(4.87%)	3(15%)	1(10%)	6(8.45%)	0.326*
Excitus n(%)		26(63.41%)	11 (55%)	7(70%)	44(61.97%)	0.785

**Fischer Exact test, SE: Standart error, n:number, RUL: right upper lobe, RML: Right middle lobe, RLL: right lower lobe, LUL: left upper lobe, LLL left lower lobe.*

Tumor localization was found to be in LUL in 8 cases (40%), RUL in 4 cases (20%), RLL in 4 cases (20%), LLL in 3 cases (15%), and RML in one case (5%). Lobectomy was performed in 17 (85%) patients, and pneumonectomy was performed in 3 (15%) patients. Among the patients, 9 (45%) were diagnosed with Stage 3A disease, while 11 (55%) were diagnosed with Stage 3B disease. Postoperative pathologic evaluation revealed single-station N2 lymph node metastasis in 14 (70%) and multiple-station N2 lymph node metastasis in 6 (30%) patients. Lymphovascular invasion was present in 18 (90%) of the 20 patients, while 3 (15%) patients showed visceral pleural invasion. A total of 70 lymph node samplings were performed in this group, and N2 station metastasis was detected in 28 (40%) of them. Skip N2 lymph node metastasis was observed in 6 (30%) patients. The median survival of this patient group was 25.967 months (95% CI: 11.220-40.713). At the end of the study, 11 (55%) patients had deceased.

3.1.3. Group 3 - "Persistent N2" "selected patients after neoadjuvant therapy"(n=10)

The mean age of the patients in this group was 59 ± 3.07 years, and all patients were male. Adenocarcinoma was the observed pathology in 8 (80%) patients, while squamous cell carcinoma was present in 2 (20%) patients. Among the patients, 4 (40%) had tumors located in the RUL, 4 (40%) in the LUL, 1 (10%) in the RML, and 1 (10%) in the LLL. Lobectomy was performed in 7 (70%) patients, while pneumonectomy was carried out in 3 (30%) patients. Based on the diagnoses, 7 (70%) patients were classified as Stage 3A, and 3 (30%) patients were classified as Stage 3B. In the postoperative pathologic evaluation, a single N2 metastasis was found in 7 (70%) patients, and multiple N2 station metastases were observed in 3 (30%) patients. Lymphovascular invasion was detected in 9 (90%) patients, and visceral pleural invasion was observed in 1 (10%) patient. N2 station metastasis was identified in 14 (15.21%) out of 92 lymph node samplings. Skip N2 lymph node metastasis was present in 6 (60%) patients. The median survival was calculated as 27.767

Table 2
Evaluation of the efficacy of parameters on survival

		n	Survival		p
			Median (month)	95% Confidence interval	
Groups	•Group 1	41	33.533	20.136-46.930	0.882
	•Group 2	20	25.967	11.220-40.713	
	•Group 3	10	27.767	0.00-60.590	
Gender	•Male	63	26.133	15.345-36.922	0.008
	•Female	8	48.183	26.849-69.442	
Histopathologic Type	•Adenocarsinoma	36	33.900	16.168-51.632	0.240
	•Squamous Cell Carsinoma	28	18.167	4.444-31.890	
	•Others	7	39.300	5.701-72.899	
Operasyon Type	•lobectomy	58	33.700	24.100-43.300	0.254
	•pneumonectomy	13	16.633	1.734-31.533	
Pathologic Stage	•3A	38	39.000	25.695-52.305	0.337
	•3B	33	20.133	8.053-32.213	
Lymphovascular invasion	•yes	57	33.533	21.333-45.737	0.800
	•no	13	33.900	11.328-56.472	
Visceral pleura invasion	•yes	6	11.700	0.000-29.656	0.100
	•no	65	33.700	23.587-43.813	

months (95% CI: 0.00-60.590). At the time the study was terminated, 7 (70%) of the patients had exited (Table 1, 2).

3.2. Statistical comparison of descriptive values of the groups

There were no statistically significant differences between the groups in terms of patient demographic information such as age and gender (p=0.946, 0.592, respectively). Additionally, no statistically significant differences were observed between the groups regarding histopathological type, size, location, pathological stage, lymphovascular invasion rate, visceral pleural invasion rate, and the type of operation performed (p=0.390, 0.369, 0.533, 0.444, 0.176, 0.326, 0.569, respectively). Similarly, there were no statistically significant differences between the groups in terms of single or multiple N2 lymph node metastases and skip metastasis rate (p=0.433, 0.157, respectively). Furthermore, there was no statistically significant difference between the groups in terms of the rate of mortality (p=0.785, respectively). However, when analyzing the ratio of N2 lymph node metastasis to the total sampled lymph node metastasis, it was found that group 2 had a significantly higher rate than the other groups (p=0.001) (Table 1).

3.3. Survival Analysis

There was no statistically significant difference in survival between the groups (p=0.882). The survival time for male patients was 26.133 months (95% CI=15.345-36.922), while for female patients, it was 48.183 months (95% CI=26.849-69.442). A gender-related survival evaluation revealed a significantly longer survival time in female patients (p=0.008). When evaluating the histopathologic types, the median survival was 33.9 months (95% CI=16.168-51.632) for adenocarcinoma, 18.167 months (95% CI=4.444-31.890) for squamous cell carcinoma, and 39.3 months (95% CI=5.701-72.899) for other types. However, the histopathologic types did not have a significant statistical effect on survival (p=0.240). Median survival was 33.7 months (95% CI=24.100-43.300) for lobectomy and 16.633 months (95% CI=1.734-31.533) for pneumonectomy, and the type of operation performed did not show a statistically significant difference (p=0.254). Postoperative pathologic cancer staging indicated a median survival of 39 months (95% CI=25.695-52.305) for stage 3A patients and 20.133 months (95% CI=8.053-32.213) for stage 3B patients. However, cancer staging did not show a significant statistical difference in survival (p=0.337). The median survival for patients with lymphovascular invasion was 33.533 months (95% CI=21.333-45.737), compared to 33.9 months (95% CI=11.328-56.472) for patients without lymphovascular invasion, indicating that the presence or absence of lymphovascular invasion had no effect on survival (p=0.800). Among the 6 patients with visceral pleural invasion, the median survival was 11.7 months (95% CI=0.000-29.656), while for the 65 patients without invasion, it was 33.7 months (95% CI=23.587-43.813). The invasion of the visceral pleura did not affect survival (p=0.100) (Table 2).

4. Discussions

N2 positivity in patients can vary from single station microscopic N2 involvement to multi-station bulky N2 positivity, and even to skip N2 involvement. Considering the clinical information of the patients, subgroups such as possible resectable N2 and surprise N2 may arise. Consequently, approaching the patient solely as an N2 positive patient in treatment decisions can be a controversial matter.

According to recent studies, the incidence of surprise N2 positivity in patients who undergo surgery following a comprehensive preoperative evaluation is around 10%[11, 12]. In our study, surprise N2 involvement was identified in 4.3% of the total cohort (n=953) who underwent resection for NSCLC, with a total of 41 cases.

The current NCCN guidelines categorize definitive concurrent chemoradiotherapy (CRT) as a 'category 1' treatment approach for

stage IIIA (N2 positive) disease. Additionally, surgery after indication chemoradiotherapy is also recommended as an alternative treatment option[13]. In cases where discrete (non-infiltrative) N2 involvement is detected prior to surgery, the ACCP guidelines suggest performing surgery after definitive CRT or neoadjuvant therapy, rather than opting for surgery alone or radiotherapy alone (grade 1A)[14]. However, despite undergoing invasive mediastinal procedures, there is still a possibility of encountering intraoperative N2 metastasis. In such instances, it is recommended to proceed with the planned resection if complete removal of the primary tumor and mediastinal lymph nodes can be achieved[14]. Detterbeck's research demonstrated that there is no significant difference in quality of life and mortality between patients who undergo thoracotomy without lung resection and those who undergo lung resection. He suggests that it is more beneficial to proceed with resection in patients who are found to have intraoperative N2 involvement, even in the absence of preoperative clinical suspicion[15]. In studies focusing on patients with surprise N2 positivity detected during surgery, the 5-year survival rate was reported to be around 20-25%[16, 17]. In your study, the median survival of patients who received adjuvant chemotherapy (n=41), which was categorized as surprise N2 involvement, was 33.5 months, consistent with findings reported in the literature.

In the existing literature, varying rates of morbidity and mortality have been reported among stage 3 (N2 positive) patients based on the specific type of surgical resection. The randomized phase 3 trial conducted by North American Intergroup (INT0139) failed to demonstrate any survival advantage associated with surgical treatment following concurrent neoadjuvant chemoradiotherapy (CRT), when compared to definitive CRT alone. The authors of this study attribute this finding to the higher occurrence of pneumonectomy cases within the surgical group. They additionally discovered elevated rates of postoperative morbidity and mortality among patients who underwent pneumonectomy following neoadjuvant CRT, as opposed to those who underwent lobectomy. Conversely, in the same study, a survival advantage was observed among patients who underwent lobectomy after neoadjuvant CRT, when compared to the group of patients who solely received definitive CRT[18]. In our study, 81.6% (n=58) of patients underwent lobectomy, while 18.3% (n=13) underwent pneumonectomy. The median survival times recorded were 33.7 months and 16.6 months, respectively, and no statistically significant difference in survival outcomes was observed between these two resection types.

Goldstraw et al. conducted a study on non-small cell lung cancer (NSCLC) and determined the median survival for Stage IIIA and IIIB as 41.9 and 22.0 months, respectively, based on clinical staging in the lung cancer staging project of the International Association for the Study of Lung Cancer (IASLC)[5]. In our study, we observed median survival values of 39.0 and 20.1 months for Stage IIIA and IIIB, respectively. When comparing the survival times between these stages, no significant difference in survival was found (p-value: 0.337).

Even if a statistically significant difference exists in the survival times of men and women, it may not hold clinical significance due to a significant disparity in the ratio of male and female individuals.

5. Conclusions

The current updated treatment of stage 3 (N2 positive) non-small cell lung cancer (NSCLC) has not yet achieved the desired survival outcomes. In cases of multiple N2 metastases, it is essential to perform a comprehensive preoperative evaluation of mediastinal lymph nodes as surgical intervention does not contribute to improved survival. However, experienced centers with a multidisciplinary treatment approach may be able to perform surgical treatment with acceptable mortality and morbidity rates. In patients with clinical suspicion of N2 positivity, particularly those with centrally located tumors, N1 metastases, absence of pathologically-sized lymph nodes in the mediastinum on thoracic CT but increased metabolic activity on PET CT, an invasive mediastinal procedure should be considered. Despite a complete invasive mediastinal procedure, intraoperative N2 positivity remains highly probable. It is crucial to define the large and heterogeneous subgroups of N2 positive patients accurately.

Therefore, further investigation is warranted on the role of surgical treatment in N2 positive NSCLC.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Çukurova University Faculty of Medicine Ethics Committee. (2018-- 80) Thesis number: 234238-2018
https://tez.yok.gov.tr/UlusalTezMerkezi/TezGoster?key=UPP_Zu9isEmWGFXFCBYascen54xi2SCrQsuqpgVznbC9U9D9PToCDnw-s-B8Ueu5

Conflict of interest statement

Author declare that they have no financial conflict of interest with regard to the content of this report.

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Author contributions

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Treatment of Primary Retroperitoneal Tumors: Single Center Experience

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Abstract

Aim: The aim of our study is to evaluate the results of patients who underwent surgery due to primary retroperitoneal tumors in order to contribute to the knowledge pool in the literature.

Methods: The data of patients who underwent surgery due to retroperitoneal tumor at Health Sciences University, Adana City Training and Research Hospital between January 2015 and January 2023 were retrospectively scanned. Approximately 54 patients with a clinical diagnosis of PRT were included in the study. Preoperative demographic characteristics of the patients, such as age at diagnosis, gender, number of surgeries for PRT, preoperative biopsy pathology and symptom status, if any, were recorded. All patients underwent computed tomography (CT) imaging with intravenous contrast. The location, size, density and presence of contrast enhancement of PRT in preoperative imaging methods were recorded. Peroperative incision type and duration, need for erythrocyte suspension transfusion, need for organ resection, complications and length of stay in the postoperative period were evaluated.

Results: The average age of a total of 54 patients who underwent surgery due to a retroperitoneal mass was 53.8±10.0 years. While 15 (27.8%) of 54 patients with a retroperitoneal mass were diagnosed incidentally, 39 (72.2%) patients were diagnosed symptomatically. The final pathological outcome of all relapsed patients was liposarcoma. The average operation time was 178.7±85.4 minutes. In 12 (22.2%) patients, adjacent organ resection was performed in addition to the mass. The average length of stay of the patients was 6.2±3.1 days. In the postoperative period, one patient required re-operation due to ileus and one patient due to bleeding. Adjuvant therapy was given to 6 (11.1%) patients after surgery. In the final pathology results of the patients, positive surgical margins were detected in 8 (14.3%) patients. Additionally, all of these patients had organ resection. In the Kaplan-Meier survival analysis, it was found that surgical margin had a statistically significant effect on average survival ($p<0.001$).

Conclusions: According to the results of our study, microscopic surgical margin positivity is the main factor affecting survival in PRT treatment and that total organ resection positively affects survival.

Keywords: *Primary retroperitoneal tumors, surgical resection, effective treatment*

1. Introduction

Retroperitoneal tumors account for less than 1% of all tumors but approximately 20% of all soft tissue tumors. It is malignant at a high rate (65-86%)[1]. They are large lesions that can be primary or secondary. Differentiating primary retroperitoneal tumors (PRT) from secondary retroperitoneal tumors is important for treatment management. The first-line treatment for lymphoma or metastatic disease is chemotherapy, while surgery is the only curative treatment option for PRT. Percutaneous biopsies may be needed from time to time to make this distinction. However, it must be differentiated from retroperitoneal non-neoplastic pathologies such as Castleman disease, extramedullary erythropoiesis, Erdheim-Chester disease and amyloidosis. Distinguishing these by characteristic imaging findings prevents unnecessary biopsies and surgeries[2]. PRT originates from soft tissues, lymphatics and neural tissue rather than the organs in the region. Symptoms are atypical and have a long growing period until symptomatic. For this reason, the diagnosis can be made either by imaging performed for other purposes or when it reaches very large sizes. Masses that reach large sizes cause symptoms to occur in the late period due to displacement of retroperitoneal structures or pressure on neighboring organs. The primary treatment is surgical resection, and the importance of removing the entire tumor has been emphasized many times in the literature[1,3,4].

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Factors such as late detection of large sizes and critical neighborhoods make treatment management difficult. Due to the limited effect of chemotherapy and radiotherapy, PRT treatment continues to be surgical even if there is a recurrence[3,4]. PRTs are a heterogeneous group of tumors. Tumors originating from different tissues have many variations even within their own subgroups. This heterogeneity is present in many studies in the literature and the number of patients generally appears to be insufficient. For this purpose, we aimed to evaluate the results of patients who underwent surgery due to RPT in order to contribute to the knowledge pool in the literature.

2. Materials and methods

After obtaining approval from the local ethics committee, the data of patients who underwent surgery due to retroperitoneal tumor at Health Sciences University, Adana City Training and Research Hospital between January 2015 and January 2023 were retrospectively scanned. Approximately 54 patients with a clinical diagnosis of PRT were included in the study. Preoperative demographic characteristics of the patients, such as age at diagnosis, gender, number of surgeries for PRT, preoperative biopsy pathology and symptom status, if any, were recorded. All patients underwent computed tomography (CT) imaging with intravenous contrast. The location, size, density and presence of contrast enhancement of PRT in preoperative imaging methods were recorded. Peroperative incision type and duration, need for erythrocyte suspension transfusion, need for organ resection, complications and length of stay in the postoperative period were evaluated. Histopathologically, tumor type, tumor grade and surgical margin status, number of recurrences and locations in the postoperative period were recorded. During their follow-up, the patients' additional treatment needs and surveys were recorded. Survey was calculated from the date of surgery to the date of death or last follow-up.

2.1. Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY). Continuous variables are presented as mean ± standard deviation and categorical variables as n (%). Kaplan Meier method and log-rank test were used to evaluate the relationship between surgical class positivity and survival rate. P <0.05 was considered statistically significant.

3. Results

The average age of a total of 54 patients who underwent surgery due to a retroperitoneal mass was 53.8±10.0 years. 30 (55.6%) of the patients were male and 24 (44.4%) were female. Needle biopsies were taken from 9 patients during preoperative evaluation. While 15 (27.8%) of 54 patients with a retroperitoneal mass were diagnosed incidentally, 39 (72.2%) patients were diagnosed symptomatically. 49 of the cases were operated once, 4 twice, and 1 three times due to recurrence. The final pathological outcome of all relapsed patients was liposarcoma. Preoperative demographic and clinical characteristics of the patients included in the study are summarized in table 1.

When intraoperative results were evaluated, median incision below and above the umbilicus was found to be the most frequently preferred approach in 21 (38.9%) patients. The average operation time was 178.7±85.4 minutes. In 12 (22.2%) patients, adjacent organ resection was performed in addition to the mass. Intraoperatively, main vessel injury occurred in 3 (5.6%) patients and pleural injury occurred in 3 (5.6%) patients and was repaired intraoperatively.

Table 1

Demographic and preoperative characteristics of the patients

Variables	Total patient, n=54
Age, year, mean±s.d.	53.8±10.0
Gender, female/male	30/24
Tumor size, cm, mean±s.d.	8.5±4.7
Preoperative biopsy, n (%)	
None	45 (83.3)
Paraganlionoroma	3 (5.5)
Ganglionoroma	3 (5.5)
Malign mesenchymal tumor	3 (5.5)
İncidental diagnosis, n (%)	15 (27.8)
Presence of contrast enhancement, n (%)	48 (88.9)
Density of mass in CT, n (%)	
Hyperdense	12 (22.2)
Hypodense	33 (61.1)
Heterogen	9 (16.7)
Anatomical location of the mass, n (%)	
Psoas anterior	36 (66.6)
Para-aortic	9 (16.6)
Renal hilum	3 (5.5)
Suprarenal	6 (11.1)

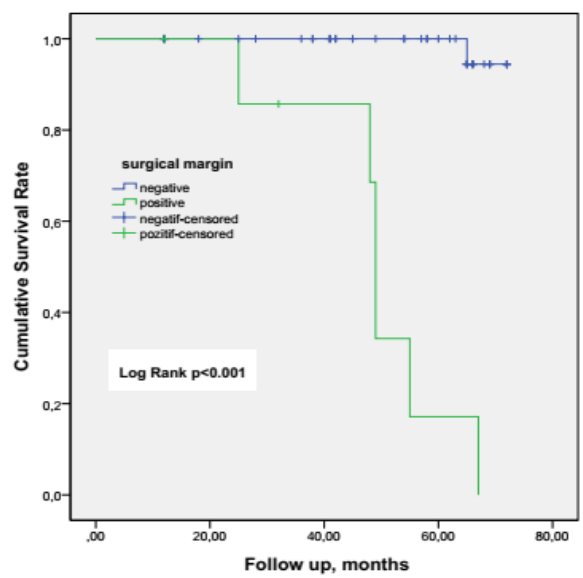
Table 2

Histological types of retroperitoneal tumor

	Frequency	Percent
Liposarcoma	22	40.7
Well differentiated		
Myxoid		
Mixed type		
Malign fibrous histiocytoma	11	20.4
Paraganglioma	6	11.2
Leimyosarcoma	3	5.6
Atypical lipomatosis tumor	3	5.6
Mature cyctic teratoma	3	5.6
Ganglionoroma	3	5.6
Schwannoma	3	5.6
Total	54	100.0

Figure 1

In Kaplan-Meier survival analysis



The average length of stay of the patients was 6.2±3.1 days. In the postoperative period, one patient required re-operation due to ileus and one patient due to bleeding. Erythrocyte suspension was given to 6 (11.1%) of the patients due to decrease in hematocrit. According to the surgical specimen results, the most frequently detected pathology was reported as liposarcoma (40.7%). 50 (92.5%) patients underwent complete resection. Total excision could be performed in 12 (100%) patients with benign pathology results and 38 (90.4%) patients with malignant pathology results. Final pathology results are presented in table 2. Adjuvant therapy was given to 6 (11.1%) patients after surgery. In the final pathology results of the patients, positive surgical margins were detected in 8 (14.3%) patients. During an average follow-up of the patients of 49.1 ± 19.2 months, cancer-specific deaths occurred in 7 (12.5%) patients. When the pathology results of 7 patients were examined, it was observed that 4 (57.1%) patients had liposarcoma and 3 (42.9%) patients had leiomyosarcoma pathology. Additionally, all of these patients had organ resection. In the Kaplan-Meier survival analysis, it was found that surgical margin had a statistically significant effect on average survival (p<0.001) (Figure 1).

Table 3

Patients underwent adjent organs resection (n = 12)

Surgery	Frequency	Percent
Nephrectomy	5	41.6
Adrenalectomy	4	33.3
Partial intestine resection	2	16.6
Splenectomy	1	8.3
Total	12	100.0

4. Discussions

PRTs are challenging cases in terms of location, slow progression, and lack of an effective treatment method other than surgery. Its treatment involves complete resection of the tumor, including the pseudomembrane, which can be seen with the naked eye and radiologically. Surgery is often performed without taking a preoperative biopsy of these masses. When we look at the literature, it is seen that 30% of cases are benign as a result of pathology, and in our study, we found this rate to be 22.2%[4]. Benign tumors generally have a well-circumscribed and distinct capsule on imaging methods. Malignant tumors tend to invade neighboring organs or have unclear borders. [one]. Both contrast-enhanced computed tomography and magnetic resonance imaging are used to evaluate the source of the mass, its relationships with neighboring organs, and its malignant potential. Both imaging provides very accurate assessment of the characteristics of these tumors[5]. Sometimes computed tomography or magnetic resonance angiography may be needed to determine adjacent vessel relationships and oral contrast-enhanced computerized tomography to determine the gastrointestinal system relationship. Preoperative detection of these relationships can help take precautions for bowel cleansing or vascular resection and reconstruction[6]. Such preoperative preparations reduce both morbidity and mortality.

Previous studies have proven that removing surrounding organs (e.g. kidney, colon, small intestine) with multivisceral resection, when necessary, contributes to an increase in the resectability rate. Invasions involving major retroperitoneal blood vessels such as the inferior vena cava, aorta, or iliac or visceral vessels require planned vascular resection[6,7]. In their study by Lee et al., 21% of adjacent organ resections were performed, consistent with our results, while operation times and average hospital stays were longer. It seems to be long (207 minutes and 18 days, respectivle). We think that the reason for this difference between the results is due to the retroperitoneal mass sizes of the patients included in both studies (13.7 cm versus 8.5 cm)[8]. When we look at the literature, it is seen that adjacent organ resections are generally performed at similar rates[4,9]. The most commonly resected adjacent organ is the kidney[1,4,8]. While this rate was 44.4% in Lee et al.'s study, it was 41.6% in our study. Our adjacent organ resection rates were consistent with the literature.

According to the results of their study, Xu et al. were able to achieve 85.5% total tumor excision. This rate was 95.6% in benign pathology results and 80.6% in malignant ones. In our study, our overall, benign and malignant pathology results and total excision rates were similar to the results of the study by Xu et al. They also performed adjacent organ resection at a rate similar to the literature and our study (20.2%). When we look at the literature, it is seen that the factor that most affects total excision is major vascular invasion. In the study conducted by Xu et al., 7 patients (4%) required major vascular reconstruction, while the results were similar to our study (5.6%). While there was a 19% recurrence rate in their study, this rate was 9% in our study. In the literature, it is seen that this rate can vary within a wide range of 40-82% between 15-44 months[4,10]. The most recurrent pathologies were liposarcoma, leiomyosarcoma and malignant hemangioendothelioma. In our study, all recurrent masses were liposarcoma[4]. In our study, we detected sarcoma at a rate of 66.6%. In the literature, this rate is seen to be around 90%[11,12]. Our complete resection rate in sarcomas is 86.1%, and in the literature this rate varies within a wide range of 40-95%[1]. Previous studies have shown that local recurrence is associated with poor prognosis. Even if there is recurrence, the primary treatment is surgery[3]. When complete resection can be performed in sarcomas, the average life expectancy is 103 months, but in cases of incomplete resection or inoperability, it can decrease to 18 months[13]. In our study, microscopic surgical margin positivity was detected in 14.3% of the patients. During an average follow-up of the patients of 49.1 ± 19.2 months, cancer-specific deaths occurred in 7 (12.5%) patients. Similar to previous studies, we found that incomplete or positive surgical margins affected median survival[4]. Surgical margin positivity is directly related to recurrence and survival. Primary versus recurrent tumor has a strong association with postoperative survival[14].

Many factors affect survey in PRT treatment. Many studies in the literature have previously focused on this issue and some results have been reached. Many factors such as the patient's age, gender, tumor size and location, laboratory parameters, and the number of PRT patients treated by the center have been found to be effective1,4,8,15. An et al. In their multivariate regression analysis with 49 patients, they reported that tumor size, macroscopic negativity of surgical margins and tumor location were factors affecting average survival[1]. However, the most important limitation in supporting these findings and verifying them with regression analysis was observed to be the limited sample size. In the Kaplan Meier analysis we conducted with 54 patients in our study, we determined that microscopic surgical margin positivity was a factor affecting survival. In addition, although it could not be verified by Cox regression analysis, we observed that 7 patients who died had leiomyosarcoma+liposarcoma pathology and that accompanying organ resection affected survival.

Our study contains some limitations. The first of these is its single center experience and retrospective design. Secondly, our sample number is small. Despite these, we think that it will contribute to the

literature since there are few studies on this subject in the literature and these are the results of the experiences of a tertiary center.

Conclusions

According to the results of our study, we think that microscopic surgical margin positivity is the main factor affecting survival in PRT treatment and that total organ resection positively affects survival, but studies with large sample sizes are still needed to support our results.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Health Sciences University, Adana City T&R Hospital Ethics Committee. (2023-2962)

Conflict of interest statement

Author declare that they have no financial conflict of interest with regard to the content of this report.

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The Effect of Hyperuricemia and Allopurinol Treament Outcome of Graft in Kidney Transplant Recipients

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Abstract

Aim: Kidney transplant recipients (KTRs) may have high levels of serum uric acid (SUA) due to graft dysfunction and immunosuppressives. This study evaluated the effect of high SUA levels and allopurinol therapy on renal functions in KTRs.

Methods: 113 of 233 KTRs had elevated SUA levels (G1) others had normal SUA (G2) . Fifty seven of G1 received allopurinol treatment(G1A+), and 56 patients (G1A--) did not. 56 of 118 patients who were followed for five years(G5) were hyperuricemic (G5-1) and 26 of G5-1 treated with allopurinol (G5-1A+) and 30 of them did not(G5-1A-). 62 patients were normourisemic(G5-2). GFR<10 ml/min was considered as graft loss.

Results: Of the 233 patients the mean age was 42.8±11.6(17-76), 164 were male (70.0%). In 2.year graft loss developed in 9 (7.5 %) and 18 (15.9%) of G2 and G1 respectively (p=0.045). Graft losses occurred 10 in the G1A+ and 8 in the G1A-(p=0,330). In G5 graft loss occurred in 12 (21%) and 9 (14%) in G5-1 and G5-2 respectively(p=0.62). Graft loss occurred in 7 (23%) and 5 (19%) in G5-1A+ and G5-1A- respectively (p=0.71). Considering the first two years, graft loss in G5-1 was higher than in G5-2(p=0.023). Higher SUA levels increased the graft loss by 3.6 times compared to normal SUA levels (95% confidence interval: 1,2-12.70).

Conclusions: There was a significant relationship between high SUA levels and graft loss in KTRs in 2 years and 5 years. Treatment of high SUA with allopurinol therapy had a protective effect on renal functions. So, treatment of hyperuricemia, such as allopurinol, can be a good option to preserve kidney function in KTRs.

Keywords: *Uric acid, kidney transplant recipient, renal dysfunction, allopurinol*

1. Introduction

There are many risk factors for graft loss. In addition to immunological factors, hypertension, increased cardiovascular disease risk, recurrence of primary kidney disease, metabolic disorders such as hyperglycemia, lipid disorders, electrolyte disorders, and hyperuricemia are also important. Hyperuricemia associated with endothelial dysfunction, mitochondrial dysfunction, glomerular capillary injury, and tubular obstruction of urate crystal formation can cause structural kidney damage[1]. Elevated serum uric acid levels (SUA) appear to be associated with accelerated renal dysfunction in chronic kidney disease (CKD) patients[2 3]. There are also arguments that there may be an additional risk factor for graft loss in KTRs[4]. Studies show the effect of high serum levels of uric acid on the loss of function in renal allograft and chronic kidney disease [6].

Allopurinol is a xanthine oxidase inhibitor that increases urinary excretion of uric acid and is well tolerated. The literature has shown contrary results on this front. Some studies have shown that allopurinol can slow GFR loss in renal KTRs[7 8], while in another study, it was ineffective in KTRs[9]. In this retrospective observational cohort study, the effects of elevated serum uric acid and reduction of serum uric acid by allopurinol on renal function were evaluated in kidney transplant recipients.

2. Materials and methods

This retrospective study included 233 KTRs who underwent routine controls in the outpatient clinic within 12 months. The level of serum uric acid > 7 mg / dL for men and > 6 mg/dl for women were considered to be high SUA (G1) (n=113). The remaining 120 patients (G2) had normal SUA levels. Allopurinol (150 mg every other day) was given to reduce the high uric acid level. Fifty-seven KTRs (G1-A+) with high SUA levels received allopurinol treatment, and 56 patients (G1-A-) did not. The 118 patients (G5) followed for more than 5 years were evaluated separately. Of these, 56 (G5-1) had high SUA levels, and 62 (G5-2) were normal. Of the 56 patients with high SUA levels, 26 (G5-1-A+) received allopurinol treatment, and 30

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(G5-1A-) did not (Table 1). Patients received triple immunosuppressive therapy (CNI+MMF or mTOR inhibitor and prednisolone) as standard therapy. In addition, patients continued antihypertensive drugs as needed.

Exclusion criteria: Patients with acute renal insufficiency, clinically overt heart failure, hepatic insufficiency, uncontrolled blood pressure (>140/90mm/Hg), and diuretic therapy were excluded from the study.

Age, sex, duration of post-transplant period, and laboratory measurements, including glucose serum uric acid, BUN, creatinine, sodium, potassium, chlorine, calcium, total protein, albumin, complete blood count, and drug levels were provided retrospectively from medical records. Control visits were recorded as 1 – Baseline, 2 – Six-month control, 3 – One-year control, 4 – Second-year control, and 5 – Fifth-year control. Glomerular filtration rate (GFR) was measured using CKD-EPI. Permanent reduction of GFR to 10 ml/min was considered graft loss.

The SPSS 20.0 Windows package program was used for the statistical analyses, and a p-value <0.05 was considered significant. Frequency analysis, chi-square test, t-test, and correlation analysis were also used. Repeated Measurements Analysis was applied to evaluate the change in the measurements obtained in the time interval.

This study was approved by Medical Faculty Clinical Research Ethics Council Meeting #91 on September 2019 Decision Number 21.

This article was previously posted to a pre-print server on April 27, 2020.

3. Results

Of the 233 patients included in the study, 164 were male (70.0%), and the mean age of all patients was 42.8±11.6 (17-76). The demographic characteristics of the patients are shown in Table 1. The serum uric acid levels and glomerular filtration rate of patients at each follow-up period are shown in Table 2. According to uric acid levels, there was graft loss in 9 patients (7.5%) from the G2 (n=120) and in 18 patients (15.9%) from the G1. In the first and second-year follow-ups, graft loss was significantly higher in G1 than in G2 (p=0.045). In G1, 10 graft losses occurred in the G1-A+ and 8 in the G1-A-; however, there was no difference between them (p=0.330).

Figure 1

According to serum uric acid levels, eGFR values of kidney transplant recipients during 2-year follow-up.

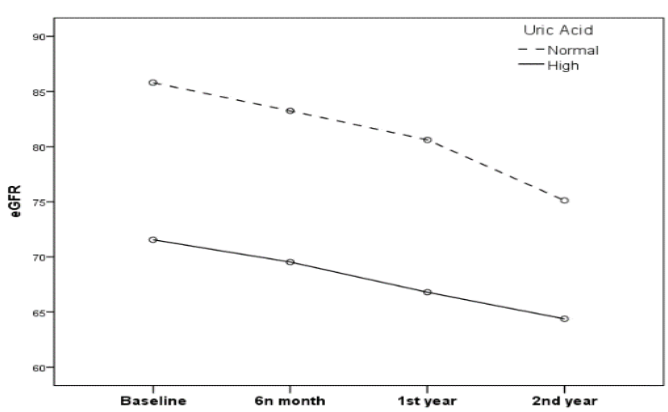


Figure 2

eGFR values according to allopurinol therapy during 2 years follow-up in kidney transplant recipients.

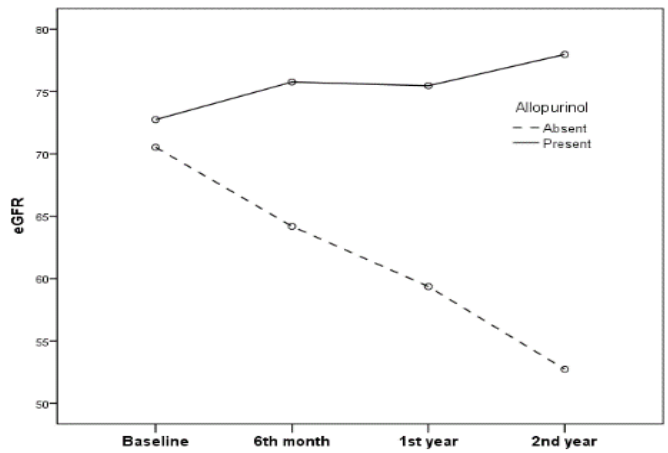


Figure 3

eGFR values during 5 years follow-up in patients

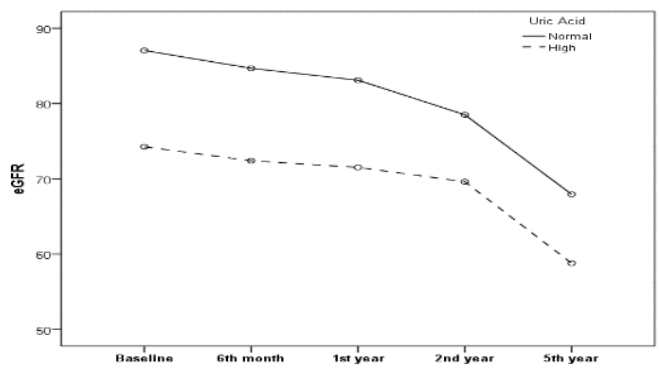
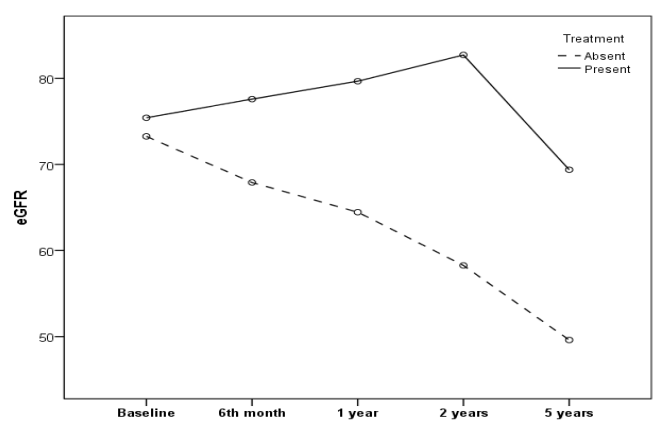


Figure 4

eGFR values according to allopurinol therapy during 5 years follow-up in kidney transplant recipients with high serum uric acid level



In the five-year follow-up group (G5, 118 patients), graft loss occurred in 12 (21%) patients from the G5-1 (n=56) and in 9 (14%) from the G5-2 (n=62). There was no statistical difference between these two groups (p=0.62). Graft loss occurred in 7 (23 %) patients from the G5-1-A+ group (30 patients) and in 5 (19%) patients from the G5-1A- group (26 patients). There was no significant difference between these two groups (p=0.71).

However, in the G5-1 (56 patients, n=118), 8 graft losses developed in the first two years, and 4 graft losses occurred between 2 and 5 years. Meanwhile, in the group with normal SUA (n=62), there were 2 graft losses in the first two years and 7 between 2 and 5 years (Table 3).

Considering the first two years in patients followed for five years, graft loss was significantly higher in G5-1 over the G5-2 (p=0.023), and higher SUA levels increased the incidence of graft loss by 3.6 times compared to normal SUA levels (95% confidence interval: 1.2-12.70).

Compared to baseline, GFR decreased in both the hyperuricemic group (G1) and normo-uricemic group (G2) followed for 2 years (p<0.001), and the decline was the same in both groups (p=0.691) (Figure 1). There was also a change in GFR in both the G1-A+ and G1-A- (p=0.043), and this change was significant in favor of allopurinol patients (p <0.001) (Figure 2).

In correlation analysis, it was found that GFR values significantly decreased in group with high uric acid (n=56) (G5-1) more than normal uric acid (n=62) (G5-2) during the 5-year follow-up (p<0.001). However, the decrease levels were similar in both groups (p=0.818) (Figure 3).

Compared to baseline, GFR values in G5-1-A+ during the 5-year follow-up decreased significantly (p=0.001). The levels of decrease of GFR were also significantly different depending on whether allopurinol treatment was provided (p=0.034). As seen in Figure 4, in patients treated with allopurinol, GFR increased in the first two years. In the second year, the reno-protective effect of allopurinol was still significant, and this effect continued into the fifth year. GFR was higher in those treated with allopurinol than those without allopurinol treatment at a difference of 20 mL/min (Figure 4).

Table 1

Groups of KTRs according to serum uric acid levels, follow-up period, and KTRs

Groups	Male	Mean age	N	Group Definition
G1	77 (%68,1)	43,2±11,6	113	Patients with high SUA levels followed for 2 years
G2	87 (%72,5)	42,6±11,7	120	Patients with normal SUA levels followed for 2 years
Total	164 (%70)	42,8±11,6	233	
G1-A+	45 (%78,9)	45,1±12,2	57	Patients with high SUA levels were treated with allopurinol and followed for 2 years.
G1-A-	32 (%57,1)	41,2±10,7	56	Patients with high SUA levels were not treated with allopurinol and followed for 2 years.
G5	85 (%72)	45,3±11,1	118	Patients followed for 5 years
G5-1	39 (%69,6)	45,2±11,5	56	Patients with high SUA levels followed for 5 years
G5-1A+	12 (%46,2)	43,7±9,6	26	Patients treated with allopurinol followed for 5 years
G5-1A-	21 (%70)	46,4±13,1	30	Patients with high SUA levels were not treated with allopurinol and followed for 5 years.
G5-2	46 (%74,2)	45,4±10,9	62	Patients with normal SUA levels followed for 5 years

Table 2

Serum uric acid levels and glomerular filtration rate of the groups at the follow-up period

		G1+G2 n=233	G1 n=113	G2 n=120	G1A+ n=57	G1A-n=56	G5 n=118	G5-2 n=62	G5-1 n=56	G5A+ n=30	G5A- n=26
1.	UA	6,6±1,8	7,94±1,2	5,16±1,0	8,2±1,5	7,5±0,9	6,6±1,9	5,3±1,1	8,2±1,5	8,6±1,6	7,6±1,1
	GFR	76,7±29,7	69,0±2,9	84,1±2,4	68,4±33,5	69,6±27,8	80,9±29,4	87,1±26,8	74,3±30,8	73,3±33,5	75,4±28,1
2.	UA	6,7±1,7	7,43±1,7	5,98±1,4	7,9±1,7	6,9±1,4	6,6±1,6	5,8±1,3	7,5±1,5	7,9±2,0	6,9±1,3
	GFR	72,9±29,2	64,0±2,8	81,2±2,3	61,5±30,6	66,6±29,7	78,8±27,1	84,7±24,6	72,4±28,4	67,9±25,6	77,6±31,0
3.	UA	6,6±1,7	7,28±1,8	5,87±1,3	7,6±2,0	6,9±1,2	6,6±1,6	5,9±1,4	7,4±1,6	7,9±1,6	6,7±1,3
	GFR	71,1±30,5	61,7±3,0	79,6±2,7	55,6±26,8	69,1±32,6	77,6±25,9	83,1±25,6	71,5±25,1	64,4±22,3	79,7±26,1
4.	UA	6,7±1,6	7,40±1,7	6,02±1,3	7,9±1,6	6,7±1,3	6,6±1,5	5,9±1,3	7,4±1,3	8,1±1,2	6,6±1,0
	GFR	70,2±31,6	64,4±3,8	75,1±3,0	52,7±30,3	78,0±31,9	74,3±28,6	78,5±24,9	69,6±31,7	58,3±28,5	82,7±30,5
5.	UA						6,9±1,6	6,6±1,7	7,4±1,4	7,5±1,2	7,3±1,5
	GFR						63,6±30,7	67,9±27,6	58,8±33,4	49,6±30,2	69,4±34,4

GFR: Glomerular filtration rate, UA: Uric acid, 1. Baseline, 2. 6. Month, 3. 1. Year, 4: 2. year, 5. 5. Year

Table 3
Graft loss of the groups at the follow-up period

Graft Loss	G2 120	G1 113	P	G1 A+	G1 A-	p	G5-2 62	G5-1 56	p	G5-1 A+ 30	G5-1 A- 26	p
2. year	9	18	0,045	10	8	0.33	2	8	0.018			
%	7.5%	15.9%	0.023									
5. year							9	12	0.062	7(23%)	5(19%)	0,71

4. Discussions

The prevalence of hyperuricemia in KTRs is 42.1 %[1º]. It can even be detected in 30-84% of patients treated with cyclosporine as a calcineurin inhibitor (CNI)[11]. Similarly, this study determined hyperuricemia to be 48.4% in KTRs. In the normal population, the prevalence is around 10-15%[11]. Factors that lead to increases in the tendency to hyperuricemia include advanced age, gender, low GFR, drugs such as diuretics, beta-blockers, CNIs (especially cyclosporine), as well as high body mass index and pre-transplant dialysis duration [7 11-13].

Uric acid is a potentially modifiable risk factor for the development and progression of CKD. Some reports suggest that hyperuricemia is related to the severity of CKD[2 3] or that it indicates progression to end-stage renal disease (ESRD)[14]. In a study, it was found that the treatment of hyperuricemia improves renal function[8]. Hyperuricemia is common in kidney transplant patients due to the use of calcineurin inhibitors and reduced kidney graft function. Allopurinol, which has been the first treatment option in patients with hyperuricemia, has considerable adverse effects, and its dosage adjustment is difficult. On renal graft survival, the effect of uric acid lowering therapy is still controversial, with some benefits, and may be the result of chronic allograft nephropathy and graft failure [15 17]. The KTRs with hyperuricemia had lower GFR, and progressive GFR loss was higher in our study. The SYMPHONY study suggests that hyperuricemia is not an independent risk factor for graft failure[18]. In addition, Kim et al. concluded that there is no risk factor for graft outcome according to the data obtained using the Marginal Structural Model[19]. According to the Korean-based meta-analysis of Miyeun et al. [4], hyperuricemia is an indicator of renal damage due to decreased excretion, and its association with normal renal function may indicate a negative endpoint, such as ESRD, similar to the present study. In a meta-analysis of Liu et al. [2º], high SUA lowering therapy with different drugs slows the development of CKD.

In the present study high SUA levels was determined as a possible risk factor for graft loss in the first two years. Treatment with allopurinol reduces the progression of kidney failure and even improves it initially. Allopurinol therapy prevented GFR loss in both the first, second, and fifth-year follow-up periods.

Uric acid itself is a source of oxidative stress and inflammation. In order to investigate the effect of elevated SUA levels on CKD progression in KTRs, multicenter studies that exclude the effect of rejection and graft dysfunction by biopsy can be used to explain the adverse effects of hyperuricemia further explain the adverse effects of hyperuricemia.

Similarly our study, it has been reported that febuxostat, another uric acid lowering drug, slowed GFR decline in 100 asymptomatic hyperuricemic chronic kidney disease patients in stages 3 and 4 over a 12-month follow-up period. Adverse events did not differ in the control group. They also titrated febuxostat dose for serum uric acid level <6 mg/dL[21]. Allopurinol therapy in KTRs with high SUA levels also positively affected renal function in our study. There are different reports about hyperuricemia and its available treatments. According to previous studies in KTRs, hyperuricemia has a negative effect on kidney function [13 2º 22], yet there is no relationship[7 9] or treatment of hyperuricemia preserves kidney function[21 23].

The limitations of our study are that it is single-centered and the number of patients is small.

In conclusion, we determined that hyperuricemia accompanied by loss of GFR and allopurinol therapy preserved renal function in kidney transplant recipients with high serum uric acid levels in follow-up 2 and 5-year periods. So, hyperuricemia should be treated, and low-dose allopurinol can be a good option, thus preventing the loss of kidney function in kidney transplant recipients.

Statement of ethics

This study was approved by Medical Faculty Clinical Research Ethics Council Meeting #91 on September 2019 Decision Number 21.

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Conflict of interest statement

Author declare that they have no financial conflict of interest with regard to the content of this report.

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Comparison of the Laboratory Values at Admission to Palliative Care Unit: Geriatric vs Non-Geriatric Patients

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Abstract

Aim: The aim of the present study is to compare the laboratory findings during the palliative care unit (PCU) admission of non-geriatric and geriatric patients and to evaluate the effects of these findings.

Methods: In the present study medical records of the patients hospitalized in PCU between 18.10.2018-18.10.2020 were reviewed. The patients were evaluated in 2 groups: Group I; 65 years and older and Group II; 18-64 years old. Demographic data and laboratory values of the patients (C-reactive protein, glucose, urea, creatinine, sodium, potassium, albumin, mean platelet volume and platelet, lymphocyte, neutrophil counts) were recorded. From these values, CRP/albumin, neutrophil/lymphocyte ratio, and platelet/lymphocyte ratio were calculated. Length of stay and mortality were also recorded.

Results: A total of 454 patients (Group I: 249 and Group II: 205) were included in the study. Blood glucose, urea, creatinine and sodium values were found to be statistically higher in Group I (p=0.027, p<0.001, p<0.001 and p=0.032, respectively). Albumin values were 2.70 g/dL (2.30–3.00 g/dL) in Group I and statistically lower than Group II (p<0.001). Albumin < 2.5 g/dL [odds ratio (OR) 2.75, 95% confidence interval (CI): 1.52–4.96, p < 0.001] was determined as an independent risk factor for mortality in Group I. While the sensitivity was determined as 79% for the albumin cut-off value of 2.5 g/dL, the specificity was determined as 66%.

Conclusions: Among the laboratory values at the time of admission of geriatric patients admitted to the PCU, only albumin has a prognostic value in poor sensitivity and specificity.

Keywords: *Palliative Care Unit, Geriatric, Mortality*

1. Introduction

In line with the recommendations of the World Health Organization (WHO), palliative care should be applied to anyone suffering from life-threatening diseases and should be started early according to the course of the disease. However, in clinical practice, palliative care is usually initiated much later and is often limited to cancer patients. Early integration of patients into palliative care is known to lead to better symptom control, prolonged survival, and better quality of life [1].

The elderly population is increasing all over the world, and the population over 65 in the United States is expected to double by 2050, from 9% in 1960 [2].

With the prolongation of average lifespan, the pressure of chronic diseases on health systems also increases [3]. This situation, which concerns the geriatric population, increases the need for palliative care units (PCU) proportionally. In addition, despite all this increase in the geriatric population, we cannot ignore the fact that the majority of the population still consists of non-geriatric people. The fact that non-geriatric people may need palliative care should not be ignored, although it is not as common as in the geriatric individuals. As a result of the combination of all these factors, the importance and requirement of PCUs are increasing day by day [4].

Geriatric care, palliative care, intensive care and home care services are intertwined in the Turkish health system and practice. The purpose of this integrated and intertwined structure is to provide patients with the necessary care in every environment. Determining the patient profiles and factors affecting the length of stay in PCUs will enable more efficient use of the limited number of PCU beds. In addition, the determination of the differences of these factors between age groups, especially between geriatric and non-geriatric patients, may be important for the goal and quality of care. For all these reasons, it is important to examine the clinical characteristics of the patients and the factors affecting the prognosis

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in PCU. Among these factors, it appears as laboratory findings that appear to be modifiable and/or correctable. In particular, the effect of laboratory findings during admission to PCU profoundly affects the initiation of treatment and palliative care.

The aim of the present study is to compare the laboratory findings during the PCU admission of non-geriatric and geriatric patients and to evaluate the effects of these findings.

2. Materials and methods

The present retrospective study was approved by the ethics committee of Selcuk University Medical Faculty (Approval date and number: 13.11.2021 and 2021/08) and the medical records of the hospitalized patients in Selcuk University Medical Faculty Hospital palliative care unit between 18.10.2018-18.10.2020 were reviewed. The present study was conducted in accordance with the principles of the Declaration of Helsinki. Patients younger than 18 years of age and patients with a diagnosis of malignancy were excluded from the study. In addition, patients with more than one admission were also excluded from the study. The patients were evaluated in 2 groups: Group I; 65 years and older and Group II; 18-64 years old. The following variables evaluated at admission to PCU were obtained from medical records: Age, gender, platelet, mean platelet volume (MPV), lymphocyte, neutrophil counts, glucose, sodium, potassium, urea, creatinine, albumin and the C-reactive protein (CRP). CRP/albumin ratio, platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR) were calculated from the data obtained from medical records. Apart from these data, length of stay in PCU and survival were also obtained from medical records. The starting point for survival was evaluated for the date of first admission to the PCU and continuing for three months.

2.1. Statistical Analysis

Statistical analysis was performed using the SPSS Version 22.0 (IBM, Chicago, IL, USA). Evaluation of data in terms of normality was performed with Shapiro–Wilk and Kolmogorov–Smirnov tests. Categorical data were expressed as number (percentages). The numerical data resulting from the descriptive statistics were expressed as the median [interquartile range (IQR)]. Patients were divided into 2 groups according to their mortality results; the survivor and the non-survivor groups. Demographic and clinical data were compared using Chi-Square or Fisher's Exact test for categorical variables and Mann-Whitney U test for numerical variables. A p value <0.05 is statistically significant. The significant parameters of univariate analysis were subjected to multivariate linear regression analysis to identify any independent risk factor associated with mortality. Receiver operating characteristic (ROC) curve analysis was performed.

3. Results

Of the 820 patients admitted to PCU between 18.10.2018-18.10.2020, 454 were eligible for inclusion criteria and analysis of data. While there were 249 patients in Group I, there were 205 patients in Group II. Comparison of laboratory values and general characteristics of two groups are presented in Table 1. A statistically significant difference was found between the groups in terms of gender distribution (p<0.001). While 51.4% of the patients in Group I were female, only 38% of the patients in Group II were female. When the groups were compared in terms of accompanying illnesses, it was seen that there was no difference only in the presence of neurological disease (p=0.153), however, diabetes, hypertension, organ failure and nutritional disorders were found to be significantly higher in Group I (<0.001, <0.001, <0.001 and 0.004, respectively).

Table 1

Comparison of General Characteristics and Laboratory Values of Two Groups

Variable	Group I (n= 249) Median (IQR), n (%)	Group II (n= 205) Median (IQR), n (%)	p
Age, year	77.00 (71.00-82.00)	44.00 (30.00-56.00)	<0.001
Gender, (M/F) n (%)	121 (48.6) / 128 (51.4)	127 (62.0) / 78 (38.0)	0.004
Length of Stay, day	12.00 (7.00-18.00)	10.00 (6.00-21.00)	0.543
Accompanying Illnesses, n(%)			
Diabetes	71 (28.5)	16 (7.8)	<0.001
Hypertension	121 (48.6)	26 (12.7)	<0.001
Neurological	115 (46.2)	81 (39.5)	0.153
Diseases	56 (22.5)	16 (7.8)	<0.001
Organ Failure	144 (57.8)	91 (44.4)	0.004
Nutritional Disorder			
Blood Glucose, mg/dL	114.00 (95.00-139.00)	108.00 (93.00-124.00)	0.027
Blood Urea, mg/dL	46.00 (32.00-68.00)	34.00 (27.00-46.00)	<0.001
Blood Creatinine, mg/dL	0.74 (0.53-1.03)	0.55 (0.40-0.75)	<0.001
Blood Sodium, mEq/L	138.00 (135.00-141.00)	137.00 (135.00-140.00)	0.032
Blood Potassium, mmol/L	3.93 (3.49-4.30)	3.98 (3.68-4.33)	0.257
Neutrophil count, (10^9 /L)	6.40 (4.23-9.40)	6.80 (5.02-10.26)	0.099
Lymphocyte count, (10^9 /L)	1.20 (0.80-1.70)	1.50 (1.00-2.10)	<0.001
Platelet count, (10^9 /L)	239000 (178000-323000)	269000 (194000-385000)	0.007
Mean Platelet Volume, fl	8.70 (7.80-9.50)	8.30 (7.70-9.15)	0.034
Neutrophil to lymphocyte ratio	5.62 (3.08-10.55)	4.58 (2.96-8.13)	0.017
Platelet to lymphocyte ratio	216.11 (140.00-310.66)	196.15 (135.76-274.54)	0.050
C-reactive protein, mg/L	4.32 (1.50-9.14)	4.98 (1.55-10.30)	0.590
Albumin, g/dL	2.70 (2.30-3.00)	2.90 (2.50-3.30)	<0.001
C-reactive protein/Albumin Ratio	1.72 (0.54-3.81)	1.68 (0.50-3.74)	0.926
Mortality, n (%)	63 (25.3)	30 (14.6)	0.005

IQR: Inter Quantile Range, M: Male, F: Female

Blood glucose, urea, creatinine and sodium values were found to be statistically higher in Group I (p=0.027, p<0.001, p<0.001 and p=0.032, respectively). The median lymphocytic and platelet counts and the MPV were higher in Group I; 1.20 (0.80–1.70), 239000 (178000–323000) and 8.70 (7.80–9.50) , respectively. Albumin values were 2.70 g/dL (2.30–3.00 g/dL) in Group I and statistically lower than Group II (p<0.001). The NLR, PLR and CRP/albumin ratio, calculated from the above laboratory values, were as follows in Group I and statistically higher than Group II: 5.62 (3.08–10.55), 216.11 (140.00–310.66) and 1.72 (0.54–3.81), respectively. The mortality rate of the patients were higher in Group I 25.3% (n =63). The patient characteristics of Group I with regard to mortality are shown in Table 2. Survivor patients of Group I, albumin values were higher (2.70 g/dL vs 2.40 g/dL; p < 0.001), than the non-survivor patients. In the non-survivor patients of Group I, blood urea values were higher (53.00 g/mdL vs 44.00 mg/dL; p=0.013), than the survivor patients.

Table 2

The Patient Characteristics of Group I in Terms of Mortality

	Univariate analysis			Multivariate analysis	
	Mortality		P	OR	P
	Survivor (n= 186)	Non-Survivor (n= 63)			
	Median (IQR), n (%)	Median (IQR), n (%)			
Age, year	76.00 (71.00-82.00)	78.00 (71.00-84.00)	0.334		
Gender, (M/F) n (%)	86 (46.2) / 100 (53.8)	35 (55.6) / 28 (44.4)	0.201		
Length of Stay, day	11.00 (7.00-17.00)	13.00 (7.00-22.00)	0.171		
Accompanying Illnesses, n(%)					
Diabetes	53 (28.5)	18 (28.6)	0.991		
Hypertension	94 (50.5)	27 (42.9)	0.292		
Neurological Diseases	91 (48.9)	24 (38.1)	0.136		
Organ Failure	46 (24.7)	10 (15.9)	0.146		
Nutritional Disorder	101 (54.3)	43 (68.3)	0.053		
Blood Glucose, mg/dL	112.00 (94.00-137.00)	122.00 (99.00-144.00)	0.118		
Blood Urea, mg/dL	44.00 (30.75-65.25)	53.00 (36.00-77.00)	0.013		NS
Blood Creatinine, mg/dL	0.76 (0.57-1.03)	0.70 (0.45-1.06)	0.089		
Blood Sodium, mEq/L	138.00 (136.00-141.00)	137.00 (134.00-141.00)	0.368		
Blood Potassium, mmol/L	3.98 (3.55-4.30)	3.85 (3.36-4.41)	0.210		
Neutrophil count, mm^3 [a]	6.40 (4.24-9.09)	7.00 (4.20-10.90)	0.243		
Lymphocyte count, mm^3	1.20 (0.80-1.70)	1.10 (0.60-1.55)	0.318		
Platelet count, mm^3	240000 (180000-324000)	222000 (154000-324000)	0.220		
Mean Platelet Volume, fl [a]	8.70 (7.90-9.60)	8.50 (7.60-9.30)	0.237		
Neutrophil to lymphocyte ratio	5.48 (3.03-9.94)	5.94 (3.18-12.48)	0.151		
Platelet to lymphocyte ratio	214.26 (138.84-311.30)	224.41 (140.00-307.50)	0.765		
C-reactive protein, mg/L [a]	4.65 (1.72-9.12)	2.80 (1.34-9.37)	0.284		
Albumin, g/dL	2.70 (2.40-3.10)	2.40 (2.00-2.90)	<0.001	2.75 (1.52-4.96)	<0.001
C-reactive protein/Albumin Ratio [a]	1.85 (0.55-3.79)	1.12 (0.46-4.41)	0.601		

The parameters in bold indicates the significant ones in univariate and multivariate analysis. a Marked parameters which were significant in univariate analysis and not associated with each other were included in the multivariate analysis. IQR: Inter Quantile Range, OR: Odds Ratio, M: Male, F: Female.

Table 3

Receiver operating characteristic analysis for the prediction of mortality in Group I. Cut-off for Survivor group versus Non-Survivor group mean Albumin based on ROC analysis

	AUC	p value	Asymptotic 95 % confidence intervals lower bound -upper bound	Cut off value
Mean Albumin	0.358	<0.001	0.227-0.443	< 2.5
		Outcome: Death		
		Yes	No	Total
Mean Albumin < 2.5 Yes		50	63	113
Mean Albumin < 2.5 No		13	123	136
Mean Albumin < 2.5 Total		63	186	249
				95 % confidence intervals
Sensitivity		0.79		0.67-0.88
Specificity		0.66		0.58-0.72
Predictive value of positive test		0.44		0.38-0.50
Predictive value of negative test		0.90		0.85-0.93
Positive likelihood ratio		2.34		1.85-2.97
Negative likelihood ratio		0.31		0.19-0.51

ROC: Receiver operating characteristic; AUC: Area Under The Curve.

Table 4

The Patient Characteristics of Group II in Terms of Mortality

	Univariate analysis			Multivariate analysis	
	Mortality		P	OR	P
	Survivor (n= 175)	Non-Survivor (n= 30)			
	Median (IQR), n (%)	Median (IQR), n (%)			
Age, year	42.00 (29.00-55.00)	55.00 (41.00-59.00)	0.006		NS
Gender, (M/F) n (%)	111 (63.4) / 64 (34.6)	16 (53.3) / 14 (46.7)	0.293		
Length of Stay, day	10.00 (6.00-20.00)	10.00 (6.00-36.00)	0.577		
Accompanying Illnesses, n(%)					
Diabetes	16 (9.1)	0	0.085		
Hypertension	21 (12.0)	5 (16.7)	0.478		
Neurological Diseases	74 (42.3)	7 (23.3)	0.060		
Organ Failure	11 (6.3)	51 (16.7)	0.059		
Nutritional Disorder	72 (41.1)	19 (63.3)	0.054		
Blood Glucose, mg/dL	107.00 (93.00-124.00)	116.00 (95.00-127.00)	0.539		
Blood Urea, mg/dL	33.00 (27.00-44.00)	35.00 (27.00-55.00)	0.320		
Blood Creatinine, mg/dL	0.55 (0.41-0.74)	0.52 (0.36-0.84)	0.955		
Blood Sodium, mEq/L	137.00 (135.00-140.00)	136.00 (132.00-139.00)	0.087		
Blood Potassium, mmol/L	4.00 (3.70-4.30)	3.78 (3.51-4.27)	0.077		
Neutrophil count, mm^3 [a]	6.80 (5.00-10.30)	6.75 (5.33-9.87)	0.926		
Lymphocyte count, mm^3	1.56 (1.10-2.20)	0.97 (0.49-1.38)	<0.001		NS
Platelet count, mm^3	273000 (198000-389000)	245000 (182000-346000)	0.204		
Mean Platelet Volume, fl [a]	8.40 (7.70-9.20)	8.20 (7.70-9.05)	0.508		
Neutrophil to lymphocyte ratio	4.25 (2.93-7.06)	7.65 (3.76-13.41)	0.004		NS
Platelet to lymphocyte ratio	187.77 (133.10-264.58)	219.97 (165.47-533.93)	0.021		NS
C-reactive protein, mg/L [a]	4.70 (1.50-10.01)	7.56 (2.40-13.67)	0.115		
Albumin, g/dL	3.00 (2.60-3.35)	2.47 (1.99-3.02)	0.002		NS
C-reactive protein/Albumin Ratio [a]	1.65 (0.50-3.42)	2.83 (0.93-5.64)	0.041		NS

The parameters in bold indicates the significant ones in univariate and multivariate analysis. a Marked parameters which were significant in univariate analysis and not associated with each other were included in the multivariate analysis. IQR: Inter Quantile Range, OR: Odds Ratio, M: Male, F: Female.

Multivariate analysis was applied for the parameters with significant results according to univariate analysis. Among the evaluated parameters, only albumin <2.5 g/dL was determined as an independent risk factor [odds ratio (OR) 2.75, 95% confidence interval (CI): 1.52–4.96, p < 0.001].

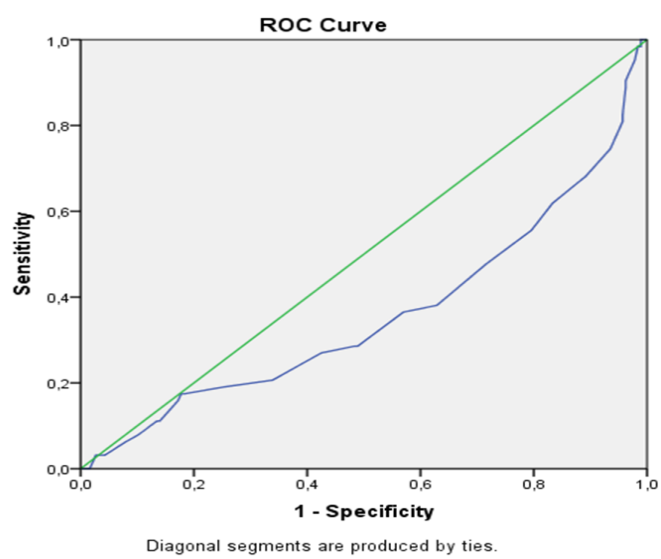
The ROC curve analysis for the prediction of cut-off value and mortality of Group I (survivor's vs non-survivor's) was performed. Albumin values obtained as a result of the ROC curve analysis are shown in Table 3. The cut-off value of mean albumin value according to the ROC curve analysis was found as 2.5 g/dL (Figure 1). Sensitivity (79%) and specificity (66%) for albumin cut-off value (2.5 g/dL) determined as a result of ROC analysis.

Positive and negative predictive values were detected as 0.44 and 0.90, respectively. Positive likelihood ratio and negative likelihood ratio were detected as 2.34 and 0.31, respectively. The area under the curve (AUC) was 0.358 and 95% CI: 0.227–0.443 (p < 0.001) (Table 3).

The patient characteristics of Group II in terms of mortality are shown in Table 4. Survivor patients of group II, lymphocyte counts were higher (1.56 mm3 vs 0.97 mm3; p < 0.001), than the non-survivor patients. In the non-survivor patients of group II, NLR, PLR and CRP/albumin ratio were higher (7.65 vs 4.25; p=0.004, 219.97 vs 187.77; p=0.021 and 2.83 vs 1.65; p=0.041, respectively), than the survivor patients.

Figure 1

Receiver Operating Characteristic (ROC) curve for mean Albumin Value



Multivariate analysis was applied for the parameters with significant results according to univariate analysis. Among the evaluated parameters none of them could be determined as an independent risk factor.

4. Discussions

In this retrospective study, laboratory values at admission to PCU of geriatric (65 years and older) and non-geriatric (18-64 years old) patients admitted were compared. Among the evaluated parameters, only albumin values were found to have an effect on predicting mortality in the geriatric patient group, but this effect was also weak. Although there are many studies to predict mortality in PCUs, most of these studies have been performed in patient populations including cancer patients. In addition, studies in which patients under the age of 65 are evaluated as a separate group are limited, since the elderly patient groups are naturally the first to come to mind when PCU is mentioned.

In a survey conducted with palliative care doctors in Canada, it was seen that there was no consensus on the tools used to predict the prognosis of patients [5]. Participants also stated that there is a need for the development of training materials and programs to optimize the understanding of prognostic information.

It was stated that the WPCBAL score developed by Niki et al. objectively predicts the prognosis of two or three weeks for terminal cancer patients in the palliative care unit [6]. The following laboratory parameters were used in the WPCBAL score: White blood cell, platelet, CRP, blood urea nitrogen, aspartate aminotransferase, and lactate dehydrogenase. It was also stated that the WPCBAL score was superior in comparison with the previously described Glasgow prognostic score (GPS) and Palliative Prognostic Index (PPI) [7,8].

Although the half-life of albumin, an acute phase protein synthesized by the liver, is 15-19 days, this period is much shorter in critically ill patients [9]. Binding, which is one of the primary tasks of albumin, gains more importance especially in the geriatric population. In hypoalbuminemia, the concentration of free drugs in the circulation increases, and as a result, increased bioavailability may cause side effects [10]. In previous studies, hypoalbuminemia was associated with increased mortality, prolonged hospital stay, and other complications [9,11]. Albumin has an increased prognostic role in patients with severe comorbidities. However, it is unclear whether it can be a marker for mortality in patients admitted to PCU. In a retrospective study evaluating the effect of albumin levels on survival at admission to PCU, it was reported that albumin levels below 3.1 g/dL were associated with poor survival [12]. In the present study, albumin values below 2.5 g/dL were found to be an independent risk factor for mortality in geriatric patients.

In a study conducted with cancer patients, young age, sodium and BUN values were found to be prognostic factors in PCU [13]. Unlike this study, it was shown inthe present study that sodium and BUN values are not a prognostic factor in both geriatric and non-geriatric patients. In addition, as another difference, mortality was lower in young patients in the present study compared to geriatric patients. We think that the reason for this fundamental difference is that cancer patients weren't included in the present study.

In a study conducted in patients with malignant hematological disorders treated in the palliative care unit, it was reported that low platelet count, high LDH, and low albumin levels were associated with poor prognosis [14].

Apart from laboratory parameters, clinical features of PCU patients were also evaluated. It has been reported that advanced pressure ulcer is the most important clinical factor prolonging the hospital stay in PCU patients [15].

The limitations of the present study are that it is retrospective, single-centered, and no scoring was applied to the patients at the time of admission to the PCU.

5. Conclusion

In non-geriatric PCU patients, routinely evaluated laboratory values during hospitalization do not have a prognostic significance, whereas in geriatric patients, only Albumin has a prognostic value in poor sensitivity and specificity. It is obvious that prospective studies with wider participation are needed on this subject.

Statement of ethics

This study was approved by Selcuk University Medical Faculty ethics committee (Approval date and number: 13.11.2021 and 2021/08)

Conflict of interest statement

Author declare that they have no financial conflict of interest with regard to the content of this report.

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Comparison of Clinical Results of Lefort and Total Colpocleisis Operations Performed in Patients with Uterovaginal Pelvic Prolapse

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Abstract

Aim: The aim of this study is to compare the clinical results and operation success of Lefort and total colpocleisis surgeries performed in patients with stage 2 and above pelvic organ prolapse (POP).

Methods: Patients who underwent Lefort and total colpocleisis surgery in our clinic between 2015 and 2022 were included in this retrospective cohort study. Demographic data of the patients, presence of relapse and de novo incontinence symptoms, postoperative complications and management, and clinical results were obtained from the hospital information system and patient files.

Results: A total of 40 patients were included in the study. The mean age of the patients was 75.7±6.7 years. At least one comorbid disease was present in 67.5% (n=27) of all population. The anatomical success rate was 95.4% in patients with total colpocleisis during the one-year follow-up and 94.4% in Lefort colpocleisis operations. The incidence of de novo stress urinary incontinence was 10% (n=4) in the one-year follow-up, and it was observed that the patients were treated with mini-sling operations.

Conclusions: Colpocleisis is a technique that can be safely applied in the elderly and sexually inactive population due to the low perioperative complications and recurrence rates and the anatomical success rate of 90% or more. It should be kept in mind that de novo incontinence may occur after colpocleisis surgery.

Keywords: *Lefort colpocleisis, urinary incontinence, pelvic organ prolapse, total colpocleisis*

1. Introduction

Pelvic organ prolapse (POP) is defined as the complete or partial protrusion of intrapelvic structures (uterus, rectum, bladder) due to insufficient pelvic floor support[1]. POP is a common condition that affects approximately 40% of the female population and negatively affects the quality of life[2]. The presence of severe POP, especially in advanced age, brings many gynecological problems, such as urinary incontinence, difficulty defecation, and sexual intercourse[3].

The reconstructive or obliterative surgical approaches are accepted in POP surgery[4]. The ideal treatment often depends on the patient's expectations and preferences. Reconstructive surgery used more frequently, aims to restore the normal vagina anatomy. However, colpocleisis is an obliterative method in which the vaginal canal is closed, and the pelvic organs are returned to the pelvis. Partly (LeFort) and complete (total) methods can perform it.

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It can be recommended in patients who do not have an active sexual life and have comorbidities. For the first time in history, Lefort colpocleisis was applied in 1877 to a patient who wanted to avoid hysterectomy, in which the vaginal entrance was closed by suturing anterior and posterior vaginal epithelium without deep pelvic dissection[4,5]. These operations also have disadvantages, such as the lack of sexual activity, development of urinary incontinence, and failure to take an endometrial biopsy because the cervical canal cannot be reached.

It is observed that the incidence of POP increases with age, reaching a high frequency, especially between the ages of 70-79[6]. The incidence of POP recurrence up to 36%, depending on risk factors, shows the importance of surgical techniques. In particular, surgery techniques such as ease of applicability, low complication, and recurrence rates are preferred, especially in the advanced age group[7]. In this study, we aimed to share our experience with the literature on the clinical results of our patients who underwent Lefort and Total Colpocleisis surgeries in our clinic.

2. Materials and methods

This retrospective observational study was initiated by the principles of the Declaration of Helsinki after the approval of the local

Clinical Research Ethics Committee. (date:28.10.2022 number: 213). All patients who underwent Lefort colpoclesis and total colpoclesis operation at University of Health Sciences, Kanuni Sultan Süleyman T&R Hospital, between January 2015 and September 2022, and whose data could be accessed were included in the study. Exclusion criteria included pelvic inflammatory disease, suspected malignancy, previous pelvic surgery, medical unsuitability for surgery, insufficient information in the medical record, and loss of follow-up.

The pelvic examination used the Pelvic Organ Prolapse Quantification System (POP-Q) to stage prolapse. Demographic data, comorbidities, POP-Q stage, presence of incontinence, perioperative complications, cure, and recurrence rates were obtained from patient records. The study group was divided into patients who underwent Lefort (partial) colpocleisis and total colpocleisis.

In the colpocleisis technique, the anterior and posterior walls of the vagina are stitched together, shortening the length of the vaginal canal and reducing the size of the vaginal opening (introitus). Thus, the development of vaginal prolapse is prevented. The lateral vaginal epithelium is formed into a canal[8]. If a hysterectomy is performed simultaneously with the operation, it is called total colpocleisis.

The urodynamic test was applied to patients with incontinence complaints prior to surgery. In our clinic, the urodynamic test is performed by reducing the prolapse with a tampon and detecting the leak with the help of the pad test. Anti-incontinence surgery was performed in addition to the operation according to the patient's symptoms and urodynamic test. Antibiotic prophylaxis was administered to all patients pre-operatively (1–2 g intra-venous cefazolin). Additionally, we administered low molecular weight heparin prophylaxis to at-risk patients in the postoperative period.

2.1. Statistical analysis

SPSS 26.0 (SPSS Inc., Chicago, USA) program was used to analyze the data. Descriptive data are expressed as number of patients, percentage, mean and standard deviation, and distribution range. The conformity of the variables to the normal distribution was evaluated analytically (Shapiro-Wilks test) and visually (histogram). Independent sample t-test was used to analyze data with normal distribution among the groups, and the Mann-Whitney U test was used to analyze data that did not show normal distribution. The Chi-square and Fisher's exact tests were used to evaluate qualitative data. The statistical significance limit was accepted as $p<0.05$

3. Results

Total colpoclesis (n=22) or Lefort colpocleisis (n=18) was performed on 40 patients with stage 2 or higher prolapse who applied to the clinic. The demographic characteristics and clinical results of the patients are summarized in Table 1. The mean age of all patients was 75.7±6.7 years. The mean age of the patients who underwent total colpocleisis was 76.9±5.1 years. The mean age of the Lefort colpocleisis group was 74.3±8.2 years. The median parity of all population was 4 (1-13). All patients had a history of normal vaginal delivery. 52% (n=21) of the patients were sexually active. There was a history of additional disease in 65% (n=26) of the patients. There was no statistically significant difference between the groups in terms of demographic and clinical characteristics (age, gravidity, parity, sexual activity, and comorbidity). Pelvic examinations to determine POP-Q staging showed that three patients were stage 2, 16 were stage 3, and 21 were stage 4.

Perioperative and postoperative variables such as recurrence, anatomical success, and complications are shown in Table 2. Patients were routinely examined at 1, 6, and 12 months postoperatively. During the follow-up, symptomatic prolapse was observed to recur in one of the two patients in both groups after six months and in the other within one year. Patients with recurrence were treated with anterior repair and recolpocleisis. Similarly, while the postoperative anatomical success rate was 95.4% in the total colpocleisis group, this rate was 94.4% in the Lefort colpocleisis group. Considering perioperative complications, hematoma, and bladder injury were detected in one patient in both groups. De novo stress urinary incontinence developed in four patients within one year, and it was decided to perform mini-sling operations at the next follow-ups. Postoperative urinary symptoms such as dysuria, urinary retention, increased frequency of voiding, and voiding difficulty were observed in four patients. Both medical treatment and spontaneous cure were provided for the symptoms. There is no difference between the groups regarding postoperative surgical success and perioperative complications. When the question 'Are you satisfied with the surgery in general' was asked of the patients, all of them responded positively.

Table 1

Demographic parameters of patients undergoing Total/Lefort Colpocleisis surgery.

	All population	Total Colpocleisis	Lefort Colpocleisis	p
Age (years)	75,7±6,7	76,9±5,1	74,3±8,2	0.245
Gravidity (median)	4 (1-14)	4,5 (3-14)	4 (1-13)	0.229
Parity (median)	4 (1-13)	4 (3-11)	3,5 (1-13)	0.180
Sexually active, n (%)	21 (52)	12 (54)	9 (50)	0.775
Comorbidity, n (%)	26(65)	14 (63,6)	12 (66,6)	0.919
Prolapse stage, n (%)				
II	3 (7,5)		3 (16,6)	
III	16 (40)	1 (4,5)	15 (83,4)	
IV	21 (52,5)	21 (95,5)		

Demographic parameters of patients undergoing Total/Lefort Colpocleisis surgery.

Table 2

Clinical outcomes of the study population

	Total Colpocleisis n(22)	Lefort Colpocleisis n(18)
Presence of prolapse recurrence	1 (4,5)	1 (5,5)
Post-operative anatomic success	21 (95,4)	17 (94,4)
Time to recurrence (months)	6%	12%
Treatment of recurrence		
Anterior repair	1(4,5)	
Re-colpocleisis		1(5,5)
De novo SUI	2(9)	2(11,1)
Perioperative complication		
Hematoma	1(4,5)	
Bladder injury		1(5,5)

Data are given as the number of patients; n (%), SUI: Stress urinary incontinence

4. Discussions

Colpocleisis always have an essential place among urogynecology surgeries. Because age is a significant risk factor, there has always been interest in this procedure's mid- and late-term outcomes in the geriatric population[9]. A study on morbidity and mortality rates related to urogynecology surgeries showed that the risk in the population over 80 years old is increased by 13.6% compared to the population under 60 years old[10]. Surgery is more difficult in elderly patients due to additional systemic diseases and the associated surgical risks. Partially easy, less invasive and less perioperative complications of colpoclesis surgeries make the surgery easier for the geriatric age group to tolerate.

Previous studies in the literature on clinical outcomes of the obliterative procedure, including its long-term effects on quality of life. Fitzgerald et al. found that the surgery success was 95%; the patients said they were either 'very satisfied' or 'satisfied' after the colpocleisis[11]. In addition, Lefort colpocleisis was preferred as the first-line treatment in patients with advanced prolapse who were not sexually active, considering low regret and up to 90% anatomical success[12,13]. This present study analyzed mid and late-term outcomes of Total colpocleisis procedures with Lefort; It was concluded that 95.4% in the Total group and 94.4% in the Lefort group were similar. It was found to be compatible with the studies performed.

Krissi et al. concluded that the risk of recurrence after colpocleisis is associated with parameters such as postoperative longer vaginal length and wider genital hiatus[14]. This means the risk increases if the vaginal introitus is incompletely closed. It has been shown that performing high perineoplasty in patients with large introitus reduces the risk. In another study, they also recommended levator ani plication performed to reduce the recurrence of postoperative rectal prolapse[15]. It has been shown that recurrence rates can reach 30% in reconstructive surgeries performed in patients with advanced prolapse[16]. Obliterative procedures should be more prominent in these patients. In our clinic, obliterative operations are preferred more than reconstructive operations because of the low recurrence rates, especially in advanced prolapse cases in the elderly age group. In our cohort, symptomatic recurrence was observed in only two patients; treated with anterior repair and recolpocleisis. Modified recolpocleisis is recommended to treat recurrent pelvic organ prolapse after colpoclesis[17].

Sexual function and body image perception are the leading factors that significantly affect patient satisfaction after Colpocleisis. There has been some concern that obliterative procedures may adversely affect vaginal function, leading to patient dissatisfaction[18,19]. In the cohort study comparing the patient groups who underwent reconstructive vaginal approach and obliterative vaginal approach, it was concluded that there was an improvement in similar quality of life, and there was no adverse effect on body image perception[18]. We did not experience any regrets about the operation in any of our patients.

Since cervical and endometrial sampling is not possible after colpocleisis, a hysterectomy is usually performed simultaneously with colpocleisis in patients with malignancy risk. In this way, some studies argue that the risk of developing pyometra is reduced[20]. In cases where the uterus will be preserved, malignancy should be excluded with preoperative cervical and endometrial sampling. Conversely, a retrospective study showed a significantly longer operative time and higher rates of pyometra and transfusion for colpocleisis with concomitant hysterectomy compared with colpocleisis without hysterectomy, and surgical success was similar[12]. In addition, it is thought that vaginal hysterectomy performed in patients whose malignancy risk has been excluded may reduce the power of vaginal tissue to close the vagina and repair sagging, increasing the likelihood of complications.

It is recommended that the urinary incontinence complaints of the patients be questioned well in the preoperative period. If necessary, urodynamic tests should be used to determine the type of incontinence. The patient may benefit from mid-urethral sling treatments in urodynamic stress urinary incontinence. Overactive bladder symptoms may increase with age. In the postoperative period, the patient should be informed that these complaints may continue and medical treatment is required. In addition, de novo stress urinary incontinence of 8% to 30% has been reported in patients who underwent colpocleisis surgery in the literature[21]. In a study conducted on 95 patients who underwent Lefort colpocleisis, it was observed that 89% of de novo urinary symptoms (urinary incontinence, urinary retention, difficulty voiding) developed spontaneously over time[15]. In the present study, de novo stress incontinence occurred in four patients and was treated with a mini-sling operation. In addition, spontaneous recovery was observed in postoperative urinary complaints (dysuria, urinary retention, increased frequency of voiding, difficulty voiding) in four patients.

The strengths of this study are that we have a good sample size to compare the results of both operations, that their operations were performed with similar techniques in the same clinic, and that we follow up postoperatively for mid-term clinical outcomes. The study's limitation is that no internationally validated and reliable survey was used to evaluate postoperative success and patient satisfaction.

5. Conclusions

Colpocleisis is a valuable POP surgery for patients who do not want to continue their sexual activity and cannot tolerate extended vaginal reconstructive operations. It is also highly effective in recurrent prolapses, especially after previous unsuccessful reconstructive surgery. Loss of coital function rarely causes regret in patients. Based on studies on the clinical results of colpocleisis operations, we believe it is effective in treating recurrent prolapse in patients with its feasibility, high satisfaction, and low recurrence rates. In our study, the presence of recurrence, anatomical success rates, de novo incontinence rates, and perioperative complications of Lefort or total colpocleisis operations were found to be similar. Although we believe that the results of our study will contribute to the literature, more prospective randomized studies are needed in the future to see the long-term effects of these operations.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by University of Health Sciences, Kanuni Sultan Süleyman T&R Hospital 2022-213.

Conflict of interest statement

Author declare that they have no financial conflict of interest with regard to the content of this report.

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Orbital Neurogenic Tumors: An Eye Care Service Experience in Turkey

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Abstract

Aim: This study aimed to evaluate the clinical and pathological features and treatment outcomes of neurogenic tumors developing in the orbit.

Methods: A retrospective study was conducted on the medical records of 23 patients diagnosed with orbital neurogenic tumors between 2008 and 2020 in the ophthalmology clinic. Clinicopathologic features and treatment results of this patient group were evaluated.

Results: Twenty-three patients, mean (SD) age 33.34±20.18 (min-max 4-60) years, were included in this study. Mean follow-up time was 56.7±42.7 (min-max 9-120) months. At the time of presentation, 15 (65%) patients had proptosis, eight (35%) patients had strabismus and reduced vision. Histopathologic diagnosis was made after lateral orbitotomy through the skin in 16 patients (69.5%) and medial orbitotomy through the conjunctiva in 4 patients (17.4%). Nine (39.1%) of the orbital neurogenic tumors were diagnosed as meningiomas based on histological and clinical findings, eight (34.8%) as optic nerve gliomas, and the other six (26%) as peripheral nerve origin tumors. Four (44.5%) of the meningiomas originated from the sphenoid wing, and five (55.5%) from the optic nerve sheath. As a treatment modality, external radiotherapy was administered to fifteen patients (65.2%), cyberknife radiosurgery to one patient (4.3%), chemotherapy to one patient (4.3%), and exenteration surgery to one patient (4.3%).

Conclusions: According to our study, meningioma, optic nerve glioma, and peripheral nerve sheath tumors were the most frequent neurogenic tumors of the orbit. With the treatments applied, survival and the visual prognosis were satisfactory.

Keywords: *Meningioma, orbit, schwannoma, neurofibroma, optic nerve glioma*

1. Introduction

Approximately 10% of all orbital tumors are primary neural tumors. Neurogenic tumors develop from cells such as leptomeningeal, schwann, ganglion, and melanocytes; they begin in the neural crest and neuroectoderm. Optic nerve/meningeal tumors accounted for 8% of all lesions in a retrospective case series of orbital tumors, while peripheral nerve tumors made up 2% of the cases[1].Meningiomas, optic nerve gliomas, neurofibromas, schwannomas, malignant peripheral nerve sheath tumors, and granular cell tumors are among the various tumor types. Benign or malignant optic nerve gliomas and optic nerve sheath meningiomas are examples of optic nerve tumors. Neurofibromas, schwannomas, granular cell tumors, and malignant peripheral nerve sheath tumors are examples of peripheral nerve tumors in the orbit. All of these neural tumors are space occupying lesions that typically present with gradual vision loss and proptosis[2]. In this study, it was aimed to assess the clinical, pathological, and therapeutic outcomes of individuals with neurogenic tumors.

2. Materials and methods

This study included 23 patients with orbital neurogenic tumor (ONT) who were admitted to the ophthalmology department of *Dr. Abdurrahman Yurtaslan Oncology T&R Hospital* between January 2008 and January 2020. Approval for the study was obtained from the ethics committee of the hospital. Age, gender, clinical findings, tumor location, pathological diagnosis, course of treatment, and prognosis were all assessed retrospectively for each patient. A thorough eye exam was done prior to treatment. Radiological techniques like magnetic resonance imaging (MRI) and computed tomography (CT), the location, size, and relationship of the tumor to the surrounding tissues were assessed. For a conclusive diagnosis, most patients underwent biopsies.

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2.1. Statistical analysis

Statistical analyses were made using with IBM SPSS 19.0 for Windows Statistical software (SPSS, Chicago, IL). Frequency and percentage were used to represent categorical variables. The numerical variables were represented as min-max and mean±standard deviation (SD).

3. Results

The mean age of the patients was 33.34±20.18 (min-max 4-60) years. Of the patients, eight (34.8%) were men and 15 (65.2%) were women. The right eye was affected in 14 patients (60.9%) and the left eye in 9 patients (39.1%). The mean follow-up period of the patients was 56.7±42.7 (min-max 9-120) months. Table 1 shows the symptoms and examination findings of the patients.

Of the patients, 20 (87%) underwent surgery for diagnosis and treatment. Three patients (13%) were diagnosed without surgery using imaging techniques. Lateral orbitotomy was performed if the mass localization was intraconal and lateral to the optic nerve, and medial orbitotomy was performed through the skin or conjunctiva if the mass was medially localized. 16 (69.5%) patients underwent lateral orbitotomy through the skin and 4 (17.4%) patients underwent medial orbitotomy through the conjunctiva. Nine patients (39.1%) underwent incisional biopsy, ten patients (43.4%) underwent total excisional biopsy, and one patient (4.3%) underwent subtotal excisional biopsy, depending on the mass's location and characteristics.

Figure 1 illustrates the distribution of orbital neurogenic tumors according to imaging and biopsy reports. Of the meningiomas, 4 (44.5%) were sphenoid wing meningiomas and 5 (55.5%) were optic nerve sheath meningiomas. Out of all the peripheral nerve tumors, plexiform neurofibroma 1 (16.7%), olfactory neuroblastoma 1 (16.7%), and schwannomas (66.6%) accounted for 4 of the tumors. Three patients (13%) had an associated type-1 neurofibromatosis (NF-1). One (4.3%) patient with NF-1 had plexiform neurofibroma, and two (8.7%) had optic nerve gliomas.

Fifteen patients (65.2%) received external radiation, one patient (4.3%), underwent cyberknife radiosurgery, and one patient (4.3%) received chemotherapy. The patient with olfactory neuroblastoma underwent exenteration because of their severe proptosis, large and diffuse localization of the mass, and lack of light sensation.

The patients pre- and post-treatment visual acuity varied from perception (-) to 5/10. A significant improvement in visual acuity was defined as a two line or greater increase in Snellen visual acuity following treatment. After treatment, 11 (48%) of the patients' visual acuity could be monitored. As a result, following treatment, two patients (9%), and nine patients (39%) reported decreased visual acuity. Two patients with sphenoid wing meningioma experienced recurrences during the follow-up period, but no deaths occurred.

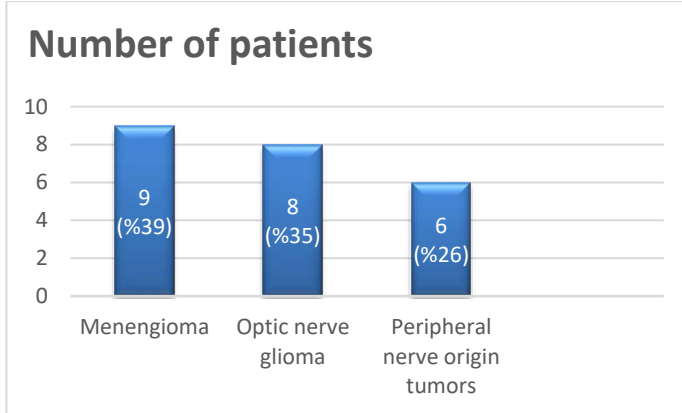
Table 1

Symptoms and examination findings of the patients

Symptoms and examination findings	Number of patients (%)
Symptoms	
Proptosis	15 (65,2)
Visual impairment	6 (26,1)
Strabismus	2 (8,7)
Examination findings	
Optic atrophy	8 (34,8)
Optic disc edema	4 (17,4)

Figure 1

Distribution of orbital neurogenic tumors



4. Discussions

Consistent with the previous reports of Shields[1] (37.5%) and Kızıltunç [3] (25.7%), optic nerve glioma was the most common neurogenic tumor in the orbit in this study (34.8%), followed by optic nerve sheath meningioma (21.7%) and sphenoid wing meningioma (17.4%). Similar rates to our study were also reported by Shields et al.[1] for optic nerve sheath meningioma in the second most common tumor (22.6%) and sphenoid wing meningioma in the third most common tumor (18.7%). The study revealed that the prevalence of schwannoma was 17.4%, whereas the rates of plexiform neurofibroma (4.3%) and olfactory neuroblastoma (4.3%) were found to be equal. Schwannoma (10.9%), plexiform neurofibroma (3.1%), and isolated neurofibroma (1.5%) were reported by Shields et al.[1]. Kızıltunç et al. reported schwannoma (17.1%) and optic nerve sheath meningioma (17.1%) as the second most common tumor. In addition to perisellar meningioma (3%), they also reported sphenoid wing meningioma (14.3%), plexiform neurofibroma (11.4%), isolated neurofibroma (5.7%), and ectopic meningioma (5.7%) [3].

Meningioma, schwannoma, and isolated neurofibroma are more common in adulthood, while optic nerve glioma and plexiform neurofibroma are more common in childhood [4]. The average age of patients with plexiform neurofibroma was 7 years, while the average age of patients with optic nerve glioma was 9 years (4–16). In adults, the mean age of orbital neurogenic tumors was 51 years for olfactory neuroblastoma, 47 years (40-52) for schwannoma, and 49 years (42-60) for meningioma.

Imaging methods are typically used to assess the diagnosis of optic nerve tumors, however certain tumor types may make the diagnosis more difficult [3].In our study, all 9 cases of meningioma were identified through biopsy, compared to 3 of the 8 patients with optic nerve glioma who were identified through imaging methods.

Gliomas of the optic nerve that affect children are known as juvenile pilocytic astrocytomas and are typically benign. Nonetheless, adult cases of malignant glioblastoma, a type of optic nerve glioma, are possible. With a median age of five years and a clinical presentation that can occur anywhere from eight months to 38 years of age, 90% of optic nerve gliomas are diagnosed within the first two decades of life. Females account for 60% of cases of these lesions, which are typically unilateral and clinically manifest as unilateral painless visual loss, proptosis, optic disc edema, or optic atrophy [5-6]. Although sporadic in most cases, 10-70% of patients diagnosed with juvenile pilocytic astrocytomas have been reported to be associated

with neurofibromatosis type 1 (NF-1). NF-1 is typically linked to bilateral optic nerve gliomas[7-8].NF-1-related tumors typically grow slowly, but sporadic tumors typically progress quickly and manifest clinically. Since the chiasm is involved in more than half of the tumors, bilateral visual field defects may be observed[9–11]. Each patient's response to treatment for optic nerve glioma is unique due to the tumor's variable growth pattern. While some tumors show rapid or slow growth patterns for many years, others remain stable for years and do not grow at all[9].

Surgery, chemotherapy, external radiation, and follow-up are all part of the treatment.

If an advanced proptosis, progressive loss of visual acuity, or an increase in tumor size is found during MRI follow-up, treatment of gliomas should be considered. Otherwise, follow-up is advised if the tumor size does not grow or progress. When a patient's tumor results in severe proptosis and deformity, severe visual loss, or severe keratopathy from lagophthalmos, surgery is performed to reduce the tumor[2].

Chemotherapy may be the preferred course of treatment for pediatric patients in order to prevent side effects from radiation. Chemotherapy combined with vincristine and carboplatin is typically regarded as first-line therapy. This treatment does not raise the risk of treatment-related death or secondary cancer, and it offers about 70% progression-free survival. About 40% of patients experience hypersensitivity reactions to carboplatin, which is the primary side effect. Additional regimens for chemotherapy consist of temozolomide, cisplatin/etoposide, and thioguanine/ procar-bazine/CCNU/vincristine (TPCV). Although these regimens have comparable survival rates, they should not be used in NF-1 patients due to the increased risk of secondary leukemia[12-13].

When chemotherapy is not an option for older children with refractory disease, external radiotherapy is advised. The goals of this treatment are to stop the tumor from growing larger and to avoid vision loss. There could be adverse effects on the central nervous system. In order to reduce the radiation dose to nearby structures, more advanced radiation therapy techniques have been developed. Conformal therapy, proton beam radiation therapy, fractionated stereotactic radiation therapy, and stereotactic radiosurgery (using a Gamma Knife) are some of these techniques[13-14]. It has been demonstrated that the VEGF inhibitor bevacizumab is useful in either halting or reducing the growth of optic nerve gliomas. It has been documented that bevacizumab is used both alone and in combination with other medications like irinotecan or vinblastine[15]. Inhibitors of the mitogen-activated protein kinase (MAPK) pathway are one class of molecularly targeted treatment that specifically targets the development and spread of cancer cells. With a specific focus on the MAPK pathway—which is hyperactive in certain cancer types—these treatments aim to slow the spread of cancer cells. The growth and division of cells depend on this pathway. Trametinib is the most commonly used MAPK inhibitor at the moment, but numerous other options are presently undergoing clinical trials[12-14].

Eight patients with optic nerve gliomas were included in our study; one patient underwent chemotherapy, one patient underwent Gamma Knife radiosurgery, and six patients underwent external radiotherapy. The survival rate was 100% and there was no recurrence.

Rare benign tumors of the central nervous system are called optic nerve sheath meningiomas (ONSM). Their location is crucial for the patient because the tumor can directly impact the visual pathway and cause severe vision loss, despite their slow but progressive growth[16–18]. These are often more prevalent in women in their middle years. They are rare, but can occur in children, though they are usually more aggressive. Ninety-five percent of ONSMs are unilateral. Patients diagnosed with type 2 neurofibromatosis may experience rare bilateral tumors. The gradual, painless, and progressive loss of vision in the affected eye is the hallmark of ONSM's natural course. This tumor can cause total blindness if treatment is not received[19–20]. Because of the tumor's close proximity to the optic nerve, it is challenging to remove the entire tumor without experiencing further complications or aftereffects. For this reason, the management of this condition is still deemed controversial. When a patient's vision is stable or good, especially when they have central visual acuity of 20/50 or better, observation is a suitable course of treatment. These patients receive close monitoring and are subjected to a thorough examination that includes optical coherence tomography of the papillary retinal nerve fibers and visual field[21-22]. Tumor follow-up with MRI is recommended every year[18,23].

On the other hand, in cases of disfiguring proptosis with markedly diminished visual function or intracranial spread, surgical resection might be warranted. ONSM can be treated if the tumor is contained within the orbit and the affected eye lacks feeling in light. However, some surgeons recommend surgical excision of the tumor to stop it from spreading to other areas. The tumor and nerve should be removed if the eye is light-sensitive and there is intracranial spread. According to some authors, surgical intervention should be the first line of treatment because it can partially reverse existing visual impairment as well as stop the disease's progression and lower the risk of future vision loss[24]. It has been demonstrated that the recently suggested transnasal endoscopic optic nerve decompression can, in certain circumstances, stabilize the condition and enhance visual acuity[25-26].

For many years, conventional radiation has been used both before and after surgery, and it has been noted that the treatment affects the preservation of visual acuity[17,27].

Recently, surgery has been replaced with stereotactic radiotherapy (STR). Since STR provides the right amount of radiation to the tumor locally, it has become the method of choice in cases of reduced visual function. Risks of radiation-induced optic neuropathy or retinopathy are frequent[28].

In our study, 5 patients with optic nerve sheath meningioma were treated with external radiotherapy. Visual acuity was stable and no recurrence was observed during a mean follow-up period of 27 months (15-72 months).

About 18% of all intracranial meningiomas are sphenoidal wing meningiomas. Because of its unique anatomical location in the sphenoid bone, the tumor's nature frequently involves periorbital tissue and bones. On imaging, hyperosteosis is frequently observed[29-30]. Because it is difficult to restore the dura mater and bony structure while maintaining key anatomical structures like the optic nerve, oculomotor nerve, trigeminal nerve, or internal carotid artery, surgical resection of sphenoid wing meningioma is technically difficult[31–32].

Recurrence after surgery is frequent. Treatment approaches include postoperative STR and maximal safe resection[33].

Individuals who have small tumors without any symptoms and cavernous sinus meningiomas can undergo annual or biannual close observation. Serial imaging with brain MRI is usually recommended as part of the follow-up.

Adjuvant therapies may be necessary in cases of incompletely resected meningiomas as well as atypical or malignant meningiomas in order to lower the recurrence rate. Patients with anaplastic meningioma who receive bevacizumab, a type of chemotherapy that targets molecular changes of vascular endothelial growth factor, following surgical resection and radiation therapy have demonstrated successful tumor regression[34]. Four sphenoid wing meningioma patients in our study had stereotactic radiotherapy after surgery to reduce the tumor. While the visual acuities of the other patients re-

ceiving stereotactic radiotherapy remained stable, the visual acuities of the other two patients showed a decline. Recurrences occurred in two patients.

Although they are uncommon in the orbit, peripheral nerve sheath tumors (PNST) account for 2% of all orbital neoplasms. Of these, 50% of the tumors are schwannomas, which are the most prevalent type. Neurilemmomas, or Schwannomas, are benign, slowly growing encapsulated tumors that originate from the Schwann cells in the peripheral nerve sheath. Most adults who experience it are between the ages of 30 and 70. In addition to the oculomotor, trochlear, and abducens nerve branches, orbital schwannomas also commonly originate from sympathetic and parasympathetic fibers, as well as the trigeminal nerve's frontal branch. The genesis of orbital schwannomas elucidates their predominant distribution in the supraorbital domain[35].

The preferred course of treatment is complete surgical resection. Even though the capsule is extremely thin, especially in tumors with cystic degeneration, the recurrence rate is almost nonexistent in the absence of a capsular breach. Restrictions on eye movement and permanent reduction in visual acuity have been reported; these depend on the surgical technique, tumor location, and degree of dissection. To assess recurrence, repeat MRIs performed over an extended period of time are advised[36].

All four of the patients in our study had total excision, and there was no sign of recurrence.

Singular, diffuse, and plexiform neurofibromas are further classifications for neurofibromas. With the exception of pleural neurofibromas, which are diagnosed in half of cases between the ages of 1 and 5, the majority of benign PNSTs affect adults between the ages of 20 and 60. No racial or gender predisposition exists. 90% of singular orbital PNSTs are not associated with NF-1, despite neurofibromas being linked to it. Benign PNSTs are typically slow-growing, non-invasive tumors whose genesis is primarily determined by where they are located in the orbit. Granular cell tumors are another type of benign nerve tumor that can develop in the orbit and are derived from peripheral nerve tissue[2].

It is uncommon for neurofibromas to transform malignantly. Plexiform neurofibromas can be challenging to completely remove due to their high vascular and infiltrative nature. Tumor reduction techniques can be used on kids who are susceptible to amblyopia. It is recommended to remove isolated benign neurofibromas completely without causing any damage to the capsule[37].

In our study, the patient with plexiform neurofibroma underwent subtotal excision with mass reduction; during follow-up, no malignant transformation was found. Due to the olfactory neuroblastoma patient's large and diffuse localization of the mass, advanced proptosis, and lack of light sensation, exenteration was performed.

In summary, ONT is not an uncommon condition, and its manifestations can vary based on the kind and location of the tumor. During follow-up, patients' radiological and clinical findings should be carefully assessed. If in doubt, a biopsy ought to be done to get an accurate diagnosis[1]. Follow-up, external radiation therapy, and chemotherapy should all be part of the treatment plan for optic nerve gliomas and optic nerve sheath meningiomas, respectively. External radiation therapy and maximally safe resection are the recommended treatments for sphenoidal wing meningiomas. For well-circumscribed peripheral nerve sheath tumors, subtotal excision is recommended, whereas total excision is advised for infiltrative tumors[2]. After receiving the right care, the prognosis for survival and vision is satisfactory.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by University of Health Sciences, *Dr. Abdurrahman Yurtaslan Oncology T&R Hospital* 2016.

Conflict of interest statement

Author declare that they have no financial conflict of interest with regard to the content of this report.

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Efficacy of Taxifolin in The Prevention of Renal Injury Due to Liver Ischemia and Reperfusion

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Abstract

Aim: During surgical procedures such as liver resection and transplantation, ischemia/reperfusion (I/R) injury and related complications may occur at a rate of approximately 10%. Our study, we planned to investigate histologically and biochemically the efficacy of Taxifolin in the prevention of renal tissue damage in liver ischemia reperfusion.

Methods: A total of 28 Wistar Albino rats with an average age of 8-10 weeks and weights of 250-300 grams were used in our study. Group 1 (n=7): control group, Group 2 (n=7): Taxifolin group; Taxifolin was administered orally at a dose of 50 mg/kg for 3 weeks, Group 3 (n=7): Liver I/R group, 30 minutes ischemia and 120 minutes reperfusion was performed. Group 4 (n=7): Taxifolin+Liver I/R group.

Results: Kidney tissues of the liver I/R group showed atrophy, degeneration of tubule epithelium and increased TNF-α expression. In addition, deterioration in renal function tests was also monitored in this group. In the Taxifolin+Liver I/R group, a significant difference was observed on both histologic and biochemical basis compared to the Liver I/R group and a positive effect was observed ($p<0.05$).

Conclusions: As a consequence of hepatic ischemia and reperfusion, impairment in the function and histological appearance of renal tissues was observed and Taxifolin was monitored to be effective in eliminating these adverse effects.

Keywords: *Liver ischemia, reperfusion, taxifolin, histopathology, immunohistochemistry, oxidative stress*

1. Introduction

During surgical procedures such as liver resection and transplantation, blood flow to the liver is temporarily interrupted. This may lead to serious complications such as ischemia/reperfusion (I/R) injury[1]. Liver I/R injury accounts for 10% of graft rejection in liver transplantation[2]. In some patients with acute renal injuries, liver injuries, acute coronary syndrome or organ transplantation, irreversible damage occurs in many organs because blood flow in the vessels stops during ischemia[3]. In addition, the integrity and function of vital organelles such as mitochondria may be disrupted during I/R injury[4]. Recent studies have also reported that mitochondria homeostasis may be disrupted as a result of I/R injury[5]. Flavonoids are a group of secondary metabolic compounds commonly found in plants as essential components of human nutrition[6]. Taxifolin, a dihydroflavone compound commonly found in Larix sibirica Ledeb, is an important substance also known as dihydroquercetin (DHQ)[7]. Flavonoids are extremely popular due to their many positive effects on health[6]. Taxifolin has antioxidant, anti-inflammatory, anti-tumor and antiviral effects, including the prevention of Alzheimer's disease[8]. In a study, it was monitored to be effective in reducing oxidase and reactive oxygen species (ROS) resulting from cerebral ischemia-reperfusion injury[9].

The cause of distant organ damage resulting from ischemia reperfusion is not yet fully understood and efforts are still ongoing to reduce the risk of its occurrence. Our study, we planned to investigate the efficacy of Taxifolin in the prevention of renal tissue damage after liver ischemia reperfusion.

2. Materials and methods

This study was approved by the Animal Experiments Local Ethics Committee (DÜHADEK, 2023/03).

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2.1. Surgical Protocol

General anesthesia was achieved by administering 90 mg/kg intramuscular Ketamine hydrochloride (Istanbul, Turkey) and 10 mg/kg Xylazine (Istanbul, Turkey) to the group to undergo liver I/R before surgical procedures. After the midline of the abdomen of the rats was shaved and laparotomy was performed, the portal triad was clamped with a microvascular clamp. After 30 minutes of hepatic ischemia, clamps were opened and reperfusion was performed for 120 minutes[10-13].

2.2. Preparation of Taxifolin

Taxifolin (Evalar, Russia) suspension prepared as described in the study by Bedir F et al. was given orally by gavage (p.o.) with a dose of 50 mg/kg in 1 cc saline for 21 days[14].

2.3. Formation of Experimental Groups

Group 1 (n=7): It is the control group and 1 cc saline was given to the rats orally by gavage as 21 days. At the last of the 21st day, the animals were sacrificed by exsanguination.

Group 2 (n=7): Taxifolin group, Taxifolin was administered p.o. with a dose of 50 mg/kg in 1 cc saline as 21 days. At the last of the 21st day, the animals were sacrificed by exsanguination.

Group 3 (n=7): Liver I/R group. After applying 30 minutes ischemia and then 2 hours reperfusion to the liver tissues, the rats were sacrificed by exsanguination.on the 1st day of the experiment.

Group 4 (n=7): Taxifolin + Liver I/R group. Taxifolin was administered p.o. a dose of 50 mg/kg in 1 cc saline for 21 days. On 21st day, the rats were administered 30 minutes ischemia and then 2 hours reperfusion to the liver tissues. Then the rats were sacrificed by exsanguination.

2.4. Measurement of Serum Malondialdehyde (MDA) Values

Serum MDA analysis was performed as described by Kei S in his study[15]. MDA results were expressed as nmol/mg protein.

2.5. Evaluation of Renal Function Tests

Blood obtained from the heart was centrifuged at 3000 rpm for 7 minutes and blood urea nitrogen (BUN) and creatinine levels were measured[16].

2.6. Histopathologic Evaluation

Kidney tissues of the rast were fixed in 10% formol for 24 hours. After fixation, the tissue samples were washed in tap water for 12 hours and then passed through increasing series of alcohol for dehydration. Sections obtained after routine histologic tissue follow-up were stained with Hematoxylin & Eosin (H&E)[17].

The scoring method in the study was used to evaluate the histologic changes in renal tissues[18]:

Grade 0: undamaged kidney tissue

Grade 1: tubular cell swelling, margin and loss of 1/3 of tubular integrity.

Grade 2: more loss of tubular integrity in addition to the findings in grade 1

Grade 3: loss of more than 2/3 of tubular integrity[18].

2.7. Immunohistochemical Evaluation

The intensity of TNF-α expression was classified as grade 0: negative, grade 1: mild, grade 2: moderate, grade 3: intense[20].

3. Results

3.1. Biochemical examinations

When the MDA levels of the biochemistry groups were analyzed, it was monitored that the MDA level of the Taxifolin group was lower than the Liver I/R group and the Taxifolin+ liver I/R group. The mean ± standard deviation of the MDA levels of the groups are declareted in Table 1.

When we compared the renal function tests, it was monitored that the BUN values of the Liver I/R group and the Taxifolin+ Liver I/R group were similar, but the BUN value of the Liver I/R group was higher than the other study groups. In terms of creatinine values, the creatinine values of the Liver I/R group and Taxifolin+ Liver I/R group were higher than the other groups. The mean and standard deviations of BUN and creatinine values of the groups are demonstrated in Table 1.

3.2. Histopathological examinations

When the kidney tissues were examined under light microscope; In the kidney tissues of the liver I/R group, glomeruli were atrophied, the epithelium in the tubule structures were degenerated and apoptosis was observed. Vascular dilatation and congestion were also observed. In the taxifolin+ liver I/R group, these histopathologic changes were milder and no congestion was observed. Kidney tissues of taxifolin+ liver I/R group were observed to be healthier. (Figure 1).

When the histopathologic damage in the kidney tissues was scored according to the scoring method in the study of Chatterjee et al. (2000), Kruskal-Wallis Test was statistically significant ($p<0.05$). In the intergroup comparison made by Mann Whitney-U test, it was observed that there was no significant difference between the control group and the Taxifolin group and the mean scores were the same ($p>0.05$). There was a significant difference between the scores of the Liver I/R group and the Taxifolin+ liver I/R group and the mean score of the Liver I/R group was higher ($p<0.05$) (Table 2).

3.3. Immunohistochemical examinations

When the intensity of TNF- α expression in the kidney tissues was equate, it was demonstrated that the most widespread expression was observed in the kidney tissues of the Liver I/R group. In the taxifolin+ Liver I/R group, the expressions were less intense (Figure 2). When the extent of TNF-α expression in kidney tissues was examined under light microscope and scored statistically, it was declareted that TNF-α expression was most intense in the Liver I/R group and the intensity of TNF-α expression was lower in the Taxifolin+ Liver I/R group compared to the Liver I/R group ($p<0.05$), (Table 2).

Table 1

Mean values and standard deviations of MDA, BUN and creatinine values of the groups.

Groups	MDA (nmol/mg)	BUN (mg/dL)	Creatinine (mg/dL)
Control	391,81±124,57	37.14±9.61	0.79±0.27
Taxifolin	355,89±245,85	41.71±6.60	0.94±0.32
Liver I/R	3308,15±2319,50	133.14±27.67	3.16±0.72
Tax+ Liver I/R	560,90±493,85	104.57±12.60	1.69±0.42

Tax; Taxifolin, I/R; Ischemia and reperfusion, MDA; Malondialdehyde

Table 2

Scoring values and standard deviations of histopathologic and immunohistochemical damage of the groups.

Groups	Histopathologic score	Immunohistochemical score
Control	0.14±0.37	0.42±0.53
Taxifolin	0.14±0.37	0.57±0.53
Liver I/R	2.28±0.48	2.28±0.48
Tax+ Liver I/R	1.28±0.48	1.28±0.48

Tax; Taxifolin, I/R; Ischemia and reperfusion.

Figure 1

C; control group, Tax; Taxifolin group, I/R; Liver ischemia and reperfusion group. Atrophy of glomeruli (yellow arrow), degeneration of tubule epithelium (black arrow), congestion (red arrow).

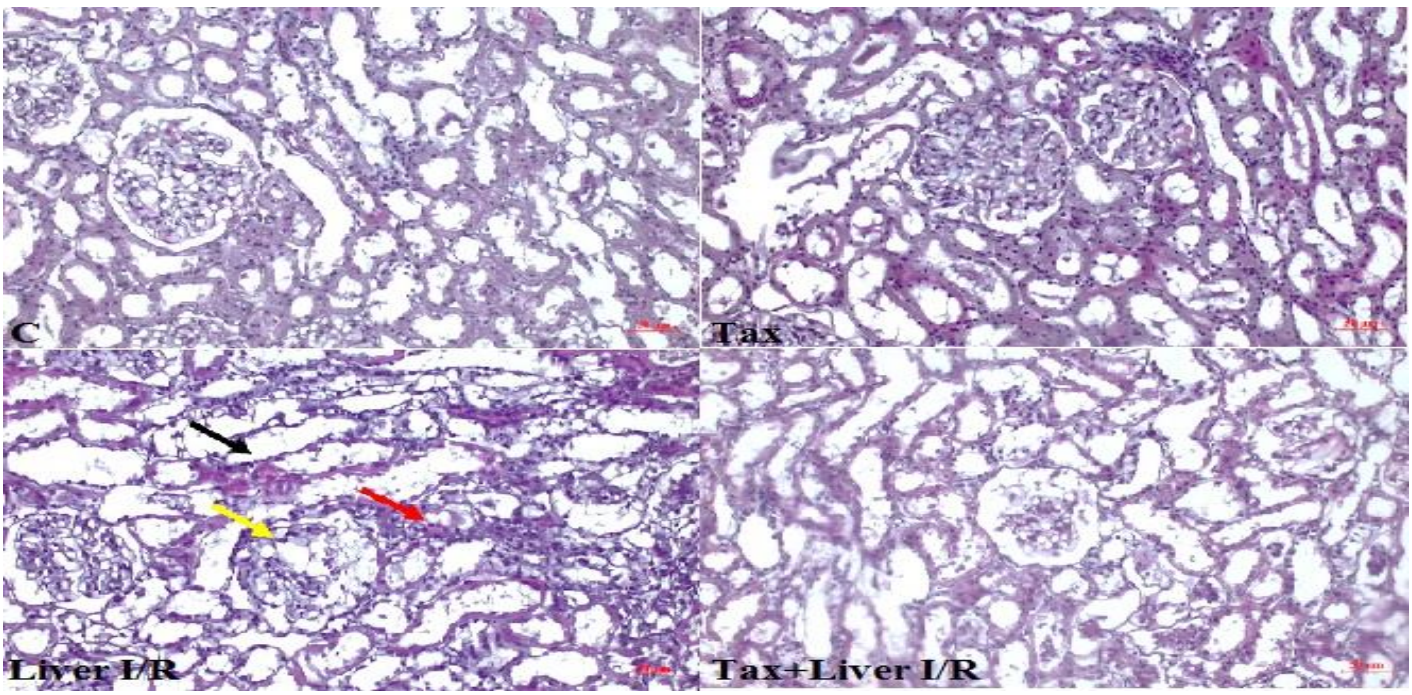
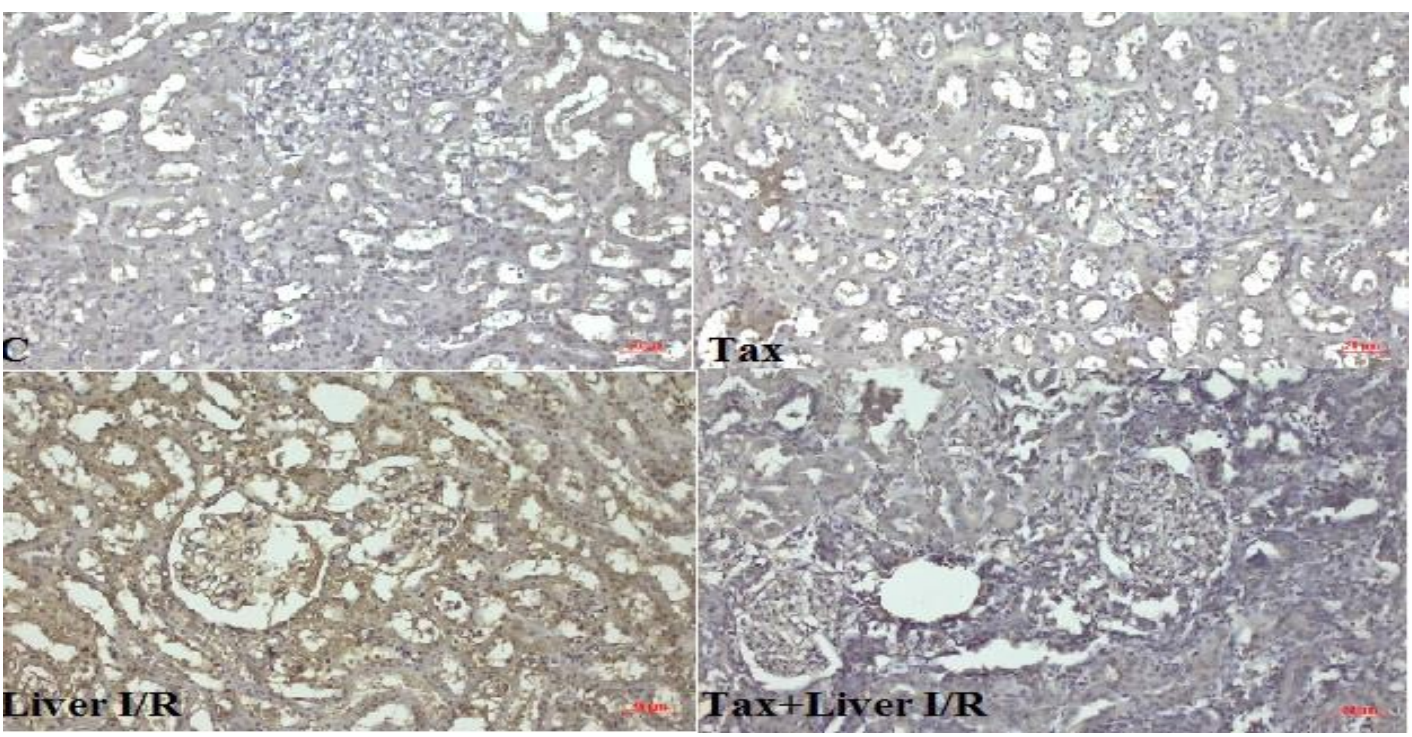


Figure 1

Figure 2

C; control group, Tax; Taxifolin group, I/R; Liver ischemia and reperfusion group.



4. Discussions

Hepatic ischemia and reperfusion injury not only results in liver damage, but also affects many distant organs such as kidneys, lungs, myocardium, adrenal glands and small intestines[21]. Acute kidney injury is a clinical picture of rapid decline in renal function in a short period of time, resulting in high mortality. It usually results in multiple organ failure and distant organ damage[22-24]. Liver I/R injury in experimental animals has been statement to result in acute kidney injury[25]. While liver I/R injury causes damage in the liver parenchyma, it also causes damage in distant organs such as kidney and lung through the production of proinflammatory mediators such as TNF-α, IL-6, IL-1 and free oxygen radicals[26,27]. Among our findings, TNF-α expression was intensely positive in the kidney tissues of the liver I/R group. An increase in serum MDA levels was also observed. Many experimental studies to date have shown that the oxidant-antioxidant status is closely related to proinflammatory cytokines[28,29].

It is also known that increased free radicals leads to an increase in proinflammatory cytokine production[30]. Taxifolin (3,5,7,3′,4′-pentahydroxy-flavanone or 2,3-dihydroquercetin) is a flavonoid with antioxidant properties that positively affects oxidative stress and proinflammatory cytokine production[31]. Previous studies have suggested that Taxifolin has a protective mechanism in the inhibition of important proinflammatory cytokines such as TNF-α and nuclear factor kappa B (NF-κB)[32]. In this study, it was monitored that TNF-α expression was increased in kidney tissue due to liver I/R, but the group that was given Taxifolin beforehand was less affected.

MDA is one of the end products of peroxidation of unsaturated fatty acids in cells. The increase in free radical production in cells leads to an increase in MDA. The level of oxidative stress, disease states, I/R, cancer and some pathologic conditions increase MDA levels[33]. Therefore, measurement of MDA level is very important in I/R studies. Studies have shown that MDA levels were increased when induced by acrylamide and proinflammatory cytokine levels such as IL-1β and TNF-α increased in renal tissues due to oxidative stress, but animals given Taxifolin were less affected or not affected[34]. In our study, in parallel with these studies, there was a significant decrease in MDA level and TNF-α expression in renal tissues of Taxifolin+ liver I/R group.

5. Conclusion

As a result of liver ischemia and reperfusion, renal tissue function is impaired and inflammatory and histopathologic changes occur. In our study, Taxifolin was demonstrated to be effective in eliminating these adverse effects.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by University of Dicle 2023-476064

Conflict of interest statement

Author declare that they have no financial conflict of interest with regard to the content of this report.

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Comparison of Modified Single Incision Two Loop Technique and Classical Three Lobe Technique in HoLEP: Experience of 200 Cases of a Single Surgeon

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Abstract

Aim: We aimed to present our single incision two-lobe technique, which we developed in our own clinic and performed by a single surgeon and to compare the results of this technique with the results of Gilling's 3-lobe technique, which we applied before.

Methods: HOLEP was performed in 200 patients with medically resistant lower urinary tract symptoms (LUTS) and BPH, regardless of prostate size, between December 2018 and August 2022 in our urology clinic. All operations in the study were performed by a single surgeon who had completed the HoLEP learning curve, was well versed in endoscopic surgery, and had high experience. The classical Gilling 3-lobe method was preferred in the first hundred cases after the cases in the first fifty cases learning curve (Group 1, n=100). Due to some difficulties in the technique after the experience in the first hundred cases, the single incision two-lobe technique, which was created by referencing and modifying Scoffone's en bloc no touch technique, was used in the next hundred cases (Group 2, n=100).

Results: The average age of a total of 54 patients who underwent surgery due to a retroperitoneal mass was 53.8±10.0 years. While 15 (27.8%) of 54 patients with a retroperitoneal mass were diagnosed incidentally, 39 (72.2%) patients were diagnosed symptomatically. The final pathological outcome of all relapsed patients was liposarcoma. The average operation time was 178.7±85.4 minutes. The average length of stay of the patients was 6.2±3.1 days. Additionally, all of these patients had organ resection. In the Kaplan-Meier survival analysis, it was found that surgical margin had a statistically significant effect on average survival ($p<0.001$).

Conclusions: In our modified single-incision two-lobe technique, the eneculation time and probe residence time are shorter than the classical gilling method.

Keywords: *HOLEP, Gilling's 3-lobe technique, the single incision two-lobe technique*

1. Introduction

Holmium laser enucleation of the prostate (HoLEP) was first introduced by Fraundorfer and Gilling as an effective transurethral treatment option in the surgical treatment of BPH[1]. In the light of literature data in the last two decades, HoLEP is considered to be a superior method to transurethral resection of the prostate (TUR-P), which is applied as a standard procedure, thanks to its advantages such as short catheterization time, short hospital stay, and less intraoperative bleeding[2,3]. In addition, the low cost of HoLEP is another advantage in terms of the results of cost analysis studies compared to other procedures[4,5]. In studies examining urodynamic outcomes, short and long-term outcomes were found to be comparable or better than TUR-P and open prostatectomy (AP)[6-8]. However, the difficulty in the learning curve of HoLEP stands out as the biggest disadvantage of this method[9,10-12]. In addition, the fact that incontinence rates after surgery are higher in some studies compared to TUR-P and AP can be considered as another important disadvantage[6,7]. Especially due to the difficulty in the learning curve, some urologists prefer more invasive and costly options such as laparoscopic or robotic simple prostatectomy instead of HoLEP to treat their patients with large prostate volumes[4,5]. After the definition of HoLEP, there have been various studies in terms of the development and differentiation of the technique. Due to some difficulties in the

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traditional three-lobed technique[13,-15] described by Gilling, necessity to develop and differentiate the technique has arisen. Especially when applying this technique, technical difficulties such as the emergence of different surgical planes due to the fact that the three incisions are sometimes not at the same depth, the risk of sphincteric injury that may occur as a result of the antegrade incision made at the twelve o'clock level, led to the need to improve the technique or to perform surgery with a different technique. In this study, we aimed to present our single incision two-lobe technique, which we developed in our own clinic and performed by a single surgeon, using Scoffone's en bloc no touch technique[16] as a reference and modified, and to compare the results of this technique with the results of Gilling's 3-lobe technique, which we applied before.

2. Materials and methods

After our study was approved by the local ethics committee of our tertiary education and research hospital, HOLEP was performed in 200 patients with medically resistant lower urinary tract symptoms (LUTS) and BPH, regardless of prostate size, between December 2018 and August 2022 in our urology clinic. Those with urethral stricture, those with a neurogenic component in the urodynamic studies, those who had previous prostate surgery, those who were diagnosed with prostate cancer based on imaging studies and transrectal ultrasonographic (TRUS) biopsy results were excluded from the study. In addition, the first fifty cases in the learning curve of the surgeon who performed the cases were not included in the evaluation, considering that this may affect the results of the study.

All operations in the study were performed by a single surgeon who had completed the HoLEP learning curve, was well versed in endoscopic surgery, and had high experience. The classical Gilling 3-lobe method was preferred in the first hundred cases after the cases in the first fifty cases learning curve (Group 1). Due to some difficulties in the technique after the experience in the first hundred cases, the single incision two-lobe technique, which was created by referencing and modifying Scoffone's en bloc no touch technique, was used in the next hundred cases (Group 2). Preoperative hemogram, routine biochemistry, chest X-ray, Electrocardiogram (ECG), coagulation parameters, ELISA tests, urine culture, urinary USG, prostate specific antigen (PSA), uroflowmetry, postresidual urine volume (PMR), international prostate symptom score (IPSS) were all patients.) were viewed. Patients with elevated PSA levels were operated one month after TRUS-guided prostate biopsy.

Patients receiving antiplatelet and anticoagulant therapy were operated after their medications were discontinued and replaced with low molecular weight heparin. The operations were performed under general anesthesia or spinal anesthesia according to the preference of the patient and the anesthesia. Surgery was performed using a 120W Holmium: yttrium-aluminum-garnet (Versa Pulse Power Suite, Lumenis, Yokneam Israel) 26 F resectoscope suitable for HoLEP, a morcellator and display screen (Richard Wolf GmbH, Knittlingen, Germany). After the surgery was completed, all tissues taken were examined histologically. A 22f 3-way Foley catheter was attached to the patients and they were washed with continuous saline until the hematuria subsided.

Control hemogram was checked on the first postoperative day. The patient was discharged after the catheter was removed 2and micturition was performed after the hematuria passed. The patients' active complaints (dysuria, filling phase symptoms, urinary incontinence, retrograde ejaculation) were recorded along with the results of PSA, uroflowmetry, IPSS, and PMR at the third month.

2.1. Surgical Technique

1. Classic Gilling's Three Lobe Technique (Group 1, n=100) The operation begins following bilateral bladder neck incisions extending antegradely from the ureteral orifices to the verumontanum. These incisions are deepen to the level of the surgical capsule at the 5 and 7 o'clock positions. After the incisions are completed, they are connected together with a transverse incision just anterior to the verumontanum. Then, starting from the middle lobe verumontanum, enucleation is performed towards the bladder neck. The lobe is separated from the bladder neck and then placed in the bladder for morcellation. Each of the lateral lobes are enucleated in several different steps. The first bladder neck expands the incision area from 12 o'clock to inferolaterally and distally at 2 and 10 o'clock positions. In this way, the upper part of both lobes is released. A surgical plan is then created at the level of the verumontanum at the 5 o'clock position to locate the surgical plane and identify the apex. Then the apical incision is continued until 2 o'clock. The upper and lower incisions are joined at the apex. Similar to lateral and median lobe enucleation, it is enucleated in the capsular plane by progressing from the top to the lower incisions. The left lateral lobe is pushed into the bladder. A surgical plan is created in the right lobe at 7 o'clock and then the apical incision is continued until 10 o'clock. The upper and lower incisions are joined at the apex. After enucleation of the right lateral lobe is completed, it is sent into the bladder for morcellation. Thus, the eneculation process of the 3 lobes is completed.

2. Our Single Incision Bilobe Modified Technique (Group 2, n=100) The operation begins with a mucosal incision just lateral to the verumontanum at the 5 o'clock position. Here, with the advantage of not having much adenoma tissue, the plane between the adenoma and the capsule can be easily entered. After expanding the surgical plan, the prostate is enucleated in the apical region from the left edge of the veru montanum along the surgical capsule to the 12 o'clock position. The urethral mucosa, which remains at the 2-12 o'clock position, is cut 1 cm away from the external sphincter by decreasing the energy. Thus, the external sphincter is freed from the prostate apex and the first part of the operation is completed. By coming back to the left side of the verumontanum, our 5 o'clock incision is advanced retrogradely to the bladder neck. Prostate tissue is enucleated from the capsule from the apex to the bladder neck at the 12 o'clock position, taking the capsule as a reference in the surgical plan. After the left lobe of the prostate is completely enucleated, eneculation is advanced antegradely from the bladder neck to the apex by passing to the right lobe of the prostate from 12 o'clock to 9 o'clock. The left lobe, which is completely enucleated from the capsule, is cut at 12 o'clock and sent into the bladder. It comes back to the veru montanum and a mucosal incision is made from the front of the verru montonum at the 5 o'clock position to the 7 o'clock position, and a surgical plane is created by entering between the prostate adenoma and the capsule. By accepting the capsule as a reference, prostate tissue is enucleated in the apical region between 7-12 o'clock, and the urethral mucosa is cut between 10-12 o'clock, 1 cm away from the external sphincter, and the sphincter and the right lobe of the prostate are freed from each other. Then, the right prostate lobe and median lobe are enucleated retrogradely from the 5 and 9 o'clock positions to the bladder neck, completely freed from the capsule and eneculation is completed.

2.2. Statistical Analysis

Statistical analysis of the data was created using SPSS (Statistical Package for the Social Sciences) 23.0 package program. Categorical measurements were determined by number and percentage, and continuous measurements were determined as mean and standard deviation (median and minimum-maximum where necessary). Categorical expressions were analyzed using the chi-square test. Shapiro-Wilk test was used to determine whether the parameters in the study showed normal distribution. Independent Student's t-test

was used for normally distributed parameters and Mann Whitney u test was used for non-normally distributed parameters. Statistical significance level was taken as 0.05 in all tests.

3. Results

The mean age of the patients was 65.5±6.8 in group 1, while it was 63.8±6.4 in group 2. There was no difference between the two groups in terms of perioperative PSA value and prostate volume. Perioperative and postoperative Hct, Qmax and IPSS scores were similar in both groups. While there was no significant difference between the morcellation time and the amount of tissue removed, the enucleation time was statistically significantly shorter in the modified technique (p<0.001). Probe residence time was significantly shorter in the modified technique compared to the classical Gilling method (p=0.003). There was no significant difference between the two techniques in terms of retrograde ejaculation and incontinence rates, which are the most important postoperative complications (Table I).

Table 1

Patients' characteristics, preoperative and postoperative datas and continence status

	Group 1 (n=100)	Group 2 (n=100)	p
Mean Age (year)	65,5±6,8	63,8±6,4	0,193[a]
Mean PSA (ng/ml)	3,59 (0,6-37)	3,15 (0,3-20)	0,586[b]
Mean Prostate Volume (ml)	89 (40-240)	90 (40-260)	0,804[b]
Eneculation time (min)	100 (45-240)	70 (35-200)	<0,001[b]
Morcelation time (min)	20 (15-30)	20 (10-40)	0,280[b]
Amount of removed tissue (gr)	72,5 (30-180)	67,5 (25-220)	0,874[b]
Preoperative Hct	42,3 (28-53,4)	42,2 (31,4-46,8)	0,972[b]
Postoperative Hct	38,4 (25,4-51,7)	39 (29-45,6)	0,785[b]
Length of catheter (h)	40 (20-120)	30 (16-90)	0,003[b]
Length of hospitalization (day)	2 (2-7)	2 (1-5)	0,061[b]
Preoperative Qmax	8,9 (4,5-16,4)	8,4 (3,7-16,4)	0,322[b]
Postoperative Qmax	24,3 (18,4-43,2)	26,2 (18,4-45,2)	0,777[b]
Preoperative IPSS	29 (22-35)	29 (21-35)	0,770[b]
Postoperative IPSS	5 (1-8)	5 (2-8)	0,620[b]
Retrograde ejaculation			
No	32	38	0,529[c]
Yes	68	62	0,654[c]
Incontinence status			
1	68	78	0,171[b]
2	26	18	0,061[b]
3	6	4	0,643[b]
4	2	0	0,447[b]

4. Discussions

HoLEP is accepted as a new standard treatment in the surgical treatment of BPH, regardless of prostate size[7,17,18]. Although its functional results are equivalent to TUR-P and open prostate according to guidelines, and even superior to the results of recent studies in many ways, it still does not take place sufficiently in the surgical treatment of BPH[19]. The most important reason for this is the challenging learning curve of HoLEP. In addition, it is a fact that surgeons are intimidated by the high rates of early postoperative incontinence. Because in studies on this subject, the prevalence of stress urinary incontinence (4.9%-12.5%) after HoLEP was found to be quite high compared to open prostatectomy and conventional TUR-P[6,7,20,21]. However, the high rates of incontinence in HoLEP led surgeons, who have great interest in HoLEP, to seek various new techniques and modifications based on the classical gilling method.

Although many physicians apply different techniques or modifications from the classical gilling technique, a standard technique has not yet been accepted[22-25]. Gong et al. reported that they reduced the rate of transient incontinence up to 2% in their external sphincter-preserving modified bilateral technique[25]. Shigemura et al. found the rates of incontinence to be less than 10% in the series of 497 patients who underwent HoLEP[26]. Endo et al. described anterior-posterior dissection in their modified technique and compared 31 HoLEP patients performed with the classical gilling method and 37 HoLEP patients performed with their own technique in terms of incontinence, and reported that incontinence rates, which were 25% in the classical method, decreased to 2% in their own technique[27]. In our study, although there was no statistically significant difference between the modified bipolar technique and the classical technique in our incontinence rates, the results were proportionally better in our modified bipolar technique. We think that in the two-lobe technique, the connection between the external sphincter and the apical prostate is cut in the first stage of the operation and the damage of the sphincter due to stretching is reduced during enucleation of the prostate, and that the antregrade incision made at 12 o'clock in the classical technique extends to the sphincter and the risk of thermal damage is not present in the modified two-lobe technique.

One of the most important criteria in modifying techniques is how the new technique affects the operation time. In this respect, the time of inoculation is important. However, the number of studies comparing operation times among HoLEP techniques is limited in the literature. Endo et al. compared the anterior-posterior dissection technique they defined with the classical gilling technique and found similar enucleation times for prostates of similar size[27]. Tokatli et al. compared the eneculation times between two-lobe, three-lobe and en-block methods. They found the eneculation times were significantly shorter in the two-lobe technique compared to the others[28]. In our study, the eneculation time was statistically significantly shorter in favor of our modified bilateral technique (p=0.003). We think that the reason for this is the use of three incisions in the classical 3-lobe method and the difference in depth between these incisions, which is related to the prolongation of eneculatation time.

The study has some limitations. First, our study is a retrospective study. Second, the study results reflect the experience of a single surgeon. Therefore, the results may have been affected by this situation. We think that our data can be more secure with multicenter studies with more patients.

5. Conclusions

In our modified single-incision two-lobe technique, the eneculation time and probe residence time are shorter than the classical gilling method. However, only two parameters do not lead to the conclusion that our technique is superior to the classical technique. Therefore, the surgeon should choose whichever technique he or she feels more successful and safe with for the HoLEP operation.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Health Sciences University, Adana City T&R Hospital Ethics Committee. (2023)

Conflict of interest statement

Author declare that they have no financial conflict of interest with

regard to the content of this report.

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Mental Health and Planetary Health

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Abstract

Aim: While the mental health burden of the COVID-19 pandemic is turning into a public health problem, the global dimension of the problem makes it necessary to address the issue in the context of planetary health for a solution. The goal of this study was to examine the contents and challenges of managing mental health issues at the planetary health level during COVID-19.

Methods: The bibliographic method was used. Thesis were searched by searching YOKSIS and PubMed for reviews with the keywords "mental health, planetary health, and COVID-19."

Results: In the search made in June 2021, from 2018 till 27.02.2022; 19 related articles have been found. The most proportion of published reviews was about patients' mental health via telehealth; only three of the reviews were about healthcare workers. Two of the researches were excluded because they were not reviewed. The same keywords are used for searching among the thesis of YOKSIS, only one research was found about fuzzy cognition maps and decision making.

Conclusions: Research on managing mental health problems and planetary health during pandemics in the family medicine discipline is far from providing sufficient literature diversity. Advances in data analytics and information technologies are opening up new medical clinical problem-solving methods. In order to measure the effects of the COVID-19 pandemics and to establish global well-being and higher planetary mood in the future, research at the level of the individual, society and planet are required.

Keywords: *Mental health, planetary health, family medicine*

1. Introduction

The global impact of the COVID-19 pandemic has made the eyes turn to the concept of planetary health, which has been predominantly included in the scientific literature so far. In this process, where the well-being of our world has a direct impact on society and individual health, the increase in the incidence of common mental illnesses draws attention. Examining the effects of planetary health on mental health during the pandemic period with an interdisciplinary perspective will help us evaluate the future of humanity and our planet in terms of health. This study aims to examine the scientific literature in the field of planetary and mental health since the beginning of the global epidemic caused by Coronavirus.

Understanding the concept of global (global) health is an important step that must be passed before working on Planetary health. The birth of the concept of global health is related to the mass experiences of humanity in the 20th century[1]. Efforts to erase the traces of global devastation and improve public health indicators after the Second World War have pushed states and international organizations to show a global reaction[2,3]. As a result of the establishment of the World Health Organization and the production of new strategies and policies, the framework of today's global health concept has been formed. Global health is defined as a developing discipline in the field of health sciences and under the wings of the branch of public health[4]. However, it is necessary to introduce interdisciplinary approaches, especially when it comes to global impact and global field solutions[5]. In the field of global health, a significant accumulation of scientific literature and theory has emerged, thus paving the way for interventions by health service providers and policy makers that have a significant impact. Access to global well-being is related to the health of nations and the demographic factors that affect them; It is also related to the health of the planet as well as all the ecological systems within it, and Planetary Health, a new field of study that will affect the 21st century, has been born.

These developments on a global scale heralded the arrival of a new concept. The article titled "From Public to Planetary Health: A Manifesto" published in the prestigious scientific journal Lancet was a milestone[6]. The traditional public health approach, with its preventive medicine mission, made significant contributions to the improvement of health indicators and the establishment of equal opportunities in health. The Planetary Health concept goes beyond this; aims to save the future of humanity and the sustainability of

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Figure 1

Network map of five or more repeated keywords and years connected exchange

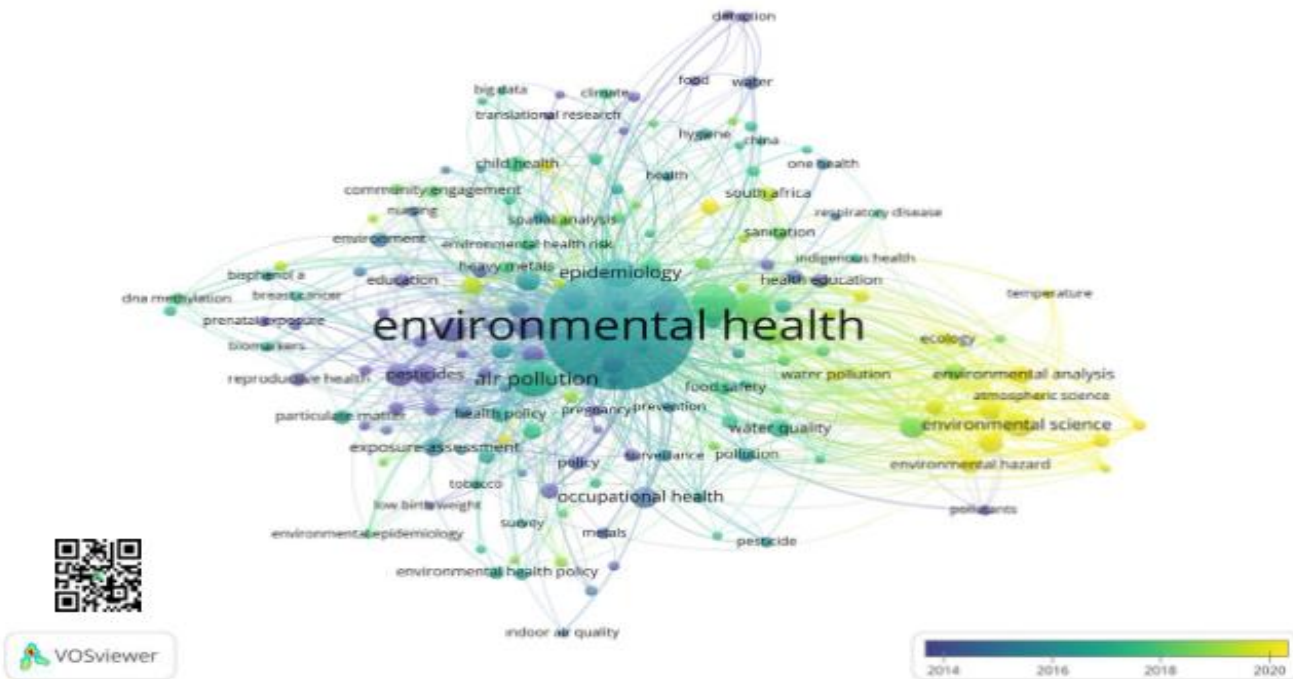
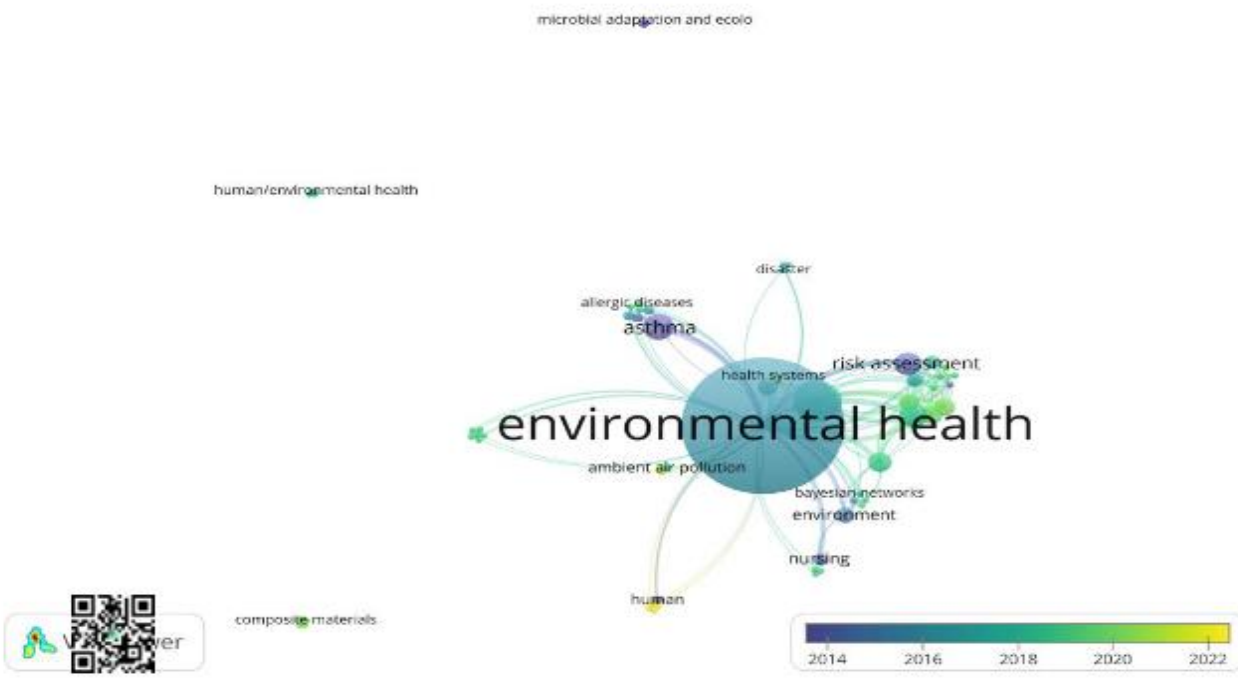


Figure 2

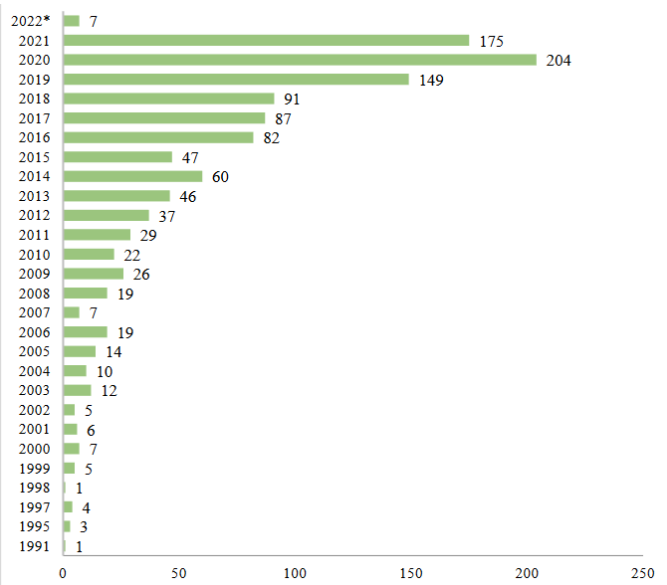
The network map of the keywords used in the articles produced in Turkey and the years connected exchange



The prevalence of mental diseases, especially depression and anxiety, has increased with a high momentum during the COVID-19 era. According to the results of a study by Xiong, Jiaqi et al. relatively high rates of symptoms of anxiety, depression post-traumatic stress disorder, psychological distress and stress are reported in the general population during the pandemic in China, Spain, Italy, Iran, the US, Turkey, Nepal, and Denmark. Female gender, younger age group (≤40 years), presence of chronic/psychiatric illnesses, unemployment, student status, and frequent exposure to social media/news concerning COVID-19 were defined as risk factors associated with distress measures[10] Today, this global crisis due to a virus has affected people's mental health, consumption and lifestyle behaviors. Tomorrow, many chemical, nuclear, economic and astronomical phenomena will affect the health of society and individuals. In this context, we aimed to compile studies dealing with planetary health and mental health in order to give a global, rapid and evidence-based reaction to public health emergencies.

Table 1

Number of articles containing the keyword "Environmental Health" by year.



*Data for only the first 11 days of 2022.

2. Materials and methods

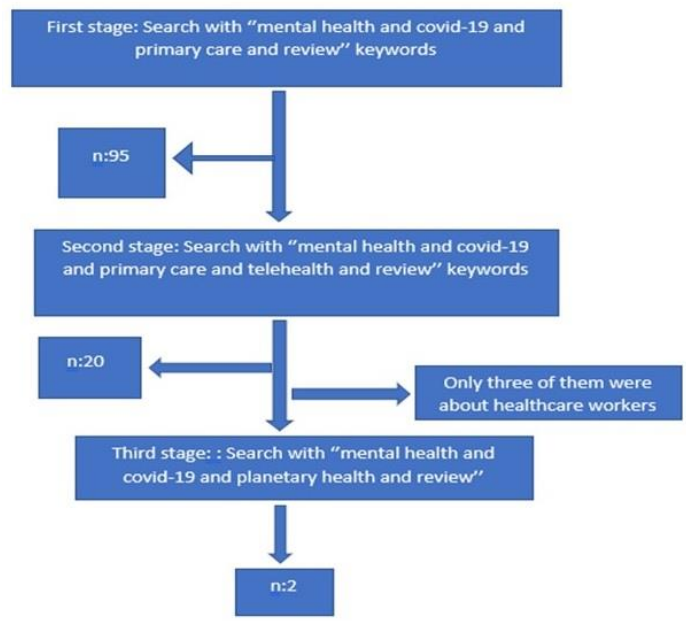
This study was proposed on the basis of the (PRISMA) guidelines for systematic review. The reviews that were published via PubMed were selected by using keywords as "mental health, planetary health and COVID-19" The same keywords used for searching among thesis of YOKSIS.

3. Results

In the search made in June 2021, from 2018 till 27.02.2022; 19 related articles have been found. The most proportion of published reviews was about patients' mental health via telehealth; only three of the reviews were about healthcare workers. Two of the researches were excluded because they were not reviewed. The same keywords are used for searching among the thesis of YOKSIS, only one research was found about fuzzy cognition maps and decision making.

The review was carried out in three main databases: Academic Search Complete, Complementary Index, and MEDLINE. According to database screenings, 118 articles were identified and 76 of them were excluded on the basis of exclusion criteria (see flowchart 1). Demographics, personal support/self-care resources, and income/financial concerns were identified as protective factors by researchers, while mental health distress, as well as two additional variables: health/social status and general knowledge/government mistrust were non-protective factors[11].

Flowchart



COVID-19 pandemics particularly effected vulnerable groups. Ma et al. (2021) conducted a systematic review and meta-analyse about mental health problems among children and adolescents in COVID-19 times[12]. The literature search was carried out in PubMed, Web of Science, PsycINFO, and two Chinese databases for researches published from December 2019 to September 2020. Twenty-three studies with 57,927 children and adolescents were listed. Depression, anxiety, sleep disorders, and posttraumatic stress symptoms were evaluated in 12, 13, 2, and 2 studies. Meta-analysis of results showed that the pooled prevalence of depression, anxiety, sleep disorders, and posttraumatic stress symptoms were 29%, 26%, 44% and 48% respectively. The subgroup meta-analysis emerged that adolescents and females have higher prevalence of depression and anxiety compared to children and males.

Another group that was primarily under scrutiny was healthcare workers, who were the pioneers of the struggle on the field. De Kock et al. discussed the implications of supports for providing psychological wellness of healthcare workers during pandemics[13].

Reaearchers searched across adatabases of Medline, EMBase, HMIC and PsychInfo. 82 studies were assessed for eligibility and only twenty-four published studies met the inclusion criteria . 22 studies directly assessed the healthcare workers' levels of psychologic symptoms. Another study expressing the universal struggle of healthcare professionals is a review by Chersich et al., in which they scanned the medical literature as of March 24, 2020[14].

As a result of the Medline (Pubmed)-based research, 88 studies were identified, some of which addressed the African experience in

the protection and care of healthcare workers in the event of an epidemic, including HIV and EBOLA infections. Another point that makes this study valuable is that the pandemic is more difficult in middle and lower income group countries and all countries are affected by this situation due to its global nature. Kola et al. evaluated the COVID-19 period in developing countries and the third world in scope of mental health[15].

4. Discussions

In order to make mental health care sustainable under prohibitions and restrictions in various regions, reviews examining digital health interventions were carried out. In study conducted by Wynn, it was underlined that video consultations between patients and physicians increased in Norway during the pandemic process, and this increase was seen especially in primary care and mental health areas[16]. In a narrative review conducted by Cunningham et al., based in the United States, telemedicine applications in the field of child mental health were reviewed[17]. 876 potential studies were included in this research, of which 55 met the inclusion criteria. A deeper reading of the available data showed that 28% to 36% of health complaints during the global pandemic were related to mental health. Digital solutions will play an important role in solving this problem.

We see that two of the remarkable studies conducted in North America were revealed in Canada. Strudwick and his friends published a rapid review on telemedicine interventions to make mental health services sustainable during the COVID-19 era[18]. This study was conducted by using several databases and popular mobile app libraries. During the closure period, 31 mobile applications and 114 web-based services consisting of websites, forums and telemedicine initiatives were identified, which were heavily used by the Canadian people and included information, suggestions and applications on mental health.. Another study was conducted by Xie et al.; has focused on publication trends titled telemedicine from past to present[19]. This study, also based in Canada, evaluated telemedicine articles in the field of mental health between 1976 and 2021. As a result of the literature review, 810 articles including 29 randomized controlled trials and 6 systematic reviews were seen. While there was one study per year in 1976, 80 publications were published in 2020. Telepsychiatry, COVID-19, mental health and primary care were prominent as the main keywords

Family Medicine and mental health care are at the intersection of all research. This situation points to family physicians as qualified pioneers of digital transformation in health. Rohilla et al., in their study published in June 2020, processed this mission within the framework of the COVID-19 projection[20]. In the pandemic conditions, many mental health problems have been solved at the initiative of primary care physicians. Sometimes they have solved problems with the remote support of a mental health professional, sometimes by themselves. The effectiveness of telemedicine applications in terms of the sustainability of community-oriented mental health services is now a reality with scientific evidence.

There are many electronic systems that offer both visual and auditory communication. There are opportunities for family physicians to access patients who cannot reach health facilities due to legal restrictions or physical barriers, and to consult with mental health professionals when necessary. Policy makers and practitioners in the field should be willing and courageous in establishing the infrastructure and remote initiatives on this issue.

Primary care physicians, who produce community-oriented solutions to daily clinical problems, can overcome global problems with planetary-oriented solutions during the pandemic process. Pescott in her study published in 2020 examined the effects of biodiversity on the immune system, especially on allergic reactions[21]. The immune system is a marker for measuring the effects of environmental factors on the human organism and a data source that reflects the distance between our current life and our evolutionary past**.** Organ systems, which are functional parts of the human organism, interact with the biological and ecological existence of the planet. Family physicians as expert generalists in medicine; will fight global problems such as epidemics and cancer by using all means, including information and communication technologies and the most up-to-date evidence-based data. Within the framework of this research, the hot topics of the emerging literature and the importance of community-oriented approaches and digital initiatives are discussed.

The richness of literature in the field of planetary health will create an area of influence that extends from the minds of researchers to the practical applications of clinicians, from humans to organic and inorganic components of the planet. Menculini and colleagues discussed the effects of the urban environment in the context of migration and air pollution[22]. 33 of 663 studies evaluated in various databases were accepted under this narrow review14 studies were related to air pollution and related factors, and 19 studies were related to the health effects of migration. Within the scope of this research, it has been observed that atmospheric particulate matter density causes viruses to stay alive longer and to transmit at longer distances. In addition, the unusual immune response of sick individuals in areas with intense air pollution; Increasing the rates of death, sequelae and intensive care unit admissions has led to the definition of air pollution as a potential risk factor for mental health.

5. Conclusions

The rapid spread of urbanization poses new health threats for vulnerable groups such as immigrants and the poor. Failure to provide standard hygiene conditions, establishment of occupational health and safety, social support programs and difficulty in accessing health institutions make the problem more complex.

Nowadays earthquakes, flood, drought are the main reasons of starvation, lack of sheltering, migration, and also more people who would be handicapped, ad/or mental problems. This field needs more evidence-based sustainable projects.

Conflict of interest statement

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