AUGUST 2023 VOL 6 ISSUE 2

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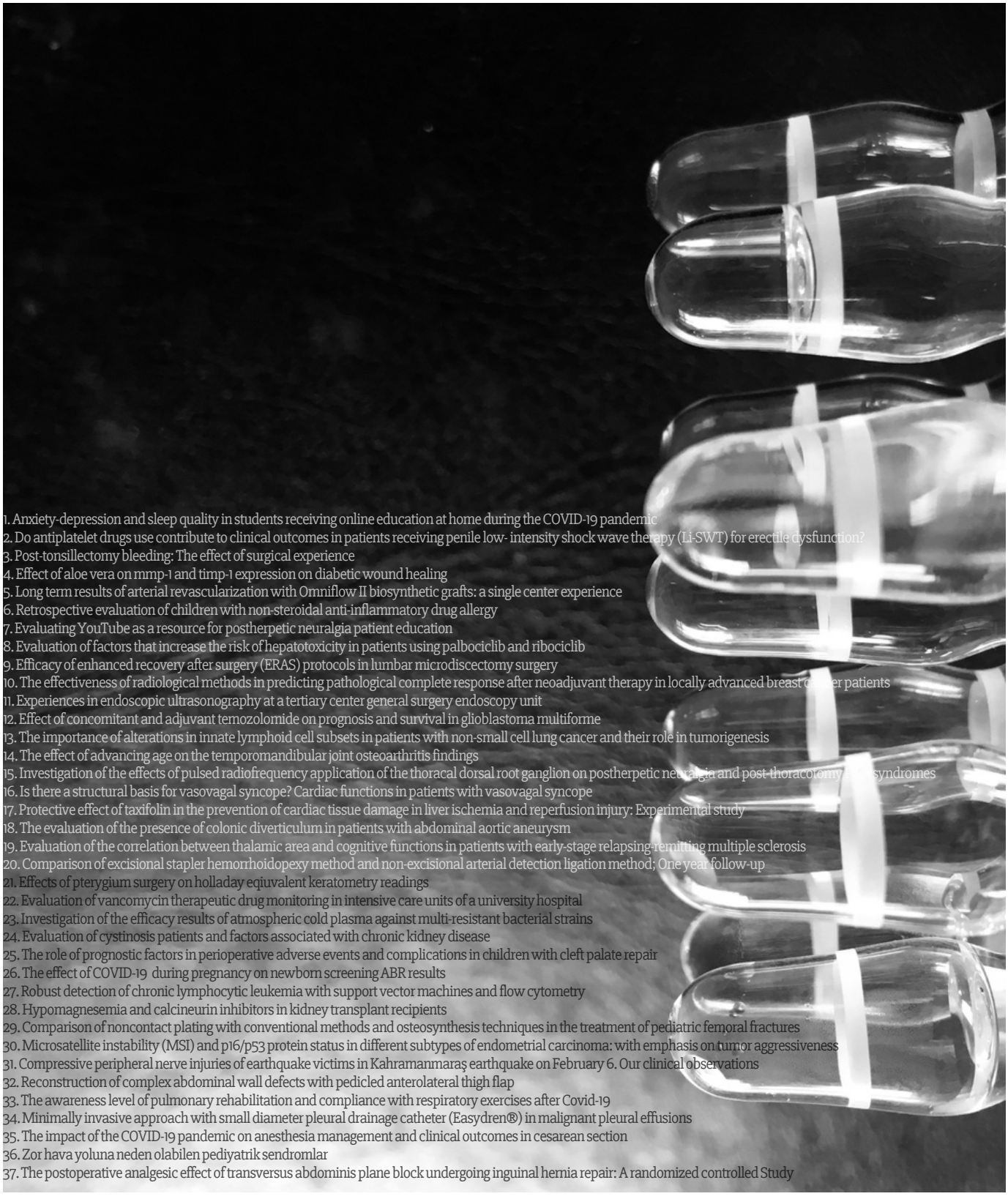

E-ISSN: 2667-498X ESTABLISHED IN 2018, PERIOD: ANNUALLY THREE ISSUES, PUBLISHER: MERTHAN TUNAY

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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.

E-ISSN: 2667-498X FOUNDED: 2018 PERIOD: 3 ISSUES PER YEAR PUBLISHER: MERTHAN TUNAY

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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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WRITING RULES

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All articles are offered under a CC license and are openly accessible. Authors must agree to the terms of open access.
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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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E-ISSN: 2667-498X ESTABLISHED IN 2018, PERIOD: ANNUALLY THREE ISSUES, PUBLISHER: MERTHAN TUNAY

ÇUKUROVA
ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ

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ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ

CONTENTS II

Anxiety-Depression and Sleep Quality in Students Receiving Online Education at Home During the Covid-19 Pandemic

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Abstract

Aim: In this study, we aimed to analyzed symptoms of anxiety and depression, excessive daytime sleepiness, and sleep habits in students during the Covid-19 pandemic.

Methods: Two hundred children who received online education at home during the COVID-19 pandemic were included in this study. The students were divided into three groups as primary school, middle school, and high school. The students completed questionnaire forms including the Epworth Sleepiness Scale (ESS), Child Sleep Habits Questionnaire (CSHQ), and Childhood Anxiety and Depression Scale (CADS)

Results: The rates of CADS and ESS did not differ according to the groups (p>0.05). The rates of anxiety disorder and daytime sleepiness according to CADS and ESS were mostly in the high school group. According to the CSHQ score, sleep quality disorder was observed with a higher rate in primary school students (p<0.005) The median ESS was found to be lower in those who had adenoidectomy compared to those who did not (p=0.011). The Median CSHQ and ESS scores were higher in the secondary school class with allergies than in those without allergies (p = 0.040). Secondary school students who are exposed to cigarette smoke at home Median CADS and CSHQ scores were higher than those who did not (p = 0.022)

Conclusions: If the children have adenotonsillar disease, performing surgery without delay by following COVID-19 precautions may contribute to increase sleep quality. We must be careful exposure to cigarettes and allergies during the Covid-19 pandemic.

Keywords: *Anxiety, Covıd-19, sleep quality*

1. Introduction

A series of unexplained cases of pneumonia were reported in Wuhan, China in December 2019[1]. The World Health Organization stated that it was caused by the virus named SARS-COV-2 and announced it as a pandemic with the spread of the virus all over the world. Very different epidemic prevention and control strategies developed in different countries. It has been observed that staying in quarantine at home for a long time, being away from the outside world, and developing extreme fear of being infected has caused both physical and mental distress in the general public.

During the coronavirus epidemic, symptoms such as fear of loneliness, panic, anxiety and depression were observed[2]. Significant anger control disorders, sleep disorders, and suicides have been reported[3].

Children are less likely to become infected with COVID-19 and have a lower mortality rate than adults. Therefore, fewer studies have been conducted on the clinical features of COVID-19 in children and its effects on children's mental and emotional health[4]. However, some studies have shown that because the emotional development of children and adolescents is not complete compared with adults, they may experience more stress during the pandemic period and may be more psychologically affected[5]. In children and adolescents, the closure of schools and transition to online education, the obligation to stay in quarantine at home, and lifestyle changes have caused negative changes in mental and emotional health[6]. Anxiety-depression symptoms were observed in children during the pandemic period and sleep problems increased[7]. Various questionnaires such as the Childhood Anxiety and Depression Scale (CADS) are used to evaluate the symptoms of anxiety and depression in childhood, to identify patients at risk, and to provide early diagnosis and treatment[7]. CADS does not diagnose anxiety but can provide information

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Received: 01.12.2022, Accepted: 02.08.2023, Available Online Date: 31.08.2023
Cite this article as: Karaoğullarından A, Erkan SO, Tuhanioğlu B, et al. Anxiety-depression and sleep quality in students receiving online education at home during the covid-19 pandemic. J Cukurova Anesth Surg. 2023;6(1):186-93.
doi: 10.36516/jocass.1213341

about anxiety levels.

Sleep problems are quite common in childhood. The most important symptoms that bring families of children with sleep problems to us as ear, nose, and throat (ENT) physicians include sleeping with mouth open, snoring, and stopping breathing during sleep. Obstructive sleep apnea (OSAS) in childhood is one of the most important and serious sleep problems, and it is seen in 2% of children aged 2-8 years[8]. The most important and most common risk factor for OSAS in children is adenotonsillar hypertrophy[8,9]. In addition, chronic diseases, allergic symptoms, and cigarette exposure increase the risk of OSAS[8]. Due to the decrease in sleep quality in children with sleep problems, excessive daytime sleepiness, learning difficulties, decrease in school success, and various mental problems can be seen. The Epworth Sleepiness Scale (ESS) can be used to evaluate daytime sleepiness in children, and the Child Sleep Habits Questionnaire (CSHQ) can be used to evaluate sleep quality[10,11].

After the 2020 spring semester, schools in Türkiye, as in many countries with the progress of the pandemic, moved to online teaching. In this study, we analyzed symptoms of anxiety and depression, excessive daytime sleepiness, and sleep habits in students who received online education at home during the COVID-19 pandemic. We examined factors that affected these and their relationship with each other. The aim of this study was to test the hypothesis that there might be negative changes in the mental health and sleep habits of students who received online education at home during the 2019 coronavirus epidemic and to compare these changes between age groups.

2. Materials and methods

Two hundred children who received online education at home during the COVID-19 pandemic were included in this study. The students were divided into three groups as primary school, middle school, and high school. The students completed questionnaire forms including the ESS, CSHQ, and CADS with the support of families for young children when necessary. The demographic data of the students, age, sex, class, allergic diseases, adenoidectomy history, tonsillectomy history, smoking exposure, and chronic diseases were questioned. Written consent was obtained voluntarily from the families and children. Children who could not complete the questionnaire completely and those whose information was incomplete were excluded from the study. The daytime sleepiness of the students was evaluated using the ESS by their families. It was developed by Johns in 1991 and adapted to Turkish and its validity and reliability tests were performed by Ağargün et al[12]. The modified ESS for children in the pediatric population was used[13]. It evaluates the state of falling asleep or sleeping in eight different daily life situations. Each item in the scale is graded as never = 0, rarely = 1, frequent = 2, and always = 3. Excessive daytime sleepiness is indicated if the total score for each condition on the scale is above 10[14]. The CSHQ was developed by Owens et al. in 2000. It is used to investigate children's sleep habits and sleep-related problems[15]. Its validity and reliability tests in Turkish have been performed[16]. The questionnaire includes questions about the child's sleeping habits and possible sleep difficulties. The scale is completed retrospectively by the parents, who are asked to evaluate the sleeping habits of the child over the previous week. It is accepted that children with a score of 42 and above have significant sleep problems[15]. Anxiety and depression symptoms were evaluated using CADS, which was developed by Birmaher et al.[17]. Its validity and reliability tests in Turkish have been performed[18]. There are 47 questions describing how children feel about themselves. Each question in the scale is graded as never = 0, rarely = 1, frequent = 2, and always = 3. A score of 25 and above indicates a significant anxiety disorder. High scores from the scale indicate more severe anxiety. This study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. This study was approved by the Ethics Committee of Medical Ethics Decision date: 13.01.2021, Number: 1258.

2.1. Statistical analyses

Statistical analyses were performed using the SPSS 21 program. Normality analyses of continuous variables were performed using the Shapiro-Wilk test. Variables were analyzed using non-parametric methods because they did not conform to normal distribution. The Mann-Whitney U test was used for comparing two independent groups, and the Kruskal-Wallis test was used for more than two groups. Spearman's correlation coefficients were calculated to determine the linear relationships between continuous variables. The Chi-square test was used in the analysis of categorical variables. The statistical significance level was taken as 0.05.

Table 1

Sex distribution of students by groups

	Male		Female		Total	
	n	%	n	%	n	%
Primary school	23	26.7	20	17.5	43	2.5
Middle school	51	5.3	55	48.2	106	53.0
High school	12	1.0	39	34.2	51	25.5
Total	86	100.0	114	100.0	200	100.0

Table 2
Results of the groups according to their CADS, CSHQ, and ESS scores

		Primary school		Middle school		High school		Total		
		n	%	n	%	n	%	n	%	p
CADS	No	14	32.6	30	28.3	9	17.6	53	26.5	0.219
	Yes	29	67.4	76	71.7	42	82.4	147	73.5	
CSHQ	No	0	0.0	1	0.9	4	7.8	5	2.5	0.017
	Yes	43	100.0	105	9.1	47	92.2	195	97.5	
ESS	No	39	90.7	99	93,4	44	86.3	182	91.0	0.343
	Yes	4	9.3	7	6.6	7	13.7	18	9.0	

p: Chi-square test, CADS: Childhood Anxiety and Depression Scale, CSHQ: Children's Sleep Habits Questionnaire, ESS: Epworth Sleepiness Scale

3. Results

Of the 200 students who participated in the study, 43 were primary school students, 106 were at middle school, and 51 were high school students. There was a total of 114 female and 86 male students (Table 1). Nearly three-quarters (73.5%) of the students had anxiety disorder, 97.5% had sleep disturbances, and 9% had excessive daytime sleepiness. The rates of CADS and ESS did not differ according to the groups (p>0.05). The rates of anxiety disorder and daytime sleepiness according to CADS and ESS were mostly in the high school group. According to the CSHQ score, sleep quality disorder was observed with a higher rate in primary school students (p<0.005) (Table 2). When evaluated in general (total), CADS scores differed according to the education group (p<0.001).

According to this, the CADS scores of high school students were found to be higher than for primary and secondary school students, and those who went to secondary school has higher CADS scores than primary school students (p<0.05). Although the CADS scores of students attending primary school did not differ according to sex, the CADS scores of female students attending secondary and high school were higher than for boys. The difference was significant p<0.05). CADS scores differed between girls according to the education group (p<0.001). The CADS scores of female high school students were higher than those at primary and secondary schools, and girls who went to secondary school were found to have higher CADS scores than primary school students (p<0.05) (Table 3).

CSHQ scores were highest in primary school and lowest in high school. CSHQ scores of high school students were found to be lower than middle school and primary school students (p=0.001). The CSHQ scores of female high school students were found to be higher than for boys (p<0.05). CSHQ scores differed among males according to the education group and the highest values were in the primary school group (p=0.001) (Table 3).

ESS scores of primary school students did not differ according to sex, but the daytime sleepiness scores of female middle and high schools students were found to be higher than for boys (p<0.05) (Table 3).

No significant relationship was found between CADS, CSHQ, and ESS among male high school students (p>0.05). A positive moderate linear relationship was found between CADS and CSHQ among female high school students (p<0.05).

A positive moderate linear relationship was found between CADS and CSHQ in high school students (p<0.05) (Table 4).

A total of 23% students had a history of allergy, 16.5% had adenoidectomy, 10% had tonsillectomy, 6.5% had chronic disease, and 25% had smoking exposure. Allergy history, adenoidectomy, and chronic disease rates did not differ according to the groups (p>0.05). The rate of having tonsillectomy varied according to the groups (p=0.038). The rate of having tonsillectomy in middle school students was higher than in high school students (p<0.05). The rate of smoking at home varied according to the groups (p=0.022). The rate of smoking in the homes of primary school students was lower than that of middle school and high school students (p<0.05). The group with the highest smoking exposure was the high school group (Table 5).

The median ESS was found to be lower in those who had adenoidectomy compared to those who did not (p=0.011) in middle school students. The median CSHQ and ESS scores were higher in middle school student with allergies than in those without allergies (p=0.040) Who are exposed to cigarette smoke at home median CAHS and CSHQ scores were higher than those who did not in middle school students. (p = 0.022). CADS, sleep habits, and daytime sleepiness did not differ in patients with tonsillectomy and the presence of chronic diseases, both in total and according to education groups (p>0.05) (Table 6).

4. Discussion

In our study, sleep habits, excessive daytime sleepiness, and anxiety-depression symptoms were investigated in students who received online education at home during the pandemic period. Sleeping habits were evaluated using the CSHQ, excessive daytime sleepiness with the ESS, and anxiety and depression symptoms using CADS. The students were divided into primary school, middle school, and high school according to their education level, and they were grouped according to their sex.

Table 3

CADS, CSHQ and ESS results of the groups by sex

	Male			Female			Total			
	Mean±SD	Median [IQR]	Min-Max	Mean±SD	Median [IQR]	Min-Max	Mean±SD	Median [IQR]	Min-Max	p1
CADS										
Primary school	35.74±19.64	38 [18-49]	0-92	29.8±13.31	29 [17.5-40.5]	9-55	32.98±17.06	33 [18-46]	0-92	0.227
Middle school	34.96±19.13	34 [21-44]	2-103	47.53±27.39	43 [24-67][a]	7-116	41.48±24.5	35 [23-59][a]	2-116	0.038
High school	27.83±13.33	23.5 [21.5-33.5]	9-62	60.23±22,92	52 [48-78][ab]	22-117	52.61±25.12	51 [31-72][ab]	9-117	<0.001
p2		0.340			<0.001			<0.001		
CSHQ										
Primary school	50.7±5.76	50 [48-51]	41-66	51.1±6.32	50 [47-55,25]	41-67	50.88±5.96	50 [47-53]	41-67	0.854
Middle school	48.51±4.54	48 [45-51]	41-62	50.51±5.99	49 [47-53]	38-66	49.55±5.41	49 [46-52]	38-66	0.081
High school	43.83±5.13	44 [41-45.75][ab]	33-54	49.69±7.66	50 [44-54]	37-73	48.31±7.53	46 [44-54]	33-73	0.010
p2		0.001			0.609			0.061		
ESS										
Primary school	5.39±3.58	7 [2-7]	0-12	4.1±4.25	2.5 [1.25-6.75]	0-17	4.79±3.91	4 [2-7]	0-17	0.188
Middle school	4.06±3.1	4 [2-6]	0-14	5.58±3.74	5 [3-7]	0-17	4.85±3.52	4 [3-6]	0-17	0.028
High school	3.17±1.9	3.5 [2-4.75]	0-6	5.,77±3.79	6 [3-9]	0-13	5.16±3.6	4 [2-9]	0-13	0.036
p2		0.155			0.087			0.720		

p1: Mann Whitney U test, p2: Kruskal-Wallis test, CADS: Childhood Anxiety and Depression Scale, CSHQ: Children's Sleep Habits Questionnaire, ESS: Epworth Sleepiness Scale

Table 4

CADS, CSHQ, and ESS effects on each other by groups and sex

Groups			Male		Female		Total	
			CSHQ	ESS	CSHQ	ESS	CSHQ	ESS
Primary school	CADS	r	0.268	0013	0.174	0156	0.203	0.149
		p	0.216	0.954	0.463	0.512	0.193	0.339
	CSHQ	r		0.397		0.725		0.564
		p		0.061		<0.001		<0.001
Middle school	CADS	r	0.444	0.046	0.365	0.285	0.396	0.218
		p	0.001	0.747	0.006	0.035	<0.001	0.025
	CSHQ	r		0.308		0.360		0.348
		p		0.028		0.007		<0.001
High school	CADS	r	0.179	-0.068	0.529	0.027	0.592	0.185
		P	0.579	0.834	0.001	0.871	<0.001	0.194
	CSHQ	r		0.471		0.002		0.166
		p		0.122		0.988		0.245

p: Spearman Correlation, CADS: Childhood Anxiety and Depression Scale, CSHQ: Children's Sleep Habits Questionnaire, ESS: Epworth Sleepiness Scale

Table 5

Allergy history, adenoid and tonsil surgery, chronic diseases, and cigarette exposure of the groups

		Primary school		Middle school		High school		Total		
		n	%	n	%	n	%	n	%	p
Allergy	No	33	76.7	83	78.3	38	74.5	154	77.0	0.869
	Yes	10	23.3	23	21.7	13	25.5	46	23.0	
Adenoidectomy	No	36	83.7	84	79.2	47	92.2	167	83.5	0.124
	Yes	7	16.3	22	20.8	4	7.8	33	16.5	
Tonsillectomy	No	41	95.3	90	84.9	49	96.1	180	90.0	0.038
	Yes	2	4.7	16	15.1	2	3.9	20	10.0	
Chronic diseases	No	40	93.0	99	93.4	48	94.1	187	93.5	0.975
	Yes	3	7.0	7	6.6	3	5.9	13	6.5	
Smoking exposure	No	39	90.7	75	70.8	35	68.6	149	74.5	0.022
	Yes	4	9.3	31	29.2	16	31.4	51	25.5	

Table 6
Factors affecting CADS, CSHQ, and ESS

	ESS			CSHQ			CADS		
	No	Yes	p	No	Yes	p	No	Yes	p
Adenoidectomy	5 (3-7)	3 (2-5)	0.042						
Middle school adenoidectomy	5 (3-6.75)	3 (1.75-4)	0.011						
Middle school allergy	4 (2-7)	5 (2.75-8.25)	0.048	48 (45-51)	50 (47-55)	0.040			
Middle school smoking exposure				48 (45-51)	51 (48-54)	0.010	34 (21-47)	51 (30-66)	0.022

CADS: Childhood Anxiety and Depression Scale, CSHQ: Children's Sleep Habits Questionnaire, ESS: Epworth Sleepiness Scale

The students smoking exposure, adenotonsillectomy, and allergy history were questioned.

The coronavirus (COVID-19) pandemic has adversely affected the mental health of all people, children, adolescents, and adults alike[19]. During the COVID-19 pandemic, children are deprived of social interaction and friendship because they are in quarantine at home and therefore their sensitivity to psychiatric disorders increases. The closure of schools and playgrounds, the fear of being infected by their parents, and the restriction of outdoor activities caused panic attacks and anxiety disorders in children[20]. In a web-based survey study conducted in India during pandemic period, it was revealed that 73.15% of children showed signs of increased anger and 51.25% of them[7]. Many studies have reported that anxiety and depression levels had increased in children and adolescents compared with the pre-pandemic period[2,21]. In a study conducted with university students during the COVID-19 pandemic in Italy, depressive symptoms were 27.8%, and anxiety symptoms were 34.3%[22]. In our study, we saw anxiety-depression symptoms with a high rate of 73.5%. The reason for this may be the different study population, quarantine conditions, survey cut-off values, and varying sociocultural differences between countries. Although questionnaires used such as CADS do not diagnose anxiety, they can provide information about anxiety levels in childhood.

The sex difference in anxiety and depression is also evident in many studies [23,24]. In our study, similar to LI Duan's study, adolescents' anxiety levels were found to be significantly higher than in children, and girls' anxiety levels were significantly higher than in boys ($p<0.001$)[1]. Having a family member or friend infected with coronavirus, residing in an urban area, the mother's occupation being related to the epidemic, and telephone and internet addiction increased levels of anxiety and depression[3]. Anxiety in city centers is higher than in rural areas; stricter implementation of quarantine in the city may be related to the fact that there are fewer open areas such as parks and gardens and the apartments are more common, and smoking exposure and allergic symptoms are more common. Our study was conducted with children living in the city, and smoking exposure increased anxiety levels, especially in the middle school group.

Children need healthy sleep to fully complete their physical, psychological, and spiritual development 25. Quality sleep means that the individual feels fit and ready for a new day after waking up. Decreased sleep quality causes daytime sleepiness in children and adolescents[25]. Excessive daytime sleepiness is an important public health problem and significantly reduces the quality of life[26]. It has been reported that children and adolescents with high daytime sleepiness have behavioral problems during the day and show lower academic success[27]. The reason for increased daytime sleepiness is poor sleep quality[28].

To evaluate the sleeping habits of children, the sleeping habits of pediatric subpopulations in Cape Verde and Mozambique were evaluated using the Portuguese version of the Child Sleep Habits Questionnaire[11]. There may be differences between studies in the prevalence of sleep disorders and the factors affecting them because children's sleep habits are highly influenced by socio-economic, psychosocial, cultural, and environmental factors.

In a survey study conducted on university students and administrative staff during the COVID-19 pandemic in Italy, it was observed that sleep was delayed, sleep quality decreased, insomnia symptoms, anxiety in-creased, and depression symptoms increased in both groups compared with the pre-pan-demic period[22]. During the COVID-19 pan-demic, it has been reported in many studies that the time spent outside and physical activity decreased, sedentary movements such as screen time increased, diet and sleep habits changed[29,30]. In our study, we found that high school girls had poorer sleep quality than high school boys and they had more excessive daytime sleepiness. The reason for this may be that, as seen in our study, the anxiety level of high school girls is higher than that of boys. It may also be because boys are more fond of games involving physical activities and girls adopt a more sedentary lifestyle.

Sleep disorders are quite common in children. One of the most common is simple snoring, but the most severe and most serious is obstructive sleep apnea syndrome (OSAS)[31]. In OSAS, upper airway obstruction, and consequently apnea attacks, hypoxia, hypercapnia, blood gas changes, and systemic complications may occur[32]. Behavioral problems, hyperactivity, and learning difficulties can be seen in

affected children. In Italy, simple snoring in children was reported as 4.9% and OSAS as 1.8%[33,34]. The most important risk factor for OSAS was adenotonsillar hypertrophy, obesity, and less frequently allergy and smoking exposure[34,35]. There are very few questionnaires that can be used to evaluate children suspected of having OSAS, but the ESS is one of them. Otorhinolaryngology physicians are vital in the evaluation of children with OSAS and adenotonsillectomy should be performed in these children when necessary[36]. It is observed that sleep apnea attacks disappear and sleep quality increases after surgery[37]. In our study, the daytime sleepiness of children who had nasal surgery was found to be significantly lower than those who did not have surgery. In our study, allergy and cigarette exposure negatively affected sleep quality and increased excessive daytime sleepiness. In children with sleep disorders, the history of allergies should be questioned, and if necessary, they should be referred to allergy polyclinics. Smoking exposure should be investigated and protective measures should be taken.

Limitation: This study has some limitations. First, data collection was performed by dis-tributing questionnaires to children and adolescents. Results may vary according to the understanding of the participants, especially for children who need their parents' assistance. This situation may have restricted the reaction of children and prevented them from expressing themselves properly. Second, our sample was from a specific area in the city center and there was a limited number of participants. For this reason, to improve further study designs and the scientific structure of their results, it is necessary to increase the sample size and catchment areas, to conduct face-to-face surveys, and to use qualitative interview methods.

5. Conclusions

The COVID-19 pandemic has caused anxiety symptoms, especially in high school girls and poor sleep quality in primary school-age boys. Although it cannot be said definitively that there may be adenoid vegetation in children in the presence of excessive daytime sleepiness, it can be a guide for us. Children should be examined and investigated in this respect. Cigarette exposure and allergies negatively affect sleep quality and cause excessive daytime sleepiness.

Acknowledgements

We thank Asena Ayça Özdemir from Mersin University for statistical analysis.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Adana City Training and Research Hospital Medical Ethics Committee with the decision no. 1258 dated 13.01.2021.

Conflict of interest statement

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

Funding source

None.

Author contributions

Concept/Design: AK, SOE, YK ; Data acquisition: AK, YK, ; Data analysis and interpretation: AK, SOE, ; Drafting manuscript: AK, BT; Critical revision of manuscript: AK, SOE, BT YK; Final approval and accountability: AK, SOE, BT, YK, OG; Technical or material support: AK, SOE ; Supervision: AK, SOE, BT, YK, OG ; Securing funding (if available): n/a.

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Do Antiplatelet Drugs Use Contribute to Clinical Outcomes in Patients Receiving Penile Low-Intensity Shock Wave Therapy for Erectile Dysfunction?

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Abstract

Aim: Low-intensity extracorporeal shock wave therapy (Li-SWT) is one of the recommended treatment options in patients with erectile dysfunction (ED). Li-SWT is safe in patients using antiplatelet drugs (APs), however, there are no specific studies on the contribution of APs use to clinical improvement in erectile function. We aimed to evaluate the early clinical results of Li-SWT administration and whether the use of APs had an additional positive contribution to clinical improvement and safe in ED patients.

Methods: Patients with ED for more than 6 months despite using (5 mg/day) PDE5i were included in our study. Patients treated with Li-SWT and using PDE5i were classified as Group 1, patients treated with Li-SWT and using APs and using PDE5i were considered Group 2. The evaluation results of the International Index of Erectile Function-Erectile Function Area (IIEF-EF) in all patients baseline and after treatment were examined.

Results: There are 25 patients in each group. Analysis of IIEF-EF scores showed significant increases in both groups after treatment [group 1 (p=0.001); group 2 (p=0.001)]. When the IIEF-EF scores of the groups before and after the treatment were compared with each other; it was shown that baseline scores were similar(p=0.746) and that APs use had no statistically significant effect on post-treatment scores (p=0.613) No side effects were seen in APs.

Conclusions: This study showed that penile Li-SWT significantly increases the IIEF-EF scores and response of (5 mg/day) PDE5i in ED patients and safe, also in AP users. However, Using AP in Li- SWT does not contribute positively to clinical results.

Keywords: *Erectile dysfunction (ED), Antiplatelet (AP), Endothelial dysfunction, Low intensity extracorporeal shockwave therapy (Li-SWT), Phosphodiesterase type 5 inhibitor (PDE5i).*

1. Introduction

Erectile dysfunction (ED) affects men of all ages. Its incidence is in the range of 30-65% in men over 40 years of age with vascular risk factors (VRF) such as metabolic syndrome, diabetes mellitus (DM) and hypertension (HT)[1,2].

Oral Phosphodiesterase type 5 inhibitors (PDE5i), hormone replacement, also in severe patients intracavernosal injections or penile prosthesis implants are used in current medical treatment (MT)[3,4]. Due to MTs does not change the underlying pathophysiology, researches has focused on the concept of "regenerative therapies (RT)". RT is based on the idea of applying low-intensity extracorporeal shock wave therapy (Li-SWT) for the restoration of the erectile mechanism[5]. Mechanical stress and micro-trauma caused by Li-SWT in the tissue provide non-enzymatic nitric oxide production, activate vascular endothelial growth factor, and cause angiogenesis[6,7]. Li-SWT is effective and safe, especially in patients with vascular-derived ED[2] and is weakly recommended in the EUA ED guideline for the treatment of mild organic ED[8].

The relationship between ED and microvascular circulation disorder, also the restorative effects of antiplatelet drugs (APs) therapy in endothelial dysfunction, as well the role of activated platelets in the pathogenesis of ischemia/reperfusion injury are known[9,10]. Studies

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Received: 29.03.2023, Accepted: 12.07.2023, Available Online Date: 31.08.2023
Cite this article as: Geyik S, Deger M, Akdoğan N, et al. Do Antiplatelet Drugs Use Contribute to Clinical Outcomes in Patients Receiving Penile Low- Intensity Shock Wave Therapy (Li-SWT) for Erectile Dysfunction? J Cukurova Anesth Surg. 2023;6(1):194-8. doi: 10.36516/jocass.1247105

have shown that Li-SWT therapy is safe in patients using APs[11], however, there are no specific studies on the contribution of APs use to clinical improvement in erectile function.

In this study, we aimed to evaluate the early clinical results of Li-SWT administration and whether the use of APs had an additional positive contribution to clinical improvement and safe in sexually active 5 mg/day PDE5i refractory ED patients.

2. Materials and methods

Patients who applied to our clinic with the complaint of erectile dysfunction for more than 6 months despite using 5 mg/day PDE5i (Tadalafil) between January 2015 and January 2021 and received penile Li-SWT were included in our study. Diabetic Patients with HbA1C levels > 7 ng/ml and patients with a history of pelvic surgery (radical prostatectomy) and neurologic mediated disease (such as Multiple Sclerosis) and patients with the International Index of Erectile Function-Erectile Function (IIEF-EF) > 26 and testosterone levels < 4 ng/ml, patients using Thiazide Diuretics and Beta Blockers (except Nebivolol) were excluded from the study.

Patient data were collected retrospectively. First examination findings, laboratory results, and 6-month follow-up results after treatment were examined. We prescribed 5 mg/day PDE5i to all patients undergoing Li-SWT during treatment and for at least the first 3 months after treatment. Patients treated with one course of Li-SWT and using PDE5i were classified as Group 1, patients treated with one course of Li-SWT and using APs (100 mg/day acetylsalicylic acid or 75 mg/day dipyridamole/clopidogrel) for other diseases and using PDE5i were considered Group 2.

We perform penile Li-SWT treatment mainly on patients with organic erectile dysfunction who do not benefit or partially benefit from 5mg/day Tadalafil treatment. To all patients Li-SWT was applied for one course which was consisted of 5 implementations 7±2 days apart. In each implementation; 1,800 shockwaves(SW)(0.09 mJ/mm^2) were applied to the distal penile shaft and 1,800 SWs to the perineal corpus cavernosum. A total of 18,000 SWs was applied to each patient at the end of one session. The treatment was administered in an outpatient setting without anesthesia, the application areas were the same, and each implementation lasted approximately 20 minutes[12].

Linear SW were applied with Renova(Initia Ltd. Petah Tikva Israel), a second generation electromagnetic energy source Li-SWT device. All sessions were conducted by the same urologist. The probe was manually supported to provide an effective tissue contact without using any stabilizers or additional accessories.

Evaluations were made baseline and after treatment with the IIEF-EF[13]. In the evaluation; the short-term clinical results of Li-SWT application were evaluated separately for both groups and whether the use of AP made a positive contribution to clinical improvement or not was evaluated by comparing the groups. Also, the safe of APs uses is evaluated with physical examination and anamnesis for each pre/post- implementation.

2.1. Statistical analyses

The SPSS 22.0(SPSS Inc. Chicago, IL, United States) software was used for statistical analysis. Continuous variables were given as mean ± standard deviation. Independent t tests were performed on these variables. P value <0.05 was considered significant.
The study which was approved by Çukurova University Clinical Research Ethics Committee with the number 120 and date 05/13/2022.

3. Results

Data of 87 patients were reviewed retrospectively and 37 patients were excluded from the study; 3 patients lacked hormonal evaluations, 4 patients had recurrent testosterone insufficiency, 7 patients had ongoing diuretics and 2 patients beta-blockers medications, 1 patient had multiple sclerosis and 4 patients had previous radical prostatectomy history, 16 patients had high HbA1C levels. 50 patients were included in the study.

There are 25 patients in each group. The mean age of Group1 was 46.7±13.2 years, and the mean age of Group 2 was 54.2±10.5 years. Mean age of group 2 was significantly higher (p=0.03). There was no statistically significant difference in terms of the demographic characteristics of the groups, except for the mean age of the patients (Table 1).

Table 1
Comparison of demographic data

	Group 1	Group 2	p value
Age (year)	46.7±13.2	54.2±10.5	0.03
Duration of ED (year)	4.64±3.58	3.84±2.56	0.368
Hypertension (n)	4	10	0.114
Diabetes mellitus (n)	8	15	0.088
Cardiovascular diseases (n)	8	15	0.088
Benign prostatic hyperplasia (n)	6	11	0.232
Benign prostatic hyperplasia surgery history (n)	0	1	1.00
Chronic kidney disease (n)	0	1	1.00
Usage of antidepressants (n)	11	4	0.062

(ED: Erectile dysfunction)

Table 2
IIEF-EF score changes of Groups

		Group 1	Group 2	p
IIEF-EF score changes in pre&post Li-ESWT	Baseline	11.68±4.22	11.32±3.57	0.746
	6th month	22.56±4.67*	21.88±4.76*	0.613

(IIEF-EF: International Index of Erectile Function-Erectile Function, Li-ESWT: Low-intensity extracorporeal shock wave therapy)

Table 3
IIEF-EF scores of patients in pre-post Li-SWT

		Group 1 Pre / post Li- SWT	Group 2 Pre / post Li- SWT	p
IIEF-EF ≥26 patients in post Li-SWT	EF 6th month (n,%)	8 / 25 (32)	6 / 25 (24)	0.754
IIEF-EF ≥26 patients in post Li-SWT (according to baseline ED grades)	Mild to moderate (n, %)	2 / 3 (66.7)	2 / 3 (66.7)	1.0
	Moderate (n, %)	5 / 15 (33.3)	3 / 13 (23.1)	0.686
	Severe (n, %)	1 / 7 (14.3)	1 / 9 (11.1)	1.0

(ED: Erectile dysfunction, EF: Erectile function, IIEF-EF: International Index of Erectile Function-Erectile Function, Li- ESWT: Low-intensity extracorporeal shock wave therapy)

Analysis of IIEF-EF scores showed significant increases in both groups after treatment [group 1, from baseline 11.68±4.22 to 22.56±4.67 at 6th month(p=0.001); group 2 from baseline 11.32±3.57 to 21.88±4.76 at 6th month(p=0.001)]. When the IIEF-EF scores of the groups before and after the treatment were compared with each other; it was shown that baseline scores were similar(p=0.746) and that APs use had no statistically significant effect on post-treatment scores(p=0.613)(Table2).Post-treatment IIEF-EF ≥26 ratios; in group 1 was %32, in group2 was %24 and in all patients was %28. The ED grades of the patients were determined according to the pre-treatment IIEF-EF score. Initially, there were 16 patients with severe ED, 28 with moderate ED, and 6 with mild-moderate ED. According to baseline ED grades post-treatment IIEF-EF ≥26 ratios; 12.5% in severe, 28.6% in moderate, and 66.7% in mild to moderate ED patients were (Table 3).

No patient during treatment and follow-up reported penile pain, skin reactions or hematuria.

4. Discussion

Current medical treatment of ED focuses on symptomatic improvement. Based on our knowledge of ED pathophysiology, the concept of regenerative therapies and Li-SWT applications have gained popularity after 2010. Recent studies have once again demonstrated that focused or linear alternatives in shockwave delivery are not superior to each other in terms of safety and effectiveness14.

ED guideline of EUA states that Li-SWT can be used in patients with mild organic ED or in poor responders to PDE5i with a weak recommendation level. In contrast the ED guideline of AUA, is still classified as investigational8.

First, in 2010, Vardi et al. reported the use of Li-SWT in the treatment of ED in a retrospective clinical study. As a result, after 6 months, with oral PDE5i therapy 10 out of 20 patients was reported better EF15. Also two years later, with a randomized, double-blind, placebo-controlled study on the same patients; it was demonstrated that Li-SWT had a physiological effect on EF and that spontaneous erection was satisfactory for penetration and sexual intercourse in 50% of patients16. Similarly, all patients of us who were initially refractory to 5 mg/day PDE5i reported that they became responsive approximately at 3th-4th weeks of the treatment with better hardness. None of them suffered from the side-effects to PDE5i because they were using at past also. The recommendation of PDE5i use to maximize the improvement in erectile function has almost standard

in Li-SWT applications17. Subsequent studies have shown that Li-SWT, which promotes angiogenesis, can restore natural and spontaneous EF by repairing penile hemodynamics and underlying pathologies, particularly in vasculogenic ED18.

In the literature, there was a recent experimental study showing that Li-SWT reversed age-related physiological changes in old rat erectile tissues partially[19]. The results are exciting for the hope that ED may be cured with Li-SWT for sure.

In aging and metabolic diseases (DM, HT, hyperlipidemia, etc.), the prevalence of cardiovascular disease increases with the emerging atherosclerosis and microvascular circulation disorders. Studies show a correlation between cardiovascular disease and the prevalence of ED **[1]**. APs, that are used in both peripheral and coronary artery diseases have restorative effects in endothelial dysfunction, as well the role of activated platelets in the pathogenesis of ischemia / reperfusion injury[9,10]. One of the mechanisms of action of Li-SWT is the increase in tissue blood supply through neoangiogenesis[7]. Since the tissue blood supply increased with the use of AP, we sought an answer to the question "Did the use of AP together with the SWs contribute positively to the clinical results?". For this purpose, we retrospectively evaluated the data of our one session Li-SWT applied patients into two groups; without AP(group 1) and while using AP(group 2). Srini et al. reported that more than 70% of patients with vasculogenic ED in the active treatment group could experience spontaneous erections with Erectile Hardness Scale (EHS) scores of 3 after treatment with focused Li-SWT[20]. Similarly, in our study, we observed that 66.67% of patients with mild-moderate ED in groups 1 and 2 reached IIEF-EF≥26 score at the end of 6 months and achieved a satisfactory sexual life. Although, ıt was safe, we could not observe the use of AP have any positive contribution on clinical results. In a meta-analysis, Lu et al., demonstrated that the therapeutic efficacy was higher in patients with mild to moderate ED than those with severe ED or severe comorbidities. They concluded that the duration of Li-SWT were closely related to the improvement of clinical outcomes and IIEF scores, and that Li-SWT and PDE5i combination therapy was more effective [21]. Similarly, in our clinic, we prescribe the PDE5i 5mg/day for during and after treatment at least 3 months in order to increase blood supply in the tissue restoration process and to improve the IIEF-EF scores and also to build of sexual life self-confidence. Our clinical experience showed that, patients who tolerate and responsive to PDE5i continue using the drug voluntarily, for a more satisfactory sexual life, without a doctor's prescription.

Jeffrey D et al. published a meta-analysis evaluating 7 randomized controlled studies with a total of 607 patients from November 2005 to July 2018)[2]. As we determined in our study, good tolerability was stated, on the other hand, it was emphasized that a specific treatment protocol and long-term follow-up results were needed.

In the evaluation, mean change in IIEF-EF scores before and after 1 month was statistically significant[2]. Similarly, our IIEF-EF scores were significantly increase at 6th month after the treatment for both groups. The mean pre-treatment IIEF-EF scores of groups were similar. However, when the additional positive contribution of the AP drugs used by the group 2 patients to the improvement of IIEF-EF was evaluated, no statistically significant difference was found in contrast our expectation.

Dimitrios Kalyvianakis et al. published the 3-month follow-up results of 35 patients with vasculogenic ED who received anti-coagulant/antiplatelet drugs during Li-SWT treatment and during the follow-up period. After each implementation and 1-3 months after treatment, all patients were evaluated by penile physical examination and ultrasound. As a result, no side effects, skin reactions or bleeding were reported[11]. Similarly, we did not observe any side effects in group 2 and this result is a second "yes" to safe of Li-SWT therapy is in patients receiving anti-coagulant/antiplatelet. We found that a single session was insufficient in patients with severe and moderate ED. These results are in line with the ED treatment guideline of EUA[8].

Hüseyin M Adeldaeim et al. reported "Prognostic Indicators for Successful Low Intensity Extracorporeal Shock Wave Therapy in Erectile Dysfunction" study, involving 425 patients with 30 months of follow-up period. As result, affecting the success in Li-SWT important factors were age, diabetes, hypertension, smoking, obesity, hyperlipidemia, pre-treatment Sexual Health Inventory for Men (SHIM) score, ED duration. At follow-up, 168(76.3%) of the Li-SWT responders reported satisfactory sexual intercourse with a SHIM score of 22-25 without using PDE5i. They reported safe and effective ED treatment during follow-up, in 39.5% successfully treated of all patients[22]. In contrast, our successful treatment rate was %28 and lower than this study, because our baseline severe grade ED patients rate were %32 and our success criteria was IIEF-EF score ≥26. Almost all studies have focused on improving EF after Li-SWT.

Olsen et al. published in 2015 a double-blind randomized prospective controlled study of Li-SWT application to patients with ED with comorbidities such as hypertension, diabetes, hyperlipidemia and coronary artery disease without giving treatment for these diseases. As a result, they reported that there was no clear information about the relationship between the clinical outcomes of Li-SWT and these comorbidities[23]. More randomized controlled prospective studies are needed to evaluate the relationship of ED with idiopathic or comorbid factors.

Under 7% HbA1C has been shown to reduce microvascular and neuropathic comp-lications of diabetes[24]. Also antihypertensive drugs are involved in the development of erectile dysfunction. The thiazide type diuretics, the aldosterone receptor blockers, and the β-adrenergic receptor blockers are the most prominent of these[25]. Due to this point of view before applying Li-SWT in our clinic; we make treatment arrangements for ED patients with comorbidities (DM, HT, cardiovascular diseases, etc.) via the consultations of the relevant specialists. With this approach, we believe that existing comorbid factors will have a minimal negative impact on the success of Li-SWT treatment.

The strengths of our study are that it is the second study on the safety of APs use in Li-SWT patients and that it is the first study to suggest that APs can contribute to tissue restoration by improving tissue perfusion and endothelial dysfunction. The limitations and weaknesses of the study are that it evaluates a small group of patients retrospectively and the lack of a penile Doppler USG control.

5. Conclusions

Our results showed that the use of APs drugs with the application of Li-SWT was safe, but might not positively contribute to clinical results. The possible contribution of APs to tissue restoration and perfusion in Li-SWT may be the subject of future experimental animal studies. In our study, we concluded that 5 mg/day PDE5i refractory ED patients will be responsive to PDE5i treatment with Li- SWT application, additionally that the treatment was most effective in patients with mild and mild- moderate ED.

Acknowledgements

None.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Çukurova University Hospital Medical Ethics Committee with the decision no. 122 dated 13.05.2022.

Conflict of interest statement

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

Funding source

None.

Author contributions

The authors confirm contribution to the paper as follows: study conception and design: SG, MD; data collection: SG; analysis and interpretation of results: NAK, NA, IOY; draft manuscript preparation: SG. All authors reviewed the results and approved the final version of the manuscript.

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Post-Tonsillectomy Bleeding: The Effect of Surgical Experience

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Abstract

Aim: We aimed to discuss and investigate the relationship between the surgeon's experience and post-tonsillectomy bleeding (PTB) in the light of the literature.

Methods: The retrospective data was obtained from 280 patients who underwent tonsillectomy (32 PTB and 248 no-PTB) operated by residents or consultant surgeons.

Results: The overall bleeding rate after tonsillectomy was 11.43% (32/280). The bleeding rate was 14.3% in the <16 age group and 9.7% in the ≥16 age group (p=0.246). While the rate of bleeding after tonsillectomy operation was 6.16% in the resident group; it was 27.53% in the consultant group (p<0.001). In patients who bled after tonsillectomy operation, the operation time was significantly shorter in the consultant group (p=0.032). Binary Logistic Regression analysis revealed that being a consultant surgeon is a risk factor for bleeding after tonsillectomy operation (p<0.001). Short operation time was a weak risk factor (p=0.048).

Conclusions: More experience in surgery does not decrease the risk for PTB, quite the reverse, it increases the PTB risk. The effort to finish surgery in a short time, and possibility of performing a less careful and more traumatic surgery might have caused this result.

Keywords: *Tonsillectomy, post-tonsillectomy bleeding, resident, consultant, surgeon's experience*

1. Introduction

Tonsillectomy is one of the most common interventions in oto-rhinolaryngology practice, comprising approximately 20-40% of the surgical procedures in this field[1,2]. Recurrent infections and airway obstruction are the primary indications for tonsillectomy in both adults and children, and more than 500.000 tonsillectomies are performed each year in patients younger than 15 years of age[3]. Tonsillectomy decreases the rate of bacterial tonsillitis, and improves overall quality of life[4,5]. Post-tonsillectomy bleeding (PTB) is divided into two main categories as primary bleeding, which happens within 24 hours after surgery and secondary bleeding that occurs >24 hours after the surgery.

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Received: 21.01.2023, Accepted: 12.06.2023, Available Online Date: 31.08.2023
Cite this article as: Delibaş V, Özdaş T, Muluk NB, et al. Post-tonsillectomy bleeding: The effect of surgical experience. J Cukurova Anesth Surg. 2023; 6(1): 199-203.doi: 10.36516/jocass.1240290

Primary bleeding rate has been reported as 0.2-2% [4] while secondary bleeding rate has been reported as 3-5%[1]. Primary bleeding is usually associated with surgical technique, while environmental factors affecting oropharyngeal healing contribute to secondary (delayed) bleeding, although the exact mechanism is not known[6,7]. Old age, recurrent tonsillitis, attention deficit hyperactivity disorder[8], 15-30 years of age [9], chronic / cryptic tonsillitis[9,10] and low household income[11] have been reported as the risk factors for PTB. The causes of secondary PTB may be solid food intake, tonsillary bed infection, postoperative use of non-steroid anti-inflammatory drugs, or it may be idiopathic[12-15].

In this study, we investigated the relationship between PTB and the surgeon's experience.

2. Materials and methods

2.1. Informed consent and ethical approval

This retrospective study was conducted at a area hospital in 2017, in accordance with the principles of the Declaration of Helsinki, by informing the patients and obtaining their consent. Ethics committee approval was obtained from ethics committee of a area hospital (Date: June 28, 2017; No:69).

2.2. Subjects

The data of the patients who underwent tonsillectomy in ENT clinic of our hospital between January 2015 and June 2017 were reviewed retrospectively, from the electronic patient recording system of the hospital. The ones with chronic disorders (asthma, hypertension, etc.) and the ones who smoked were excluded, and the remaining 280 patients were reviewed. The patients did not use drugs before the operation, and the same recommendations were made and implemented in terms of post-operative nutrition.

There was PTB in 36 patients; one patient was excluded for not taking prescribed antibiotics postoperatively, and three patients were excluded for not obeying their post-tonsillectomy diet, and finally 32 patients who had PTB were included in the study (PTB group). The remaining 248 patients who met the inclusion criteria and did not have PTB were included in no-PTB group. At the end, the study population included 280 patients who had tonsillectomy.

The PTB and non-PTB groups were further divided into two subgroups to investigate the role of the surgeon's experience on PTB, as the patients in whom surgical procedures were performed by consultant surgeons, and the patients in whom the surgical procedures were performed by the residents under the supervision of consultants.

2.3. Preoperative investigations, surgical technique and postoperative care

Complete blood count, routine blood chemistry, prothrombin time (PT) and international normalized ratio (INR) were done in all patients preoperatively, and were in normal limits in all patients included in the study.

Tonsillectomy was performed with cold dissection and snare method, under general anesthesia. Hemostasis was achieved using bipolar diathermy, if necessary. None of the patients had an additional surgical procedure, such as adenoidectomy or ventilation tube insertion.

The patients were administered paracetamol (10 mg/kg q.i.d. for children, 500 mg q.i.d. for adults, both in suspension form) and amoxicillin (50 mg/kg b.i.d. for children, 750 mg b.i.d. for adults, both in suspension form) postoperatively. All patients were given a diet postoperatively, and hot and solid food was avoided between postoperative 0-10th days. All patients were discharged from the hospital the next day after surgery.

2.4. Parameters investigated

The demographic characteristics of the patients, duration of surgery, the experience of the surgeon who performed surgery (consultant surgeon or resident under the supervision of the consultant surgeon), date of re-admission for bleeding, and the hemoglobin level at the time of bleeding were noted.

2.5. Statistical Analysis

SPSS package program (version 16.0) was used for statistical analysis. Chi-square test, Wilcoxon Signed Ranks Test, Independent Samples t-Test, Mann Whitney U test, Spearman's correlation test and Binary Logistic Regression (Backward LR) were used where appropriate. A p value <0.05 was considered as statistically significant. The study population was determined as 5320 with G-power program by taking impact size 0.362, α=0.05, power (1-β) =0.80 at a confidence level of 95% and a substitute group composing of 280 individuals was added.

3. Results

3.1. Comparison of the PTB and no-PTB groups

The characteristics and the comparisons of PTB and no-PTB groups are presented in Table 1. Among 280 patients who had tonsillectomy, 32 (11.43%) patients had PTB. One (3%) patient had primary bleeding (consultant group) and 31 patients (97%) had secondary bleeding. The mean postoperative day for PTB was 7.77±3.28 (range: 1-15 days).

There were 20 males and 12 females in PTB group, and 124 males and 124 females in no-PTB group; two groups were similar for gender distributions (p=0.184). The mean age was not different in PTB no-PTB groups (18.5±11.5 years in PTB, and 22.5±14.6 years in no-PTB group, p=0.347) (Table 1).

In the PTB group, the mean duration of surgery was 35.46±9.18 minutes (range: 20.0-55.0 minutes). In the no- PTB group, the mean duration of surgery was 35.06±8.91 minutes (range: 15.0 -75.0 minutes). The mean durations of surgery were similar in PTB and no-PTB groups (p=0.808) (Table 1). There was no significant correlation between PTB and duration of surgery (r= 0.026, p=0.669). The day of PTB and duration of surgery were not significantly correlated, either (r= - 0.68, p=0.716).

3.2. Comparison of Resident and Consultant Surgeon groups for PTB

Residents performed tonsillectomy in 211, and consultants performed tonsillectomy in 69 patients. Among 32 patients with PTB, residents performed surgery in 13 (40.6%), and consultants performed surgery in 19 (59.4%) patients. PTB rate was 6.16% (13/211) in the resident group, and 27.53% (19/69) in the consultant group. In consultant group, PTB was significantly more frequent than the resident group (p<0.001, r=0.290) (Table 2).

The mean ages of the patients with PTB were 23.62±11.77years and 15.05± 10.25 years in in resident and consultant groups, respectively (p=0.044) (Table 2).

Table 1

The characteristics of PTB and no-PTB groups.

	PTB group	No-PTB group	Total	p
Number	32 (11.43%)	248 (88.57%)	280	
Mean age (years)	18.5±11.5	22.5±14.6	22.06	0.347
Male	20	124	144	0.184
Female	12	124	136	
Mean surgery time (min)	35.46±9.18	35.06±8.91	35.11±8.93	0.808

PTB: Post-tonsillectomy bleeding.

Table 2
Comparison of resident and consultant surgeon groups for PTB

	RES group	CONS group	p
PTB rate	6.16%	27.53%	<0.001
Age (years)	23.62±11.77	15.05±10.25	0.044
Mean surgery time (min)	39.61±7.49	32.63±9.33	0.032

PTB: Post-tonsillectomy bleeding; RES: Resident group; CONS: Consultant group

Table 3
Risk factors for PTB.

	S.E.	Wald	Exp(B)	p
Being a resident or attending surgeon	0.427	21.931	7.384	0.000
Duration of surgery	0.022	3.898	1.044	0.048
Age	0.016	2.754	0.973	0.097

S.E.: Standard Error Difference; Exp(B): exponentiation of the B coefficient; PTB: Post-tonsillectomy bleeding.

When all patients who had tonsillectomy were taken into account, the mean duration of surgery was 36.45±8.60 minutes (range: 20.0 - 75.0 minutes) in the resident group, and it was 31.01±8.72 minutes (range: 15.0- 55.0 minutes) in the consultant group (p<0.001). When only the patients with PTB were taken into account, the mean duration of surgery was 39.61±7.49 minutes in the resident group, and 32.63±9.33 minutes in the consultant group, and the duration of surgery was significantly shorter in consultant group in patients with PTB (p=0.032) (Table 2).

To determine the confounding variables on PTB, Binary Logistic Regression (Back-ward LR) analysis was performed (Table 3). Confounding variables were age, duration of surgery, and experience of the surgeon (being a resident or a consultant surgeon). Binary Logistic Regression analysis revealed that being a consultant surgeon was risk factor for PTB (p<0.001, Exp(B): 7.38, Wald=21.93). Duration of surgery was a weak risk factor (p=0.048, Exp(B): 1.044, Wald=3.898).

4. Discussion

In this study, we investigated the experience of surgeons on PTB, and found that being an experienced surgeon increased the risk of bleeding following tonsillectomy.

PTB is the most common complication of tonsillectomy. Primary bleeding is thought to be due to inadequate hemostasis during surgery while the cause of secondary bleeding has not been yet not fully understood [16]. Most of our patients (97%) had secondary PTB.

Since PTB may be a life-threatening complication, a number of surgical techniques have been compared for PTB rate. Ali et al. [17] reported that in 494 patients, 33 patients (6.68%) had PTB, 3 being primary and 30 being secondary. The most frequently used surgical technique was cold-steel dissection with bipolar diathermy for hemostasis (55.87%). The lowest PTB rate was observed with cold dissection technique (3.14%) while the highest PTB rate was seen after bipolar diathermy tonsillectomy (8.47%). In our study, we used cold dissection technique for tonsillectomy, and our overall PTB rate was 11.43%.

Age has been suggested as a risk factor for PTB. Ali et al. [17] reported that the highest PTB rate was above 15 years of age (9.41%), followed by the 10-14-year-old (8.75%) and the < 5-year-old age (5%) groups. They found the lowest PTB rate in the 5-9-year-old age group (3.66%). Lee, et al. (4) investigated retrospective data of 8347 patients who underwent tonsillectomy. The overall bleeding rate was 1.3%. Patients ≥12 years old had a significantly higher bleeding rate when compared to the younger group. PTB rates were 0.5% for patients <12 years, and 3.2% for those ≥ 12 years of age (p<0.0001). Kim et al. [18] provided data on 1489 patients who underwent tonsillectomy. PTB rates were 3.1%, 2.5% and 10.8% in younger children (under 11 years), older children (12-15 years) and adults (over 15 years old). After tonsillectomy, the bleeding was more common in adults compared to children. In our study, the mean ages were similar in PTB no-PTB groups (p=0.347, Table 1). We divided our study population into two, as the ones <16 years of age and the ones ≥16 years of age, however the two age groups were also similar for PTB rate (p=0.246), and we did not determine age as a risk factor for PTB (p=0.203, r= -0.076). Since the mean age our study population was 22.06 years, our high PTB rate may be related to older age of our study group.

The effect of the experience of surgeons on PTB has been studied, and a number of studies reported that surgeon's experience did not affect PTB rate [4,12,15,19-21]. Lee et al. [4] reported that there was no significant difference of bleeding rates in tonsillectomy procedures performed at academic versus community sites in the data of 8347 tonsillectomies (p =0.59). Similarly, Leader et al. [21] reported that consultants performed tonsillectomy quicker, and concluded that residents and attending surgeons were similar for readmission or postoperative hemorrhage rates. On the other hand, Hinton-Bayre et al. [22] reported that primary PTB rate was similar in trainees and consultants, however secondary PTB was seen less after tonsillectomies performed by experienced surgeons (3.3% vs. 10%). Similarly,

Manimaran et al. [23] reported that 69.5% of the patients with PTB were operated on by trainees, while 30.5% were operated on by consultants (p=0.03), and there was a negative correlation between experience and PTB.

In this study, we investigated the effect of the surgical experience on postoperative bleeding rates in tonsillectomy. Among 32 patients in which PTB was detected, 40.6% was operated by residents, and 59.4% was operated by the consultant ENT surgeons. The bleeding ratio was significantly higher in the consultant group compared to the resident group (27.53% vs. 6.16%, p<0.001). Logistic regression analysis showed that being a consultant surgeon was a risk factor for PTB (p<0.001). The reason for this result may be the slower and more careful surgery of the residents causing less trauma to the tonsillary bed, since duration of tonsillectomy was significantly longer in the resident group. The consultant surgeons might have had overconfidence while performing tonsillectomy and had the anxiety for finishing surgery in a short time, resulting in reduced attention and a more traumatic surgery causing PTB.

Our study has some limitations. Since it is a retrospective study, we could not perform a histopathological analysis to show whether tonsillectomy materials included surrounding muscle tissue, indicating a more traumatic tonsillectomy in the consultant surgeon group.

4.1. Limitations

Classifying the patients we included in the study as adults and pediatrics would have enabled us to obtain more precise results, but the insufficient number of our patients did not allow us to make this distinction. Not all operations were performed by a single surgeon.

5. Conclusions

We concluded that expertise in surgery does not decrease the risk for PTB, quite the reverse, it increases the PTB risk. The effort to finish surgery in a short time, and possibility of performing a less careful and more traumatic surgery might have caused this result. Further prospective studies on larger cohorts are needed to make more clear conclusions.

5.1 Implications

- The result we obtained at the end of our study is that surgical experience has no effect on bleeding after tonsillectomy operation.
- Tonsillectomy operation is a common procedure in ENT practice.
- Bleeding after tonsillectomy can cause serious loss of work and time, and even a small amount of mortality.

Acknowledgements

None.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by SBÜ. Adana City E&R Hospital ethics committee(Date: June 28, 2017; No:69).

Conflict of interest statement

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

Funding source

None.

Author contributions

All authors contributed to the study conception and design.

All authors read and approved the final manuscript.

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Effect of Aloe Vera on MMP-1 and TIMP-1 Expression on Diabetic Wound Healing

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Abstract
Aim: The aim of this study is to investigate the healing aspect of aloe vera in diabetes mellitus, which inhibits wound healing.
Methods: Diabetes model was created with streptozotocin. At the end of the 14-day experiment, blood glucose was measured from the tail vein of animals in all groups and blood was taken from the heart and sacrificed. Histopathology and immunohistochemical statistics and evaluation were performed.
Results: Pycnosis and degeneration of epithelial cells were observed in diabetes groups. Leukocyte infiltration in the dermal papilla, degeneration of collagen fibers and an increase in the extracellular matrix were observed. It was observed that the epithelial layer in the aloe vera group was histologically close to the control group. It was observed that decreased inflammation in the dermal papilla and decreased in organized collagen fibers and vessel dilatation were observed. In the control group, MMP-1 and TIMP-1 expression were positive in the epidermis and dermis layers. In the diabetes group, weak expression of MMP-1 and TIMP-1 was observed in cells in the epidermis and dermis. The expression of MMP-1 and TIMP-1 in the surface epithelium in the aloe vera group was increased compared to the diabetes group.
Conclusions: Aloe vera accelerated cell and extracellular matrix regeneration with its anti-oxidative activity.
Keywords: *Diabetes, wound healing, MMP, Aloe Vera, TIMP-1*

1. Introduction

Diabetes Mellitus is a lifelong disease that develops when the pancreatic gland does not produce enough insulin hormone or the insulin hormone it produces is not used effectively. Diabetes is responsible for the delayed or incomplete wound healing process seen in patients and often leads to the formation of chronic ulcers[1]. Matrix metalloproteinases (MMPs) cleave the peptide bonds of extracellular matrix proteins such as collagen, laminin, elastin and fibronectin. This family of proteinases plays a critical role in morphogenesis, development, wound healing, reproduction, and neovascularization. Also, this proteolytic enzyme activity is controlled by another family of proteins, tissue metalloproteinase inhibitors (TIMPs). The imbalance between MMPs and TIMPs plays a role in many pathological processes such as cancer metastasis, arthritis, inflammation, periodontal diseases, corneal ulceration and cardiovascular diseases. In the skin, this enzyme is synthesized by fibroblasts and keratinocytes and plays an important role in the amount of dermal collagen in the tissue[2]. In a previous study evaluating wound healing in humans, it was shown by protein analysis that the balance between MMP-1 and TIMP-1 plays an important role[3]. Many clinical and experimental studies examining the effects of herbal extracts on acute or pathological wound healing have been conducted and discussed. Aloe Vera produces gel and latex, two substances used to make medicine. Aloe Vera gel is a clear, jelly-like substance found on the inside of the Aloe plant leaf[4]. Aloe latex is a yellow substance located just below the plant membrane. Studies have shown that Aloe Vera moisturizes the skin, is good for sunburn and skin wrinkles, helps to maintain the elasticity and freshness of the skin, and to control acne and eczema. In addition, the healing power of Aloe Vera on the skin is due to the increase in the amount of oxygen and collagen synthesis in the skin[5]. In this study, the effectiveness of aloe vera on the balance of MMP-1 and TIMP-1 in rats with experimental diabetic wound model was investigated by histopathological and immunohistochemical methods.

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Received: 21.03.2023, Accepted: 24.05.2023, Available Online Date: 31.08.2023
Cite this article as: Seyrek R, Soker S, Kaplan O, et al. Effect of Aloe Vera on Mmp-1 and Timp-1 Expression on Diabetic Wound Healing. J Cukurova Anesth Surg. 2023; 6(1): 204-9. doi: 10.36516/jocass.1268067

2. Materials and methods

This study was carried out within the framework of the permission dated 29.04.2020 and numbered 2020/09, obtained from the Dicle University Animal Experiments Local Ethics Committee. In our study, 21 Wistar Albino female rats, 15-16 weeks old and weighing between 190-210 g, were used. Rats were divided into 3 groups.

1. Sham group: A wound model with a diameter of 1 cm was created on the dorsal skin in the lumbosacral vertebral region of the animals.

2. DM group: STZ-induced diabetes was induced by intraperitoneal administration of 45 mg/kg streptozotocin (STZ) dissolved in cold 0.1 M citrate buffer (pH=6.0).72 hours later, those with a glucose level > 240 mg/dl measured with a glucometer from the tail vein were considered Type 2 diabetic[6].A wound model with a diameter of 1 cm was created on the dorsal skin in the lumbosacral vertebral region of the animals.

3. DM+Aloe vera group: STZ-induced diabetes was induced by intraperitoneal administration of 45 mg/kg streptozotocin (STZ) dissolved in cold 0.1 M citrate buffer (pH=6.0).72 hours later, glucose levels > 240 mg/dl measured with a glucometer from the tail vein were considered Type 2 diabetic. Aloe vera extract was dissolved in distilled water and 300 mg/kg daily was given as 0.5 ml suspension by oral gavage. A wound model with a diameter of 1 cm was created on the dorsal skin in the lumbosacral vertebral region of the animals.

At the end of 14 days, blood glucose was measured from the tail vein and blood was taken from the heart and sacrificed. Tissues were excised and removed and skin samples were fixed in 10% formol. Skin samples were dehydrated and incubated in xylene. The tissue samples were then embedded in paraffin blocks. Skin tissue sections taken from paraffin blocks were stained with Hematoxylin-Eosin (HE), Alcian Blue and immunohistochemistry[7].

2.1. Immunohistochemical staining

Sections were deparaffinized in xylene for 3x15 minutes. Sections were passed through the decreasing alcohol series for 10 minutes and put into water. Sections were washed 3x5 minutes in phosphate buffer solution (PBS). Sections were taken in ethylenediamine tetraacetic acid (EDTA) buffer solution (pH:8.0, catalog no: ab93680, Abcam, Cambridge, USA) and retrieval of the heat-induced epitope was performed. Hydrogen peroxide solution (catalog no: TA-015-HP, ThermoFischer, Fremont, CA, USA) was dripped onto the sections and left for 20 minutes. It was kept in Ultra V Block (catalog no: TA-015-UB, ThermoFischer, Fremont, CA, USA) solution for 7 minutes. Sections were kept at +4°C overnight with antibodies to MMP-1 (catalog no:bs-0463R) and TIMP-1 (catalog no:orb-195994). Biotin-containing secondary antibody (catalog no: TP-015-BN, ThermoFischer, Fremont, CA, USA) was dripped onto the sections and left for 14 minutes. Then, streptavidin-peroxidase (catalog no: TS-015-HR, ThermoFischer, Fremont, CA, USA) was dripped and left for 15 minutes. Diaminobenzidine (DAB) (catalog no: TA-001-HCX, ThermoFischer, Fremont, CA, USA) was dropped on the sections washed with PBS. After counterstaining with Harris hematoxylin, the sections were covered with entellan (catalog no:107961, Sigma-Aldrich, St. Louis, MO, United States). They were evaluated and visualized under a Zeiss Imager A2 photomicroscope.

2.2 Statistical Analysis:

IBM SPSS version 25 software program was used for statistical analysis. Multiple comparisons between groups before and after the experiment were made according to Kruskal Wallis and post hoc Tamhane's T2 test. $P<0.05$ was considered statistically significant and the results were shown as mean ± standard deviation (SD).

3. Results

3.1. Blood Glucose Level

Numerical and graphical data on blood glucose levels are shown in Table 1 and Figure 1. Pre-experimental blood glucose levels were 110.71 ± 11.29 mg/dl in the sham group, 118.00 ± 25.51 mg/dl in the diabetes group, and 119.57 ± 16.97 mg/dl in the diabetes+aloe vera group. and no statistically significant difference was found between the groups ($p>0.05$). At the end of the experiment, the blood glucose level of the diabetes group was found to be 367.86 ± 113.55 mg/dl and significantly higher than the sham group ($p<0.01$). It was determined that the blood glucose level of the diabetes+aloe vera group was 220.86 ± 5.49 mg/dl and was significantly different from the sham group ($p<0.01$) and diabetes group ($p<0.05$).

3.2. Histopathological Findings

Hematoxylin staining (a-c) and alcian blue (d-f) stainings of Sham, diabetes and aloe vera groups are shown in Figure 2.

Sham Group: Cells were observed in the epidermis layer with normal appearance. A tight connective tissue and hair follicle structures were observed in the dermis region. Vascular structures were observed regularly in the dermis (Figure 2a).

Diabetes Group: Degeneration loss in epithelial cells and pycnosis in nuclei were observed. Thinning and separations were detected in the epidermis structure. Leukocyte infiltration was observed in the dermal papilla, slight degenerations were observed in collagen fibers and fibrosis began. Degenerative changes were observed in hair follicles. Apoptotic changes were detected in the nuclei of connective tissue cells (Figure 2b).

Aloe Vera Group: Thickness was detected in the epidermis layer. Collagens were detected regularly in the dermis layer. Mild hypertrophy was observed in connective tissue cells, vessels were dilated and mild leukocyte infiltration was detected (Figure 2c).

Control Group: Epidermis layer was observed regularly. It was observed that there was an irregular tight connective tissue between the collagen fibers rich in dermal papilla ESM.

Table 1

Blood glucose levels before and at the end of the experiment

	Sham	Diabetes	Diabetes+Aloe vera
Pre Experiment	110,71 ± 11,29a	118,00 ± 25,51a	119,57 ± 16,97a
Post experiment	107,57 ±7,28a	367,86 ± 113,55c	220,86 ± 5,49b

Note :Different superscripts indicate significant difference between groups: a-bp<0.01, a-cp<0.01, b-cp<0.05.

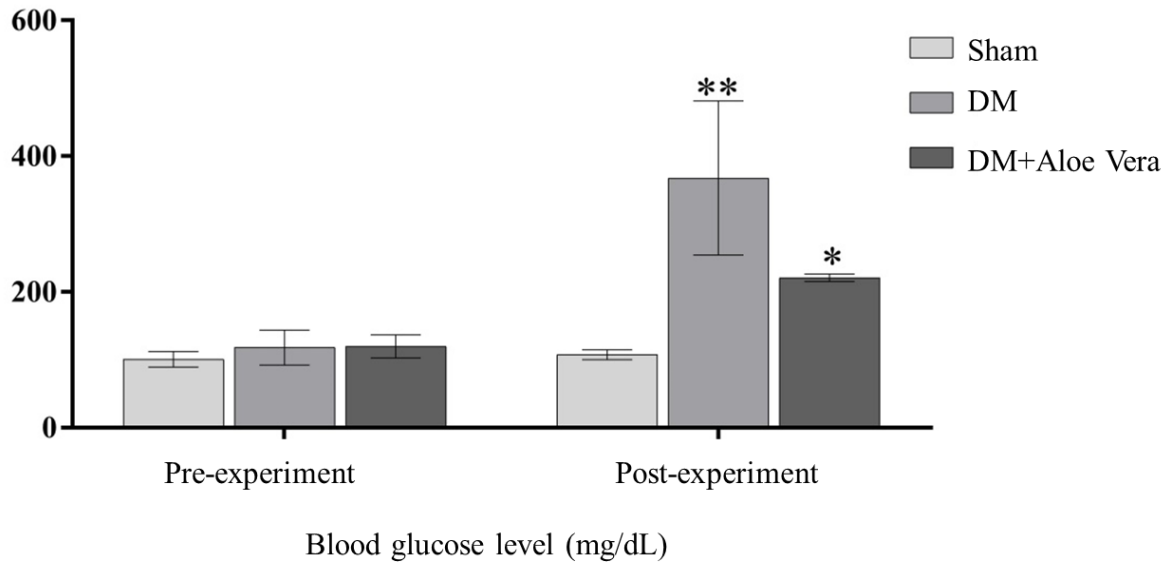

Figure 1

Graphical presentation of the statistical analysis of the Pre-Experimental and Pre-Sacrification Blood Glucose Levels of the Groups. According to Sham group *p<0.01, **p<0.01. */**p<0.05.

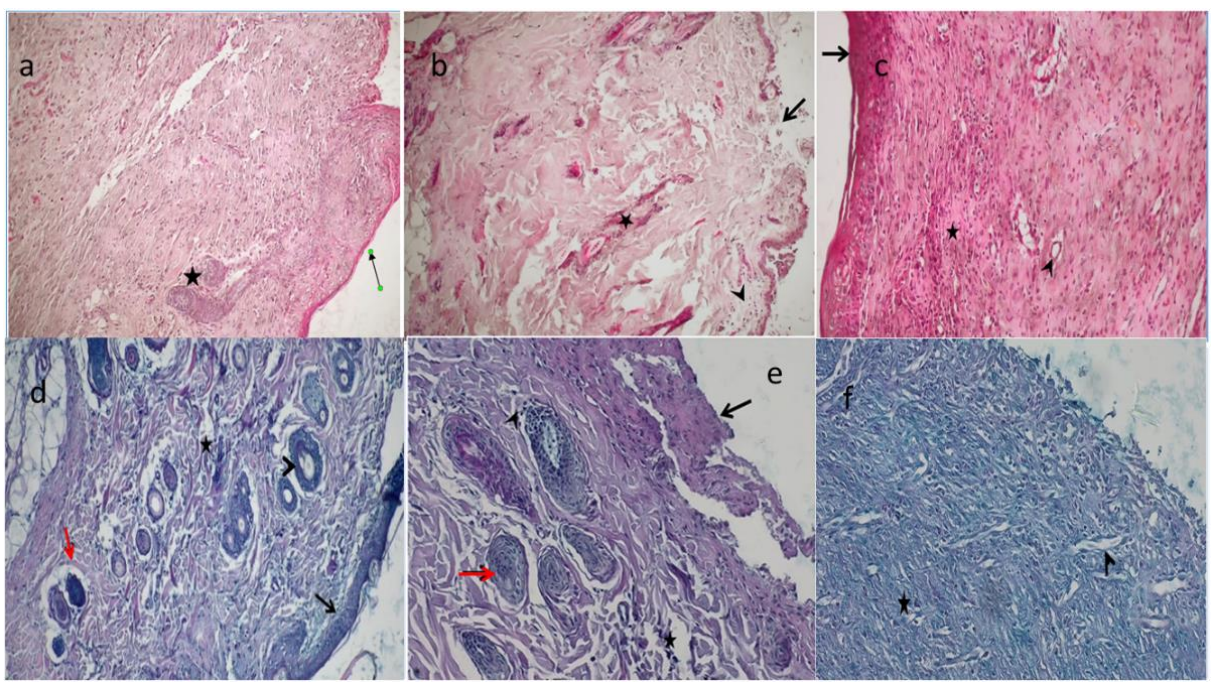

Figure 2

a) Control Group: Epidermis (arrow) follicle (star), b) Diabetes group: Epidermis (arrow) leukocyte infiltration (arrowhead), collagen structure (star); c) Aloe vera group: Epidermis (arrow), fibroblasts (star), vascular structure (arrowhead) Bar: 100μm Hematoxylin eosin 10X d) Control Group: Epidermis (arrow), collagen fiber (star), hair follicle (arrowhead), musculus erector pili muscle (red arrow); e) Diabetes Group: Epithelium (arrow), leukocyte cells (arrowhead), hair follicle (red arrow), collagen fibers (star). f) Aloe Vera Group: Collagen fibers (star), vessel dilatation (arrowhead) Bar: 100μm Alcian Blue 10X

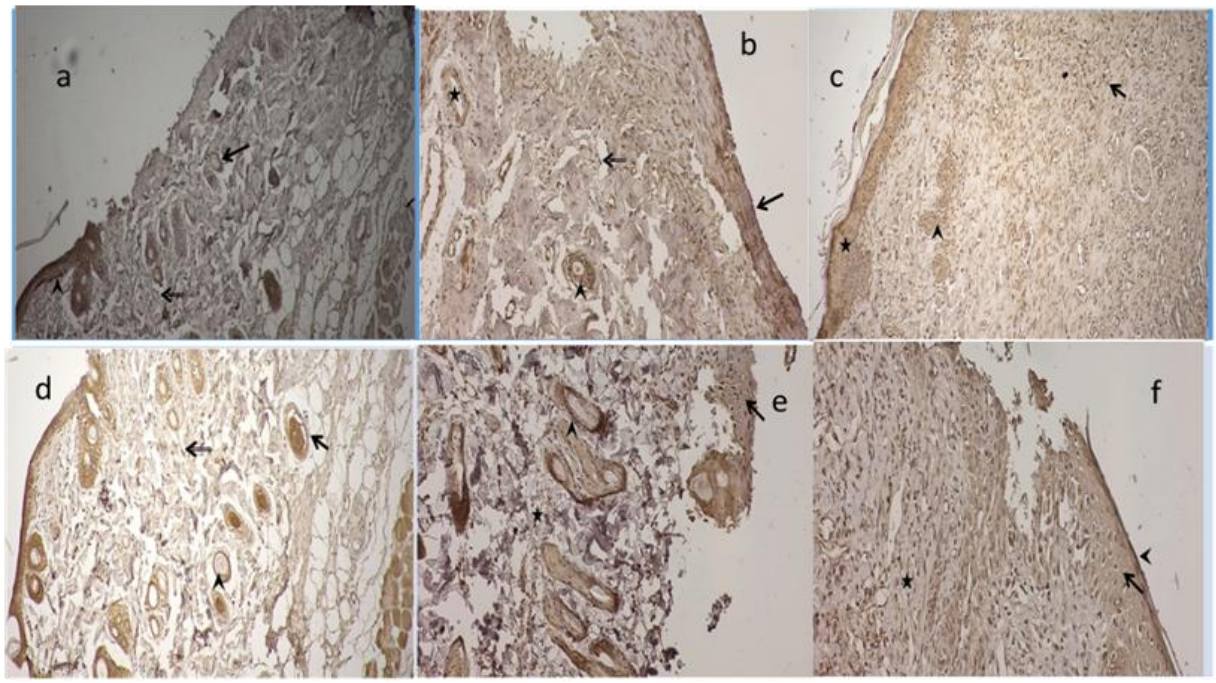

Figure 3

a) Control Group: Basal lamina (arrowhead) in the epidermis, fibroblast (double-tailed arrow) and in hair follicles (arrows) positive MMP-1 expression (arrows) b) Diabetes Group: Epidermis (arrow), in the basal lamina of the vessels (star), hair follicles (arrowhead), fibroblast cells (double-tailed arrow) MMP-1 positive expression. c)Aloe Vera Group: Granulosa cells (star), hair follicle (arrowhead), fibroblast cells (arrow) positive MMP expression. d) Control Group: in hair follicles (arrow), in Huxley layer (arrowhead) and fibroblasts (double-tailed arrow) positive TIMP-1 expression; e) Diabetes Group: Positive TIMP-1 expression in granulosa cells (arrow), connective tissue (star), hair follicles f) Aloe Vera Group: It was determined that TIMP-1 reaction was intense in the epidermis (arrow), in keratinized areas (arrowhead), fibroblasts and other connective tissue cells (star). Bar: 100μm 10X. Immunohistochemical Staining

The outer hair follicles were seen in normal appearance. The musculus erector pili muscle was located parallel to the hair follicle (Figure 2d).

Diabetes Group: Epithelial loss was observed. Leukocyte cells were detected in the dermis layer. Apoptotic changes were observed in the hair follicle. Degenerative changes were seen in collagen fibers, an increase in ESM structure was observed. The vessels are slightly dilated (Figure 2e).

Aloe Vera Group: A significant decrease was observed in the connective tissue between the collagen fibers in the dermis. Connective tissue cells were prominent in the dermis, with a marked reduction in dilatation and inflammation (Figure 2f).

3.3 Immunohistochemical Findings

Figure 3 shows MMP1 (a-c) and TIMP1 (d-f) stainings of Sham, diabetes and aloe vera groups. Control Group: MMP-1 expression in the basal lamina region of the epidermis, hair follicles and fibroblast cells was evaluated as positive (Figure 3a). Diabetes Group: It was determined that MMP-1 expression was positively stained in epidermis cells, hair follicles, and fibroblast cells (Figure 3b). Aloe vera group, It showed a very intense increase in MMP-1 expression in the surface epithelium, hair follicle and fibroblast cells (Figure 3c). Control Group: TIMP-1 expression intensity was observed in hair follicles, Huxley layer, fibroblasts in the dermal papilla region (Figure 3d). Diabetes Group: TIMP1 expression was positive in the epidermis, connective tissue cells and hair follicles (Figure 3e). Aloe vera Group: TIMP-1 reaction was found to be positive in the epidermis, fibroblasts and other connective tissue cells (Figure 3f).

4. Discussion

Wound healing is a natural process involving complex cellular and biomolecular steps that are shaped to restore the tissue to its former state after damage. Basically, the biological wound healing process takes place through the regulation of homeostasis, inflammation, cell migration and proliferation, and remodeling. Proper wound healing leads to rapid wound closure and minimal or aesthetically acceptable scarring without regeneration for the acute wound [However, while this process occurs at an optimal rate and in an optimal manner in healthy individuals, in people with diabetes, wound healing is impaired or disrupted[8].

DM is a metabolic disease characterized by high blood glucose levels caused by a decrease in insulin secretion and/or a decrease in the effect of insulin. Various factors such as environmental, genetic and lifestyle factors have been reported to contribute to the development of DM[9]. DM, which is a progressive disease, becomes a major health problem for society and the individual, leading to increased morbidity and mortality with serious complications if not controlled[5].

Many factors that inhibit the wound healing process at various stages lead to delayed wound healing and an increase in mortality and morbidity[10]. Although the adverse effects of DM on wound healing have not been fully explained, high blood glucose levels are thought to be the underlying cause of this condition by inhibiting cell proliferation and collagen production, decreasing fibroblast formation and growth factors, increasing apoptosis in wound tissue cells, increasing infection formation due to decreased angiogenesis,

granulation tissue formation, chemotaxis and phagocytosis[11]. DeClue and Shornicks reported that diabetic wound healing is associated with excessive release of proinflammatory cytokines such as IL-1β, IL-6 and TNF-α[12]. Qui et al. reported that diabetic patients with high blood glucose levels had decreased cell proliferation and decreased collagen production and growth factors in the wound healing process[13]. Decreased angiogenesis and decreased growth factors such as VEGF and TGF-1β are thought to be associated with the non-healing process of diabetic wounds[14].

The use of medicinal plants for healthy living, treatment and care of various diseases has increased rapidly worldwide in recent years. 60% of the world population and 60-90% of developing countries use traditional medicinal plants in primary health care[15]. However, one out of every three drugs used in traditional medicine is used in wound and skin diseases, while only 1-3% of synthetic drugs are used in these diseases[16]. All these suggest that medicinal plants used in wound treatment may have the potential to be therapeutic alternatives to synthetic drugs.

Aloe vera (yellow patience) belonging to the Liliaceae family is known to have wound healing properties and has been used for thousands of years for this purpose[17, 18]. Atiba et al. examined the effects of oral Aloe vera application on diabetic wounds in a study on type II diabetic rat models and reported that this application increased inflammatory cell infiltration, angiogenesis, extracellular matrix deposition and epithelialization and accelerated wound contraction, and also increased TGFβ-1 and VEGF protein-positive cells[19]. In another study, the positive effects of oral and topical Aloe vera application on the wound were shown on diabetic rat models[20]. In the rats treated with Aloe vera, the wound patency level was visibly between the levels in the sham and diabetes groups. In microscopic examination, macrophage and lymphocyte infiltration was quite intense in the wound tissue in the sham group and regeneration of epithelial and connective tissue elements was detected. In the diabetes group, the epidermis layer could not reach a compact state, intense edema accumulated in the wound area and the general structure of the scar tissue was observed. In the diabetes group of our study, loss of epithelial cells in the epidermis, pyknotic leukocyte infiltration in the nucleus and solitary leukocyte infiltration in the dermal papilla region, degeneration of collagen fibers, and cell disruption and apoptotic changes in the hair follicles were observed (Figure 2b,2d). Although cell nucleus shrinkage was observed due to the effect of diabetes, degenerative changes increased and apoptotic changes accelerated. In the group treated with aloe vera, epithelium size and nucleus size were close to the sham group and regular, inflammation in the dermal papillae decreased, collagen fibers were regular, vascular dilatation decreased and hair follicles started to improve. It was thought that the tightening property of aloe vera especially in the dermis region was important in terms of collagen reorganization (Figure 2c,2f).

It is known that the amount of MMP in the tissue decreases over time in the normal wound healing process, but in chronic wounds, there is an increase in proteases as well as proinflammatory cytokines and the amount of growth factors decreases[21-23]. Lobmann et al. In their study, Lobmann et al. reported that the expression level of MMP-1, MMP-8 and MMP-9 and the level of active MMP-2 increased significantly in diabetic ulcers, whereas the level of TIMP-2, the tissue inhibitor of MMP-2, decreased. Muller et al. examined the levels of various MMP and TIMP-1 in cutaneous tissue fluid in diabetic patients with foot ulcers. As a result of their study, they reported that the amount of MMP-1 and TIMP-1 in the tissue fluid of patients with good wound healing increased by the 2nd week, but both MMP-1 and TIMP-1 levels tended to decrease in the following weeks. The researchers stated that in patients in whom wound healing did not progress normally, the TIMP-1 level remained almost constant during the 12-week study, but after the 12th week, there was an increase in MMP-1 level and a decrease in TIMP-1 level. The researchers reported that MMP-1 and TIMP-1 play an active role in the wound healing process and that an increase in both the amount of MMP-1 and the MMP-1/TIMP-1 ratio may provide information about the healing of diabetic ulcers in patients whose wound healing process is clinically well evaluated[24].

In our study, when the cutaneous wounds of animals with experimental diabetes model were compared with the cutaneous wounds of non-diabetic animals at the end of the 14-day follow-up, it was found that MMP-1 immunoexpression was significantly increased and TIMP-1 expression was decreased. In animals in which we administered 300 mg/kg Aloe vera oral gavage for 14 days, it was observed that both MMP-1 and TIMP-1 expression levels were at a level between the sham and diabetes groups. In the sham group, MMP-1 and TIMP-1 expression in the epidermis and dermis, especially in the regions where extracellular matrix was dense and in the external membrane of the hair follicle was prominent (Figure 3a,3d). In our study, it was found that both cellular and fibrous structuring decreased in both epidermis and dermis in diabetes-induced wound healing, and the matrix metalloprotein family showed a significant decrease in membranes in terms of both hair follicle and collagen fibers in both dermis and epidermis. Weak MMP-1 and TIMP-1 expression was observed in epidermis and dermis cells in the diabetes group (Figure 3b,3e). Although topical application of aloe vera is widely used under normal conditions, in our study, it was observed that the plant spread over a certain time interval in wound healing as a result of oral administration, but regional diffusion was slightly delayed. It was thought that the delay in wound healing with diabetes may be related to the inhibition of diabetes in two different regions in both epidermis and dermis. Although the effect of aloe vera has been shown in many studies, it was understood that it induced the reorganization of cells in the epidermis and the extracellular matrix and collagen fiber structuring model in the dermis. The fact that the extracellular matrix density in the Aloe vera group appeared close to the sham group, especially in terms of MMP-1 and TIMP-1, was considered as a signal of the connective tissue reorganization process. The increase in MMP-1 and TIMP-1 expression in the aloe vera group (Figure 3c,3f) was shown to be an important feature of tightening and repair in the dermis.

5. Conclusions

As a result of the anti-oxidative effect of aloe vera, it has been observed that the restructuring of cells and the development of extracellular matrix organization, depending on the decrease in oxidative stress, accelerated and the effect on skin tightening began to increase. Aloe vera administration alleviated pathology and promoted cell proliferation induced by diabetes with its anti-oxidative activity.

Acknowledgements

None.

Statement of ethics

This study was approved by Dicle University Faculty of Medicine Ethics Committee for Animal Experimentation with the protocol number (2020/09).

Conflict of interest statement

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

Funding source

This study was supported by Dicle University Scientific Re-

search Projects Commission with project number TIP.20.027

Author contributions

All authors contributed to the study conception and design.

All authors read and approved the final manuscript.

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Long Term Results of Arterial Revascularization with Omniflow II® Biosynthetic Grafts: A Single Center Experience

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Abstract

Aim: The aim of this study is to analyze the long-term outcomes of above-knee femoro-popliteal bypass procedures with Omniflow® II biosynthetic grafts. Primary patency and graft related complications were the end points of the study.

Methods: Between January 2012 and January 2021, a total of 50 patients (42 males, 8 females) were revascularized using an in-situ Omniflow® II graft. Demographic, clinical, operative and postoperative characteristics of the patients were analyzed retrospectively.

Results: Mean age was 63.8±10.1 (range 40-82) years. Fifty above-knee femoropopliteal bypass procedures were performed. Four patients (8%) were operated on due to a previous vascular graft infection where 8 (16%) were operated on due to a previous occlusion. Primary patency rate was 88%. Early graft thrombosis occurred in 2 (4%) patients where late graft stenosis unrelated to the anastomotic sites was encountered in 1 (2%) patient. An endarterectomy on either the proximal or distal site of the anastomosis were performed in 12 (24%) patients. Mean follow-up was 32.9±20.8 (range 12-90) months. Three (6%) patients died due to a COVID-19 infection. No graft infection nor mortality related to arterial bypass procedures was encountered.

Conclusion: The Omniflow® II biosynthetic graft provides superior results in treatment of above-knee femoro-popliteal bypass procedures with high patency rates and low incidence of graft infection and aneurysm formation.

Keywords: *Biosynthetic graft, vascular grafting, revascularization, peripheral arterial disease*

1. Introduction

Patients with peripheral arterial disease (PAD) have a poor circulation due to decreased arterial perfusion. The arterial blood flow to the distal extremity is restricted most frequently by systemic atherosclerosis. Its prevalence is 3-10% between 40-59 years and 15-20% over 70 years[1]. The most significant risk factors for PAD are diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL), chronic kidney disease (CKD), and smoking[2]. In addition, there is an increased rate of myocardial infarction, ischemic stroke, and cardiovascular death in patients with PAD[3].

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Received: 03.04.2023, Accepted: 01.06.2023, Available Online Date: 31.08.2023
Cite this article as: Simsek B, Azboy D, Temiztürk Z. Long term results of arterial revascularization with Omniflow® II biosynthetic grafts: a single center experience. J Cukurova Anesth Surg. 2023; 6(2): 210-4. doi: 10.36516/jocass.1276127

There is a remarkable elevated risk of adverse limb events like ischemic ulceration and gangrene unless treated. Revascularization deemed mandatory, particularly in patients with more advanced symptoms and presentations. Duplex ultrasonography, computed tomography angiography (CTA), magnetic resonance angiography or conventional peripheral angiography should be performed to diagnose and define the anatomy before revascularization. Though endovascular approaches have extended the invasive treatment modalities in peripheral arterial occlusive disease, surgical interventions must be considered especially for long occlusive disease, aneurysm formation, vascular graft infection and failure of endovascular treatment.

Despite the fact that superiority of the autogenous grafts are well-known, prosthetic grafts should be the selected conduit type in a variety of patients especially when autogenous grafts are not accessible, available or suitable[4]. Since 1983, the Omniflow® vascular grafts have been in clinical practice and advances in technology throughout this time period led to the current Omniflow® II vascular graft (OVG)[5-7]. Omniflow® II (Bio Nova International, Victoria, Australia) is created by using cross linked ovine collagen and an endoskeleton made of polyester mesh which

suggests superior long-term patency and low degeneration rates with a decreased vulnerability to infection[8,9].

The aim of the present study was to analyze the experience and long-term outcomes of patients with above-knee femoropopliteal bypass procedures with OVG.

2. Materials and methods

50 patients who underwent peripheral arterial revascularization with an OVG between January 2012 and January 2021 were identified from our vascular database. This was a retrospective and single-center study which was approved by the local Ethics Committee (protocol no: 18.03.2021-2021/04-05) and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consents were obtained from the participants of the study. Parametric data is presented as mean and standard deviation, non-parametric data is presented as interquartile range, where applicable.

2.1. Patients and data

This study retrospectively reviewed the medical records of 50 patients (42 males, 8 females) with a mean age of 63.8±10.1 years (range 40-82) who had undergone above-knee femoro-popliteal bypass surgery. The conduit preference was Omniflow® II (Bio Nova International, Victoria, Australia) when autogenous grafts were not accessible, available or suitable. Patients who had undergone a re-do surgery with OVG due to either previously infected grafts or occluded grafts were also included in the study. Patients' demographic, clinical, perioperative and postoperative follow-up data including complications were assessed in a retrospective design. Data included age, gender, history of DM, coronary artery disease, carotid artery disease, HT, HL, CKD, smoking, chronic obstructive pulmonary disease (COPD) and follow-up time. The baseline characteristics of the patients are demonstrated in Table 1. Symptomatical and descriptive classification of the patients were assessed according to the Rutherford Classification and Global Limb Anatomic Staging System (GLASS), where patients with previous infected grafts were graded with wound, ischemia, foot infection (WIfI) composite scores which are demonstrated in Table 2[10-12]. CTA and/or conventional peripheral angiography was performed to define the anatomy and decide the right surgical strategy before revascularization.

2.2. Surgical technique

Surgery was performed either under general or spinal anesthesia. A 6-mm OVG was preferred in above-knee femoropopliteal bypass procedures (Image 1-2). The OVG was rinsed following the manufacturer's implantation protocol. After intravenous administration of 5000 units of heparin and confirming an activated clotting time >200 seconds, anastomoses were constructed in an end to side fashion both in distal and proximal sites. Heparin was not reversed with protamine. During the first 24 hours, 1 mg/kg intravenous heparin infusion was administered. Thereafter, the treatment switched to therapeutic subcutaneous low molecular weight heparin (LMWH) with warfarin and Aspirin up to discharge. After reaching an International Normalized Ratio (INR) >2, LMWH quitted. The targetted INR was 3 for the patient group. Warfarin treatment was quitted at the end of the first year of surgery where Aspirin was administered life-long. In the presence of contraindications to oral anti-coagulation, long-term anti-platelet medication was administered.

In cases of 4 infected previously expanded polytetrafluoroethylene (ePTFE) bypass grafts which were occurred lately after initial bypass, all grafts were removed with infected tissue debridement. Revascularization was performed with OVG by using fresh anastomotic sites through uninfected tissue planes.

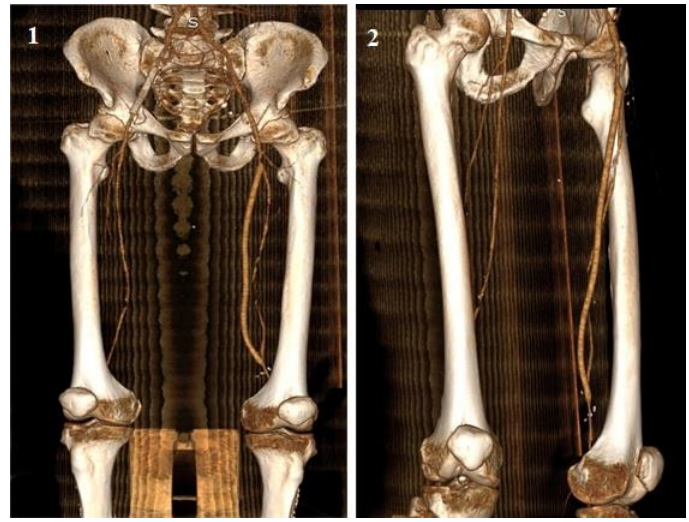

Image 1-2

1 Postoperative third year control computerized tomographic angiographic evaluation of a 6-mm Omniflow® II biosynthetic vascular graft in above-knee femoropopliteal position

2 Postoperative fourth year control computerized tomographic angiographic evaluation

In cases of 4 infected previously expanded polytetrafluoroethylene (ePTFE) bypass grafts which were occurred lately after initial bypass, all grafts were removed with infected tissue debridement. Revascularization was performed with OVG by using fresh anastomotic sites through uninfected tissue planes. Depending on the patient's condition, preoperative broad spectrum antimicrobial treatment was administered with a postoperative adaptation due to identification of the causative microorganisms. The duration and type of the antimicrobial treatment was determined within an infectious disease specialist consultation.

Primary patency is described as the period from the bypass procedure till any necessary intervention needed to reestablish or maintain patency. Bypass patency was evaluated by physical examination and duplex ultrasonography at first, third and sixth months and yearly afterwards in the outpatient clinic. The control CTA evaluations were performed in the first year of surgery and yearly afterwards as long as our patients remain symptom-free.

3. Results

A total of 50 patients (42 males, 8 females), with a mean age of 63.8±10.1 years (range 40-82) were identified. Fifty OVGs were implanted in the above-knee femoropopliteal position The indication for initial biosynthetic graft implantation was occlusive disease in 46 (92%) patients. Four patients (8%) were operated on due to a previous ePTFE graft infection which were implanted in other centers. The causative microorganisms were coagulase-negative Staphylococci in 3 patients and Staphylococcus aureus in 1 patient. Preoperative broad spectrum antimicrobial treatment was administered with a postoperative adaptation due to identification of the causative microorganisms. The duration of the anti-infective treatment after discharge was determined individually according to the recommendation of the infectious diseases specialist. No clinical evidence of graft re-infection encountered in the follow-up period.

Table 1
The baseline characteristics

Variable	n	%	Mean±SD
Total number of patients	50	100	
Age (years)			63.8±10.1 (range 40-82)
Male sex	42	84	
Hypertension	17	34	
Diabetes mellitus	30	60	
Smoking history	34	68	
Hyperlipidemia	35	70	
Coronary artery disease	25	50	
Carotid artery disease	3	6	
Chronic kidney disease	2	4	
COPD	6	12	
Follow-up (months)			32.9±20.8 (range 12-90)

COPD: Chronic obstructive pulmonary disease, SD: standard deviation

Table 2
Symptomatical and descriptive classification of the patients

	n	%
Rutherford stage		
Stage 1	1	2
Stage 2	8	16
Stage 3	18	36
Stage 4	22	44
Stage 5	1	2
GLASS score		
Stage 1	9	18
Stage 2	29	58
Stage 3	12	24
WifI score		
1	8	16
2	40	80
3	1	2
4	1	2

GLASS: Global Limb Anatomic Staging System, WifI: Wound Ischemia Foot Infection

Eight patients (16%) were operated on due to a previously occluded ePTFE grafts in above-knee femoropopliteal position without any acute ischemic status. An endarterectomy on either the proximal or distal site of the anastomosis were performed in 12 (24%) patients.

There was either perioperative morbidity or mortality among the patient group. Delayed wound healing was encountered in 4 (8%) patients. None of the patients needed surgical revision due to bleeding or hematomas. Early postoperative graft occlusion within 30 days occurred in 2 (4%) above-knee femoropopliteal bypass patients which was managed by successful surgical thrombectomy. Late graft stenosis unrelated to the anastomotic sites was encountered in 1 (2%) femoropopliteal bypass patient, which was managed by a resection and replacement within a new OVG 44 months after the initial bypass procedure. Three (6%) patients died due to a COVID-19 infection. There was neither aneurysmal dilation nor graft aneurysm formation detected at anastomotic sites. No graft infection nor mortality related to arterial bypass procedures was encountered. The overall primary patency rate was 88%. Mean follow-up was 32.9±20.8 (range 12-90) months.

4. Discussion

The OVG which was designed to overcome the drawbacks of synthetic and biological conduits, has been off the shelf for about 30 years but there have been few studies published on complication and long term patency rates[4,9,13]. The graft was created by inserting polyester scaffolded silicone mandrels into sheep to produce a wound healing counteraction that integrates the polyester mesh. This tissue-engineered product which is cross-linked with glutaraldehyde led to a non-antigenic vascular conduit. In contrast with other approaches, the incorporated polyester mesh contributes structural stability for the vascular wall and the blood flow surface which was assumed to be smooth and non-thrombogenic[5]. Anticoagulant and antiplatelet medications have been reported to improve bypass graft patency. It should be kept in mind when implanting the OVG, a higher anticoagulation management in the early postoperative period might be considered[14]. Discontinuation of oral anticoagulation might be a potential reason for acute graft failure. Nevertheless, till today we have more detailed information about the above-knee femoropopliteal bypass graft patency with the OVG rather than crural position[9,15]. Primary and secondary patency rates were 48% and 71% with the composite bypasses with autologous vein and OVG as the proximal part of such bypasses in below-knee anatomic positions[8,16]. Another reason to prefer the OVG is the polyester mash which provides more resistance to external compression in order to prevent potential kinking. Toktas et al. reported 98% patency rate at third year, 95% at fourth year and 78% at fifth year follow-up in the above knee femoro-popliteal bypass groups with OVG[13]. Yet the OVG was used as a carotid patch and also reported for hemodialysis access with promising results[17,18].

Despite the fact that the preferred graft to revascularize the lower limbs is the autologous saphenous vein, in up to 45% it may not be accessible, available or suitable due to previous coronary or lower limb bypass procedures, varicose veins of the lower limbs, previous surgery for varicose veins or mismatches in diameter and length[19,20]. In these kind of situations, alternative graft usage should be considered. Although ePTFE has been the most preferred prosthesis, the systematic review and meta-analysis by Wilasrusmee et al. revealed that there is a 54% higher graft patency in biological grafts compared to ePTFE in femoropopliteal bypass procedures and vascular access grafts[21].

Vascular graft infection is a rare but dreaded complication with significant morbidity and mortality which is associated with the use

of prosthetic grafts, postoperative hematoma, superficial wound infection, lymphocele, lymphorrhea and medical comorbidities[22]. Prosthetic vascular grafts are mostly infected in the perioperative stage. Accomplishing asepsis is essential in terms of avoiding vascular graft infection. Though, the graft might be infected despite excellent asepsis techniques. Autologous veins are suggested as the first choice graft material in terms of infection[23]. Autogenous veins are the most common grafts which are used for in situ revascularization for infected vascular grafts; however it may be unavailable or unsuitable. Once the graft infection develops, the most suitable treatment is removing the infected graft. The OVG seems to be promising for peripheral arterial reconstruction in case of infection. Results from clinical practice have proven a good infection resistance[4,9,24]. On the other hand, there have been concerns about its resistance to bacterial colonization regarding animal studies[25]. There is strong evidence that redo surgery is related to increased risk of prosthetic vascular graft infection[24,26,27,28]. We replaced 4 infected ePTFE grafts in the above-knee femoropopliteal position with an OVG with no reinfections in a 5-years follow-up period. We propose that the OVG may be a good choice to replace an infected graft material.

An aneurysm is a vascular condition which can be defined as localised dilation due to weakness. Infection, intraoperative damage, improper sterilization or storage, expansion of the polyester mesh, trauma, anastomotic failures are the main reasons of aneurysm formation. The possibility of late aneurysmal degeneration has always been a debate in biological grafts as all biologic materials are subject to probable biodegredation with consequent aneurysm formation[4,29]. Nevertheless, the anatomic position of the graft in the extremity, the patient's systemic diseases, such as autoimmune diseases, hypertension and dyslipidemia may also contribute to aneurysmal dilation. Aneurysmal degeneration may impair graft patency by leading to thrombosis as well as local symptoms[30]. In case of thrombus formation, early replacement might be kept in mind to avoid possible embolization. Such different rates were reported for aneurysm formation following bypass procedures with OVG. Koch et al. reported only 1.1% in 267 cases where Van de Laar et al. reported 8% in 25 patients[9,31]. We detected no graft aneurysm formation in the follow-up period. Patients should be followed-up regularly with duplex ultrasound and physical examination not to overlook a degenerative aneurysm.

4.1. Study Limitations

The small number of patients might be a limitation. Thus, further prospective studies in order to compare the results with different types of synthetic vascular graft materials in terms of infection may help to provide further insight with regard to patency rates, incidence of graft infection and aneurysm formation. The retrospective nature of the study is another limitation.

5. Conclusions

The Omniflow® II biosynthetic vascular graft provides encouraging results in treatment of above-knee femoro-popliteal bypass procedures with high patency rates and low incidence of graft infection and aneurysm formation. Peripheral vascular reconstruction with the Omniflow® II biosynthetic vascular grafts appears to be feasible, safe and acceptable for revascularization when autogenous vein grafts are not accessible, available or suitable.

Acknowledgements

None.

Statement of ethics

This was a retrospective and single-center study which was approved by the Fırat University local Ethics Committee (protocol no: 18.03.2021-2021/04-05) and was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

BS: Design, writing the article, literature review, critical review, DA: Idea/concept, data collection, analysis and interpretation, ZT Data collection, control/supervision, analysis and interpretation

All authors read and approved the final manuscript.

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Retrospective Evaluation of Children with Non-Steroidal Anti-Inflammatory Drug Allergy

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Abstract

Aim: Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs and are among the drug-related hypersensitivity reactions after antibiotics. There are limited studies evaluating nonsteroidal drug reactions in children. In this study, we aimed to evaluate the concomitant atopic diseases, admission clinic, laboratory findings and drug provocation test results of children with a pre-diagnosis of nonsteroidal drug reaction and who underwent allergy tests, retrospectively.

Methods: In this study, patients who applied to the pediatric allergy outpatient clinic due to nonsteroidal drug reaction were included. In this group of patients, age, gender, fx5 (nutrient mix specific IgE), phadiatop (inhalant allergen mix specific IgE), skin prick tests and drug provocation tests were recorded from their files. Demographic and clinical features of the cases were compared.

Results: 61 patients with suspected NSAIDs allergy were included in the study. When the admission clinics of the patients were evaluated, 54% (n:33) had urticaria, 22.9% (n:14) had isolated angioedema, 6.5% (n:4) had urticaria angioedema, 14.7% (n:9) had maculopapular eruption. Only 1 patient presented with anaphylaxis. NSAIDs allergy was confirmed in 16.3% (n:10) of the patients.. Single ibuprofen sensitivity was detected in 13.1% of patients (n:8), both paracetamol and ibuprofen sensitivity were detected in 1 patient (1.6%), and single paracetamol sensitivity was detected in 1 patient (1.6%).

Conclusions: It is usually not easy to detect drug allergies in patients. These patients may usually be misdiagnosed as NSAIDs allergy. In our study, it was revealed that drug provocation tests should be performed to confirm the diagnosis in case of suspected NSAIDs allergy.

Keywords: *Non-steroidal anti-inflammatory drug allergy, isolated angioedema, drug provocation test*

1. Introduction

The WHO (World Health Organization) describes adverse drug reaction as noxious and unintended events which occurs at the appropriate doses of medicines used for diagnosis/treatment[1]. Unexpected and not dose-related effects in only susceptible individuals are classified as drug hypersensitivity reactions[2]. Drug hypersensitivity reactions that occur through immunologic mechanisms constitute drug allergies[3]. The incidence of drug hypersensitivity events is not clearly known, but it is reported that these reactions result in significant public health problems in terms of morbidity, mortality, and socioeconomic burden[4,5]. Drug allergies account for 6-10% of adverse drug reactions.

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Received: 01.02.2023, Accepted: 22.04.2023, Available Online Date: 31.08.2023
Cite this article as: Aydogdu AK, Cam NY. Retrospective evaluation of children with non-steroidal anti-inflammatory drug allergy. J Cukurova Anesth Surg. 2023;6(2):215-9. doi: 10.36516/jocass.1246401

Beta-lactam antimicrobial agents and NSAIDs are the most common causes of drug allergy. The clinical presentation of drug allergies is frequently associated with skin involvement including maculopapular erythematous rash and urticaria[6]. A number of diagnostic tests are performed in cases with a preliminary diagnosis of drug allergy based on the detailed clinical history and physical examination[7]. Among these tests, the drug provocation test is considered as the gold standard method and is the controlled administration of the suspected drug to the patient.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the second most common cause of drug-related hypersensitivity reactions following antibiotics. It causes hypersensitivity reactions that occur with vaying courses in reaction time, organ involvement, and severity in individuals who develop sensitivity.

The reported prevalence of hypersensitivity reaction to NSAIDs is 0.3% both in adult and childhood population[8]. Hypersensitivity reactions to NSAIDs have been classified based on clinical findings, the presence of comorbidities and cross-reaction history with other cyclooxygenase-1 (COX-1) inhibitors[9]. In patients with a history of hypersensitivity to NSAIDs, allergic reaction through type 1 IgE-mediated mechanism is rarely observed. In this group of patients, a hypersensitivity reaction to a single drug or drugs in the same chemi-

cal group develops, while drugs with different chemical structures are well tolerated. This type of reaction is caused by an immunological mechanism and is called an allergic reaction. The most described hypersensitivity reaction mechanism is related to the inhibition of COX-1 which is involved in the mechanism of action of NSAIDs, characterized by cross-reactions to different NSAIDs. This reaction occurs through a non-immunologic mechanism. COX-1 inhibition decreases prostagladins, which are regulators of mediator release from mast cells, and increases cysteinyl leukotrienes, leading to an allergic drug reactions. This increase may cause clinical signs of urticaria, angioedema, rhinitis, and bronchospasm. Although the primary goal is to determine whether the clinical findings develop due to drug allergy in patients who present with suspected allergy after drug use, it is also necessary to determine a alternative drug that will not cause an allergic reaction to the patient in case the allergy is confirmed. It is essential to make a definitive diagnosis of patients with suspected NSAID allergy in children, because the new COX-2 inhibitors, which are frequently used as an alternative in the diagnosis of cross-reactive NSAID allergy in adults, have not been approved for pediatric use, and these drugs are not available in syrup form. Detailed patient history, physical examination, and evaluation of the patient with standardized diagnostic tests are recommended for the diagnosis. An oral drug provocation test is recommended for the definitive diagnosis of NSAID reaction under appropriate settings and conditions[8,9]. In a drug provocation test, a drug suspected of causing allergy is administered in a controlled manner gradually. There have been limited number of publications evaluating non-steroidal drug reactions worldwide and from our country. In this study, we aimed to retrospectively analyze the comorbid atopic diseases, clinical presentation at the admission, laboratory findings and drug provocation tests of children who were admitted to our clinic with a prediagnosis of non-steroidal drug reactions, and underwent allergy tests.

2. Materials and methods

The medical records of 61 patients admitted to the Pediatric Allergy-Immunology Clinic of Mersin City Hospital between May 2020 and May 2022 due to non-steroidal drug reactions were retrospectively investigated. Date of birth, gender, presence of concomitant allergic conditions, physical examination findings, fx5 (food mix specific IgE), phadiatop (inhalant allergen mix specific IgE), skin prick tests, and drug provocation tests were evaluated from the records of the patients. Eosinophilia was defined when the eosinophil level was above 4% in the complete blood count. Total lgE levels greater than 100 KU/L were considered positive. ImmunoCAP method was used for serum specific IgE levels. Food and inhalant specific IgE values ≥0.35 kU/l were considered positive. Skin prick test was performed by epidermal application with Dermatophagoides pteronyssinus, Dermatophagoides farinae, alternaria, cat and dog epithelium, meadow and cereal pollen mix, weed mix, tree pollen mix, olea, milk, egg, wheat, soy, peanut, hazelnut, beef, chicken meat, fish mix (alk) antigens. In skin prick test, histamine was used as positive control and sterile saline as negative control. Histamine was considered positive when >5 mm edema accompanied by erythema appears and was considered as the criterion for the test validation. The presence of erythema with edema diameter ≥3mm compared to the negative control was considered positive for allergens applied for the skin prick test[10].

Testing for the diagnosis of NSAID allergy was scheduled 6 weeks after the onset of allergic symptoms. Patients were asked not to use antihistamines in the week before the allergy test if they were receiving any. If the skin prick test with the suspected drug was negative, an intradermal test was performed. The test result was evaluated at the 20th minute of the intradermal administration of the drug and the resulting edema diameter 3 mm or more compared to the negative control was considered positive. Drug provocation test (DPT) was performed to confirm drug allergy in patients with negative skin tests. Written informed consent was obtained from parents. The test was performed by starting with a dose calculated between 1/1000 and 1/10 of the targeted drug dose, considering the severity of allergic symptoms. After the initial dose, the test was gradually maintained by administering the drug every 30-60 minutes until reaching the targeted drug dose. If objective findings were detected during or after the test, the test was considered positive and terminated. If no reaction was observed in the patients followed during this period of time, they were considered to have no allergies to NSAIDs[11].

The study was approved by the University of Toros Ethics Committee (September 2022/156). Statistical analysis was performed using SPSS 26.0 (Statistical Package for the Social Sciences Version 26.0) package program.

3. Results

Sixty-one patients with suspected NSAID allergy were included in the study. 59% (n:36) were boys with 1.44 boy/girl ratio. The mean age of the patients was 5.2 years (P^{25}-P^{75}:2.5-8). The evaluation of clinical presentations at the admission demonstrated that 54% (n:33) presented with urticaria, 22.9% (n:14) with isolated angioedema, 6.5% (n:4) with urticaria-angioedema and 14.7% (n:9) with maculopapular eruption. Only 1 patient presented with anaphylaxis.

Table 1

Demographic and Clinical Characteristics of the Patients

	Frequency(n)	Percentage(%)
Age(year)*	2.5-8*	0-16*
Gender		
Female	25	41
Male	36	59
Existence of Allergic diseases		
No	46	75.4
Allergic rhinitis	10	16.3
Asthma	3	4.9
Recurrent urticaria	2	3.2
Symptoms		
Urticaria	33	54
Urticaria angioedema	4	6.5
Angioedema	14	22.9
Maculopapular exanthema	9	14.7
Anaphylaxis	1	1.6
Eosinophil		
<%4	51	83.6
≥%4	10	16.4
Total IgE		
≤100	34	65.4
>100	18	34.6
FX5		
Negative	44	97.7
Pozitive	1	2.3
Phadiatop		
Negative	35	77.7
Pozitive	10	22.3

* P25-P75:2.5-8

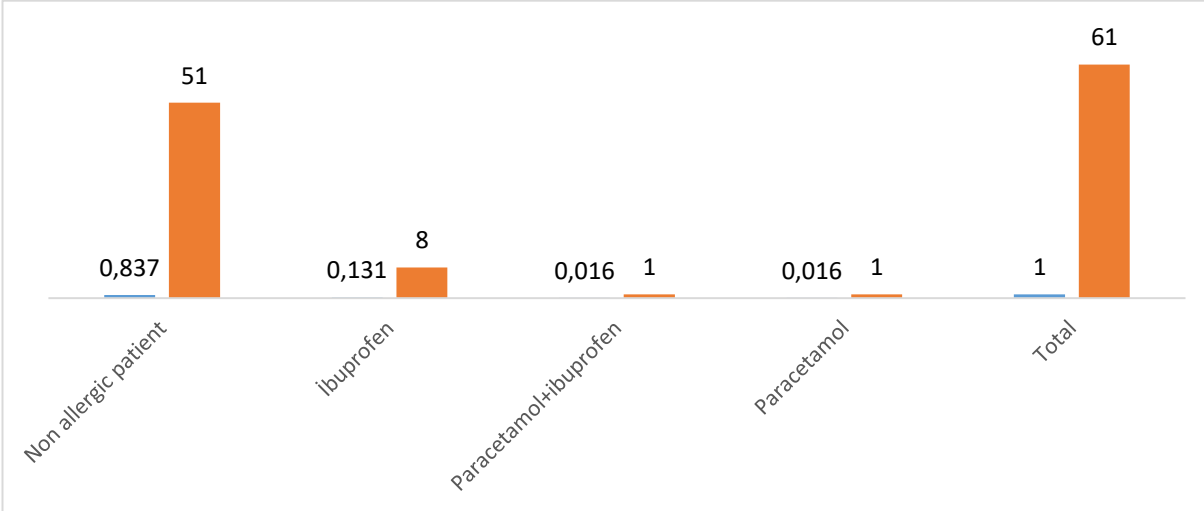

Figure 1
Confirmed drug allergies

There was no history of atopic disease in 75.4% (n:46) of the patients. Among the patients with atopic disease, 16.3% (n:10) had allergic rhinitis, 4.9% (n:3) had asthma, and 3.2% (n:2) had recurrent urticaria. Fx5 and phadiatop were examined in 45 patients, and fx5 was positive in only 1 patient, whereas phadiatop was positive in 16.3% (n:10). Total IgE was analyzed in 52 patients and found to be elevated in 18 patients (34.6%; min-max 18-1280; mean:146). Eosinophil elevation was detected in 10 patients (16.4%; min-max:0.1-7.7,mean: 2.37). (Table1) NSAID allergy was confirmed in 16.3% (n:10) of the patients. There were 5 patients with urticaria, 3 patients with urticaria angioedema, and 2 patients with angioedema in proven NSAID allergy. Ibuprofen-induced sensitivity was detected in 13.1% (n:8) of the patients, while 1 patient (1.6%) had both paracetamol and ibuprofen sensitivity and 1 patient (1.6%) had only paracetamol sensitivity (Figure 1).

4. Discussion

In this study, drug allergy was commonly observed to ibuprofen among suspected non-steroidal drug reactions.

Although literature on NSAID allergy in childhood is limited[12], beta-lactam antibiotics have been found to be the most common causative agents in drug-induced anaphylaxis in France and Portugal. In both studies, NSAIDs were the second most common causative agents[13,14]. Similarly, the most common causative agents in the US are beta-lactam antibiotics, followed by NSAIDs[15]. A recent study reported that beta-lactam antibiotics were the most common causative agents with a rate ranging from 35.5-66.6%[16]. In the same study, NSAIDs followed beta-lactam antibiotics with a rate of 21.5-28.5%.

In population-based prevalence screening studies, NSAID allergy was reported to be 0.3% in children and 5% in children with asthma[17]. In our study, we found NSAID allergy at a rate of 16%. Different rates have been reported in the literature. Ibuprofen allergy was 14.7% and paracetamol allergy was 3.2% in our study. The majority (90%) of the cases were due to ibuprofen, while paracetamol sensitivity was detected in 20% of allergic patients. Our results seem to be consistent with the literature[8,13,17]. In our study, ibuprofen was detected most frequently both as a suspected drug and as an NSAID to which allergy was confirmed. Similar reports were observed in previous studies[17,18,19]. Reactions with paracetamol in patients with NSAID allergy have been reported at rates between 0-25%[20,22]. It was 3.2% in our study.

Several studies have shown an association between NSAID allergy and allergic diseases (asthma, rhinitis)[19,20,21]. Similarly, in our study, 50% (n:5) of patients with confirmed NSAID allergy had allergic rhinitis and 10% (n:1) had asthma, whereas in the group with negative NSAID allergy result, 10% (n:5) had allergic rhinitis and 4% (n:2) had asthma. 59% of our participants were male (n:36). There is a male dominance (n:8, 80%) among patients with NSAID allergy. Similar findings were reported in previous studies[18,20]. The most common clinical presentation was urticaria. It was observed that 54% of the patients presented with urticaria and 6.5% with urticaria angioedema and this was consistent with the literature[20,22].

Isolated angioedema is a common presentation in patients who develop NSAID allergy. This requires the meticulous differential diagnosis of hereditary angioedema, another cause of isolated angioedema. Because both diagnostic and therapeutic approaches are completely different[23]. Different prevalence rates have been reported in previous studies[9,24,25]. In our study, isolated angioedema developed in 22.9% of the patients. Patient number 22 was admitted to the emergency department with a clinical presentation of viral infection. Renal function, total protein and albumin values were examined to understand underlying etiology of edema. Since findings were normal, pediatric allergy consultation was obtained, and detailed patient history revealed that the symptoms developed after non-steroidal drug intake and the patient was treated accordingly. This case suggests that emergency and family physicians should have increased awareness of diseases that may cause edema in patients presenting with isolated angioedema, as they are usually the first physicians to see patients.

Although history, physical examination and skin prick tests are performed in the investigation of drug allergy, drug provocation tests are considered as the gold standard [26,27,28]. Drug provocation tests are important to prevent unnecessary diagnosis of drug allergy. Indeed, drug allergy was reported as 17.7% in a study conducted by Tuğcu et al.[29]. In a study by Yılmaz et al.[30], NSAID allergywas 14%. Alves et al.[18] confirmed the drug allergy in 7.6% of patients evaluated for suspected NSAID allergy. In our study, NSAID

allergy was confirmed in 16.4% of patients.

5. Conclusions

Investigation of patients with suspected drug allergy is challenging. Confirmation of suspected cases require a detailed medical history, physical examination and specific tests. Tests to detect the presence of drug allergy should be performed by trained personnel, in an appropriate clinical setting, and are contraindicated in some cases. They are, therefore, not widely performed. This issue not only causes patients to be misdiagnosed as having drug allergy, but also leads to administration of drugs that are less effective or have more side effects as an alternative to patient's treatment. In addition, it has been observed that some of the patients who are allergic to NSAIDs present with isolated angioedema signs and it is crucial to differentiate it from other isolated angioedema diseases such as hereditary angioedema. Our study revealed that drug provocation tests should be performed to confirm the diagnosis in case of suspected NSAID allergy.

Acknowledgements

None.

Statement of ethics

The study was approved by the University of Toros University Ethics Committee (September 2022/156) and was conducted in accordance with the Declaration of Helsinki.

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

All authors contributed to the design and writing of the study. All authors reviewed and accepted the final version of the study.

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https://doi.org/10.1111/all.12266

Evaluating Youtube as a Resource for Postherpetic Neuralgia Patient Education

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Abstract

Aim: Postherpetic neuralgia (PHN) is one of the common complications of herpes virus and is the most common neuropathic pain syndrome after an infectious disease. YouTube is a widely used source for information, but the quality of YouTube videos in terms of medical content is questionable. Therefore, our aim was to evaluate the PHN-related quality of YouTube videos.

Methods: This study was carried out by evaluating YouTube videos up to April 2023. A total of 65 videos were evaluated. The number of views and duration of the videos, the number of likes and views, the number of comments, the age of the videos and the source of the videos were recorded. We evaluated all videos for overall educational quality and creator bias. Content creators were categorized as physicians, health-related websites, and patients, and we compared overall DISCERN scores and bias scores between creator type and search term.

Results: The average view count of the videos was 119224.62. The mean DISCERN and DISCERN Bias Scores were 2.01 and 2.14 respectively. Most of the videos were uploaded by the physicians. The DISCERN and DISCERN Bias scores were significantly higher in the videos uploaded by physicians ($p<0.001$, p:0.002 respectively).

Conclusions: Educational value of YouTube videos about PHN uploaded by different sources is poor or moderate. Although physician-created videos have higher quality and less bias, health-professionals should warn their patients to be cautious when referring to social media platforms about their disease.

Keywords: *Postherpetic Neuralgia, YouTube, video*

1. Introduction

Postherpetic neuralgia (PHN) is defined as neuropathic pain in a dermatomal distribution that persists for three months or more after the acute onset of herpes zoster. It is the most common long-term complication of herpes zoster and the most frequently seen neuropathic pain syndrome after an infectious disease[1]. Data from the UK database showed that the incidence of postherpetic neuralgia increases from 8% in early 50s to 21% in early 80s[2]. It is also shown that patients with chronic diseases or immunodeficiency are more likely to develop PNH[3,4]. The pain often affects individuals' quality of life, psychological and functional status and poses a significant health burden[1,5]. In the last decades, in conjunction with the progress of social media, patients often use online tools in a manner to learn more about their disease.

YouTube is the biggest video platform in the world, which is widely preferred for obtaining medical information due to its rapid accessibility. Various studies have examined the credibility of YouTube videos in patient education regarding several pain syndromes like fibromyalgia, migraine, or trigeminal neuralgia[6-8]. Since postherpetic neuralgia is a serious problem in elderly or immunocompromised patients, we should know the reliability of social media content on this subject. Therefore, in the present study our aim was to evaluate the educational value of YouTube videos about PHN.

2. Materials and methods

2.1. Video selections

This cross-sectional study was conducted through April 2023 by searching the phrases "postherpetic neuralgia", "zoster pain" and "herpes neuralgia" on YouTube (www.youtube.com). Ethics committee approval is not required as there are no human or animal participants. For each of these phrases the top 20 videos were evaluated based on views and relevance (top 20 videos sorted by views and top 20 videos sorted by relevance). Search history was reset prior to initiation of the study and a total of 120 videos were planned to be reviewed. Only English videos were included. Duplicate videos, videos without audio or subtitles were excluded.

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Received: 13.04.2023, Accepted: 07.07.2023, Available Online Date: 31.08.2023
Cite this article as: Sacaklidir R, Ozturk EC. Evaluating YouTube as a Resource for Postherpetic Neuralgia Patient Education. J Cukurova Anesth Surg. 2023; 6(1): 220-3. doi: 10.36516/jocass.1268067

2.2. Video features

The number of views and duration of the videos, the number of likes and comments, the rate of views (number of views / day), the age of the video and the uploaded source were recorded. The uploaded source was categorized as physician, patients, and health-related websites.

2.3. Assessment of video quality

Video contents were evaluated by two pain medicine specialists. The DISCERN scale, consisting of 16 questions, was used to evaluate the quality of the videos[9]. Each question is scored between 1-5 and higher scores refer to better quality of the video. An average of 16 questions was determined as one DISCERN score for the present analysis with respect to previous research. Besides, a DISCERN bias score of 1 indicates a completely biased source, while 5 indicates a completely unbiased source of information[7].

2.4. Statistical analysis

The Shapiro-Wilk test was used to assess the normality of the data. Mean and standard deviation (SD), minimum and maximum values and frequency were used when expressing continuous variables. The Kruskal-Wallis test was used to detect statistical differences between more than two independent variables. Inter-rater agreement was evaluated with the kappa coefficient. A p value of <0.05 was considered statistically significant for the study.

3. Results

A total of 120 videos were evaluated, 65 (54%) videos were unique, the rest were duplicate. The mean time passed since the videos were uploaded was 58.62 months. The average view count of the videos was 119224.62. The mean video duration was 3919.22 seconds. The mean number of comments and likes were 312.69 and 939.09, respectively. DISCERN treatment and quality scores were 2.11 and 2.07, respectively. The mean DISCERN and DISCERN Bias Scores were 2.01 and 2.14 respectively (Table 1). The Cohen kappa score was calculated as 0.866 for the mean DISCERN score and 0.845 for the DISCERN Bias Scores. The mean DISCERN and DISCERN Bias Scores were highest for the search phrase herpes neuralgia. In addition, videos sorted for this search phrase were mainly uploaded by physicians (75%). The highest number of likes were seen for the search phrase zoster pain (Table 2).

Table 1

General Features and Video Quality of the Videos

Video features (n:65)	Mean	Min–Max
Duration (s)	3919.22	43-216000
Time since upload (m)	58.62	1-168
Number of views	119224.62	126-850000
View ratio	93.25	0.63-1075
Number of comments	312.69	0-4295
Number of likes	939.09	0-10000
Mean DISCERN	2.01	1-4.2
Mean DISCERN Bias score	2.14	1-4
Mean DISCERN treatment	2.11	1-4
Mean DISCERN quality	2.07	1-5

The DISCERN and DISCERN Bias scores were significantly higher in the videos uploaded by physicians (p<0.001, p:0.002 respectively). There was no significant difference between the video sources in terms of number of likes, views, duration and age of the videos (Table 3). Most of the physicians who created videos were pain medicine specialists (37%). Other videos were uploaded by physiatrists (4), neurologists (2), dermatologists (4), an ophthalmologist (1) and a rheumato-logist (1). The current study is the first to assess medical content on YouTube related to postherpetic neuralgia. The mean DISCERN and DISCERN bias scores of all videos subject to this analysis were 2.01 and 2.14 (out of 5) respectively. The highest DISCERN and DISCERN bias scores which were 2.31, and 2.48 respectively, pertained to videos created by physicians.

Table 2

Vıdeo Characterıstıcs By Search Term

Search Term	Mean DISCERN Score	Mean Views	Made by Physician (%)	Mean DISCERN Bias Score	Mean Video Age (m)	Number of likes
Postherpetic neuralgia	1.99 ± 0.88	120845.9 (126-815000)	43	2.11 ± 0.96	63.89 (1-168)	941.2 (0-10000)
Zoster pain	1.85 ± 0.68	247236.0 (4900-815000)	45	2.00 ± 0.76	59.28 (6-120)	1811.3 (80-10000)
Herpes neuralgia	2.31 ± 0.95	31289.0 (126-327000)	75	2.33 ± 1.09	39.63 (1-144)	317.0 (2-3700)
All terms combined	2.01 ± 0.85	119224.62 (126-850000)	54	2.14 ± 0.94	58.62 (1-168)	939.09 (0-10000)

Table 3
Video quality assessments according to the source of the videos

	Mean DISCERN Score	Mean DISCERN Bias Score	Number of likes	Mean Views	Mean Video Age (m)	Duration
Physician (35)	2.31± 0.95	2.48 ±1.01	828.7 (0-10000)	108713.2 (126-815000)	58.91 (1-144)	7019.9 (43-216000)
Health-related Websites (22)	1.49 ± 0.49	1.77± 0.63	1213.1 (0-5300)	153401.6 (437-815000)	53.27(1-168)	277.6 (58-606)
Patient (8)	1.28 ± 0.30	1.37 ± 0.51	668.8 (24-2600)	71225.0 (4500-283000)	31.87 (12-120)	367.6 (73-802)
p	0.001	0.002	0.460	0.301	0.553	0.710

4. Discussion

Even from an optimistic point of view these results demonstrate that YouTube videos regarding postherpetic neuralgia have significant shortcomings and barely reach moderate quality.

As patients do not always have opportunity to contact with health professionals, they tend to seek information from unprofessional sources without concerning the accuracy of the data. The widespread use of the Internet and the inevitable rise of social media platforms provide quick access to information on health-related issues. However, the quality of the medical content on social media needs to be questioned. When it comes to the most popular video-sharing platform, YouTube lacks any reviewing process for the informative videos about medical conditions. Inaccurate, exaggerated or overlooked medical information may interfere with patients' decision-making process, leading to long-term effects on their physical or mental health.

To date several studies were conducted regarding informative YouTube videos about chronic pain syndromes. Hornung et al. investigated videos about low back pain and found the overall quality and reliability unsatisfactory[10]. Similarly, Zhang et al analyzed the videos related to neck pain and indicated low quality and reliability[11]. In contrast, Altun et al. showed that the quality of complex regional pian syndrome videos were partially sufficient[12]. Chaudhry et al. reviewed the videos on cluster headache and reported 52% of the videos were of low quality.

PHN is a disabling chronic neuropathic pain syndrome that is often accompanied by depression, anxiety, and sleep disturbances[13]. For patients suffering from a chronic neuropathic pain syndrome, it is of utmost importance to attain correct and complete information about the course of their disease[14]. As previously offered official health organizations may provide online, easily accessible, educational tools (official YouTube channels etc.) for patients while ensuring a thorough reviewing process[15]. A standardized criteria should also be utilized for medical YouTube videos uploaded by health professionals as the present study established that even PHN videos created by physicians could not exceed moderate quality.

As far as know this is the first analysis to investigate the educational value of YouTube videos related to PHN. Including only English videos, utilizing a scale (DISCERN) created for written material are the main limitations of our study. Furthermore, although we assessed the top results concerning view number and relevance separately, the top list sorted by relevance may change over time due to YouTube algorithm.

5. Conclusions

In conclusion, the educational value of YouTube videos about PHN uploaded by different sources is poor or moderate. Although physician-created videos have higher quality and less bias, health-professionals should warn their patients to be cautious when referring to social media platforms about their disease. Official health organizations should also consider providing easily accessible educational material for patients with PHN

Acknowledgements
None.

Statement of ethics
This is a cross-sectional study that included no human or animal participants, so ethical approval was not required and consent was waived.

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

Funding source
The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions
Concept: RS, ECÖ; Design: RS, ECÖ; Supervision: RS, ECÖ; Data Collection and/ or Processing: RS; Analysis and/ or Interpretation: RS; Literature Search: RS, ECÖ; Writing Manuscript: RS, ECÖ Critical Review: RS, ECÖ

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Evaluation of Factors That Increase the Risk of Hepatotoxicity in Patients Using Palbociclib and Ribociclib

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Abstract

Aim: In patients with hormone receptor-positive and HER2-negative metastatic breast cancer, the use of CDK 4/6 inhibitors in combination with endocrine therapy have become a standard of care.

Methods: This was a retrospective study involved patients over the age of 18 years, who had de novo metastatic or locally breast cancer progressed to the metastatic stage and were treated with ribociclib and/or palbociclib.

Results: The mean age of a total of 73 patients included in the study was 57.0±10.3 years. Thirty-four (46.6%) patients were treated with palbociclib, 35 (47.9%) patients with ribociclib, 4 (5.5%) with palbociclib and ribociclib. Twenty-five (34.2%) of the patients developed any grade of hepatotoxicity, 12 (16.4%) of them was grade 2 hepatotoxicity. Of these patients, 11 (44%) received palbociclib, 13 (52%) received ribociclib, and 1 (4%) received palbociclib and ribociclib. In patients who were treated with palbociclib, 1 (2.9%) developed grade 3 hepatotoxicity and 1 (2.9%) developed grade 4 hepatotoxicity. Of those who received ribociclib, 3 (8.5%) developed grade 3 hepatotoxicity and 2 (5.7%) developed grade 4 hepatotoxicity.

Conclusions: In conclusion, it can be stated that ribociclib is more toxic to the liver than palbociclib, since patients who received ribociclib and developed grade 3-4 hepatotoxicity had no disease that facilitates hepatotoxicity. We believe that more comprehensive studies are needed to determine the factors that facilitate hepatotoxicity such as liver metastasis and to select the drug accordingly will prevent patients from being devoid of this group of drugs and discontinuing their treatment due to toxicity.

Keywords: *Ribociclib, palbociclib, breast cancer, hepatotoxicity*

1. Introduction

Breast cancer is the most common cancer in women[1]. Nearly 75% of patients with breast cancer are hormone receptor-positive and human epidermal growth factor receptor 2 (HER2)-negative[2]. The 5-year survival rate for patients with stage 4 breast cancer is 20%[3]. While these patients are sensitive to endocrine therapies, they show progression after acquiring resistance[4,5]. Cyclin-dependent kinase (CDK) 4/6 inhibitors used with endocrine therapies have been shown to prolong progression-free survival (PFS) and overall survival (OS) in patients with metastatic breast cancer[6-9].

If there is no visceral crisis in patients with hormone receptor-positive and HER2- negative metastatic breast cancer, the use of CDK 4/6 inhibitors in combination with endocrine therapy have become a standard of care[10]. These drugs have brought about their specific side effects along with efficacy. The aim of this study is to evaluate hepatotoxicity with a moderate frequency in patients using palbociclib and ribociclib and factors that increase its risk.

2. Materials and methods

A total of 1152 patients who were admitted to Adana City Training and Research Hospital Medical On- cology Outpatient Clinic with a diagnosis of breast cancer between 01 January 2017 and 01 January 2022 were included in the retrospective analysis. Those with unavailable pathology information were excluded from the study. The treatments of patients with a pathological diagnosis of primary or metastatic breast cancer were evaluated. The study included a total of 73 patients over the age of 18 years who had de novo metastatic or locally advanced disease progressed to the metastatic stage and were treated with ribociclib and/or palbociclib. Informed consent was obtained from all individual participants or relatives

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Received: 11.04.2023, Accepted: 30.05.2023, Available Online Date: 31.08.2023
Cite this article as: Ata S, Araz F, Çil T, et al. Evaluation of Factors That Increase the Risk of Hepatotoxicity in Patients Using Palbociclib and Ribociclib. J Cukurova Anesth Surg. 2023; 6(2): 224-8. doi: 10.36516/jocass.1279677

included in the study. Patient data were analyzed through patient follow-up files and the hospital management system. The reported results of abdominal ultrasound examinations performed in the past 6 months before ribociclib or palbociclib treatment were evaluated. The hepatic steatosis grades of the patients were determined by taking into account the hepatic steatosis grades in abdominal ultrasound reports closest (0-3 months) to the time of drug initiation. Other toxicity grades were determined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

2.1. Statistical analysis

SPSS (Statistical Package for the Social Sciences) version 23.0 software package was used for statistical analysis of the data. Categorical measures were summarized using numbers and percentages, while continuous measures were summarized using the mean and standard deviation (median and minimum-maximum where appropriate). Chi-square and Fisher's exact tests were used to analyze categorical expressions. Shapiro-Wilk test was used to check whether the parameters included in the study follow a normal distribution. When parameters did not follow a normal distribution, Mann-Whitney U test was used for binary variables and Kruskal-Wallis tests were used for more than two groups. The level of statistical significance was set at 0.05 in all tests.

3. Results

The mean age of a total of 73 patients included in the study was 57.0±10.3 years. Of the patients, 68 (93.2%) were female and 5 (6.8%) were male. Thirty-four (46.6%) patients were treated with palbociclib, 35 (47.9%) patients with ribociclib, 4 (5.5%) with palbociclib and ribociclib. In patients who could not continue treatment due to toxicity even though there was no progression after the initiation of treatment, the treatment was switched, provided that consent for off-label use of another CDK inhibitor was obtained within the scope of the rules of the medicines regulatory authority. Therefore, 4 patients used both agents. In the same way, consent for off-label use was obtained for male patients. Of the patients, 22 (30.1%) had liver metastases, while 51 (69.9%) did not. Twenty-five (34.2%) of the patients developed any grade of hepatotoxicity, while 48 (65.8%) did not have any grade of hepatotoxicity. The median time from the end of cytotoxic chemotherapy to the initiation of CDK 4/6 inhibitor was 10 (0-120) months. The demographic characteristics and laboratory data of the patients are illustrated in Tables 1.

The mean age of the patients who developed hepatotoxicity was 56.3±8.3 years. Of these patients, 11 (44%) received palbociclib, 13 (52%) received ribociclib, and 1 (4%) received palbociclib and ribociclib. Out of these patients, 4 of patients using palbociclib; 5 of the patients using ribociclib were using concomitant fulvestrant treatment. Of those who were treated with palbociclib, 1 (2.9%) developed grade 3 hepatotoxicity and 1 (2.9%) developed grade 4 hepatotoxicity. Of those who received ribociclib, 3 (8.5%) developed grade 3 hepatotoxicity and 2 (5.7%) developed grade 4 hepatotoxicity. The demographic characteristics and laboratory data of the patients who developed hepatotoxicity are shown in Tables 2 and 3, respectively.

4. Discussion

In previous studies the 5-year survival rate for patients with metastatic breast cancer is around 20%[3]. While new targeted therapies have been introduced for the treatment of patients with HER2-positive metastatic breast cancer, the search for new treat-

Table 1

Demographic characteristics of patients

		Frequency (n)	Percentage (%)
Sex			
	Female	68	93.2
	Male	5	6,8
Ditribution of treatments			
	Palbociclib	34	46,6
	Palbociclib&Ribociclib	4	5.5
	Ribociclib	35	47.9
Liver metastasis			
	Yes	22	30.1
	No	51	69.9
Hepatosteatosis			
	Grade 1	15	20.5
	Grade 2	12	16,4
	No	46	63.0
HbsAg			
	Negative	70	95.9
	Positive	3	4,1
Anti-Hbs			
	Negative	44	60.3
	Positive	29	39.7
Anti-HCV			
	Negative	71	97.3
	Positive	2	2,7
Anti-Hbc IgG			
	Negative	57	78.1
	Positive	16	21.9
De novo Metastasis			
	Yes	44	60.3
	No	29	39.7
Anthracycline and Taxane Use			
	No	31	42,5
	Yes	42	57.5
Comorbidity*			
	No	37	50.7
	Yes	36	49.3
Additional drug use			
	No	3	4,1
	Yes	70	95.9
Neutropenia in Follow-up			
	Yes	51	69.9
	No	22	30.1
Hepatotoxicity			
	Yes	25	34,2
	No	48	65.8

* Diabetes, hypertension, hyperlipidemia, asthma

Table 2
Laboratory data of patients

	Mean±SD	Median (Min-Max)
Estrogen receptor (%)	85.6±17.2	90 (0-100)
Progesterone receptor (%)	49.8±38.3	60 (0-100)
Ki-67 (%)	20.6±15.7	20 (1-70)
Time from cytotoxic chemotherapy to CDK* 4/6 inhibitor (months)	22,5±30.3	10 (0-120)
Aspartate aminotrasferase (U/L)	324,3±724,9	62 (17-2656)
Alanine aminotransferase (U/L)	190.6±241.9	95 (14-912)
Total bilirubin (mg/dL)	6,55±4,4	5.2 (2,3-12,4)
Direct bilirubin (mg/dL)	3.5±2,37	2,85 (1.1-6,8)

* cyclin-dependent kinase

Table 3
Demographic data of patients with and without hepatotoxicity

		Patients with hepatotoxicity	Patients without hepatotoxicity	p-value
Sex	Male	23 (29.5)	45 (70.5)	0.770
	Female	2 (40)	3 (60)	
Palbosilib/Ribocilib	Palbociclib	11 (32.3)	23 (67.7)	0.845
	Palbociclib&Ribociclib	1 (25)	3 (75)	
	Ribociclib	13 (37.1)	22 (62.9)	
Liver metastasis	Yes	12 (54,5)	10 (45.5)	0.016
	No	13 (25.4)	38 (74,6)	
Hepatosteatosis	Grade 1	6 (40)	9 (60)	0.667
	Grade 2	5 (41.6)	7 (58,4)	
	No	14 (30.4)	32 (69.6)	
HbsAg	Negative	24 (34,2)	46 (65.8)	0.973
	Positive	1 (33,3)	2 (66,7)	
Anti-Hbs	Negative	16 (36.3)	28 (63,7)	0.639
	Positive	9 (31)	20 (69)	
Anti-Hcv	Negative	24 (3,8)	47 (66.2)	0.634
	Positive	1 (50)	1 (50)	
Anti-Hbc IgG	Negative	18 (31.6)	39 (68.4)	0.365
	Positive	7 (43,7)	9 (56.3)	
De novo Metastasis	Yes	14 (31.8)	30 (68.2)	0.590
	No	11 (37.9)	18 (62.1)	
Anthracycline and Taxane Use	No	10 (32.2)	21 (67.8)	0.758
	Yes	15 (35.7)	27 (64,3)	
Chemotherapy in the Meta-static Stage	Yes	17 (47.2)	19 (52.8)	0.021
	No	8 (21.6)	29 (78.4)	
Comorbidity*	No	15 (40.5)	22 (59.5)	0.251
	Yes	10 (27.7)	26 (72.3)	
Additional Drug Use	No	24 (34,2)	46 (65.8)	0.973
	Yes	1 (33,3)	2 (66.7)	
Neutropenia	Yes	19 (37.2)	32 (62.8)	0.410
	No	6 (27.3)	16 (72.7)	

* Diabetes, hypertension, hyperlipidemia, asthma

Table 4
Laboratory data of patients with and without hepatotoxicity

	Patients with hepatotoxicity	Patients without hepatotoxicity	p-value
Estrogen receptor (%)	88.4±20.9 90 (0-100)	83,9±14,7 90 (40-100)	0.336
Progesterone receptor (%)	56.5±35.3 62.5 (0-100)	45.9±39.9 55 (0-100)	0.308
Ki-67 (%)	19.9±10.6 20 (2-40)	20.9±8.0 15 (1-70)	0.823
Time from cytotoxic chemotherapy to CDK* 4/6 inhibitor (months)	11.9±3,1 8 (0-52)	28.2±35.2 11 (0-120)	0.046
Aspartate aminotrasferase (U/L)	327.2±739.7 62 (17-2656)	252±0.0 252 (252-252)	0.921
Alanine aminotransferase (U/L)	182.0±243,1 92.5 (14-912)	397±0.0 397 (397-397)	0.395
Total bilirubin (mg/dl)	6.55±4,4 5.2 (2.3-12.4)	-	NA
Direct bilirubin (mg/dl)	3,5±2.3 2.85 (1.1-6.8)	-	NA

* cyclin-dependent kinase

-ments for hormone receptor-positive and HER2-negative patients continues[11].

Finally, CDK 4/6 inhibitors have been used in combination with hormone therapies in this group of patients, which increased survival rates.

Ribociclib, palbociclib, and abemaciclib are CDK 4/6 inhibitors that are in use at present. With the introduction of these drugs, PFS for metastatic breast cancer patients increased from 6.1 to 24.8 months[12], while OS increased from 15.4 months to 53.7 months[13]. Side effects associated with these drugs vary depending on the

affinity of the drugs to different CDKs. While the most common side effect of ribociclib and palbociclib is neutropenia, diarrhea has been reported as the most common side effect associated with abemaciclib[6,8,9].

The incidence of hepatotoxicity seems to be higher in patients using ribociclib than in patients using the other drugs. These patients should be followed up with ALT and AST values. The median time to severe hepatotoxicity (≥ grade 3) is 85 days, regardless of the endocrine therapy used with ribociclib, and the median time to resolution to ≤ grade 2 is 22 days after the discontinuation of the drug[14]. ALT and AST values rapidly increase to critical levels in patients who are reinitiated on ribociclib[15].

In our study, 32.3% of the patients receiving palbociclib and 37.1% of the patients receiving ribociclib developed hepatotoxicity (p=0.676). While grade 3-4 ALT elevation was observed in 5 (14.2%) patients among those receiving ribociclib, grade 3-4 ALT elevation was observed in 2 (5.8%) patients among those receiving palbociclib (p=0.226). The MONALEESA 2-3-7 studies evaluating the efficacy and side effects of ribociclib showed grade 3-4 ALT elevations in 9.3%, 8.5%, and 5% of patients, respectively, while the PALOMA 3 study evaluating the efficacy and side effects of palbociclib found grade 3-4 ALT elevation in 2% of patients16. In our study, all patients with grade 3-4 ALT elevations had liver metastases. On the other hand, 12 (54.5%) of the patients with liver metastasis developed ALT elevation, while 7 (58.3%) of them developed grade 3-4 ALT elevation. This result shows that liver metastasis can increase hepatotoxicity and that these drugs should be preferred more carefully in the group of patients with liver metastasis. Since the phase studies of CDK 4/6 inhibitors did not indicate whether the patients with hepatotoxicity had liver metastases, we are of the opinion that this should be clarified with a subgroup analysis.

Of the 73 patients included in the study, 46 (63.0%) had an abdominal ultrasound report that met the criteria. Six of the 7 patients who were treated with ribociclib or palbociclib and had grade 3-4 hepatotoxicity had an abdominal ultrasound imaging. While 1 patient who received ribociclib with grade 3 hepatotoxicity had grade 2 hepatic steatosis, the other 5 patients did not have hepatic steatosis. Since there was only one patient with hepatic steatosis, it could not be speculated on whether hepatic steatosis triggered hepatotoxicity.

The evaluation of the comorbid diseases of 7 patients with grade 3-4 hepatotoxicity revealed that 1 patient had diabetes mellitus and 1 patient had hypertension, both of whom were on palbociclib. Five patients who had grade 3-4 ALT elevation and were on ribociclib had no comorbid disease. It can be stated that ribociclib is more toxic to the liver than palbociclib, since patients who received ribociclib and developed grade 3-4 hepatotoxicity had no disease that facilitates hepatotoxicity.The evaluation of the same 7 patients with grade 3-4 hepatotoxicity unveiled that 2 (100%) patients with palbociclib-induced hepatotoxicity had increased total and direct bilirubin values (total bilirubin 11.6-12.4), while 2 (40%) of 5 patients using ribociclib had increased levels of total and direct bilirubin (total bilirubin 5.9-6.4). Although the rate of hepatotoxicity was higher with ribociclib

than with palbociclib, the rate of elevated levels of bilirubin was observed to be higher in the palbociclib group. It has been shown in the literature that hepatotoxicity does not develop with the other drug when switching between CDK 4/6 inhibitors due to hepatotoxicity. This suggests that the hepatotoxicity mechanism of these two drugs may be different[16,17].

With regard to neutropenia side effect, 7 (20.5%) of the patients using palbociclib and 13 (37.1%) of the patients using ribociclib developed grade 3-4 neutropenia. While 2 patients who received palbociclib and developed grade 3-4 hepatotoxicity had grade 3-4 neutropenia (100%), 2 of the 5 patients who received ribociclib and developed grade 3-4 hepatotoxicity had grade 3-4 neutropenia (40%). This suggests that these two toxicities may develop concurrently in patients receiving palbociclib, and when one develops, the patient should be followed up closely for the other toxicity.

Of the 25 patients who developed hepatotoxicity of any grade while using ribociclib or palbociclib, 1 were HBsAg-positive and 8 were antiHBs and antiHBc IgG positive. One of the 5 patients with ribociclib-induced grade 3-4 toxicity and 1 of the 2 patients with palbociclib-induced grade 3-4 toxicity was anti-HBc IgG-positive. All patients who were positive for anti-HBc IgG were initiated on prophylactic treatment for hepatitis.

5. Conclusions

In conclusion, the severity of hepatotoxicity may require discontinuation of treatment in a limited number of patients. It can be stated that ribociclib is more toxic to the liver than palbociclib, since patients who received ribociclib and developed grade 3-4 hepatotoxicity had no disease that facilitates hepatotoxicity. We believe that more comprehensive studies are needed on this issue to determine the factors that facilitate hepatotoxicity such as liver metastasis and to select the drug accordingly will prevent patients from being devoid of this group of drugs and discontinuing their treatment due to toxicity.

Acknowledgements

None.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Adana City Training and Research Hospital Hospital Medical Ethics Committee with the decision no. 1473 dated 01.07.2021.

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Serdar Ata, Filiz Araz, Timuçin Çil and Berna Bozkurt Duman. The first draft of the manuscript was written by Serdar Ata and all authors commented to previous versions of the manuscript. All authors read and approved the final manuscript.

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Efficacy of Enhanced Recovery After Surgery (ERAS) Protocols in Lumbar Microdiscectomy Surgery

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Abstract

Aim: This study aimed to assess the efficacy of enhanced recovery after surgery (ERAS) protocols in lumbar discectomy surgeries.

Methods: Data was obtained from 92 patients who underwent lumbar microdiscectomy surgery at a single institution between January 2021 and January 2023. Then, the patients were divided into two groups: ERAS protocol group (n=60), and conventional surgery group (n=32).

Results: The mean age of the patients was 49.4±14.0 years. Among these, 31 were females, and 61 were males. The demographic, surgical, and outcome parameters of the two groups were compared. There were statistically significant decreases in length of stay and spondylodiscitis rates in the ERAS protocol group. Length of stay was found 25.5±12.5 hours in the ERAS group, and 34.0±20.1 hours in the conventional surgery group (p=0.002). Spondylodiscitis rates were 3.3% and 15.6% in the ERAS and conventional surgery groups, respectively (p=0.034).

Conclusions: This study revealed that ERAS protocol reduces length of stay in hospital, and spondylodiscitis rates in lumbar microdiscectomy surgery. We conclude that ERAS protocols should be encouraged and applied more widely in spine surgeries.

Keywords: *Enhanced recovery after surgery, ERAS, spine, lumbar microdiscectomy, spondylodiscitis*

1. Introduction

ERAS (Enhanced Recovery After Surgery) protocol, which is a multidisciplinary approach consisting of evidence-based practices that are recommended to be applied before, during, and after surgery by many surgical departments, was first introduced by Kehlet et al. in 1997[1-3]. In the last two decades, much more comprehensive studies were carried out with large study groups[1,2,4,5]. ERAS protocols aim to optimize the process from the preoperative hospitalization to the postoperative discharge of a patient who is planned for surgical intervention.

The goals of these protocols are to reduce the metabolic stress in the human body as a result of surgical trauma, to enable patients to return to their daily life activities as soon as possible, and to reduce health expenditures[1,5,6]. This study aimed to assess the results of patients who underwent lumbar discectomy surgery with and without ERAS protocols.

2. Materials and methods

The research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013), and Institutional Review Board approval was obtained. This study included 92 patients who underwent lumbar microdiscectomy surgery at a single institution between January 2021 and January 2023. The patients with recurrent/residual disc herniations, a history of posterior lumbar surgery or in need of posterior instrumentation, and the patients who were suffering from infectious or immunodeficiency diseases at the time of enrollment were excluded from the study. Patient data including age, gender, body mass index, comorbidities, tobacco use, American Society of Anesthesiologist (ASA) classification scores, symptoms, preoperative and postopera-

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Received: 29.05.2023, Accepted: 13.08.2023, Available Online Date: 31.08.2023
Cite this article as: Ilgınel MT, Oktay K, Ilgınel ÖÖ, et al. Efficacy of Enhanced Recovery after Surgery (ERAS) Protocols in Lumbar Microdiscectomy Surgery. J Cukurova Anesth Surg. 2023; 6(2): 229-34.
doi: 10.36516/jocass.1286977

tive visual analog scale (VAS) scores, surgery levels, complications, length of stay (LOS) in hospital, and patients' follow-up examinations were retrospectively gathered. ERAS protocols that are applied in the present study, are mentioned in Table 1.

2.1. Statistical analysis

Statistical Package for the Social Sciences (SPSS) software version 25.0 (IBM Corporation, Armonk, New York, United States) was used to analyze the variables. The Kolmogorov–Smirnov test was used to determine whether the parameters in the study showed normal distribution. Independent student t-test was used for parameters showing normal distribution, and Mann- Whitney U test was used for parameters not showing normal distribution. The quantitative variables were presented as mean ± SD (standard deviation) and the range (maximum-minimum) and categorical variables as n (%). The Pearson chi-square and Fisher's exact tests were used to compare the treatment and control groups in terms of the categorical variables. Spearman correlation analysis was used to identify risk factors for prolonged LOS. The variables were examined at 95% confidence level, and $p<0.05$ was considered significant.

3. Results

In the present study, 92 patients were enrolled with 60 (65.2%) patients classified into the surgery with ERAS protocol group, and 32 (34.8%) patients classified into the conventional surgery group. The mean age of the patients was 49.4±14 years (20-86 years). Among the 92 patients, 31 (33.7%) were females, and 61 (66.3%) were males. Patients' demographic data; including age, gender, body mass index, comorbidities, ASA scores, tobacco usage, and surgery levels, were compared between two groups and shown in Table 2. There were no statistically significant demographic differences between ERAS and conventional surgery groups (Table 2).

The surgical and outcome parameters of the two groups were compared (Table 3). There were statistically significant decreases in LOS (p=0.002) and spondylodiscitis rates (p=0.034) in the ERAS protocol group. LOS was found 25.5±12.5 hours in the ERAS group, and 34.0±20.1 hours in the conventional surgery group. There was not any statistically significant difference in the other parameters between two groups (Table 3). Prolonged surgical time (p=0.043) and diabetes mellitus presence (p=0.014) were identified to be the main risk factors for prolonged LOS.

The mean follow-up period of the patients was 14.7±7.2 months (3-27 months). Preoperative and postoperative VAS scores were compared between two groups and no statistically significant difference was found (Table 4). Among complications developed; there were 2 spondylodiscitis, 2 durotomy, and 1 reoperation in the ERAS group, and 5 spondylodiscitis, 2 durotomy, and 2 reoperation in the conventional surgery group. Spondylodiscitis rates were 3.3% and 15.6% in the ERAS and conventional surgery groups, respectively (p=0.034).

4. Discussion

ERAS pathways combine optimized clinical procedures with improved logistics and should cover preoperative and postoperative phases. It is very important to provide information about the disease, the complications of the operation, and the postoperative recovery process after a patient is diagnosed and decided to undergo surgery. There are studies in which there is strong evidence that knowing the current condition and postoperative events reduces the patient's anxiety[7-9]. In addition, it was observed that preliminary information significantly increased compliance with the preoperative and postoperative treatment process and decreased the need for perioperative narcotic and non-steroidal anti-inflammatory analgesics[8-11].

Comorbidities and smoking-alcohol usage should be carefully questioned before surgery. In the literature, there are studies with a high level of evidence, that quitting smoking and alcohol 4-8 weeks before the operation reduces the complications of the surgery.[10,12] The presence of preoperative malnutrition increases the risk of postoperative morbidity and mortality. In studies evaluating patients with serum-albumin levels below 3 g/dl, a significant relationship was found between postoperative infection and malnutrition.[13] It is recommended to evaluate the preoperative nutritional status and to start nutritional support 7-10 days before the operation[1].

Table 1

ERAS protocols that are applied in the present study

ERAS Protocol		
Preoperative	**Perioperative**	**Postoperative**
Preliminary information	Standard anesthesia protocol	Early mobilization
Preoperative nutritional evaluation and supplementation	Antimicrobial prophylaxis	Prompt nutrition
Prehabilitation	Optimal fluid management	Avoidance of nausea and vomiting
Tobacco and alcohol quitting	Opioid free analgesia	Opioid free analgesia
Anemia assessment	Small skin incision	
Carbonhydrate loading	Avoidance of surgical drain and Foley catheter	
Shortened fasting	Avoidance of hypothermia	
Optimal analgesia		

ERAS: Enhanced recovery after surgery

Table 2
Demographic data and patient characteristics

		ERAS (+) n=60 (%)	ERAS (-) n=32 (%)	Total n=92 (%)	p
Age (years)	Mean±SD	48.9±13.7	50.2±14.7	49.4±14	0.663
	Median (min-max)	50.5 (20-81)	47.5 (30-86)	49.5 (20-86)	
Gender (%)	Female	22 (36.7)	9 (28.1)	31 (33.7)	0.409
	Male	38 (63.3)	23 (71.9)	61 (66.3)	
Body mass index (kg/m2)	Mean±SD	27±4.5	27.4±4.5	27.1±4.5	0.699
	Median (min-max)	26.6 (18.7-37.9)	28.2 (18-34.8)	27.5 (18-37.9)	
ASA (%)	1	19 (31.7)	11 (34.4)	30 (32.6)	0.570
	2	37 (61.7)	17 (53.1)	54 (58.7)	
	3	4 (6.6)	4 (12.5)	8 (8.7)	
DM (%)	yes	51 (85)	26 (81.3)	77 (83.7)	0.643
	no	9 (15)	6 (18.7)	15 (16.3)	
Smoking (%)	yes	51 (85)	24 (75)	75 (81.5)	0.239
	no	9 (15)	8 (25)	17 (18.5)	
Spine level (%)	L5-S1	22 (36.7)	8 (25)	30 (32.6)	0.444
	L4-5	31 (51.7)	20 (62.5)	51 (55.4)	
	L3-4	4 (6.6)	4 (12.5)	8 (8.7)	
	L2-3	2 (3.3)	-	2 (2.2)	
	L1-2	1 (1.7)	-	1 (1.1)	

ERAS: Enhanced recovery after surgery, ASA: American Society of Anesthesiologist, DM: Diabetes mellitus, SD: Standart deviation

Table 3
Surgical and outcome parameters

		ERAS (+) n=60 (%)	ERAS (-) n=32 (%)	Total n=92 (%)	p
Surgical time (minutes)	Mean±SD	61.5±28.9	68.3±28.5	63.0±28.8	0.182
	Median (min-max)	50 (25-150)	59 (35-135)	53.50 (25-150)	
Blood transfusion (%)	yes	59 (98.3)	30 (93.8)	89.0 (96.7)	0.276
	no	1 (1.7)	2 (6.2)	3 (3.3)	
LOS (hours)	Mean±SD	25.5±12.5	34±20.1	28.5±15.9	0.002
	Median (min-max)	23 (14-96)	26 (16-98)	24 (14-98)	
Spondylodiscitis (%)	yes	58 (96.7)	27 (84.4)	85 (92.4)	0.034
	no	2 (3.3)	5 (15.6)	7 (7.6)	
Reoperation (%)	yes	59 (98.3)	30 (93.8)	89.0 (96.7)	0.276
	no	1 (1.7)	2 (6.2)	3.0 (3.3)	
Follow-up (months)	Mean±SD	14.1±7.8	15.9±5.7	14.7±7.2	0.323
	Median (min-max)	14.5 (3-27)	17 (4-24)	16 (3-27)	

ERAS: Enhanced recovery after surgery, LOS: Length of stay, SD: Standart deviation

Table 4
Preoperative and postoperative VAS scores

		ERAS (+) n=60	ERAS (-) n=32	Total n=92	p
Preop VAS (Lumbar)	Mean±SD	7.5±1.1	7.9±0.9	7.6±1.1	0.540
	Median (min-max)	8 (6-10)	8 (6-10)	8 (6-10)	
POD 1 VAS (Lumbar)	Mean±SD	3.6±1.2	3.2±0.9	3.4±1.1	0.101
	Median (min-max)	3 (2-7)	3 (2-6)	3 (2-7)	
POD 10 VAS (Lumbar)	Mean±SD	2.6±1.1	2.6±0.9	2.6±1.1	0.763
	Median (min-max)	2 (1-5)	3 (1-5)	2 (1-5)	
POD 45 VAS (Lumbar)	Mean±SD	2.0±0.9	2.4±1.5	2.1±1.1	0.173
	Median (min-max)	2 (1-5)	2 (1-6)	2 (1-6)	
Preop VAS (Radiculopathy)	Mean±SD	9.2±0.90	9.1±0.8	9.1±0.9	0.778
	Median (min-max)	9 (7-10)	9 (7-10)	9 (7-10)	
POD 1 VAS (Radiculopathy)	Mean±SD	2.7±0.8	2.4±0.8	2.6±0.8	0.091
	Median (min-max)	3 (1-5)	2 (1-5)	3 (1-5)	
POD 10 VAS (Radiculopathy)	Mean±SD	1.9±0.9	1.8±0.8	1.9±0.9	0.653
	Median (min-max)	2 (1-5)	2 (1-4)	2 (1-5)	
POD 45 VAS (Radiculopathy)	Mean±SD	1.5±0.7	1.6±0.8	1.5±0.7	0.592
	Median (min-max)	1 (1-4)	1 (1-4)	1 (1-4)	

ERAS: Enhanced recovery after surgery, VAS: Visual analog scale, POD: Postoperative day, SD: Standart deviation

It has been reported that patients with hemoglobin levels below 13 mg/dl are risky in the perioperative and postoperative periods. Anemia is a high-risk factor for postoperative complications and mortality[14,15]. ASA reported that hemoglobin levels above 8 mg/dl reduce the risk of perioperative complications in surgical patients with cardiac, renal, or pulmonary comorbidities[1,16]. In patients with preoperative electrolyte disorders, the preoperative fluid balance may not be achieved, and adverse events such as diabetes insipidus and inappropriate antidiuretic hormone secretion may develop during and after the operation, leading to serious morbidity or mortality. Preoperative patients should not remain dehydrated in terms of both preserving kidney functions and maintaining electrolyte balance[12]. Therefore, preoperative normovolaemia should be ensured and any fluid-electrolyte imbalance should be treated[17].

It is recommended to avoid long-term fasting before the operation, to consume light solid food up to 6 hours before the operation, or to provide oral carbohydrate support before the operation[1,16]. It has been reported that consumption of 400 ml oral carbohydrate-rich drink (400 ml water, 50 g glucose) 2-3 hours before anesthesia, and 800 ml carbohydrate-rich drink at night before the surgery provides decreased postoperative insulin resistance, muscle strength, and body weight protection, increased cardiac activity, and decreased myocardial damage.[18] It has been observed that the administration of prophylactic intravenous antibiotics approximately 30 minutes before the incision reduces the surgical site infection rates[16].

It is aimed to prefer short-acting general anesthetic agents such as propofol so that the patients wake up quickly with minimal residual effect. Sevoflurane or desflurane, which is short-acting inhalation anesthetic agents, are preferred for maintaining anesthesia. The use of nitrous oxide is not recommended because of the delayed residual effect and the high probability of postoperative nausea and vomiting[19,20]. Intraoperative fluid therapy aims to provide intravascular volume, cardiac output, and tissue perfusion while preventing sodium and fluid overload. Crystalloid and colloid-derived fluids may be preferred according to the cardiac capacity and bleeding volume of the patients. Inotropic agents such as Dopamine, can be used in case of excess fluid imbalance to increase intravenous volume[16].

The decrease in room temperature, blood loss, the effect of the anesthetic agents on the thermoregulation center, and the direct or vascular involvement of the hypothalamus in the intracranial tumor, arteriovenous malformation, and aneurysm surgeries increase the possibility of hypothermia in patients[16]. It is recommended to heat anesthetic gases and intravenous fluids and to use heater blankets to maintain body temperature. Studies have shown that the use of surgical drains is not associated with reoperation or mortality rates. However, routine use of drains is not recommended because of increased infection rates[16].

The persistence of postoperative nausea and vomiting may cause many problems. Dehydration of patients due to excessive fluid loss and restriction in water intake, and delayed feeding cause a lack of nutritional support and lengthen patients' discharge time. Prevention of nausea and vomiting begins in the preoperative period. Avoiding the use of nitrous oxide and opioid analgesics reduces the risk of nausea and vomiting[21-23]. Some studies have shown that preoperative oral carbohydrate support can reduce the rate of postoperative nausea and vomiting[16]. It is recommended to start oral intake 4 hours after the operation[16,24,25]. It has been stated that oral fluid intake should be started 4 hours after surgery, and soft solid foods or nutritional support fluids can be given after an average of 8 hours[23].

Accurate analgesic treatment is important for postoperative bowel

function recovery, early mobilization, decreased complication rates, and shorter hospital stay. It is aimed to reduce the side effects of each drug by using various pain mechanisms with multimodal analgesia[26]. Urinary catheterization is directly related to infection and delayed postoperative mobilization. Early removal of the urinary catheter can significantly reduce the risk of urinary infection and it is recommended to remove the urinary catheter within 1 to 3 days after the surgery[16,21-23].

Patients with high-risk factors such as iatrogenic neurodeficits, obesity, steroid use, advanced malignancy, cardiac arrhythmias, and genetic diseases affecting the coagulation cascade should be followed carefully for possible thromboembolism in the postoperative period[16]. There are medical and mechanical treatment options for postoperative thromboembolism prophylaxis. Anti-embolism stockings and intermittent pneumatic compression devices are recommended for mechanical prophylaxis. Pharmacological thromboprophylaxis with low molecular weight heparin has been shown to reduce the incidence of symptomatic venous thromboembolism and also overall mortality with a very low risk of bleeding complications[16,27]. Early mobilization is an important predictor for the rapid recovery of patients after surgery. Prolonged bed rest has disadvantages including decreased muscle strength, insulin resistance, and increased thromboembolic and pulmonary complications[27].

The retrospective nature of the study and the relatively small sample size are the main limitations of the present study. The lack of 5-year follow-up of all patients is also another limitation. Nonetheless, this study also has several strengths. Demographic data of the patient groups are similar, there is no statistically significant difference between the patient groups, and all surgeries were performed by the same surgeon group in the same period.

5. Conclusions

ERAS protocols are designed to reduce the complication rates of surgical interventions and health expenditures. The present study also demonstrates that ERAS protocol reduces LOS in hospitals, and spondylodiscitis rates in lumbar microdiscectomy surgery. Reduction in these parameters may decrease health expenditures in accordance with the literature. We conclude that ERAS protocols should be encouraged and applied more widely in spine surgeries.

Acknowledgements

None.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Cukurova University Hospital Medical Ethics Committee with the decision no. 133 dated 2023.

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

All authors contributed to the study conception and design. All authors read and approved the final manuscript.

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The Effectiveness of Radiological Methods in Predicting Pathological Complete Response After Neoadjuvant Therapy in Locally Advanced Breast Cancer Patients

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Abstract

Aim: The current innovations in breast cancer treatment have led to an increased utilization of neoadjuvant therapy. Pathological complete response (PCR) following neoadjuvant therapy is a crucial prognostic factor for predicting survival. The objective of this study is to demonstrate the efficacy of radiological methods in predicting PCR in our patients with locally advanced breast cancer.

Methods: The medical records of patients who received treatment for breast cancer at our hospital between January 2017 and January 2022 were retrospectively reviewed. The study included female patients over the age of 18 with locally advanced unifocal breast cancer who underwent neoadjuvant chemotherapy. Demographic information, menopausal status, molecular subtypes, radiological results, disease stage, treatment and surgical methods, and pathology results were recorded.

Results: A total of 4474 patients were treated for breast cancer out of which 94 patients met the criteria for this study. The mean age of the patients was 49.9 ± 11.1 years. Ultrasonography was performed on all patients, while FDG-PetCT was performed on 47 (50%) patients and magnetic resonance imaging (MRI) was performed on 31 (33%) patients for radiological response evaluation. The radiological complete response was highest in the FDG-petCT group (39.4%). The rate of pathological complete response was 35.1%.

Conclusion: Although FDG-PETCT has high sensitivity in predicting pathological complete response after neoadjuvant chemotherapy in locally advanced breast cancers, the common use of ultrasonography, FDG-PETCT, and magnetic resonance imaging is more advantageous due to their different benefits.

Keywords: *Breast; breast cancer; neoadjuvant therapy*

1. Introduction

Breast cancer is the most common malignancy among females and is the second most common cancer after lung cancer. With recent advancements, radical surgeries for the treatment of breast cancer have decreased and the use of minimally invasive surgeries has increased[1]. Locally advanced breast cancers are classified as Stage 2b and Stage 3 tumors according to the TNM 2003 classification[2]. Locally advanced breast cancer is a heterogeneous group of diseases that includes both aggressive and slow-progressing tumors. In developed countries, 5-25% of all breast cancers are classified as locally advanced, while in developing countries, this rate can be as high as 73%. The reason for this difference is thought to be due to differences in educational levels and lack of screening programs[3,4].

Although adjuvant chemotherapy (CT) and radiotherapy (RT) can be administered after surgery in operable locally advanced breast cancer patients, neoadjuvant chemotherapy (NACT) has become the standard treatment. This treatment offers advantages such as reducing the stage of the disease, rendering inoperable tumors operable, destroying micrometastases, and evaluating chemo-resistance.

Thanks to this treatment, patients who were candidates for mastectomy can undergo breast-conserving surgery[5]. In addition to the advantages of neoadjuvant therapy, there are also disadvantages such as changes in the biological characteristics of the primary tumor, overtreatment, increased risk of local recurrence, and disease progression during preoperative treatment. Furthermore, studies

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Received: 09.05.2023, Accepted: 01.06.2023, Available Online Date: 31.08.2023
Cite this article as: Erkan S, Yabanoğlu H, Gündoğdu R, et al. The Effectiveness of Radiological Methods in Predicting Pathological Complete Response After Neoadjuvant Therapy in Locally Advanced Breast Cancer Patients. J Cukurova Anesth Surg. 2023; 6(2): 235-40. doi: 10.36516/jocass.1294672

have shown that neoadjuvant therapy does not confer a survival advantage[6]. Many treatment guidelines recommend anthracycline-containing chemotherapy regimens as an initial treatment[7].

The evaluation of response to treatment is based on anatomical changes observed through imaging methods. The "Response Evaluation Criteria in Solid Tumors (RECIST)" were updated by the World Health Organization in 2009[8]. Functional assessments of metabolic activity can be performed by positron emission tomography (PET). Positron Emission Tomography Response Criteria (PERCIST) for solid tumors were developed in 2009 in order to standardize this evaluation[9]. Positron emission tomography (PET) can be utilized for the functional assessment of metabolic activity. In 2009, Positron Emission Tomography Response Criteria (PERCIST) were developed to standardize the evaluation of solid tumors. The pathological response that occurs after neoadjuvant chemotherapy in patients with locally advanced breast cancer is the most significant prognostic factor for evaluating survival rates[10]. Several quantitative and categorical methods, such as the Chevalier Scoring System, have been developed to characterize the pathological response to neoadjuvant chemotherapy. In our study, we aimed to present the effectiveness of radiological methods in predicting pathological complete response (PCR) in patients with locally advanced breast cancer who were treated at our clinic, in the literature.

2. Materials and methods

2.1. Sample

For this study, the Baskent University Medical and Research Council's 22.03.2023 history and KA22/457 the protocol approval has been obtained and the study has been designed in accordance with the Helsinki Declaration. The medical records of patients who underwent treatment for breast cancer at our hospital from January 2017 to January 2022 were retrospectively reviewed. Female patients over 18 years old, diagnosed with locally advanced unifocal breast cancer, and who received neoadjuvant chemotherapy were included in the study. Breast cancer cases with multiple data deficiencies, except for multisentric and locally advanced breast cancer, were excluded from the study. After pretreatment imaging of the patients, all of them received anthracycline and taxane-based neoadjuvant chemotherapy (NACT), and surgery was performed after radiological response evaluation. Following surgery, 50 Gy radiation therapy was administered to the breast/chest wall and axilla. Radiological complete response was defined as the absence of significant mass in the breast and the disappearance of abnormal features in the armpit lymph nodes. Pathological complete response was defined as the absence of residual invasive tumors in the breast or armpit nodes. Clinicopathological characteristics were documented for each patient, including demographic data, menopause status (the age range of 45 to 55 is considered as perimenopause), molecular subtypes, radiological results, disease stage, treatment and surgery methods, and pathology results.

2.2. Statistical analysis

The statistical analysis of the data was conducted using the Statistical Package for the Social Sciences (SPSS) version 25.0. The performance measures of radiological and pathological tests were evaluated through Receiver Operating Characteristic (ROC) analysis, and the statistical analyses were tested at a significance level of $p < 0.05$.

3. Results

A total of 94 female patients were included in the study, with a mean age of 49.9±11.06 years. Most patients were in the premenopausal group of the patients (48.9%). Regarding their molecular subtyping, luminal b patients were the most common subgroups (51.1%). Stage 2B disease was 95.7% frequency (Stage2B/-Stage3:90/4). The least types of surgeries performed were modified radical mastectomy + axillary lymph node dissection(6.4%). (Table 1).

Table 1

Demographic and clinical characteristics of the patients

Patient Characteristics		n (%)
The average age	49,96±11.06 year	
Menapouse	Menapausal	27 (%28.7)
	Premenopausal	46 (%48.9)
	Postmenopausal	21 (%22.3)
Reseptor	Luminal A	15 (%16)
	Luminal B	48 (%51.1)
	Triple -	16 (%17)
	HER +	15 (%16)
Stage	Stage2B	90 (%95.7)
	Stage3	4 (%4.3)
Surgery	SM+SLN	43 (%45.7)
	BM+SLN	34 (%36.2)
	SSM+SLN	11 (%11.7)
	MRM+AD	6 (%6.4)

SM:Segmental Mastectomy SLN:Sentinel Lenf Node Bıopsy BM:Basic Mastectomy SSM:Skin Sparing Mastectomy MRM:Modifiye Radical Mastectomy AD:Aksiller Dissection

Table 2

Statistical evaluation of pathological and radiological complete response

Chevalier	USG	MRI	Fdg-PET
AUC	0.61	0.66	0.61
%95 confidence range	0.51 – 0.71	0.45 – 0.87	0.51 – 0.72
p	0.033	0.163	0.028
Sensitivity	0.46	0.60	0.94
Spesifity	0.77	0.71	0.29
PPV	0.52	0.50	0.41
NPV	0.72	0.79	0.90

AUC: Area under the curve, PPV:Positive predictive value, NPV:Negative predictive value

Ultrasonography (USG) was performed on all patients, FDG-PetCT was performed in 47 (50%) patients and magnetic resonance imaging (MRI) was performed in 31 (32.9%) patients for radiological response evaluation. In terms of radiological complete response evaluation, FDG-petCT showed the most complete response (39.3%). In terms of pathological complete response evaluation, 34 (36.1%) patients achieved PCR. The performance of complete response for pathological and radiological tests was evaluated using ROC analysis (Table 2). The AUC value for ultrasonographic radiological response evaluation was 0.61 (p=0.033) (Figure 1), and the success rate of determining complete response for the test was 46%, with a success rate of determining no response of 77%.

Those who had a complete response in radiology actually had a 52% probability of having a pathological complete response (positive predictive value=PPV), while those who did not have a complete response with USG actually had a 72% probability of not having a complete response in pathology (negative predictive value=NPV). The AUC value of magnetic resonance imaging was 0.66 (p=0.163) (Figure 2), the success of the test in determining the complete response was 60%, the success in determining no response was 71%. Those with a complete radiological response had a 50% probability of actually having a pathological complete response (PCR), while those without a response had a 79% probability of actually not having a response in pathology (NPV). The AUC value of FDG-PetCT was 0.61 (p=0.028) (Figure 3), the success rate of determining the complete response of the test was 94%, and the success rate of determining no response was 29%.

Table 3

Prediction of pathological response by USG

Chevalier-Usgp	Luminal B	Triple -	Her +
AUC	0.56	0.67	0.75
%95 Confidence range	0.41 – 0.72	0.42 – 0.92	0.57 – 0.94
p	0.423	0.17	0.008
Sensitivity	0.39	0.55	0.51
Spesifity	0.74	0.80	0.98

AUC: Area under the curve

The probability of pathological complete response for those with radiological complete response was 41% (PKD), and the probability of non-response not being a response in pathology was 90% (NKD) (Figure 1). When the evaluation was made according to the receptor status, it was possible to make an evaluation only in the USG group due to the number of samples. While there was no PTY in the Luminal A group, the results were statistically meaningless in the Luminal B group and the Triple group. In each 2+ group, the AUC value was 0.75 (p=0.008), the success of determining the complete response of the test was 51%, and the success of determining no response was 98% (Table 3).

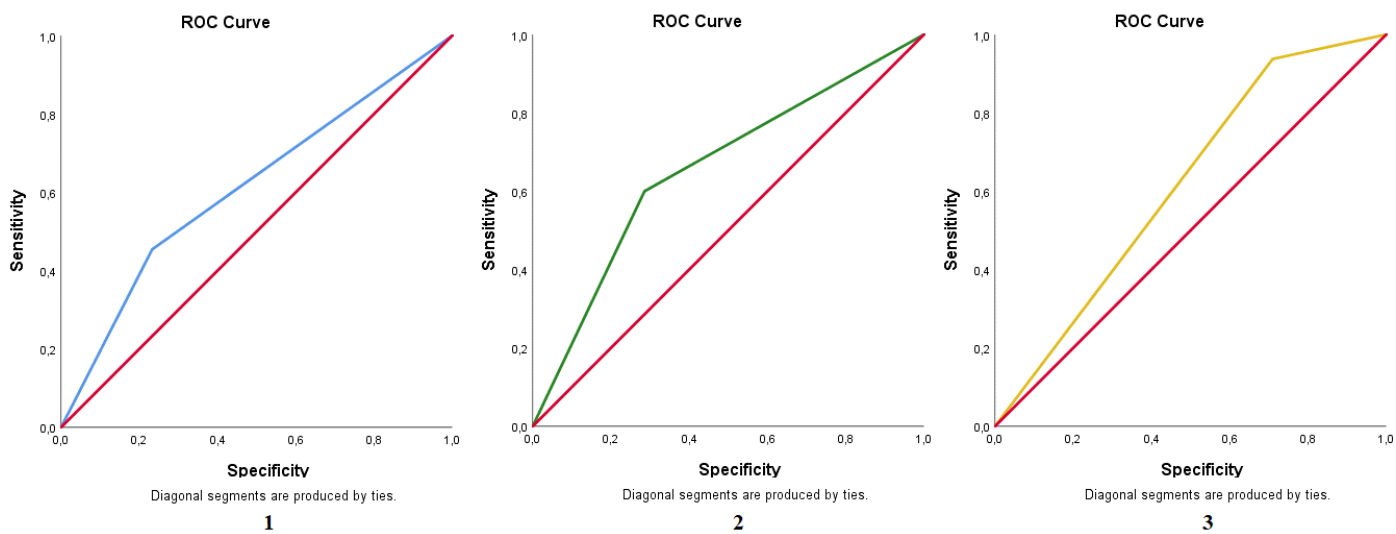

Figure 1-2-3

1. Evaluation of radiological response with USG and ROC analysis of the relationship between pathological response (AUC:0.61)
2. Evaluation of radiological response with MRI and ROC analysis of the relationship between pathological response (AUC:0.66)
3. Evaluation of radiological response with FDG-petCT and ROC analysis of the relationship between pathological response (AUC:0.61)

Table 4
Pathological complete response rates

Author	Year	Patients number	PCR(%)	Worst response	Best response
Houssami N et al (17)	2012	11695	31.1	Luminal A	Her2+
Boughey JC et al (18)	2014	694	28	Luminal	Her2+
Haque W et al (16)	2018	13939	19	Luminal A	Her2+
Agrawal R et al (19)	2020	224	46	Luminal	Triple -
Müller C et al (20)	2021	205	47	Luminal A	Her2+

Table 5
Radiological complete response comparison

Author	Year	Patients number	Comparison	Result
Tateishi U et al (24)	2012	142	MRG/FDG-pet	FDG-pet sensitive ve spesific
S You et al (28)	2015	139	USG/MRG/FDG-pet	All sensitive /FDG-pet specific
Ann YY et al (25)	2015	20	MRI/FDG-PET	MRI sensitive ve spesific
Chen L et al (29)	2017	527	MRI/FDG-pet	FDG-pet sensitive/MRI spesific
Evans A et al (26)	2018	80	USG/MRI	MRI sensitive ve spesific
Huimin Lİ et al (30)	2018	575	MRI/FDG-pet	MRI sensitive/FDG-pet spesific
Sanei Sistai S et al (27)	2020	3248	USG/MRI	USG=MRI

USG:Ultrasonography MRI:Mangetic Resonanse Imaging

4. Discussion

Increasing preventive medicine activities in recent years have led to the detection of many malignancies at an early stage and increased survival rates. Due to this, although the rates of locally advanced breast cancer have decreased, the rates are still high in communities of people with low economic and sociocultural levels. Many studies have been conducted related to the treatment systematics of locally advanced breast cancer. As a result of these studies, it has been proven that neoadjuvant therapy has a positive effect on the results in appropriate patient groups. The compatibility of radiological response and pathological response is very valuable in the evaluation of response to treatment. In our study, we evaluated the follow-up and treatment results of locally advanced breast cancer patients treated in our clinic. Our correlation rates between the results were similar to those reported in the literature.

While the incidence of premenopausal breast cancer has risen in recent years, breast cancer is still more common in patients aged 50 and older. In our study, the median age of patients was 49.9±11.06, which is consistent with the literature. Early detection rates of breast cancer have increased in recent years due to improved screening methods. The number of premenopausal (38.2%) and perimenopausal (29.7%) patients was higher than that of postmenopausal patients. We believe that the increase in breast cancer frequency and improved early screening methods are contributing factors to this trend.

The response to neoadjuvant chemotherapy in terms of pathological complete response rate is influenced by various factors, such as age, tumor size, nodal status, and receptor status[11]. According to a meta-analysis conducted by Von Waldenfels G. and colleagues in 2018, among 8,949 patients, the lowest pathological complete response rate was observed in patients over the age of 65 (11.7%), while the highest response rate was observed in patients under the age of 40 (20.9%)[12]. In our study, we found that the pathological complete response rate was 18% in premenopausal patients, 9.5% in perimenopausal patients, and 8.5% in postmenopausal patients. These findings are consistent with the literature, indicating a decrease in response rate with increasing age. The results of the study were consistent with the literature, with the worst outcomes observed in the postmenopausal group.

Tumor receptor status is an important indicator of the biological function of the tumor, and different frequency rates have been reported in breast cancer patients based on receptor status in various studies in the literature. For instance, Caiyun et al. reported that patients with Luminal B tumors comprised 50% of all patients in their study with 220 patients in 2018, followed by Luminal A and other types[12]. Akoz et al. found Luminal B (32.3%), Luminal A (24.5%), Triple-negative (14.1%), and HER2-positive (29%) in a different study conducted in 2018[14]. In a review study conducted in 2001, Chu and colleagues also found the ER+/PR+ patient group to be the most common molecular type, accounting for 63.9%[15]. In our study, we observed a similar distribution, with 15.9% of patients having Luminal A, 51% having Luminal B, 17% having Triple-negative, and 15.9% having HER2-positive breast cancer.

In a study conducted by W. Haque et al. on 14,000 patients, the overall PCR rate was 19%, with the lowest rate found in the Luminal A group (0.3%) and the highest rate in the Her2+ group (38.7%)[16]. A meta-analysis by Houssami et al. on 11,695 patients reported PCR rates of 8.3% for Luminal A, 18.7% for Luminal B, 38.9% for Her2+,

and 31.1% for Triple-negative breast cancer[17]. In our study, of the 34 patients who achieved PCR, 1 (7.6%) had Luminal A, 13 (26%) had Luminal B, 11 (68.7%) had Triple-negative breast cancer, and 9 (60%) had the Her2 molecular subtype, consistent with the literature (see Table 4).

In a study by Gajdos C et al. on 144 patients, it was shown that smaller tumors were more likely to respond to chemotherapy than larger tumors[21]. In another study involving 165 patients, Bonadonna and colleagues found an inverse relationship between the degree of response and tumor size for tumors larger than 3 cm.

A study by Smith et al.[22] found that as tumor size increased, the response to treatment decreased. Among patients who received transplantation, pathological complete response was observed in 3 of the 6 patients with tumors larger than 5 cm, 34 of the 76 patients with tumors 2-5 cm, and 3 of the 12 patients with tumors 0-2 cm. When accounting for the excess number of Her2+ and Triple-negative breast cancer patients with treatment response, we believe that factors other than size may have contributed to these results.

Various imaging methods can be used to assess radiological complete response. Ultrasound (USG), computed tomography (CT), and magnetic resonance imaging (MRI) provide anatomical response evaluation, while FDG-PETCT is used to evaluate metabolic complete response[23]. In a study by Tateishi et al., contrast-enhanced MRI and FDG-PETCT were compared, and the sensitivity and specificity values were found to be 45.5% and 85.5% for MRI, and 70.4% and 95.7% for PETCT, respectively[24]. In another study by Yeng Yi Ann et al., the response to neoadjuvant chemotherapy was evaluated with MRI and FDG-PETCT. They found that contrast-enhanced MRI, diffusion-weighted MRI, and FDG-PETCT had the highest diagnostic performance, with contrast-enhanced MRI showing the best results. Although there was no statistically significant difference between FDG-PETCT and diffusion-weighted MRI, their combined use improved specificity[25]. In their study of 80 patients, Evans et al. compared ultrasonography and MRI and found the sensitivity and specificity values to be 78%-81% and 91%-95%, respectively. The ROC analysis revealed AUC values of 0.91 for USG and 0.96 for MRI[26]. Sheikhbahaei et al. analyzed 10 different studies and showed that MRI has higher sensitivity (88% vs. 71%) than petCT imaging alone, but lower specificity (55% vs. 77%), with AUC values also found to be higher on MRI[27]. In our study, PETCT (94%) was the evaluation method with the lowest specificity, although it had the highest sensitivity, making it the best test for detecting those with the disease. The best test for specificity was ultrasonography, which distinguished those who did not have the disease the best. Although MRI appeared to have the best value in test distinctiveness, this was not statistically significant.

In the evaluation of pathological complete response in receptor groups, PCR is higher in Triple-positive and Her2-positive tumors, while it is lower in luminal group tumors[31,32]. Due to insufficient sample size and lack of data, statistical evaluation could not be performed according to receptor status in patients who underwent FDG-PET/CT and MRI. In the ultrasound group, there was no pathological complete response in the Luminal A group, and the results were statistically insignificant in the Luminal B and Triple-positive groups. The sensitivity was 51% and the specificity was 98% in the Her2-positive group.

Our study had limitations, such as a small sample size due to being a single-center retrospective study and the lack of standardization in radiological follow-up methods after treatment, resulting in insufficient data.

5. Conclusions

In conclusıon a significant survival advantage has been achieved with the introduction of a multidisciplinary approach and chemoradiotherapy in the treatment of locally advanced breast cancer. Radiological evaluation performed after neoadjuvant therapy is of great importance in surgical planning. As a result of our study, although the MRI test seemed to be superior to the others in terms of its performance among the radiological evaluations after treatment, the results were not statistically significant. Although the sensitivity and specificity values of all three tests are not at the desired level, we believe that their combined use can improve the specificity of predicting pathological response.

Acknowledgements

None.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by for this study, the Baskent University Medical and Research Council's 22.03.2023 history and KA22/457.

Conflict of interest statement

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

Funding source

Baskent University project number KA22-457

Author contributions

All authors contributed to the study conception and design. All authors read and approved the final manuscript.

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Experiences in Endoscopic Ultrasonography at a Tertiary Center General Surgery Endoscopy Unit

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Abstract

Aim: Endoscopic ultrasonography (EUS) is used for diagnosing pathologies in the gastrointestinal system and surrounding organs. This study aims to share the experiences and results of EUS and biopsy at a tertiary center general surgery endoscopy unit, in the context of the literature.

Methods: Patients who underwent EUS imaging at the general surgery endoscopy unit between January 2021 and January 2022 were retrospectively reviewed. Demographic characteristics, EUS biopsy indications, clinical pre-diagnoses, preoperative imaging methods, biopsy counts, and results, as well as complications, were analyzed.

Results: The mean age of the 292 patients was 56.5±15.5 years, with 157 (53.8%) being male. The most common EUS indication was a mass in the pancreas, accounting for 181 (62%). Endoscopic fine-needle aspiration biopsy was performed on 127 (43.4%) patients, and the mean diameter of biopsied masses was 35.1±27.7 mm. Malignancy was detected in 74 (58.2%) of the biopsied patients. Based on biopsy and lesion characteristics, 49.3% of patients were followed up, 80 (27.4%) underwent surgery, 45 (15.4%) received oncological treatment, and 23 (7.9%) were given endoscopic retrograde cholangiopancreatography.

Conclusion: The role of EUS in the diagnosis and treatment of gastrointestinal malignancies, pancreatic diseases, and biliary diseases continues to evolve. We believe that EUS plays a key role in the multidisciplinary management of complex surgical and oncology patients and those with pancreatobiliary disorders.

Keywords: *Endoscopic ultrasonography, fine needle aspiration biopsy, pancreatic tumor, gastrointestinal mass, biliary obstruction*

1. Introduction

Endoscopic ultrasonography (EUS) provides high-resolution, simultaneous imaging of the gastrointestinal system and surrounding extramural structures. It is an effective, efficient, and cost-effective method for evaluating a wide range of benign and malignant gastrointestinal diseases. In recent years, EUS has played an increasingly important role as an adjunct or alternative to traditional surgical treatments.

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Received: 05.05.2023, Accepted: 01.06.2023, Available Online Date: 31.08.2023
Cite this article as: Yuksel S, Topal U, Uzunkulaoğlu M, et al. Experiences in endoscopic ultrasonography at a tertiary center general surgery endoscopy unit. J Cukurova Anesth Surg. 2023; 6(2): 241-4.
doi: 10.36516/jocass.1292736

EUS initially served as a diagnostic tool in the 1980s, but it has gradually transitioned into a therapeutic modality. The evolution of therapeutic procedures guided by EUS has progressed steadily due to reported high technical and clinical success rates. Treatment methods applied with EUS include gastrojejunostomy creation, gallbladder drainage (GBD), angiotherapy, drainage of postoperative fluid collections, portal vein (PV) sampling, and liver biopsy[1,2]. EUS has been reported in the literature to have significantly changed the management of nearly half of the patients with various diseases. However, making an accurate diagnosis using only traditional B-mode EUS imaging can often be challenging. Tissue biopsy guided by EUS is usually required. Vilmann et al. reported the first case of EUS-guided fine-needle aspiration cytology/biopsy (EUS-FNA) in 1992; EUS and EUS-FNA have become indispensable examinations in the clinical field as their applications have expanded[3]. Today, the accuracy of biopsy under EUS guidance is quite high, with sensitivities ranging from 80% to 85% and specificities approaching 100%[4,6].

Various indications exist for EUS procedures. However, some contraindications apply to therapeutic EUS-guided procedures, including hemodynamic instability, inability to visualize the target access

region or find a window due to intervening vessels, and severe, uncorrectable coagulopathy[7]. While several retrospective case series and meta-analyses worldwide have described EUS-guided drainage procedures and EUS outcomes, there is a lack of large-scale, high-volume center results from our country[3,7-11].
In this article, we aimed to share the EUS biopsy experiences and results of a tertiary advanced center general surgery endoscopy unit in the context of the literature.

2. Materials and methods

Following the approval from the local ethics committee (CREB/2022.01.29), patients who underwent EUS (Endoscopic Ultrasound) for various indications in the general surgery endoscopy unit between January 2021 and January 2022 were included in the study. Approximately 300 EUS imagings have been performed per year in this high-volume endoscopy unit. Patients under 18 years of age and those with incomplete clinical data were excluded. Data were retrospectively analyzed from the dataset created using hospital information systems, nurse observation forms, and pathology results. Patients' demographic characteristics, EUS and biopsy indications, clinical pre-diagnoses, pre-procedural imaging methods, number of biopsies, and results, as well as complication status, were analyzed.
All procedures were performed by the same endoscopist (HB). Technical success of EUS-FNA (Endoscopic Ultrasound-Guided Fine Needle Aspiration) was defined as the presence of visible tissue after biopsy. Clinical success was defined as the presence of a sufficient sample for histological or cytological diagnosis.

2.1. Technique

The procedure was conducted in a fasted state, with patients receiving instructions to abstain from oral ingestion of food starting from midnight on the night preceding the procedure. Sedation was administered to patients with midazolam or a combination of midazolam-propofol-fentanyl prior to EUS, and the EUS procedure was performed in the left lateral position. A Fujinon EG-530UT linear echoendoscope was used for the procedure. The EUS evaluation with the Fujinon EG-530UT linear echoendoscope involved examining all areas of the pancreas by withdrawing the scope from the duodenum to the gastric corpus. A linear EUS (Fujinon EG-53UT) device was employed for the aspiration biopsy procedure. Platelet count, activated partial thromboplastin time, and prothrombin time were measured in patients before the procedure. Patients were questioned regarding coagulopathy, anticoagulant, and/or antiplatelet use. Vascular structures were identified using color Doppler ultrasonography prior to the procedure. Fine-needle aspiration was performed using 22 or 25 gauge needles with either "slow pull" or syringe suction, at the discretion of the endoscopist. After the procedure, patients were observed for 2-3 hours in the Endoscopy Unit and discharged if no signs of complications were observed.

2.2. Statistical analysis

IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA) software package was used for the statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, while continuous measurements were presented as means and standard deviations (medians and minimum-maximum values, where necessary).

3. Results

Our study included 292 patients, 157 (53.8%) of whom were male with an average age of 56.5±15.5. The most commonly applied preoperative imaging method was computed tomography (CT), accounting for 107 (36.7%). Demographic and clinical data are shown in Table 1.

Examining the application indications, the most common causes were pancreatic mass 181 (62%), gastric mass 31 (10.6%), and biliary obstruction 23 (7.9%). Indications are shown in Table 2. The average diameter of the detected lesions was 35.1±27.7 mm, and biopsy was performed on 127 patients. No procedural complications were detected in any of the patients. Biopsy results indicated malignancy in 74 (58.2%) cases, and nondiagnostic results were observed in 5 (4%) patients.

Table 1
Demographic and Clinical Data

Variables	n:292
Age mean+std (min-max)	56.5 + 15.5 (19-98)
Gender	
Female	135 (46.2%)
Male	157 (53.8%)
Pre-procedural imaging method	
CT	107 (36.7%)
CT and MRI	91 (31.2%)
MRI	46 (15.8%)
Gastroscopy	25 (8.5%)
CT and PET	12 (4.1%)
CT, MRI, and PET	11 (3.7%)

CT: Computed Tomography, MRI: Magnetic Resonance Imaging, PET: Positron Emission Tomography

Table 2
Indication

Indication	n:292
Pancreatic mass	181 (62%)
Gastric mass	31 (10.6%)
Biliary obstruction	23 (7.9%)
Esophageal mass	18 (6.1%)
Duodenal mass	14 (4.8%)
Common bile duct mass	12 (4.1%)
Intra-abdominal mass	5 (1.9%)
Mediastinal mass	3 (1%)
Adrenal mass	3 (1%)
Rectal mass	1 (0.3%)
Ascites	1 (0.3%)

Table 3
Procedures and outcomes

Variables	n:292
Lesion diameter (mm) mean+std (min-max)	35.1+27.7 (4-160)
Number of patients who underwent biopsy.	127 (43.4%)
Procedure-related complications	0
Biopsy result	
Malignancy	74 (58.2%)
Benign lesion	48 (37.8%)
Non-Diagnostic	5 (4%)
Decision	
Medical Follow-up	144 (49.3%)
Surgical Treatment	80 (27.4%)
Medical Oncology	45 (15.4%)
ERCP	23 (7.9%)

ERCP: Endoscopic Retrograde Cholangiopancreatography

Treatment determinations were established considering the biopsy and lesion characteristics, with 144 (49.3%) patients undergoing follow-up, 80 (27.4%) receiving surgical intervention,45 (15.4%) receiving medical oncology, and 23 (7.9%) undergoing endoscopic retrograde cholangiopancreatography (ERCP). The applied procedures and results are shown in Table 3.

The probability of pathological complete response for those with radiological complete response was 41% (PKD), and the probability of non-response not being a response in pathology was 90% (NKD) (Figure 1). When the evaluation was made according to the receptor status, it was possible to make an evaluation only in the USG group due to the number of samples. While there was no PTY in the Luminal A group, the results were statistically meaningless in the Luminal B group and the Triple group. In each 2+ group, the AUC value was 0.75 (p=0.008), the success of determining the complete response of the test was 51%, and the success of determining no response was 98% (Table 3).

4. Discussion

Endoscopic ultrasonography (EUS) was first performed by Jenssen C and colleagues in 1980 at the Wolfgang von Goethe University in Frankfurt, Germany, and the Mayo Clinic in Rochester, USA, using a rotating mechanical ultrasound scanner or an electronic linear ultrasound array with side-viewing gastroscopes (Olympus GF-B3; ACMI FX-5)[2,4]. The clinical use of these early echoendoscopes had limitations such as the length (80 mm) and diameter (13 mm) of their rigid tips. Due to this limited flexibility, endoscopists struggled to pass the pyloric canal, but they did not define any complications despite mechanical disadvantages. Today, 60% of gastroenterologists in the United States use EUS, and approximately 43% of gastroenterologists and visceral surgeons in four European countries have access to EUS[8].

In a study presenting EUS results of 732 patients in the literature, the average age was 51, and the female gender was dominant at 62%. In this study, with a success rate of 97.7%, EUS changed clinical management in 58.7% (430/732) of cases overall. Management plans were altered in 26.0% of choledocholithiasis cases, 91.2% of malignancy investigation cases, and 72.7% of other benign conditions such as pancreatic, hepatic, and biliary diseases[12]. In our series, the male gender was dominant, which was related to the disease population, and our average age was consistent with the literature. In our series, EUS changed management in many diseases, and particularly in all cases of choledocholithiasis, it constituted an indication for ERCP. It played a key role in making follow-up decisions for submucosal lesions and management of malignant pancreatic masses.

EUS (Endoscopic Ultrasound) presents multiple advantages over other imaging modalities. It does not involve radiation, as is the case with computed tomography (CT) or positron emission tomography (PET), and is not subject to contraindications related to magnetic resonance imaging (MRI), such as the presence of metal implants or claustrophobia. EUS provides high-resolution real-time imaging and can be combined with Doppler ultrasound to assess vascular structures and perform diagnostic procedures, angiotherapy, fine-needle aspiration biopsy, and core biopsy for tissue diagnosis. Furthermore, EUS permits therapeutic interventions[13]. In selecting patients for EUS procedures, we identified the use of several pre-procedural imaging methods. In our study, CT was the most frequently employed imaging method, which we associated with the use of EUS as a therapeutic and advanced diagnostic tool.

In the literature, the indications for the use of EUS in the upper gastrointestinal system have been examined under three main categories: esophageal and gastric malignancies, submucosal tumors, and pancreatobiliary diseases. Focusing on these indications sequentially, EUS can be used to identify benign tumors of the upper gastrointestinal system, including submucosal esophagogastric tumors. EUS-guided fine-needle aspiration and biopsy can aid in the cytohistological diagnosis of solid esophagogastric subepithelial lesions. EUS is routinely employed in the diagnosis and staging of malignant esophageal tumors[14].

EUS is more sensitive, specific, and accurate than high-quality cross-sectional imaging for the detection of pancreatic lesions. Numerous studies have demonstrated the high sensitivity (92-100%), specificity (89-100%), and accuracy (86-99%) of EUS in detecting pancreatic malignancies. In particular, it yields better results for small-sized lesions compared to cross-sectional imaging[15]. Biliary obstructions can result from a wide spectrum of diseases, ranging from benign to malignant causes. In our indications, pancreatic masses constituted the largest portion. We performed procedures to detect pancreatic masses, aspirate cysts, and obtain tissue diagnoses. In cases of biliary obstruction, we used EUS to detect choledocholithiasis prior to ERCP in suspicious cases and to rule out malignant causes. We also employed the procedure to identify the originating layer of upper gastrointestinal subepithelial lesions and for fine-needle aspiration biopsy.

Previous studies describing the diagnostic performance of EUS-FNA for pancreatic tumors have reported sensitivities of 54-95%, specificities of 71-100%, and overall accuracy rates of 65-96%[16]. In our series, biopsies were performed on 43% of the patients. Biopsy results indicated malignancy in 58% of cases, which we attributed to the high prevalence of pancreatic diseases in our patient population.

5. Conclusions

The role of EUS in the diagnosis and treatment of gastrointestinal malignancies, pancreatic diseases, and biliary diseases continues to evolve. Therapeutic EUS procedures for various pancreas and biliary tract indications can be performed with high technical and clinical success rates, along with low rates of adverse effects. We believe that EUS plays a pivotal role in the multidisciplinary management of

complex surgical and oncology patients and those with pancreatobiliary disorders.

Acknowledgements

None.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by for this study the Başakşehir Çam ve Sakura Şehir Hastanesi Klinik Araştırmalar Etik Kurulu (CREB/2022.01.29).

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

Collection of the data, draft: MU, SS, Writing of the article, performed the analysis, review of the literature: SY, EA, Critical review of the article, design of the study: HB,UT,EK
All authors read and approved the final manuscript.

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Effect of Concomitant and Adjuvant Temozolomide on Prognosis and Survival in Glioblastoma Multiforme

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Abstract

Aim: Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor in adults. The most common problem in the follow-up after GBM treatment is the lack of local control. This study aims to evaluate the efficacy and safety of Temozolomide (TMZ) in cases who received post-surgical radiotherapy and TMZ treatment in GBM compared to cases who received only radiotherapy treatment after surgery.

Methods: The cases diagnosed with GBM were divided into two groups. The first group was divided into cases that received only radiotherapy after surgery, and the second group (combined treatment group) was divided into cases that received post-surgical radiotherapy and TMZ treatment. 28 cases who received radiotherapy and TMZ treatment after surgery and 26 cases who received only radiotherapy after surgery were included in the study. Local fractionated radiotherapy (60 Gy total dose: 2 Gyx5 days/week for 6 weeks) was applied to all cases. Only in the second group, 75 mg/m^2/day 7 days/week orally, 200 mg/m^2/day 5 days as monotherapy for 6 weeks, and six cycles of TMZ every 28 days were administered concomitantly. In addition to the effect of TMZ on prognosis and survival, the effects of age, gender, and resection size on progression-free survival (PSS) and overall survival (GSS) were evaluated in both groups.

Results: There was no statistically significant benefit in terms of both PFS and OS in both groups for age and gender, a statistically significant benefit was found for resection size (total-subtotal). At the end of the study, PFS was 14 months in the combined treatment group and 6 months in the radiotherapy alone group (P<0.0001). OS was 16 months in the combined treatment group and 12.5 months in the radiotherapy alone group (P=0.0354).

Conclusion: Combined (RT + TMZ) treatment after total surgical treatment was found to be more effective on prognosis and survival than radiotherapy alone.

Keywords: *Glioblastoma multiforme, temozolomide, radiotherapy, surgery*

1. Introduction

According to the World Health Organization, one of the top three causes of death in both developed and developing countries after the first 5 years of age is cancer-related deaths.

Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults and is one of the most rapidly progressing and deadly tumors known[1]. GBM is the most common primary brain tumor that can be seen at any age. The median survival after diagnosis is less than one year. In the most appropriate treatment conditions, this period can be extended to two years. Intracranial tumors account for 14% of all tumors and 48% of malignant central nervous system tumors. It is responsible for approximately 1.5% of all cancers and 2% of all cancer-related deaths. It ranks fourth in cancer-related deaths[2-4].

Despite improvements in treatment modalities, there has been no significant change in GBM treatment outcomes. Therefore, preclinical and clinical studies are increasingly continuing to develop other treatment strategies that may be beneficial when combined with RT in malignant gliomas[5].

Temozolomide (TMZ) is an alkylating agent that converts alkyl

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Received: 23.06.2023, Accepted: 25.07.2023, Available Online Date: 31.08.2023
Cite this article as: Sezer C, Acikalin R, Bilgin E, et al. Effect of Concomitant and Adjuvant Temozolomide on Prognosis and Survival in Glioblastoma Multiforme. J Cukurova Anesth Surg. 2023; 6(2): 245-50.
doi: 10.36516/jocass.1318903

groups to guanine bases in the cell, causing DNA damage and causing apoptosis6. It can be taken orally due to its small molecular structure (194.151 g/mol) and lipophilicity. The plasma half-life is about 2 hours. However, crossing the blood-brain barrier has only 20% bioavailability[6].

Standard treatment in cases with GBM; surgery (CER) + radiotherapy (RT) ± chemotherapy (CT). Since the beginning of the 2000s, TMZ has taken its place in standard treatment as a chemotherapeutic agent in cases with GBM. Despite these advances, KT has a limited role in the adjuvant treatment of primary disease or after relapse[7]. Different multimodal treatment approaches have been developed to prolong survival. High-dose RT, adjuvant CT, alternative fractionation regimens in radiotherapy, heavy particle therapy, use of radiosensitizers together with RT, interstitial brachytherapy, radiosurgery, stereotactic fractionated RT, and intensity modulated RT are some of the treatment modalities that are being developed[8-10]. In this study, we aimed to determine the effect of TMZ, which we use as a chemotherapeutic agent following post-surgical radiotherapy in standard treatment protocols, on prognosis and survival, by comparing it with the cases in which we gave only radiotherapy after surgical treatment in previous years.

2. Materials and methods

Twenty-eight patients who received post-surgical radiotherapy and chemotherapy treatment at Çukurova University Faculty of Medicine Neurosurgery Clinic between May 2006 and March 2010 were randomized to this study. Between 2000 and 2005, 26 patients who received only radiotherapy after surgery were randomly selected.

Cases with histological diagnosis of glioblastoma were divided into two groups. The first group was divided into cases that received only radiotherapy after surgery, and the second group was divided into cases that received post-surgical radiotherapy and TMZ treatment. Radiotherapy consists of administering a dose of 2 Gy/fraction five days a week (Monday to Friday), once a day for a total of 45 days over 6 weeks, with an additional dose of 46 Gy to the whole brain and 20 Gy to the tumor bed, giving a total dose of 66 Gy, we applied conventional fractionated irradiation. Preoperative CT or MRI was used to determine the target volume while applying an additional dose to the tumor site. Since the target volume is whole brain irradiation; It was determined as an area of 2 cm from the tumor border. According to tumor location, different field entrances were used to distribute the dose; supplemental dose areas vary. Chemotherapy with TMZ was administered at a dose of 75 mg/m^2/day, 7 days a week, for a total of 49 days from the first day to the last day of radiotherapy. After a 4-week break, patients received adjuvant TMZ therapy at a dose of 150 mg/m^2/day for 5 days every 28 days, the standard regimen for six cycles (Figure 13). The anti-edema treatment, which was started parenterally from the beginning of the treatment, was discontinued by reducing the dose within 1-2 months after radiotherapy. Anti-epileptic therapy was continued uninterrupted. As anti-emetic prophylaxis, selective 5-HT3 (5-hydroxytryptamine) receptor antagonists have been used at initial doses of concomitant TMZ therapy and during 5-day adjuvant TMZ administration. Side effects during post-surgical radiotherapy (with or without concomitant TMZ), during the adjuvant treatment period, and throughout the study period (from enrollment to disease progression or final follow-up) were evaluated separately.

Observation and Follow-up During radiotherapy (with or without TMZ), patients were checked every week. During the controls, the neurological status of the patients along with their complaints was examined and complete blood counts were checked. The patients were called for their first controls 4 weeks after the end of radiotherapy, and their neurological and general conditions were evaluated, and the tumor response was checked with control CT or MRI. Thereafter, clinical and radiological examinations were performed at 3-month intervals as long as they were asymptomatic. During adjuvant TMZ therapy, patients were clinically evaluated monthly and subjected to a comprehensive investigation including CT or MRI at the end of cycles 3 and 6. Response criteria were evaluated based on clinical response together with the results of radiological neuroimaging studies and according to the US Medical Research Council's neurological scale and corticosteroid requirement. Responses were then grouped into four categories: 1) Complete response 2) Partial response 3) Stable disease 4) Progressive disease. Toxic effects are graded according to the National Cancer Institute General Toxicity Criteria version 2. Grade 1 indicates mild adverse effects, Grade 2 indicates moderate adverse effects, Grade 3 indicates serious adverse effects, and Grade 4 indicates life-threatening adverse effects.

Radiotherapy time frame; is defined as the time from day 1 of radiotherapy to day 28 after the last day of radiotherapy or to the first day of adjuvant TMZ therapy. The adjuvant chemotherapy segment; is defined as the period from the first day of adjuvant TMZ therapy to 35 days after the first day of the last TMZ course.

Progression-free survival (PFS); was determined as the time from the start of treatment to the date of progression of the disease, the date of the last control in patients without progression, and the date of death in patients who died without progression. Overall survival (OS); was defined as the time from the start of treatment to death.

2.1. Statistical analysis

The X-test (gender, age, type of surgery, KPS) and t-test were used when comparing patient characteristics that have an impact on prognosis. Kaplan-Meier method was used to calculate PFS and OS. The log-rank test was used when comparing the PFS and OS groups. Hazard Ratio and 95% CI (confidence interval) calculated p values were found. Statistical calculations were made using SPSS 11.0 program. $P<0.05$ was considered statistically significant.

3. Results

There was no significant difference in demographic and baseline characteristics between the two treatment groups. In the post-surgical radiotherapy-only (CER + RT) group, 14 (54%) cases were male, and 12 (46%) were female. Karnofsky performance scale values of all patients were evaluated as ≥80 before treatment (Table 1). In the group that received TMZ (CER + RT + TMZ) together with postoperative radiotherapy, 15 (53%) of the cases were male and 13 (47%) were female. In the CER + RT group, the youngest patient was 24 years old and the oldest was 71 years old; the mean age (± standard deviation) was 52.05 ± 13.02, and the median age was 50.5 ± 5. In the group receiving CER + RT + TMZ, the youngest patient was 25 years old and the oldest was 69 years old; the mean age (±standard deviation) was 49.65 ± 12.42, and the median age was 48.5 ± 4.4. Total excision was performed in 15 (57%) cases and subtotal excision was performed in 11 (43%) cases in the CER + RT group. In the group receiving CER + RT + TMZ, total excision was performed in 15 (53%) patients, and subtotal excision was performed in 13 (47%) cases. The median time from diagnosis to the start of treatment was calculated as 11.2 days in the CER + RT + TMZ group and 10.3 days in the CER + RT group. The mean duration of radiotherapy was 41.2 days in the CER + RT + TMZ group and 42.1 days in the CER + RT group (P=0.92).

Headache was the most common complaint in the study group at the time of admission to our clinic. Symptoms such as loss of

strength, epilepsy, forgetfulness, nausea-vomiting, and loss of consciousness were observed depending on factors such as the size of the mass lesion, the age of the case, and the location of the lesion. All subjects in the CER + RT group received radiotherapy at a total dose of 66 Gy (46 Gy to the whole brain + 20 Gy to the tumor bed) as planned. All patients in the CER + RT + TMZ group completed both radiotherapy and TMZ treatment as planned. The adjuvant TMZ cycle was applied to 28 cases in the CER + RT + TMZ group. Adjuvant TMZ could not be given to 1 of the cases after radiotherapy due to disease progression, 2 cases could not complete 6 cures of adjuvant TMZ treatment due to progression, and adjuvant TMZ treatment was terminated in 3 cases due to toxic effects. A total of 22 cases completed six treatment cycles as planned. Hematological side effects were not observed in the CER + RT group. CER + RT + TMZ (concomitant and sequential) was well tolerated. The main side effect was myelosuppression. In the concomitant RT + TMZ phase after surgery; Grade 3 and 4 thrombocytopenia occurred in 1 case, and Grade 2 anemia in 1 case. During adjuvant TMZ treatment; Grade 3 thrombocytopenia was found in 2 cases, grade 2 anemia in 1 case, and Grade 2 leukopenia in 1 case. No mortality due to treatment toxicity was observed.

Non-hematological toxicity was mild. In the combined treatment group, treatment-related rash was seen in 3 cases, constipation in 2 cases, and arthralgia in 1 case. No late-term neurological side effects were observed. As a non-hematological side effect in the CER + RT group; Grade 1 acute skin reaction was observed in 9 cases, grade 1 nausea and vomiting in 3 cases, and fatigue in 3 cases.

3.1. Treatment After Disease Progression

A second surgery was performed on 1 patient in the CER + RT group and 2 patients in the CER + RT + TMZ group who progressed. Rescue chemotherapy was not applied to any of the cases.

3.2. Survival Results in Patient Groups

When this study conducted in our clinic was evaluated in January 2010 during the data analysis phase, 26 (100%) of 26 patients in the CER + RT group died. Twenty-four (86%) of 28 cases in the CER + RT + TMZ group died, and 4 cases were still alive. There was progression in 3 (75%) of these 4 cases. The follow-up period of the cases in the CER + RT group; had a mean of 13.5 months (3-48 months), and a median of 13.70 (95% CI; 11.38 - 15.20) months. The follow-up period of patients in the CER + RT + TMZ group; had a mean of 14.32 (3-48 months), the median of 13.80 months.

The median PFS was 14 months in the CER + RT + TMZ group and 6 months in the CER + RT group (95% CI 0.05732 - 0.2742) **(**Figure 1). The log-rank test showed a significant PFS difference between the two groups (P < 0.0001). Median OS was 16 months in the CER + RT + TMZ group and 12.5 months in the CER + RT group (95% CI 0.3213–0.7654) **(**Figure 2). The log-rank test showed a significant difference in survival between the two groups (P= 0.0354).

3.3. Prognostic Factors

The effects of age, gender, and resection size, which are considered to be important prognostic factors, on PFS and OS were investigated as a stand-alone factors in both groups.

3.4. Survival Results in the CER + RT Group by Age

When examined by age, the median PFS in the CER + RT group was; It was found to be 5.6 months for those over 50 years of age and 7 months for those 50 years and younger (95% CI: 0.3276-2.357). This result was not statistically significant (P=0.5168). When analyzed by age, the median OS in the CER + RT group was 10 months in those over 50 years of age and 12.6 months in the group 50 years and younger (95% CI: 0.2436 - 2.251). This result was not statistically significant (P = 0.5842).

3.5. Survival Results in the CER + RT Group by Gender

When analyzed by gender, the median PFS in the CER + RT group was 6 months in female patients and 5 months in male patients (95% CI: 0.2946-2.5440). This result was not statistically significant (P=0.7568). OS was 13 months in female patients and 10.5 months in male patients (95% CI: 0.2865-2.216). This result was not statistically significant (P=0.7462).

3.6. Survival Results in the CER + RT Group by resection size

When analyzed according to resection size, the median PFS in the CER + RT group was 8 months in total resection and 5 months in subtotal resection (95% CI: 0.2567-2.867). This result was statistically significant (P=0.02). Median OS was 15 months for total resection and 8 months for subtotal resection (95% CI: 0.3257 - 3.584). This result was statistically significant (P< 0.01).

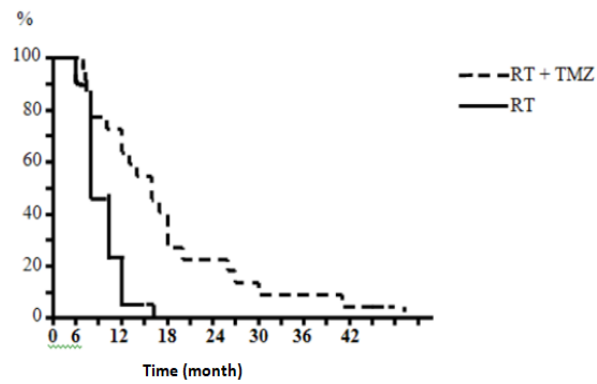

Figure 1
Progression-free survival in all patients

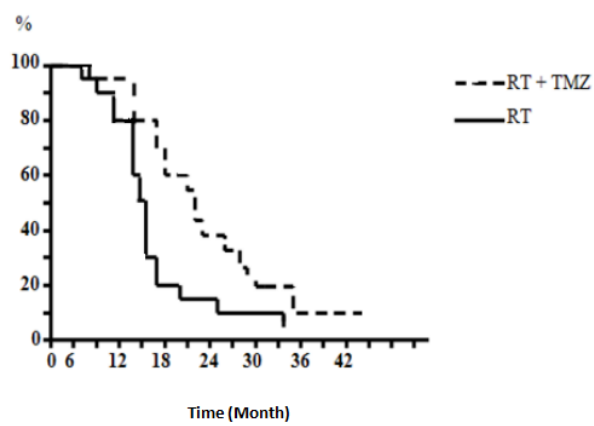

Figure 2
Overall survival in all patients

Table 1
Baseline demographic characteristics of the cases

		CER + RT	CER + RT + TMZ	P
Gender	Male	14	15	0.65
	Female	12	13	
Age	≤ 50	12	12	0.62
	> 50	14	16	
	Average ± SEM	52±13	49 ± 12.4	0.43
	Median ± CI	50,5±5	48.5 ± 4.4	
Surgery Type	Total	15	15	0.21
	Subtotal	11	13	
From diagnosis to treatment elapsed time (days) (Average)		10,3	11.2	

3.7. Survival Results in CER + RT + TMZ Group by Age

When analyzed according to age, the median PFS in the group receiving CER + RT + TMZ was found to be 9 months in those over 50 years of age and 13.5 months in those aged 50 and younger (95% CI: 0.8741–4.376). This result was not statistically significant (P =0.1363). Median OS was 16 months for those over 50 years of age and 18.6 months for those 50 years or younger (95% CI; 0.5965 vs 3.897). This result was not statistically significant (P=0.2865).

3.8. Survival Results in CER + RT + TMZ Group by Gender

When analyzed by gender, the median PFS in the group receiving CER + RT + TMZ was 12 months in female patients and 11 months in male patients (95% CI; 0.5359-3.965). This result was not statistically significant (P=0.4365). The median OS was 22 months in female patients and 20 months in male patients (95% CI; 0.3465-2.645). This result was not statistically significant (P=0.4985).

3.9. Survival Results in CER + RT + TMZ Group by Resection Size

When analyzed according to the size of the resection, the median PFS was found to be 14.5 months in the CER + RT + TMZ group, in those who underwent total resection, and 8 months in those who underwent subtotal resection (95% CI; 1.5641-2.385). Statistically significant (P = 0.012). Median OS was 18.5 months for total resection and 13 months for subtotal resection (95% CI; 0.1259 - 1.8649). This result was statistically significant (P = 0.03).

4. Discussion

GBM is the most lethal and least controllable primary CNS tumors. Despite various treatment approaches, the most important reason for failure in high-grade brain tumors is failure to achieve local control of the tumor. Despite advances in imaging, surgery, and radiotherapy techniques, patients with GBM have a poor prognosis. Therefore, the search for more effective chemotherapeutic agents is of great interest. It is important to determine the tumor size in planning the surgery and/or radiotherapy to be applied in the treatment of brain tumors, evaluating the response to treatment, and predicting the prognosis. It has been reported in the literature that tumor size before surgery + adjuvant treatment has a positive effect on survival, and the prognosis is poor if the tumor size is large enough to involve more than one lobe. Another factor that has an impact on survival is the location of the tumor. In brain tumors, the localization of the tumor, the extent of local spread, and its proximity to vital areas of the brain are important in terms of the degree of neurological damage [10-12]. In our cases, we get better results in more appropriately located cases such as the frontal and temporal lobes.

In many retrospective studies in the literature, it has been stated that aggressive tumor resection is a factor that prolongs survival in high-grade gliomas, the residual tumor size on postoperative CTs is more important than the preoperative size, and it correlates with the time of progression and prognosis of the tumor[11,12]. In brain tumors, factors such as tumor size before treatment and tumor size after surgery and/or radiotherapy, which have prognostic value, are still discussed. Post-surgical changes have a feature such as retention of contrast material in radiological examinations. Therefore, it is very difficult to distinguish between postoperative changes and residual tumors. In the studies, it was concluded that the radiological determination of the residual tumor is more appropriate in the first 3 days postoperatively. Because the postoperative changes start to hold the contrast agent as early as the 3rd day and the uptake peaks after approximately 2 weeks. This takes up to 45 days. Therefore, MRI should be performed in the first three days or 45 days after the treatment to detect the tumor size[13]. We did not evaluate our cases with MRI in the early period. We made a total-subtotal distinction only with cerebral CT. We found higher rates of PFS and OS in patients who underwent total resection in both of our study groups.

In a randomized phase III study conducted by the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC), the combined use of CER + RT and TMZ has been shown to prolong survival in patients with GBM[14]. In this study, 573 cases were randomized into two groups as only CER + RT and CER + RT with simultaneous TMZ and then adjuvant TMZ application. RT was administered 2 Gy/day x 30 fractions, a total of 60 Gy, within 6-7 weeks, excluding weekends. Simultaneous administration of TMZ at a dose of 75 mg/m^2/day from the first day to the last day of RT for a total of 49 days, including the

weekend, and adjuvant administration 4 weeks after the end of RT (150-200 mg/m^2/day) every 4 weeks 6 cycles were applied for 5 days. As a result of this study, While the median OS was 12 months in patients who received only CER + RT, it was 15 months in the arm combined with TMZ. While the 2-year OS was only 10% in the CER + RT group, this rate was 26% in the arm combined with TMZ. The median PFS was 5 months in the CER + RT arm alone, and 6.9 months in the TMZ combined arm. The 1- and 2-year PFS rates were 9% and 2% in patients who received CER + RT alone, compared to 27% and 11% in the arm combined with TMZ (P<0.0001). In this phase III study, a significant improvement in survival was demonstrated by combining CER + RT with TMZ in newly diagnosed GBM patients. Similar values were determined in our study, and we obtained similar results in our study.

Reardon et al[15] performed TMZ before post-surgical RT in patients with newly diagnosed GBM. Patients received four cycles of TMZ. At the end of the treatment, a reduction in tumor size was found in 52% of patients with GBM. 9% (3/33) of patients showed complete remission (radiologically no tumor detected), 42% (14/33) showed a partial reduction in tumor size, and only 12 (36%) of patients progressed.

In a phase II study by Athanassiou et al[16], 110 patients received 60 Gy RT after CER alone in one arm and TMZ at a dose of 75 mg/m^2/day concurrently with CER + RT in the other arm, followed by 150 mg/m^2/day 1-5 and 15 6 courses of adjuvant TMZ were applied every 28 days, between -19 days. In the results of this study, the median PFS was 5.2 months versus 10.8 months; 1-year PFS was 7.7% versus 36.6%, OS 7.7 versus 13.4 months, and 1-year OS 15.7% versus 56.3%. Toxicity was mostly hematological, and it was reported that 1 patient died due to grade IV myelotoxicity resulting in sepsis. Our PFS and OS results are in agreement with this study.

In the study of Huang et al[17], while the median PFS was 15 months in the 1st group in which 6 cycles of TMZ were given, the median PFS was 20.1 months in the 2nd group in which they gave more than 6 cycles of TMZ. The median OS in group 1 was 19.4 months. OS was 25.6 months in Group 2. Groups 1 and 2 had a 2-year survival rate of 36% and 66%, respectively (P=0.02). and 5-year survival was 7% in both. According to this study, the TMZ dose we applied to our patients seems to be sufficient.

In our study, as in other studies[14-17], toxicity was higher in the group in which adjuvant therapy was applied, but it was at acceptable levels. Nausea and vomiting, which were the most common side effects, were generally mild.

In our study, we made our subgroup analysis evaluations for age, gender, and surgical resection according to prognostic factors in both groups. Our results showed a statistically insignificant difference in both PFS and OS for age and gender. In terms of the amount of resection, a statistically significant difference was found in both groups in terms of both PFS and OS. In the first group, PFS was determined as 5 months and OS as 8 months in patients who underwent subtotal surgical treatment, while this period was 8 months and 15 months, respectively, in patients who underwent total surgical treatment. In the second group, PFS was determined as 8 months and OS as 18.5 months in patients who underwent subtotal surgical treatment, while this period was found to be 14.5 months and 3 months, respectively, in patients who underwent total surgical treatment. These results are consistent with the literature[18-20].

5. Conclusions

Although the number of cases in our study is lower than in other studies, it shows that 6 cycles of TMZ treatment following post-surgical RT combined with TMZ may be an effective agent by prolonging survival in newly diagnosed cases with GBM. It also demonstrates that it is important to start chemotherapy early in the disease to allow time for the drug to act against the rapidly growing tumor. It supports that it is superior to CER + RT therapy alone. With this treatment regimen, both PFS and OS will be improved and this beneficial effect will be achieved with a safe and tolerable chemotherapeutic agent. In these cases, this intensive and continuous treatment was generally applied without any problems. However, considering the cost of this treatment, it may be thought that the expected results would be much more acceptable (cost/benefit ratio). However, the presence of such adjuvant treatments in these tumors with a very poor prognosis gives hope for the development of other treatment modalities.

Acknowledgements

None.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by for this study the Cukurova University Institution Ethics Committee (2010-Thesis number 247902).
https://tez.yok.gov.tr/UlusalTezMerkezi/tezDetay.jsp?id=F_E_jXAckxV6q8q2gxDqXg&no=LFoKzqq7GW9ilSrzaL1JLg

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

Collection of the data, draft: MU, SS, Writing of the article, performed the analysis, review of the literature: SY, EA, Critical review of the article, design of the study: HB,UT,EK

All authors read and approved the final manuscript.

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The Importance of Alterations in Innate Lymphoid Cell Subsets in Patients with Non-Small Cell Lung Cancer and their Role in Tumorigenesis

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Abstract

Aim: Non-small cell lung cancer (NSCLC) is one of the leading causes of cancer-related morbidity and mortality. Diverse functions of innate lymphoid cells (ILCs) and NK cell subsets are investigated thoroughly in cancer immunotherapy. ILC and recently described NK cell subsets in NSCLC patients' blood samples and tumor draining lymph nodes were investigated.

Methods: The study included chemotherapy and/or radiotherapy-naive NSCLC patients with clinical stage T1-4N0-2M0 who underwent video-assisted mediastinal lymphadenectomy and 14 healthy controls. Mononuclear cells were isolated from peripheral blood of both groups and mediastinal lymph nodes of NSCLC patients. NK cells and ILC subsets were analyzed by flow cytometry.

Results: Total NK cells are shown to be increased in peripheral blood of NSCLC patients compared to lymph nodes while the ratio of $CD56^{dim}CD16^{-}$ exhausted NK cells is higher in lymph nodes than in blood samples of NSCLC patients. Compared to control group, peripheral blood ILC1 cells were lower in NSCLC patients, however ILC2 and ILC3 cells were significantly increased. However, mediastinal lymph nodes of NSCLC patients had decreased ratio of ILC2 and increased ratio of ILC3 cells than in peripheral blood of patients. NSCLC patients had significantly increased ratio of $NKp44^{-}$ILC3 cells and decreased ratio of $NKp44^{+}$ILC3 in lymph nodes.

Conclusion: Decreased ratio of ILC1 cells is an important indicator of impaired anti-tumoral response. Increased in the ratio of $NKp44^{-}$ILC3 cells in NSCLC patients may potentially contribute to tumor progression. These findings highlight the distinct roles of ILCs, which play a pivotal role in the pathogenesis of lung cancer.

Keywords: *NSCLC, NK cells, ILC1, ILC2, ILC3, immunotherapy*

1. Introduction

The goal of cancer treatments is to improve survival rates, and recent advancements in immunotherapies and our understanding of tumor immunity have been considered in a new era in cancer - treatment. However, lung cancer has still high mortality rates[1-2].

Histologically, lung cancer can be divided into two main groups: Non-Small Cell Lung Cancer (NSCLC), which accounts for approximately 85% of all cases, and Small Cell Lung Cancer (SCLC), which represents about 15% of all lung cancers[3]. Nonmetastatic (stage I-IIIA) NSCLC is generally treated with multimodality treatment approaches including surgery, radiotherapy, chemotherapy, and immunotherapy[4-5]. Unfortunately, the majority of lung cancer cases are diagnosed at late stages (stage IIIB-IV) with distant metastasis and/or local invasion. As a result, there is currently significant research focus on enhancing antitumoral immunity in the field of oncology[6].

Recent studies have revealed the significance of innate immunity, and its contribution to antitumor immunity. A distinct subset of lymphocytes known as innate lymphoid cells (ILCs) has gained attention in this context. ILCs encompass a diverse group of cells, in-

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Received: 03.07.2023, Accepted: 18.07.2023, Available Online Date: 31.08.2023
Cite this article as: Cikman DI, Aktas EC, Gelmez YM, et al. The importance of alterations in innate lymphoid cell subsets in patients with non-small cell lung cancer and their role in tumorigenesis. J Cukurova Anesth Surg. 2023; 6(2): 251-7. doi: 10.36516/jocass.1321787

cluding cytokine-producing ILCs and natural killer (NK) cells. They are recently classified into three different subgroups according to their cytokine secretion and transcription factor expression: group 1 ILC (comprising ILC1s and NK cells), ILC2 and ILC3. Lymphoid tissue inducer cells (LTi) are a distinct group of ILCs but thought to belong to group-3 ILCs[7]. There is homology between T helper cell subsets and ILCs. Group 1 ILCs is a counterpart of Th1 consist of NK and ILC1 cells. These cells secrete tumor necrosis factor (TNF)-α and interferon (IFN)-γ, playing a key role in antitumor immunity. However, unlike ILC1s and other ILCs, NK cells possess cytotoxic functions. While NK cells can circulate in the bloodstream, ILC1 cells predominantly reside in various tissues[7-8]. NK cells employ several mechanisms in their antitumor activity, including antigen-dependent cell cytotoxicity, induction of target cell apoptosis via FASL and TRAIL signaling, and target cell lysis using cytolytic granules containing molecules such as perforin and granzyme[9]. The overall effect of NK cells is the enhancement of both innate and adaptive immunity, leading to a robust antitumor response.

ILC2 cell subset, similar to Th2 cells, secrete cytokines such as IL-4, IL-5 and IL-13 which contribute to type 2 immune responses. ILC2 cells originate from the progenitors in bone marrow and are found in various organs such as lung, intestines, adipose tissue, and the skin[11]. It has been shown that an increased ratio of ILC2s in gastric cancer patients creates an immunosuppressive microenvironment that facilitates tumorigenesis in this group[12]. ILC3 cells functionally resemble Th17 cells and secrete IL-17 and IL-22. A unique subgroup of ILC3s, lymphoid tissue inducer cells (LTi) that play a role in modulating lymphoid tissues during inflammatory conditions and even in embryological development[7]. Additionally, ILC3 cells expressing the Natural Cytotoxicity Receptor (NCR) have been found to enhance antitumoral immunity by promoting the formation of ectopic lymphoid structures in NSCLC patients. These findings are associated with a better prognosis in terms of clinical outcomes for lung cancer patients[13].

ILCs play critical regulatory roles in various inflammatory conditions including autoimmune diseases, infections, and cancer. They exhibit distinct functions depending on the specific tissue and context in which they are found[14]. Recent research has shown that ILCs possess plasticity, meaning they can convert from one subgroup to another, further complicating the categorization of their roles[15]. This study focuses on the identification of distinct subgroups of innate lymphoid cells (ILCs) and examines their distribution in the peripheral blood of both non-small cell lung cancer (NSCLC) patients and healthy controls. Additionally, the presence of ILC subgroups in the tumor draining lymph nodes of NSCLC patients was investigated. The primary objective of this study was to gain insight into the potential impact of alterations in ILC and natural killer (NK) cell subsets on tumorigenesis in NSCLC patients. In addition to the primary objective, this study also aimed to explore and compare the differences between the distribution of ILC subgroups in the peripheral blood and tumor draining lymph nodes of NSCLC patients. By examining these distinct anatomical sites, the secondary outcome was to provide a comprehensive understanding of the potential variances in ILC composition within the same individuals affected by NSCLC.

2. Materials and methods

2.1. Study Population

Thirteen patients diagnosed with operable non-small cell lung cancer (NSCLC) and scheduled to undergo Video-Assisted Mediastinal Lymphadenectomy (VAMLA) between January 2018 and December 2019 were prospectively enrolled in the study. Prior to surgery, all patients underwent a comprehensive preoperative staging evaluation, including transthoracic or bronchoscopy-assisted biopsy, computed tomography, positron emission computed tomography, and cranial magnetic resonance imaging. Staging of the patients was performed according to the 8th edition of the TNM staging system for lung cancer, and they were classified as having a disease stage of cT1-4N0-3M0-1A. None of the patients had a history of chemotherapy or radiotherapy. Bilateral mediastinal lymph node dissection was performed using the VAMLA technique for all patients. Fourteen age- and sex-matched healthy individuals with no history of malignancy or self-reported chronic diseases were included as the control group (Table 1), and peripheral blood samples were collected from these individuals. The study protocol was approved by the institutional review board (document 2017/262587) and adhered to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.2. Isolation of peripheral blood mononuclear cells

Peripheral blood mononuclear cells (PBMCs) were isolated from heparinized blood samples using density gradient centrifugation with Ficoll-Paque (Histopaque-1077; Biochrom, UK). Heparin-anticoagulated blood was centrifuged at 800 × g for 20 minutes to remove plasma. The remaining blood was diluted with an equal volume of phosphate-buffered saline solution (PBS) (Biochrom, UK). The cells were then adjusted to a final concentration of 1 × 106 cells/mL in complete RPMI-1640 medium, which consisted of RPMI supplemented with 10% fetal calf serum, 1% L-glutamine, and 1% anti-mycotic and antibiotic solutions (all from Sigma Chem. Co., Germany).

2.3. Isolation of lymphocytes from mediastinal lymph nodes

The lymph node samples after VAMLA procedure were transferred to pathologist to assess the presence of any tumor involvement or other pathologic conditions. Remaining lymph nodes that were not needed for pathological evaluation were transferred to the laboratory in complete RPMI-1640 medium. The lymph nodes were transferred to a sterile petri dish, crushed into smaller pieces using a sterile scalpel on ice, and the crushed lymph node samples were filtered through a 70-µm cell strainer (BD Biosciences, USA). To isolate mononuclear cells, cell suspension was centrifuged by the Ficoll-Hypaque gradient and centrifuged at 800xg for 20 minutes.[16] After centrifugation, lymphocyte-rich mononuclear layer was collected. The washing process was repeated two times then the cells were re-suspended in a complete RPMI-1640 culture medium.

2.4. Determination of NK cell subsets from peripheral blood and lymph nodes

Freshly isolated mononuclear cells from peripheral blood and mediastinal lymph nodes were washed and re-suspended in staining buffer (PBS containing 2% fetal calf serum) and surface staining was done using fluorochrome-conjugated anti-human CD3-FITC, anti-human CD16-Alexa Fluor 700 and anti-human CD56-PerCp (all from Biolegend, USA) monoclonal antibodies. Specific subpopulations were identified by comparison to autofluorescent controls. Tubes were incubated for 30 min at room temperature and were washed with staining buffer. After washing twice with staining buffer, cells were re-suspended in 500 µL PBS with 1% paraformaldehyde and acquired on FACSAria II (Becton Dickinson, San Jose, CA, USA). This instrument allows for the analysis of individual cells based on their fluorescence properties. The acquired data were analyzed using FACS DIVA (BD Biosciences, USA) software. FlowJo software (BD Biosciences, USA) was used for further analysis of the flow cytometric data. NK cell subsets were further divided based on the expression levels of CD16 and CD56 into six subsets:

$CD56^{bright}CD16^{-}$, $CD56b^{bright}CD16^{dim}$, $CD56^{dim}CD16^{-}$, $CD56^{dim}CD16^{dim}$, $CD56^{dim}CD16^{bright}$ and $CD56^{-}CD16^{bright}$ cells[17].

2.5. Flow cytometric determination of ILC subsets from peripheral blood and lymph nodes

PBMCs were isolated from heparinized blood and lymph node

samples and the cells were labeled a panel of conventional FITC labeled lineage negative markers (anti-human CD1a, anti-human CD4, anti-human TCRαβ, anti-human TCRγδ, anti-human CD3, anti-human CD11c, anti-human CD14, anti-human CD94, anti-human CD19, anti-human CD123, anti-human CD303, anti-human CD34, anti-human FcεR1, anti-human CD16), Viability Dye-APC/CY7, anti-human NKp44-PE, anti-human CD161-PerCp.Cy5.5, anti-human CD127-PE/Cy7, anti-human CRTH2 (CD294)-APC, anti-human c-kit (CD117)-BV421 and anti-human CD45-BV510 monoclonal antibodies (All from Biolegend, San Diego, CA, USA) and incubated for 30 min at room temperature in the dark. After incubation, cells were washed by PBS and fixed in PBS with 1% paraformaldehyde. The auto-fluorescent tube was used as an isotypic control for analysis. Data were acquired on a FACSAria II by using the FACSDiva operating system software (BD Biosciences, San Jose, CA, USA). Flow cytometric analyses were performed using FlowJo software (BD Biosciences, USA).

2.6. Statistical Analysis

The data analysis was performed using IBM SPSS (Statistical Package for Social Sciences) for Mac 21.0 software. The normality of the data distribution was assessed using the Kolmogorov-Smirnov test. The comparison of independent variables was conducted using the Mann-Whitney U test. Statistical significance was determined at a p-value < 0.05. Graphical representations were generated using GraphPad Prism 9.0 software (GraphPad Software Inc., La Jolla, USA).

3. Results

3.1. NK cells with exhausted phenotype increased in mediastinal lymph nodes of NSCLC patients

The ratio of total NK cells was significantly lower in the tumor draining mediastinal lymph nodes of the patients compared to their blood levels (p<0.001). The ratio of $CD56^{bright}CD16^{-}$ cytokine-secreting NK, $CD56^{bright}CD16^{dim}$ NK, $CD56^{dim}CD16^{bright}$ mature cytotoxic NK and $CD56^{-}CD16^{bright}$ NK cells were significantly reduced in the tumor draining mediastinal lymph nodes of the patients compared to their peripheral blood levels (p=0.001, p=0.001, p<0.001 and p=0.005, respectively). $CD56^{dim}CD16^{-}$ exhausted NK cells increased in the tumor draining mediastinal lymph nodes compared to peripheral blood of patients and healthy controls (p<0.001 and p<0.001, respectively). $CD56^{-}CD16^{bright}$ NK cells were increased (p=0.003), while $CD56^{dim}CD16^{bright}$ NK cells were decreased in the peripheral blood of the patients compared to healthy controls (p=0.008) (Figure 1).

3.2. Diminished ILC1 but increased ILC2 and ILC3 cells in active NSCLC patients

The ratio of the total ILCs did not change between the peripheral blood of the patients and their mediastinal lymph nodes or control blood. However, the distribution of the ILC subsets varied significantly in patients and controls. The ratio of $CD45^{+}Lineage^{-}CD127^{+}CD161^{+}CRTH2^{-}c\text{-}kit^{-}$ ILC1 cells was significantly reduced in the peripheral blood and mediastinal lymph nodes of the patients compared to the controls (p=0.018 and p=0.014, respectively). This is functionally relevant, as ILC1 cells represent IFN-g secreting population of ILCs and have important antitumoral functions. Interestingly, the ratio of $CD45^{+}Lineage^{-}CD127^{+}CD161^{+}CRTH2^{+}c\text{-}kit^{+}$ ILC2 cells was significantly higher in the peripheral blood of the patients compared to healthy subjects, while it was significantly lower in the mediastinal lymph nodes of the patients. The expression of $CD45^{+}$ $Lineage^{-}CD127^{+}CD161^{+}CRTH2^{-}c\text{-}kit^{+}$ ILC3 cells increased significantly in the peripheral blood of the patients compared to the healthy individuals (p=0.006) and was further increased in the mediastinal lymph nodes of the patients compared to their blood levels (p=0.022). ILC3 cells have also two distinct subtypes according to their cytokine patterns. NCR negative ILC3 cells increased in the peripheral blood and mediastinal lymph nodes of the patients compared to controls (p=0.035 and p=0.030, respectively). The ratio of IL-22 secreting NCR positive $NKp44^{+}$ILC3 cells decreased in the peripheral blood and mediastinal lymph nodes of the patients compared to control blood (p=0.022 and p=0.017, respectively) (Figure 2A and 2B).

Table 1

Demographic data of study and control groups

	Patients (n=13)	Controls (n=14)
Gender		
• Female, n (%)	2 (15)	4 (28.6)
• Male, n (%)	11 (85)	10 (71.4)
Age (years, mean ± SD)	64.2 ± 6.1	54.3 ± 8.7
Diagnosis		
• Adenocarcinoma	4 (30.7%)	-
• Squamous cell carcinoma	6 (46.2 %)	-
• NSCLC, not otherwise classified	3 (23.1%)	-
Clinical Stage		
• Stage I	4 (30.7%)	-
• Stage II	1 (7.7%)	-
• Stage III	5 (38.5%)	-
• Stage IV	3 (23.1%)	-
Surgery		
Lobectomy	4 (66.6%)	
Bilobectomy	1 (16.6%)	
Pneumonectomy	1 (16.6%)	

SD; standard deviation, NSCLC; non-small cell lung cancer

4. Discussion

Immunotherapies are widely used in the treatment of various cancers, including lung cancer. These treatments primarily involve targeting inhibition of immune checkpoint receptors on T lymphocytes to enhance the immune response against cancer cells[18]. However, despite significant treatments, effectively treating cancer remains a challenging task. In recent years, the importance of innate immunity has been well demonstrated, shedding light on the importance on ILC and NK cells[19]. This study investigated the ratio of NK and ILC subsets within peripheral blood and tumor draining lymph nodes of NSCLC patients. The findings revealed remarkable changes in the expression of both NK cells and ILC subsets in these patients. NK cells, unlike T lymphocytes can recognize target cells without the need for interaction with MHC molecules[20]. Studies have shown that increased number of NK cells within the tumor microenvironment (TME) in solid tumors, including lung cancer and colon cancer, is associated with better prognosis, regardless of the ongoing cancer treatments[21-23].

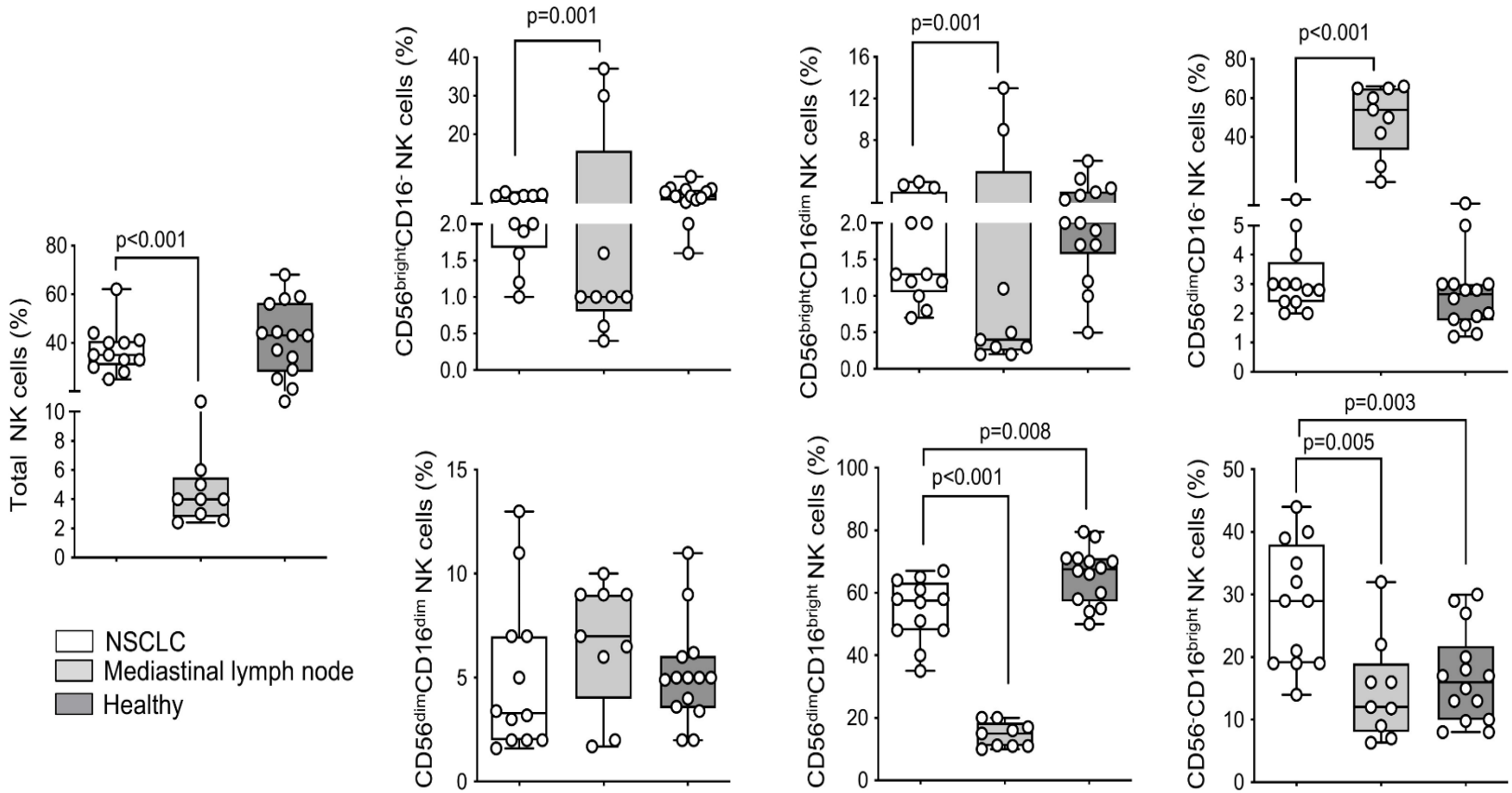

Figure 1

Percentages of six different NK cell subsets in peripheral blood and lymph node samples in NSCLC and healthy subjects. NK cells were classified into six subsets as follows: $CD56^{bright}CD16^{-}$, $CD56^{dim}CD16^{dim}$, $CD56^{bright}CD16^{dim}$, $CD56^{dim}CD16^{bright}$, $CD56^{dim}CD16^{-}$ and $CD56^{-}CD16^{bright}$ NK cells. Percentages of the six different NK subsets and total NK cells in peripheral blood and mediastinal lymph nodes of NSCLC patients and peripheral blood of controls were shown as bar graphs. Differences were considered significant when $p < 0.05$.

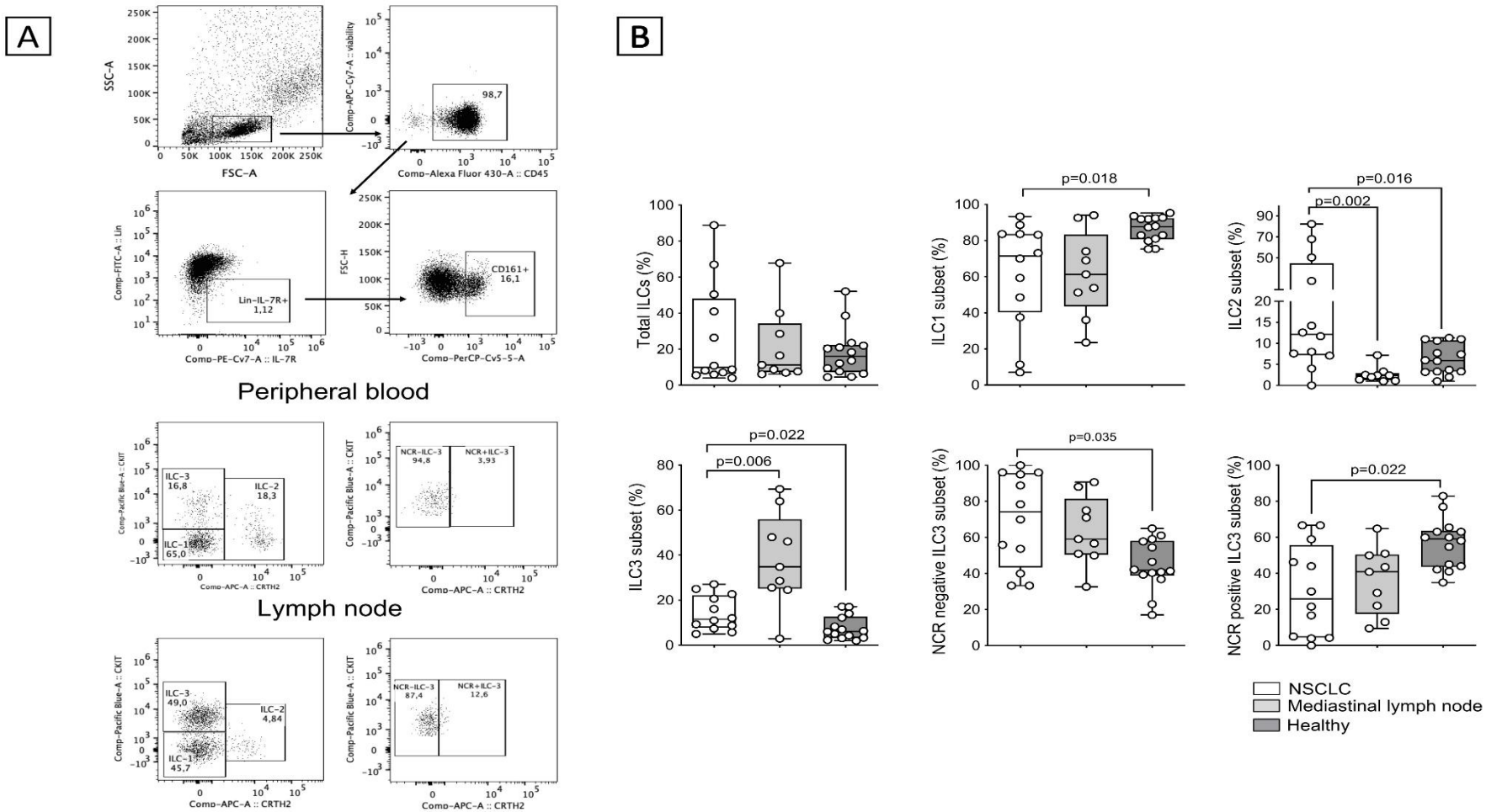

Figure 2

Flow cytometric gating strategy for identifying peripheral blood and lymph node ILC subsets. CD45+ cells were gated by excluding dead cells within the lymphocyte gate. ILCs were defined as Lineage-CD127+ cells. The CD161+ cells were selected as the total ILC gate. ILCs were further classified into ILC1, ILC2, and ILC3 subsets based on the expression of c-kit and/or CRTH2. Within the ILC3 subset, cells were further divided into NKp44-ILC3 and NKp44+ILC3 subsets based on NKp44 expression. (A) The percentages of total ILC, ILC1, ILC2, ILC3, and ILC3 subsets (NKp44+ILC3 and NKp44-ILC3) were analyzed in peripheral blood and lymph nodes of NSCLC patients and healthy subjects. (B) The median values are presented as bars. Statistical analysis was performed using the Mann Whitney U-test, and differences were considered significant when $p < 0.05$.

It is not only the number of NK cells present in the TME that influences antitumor immunity, but also the functionality of these NK cells. A population study conducted in Japan showed that patients with decreased NK cell cytotoxic activity have a higher probability of developing cancer.[24] Consistent with these findings, the current study showed a decreased ratio of cytotoxic $CD56^{dim}CD16^{bright}$ NK cells in the peripheral blood of NSCLC patients compared to healthy controls. Furthermore, we found a significant increase in exhausted $CD56^{dim}CD16^{-}$exhausted NK cells and a significant reduction in mature cytotoxic $CD56^{dim}CD16^{bright}$ NK cells in the mediastinal tumor draining lymph nodes of NSCLC patients. These findings suggest that cytotoxic and cytokine-secreting NK cells play crucial roles in antitumor immunity and are significantly diminished in NSCLC patients. The dominant NK cell subset observed in NSCLC patients is the exhausted NK cell phenotype. Overcoming NK cell exhaustion may represent a potential future treatment approach for NSCLC patients.

ILC1 cells play a vital role in promoting antitumor immunity by reducing the risk of progressive disease and the development of distant metastasis through their secretion of IFN-γ.[25] Verma et al[26], showed that ILC1 cells secreting IFN-γ are crucial for maintaining antitumor immunity, while ILC1 cells that produce low levels of IFN-γ possess tumor-promoting capabilities and are associated with a worse prognosis in patients with NSCLC. In our own investigation, we observed a significant decrease in the ratio of ILC1 cells in the peripheral blood and tumor draining mediastinal lymph nodes of NSCLC patients. These findings indicate that lower levels of ILC1 cells are linked to impaired antitumor activity.

ILC2 cells play important roles in type 2 immune responses, but their exact roles in anti-tumoral immunity are complicated and not fully understood. Recent studies have produced conflicting results, suggesting that ILC2 cells can have both anti-tumoral and tumor-promoting effects. Lung cancer, patients with a higher ratio of ILC2 cells have shown improved antitumor immunity and a decreased risk for distant metastasis.[27] However, in bladder cancer patients, pro-tumorigenic cytokines such as IL-4 and IL-13 secreted by ILC2 cells have been found to promote an immunosuppressive TME. This leads to a higher risk of recurrence and a poor prognosis.[28] In our current study, we demonstrated that a significantly higher ratio of ILC2 cells in the peripheral blood of NSCLC patients compared to healthy controls. This suggests that ILC2 cells may have tumor-promoting effects in NSCLC. Similar to our findings, Zhang et al. demonstrated in their study that the ratio of ILC2 cells in the peripheral blood and tumor tissue of NSCLC patients was higher compared to healthy controls.[29] Intriguingly, our study revealed that the ratio of ILC2 cells in tumor-draining lymph nodes was lower compared to the peripheral blood of NSCLC patients. Our findings suggest that higher ILC2 cells in peripheral blood of patients may have tumor promoting effects.

ILC3 cells comprise a significant subgroup of including NCR^{+}ILC3, NCR^{-}ILC3 and LTi cells. These cells have been found to exhibit dual effects, with both tumor-promoting and antitumor functions in different cancer types.[30] $NKp44^{-}$ILC-3 cells, which are a subset of NCR^{-}ILC-3 cells, are known to predominantly secrete IL-17. Studies have shown that IL-17-secreting NCR^{-}ILC3 cells can play a role in promoting tumor growth, particularly in a mouse model of hepatocellular carcinoma.[31] In human colorectal cancers, it has been observed that NCR^{-}ILC3 cells have tumorigenic functions and are associated with worse clinical outcomes.[32] Consistent with these previous observations, our study demonstrated that the ratio of NCR^{-}ILC-3 cells were higher in the peripheral blood and mediastinal lymph nodes of the patients compared to the controls. These findings suggest a potential role for NCR^{-}ILC3 cells in promoting tumor growth and progression in NSCLC. Recent evidence has revealed the crucial role of $NKp44^{+}$ILC-3 cells (NCR^{+}ILC-3 cells) in secreting IL-22 while exhibiting minimal expression of IL-17. It has been observed that tertiary lymphoid structures, primarily formed by NCR^{+}ILC-3 cells, and an increased infiltration of higher NCR^{+}ILC-3 cells within these structures are associated with early-stage tumors and improved prognosis.[13] Similarly, in this study we demonstrated that the ratio of NCR positive $NKp44^{+}$ILC-3 cells were lower in both peripheral blood and mediastinal lymph nodes of the patients compared to healthy controls.

One limitation of this study is the ethical consideration that prevents the excision of healthy mediastinal lymph nodes for direct comparison with the lymph nodes of NSCLC patients. Due to ethical constraints, it was not feasible to obtain healthy lymph nodes for analysis. Consequently, the study was unable to directly investigate the differences in ILC distribution between healthy and tumor draining lymph nodes, which could have provided valuable comparative insights.

On the other hand, a significant strength of this study lies in its comprehensive assessment of ILC distribution. By examining not only the peripheral blood but also the lymph nodes of NSCLC patients, the study offers a more holistic understanding of ILC involvement in the disease. Furthermore, the study benefits from incorporating the most current classification of NK cells, facilitating a clearer demonstration of the increased exhausted pattern observed in NSCLC patients. This comprehensive approach enhances the significance and relevance of the study's findings.

5. Conclusions

Our study demonstrated an increased exhausted phenotype of ILCs and a decreased ratio of effector ILCs in NSCLC. We observed a decreased ratio of ILC1 cells and $NKp44^{+}$ILC-3 cells, along with an increased ratio of $NKp44^{-}$ILC-3 cells, which suggests tumorigenic changes in the innate immune response of NSCLC. Similar to changes in ILCs, NK cells showed a significant functional change from cytotoxic phenotype to exhausted phenotype. These alterations may contribute to a shift in the TME from an antitumor state to a tumorigenic state for innate immune cells. However, further studies are needed to explore strategies for revitalizing ILCs and NK cell function and enhancing their antitumor capabilities in the context of NSCLC.

Acknowledgements

None.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by for this study the Cukurova University Institution Ethics Committee (2010-Thesis number 247902).

Conflict of interest statement

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

Funding source

This work was supported by the Research Fund of Istanbul University (Grant No: TOA-2017 20591).

Author contributions

Collection of the data, draft: MU, SS, Writing of the article,

performed the analysis, review of the literature: SY, EA, Critical review of the article, design of the study: HB,UT,EK

All authors read and approved the final manuscript.

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The Effect of Advancing Age on the Temporomandibular Joint Osteoarthritis Findings

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Abstract

Aim: The aim of this study is to evaluate temporomandibular joint osteoarthritis (TMJ OA) findings in elder patients with cone beam computed tomography.

Materials and methods: One hundred and sixty-seven patients (136 women, 31 men) participated in the study. Three hundred and thirty-four joints were evaluated in the study. According to the presence of OA, TMJs were divided into two groups as "with osteoarthritis" and "without osteoarthritis". When any of the osteoarthritis findings were present, the joint was included in the "with osteoarthritis" group. OA findings were listed as osteophyte, erosion, flattening, sclerosis and pseudocyst. Also, TMJs were divided into two age groups: Group 1 (50-64 years old) and group 2(65-81 years old) For statistical analysis, SPSS v20 were used.

Results: There was no significant difference between genders for the presence of OA (p>0.005). There were significant differences between group 1 and group 2 for erosion, flattening and sclerosis (p<0.005). There was no significant difference between group 1 and group 2 for osteophyte and pseudocyst (p>0.005).

Conclusion: Radiological findings like erosion, flattening and sclerosis can be seen more common with advancing age.

Keywords: *Osteoarthritis, cone beam computed tomography, geriatrics*

1. Introduction

Temporomandibular joint osteoarthritis (TMJ OA) is a subgroup of diseases which was under the umbrella term of temporomandibular disorders[1]. It is characterized by erosion, osteophyte formation, subchondral sclerosis, pseudocyst, flattening. It is known that osteoarthritis is an age-related disorder and more common in female patients compared to men[2,3]. Cone beam computed tomography (CBCT) is the method of choice to evaluate degenerative bone changes in TMJ due to osteoarthritis. It provides excellent diagnostic quality images with low-radiation dose compared to computed tomography[4]. Prevalence of TMJ OA in elder patients is not well documented in the literature. With the widespread use of CBCT, objective incidental findings began to be observed more frequently by clinicians. It was reported that available database on clinical examination for degenerative joint diseases is insufficient[5]. TMJ is one of the most commonly used joints in the human body and in close relationship with other vital functions such as chewing and speaking. Since TMJ OA may affect the quality of life of elder patients, the diagnosis and management should be performed carefully and objectively. The purpose of the present study is to evaluate TMJ OA findings in older patients with cone beam computed tomography.

2. Materials and methods

The presented retrospective study was carried out at Çukurova University Faculty of Dentistry Department of Dentomaxillofacial Radiology. It was approved by Çukurova University Clinical Researches Ethics Committee. A written consent form was obtained from all participants. Patients who had a CBCT scanning due to various reasons (scannings which include TMJ region) were included in the present study. Previous surgical procedures in temporomandibular joint, trauma, patients with rheumatic diseases (which can affect OA severity) and low-quality images with artefacts were listed as exclusion criteria.

One hundred and sixty-seven patients (136 women, 31 men) were included in the study. A total of 334 TMJs were evaluated in the study. The maxillofacial imaging of the patients was performed with CBCT device (Planmeca ProMax® 3D Mid, Helsinki, Finland; exposure parameters: 90 kV, 10 mA, 27 s scan time, voxel size: 0.4 mm3).

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Received: 05.07.2023, Accepted: 08.08.2023, Available Online Date: 31.08.2023
Cite this article as: Cabuk DS, Yuksel HD. The Effect of Advancing Age on the Temporomandibular Joint Osteoarthritis Findings. J Cukurova Anesth Surg. 2023; 6(2): 258-61. doi: 10.36516/jocass.1322183

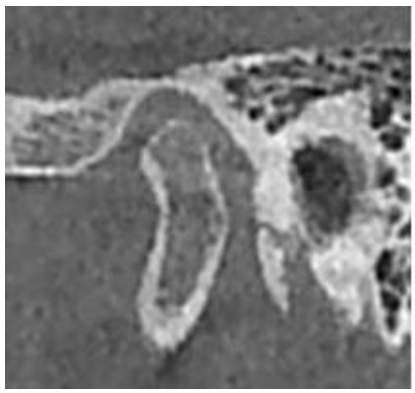

Figure 1
The view of a normal condyle in sagittal CBCT sections.

Image analysis were performed using the Planmeca, Romexis viewer software in a dark and quiet room. All categorical evaluations were performed by two maxillofacial radiologists with 20 days interval. The differences were discussed and reconsidered, and a consensus was reached.TMJs were classified into two groups as the osteoarthritis group and without osteoarthritis group. If any of the osteoarthritis findings were present, TMJ was included in the "with osteoarthritis" group. Osteoarthritic bone changes were examined according to the following definitions. Normal condyle was defined as mandibular condyle without any osteoarthritic findings (Figure 1).

Erosion was defined as the visible breaks of continuity in cortical bone. Osteophyte was defined as a bony exostosis developed on the margin of the condyle. Sclerosis was defined as increased thickness of cortical bone. Flattening was defined as the flat bony contour of mandibular condyle due to degenerative changes. Pseudocyst was defined as a radiolucent degeneration area in the subchondral trabecular bone.

According to patients' age groups, TMJs were divided into two groups: Group 1 consisted of patients younger than 65 years old. Group 2 consisted of patients aged 65 and older.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

2.5. Statistical Analysis

IBM SPSS 20.0 (IBM Corp., Armonk, NY) statistical program was used for statistical analysis. Significance level was determined as $p<0.05$. Categorical data were summarized as n (%), age data as mean±standard deviation. Possible associations between osteoarthritis findings and gender/age groups were analyzed by chi-square or Fisher's exact test. Inter-observer agreement was assessed by Kappa (κ) analysis.

3. Results

There was a high level of agreement for all categorical assessments [minimum κ value 0.92 ($p<0.001$)]. Demographic information is shown in Table 1.

Table 1
Demografic Data

Age groups	n	Number of joints (male/female)	Age
65 years<	234	(36/198)	57.41±4.37
65 years≥	110	(26/84)	69.97±4.69

Table 2
Osteoarthritis findings according to genders

		Genders			
		Female	Male	Total	p
Osteophyte	Absent	145(51.4)	33(53.2)	178(51.7)	0.797Ω
	Present	137(48.6)	29(46.8)	166(48.3)	
Flattening	Absent	205(72.7)	46(74.2)	251(73)	0.810Ω
	Present	77(27.3)	16(25.8)	93(27)	
Sclerosis	Absent	216(76.6)	42(67.7)	258(75)	0.145Ω
	Present	66(23.4)	20(32.3)	86(25)	
Erosion	Absent	174(61.7)	36(58.1)	210(61)	0.595Ω
	Present	108(38.3)	26(41.9)	134(39)	
Pseudocyst	Absent	266(94.3)	58(93.5)	324(94.2)	0.767§
	Present	16(5.7)	4(6.5)	20(5.8)	
Total		282(100)	62(100)	344(100)	

Data are shown as n (%). Ω Chi-square test. § Fisher's exact test.

Table 3
Osteoarthritis findings according to age groups.

		Age groups			
		65 years<	65 years≥	Total	p
Osteophyte	Absent	123(52.6)	55(50)	178(51.7)	0.657
	Present	111(47.4)	55(50)	166(48.3)	
Flattening	Absent	192(82.1)	59(53.6)	251(73)	<0.001*
	Present	42(17.9)	51(46.4)	93(27)	
Sclerosis	Absent	195(83.3)	63(57.3)	258(75)	<0.001*
	Present	39(16.7)	47(42.7)	86(25)	
Erosion	Absent	153(65.4)	57(51.8)	210(61)	0.016*
	Present	81(34.6)	53(48.2)	134(39)	
Pseudocyst	Absent	222(94.9)	102(92.7)	324(94.2)	0.428
	Present	12(5.1)	8(7.3)	20(5.8)	
Total		234(100)	110(100)	344(100)	

Data are shown as n (%). Chi-square test (*p<0.05).

Three hundred and thirty-four joints were evaluated. Table 1 shows the distribution of age and gender of the patients. While the mean age of group 1 was 57.41±4.37, the mean age of group 2 was 69.97±4.69.

Table 2 shows the distribution of osteoarthritis findings according to genders. There was no statistically significant relationship between gender and osteoarthritis findings.

The prevalences of flattening, sclerosis, and erosion were significantly higher in group 2 (46.4%, 42.7%, and 48.2%, respectively) compared to group 1(17.9%, 16.7%, and 34.6%, respectively) (p<0.001, respectively). p<0.001 and p=0.016). There was no statistically significant relationship between age groups and osteophytes and pseudocysts (Table 3).

4. Discussion

Epidemiological studies exhibited a high prevalence of temporomandibular disorder (TMD) for all age groups[6]. The prevalence of TMD is a matter of controversy in the literature. While some studies suggested that the frequency of TMD symptoms were similar among all age groups[7], other authors had found it lower in older people[8]. TMJ OA is one of the diseases under the umbrella term of TMD. It led clinicians to seek for a more objective assessment area. A clinical examination based diagnosis of OA is reported to be uncertain and unreliable[9].

Many imaging methods can be used to evaluate TMJ OA such as panoramic radiography, computed tomography and magnetic resonance imaging. CBCT, which has become increasingly popular in recent years, has been used as a reliable imaging method for the evaluation of TMJ OA[10]. CBCT provides high-quality images for the diagnosis of degenerative changes in TMJ with relatively lower radiation dose[11]. It was reported that CBCT is better to exhibit bony changes like bone destruction, cortical integrity changes, erosion, osteophyte and flattening[4,11]. In the presented study, CBCT is used due to above-mentioned features.

OA is the most common disease that can be observed in any joint including temporomandibular joint. It is an age-related disease in the articular cartilage and subchondral bone in synovial joints[12]. TMJ OA is known to have certain bone features like erosion, osteophyte, flattening, subchondral sclerosis and pseudocyst. Also, joint space narrowing, articular disc displacements may accompany this process[13].

Widmalm[14] and Ishibashi[15] reported that TMJ OA was more common in older patients compared to young patients. While only older patients were included in the present study, Kiliç et al.[10] included patients who were aged between 14-73 years old. Since osteoarthritis is an age-related disease, further studies should be conducted in the characterized osteoarthritis findings of older patients for different age groups.

In this study, no statistical difference was found between genders for the OA findings. A previous study reported that TMJ OA is more common in women due to the potential role of sex hormones[16]. Kiliç et al[10]. investigated 117 TMJs in their CBCT study. In controversy with our findings, they reported that OA was more common in female patients. This difference may be attributed to the study population and different methodology used.

The radiological findings of osteoarthritis were investigated in CBCT records in the present study. Significant differences were found between group 1 and group 2 for erosion, flattening and sclerosis. There was no significant difference between group 1 and group 2 for osteophyte, and pseudocyst. OA findings may display different stages of the degenerative disease. While erosion may indicate the acute phase of degenerative disease, sclerosis and flattening may indicate a bone repair stage[3]. According to the present study findings, erosion, flattening and sclerosis were found significantly higher in group 2.

There were some limitations to this study. First, male patients were lower in the study population. Also, the overall study population can be enlarged to a higher number. To identify different osteoarthritis stages (acute phase, chronic phase, reparative bone phase), an elder patient population with larger numbers should be evaluated. Another limitation is that the study was conducted in a

single center. Multicenter studies with more patients should be carried.

5. Conclusions

CBCT is a useful imaging modality to evaluate radiological findings of TMJ OA. In elder patients, erosion, flattening and sclerosis can be seen more common with advancing age.

Acknowledgements

None.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved was approved by Çukurova University Clinical Researches Ethics Committee. (Date: June 11, 2021; No:112).

Conflict of interest statement

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

Funding source

None.

Author contributions

All authors contributed to the study conception and design.

All authors read and approved the final manuscript.

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Investigation of the Effects of Pulsed Radiofrequency Application of the Thoracal Dorsal Root Ganglion on Postherpetic Neuralgia and Post-thoracotomy Pain Syndromes

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Abstract

Aim: The causative agent of herpes zoster (HZ) is the reactivated varicella-zoster virus. HZ leads to severe and painful rashes that can be accompanied by long-term pain, i.e., postherpetic neuralgia (PHN). According to the International Association for the Study of Pain (IASP), post-thoracotomy pain syndrome (PTPS) is defined as "recurrent or persistent pain along the thoracotomy incision at least two months after surgery"[8].

Methods: In this study, the medical records of all the patients were reviewed for age, gender, size, thoracic level, cause of pain, and visual analog scale (VAS) and DN4 scores from the patient files maintained in the archive of the Department of Algology. Two cycles of pulse radiofrequency (PRF) were administered for 2 min each. Then, a total of 5 ml of dexamethasone, lidocaine, bupivacaine, and isotonic solutions of 4 mg, 20 mg, 5 mg, and 5 mg, respectively, were added through the RF cannula at the DRG level in each application.

Results: In total, 40 patients, including 25 men (62.5%) and 15 women (37.5%), were analyzed in this study. The mean age of the patients was 60.5 ± 12.4 years, and the median duration of pain was 2 years (0.2–15 years). When PHN and PTPS groups were compared on the basis of the pain etiology, the VAS values before treatment were not statistically different (p = 0.129), whereas the VAS values after treatment were significantly lower in the PTPS group than in the PHN group (p = 0.001).

Conclusions: This study aimed to investigate the effectiveness of DRG PRF therapy on the causes of chronic thoracic pain and in different etiologies. The results revealed that PRF therapy is more effective in treating patients with PTPS than those with PHN. We also found that factors such as age, gender, and size did not significantly affect the treatment.

Keywords: *Postherpetic neuralgia, post-thoracotomy pain syndrome, pulsed radiofrequency*

1. Introduction

The causative agent of herpes zoster (HZ) is the reactivated varicella-zoster virus. This virus is known to cause dorsal root ganglion inflammation along with peripheral nerve and local tissue injury along the descending sensory nerve. HZ leads to severe and painful rashes in older patients; these rashes can be accompanied by prolonged pain, i.e., postherpetic neuralgia (PHN). The incidence of HZ has been reported to be 2.5–5.8/1000 person-years[1,2], and 5%–30% of these patients develop PHN[3]. Moreover, the incidence of HZ has been reported to be higher in people aged >50 years[4,7]. PHN exhibits a complex etiology and is difficult to treat; therefore, new treatment modalities need to be developed.

According to the International Association for the Study of Pain (IASP), post-thoracotomy pain syndrome (PTPS) is defined as "recurrent or persistent pain along the thoracotomy incision at least two months after surgery"[8]. The primary causes of PTPS include acute postoperative pain, surgery-related nerve damage, and changes in neuroplasticity in the central nervous system[9-12]. Management of PTPS is difficult, and several modalities, including epidural analgesia, preemptive gabapentinoids, and intravenous ketamine, can prevent its development. Antineuropathic medications and lidocaine or 8% capsaicin patches are used as the current standard treatment for PTPS[13,14]. However, pharmaco-

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Received: 20.05.2023, Accepted: 07.07.2023, Available Online Date: 31.08.2023
Cite this article as: Kucukbingoz C, Marufoglu F, Bayram T, et al. Investigation of the Effects of Pulsed Radiofrequency Application of the Thoracal Dorsal Root Ganglion on Postherpetic Neuralgia and Post-thoracotomy Pain Syndromes. J Cukurova Anesth Surg. 2023; 6(2): 262-6. doi: 10.36516/jocass.1299024

therapy may be inadequate for treating PTPS, and interventional pain procedures ranging from nerve blocks to nerve ablation and neuromodulation may be required[15-17].

The dorsal root ganglion (DRG) contains primary sensory afferent neurons. These neurons transmit peripheral nerve impulses to the spinal cord and central nervous system. Therefore, DRG has become a crucial target area for treating PHN and PTPS[1,9]. Pulse radiofrequency (PRF) uses intermittent (4*120 msec) RF current (300–500 kHz) for sufficient heat dissipation time for temperatures below 42°C to ensure preservation of the structure and function of nerve fibers[15]. This procedure has the following advantages: minimal invasiveness; monitoring of the electrical stimulation and measurement of impedance to locate specific nerves; neuromodulation effect that does not cause nerve damage or complications, such as decreased sensation and skin numbness; and easy repeatability of the treatment if needed. PRF has been widely applied in various painful conditions, including intractable lower back pain and joint pain[16-18]. However, the therapeutic effects of PRF reported in the literature are contradictory, and effective guidelines on the treatment parameters are still lacking[19].

This study aimed to retrospectively compare the effectiveness of DRG PRF treatment based on the visual analog scale (VAS) and Douleur Neuropathique 4 Questions (DN4) results in patients diagnosed with PHN and PTPS in the Cukurova University Algology Department between 2019 and 2022.

2. Materials and methods

The medical records of the patients were scanned for age, gender, size, thoracic level, cause of pain, and VAS and DN4 scores from the patient files in the archive of the Department of Algology. Patients included in the study were >18 years of age, with unilateral and neuropathic pain in thoracic dermatomes. (T2–T12). They were unresponsive to medical treatment and were suffering from pain for over 6 months. They had a VAS score of ≥5. The VAS and DN4 scores before and 1 month after Thoracal DRG PRF treatment were recorded and compared. For our study, we received the ethics committee decision numbered 6.1.2023-129 from the Cukurova University Ethics Committee.

Patients with local pathology, such as infection at the needle insertion site, and abnormal anatomy of the thoracic vertebrae, such as scoliosis or severe kyphosis; pregnant women; and patients with uncorrected coagulopathy and hypersensitivity to the drugs used in the procedure were excluded from the study.

The enrolled patients were taken to the pain intervention room that consisted of an anesthesia machine, monitor, fluoroscopy, and RF devices. They were placed on the surgical table in the prone position and basic monitoring (pulse oximetry, electrocardiogram, and noninvasive blood pressure) was performed. Oxygen was administered at a flow rate of 4 L/min. An intravenous cannula was inserted and 1 mg of dormicum was administered for sedation. Then, the thoracic spine was disinfected and draped. On counting from top to bottom, the first thoracic vertebra was identified by the characteristic features that distinguished it from the last cervical vertebra.

For the DRG PRF procedure, an anteroposterior (A–P) image was obtained. Then, the C-arm was caudocephally adjusted to align the endplate of the vertebra of interest. Later, the image of the rib was superimposed on the image of the transverse process, following which the C-arm was oriented obliquely by approximately 20–25 degrees. The skin entry point was determined just below the pedicle of the relevant level. The skin was infiltrated with 2 mL of 2% lidocaine at the entry point and a 22-G RF needle (10 cm) was inserted under the active straight tip, 1-cm C-arm (Figure 1). It was obtained so that the needle tip could be seen just behind the posterior border of the foramen when viewed from the side. In this position, 0.2 mL of radiopaque material was injected to observe it spread laterally under the pedicle, and the opaque material outlined the medial border of the pedicle and spread upward (characteristic image of a transforaminal epidural). After the opaque material was observed as a vertical line behind the foramen when viewed from the side, the sensory stimulation threshold at this point was aimed to be <0.5 volts in all cases. PRF was delivered for two cycles of 2 min each, with pulses of 20 ms every 500 ms (20 ms 500-kHz RF pulses delivered at a frequency of 2 Hz). The maximum temperature voltage was automatically set to 42°C. After the procedure, a total of 5 ml of dexamethasone, lidocaine, bupivacaine, and isotonic solutions of 4 mg, 20 mg, 5 mg, and 5 mg, respectively, were added through the RF cannula at the level of DRG in each application (Figure 2)

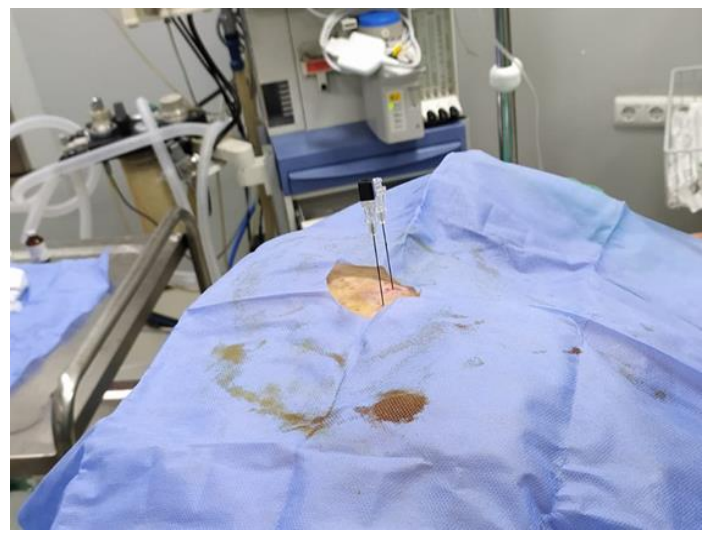

Figure 1
Thoracic DRG Skin Entry

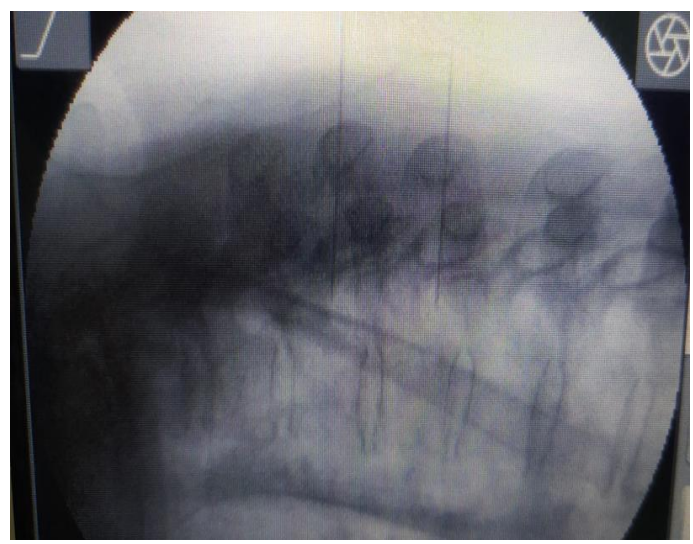

Figure 2
Thoracic DRG Skin Entry

2.1. Statistical analysis

Statistical analysis was performed using SPSS software (Version 25.0, SPSS Inc., Chicago, IL, USA). All numerical data are expressed as median values (Minimum-Maximum). For each continuous variable, normality was checked by Kolmogorov Smirnov and Shapiro-Wilk tests and by histograms. Comparisons between groups were applied using Kruskal Wallis test and post-analysis Mann Whitney U test were used for the data not normally distributed. Pre-post measures data were analysing Wilcoxson test and Repeated Measures Analysis for group comparison. Values of $p < 0.05$ were considered statistically

3. Results

This retrospective study analyzed data collected from patients with chronic pain in the thoracic region who had undergone thoracic DRG PRF treatment. In total, 40 patients, including 25 men (62.5%) and 15 women, (37.5%) were analyzed in this study. The mean age of the patients was 60.5 ± 12.4 years, and the median duration of pain was 2 years (0.2–15 years) (Table 1).

Table 1

Demographic and Clinical Characteristics of the Patients

	Min–Max	Mean ± SD	Median
Age	30–82	60,5 ± 12,4	62
Pain duration (years)	0,2–15	3,6 ± 3,9	2
Gender, n (%)			
• Men		25	62,5
• Women		15	37,5
Side			
• Right		19	47,5
• Left		21	52,5
Medical treatment			
• Gabapentin		21	52,5
• Pregabalin		19	47,5

A total of 23 patients had PHN (57.5%), 15 had thoracotomy pain (37.5%), and 5 (5%) had pain after video-assisted thoracic surgery (VATS). The mean time to treatment admission was 2 years (0.2–15 years). Patients with PHN and PTPS did not differ in terms of demographic characteristics (age, gender, and pain duration). The areas treated ranged from T2 to T12, with different levels and ranges for each patient. T6–T8 level was the most treated level (12 patients). The procedure was performed on the right side in 19 patients (47.5%) and on the left side in 21 patients (52.5%).

Table 2

Etiologic Distribution of Patients

Diagnosis	n	%
Postherpetic Neuralgia	23	57,5
Thoracotomy	15	37,5
VATS	2	5,0

VATS: Video-assisted thoracic surgery

Table 3

Effect of Thoracic DRG on VAS and DN4 Scores

	Before Procedure	After Procedure	P
VAS score	7(5-9)	3(0-7)	0,0001
DN4 score	5(2-7)	2(1-5)	0,0001

VAS: Visual analog scale, DN4: Douleur Neuropathique 4 Questions

After PRF treatment, the patients were re-evaluated at 1-month follow-up for the chronic analgesic effect. The mean VAS scores before and after the procedure were 7 (5–9) and 3 (0–7), respectively. The mean DN4 scores before and after the procedure were 5 (2–7) and 2 (1–5), respectively. The VAS and DN4 scores had decreased significantly after treatment in all patients ($p = 0.0001$) (Table 3). Regardless of gender and size, both in the PHN and PTPS groups, the VAS and DN4 scores of the patients decreased significantly ($p = 0.0001$). In other words, the VAS and DN4 scores of the patients decreased after treatment, regardless of their size and gender.When the correlations between other variables were analyzed, no statistically significant correlation was observed between age and pain duration until treatment and between pretreatment and post-treatment VAS and DN4 scores. However, a positive correlation was observed between VAS and DN4 scores after the treatment ($r = 0.66$, $p = 0.0001$). In summary, when VAS scores decreased after treatment, the DN4 scores also decreased significantly.

When the PHN and PTPS groups were compared based on the etiology of pain, no significant difference in the VAS scores before treatment was observed ($p = 0.129$), whereas the VAS scores after treatment were significantly lower in the PTPS group than in the PHN group ($p = 0.001$). When evaluated before and after treatment, the decrease in VAS score was found to be greater in the PTPS group than in the PHN group. When DN4 scores before and after treatment were evaluated, it was found that DN4 scores before the procedure were significantly lower in the PTPS group than in the PHN group ($p = 0.001$). Hence, the change in DN4 scores after the procedure was not statistically significant ($p = 0.162$) (Table 4).

Table 4

Effectiveness of Thoracic PRF DRG on Etiology

	Postherpetic Neuralgia	Thoracotomy	p	p*
VAS Before	8 (6–9)	7 (6–8)	0,129	0,016
VAS After	4 (1–7)	2 (1–5)	0,001	
DN4 Before	6 (5–7)	5 (2–6)	0,001	0,162
DN4 After	3 (1–5)	2 (1–3)	0,041	

4. Discussion

This study aimed to investigate the effectiveness of DRG PRF therapy on the causes of chronic thoracic pain and in different etiologies. The results revealed that PRF therapy is more effective in treating patients with PTPS than those with PHN. We also found that factors such as age, gender, and size did not have a significant effect on the treatment.

Radiofrequency treatments are applied to DRG for several different pain syndromes. Its popularity has recently increased because it is a clinically safe and effective treatment[20]. It can rapidly change the electrical field in neuronal membranes and alter electrolyte conduction and ongoing depolarization; these characteristics play a role in the treatment mechanism[21].

Severe PHN is persistent pain that is difficult for patients to tolerate[22]. In PHN, many inflammatory cells invade the DRG, and inflammatory mediators released from these cells cause central sensitization and pain. PRF therapy is also involved in the modulation of neuropathic pain by activating descending serotonergic and noradrenergic inhibitory pathways[23]. Because PRF therapy is a minimally invasive and selective targeted therapy, it can be used for PHN pain[24]. Utilizing these effects, PRF therapy has been applied in treating PHN. In a study by Ding et al., it was shown that DRG PRF treatment of PHN at different stages under computed tomography guidance was effective and safe. In addition, this treatment caused a significant decrease in the VAS scores of patients[25]. In a retrospective study of 58 patients with herpetic neuralgia, patients were divided into two groups, namely the early-stage patient group (within the first 90 days of the onset of shingles zoster) and the PHN patient group, and DRG PRF treatment was applied. There was a significant decrease in numerical rating scale scores after treatment in both groups[26]. In this study, it was found that the VAS and DN4 scores of the patients decreased significantly after DRG PRF treatment in the PHN patient group.

Post-thoracotomy pain can transform into chronic pain in 22%–67% of patients, depending on the surgical procedure. Considering the increase in the geriatric population and the increasing life expectancy of cancer patients, the treatment of chronic post-thoracotomy pain unresponsive to medical treatment gains importance. In a study of 49 patients with chronic thoracic pain after surgical interventions, such as thoracotomy, sternotomy, and mastectomy, the effectiveness of DRG PRF, intercostal nerve PRF, and medical therapy was compared. In the sixth week of follow-up, no difference among the treatments was observed. However, in the 3rd month of follow-up, the treatment success rate was significantly higher in the group receiving DRG PRF than in the group receiving intercostal nerve PRF and medical treatment[27]. In this study, the VAS scores decreased significantly in the PTPS group in the 1st-month follow-up after DRG PRF treatment. At the same time, when post-thoracotomy pain and PHN were compared, it was found that the decrease in VAS scores after treatment was greater in the post-thoracotomy pain group than in the PHN group. When DN4 scores before and after treatment were evaluated, it was found that DN4 scores before the procedure were significantly lower in the PTPS group than in the PHN group. Therefore, the change in DN4 scores after the procedure was not statistically significant.

In the pathophysiology of PHN, the fact that a viral agent occurs after a long DRG latency period may cause high pain severity and treatment resistance. On the other hand, in PTPS, there is a condition that develops secondary to surgery and occurs in a shorter time than PNH. We attribute the significant differences in the results of our study to this.

5. Conclusions

DRG PRF treatment is an effective and safe method for treating patients with PTPS and PHN. However, the higher treatment success in favor of the post-thoracotomy group can be explained by the difference in the pathophysiology of chronic pain. Further randomized controlled trials are needed to demonstrate the short and long-term analgesic effects of this treatment in different chronic pain syndromes.

Acknowledgements

None.

Statement of ethics

The study was approved from Cukurova University Ethics Committee (6.1.2023-129)and was conducted in accordance with the Declaration of Helsinki.

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

All authors contributed to the design and writing of the study. All authors reviewed and accepted the final version of the study.

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Is There a Structural Basis for Vasovagal Syncope? Cardiac Functions in Patients with Vasovagal Syncope

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Abstract

Aim: The pathophysiology of vasovagal syncope (VVS) is not completely understood. Some echocardiographic parameters have been defined to contribute to its pathophysiology. However. whether right atrial (RA) and right ventricular (RV) functions have any impact on development of VVS is not well known. In this study we aimed to evaluate the baseline echocardiographic parameters in patients with VVS with special focus on right ventricle and atrium functions.

Material and methods: We evaluated the medical records of 42 patients with VVS and 41 age and sex matched healthy subjects. Patients with at least two syncopal attack and positive head-up-tilt test were enrolled in the study. All medical records of echocardiography and head-up-tilt test were obtained.

Results: Among left ventricular function parameters, there were no significant difference between the groups. Right ventricle myocardial performance index (p= 0.003) and maximal pulmoner systolic flow velocity (PVmax) (p=0.03) were significantly differ between the groups. RAA was significantly larger (p=0.04) and the ratio of tricuspid filling velocities (E/A), (p=0.01) was significantly lower in VVS group.

Conclusions: The findings of the present study indicate a subtle RA diastolic dysfunction in patients with VVS. Decreased RA contribution to RV filling may cause a lower RV stroke volume which explains the lower PVmax values in our VVS group. All together, those findings may serve for a tendency to low output states and hypotension as in VVS.

Keywords: *vasovagal syncope, right ventricle, right atrium, head-up-tilt test*

1. Introduction

Syncope is a frequent clinical issue, with an occurrence rate of 1.3 to 2.7 per thousand population[1]. Vasovagal syncope (VVS) is the most frequent source of syncope and is also the most recurrent type. From a clinical perspective, these episodes can be either a single incident with an identifiable cause or a series of multiple episodes that needs thorough analysis. VVS is the most common reflex syncope in young patients. Clinical investigations demonstrate that the highest number of cases occur between the ages of 10 and 30[2,3]. Age-dependent differences in syncope epidemiology exist: neural-mediated mechanisms are more prevalent among the young, while cardiovascular causes are more common in the elderly. Elderly people tend to have cardiac issues, orthostatic and postprandial hypotension, and medication side effects as a cause of syncope, whereas VVS is less likely to be seen in this age group [4]. The diagnostic process is more convoluted in elderly patients and the prognosis is poor while in younger patients, VVS is more prevalent and the treatment is uncertain.

The pathophysiology of VVS is not fully understood. Basically, it is related to a drop in cerebral perfusion pressure that results in a syncope episode caused by a failure in the autoregulation of blood pressure and, ultimately, a transient loss of consciousness. Many complex and interrelated mechanisms are responsible. However, the most frequently emphasized mechanism is related to the reflex arc in the afferent and efferent nerve pathways of the autonomic nervous system, which is activated by an external stimulus. Increased cardiac contractility due to hypovolemia stimulates the vagal system, resulting in a decrease in heart rate, cardiac output, vascular resistance and a decrease in central blood pressure[5] .

Echocardiographic evaluation is an important part of the assessment of patients with syncope, but its use in the evaluation of patients with VVS is not common. Some echocardiographic parameters have been described to contribute to the pathophysio-

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Received: 20.07.2023, Accepted: 22.08.2023, Available Online Date: 31.08.2023
Cite this article as: Alpaslan E, Tas U,Tas S et al. Is There a Structural Basis for Vasovagal Syncope? Cardiac Functions in Patients with Vasovagal Syncope. J Cukurova Anesth Surg. 2023; 6(2): 267-71. doi: 10.36516/jocass.1330346

logy of VVS, such as reduced left atrial contribution to left ventricular filling, small left atrial size, small left ventricular size and increased left ventricular contractility[6,7]. There are limited studies in the literature on whether RA and right ventricular function influence the development of VVS[8] . There are limited demographic and clinical factors identified to predict VVS[9,10] . We used echocardiography as one of the predictive factors because it is simple and easily accessible. In our opinion, there are no studies investigating the relationship between VVS and cardiovascular function and evaluating this relationship as a predictive factor for right heart echocardiographic parameters. Therefore, in this study, we aimed to evaluate basic echocardiographic parameters in patients with VVS, with a particular focus on RV and RA function.

2. Materials and methods

2.1. Patient population

This retrospective study was designed and conducted in accordance with the Declaration of Helsinki and approved by an institutional ethics committee of Dokuz Eylül University (Date and decision number: 2023/14-29). Forty-two patients who had at least two syncope episodes without an apparent cause and who were admitted to our clinic between 2012 and 2015 and 41 age- and sex-matched healthy individuals as the control group were retrospectively evaluated. Personal information and medical history of the patients were obtained from medical records.

Subjects underwent routine cardiologic evaluation and complete physical examination, including evaluation for orthostatic hypotension and carotid hypersensitivity, followed by 12-lead electrocardiography and data recorded. Subjects underwent echocardiographic examination before the procedure. In all subjects, laboratory samples were taken after a 12-hour overnight fast to exclude metabolic abnormalities for syncope. In addition, neurological and psychiatric evaluations were performed by relevant departmental experts to exclude psychological/ neurological etiologies of syncope. Data were collected from all patients who met the criteria, had no proven cause of syncope and underwent the tilt table test. The data were then compared between the two groups

2.2. Exclusion criteria

Exclusion criteria (1) presence of structural heart disease, diabetes mellitus, hypertension, coronary artery disease, chronic kidney disease, chronic obstructive pulmonary disease, asthma, anemia, hyperthyroidism, hypothyroidism, goiter and other thyroid diseases; (2) Using drugs with potential chronotropic effects

2.3. Head-up Tilt Test

The protocol of the head-up tilt-test[11] applied to the patients was as follows: The patients were put in a supine position on the tilt table, and an intravenous catheter was inserted into the peripheral vein following a 6-hour fast. An electrocardiography was used for continual monitoring and BP readings were taken non-invasively with an automated cuff sphygmomanometer at 2-minute intervals. Initially, patients were lying down for 10 minutes and their vital signs including blood pressure and pulse rate (PR) were monitored at one-minute intervals. The table was slanted to the horizontal plane and subjects were angled in a 70-degree head-up position for 20 minutes, with their feet held in place by the foot board for assistance. Blood pressure, PR, and subjective symptoms were observed every 2 minutes to look for potential signs of hypotension or bradycardia. If a positive response was obtained during upright tilt, the protocol was terminated by returning patients to the supine position. If no positive response happened after this phase, patients were put back in supine position and 1 µg/min isoproterenol infusion was initiated. Subsequently, the head-up tilt of 70 degrees was repeated for 10 minutes. If a positive reaction was recorded, the subjects were laid down and the protocol was completed. A positive response (with or without concurrent isoproterenol infusion) was defined as follows: A sudden drop in systolic blood pressure to < 70 mm Hg or the development of syncope or presyncope with bradycardia (PR < 40/min), as well as the presence of relevant clinical symptoms in the patient.

2.4. Echocardiography

Transthoracic echocardiogram was executed with the Philips HD11XE and frequencies of 2.5 or 3.5 mHZ transducers with tissue velocity imaging according to the patient's age. The systolic pulmonary artery pressure was calculated by combining the estimated RA pressure with the maximum speed of tricuspid regurgitation. Ejection fraction was computed by means of M-mode echocardiography and the Teichholz technique[12]. Pulsed Doppler method was used for blood flow measurements through the heart valves (mitral, aortic, tricuspid and pulmonary): flow velocity (E) during early filling, flow velocity (A) during atrial contraction, and ejection time (ET) were measured, and then E/A was calculated. Tissue doppler imaging (TVI) measurements were measured from the basal segments of the lateral LV wall, septal wall and RV free walls. Mitral annular early (Em) and late (Am) diastolic velocity and tricuspid annular early (Et) and late (At) diastolic velocity were measured. The ratio between early mitral flow velocity and mitral annular early diastolic velocity (E/Em) and the ratio between early tricuspid flow velocity and tricuspid annular early diastolic velocity (E/Et) were calculated. RV myocardial performance index (RV MPI index) was calculated according to the following formula[13] (Figure 1).

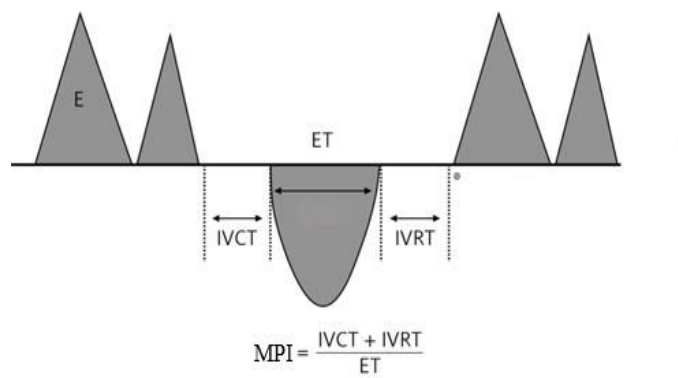

Figure 1

Method of MPI measurement. IVCT – isovolumetric contraction time, IVRT – isovolumetric relaxation time, ET – ejection time, AoVF – flow through aortic valve

2.5. Statistical analysis

Statistical Package for Social Sciences 22.0 software was used to carry out statistical analyses. (SPSS, Chicago, Illinois, United States of America). The Kolmogorov-Smirnov test was used to confirm whether the distribution of continuous variables was normal. According to the distribution pattern of continuous variables, the choice of independent sample t-test or Mann-Whitney U-test was made. Mean and standard deviation were utilized to express continuous variables while number and percentage were employed to express categorical variables, in accordance with the distribution pattern. Chi-square test was performed to analyze categorical variables. P value below 0.05 was taken as significant.

3. Results

The mean age of the patient group and the control group were 39.1±13.8 and 36.8±7.4 years, respectively. The patient group had a greater BMI than the control group, without any significant difference. The main clinical characteristics of the patients are presented in Table 1. Among the left ventricular function parameters, only two parameters differed between the groups: mitral early filling rate (E) (p= 0.007) was significantly lower and deseleration time (DT) (0.003) was significantly higher in the VVS group compared to the control group (Table 2). Right atrium area was significantly larger in the VVS group compared to the control group (p= 0.04). Similarly, RV MPI was significantly higher in patients with VVS compared to controls (p= 0.003). In addition, the ratio of maximal pulmonary systolic flow velocity (PVmax) (p= 0.004) and tricuspid filling velocities (E/A) (p= 0.01) were significantly lower in the VVS group. Except for the variables mentioned above, the right ventricular function parameters showed no significant difference between the two groups (Table 3).

Table 1

The baseline characteristics of the participants

	patient	control	P value
Age	39,1±13,8	36,8±7,4	0.126*
Sex (M, %)	12 (%28.6)	15 (%36.6)	0.43¥
Smoking (n,%)	11 (%26.2)	7 (%17.1)	0.31¥
BMI	25,3±3,1	24,5±3,7	0.13*

¥ Chi-square test, *Independent t-test, M: Men, BMI: Body mass index

4. Discussion

The primary findings of our study were as follows: (i) A slight degree of RV diastolic dysfunction and decreased RV outflow was common in in VVS patients and was associated with HRV, LV E/A ratio and RV MPI. (ii) Lower PVmax and higher RV MPI values were observed among the VVS group. (iii). There were no significant differences evaluating in terms of LV functions

Vasovagal syncope occurs as a reflection of decreased blood distribution to the brain. Different theories have been suggested to account for the hemodynamic transformations leading to syncope, such as ventricular theory, baroreflex malfunction theory, low blood volume theory, and neurohumoral theories, but the mechanism of VVS has not been clearly elucidated[14,15] . Echocardiographic examination has a great role in explaining the "ventricular theorem" which is considered to be the most common pathophysiologic cause of neurogenic syncope. Shaley et al. demonstrated a significant decrease in left ventricular systolic diameters and a significant increase in myocardial contractility in patients who experienced syncope with passive or isoproterenol provocation in the oblique table test compared to non-syncope or control group[16] . In the study by Moon et al.[17], echocardiography was performed during tilt table testing and left ventricular hypercontractility was observed immediately after passive tilting in patients who developed neurogenic syncope due to tilt table testing. In another study, patients were evaluated by strain echocardiography 6 months after tilt table testing. They found a decrease in myocardial strain as a predictor of positive tilt test[18]. In our study, echocardiography was performed at rest before the procedure. In line with the findings of Goel et al., we also found decreased RV function in patients with VVS compared to healthy controls. It is possible that VVS-prone individuals show a decreased myocardial tension at rest, but increased tension and contractility with provoking stimuli[8]. Based on the above mechanisms, the common approach to the treatment of VVS in syncope clinics is to increase dietary salt and water intake. On the other hand, there is not much proof to corroborate this strategy. Bellard et al.[19] suggested that this strategy may be explanatory in the short term, but increased hydration alone does not improve orthostatic intolerance. The other approach that may help VVS is various physical therapies and maneuvers. One of these is exercise training. The evidence for the effectiveness of exercise training in the prevention of syncope is inconclusive, yet its ability to increase blood volume and change baroreceptor function is evident [20,21] .

Table 2

The comparation of LV functions between the groups

	Patient	Control	P value
LVESD	27 ± 6	26 ± 5	0.07*
LVEDD	44 ± 7	44 ± 6	0.59*
LAA	15.5 ± 2.8	15.0 ± 2.5	0.41*
Mitral E/A	1.2 ± 0.34	1.6 ± 1.1	0.20*
LV Em	7.2 ± 2.8	7.0 ± 1.7	0.67*
LV Sm	9.0 ± 3.0	9.6 ± 3.9	0.39*
Mitral E	82.2 ± 21.2	93.2 ± 13.6	0.007*
Mitral DT	150.8 ± 28.3	129.2 ± 33.3	0.003*

*Independent t-test, DT: Decelaration time, E: Transmitral early diastolic wave velocity, E/A: The ratio of transmitral early and late diastolic wave velocity. Em: Mitral annular early diastolic wave velocity, LAA: Left atrium area, LV: Left ventricle, LVESD: Left ventricular end systolic diameter, LVEDD: Left ventricular end diastolic diameter, Sm: Systolic motion, VVS: Vasovagal syncope

Table 3

The comparation of RV functions between the groups

	patient	control	P value
RV E/A	1.1 ± 0.44	1.4 ± 0.35	0.01*
RAA	13.9 ± 3.3	12.6 ± 2.5	0.04*
PVmax	0.9 (0.2)	1.0 (0.2)	0.004#
TAPSE	22.4 ±2.8	23.3 ± 2.5	0.13*
RV Sm	14.6 ± 3.6	14.0 ± 3.2	0.46*
RV Em	4.7 ± 1.02	4.4 ± 1.2	0.32*
RV MPI	0.50 ± 0.13	0.42 ± 0.03	0.003*

*Independent t-test, #Mann Whitney-U test, Em: Tricuspid annular early diastolic wave velocity, E/A: The ratio of transtricuspid early and late diastolic wave velocity, MPI: Myocardial performans index, RAA: Right atrium area, PVmax: Maximum pulmonary flow velocity, TAPSE: Tricuspid Annular Plane Systolic Excursion, RV: Right ventricle, Sm: Tissue Doppler systolic motion, VVS: Vasovagal syncope

Isometric exercise has been shown to improve arterial blood pressure and cardiac output[22-24] . The basis of these therapeutic approaches is to increase blood flow to the heart and blood flow to the end organs. When the above-mentioned therapeutic approaches are considered together, one of the main problems is RV diastolic function, RA size and function, which can lead to decreased venous return and cardiac output. In this study, we found that the RAA was significantly larger than in the control group. Besides atrial fibrillation, any change in right ventricular function can cause volume overload, increased pressure and enlargement of the RA. We found that the ratio of tricuspid filling rates (Et/At), which is an indicator of right ventricular diastolic function, was lower in patients with VVS. Sotiriadou et al.[25] suggested that the contribution of the atria to ventricular filling is higher in young people and atrial function is better than in older people. In contrast to Sotiriadou et al, we found differences in RV function between similar age groups in our study. We found that the RV MPI value, an indicator of global right ventricular function, was higher in patients with syncope than in controls. This result suggests that right heart function is worse in patients with positive oblique table test. This results in a much stronger preload reduction, probably due to any reduction in mechanical function, and hence syncope. During the tilt-table test, LV contractility is already increased and diameters are shortened. In patients with RV dysfunction, volume overload and increased pressure in the atria worsen this condition and increase the tendency to syncope. We also found that Et/At and PVmax, indicators of RV function, were significantly lower in patients with VVS. The enlargement of RA in patients with VVS compared to controls may be explained by decreased RV function. Inconsistent findings regarding the response to blood volume expansion in patients with VVS have been reported in the literature. These inconsistent findings support the suspicion that there may be another pathophysiologic mechanism rather than volume deficit.

Our study has some limitations. Most importantly, it included a small number of patients and was single centered. Secondly, echocardiography was performed before the procedure. Since echocardiography was not performed during the tilt table test, we do not have data on cardiac function during the procedure.

5. Conclusions

This research points to a slight degree of RV diastolic dysfunction in VVS patients, which likely reduces the RV stroke volume due to the lesser RA contribution to RV filling, thus elucidating the lower PVmax values observed among the VVS group. Taken as a whole, these results may lead to conditions of reduced cardiac output and hypotension, such as in VVS. Further research is required to gain a better understanding.

Acknowledgements

None.

Statement of ethics

The study was approved from Dokuz Eylul University Ethics Committee (2023-14-29) and was conducted in accordance with the Declaration of Helsinki.

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

EA, data collection, literature review, writing of the study, UT, hypothesis, data collection and statistics, writing of the study, ST, data collection, writing of the study, literature review, hypothesis.

All authors reviewed and accepted the final version of the study.

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Protective Effect of Taxifolin in The Prevention of Cardiac Tissue Damage in Liver Ischemia and Reperfusion Injury: Experimental Study

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Abstract

Aim: Liver ischemia and reperfusion (I/R) is a serious, irreversible health problem in clinical practice. Taxifolin (Tax) is an easy to obtain and use agent found in maritime pine bark, Douglas fir bark and Siberian larch wood. In this study, we examined the protective efficacy of Taxifolin in the correction of cardiac tissue damage that may develop in liver I/R damage.

Methods: In our study, a total of 28 Wistar Albino rats, 8-10 weeks old, weighing 250-300 grams, were used. Group 1 (n=7): control group, Group 2 (n=7): Tax group with 50 mg/kg dose orally for 3 weeks, Group 3 (n=7): Liver I/R group for 30 minutes ischemia and 120 minutes of reperfusion were performed. Group 4 (n=7): Tax+Liver I/R group.

Results: In our study, MDA analysis was performed to evaluate oxidative stress. In the statistical analysis of MDA values, we observed that there was a statistically significant difference between the serum MDA values of the Tax group and the Tax+Liver I/R group, and the MDA level of the Tax group was lower ($p<0.05$). In myocyte damage scoring, we observed that the liver I/R group had the highest damage score, while the damage score of the Tax+Liver I/R group was significantly lower than the I/R group ($p<0.05$).

Conclusion: As a result of our study, we observed that there was an increase in serum MDA levels as a result of liver I/R and histopathological changes occurred in the heart tissue. However, Taxifolin has been successful in ameliorating this situation.

Key Words: *Taxifolin, Oxidative Stress, Liver ischemia and reperfusion, Heart*

1. Introduction

Ischemia and reperfusion consist of two stages. While hypoxia and cell damage occur during ischemia, oxygen is provided again during reperfusion[1]. For example, it occurs during liver transplantation (cold ischemia period after resection until reanastomosis is performed) and liver resection, after which many mechanisms are activated[2]. Numerous cellular components and mediators are involved in its mechanism. These include reactive oxygen species (ROS), neutrophil infiltration and microcirculatory failure[3,4]. The resulting toxic products cause damage in distant organs such as the lung, heart, brain and kidneys and may lead to multiple organ failure that may require long-term intensive care follow-up[5,6]. Liver ischemia and reperfusion (I/R) may cause irreversible serious health problems in clinical practice[7]. Flavonoids are widely used plant-based agents due to their wide distribution and strong antioxidant properties[8]. Dihydroflavonols, which are among flavonoids, are effective in the elimination of ROS. Taxifolin is one of the dihydroflavonols[9]. Taxifolin (Tax) is an easy-to-obtain and easy-to-use agent found in maritime pine bark, Douglas fir bark, Siberian larch bark, citrus fruits, grapes, olive oil and onions[10]. In this study, we investigated the protective efficacy of Taxifolin in the correction of cardiac tissue damage that may develop in liver I/R injury.

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Received: 23.05.2023, Accepted: 27.07.2023, Available Online Date: 31.08.2023
Cite this article as: Bilge H, Yildizhan I, Ulger BV, et al. Protective Effect of Taxifolin in The Prevention of Cardiac Tissue Damage in Liver Ischemia and Reperfusion Injury: Experimental Study. J Cukurova Anesth Surg. 2023;6(2):272-5. doi:10.36516/jocass.1300968

2. Materials and methods

For this study, ethics committee approval was obtained from Dicle University Animal Experiments Local Ethics Committee (DÜHADEK) with protocol number 2023/03.

2.1. Liver I/R Surgery Protocol

The rats were anesthetized with 90 mg/kg intramuscular Ketamine hydrochloride (Ketalar; Pfizer, Istanbul, Turkey) and 10 mg/kg Xylazine (Rompun; Bayer, Istanbul, Turkey) under aseptic conditions before surgical procedures in the liver I/R group. The abdominal hair of the rats was shaved and whisked with iodine solution. After midline laparotomy, the portal triad (hepatic artery, portal vein and common bile duct) was clamped with a microvascular clamp. Complete hepatic ischemia was maintained for 30 minutes and then the lamps were removed and 120 minutes of reoxygenation (reperfusion) was ensured[11-13].

2.2. Preparation of Taxifolin

Taxifolin (Evalar, Russia) was obtained and administered orally with a dose of 50 mg/kg in 1 cc saline for 21 days[14].

2.3. Setting of Experimental Groups

A total of 28 Wistar Albino rats with an average age of 8-10 weeks and weighing 250-300 grams were used in our study. The rats were housed in steel cages with 12 hours of light and 12 hours of daylight and were fed freely without feed and water restriction[15].

Group 1 (n=7): Control group; rats were given saline orally by 1 cc gavage for 3 weeks.

Group 2 (n=7): Tax group; 50 mg/kg dose in 1 cc saline was administered orally by gavage for 3 weeks,

Group 3 (n=7): Liver I/R group; On the first day of the experiment, liver tissues were subjected to 30 minutes of ischemia followed by 120 minutes of reperfusion by applying the appropriate surgical protocol.

Grup 4 (n=7): Tax+Liver I/R group; Taxifolin was administered orally by gavage with a dose of 50 mg/kg in 1 cc saline for 3 weeks. At the end of the 3rd week, liver tissues were practiced to 30 minutes of ischemia followed by 120 minutes of reperfusion by applying the appropriate surgical protocol.

At the last of the 3rd week, all experimental animals were sacrificed by exsanguination of the heart. The heart tissues were placed in 10% formaldehyde solution and sent to the Histology laboratory. Blood samples were centrifuged at 4500 rpm for 5 minutes, separated into serum and sent to the biochemistry laboratory for biochemical analysis.

2.4. Measurement of Serum Malondialdehyde (MDA) Values

Serum MDA analysis was performed as shown in the study by Kei S[16]. MDA consequence was defined as nmol/mg protein.

2.5. Histopathological examinations

Heart tissues were fixed in 10% Formaldehyde, washed in tap water for 12 hours after fixation and the tissue samples were passed through increasing series of alcohol (50-70-80-96% alcohol) for dehydration. After embedding in paraffin blocks, 5 µm thick sections were taken, stained with Hematoxylin & Eosin (H&E) and visualized with a rotary micro-tome (Leica Biosystems, USA).

Detected myocardial degeneration was evaluated between 0 and 3 points[17]. The severity of damage was graded as follows: 0 (normal): no degeneration of myocytes, 1 (mild): few degenerated myocytes, 2 (moderate): around 50% myocyte degeneration, 3 (severe): more than 50% myocyte degeneration.

2.6. Statistical Analysis

Statistical analysis of the data was performed using SPSS for Windows version 20 (SPSS Inc., Chicago, IL, USA) statistical program.. Kruskal Wallis-H test was used to the scoring values that did not show normal distribution, and Mann Whitney-U test was maked between paired groups for the discriminations between the significant variables. A value of $p<0.05$ was considered significant.

3. Results

3.1. MDA Analysis

In our study, MDA analysis was performed to evaluate oxidative stress. The graphical change obtained as a result of this is given in Figure 1.

In the statistical analysis of MDA values, we examined that there was a markedly significant difference between the serum MDA values of the Tax group and the Tax+Liver I/R group, and the MDA level of the Tax group was lower ($p<0.05$). We observed that administration of Tax for 21 days before liver I/R positively affected the serum MDA levels of rats (Figure 1).

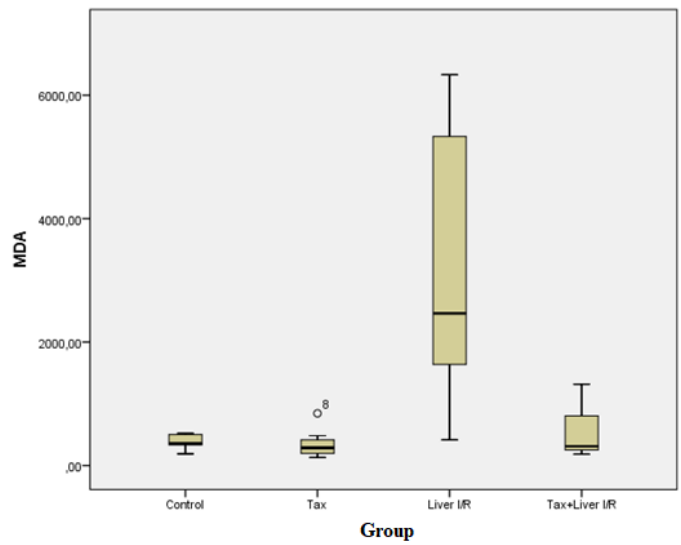

Figure 1

Graphical distribution of the mean MDA analysis of the groups.

3.2. Histologic Evaluation

Mean±standard deviation values of myocyte damage detected by light microscopic examination of heart tissues are given in Table 1.

In myocyte damage scoring, the highest damage scoring was observed in the liver I/R group, while the damage scoring of the Tax+Liver I/R group was markedly lower than the I/R group ($p<0.05$).

Table 1

Statistical difference of myocyte damage between groups and Mean±Standard deviation values of damage scoring.

Groups	Myocyte Injury Scoring
Control	0.28±0.48c,d
Tax	0.42±0.53c,d
Liver I/R	2.71±0.48a,b,d
Tax+Liver I/R	1.57±0.53a,b,c

Tax; Taxifolin group, I/R; Ischemia and Reperfusion group, a; different from control group, b; different from Taxifolin group, c; different from liver I/R group, d; different from Taxifolin+ Liver I/R group ($p<0.05$).

Nevertheless, there was no significant difference between the damage scoring of the control group and the Tax group ($p>0.05$) (Table 1).

When we researched the histopathologic changes in the heart

tissue, the light microscopic images of the control group and Tax group were found to be normal. In the heart tissues of the liver I/R group, hemorrhage, congestion, damage to myocytes and pyknotic appearance were observed. However, in the Tax+Liver I/R group, these histopathologic changes decreased but did not completely disappear. In terms of statistical scoring, it had a lower score than the Liver I/R group (Figure 2).

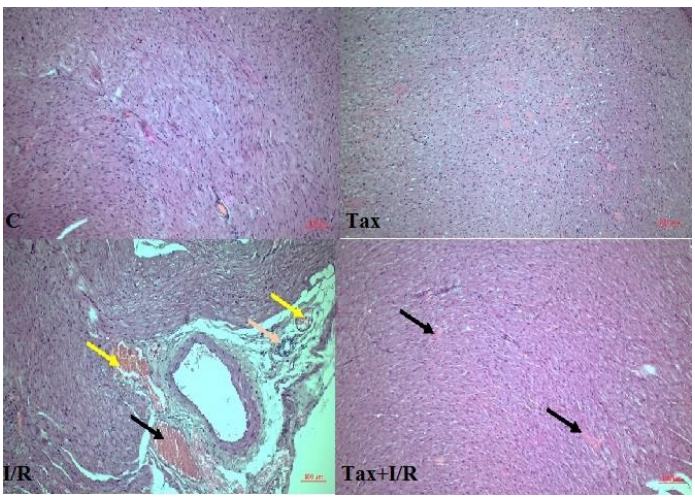

Figure 2

C; Control, I/R; Liver ischemia and reperfusion, Tax; Taxifolin group. Heart tissues of the control group and Taxifolin group appear normal. Mononuclear cell infiltration (orange arrow), congestion (black arrow), hemorrhage (yellow arrow) and pyknosis and degeneration of myocytes in the tissues of the liver I/R group (H&E, 100µm).

4. Discussion

Since there is no substance with a proven effect in reducing oxidative stress due to liver I/R injury, studies on this subject have been ongoing for a long time[18]. Free radicals released due to increased oxidative stress cause various diseases[19]. The pathologic conditions that occur induce the electron transport chain of mitochondria and lead to the formation of large amounts of superoxides, which in turn cause cardiomyocyte damage and increase the likelihood of developing acute myocardial infarction[20,21].

Seker U et al. showed that MDA levels in the testicular I/R group were higher than the other study groups in their study[22]. Similarly, Hüseyin O et al. observed that the MDA levels of the group in which brain trauma was induced were higher than the other study groups[23]. In our study, serum MDA levels in the group that underwent liver I/R were higher than the other study groups.

Taxifolin is a flavonoid found in milk thistle plant and onion and is an antioxidant and anti-inflammatory agent with protective effect against liver I/R injury[24,25]. In one of the studies on Tax, cerebral I/R was induced and it was examined that it inhibited the free radicals released during the apoptosis phase[26]. It is also known to have anticancer and neuroprotective effects[27]. Zhou et al. reported that Taxifolin has high antioxidant capacity in their study[28]. In another study, Eken H. et al. It was shown that there was an improvement in serum MDA levels in the taxifolin-treated group against liver I/R injury and that there was a difference between the taxifolin group and the sham group[29]. In our study, Taxifolin showed efficacy in successfully correcting MDA levels, which is a free radical marker released due to liver I/R injury. Moreover, our findings were consistent with the histopathologic results. Taxifolin showed protective activity in the successful recovery of liver I/R-induced myocyte injury in cardiac tissue.

5. Conclusions

In this study, it was examined that serum MDA levels increased and histopathologic changes occurred in the heart tissue as a result of liver I/R. However, Taxifolin has successfully shown efficacy in correcting this condition.

Acknowledgements

None.

Statement of ethics

The study was approved by the University of Toros University Ethics Committee (September 2022/156) and was conducted in accordance with the Declaration of Helsinki.

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

All authors contributed to the design and writing of the study. All authors reviewed and accepted the final version of the study.

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The Evaluation of The Presence of Colonic Diverticulum in Patients with Abdominal Aortic Aneurysm

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Abstract

Aim: The evaluation of the relationship between the aortic aneurysm and colonic diverticulum in the tomography images of the patients followed-up for abdominal aortic aneurysm

Methods: The tomographic images of 97 patients (Female/Male:20/77) aged between 40-88 years with/without abdominal aortic aneurysm and colonic diverticulum were analyzed. Abdominal aortic diameters were analyzed by categorizing them as 20-29 mm, 30-49 mm, and 50 mm over, and the presence of colonic diverticulum in the abdominal aorta with these diameters. The presence of plaque, narrowing, and dilatation in ascending, descending, and abdominal parts of the aorta was evaluated, and the levels of arterial plaque, narrowing, and stenosis in the inferior and superior mesenteric arteries supplying the intestine were assessed.

Results: The rate of colonic diverticulum was found to be significantly lower in the tomographic images of the patients with normal abdominal aortic diameter. It was found that the frequency of colonic diverticulum increased as the abdominal aortic diameter increased from 29 mm to 50 mm and above.

Conclusion: The probability of detection of colonic diverticulum increases as the diameter of the abdominal aorta increases.

Keywords: *Abdominal aortic aneurysm, colonic diverticulum, tomography*

1. Introduction

An abdominal aortic aneurysm (AAA) is a disease characterized by progressive enlargement of the abdominal aorta. The aneurysm may be initially asymptomatic. Subsequently, various gastrointestinal complaints may develop. Endoscopic examination performed to clarify these complaints may reveal the presence of colonic diverticulum due to hypoperfusion that takes place in the etiology of the aneurysm. Aneurysm pathophysiology is degeneration in the aortic wall, weakening of the connective tissue, loss of elasticity, and consequently, dilatation secondary to inflammation. There is a relationship between atherosclerosis and aneurysm development[1]. The development of aneurysm involves vascular wall weakening due to wall degeneration and aortic wall enlargement due to dilatation[2]. Atherosclerosis and secondary degeneration develop in the majority of aneurysms as age advances. The pathological aging process presents intimal thickening, lipid deposition, calcification, and eccentric fibrosis. That leads to the weakening of the vascular wall and dilatation. Abdominal aortic aneurysm usually begins infrarenally beneath the diaphragm and continues until the bifurcation of common iliac arteries[3].

Diverticulum is characterized by an outpouching of the gastric or intestinal wall[4]. Diverticula are the mucosal outpouchings acquired due to gastrointestinal peristaltic contractions and high intraluminal pressures. The mucosal and submucosal layers of the gastrointestinal system wall are protruded. Colon is the most common location of the diverticula in the gastrointestinal system[5]. The second most common location is the duodenum[6]. Diverticular disease may be symptomatic with complications such as acute diverticulitis or diverticular hemorrhage, or it may develop asymptomatically. Acute colonic diverticulitis is seen in approximately 10-25% of the patients[7]. Diverticula may be coincidentally detected and diagnosed, or encountered by endoscopy performed for colonic diverticula. Tomography is not a routine procedure in the diagnosis of a diverticulum. However,

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Received: 28.05.2023, Accepted: 10.08.2023, Available Online Date: 31.08.2023
Cite this article as: Cakirkose O, Dulder AC,Seven D, et al. The Evaluation of The Presence of Colonic Diverticulum in Patients with Abdominal Aortic Aneurysm. J Cukurova Anesth Surg. 2023;6(2):276-9. doi:10.36516/jocass.1298353

tomography must be performed in the presence of acute diverticulitis[7]. In contrast, tomography is routinely performed for follow-up of aortic aneurysm. Colonic diverticulum and abdominal aortic aneurysms are initially asymptomatic, and both are frequently seen in the 5th and 6th decades. The relationship between aortic aneurysm and diverticulum has been shown in the literature[8]. However, no study reported comorbidity of abdominal aortic aneurysm and colonic diverticulum was found in the literature. The presence of colonic diverticulum in patients presenting with the clinical picture of abdominal aortic aneurysm and diagnosed by tomography contributes significantly to the diagnosis and treatment of the disease. Aortic wall weakness, endothelial malnutrition, and the mechanism alteration caused by inflammation and hypoperfusion may predispose to the development of diverticulum due to alterations in the vascular structures that supply the stomach.

We encountered the presence of colonic diverticulum in the tomographic images of most patients followed-up for abdominal aortic aneurysm. We hypothesized that aortic wall weakening, endothelial malnutrition, the alteration mechanism due to inflammation, and hypoperfusion, as etiological factors for aortic aneurysm, may predispose to the development of diverticulum due to alterations in the vascular structures that provide colonic perfusion. Hence, we analyzed the tomographic images of the patients with aneurysm concerning the colonic diverticulum.

2. Materials and methods

Our study analyzed 97 patients admitted with clinical picture of aortic aneurysm to the Department of Cardiovascular Surgery between 2019-2021. Those were the patients with aortic aneurysm aged between 40-88 years that were recently diagnosed or followed up. We analyzed the abdominal tomographic images of the patients with aneurysm concerning the colonic diverticulum (Table 1). We assessed the severity of aortic narrowing and stenosis as well as the severity of plaque, narrowing, and stenosis (Table 2) in the superior and inferior mesenteric artery (SMA and IMA) branches of the abdominal aorta that supply the intestine.

Twenty of the patients included in our study were those were initially admitted to the General Surgery Clinic with a diagnosis of diverticulitis and were evaluated for aorta by tomography.

2.6. Statistical Analysis

We analyzed study data using SPSS Version 21 software package. We applied the t-test and Chi-Square test for the variables with normal distribution according to the distribution normality analysis of the obtained data. We determined the statistical significance level as the p value= 0.05. We interpreted the $p<0.05$ value as the presence of a statistically significant difference, whereas we evaluated the $p>0.05$ value as the absence of a significant difference.

Table 1

Statistical difference of myocyte damage between groups and Mean±Standard deviation values of damage scoring.

		DIVERTICULUM (D)						Chi-Square Analysis	
		D		D-NO		Total			
		n	%	n	%	n	%	Chi-Square	p
Ascending Aort Diameter	30-39 mm (Normal)	30	75,0	10	25,0	40	100,0	2,5	0,287
	40-49 mm (aneurysm)	34	72,3	13	27,7	47	100,0		
	50+	5	50,0	5	50,0	10	100,0		
	Total	69	71,1	28	28,9	97	100,0		
Plate Degree	No plate	38	66,7	19	33,3	57	100,0	0,735	0,391
	little	30	76,9	9	23,1	39	100,0		
	Total	68	70,8	28	29,2	96	100,0		
Descending Aort Diameter	-30 mm	19	65,5	10	34,5	29	100,0	-	0,691
	30-50mm	46	73,0	17	27,0	63	100,0		
	50+ mm	4	80,0	1	20,0	5	100,0		
	Total	69	71,1	28	28,9	97	100,0		
Plate	no	12	66,7	6	33,3	18	100,0	0,031	0,861
	yes	57	72,2	22	27,8	79	100,0		
	Total	69	71,1	28	28,9	97	100,0		
Abdominal Aort Diameter	20-29 mm	19	55,9	15	44,1	34	100,0	6,03	0,047
	30-49 mm	27	81,8	6	18,2	33	100,0		
	50+ mm	23	76,7	7	23,3	30	100,0		
	Total	69	71,1	28	28,9	97	100,0		

$p<0.05$ statistically significant

Table 2
Relationship between abdominal vascular nutritional status and presence of colonic diverticulum

		DIVERTICULUM						Chi-Square Analysis	
		D		D-NO		Total			
		n	%	n	%	n	%	Chi-Square	p
	no	3	50,0	3	50,0	6	100,0		
	yes	58	71,6	23	28,4	81	100,0		
Plate	middle	4	66,7	2	33,3	6	100,0	-	0,408
	heavy	4	100,0	0	0,0	4	100,0		
	Total	69	71,1	28	28,9	97	100,0		
	no	42	71,2	17	28,8	59	100,0		
	little	21	75,0	7	25,0	28	100,0		
Gastrointestinal Impact Number	middle	5	62,5	3	37,5	8	100,0	-	0,905
	heavy	1	50,0	1	50,0	2	100,0		
	Total	69	71,1	28	28,9	97	100,0		
	no	42	71,2	17	28,8	59	100,0		
Gastrointestinal Impact Number	yes	27	71,1	11	28,9	38	100,0	0	1
	Total	69	71,1	28	28,9	97	100,0		
	no	30	63,8	17	36,2	47	100,0		
Sma Plate	yes	39	78,0	11	22,0	50	100,0	1,7	0,189
	Total	69	71,1	28	28,9	97	100,0		
	yok	30	63,8	17	36,2	47	100,0		
	little	31	75,6	10	24,4	41	100,0		
Sma Plate %	middle	7	87,5	1	12,5	8	100,0	-	0,389
	heavy	1	100,0	0	0,0	1	100,0		
	Total	69	71,1	28	28,9	97	100,0		
	no	45	71,4	18	28,6	63	100,0		
İma Plate	yes	24	70,6	10	29,4	34	100,0	0,008	0,931
	Total	69	71,1	28	28,9	97	100,0		
	plate no	45	71,4	18	28,6	63	100,0		
	little	2	40,0	3	60,0	5	100,0		
İma Plate %	middle	5	100,0	0	0,0	5	100,0	-	0,378
	heavy	3	75,0	1	25,0	4	100,0		
	fully obstructed	14	70,0	6	30,0	20	100,0		
	Total	69	71,1	28	28,9	97	100,0		

p>0.05 not statistically insignificant SMA: superior mesenteric artery, İMA: inferior mesenteric artery

3. Results

The rate of diverticulum (D) in those with an abdominal aortic diameter of 20-29 mm was found to be significantly lower than the groups with an abdominal aortic diameter of 30-49 mm and 50+ mm (Table 1) (p<0.05). Aortic degeneration may start with endothelial malnutrition, atherosclerosis, and plaque formation and progress to narrowing and stenosis.

There was no relationship between the presence/absence of plaque and the presence of diverticulum (p>0.05). We determined no relationship also between normal and aneurysmatic diameters Dilatation and aneurysmatic wall weakness may develop a progressive process. In this respect, the presence of colonic diverticulum was evaluated based on the severity of plaque formation in vascular involvement and the degree of dilatation across several diameters. of ascending and descending aorta with the formation of the diverticulum (p>0.05). On the other hand, there was no relationship between the normal abdominal aortic diameter of 20-29 mm and the development of a diverticulum, whereas the detection rate increased as abdominal aortic diameter (30-49mm,

50+ mm) increased. We found this relationship statistically significant ($p<0.05$). Increased pressure, as one of the etiological factors in the development of an aneurysm, may be associated with increased colonic intraluminal pressure that leads to the development of the diverticulum (Table 1).

We evaluated vascular involvement concerning the level of plaque formation in SMA and IMA of the abdominal aorta that supplies the intestine (Table 2). We determined no statistically significant relationship between the plaque formation level and colonic diverticulum presence.

As vascular degeneration reached aneurysmal dilatation of abdominal aortic diameter, the probability of colonic diverticulum development was found to increase statistically significantly. (Table 2). Total stenosis in the SMA and IMA was not found to increase the likelihood of diverticula formation. That outcome supports the consideration that the development of diverticulum is associated with increased pressure rather than malnutrition.

4. Discussion

Atherosclerosis is accepted as an independent risk factor in aortic aneurysm development[9]. Also, in our study, no correlation between plaque formation that supports atherosclerosis and aneurysm was found. Consequently, the incidence of colonic diverticulum did not increase in patients with plaque lesions.

According to Laplace's law, increased pressure is the etiological factor in aneurysm development[10]. Increased colonic pressure is also effective in the development of the colonic diverticulum[11]. Increased pressure causes the weakening of circular colonic muscles. Pericolic fat tissue out of these weakened colon muscles protrudes together with colonic muscularis mucosa. An increase in ascending or descending aortic aneurysms did not increase the tendency for colonic diverticulum formation, but it is increased in abdominal aortic aneurysms.

This situation suggests that elevated intra-abdominal pressure results in the development of aneurysms at the vascular level and diverticula at the organ level. The increased detection of colonic diverticulum in patients with abdominal aortic aneurysm additionally suggests this in our study.

5. Conclusions

We concluded that patients who underwent tomography control due to an aneurysm should also be evaluated for the presence and treatment of colonic diverticulum.

Acknowledgements

None.

Statement of ethics

The study was approved by the University of Giresun Ethics Committee (05.12.2019-04) and was conducted in accordance with the Declaration of Helsinki.

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

All authors contributed to the design and writing of the study. All authors reviewed and accepted the final version of the study.

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Evaluation of the Correlation Between Thalamic Area and Cognitive Functions in Patients with Early-Stage Relapsing-Remitting Multiple Sclerosis

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Abstract

Aim: The aim of this study is to investigate the presence of cognitive dysfunction and deep gray matter involvement in the early-stages of Relapsing-Remitting Multiple Sclerosis (RRMS) disease and examine the relationship between them.

Methods: Thirty-four patients and 23 healthy individuals were included in the study. Patients diagnosed with RRMS according to the Revised 2010 and 2017 McDonald criteria, aged between 18-50, were enrolled in the study. The control group consisted of 23 healthy individuals with normal neurological examination, cranial magnetic resonance imaging (MRI), and cognitive functions. All participants underwent a neuropsychological test battery that covers memory, executive functions, language, and visuospatial domains, and the results of these tests were compared among the study groups. The data on MRI parameters, including the areas of the thalamus and corpus callosum as well as the width of the third ventricle, were compared among the study groups. Finally, the relationship between neuropsychological test results and MRI parameters was investigated in patients with early-stage RRMS.

Results: The mean duration of the disease for MS patients was 3.53 years, and their median EDSS score was 2. It was observed that memory, executive functions, and fine motor skills were affected in early-stage RRMS patients. This impairment correlated with a decrease in the thalamus and corpus callosum areas and an increase in the third ventricle width.

Conclusions: The MRI parameters defined as biomarkers for potential cognitive impairments in RRMS have critical importance in predicting the prognosis of the disease and taking early measures against future cognitive dysfunction.

Keywords: *Multiple Sclerosis, deep gray matter, thalamus, cognitive dysfunction*

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system, and is characterized by inflammation, degeneration, axonal loss, and gliosis in both gray and white matter [1]. In MS, the onset age is 20-40 years in 2/3 of patients, and the female-to-male ratio is 2-3/1. Although the exact cause is unknown, autoimmune mechanisms triggered by genetic and environmental factors are thought to play a role in the pathogenesis [2].

Some symptoms which occur due to impairments in motor, sensory, visual, cerebellar, and cognitive functions can be explained by the location, distribution, or burden of plaques in the central nervous system in MS [3]. However, rather than demyelinating plaques, progressive neuronal/axonal loss has recently been identified as a cause of neurological disability [4].

The prevalence of cognitive impairment in MS varies between 40-70%. According to recent studies, the information processing capacity (information processing speed and working memory), episodic memory, verbal fluency, and executive functions are the most affected cognitive parameters in MS, as in subcortical dementia [5–7]. As a result, the form of the disease and the period elapsed until diagnosis play a greater role in predicting the cognitive impairment that the disease may cause in the future, compared to the degree of physical disability caused by the disease or the period elapsed after the diagnosis of the disease [8,9]. Neuropathological processes such as demyelination, neuroaxonal loss, and synaptic loss in cortical and deep gray matter,

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Received: 27.07.2023, Accepted: 22.08.2023, Available Online Date: 31.08.2023
Cite this article as: Ayas S, Canbaz Kabay S. Evaluation of the correlation between thalamic area and cognitive functions in patients with early-stage relapsing-remitting multiple sclerosis. J Cukurova Anesth Surg. 2023; 6(2): 280-9..doi: 10.36516/jocass.1333415

particularly in the thalamus, have recently been shown as causes of cognitive impairment in MS [10–12]. Thalamus plays an important role in cognitive functions such as arousal, executive functions, emotional and episodic memory, spatial learning and memory, and recollective-based and familiarity-based recognition via its connections between the hippocampus, amygdala, cingulate cortex, orbitofrontal cortex, retrosplenial cortex, and inferior parietal lobule [13,14]. One of the most affected parameters among cognitive functions in MS is the process of encoding and recalling information. It is deteriorated as a result of damage of the anterior thalamic region, hippocampus, or any of the remaining other components of the Papez cycle [15]. It has been shown that thalamic atrophy is closely linked to cognitive impairment [16]. Reduced brain volume is also strongly linked to cognitive impairment.

The atrophy that occurs in cortical and subcortical gray matter structures can be observed in the early stages of MS and is an early indicator of cognitive impairment. Therefore, it has significant importance in predicting the prognosis of the disease. The detection of this atrophy through various imaging methods may assist in taking preventive measures against the progression of potential cognitive impairment that may develop from the onset of the disease. Therefore, in this study, we aim to investigate the role of imaging methods in predicting cognitive impairment that may develop in the early stages of MS. We aim to determine the relationship between the degree of cognitive impairment and physical disability in early-stage Relapsing-Remitting Multiple Sclerosis (RRMS) patients and also to determine the correlation between cognitive impairment and the atrophy of the thalamus and cerebral cortex (central atrophy- third ventricle width, corpus callosum area).

2. Materials and methods

2.1. Participants

After the approval of Dumlupınar University, Faculty of Medicine, Clinical Research Ethics Committee (Date: 29.07.2016, No: 2015-KAEK-86/09-178), the study was organized according to the Principles of the Declaration of Helsinki. Between August 2016 and October 2016, patients between the ages of 18 and 50 who were diagnosed with RRMS based on the revised 2010 McDonald criteria and had undergone a cranial magnetic resonance imaging (MRI) within the past three months were included in the study at our clinic. In addition, all patients fulfilled the 2017 McDonald criteria for RRMS. Patients with RRMS who experienced relapse or received steroid therapy in the past three months, as well as those with Primary and Secondary Progressive Multiple Sclerosis (PPMS and SPMS), were excluded from the study. And also, patients with other neurological diseases such as cerebrovascular disease and brain tumors, metabolic disorders (thyroid dysfunction, severe vitamin B12 deficiency, folic acid deficiency), antipsychotics use, alcohol consumption, severe depression (Beck Depression Scale score 21 and above), learning difficulties that may affect cognition, advanced visual defects, and upper extremity motor dysfunction were excluded from the study. Patients were informed about the study, and their written informed consent was provided. Disease severity was evaluated with the Expanded Disability Status Scale (EDSS).

The control group consists of healthy individuals who presented to our outpatient clinic with complaints of headache during the same time period and underwent cranial MRI within the past three months. Having a neurological disease, a major psychiatric disorder, antipsychotics use, chronic alcohol consumption, and a pre-existing learning disability was defined as the exclusion criteria for healthy individuals. Their neurological examination and cranial MRI were normal. Also, their written informed consent was provided. In the Beck Depression Scale, which is administered to all participants and consists of 21 items, each item is scored on a scale of 0 to 3. While the lowest score was 0, the highest score was 63. The range of 0-4 points indicates the absence of depression, while the range of 5-13 points indicates mild depression, the range of 14-20 points indicates moderate depression, and a score of 21 points or higher indicates severe depression [17]. In our study, we excluded participants with severe depression (21 points or higher). In the study, demographic characteristics including age, gender, and education level of the participants were evaluated. A neuropsychological test battery, which included tests assessing attention, memory, language functions, executive functions, visuospatial perception, and structural functions, was administered to all the participants by a neurologist experienced in cognitive tests.

2.2. Neuropsychological evaluation

The Edinburgh Handedness Inventory (EHI) was used to determine the handedness of the participants. The Standardized Mini-Mental State Examination (SMMSE) was applied to the participants for general cognitive assessment. Delphiforfun reaction time test (DRT) was used to evaluate the simple reaction time. Digit Span Test (DST) was used to evaluate verbal attention, and Corsi Block Test (CBT) was used to evaluate visual attention. Both tests assess verbal and visual simple attention, complex attention, short-term memory, and working memory. Oktem verbal memory processes test (OVMPT), Wechsler memory scale visual reproduction (WMS-VR) and logical memory (WMS-LM) subtests were applied to assess short and long-term verbal and nonverbal memory. Each participant's short-term memory score and long-term memory recall+recognition score were determined by the results of these tests. OVMPT is a test used frequently in our country to evaluate verbal memory [18]. The test assesses short-term memory, acquisition of information, keeping the information in the mind, and recalling information by spontaneous or recognition. Pacet Auditory Serial Addition Test (PASAT) was performed to evaluate working memory, calculation ability, and complex attention. Visuospatial perception and construction functions were evaluated with the Benton facial recognition test (BFRT), the judgment of line orientation test (JLOT), and the cube drawing test (CDT). The modified Boston diagnostic aphasia examination (BDAE) and Boston naming test (BNT) were used to evaluate language functions. Clock drawing test, Stroop Color and Word Test (SCWT), Trail Making Test (TMT) Parts A & B, and categorical and lexical verbal fluency (CVFT/LVFT) tests were performed for frontal executive functions. Fine motor skills were evaluated with the nine-hole peg test (NHPT). Abstract thinking and reasoning ability from higher cortical functions were evaluated with verbal comprehension subtests of the Wechsler Adult Intelligence Scale–Revised (WAIS-R), similarities and comprehension. The calculation ability was evaluated with the calculation subtest of the Short Test of Mental Status (STMS). The results of all neuropsychological evaluations were compared between the patient and control groups.

2.3. Magnetic Resonance Imaging

Cranial MRIs of all the participants which were performed between May 2016 and July 2016 in Dumlupınar University Faculty of Medicine, Evliya Celebi Training and Research Hospital, were evaluated.

All cranial MRIs were obtained with a 1.5 T GE Excite (GE Healthcare Technologies, Waukesha, WI, USA) MRI device, and a standard 8-channel head coil was used. Sequence features are as follows; T1-weighted (TR/TE 600/14), T2-weighted (TR/TE 5400/99) and FLAIR images (TR/TE/TI 9000/110/2100) in the axial plane, T2-weighted images in the sagittal-coronal plane. Matrix 256×256, FOV 22 or 24 cm, section thickness 5 mm, cross section spacing 1 mm. Measurements were made manually via the hospital automation system (Siso Viewer - V2.9) by a neuroradiology specialist who is blinded to the clinical status of participants. The width of the third ventricle is the marker that shows the best correlation with the brain parenchymal fraction in cross-sectional studies and is used to evaluate

whole brain atrophy (cerebral atrophy) or central atrophy [19]. In addition, the width of the third ventricle is associated with neocortical volume and is an important marker for cognition [20]. The increase in width of the third ventricle, whose lateral walls are formed by the dorsomedial thalamic nucleus, may represent selective thalamic atrophy. So, it has a strong relationship with many neuropsychological tests. Therefore, we used the width of the third ventricle to evaluate cerebral atrophy in our study. The width of the third ventricle was calculated by measuring the length of a second line drawn perpendicular to the midline of the line drawn parallel to the interhemispheric fissure along the long axis of the third ventricle in the T1-weighted axial section where the third ventricle was best visualized (Figure 1).

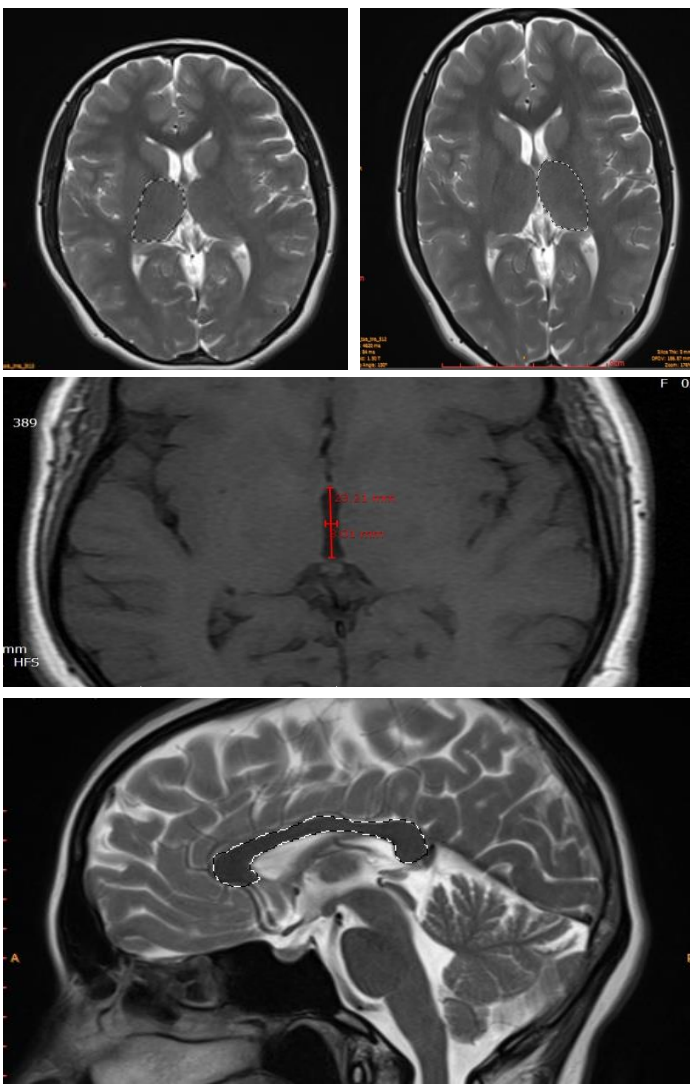

Figure 1
Thalamus Area, Third Ventricular Width and Corpus Callosum Area Measurements

In a study performed by Müller et al. a control group consisting of 70 healthy individuals and a group consisting of 54 patients with RRMS were compared. The upper limit of the normal width of the third ventricle in the control group was determined as 5.06 mm by adding 2 standard deviations (SD) to the mean value, and this value was used as the cut-off value in the study [21]. In a study by Karakaş et al. from Turkey, the normal width of the third ventricle was determined as 3.79±0.85 mm in females and 4.12±0.94 mm in males [22]. According to these results, in our study, the upper limit of the normal value of the width of the third ventricle was defined as 0.5 cm to evaluate cerebral atrophy. The area of the corpus callosum, viewed in the midsagittal plane on T1 or T2 weighted images, was obtained after its circumference was drawn manually. On T2 axial-weighted images, the area of the thalamus was obtained by drawing manually its circumference at the level of the foramen Monro.

2.4. Statistical analysis

All analyses were done with "SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc, Chicago, IL)". Descriptive statistics were presented as mean±standard deviation, frequency distribution, and percentage. Pearson Chi-Square Test and Fisher's Exact Test were used to evaluate categorical variables. The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Shapiro-Wilk Test). According to the results of the normal distributions of the variables, Mann-Whitney U Test was used to compare nonparametric data, and Student's T-Test was used to compare parametric data. The relationship between the variables was evaluated with Spearman Correlation Analysis. Last, in RRMS patients, during the correlation analyses between the results of neuropsychological tests and MRI parameters, the partial correlation analyses were applied to keep under control some demographic data that may affect the neuropsychological tests including age, gender, education period, and Beck Depression Scale scores. Statistical significance level was accepted as $p<0.05$.

3. Results

34 patients and 23 healthy individuals were included in the study. The demographic and descriptive characteristics of the patient and control groups, including age, gender, education period, handedness, and Beck Depression Scale scores, were similar. In addition, the patients' mean disease duration was 3.5 years, and their median EDSS score was 2 (Table 1).

The distribution of neuropsychological evaluation results between the study groups is presented in Table 2. The long-term memory scores of OVMPT, WMS-VR, and WMS-LM, as well as the short-term memory score of WMS-LM, were found lower in patients with RRMS.

Table 1
Distribution of some demographic and descriptive characteristics between study groups

	RRMS patients (n=34)	Control group (n=23)	p
Age (years), $\bar{X}$±S	35,32±8,04	32,57±7,45	0,196a
Gender, n (%)			
Female	27 (79,4)	17 (73,9)	0,627b
Male	7 (20,6)	6 (26,1)	
Education period, n (%)			
≤8 years	19 (55,9)	8 (34,8)	0,118b
>8 years	15 (44,1)	15 (65,2)	
Duration of disease (years), $\bar{X}$±S	3,53 (3,48)	----------	-------
Severity of disease (EDSS), M(IQR)	2 (0,5-2)	----------	-------
Beck Depression Scale score, $\bar{X}$±S	6,94 (5,03)	7,61 (6,33)	0,800c
The handedness (EHI)			
Right	33 (97,1)	21 (91,3)	0,559d
Left	1 (2,9)	2 (8,7)	

Table 2
Distribution of neuropsychological evaluation results between study groups

	RRMS patients (n=34) $\bar{X}$±S	Control group (n=23) $\bar{X}$±S	P
General Cognitive Assessment			
SMMSE	27,38±1,79	28,30±1,55	0,032[b]
Reaction Time			
DRT-Auditory Modality(s)	0,43±0,10	0,40±0,11	0,084[b]
DRT- Visual Modality(s)	0,36±0,08	0,34±0,04	0,714[b]
Attention			
Digit Span Test	9,15±1,91	9,61±2,10	0,399[b]
Forward-Backward Difference ≤2, n (%)	31 (91,2)	22 (95,7)	0,641[c]
Forward-Backward Difference>2, n (%)	3 (8,8)	1 (4,3)	
Corsi Block Test	11,12±1,59	11,09±1,24	0,938[a]
Forward-Backward Difference ≤2, n (%)	32 (94,1)	23 (100)	0,510[c]
Forward-Backward Difference>2, n (%)	2 (5,9)	0	
Memory			
OVMPT- Short Term Memory	111,91±20,30	120,13±14,18	0,157[b]
OVMPT- Long Term Memory/Recall	12,0±2,93	12,78±1,91	0,497[b]
OVMPT- Long Term Memory/Recognition	2,50±2,26	2,22±1,91	0,811[b]
OVMPT- Long Term Memory/Total Score	14,50±1,46	15,00±0	0,013[b]
WMS-VR- Short Term Memory	9,27±3,36	10,09±2,73	0,342[b]
WMS-VR- Long Term Memory/Recall	7,27±3,70	8,91±3,19	0,087[a]
WMS-VR- Long Term Memory/Recognition	2,88±2,76	4,00±3,38	0,205[b]
WMS-VR- Long Term Memory/Total Score	10,15±4,02	12,91±1,99	0,005[b]
WMS-LM- Short Term Memory	6,27±3,06	8,00±2,52	0,028[a]
WMS-LM- Long Term Memory/Total Score	4,71±3,34	6,39±2,41	0,042[a]
Working Memory			
PASAT	33,21±12,61	42,87±11,45	0,005[a]
Visuospatial perception and construction			
Benton Facial Recognition Test	41,18±4,35	42,52±3,46	0,233[b]
Judgment of Line OrientationTest	19,21±5,88	21,65±4,88	0,105[a]
Cube Drawing Test	4,44±0,79	4,57±0,73	0,538[b]
Language Functions			
Boston Naming Test	28,97±1,43	29,48±0,90	0,142[b]
Frontal Executive Functions			
Clock Drawing Test	3,79±0,54	4,00±0	0,057[b]
Stroop Color and Word Test-1 (s)	9,74±3,43	8,43±0,99	0,143[b]
Stroop Color and Word Test-2 (s)	12,27±3,32	10,39±1,92	0,010[b]
Stroop Color and Word Test-3 (s)	16,85±4,69	14,17±3,61	0,014[b]
Stroop Color and Word Test-4 (s)	24,21±7,47	24,13±6,94	0,896[b]
Trail Making Test-A (s)	41,06±21,82	30,43±13,21	0,028[b]
Trail Making Test-B (s)	103,85±54,42	76,04±31,95	0,018[b]
Categorical Verbal Fluency	21,06±4,74	22,35±5,91	0,366[a]
Lexical Verbal Fluency	12,53±5,52	13,13±5,14	0,680[a]
Fine Motor Skills			
Nine Hole Peg Test-Dominant Hand (s)	16,97±2,74	15,52±1,44	0,029[b]
Nine Hole Peg Test-Nondominant Hand (s)	18,97±2,52	16,57±0,99	<0,000[b]
Higher Cortical Functions			
WAIS-Verbal Comprehension/Similarities	15,56±4,27	16,00±3,84	0,833[b]
WAİS-Verbal Comprehension/Comprehension	14,41±3,47	14,87±3,88	0,643[a]
STMS- Calculation	5,82±2,05	6,43±2,08	0,202[b]

$\bar{X}$: Mean; S: Standard Deviation, SMMSE: Standardized Mini-Mental State Examination; DRT: Delphiforfun Reaction Time Test; OVMPT: OktemVerbal Memory Processes Test; WMS-VR: Wechsler Memory Scale-Visual Reproduction; WMS-LM: Wechsler Memory Scale-Logical Memory; PASAT: Pacet Auditory Serial Addition Test; WAIS: Wechsler Adult Intelligenc eScale; STMS: Short Test of Mental Status, aStudent's T Test, bMann-Whitney U Test; cFisher'sExact Test

Table 3
Distribution of results of MRI measurement between study groups

	RRMS patients (n=34)	Control group (n=23)	P
MRI measurements			
Left thalamus area (cm2), $\bar{X}$±S	5,19±0,76	6,02±0,73	<0,000a
Right thalamus area (cm2), $\bar{X}$±S	5,23±0,76	6,08±0,68	<0,000a
Corpus Callosum area (cm2), $\bar{X}$±S	5,51±1,01	6,06±0,70	0,017a
The width of third ventricle (cm), $\bar{X}$±S	0,43±0,23	0,27±0,14	0,005b
Cerebral atrophy (>0,5 cm), n (%)	11 (32,4)	1 (4,3)	0,018c

$\bar{X}$: Mean; S: Standard Deviation, aStudent's T Test;bMann-Whitney U Test; cFisher's Exact Test

Table 4
The relationship between the demographic characteristics of the control group and their MRI parameters

Control group (n=23)	Age (years)	Gender (female / male)	Education period (≤8 years / >8 years)	Beck depression scale score
	r	r	r	r
MRI measurements				
Left thalamus area (cm^2)	-0,059	0,194	-0,096	-0,031
Right talamus area(cm^2)	-0,155	0,224	-0,041	-0,157
Corpus Callosum area (cm^2)	-0,058	-0,179	-0,385	-0,148
The width of third ventricle (cm)	0,213	0,479*	0,200	0,046

*p<0,05; r: Spearman Correlation Coefficient. MRI: Magnetic Resonance Imaging

Table 5
The relationship between the demographic characteristics of the RRMS patients and their MRI parameters

RRMS patients (n=34)	Age (years)	Gender (female / male)	Education period (≤8 years / >8 years)	Beck depression scale score	Duration of disease (years)	Severity of disease (EDSS score)
	r	r	r	r	r	r
MRI measurements						
Left thalamus area (cm^2)	-0,274	0,185	0,229	-0,130	-0,322	-0,308
Right talamus area(cm^2)	-0,301	0,211	0,236	-0,096	-0,296	-0,288
Corpus Callosum area (cm^2)	0,048	0,063	-0,190	-0,070	-0,241	-0,273
The width of third ventricle (cm)	0,283	0,126	-0,151	0,126	0,429*	0,226

*p<0,05; r: Spearman Correlation Coefficient, MRI: Magnetic Resonance Imaging

In addition, the scores of SMME and PASAT were detected lower in the patients. The completion durations of tests including SCWT-2/3, TMT-A/B, and NHPT-Dominant/Nondominant hand were longer in the patients (p<0.05, Table 2). Other neuropsychological test results were statistically similar between groups.

In the patients, the areas of the right thalamus, left thalamus, and corpus callosum were lower, while the width of the third ventricle was higher (p<0.05, Table 3). In proportion to the increase in the width of the third ventricle, the percentage of RRMS patients with cerebral atrophy was significantly higher than in the control group (32.4% vs. 4.3%, p=0.019, Table 3).

In healthy individuals, the width of the third ventricle tended to be higher in the male population (r=0.479, p<0.05, Table 4).

However, in the patients, when the relationship between MRI parameters and demographic data was evaluated, only the width of the third ventricle showed a significant moderate positive correlation with disease duration (r=0.429, p<0.05, Table 5).

In the patients, the relationship between neuropsychological test results and MRI parameters was investigated through partial correlation analysis, controlling for demographic variables such as age, gender, education period, and Beck Depression Scale score that could affect the neuropsychological test results (Table 6).

In the patients with RRMS, based on the neuropsychological tests that were shown to be affected compared with the tests results of the healthy individuals (Table 2), a moderate positive correlation between OVMPT- Long-term memory total score and the areas of right and left thalamus (r=0.471, r=0.414, respectively), as well as a moderate positive correlation between PASAT score and right thalamus area was detected (r=0.395). In addition, while the completion durations of SCWT-2 and TMT-A showed a moderate positive correlation with the width of the third ventricle (r=0.372, r=0.423, respectively), TMT-B completion duration showed a negative, moderate correlation with the areas of the right and left thalamus (r=-0.538, r=-0.500, respectively). Finally, it was detected that there was a negative, moderate correlation between the completion duration of the NHPT-Dominant hand and the areas of the right thalamus, left thalamus, and corpus callosum (r=-0.476, r=-0.466, r=-0.631, respectively) and a negative, moderate correlation between the completion duration of the NHPT-Nondominant hand and the areas of the right thalamus and corpus callosum (r=-0.441, r=-0.534, respectively).

In addition, a correlation was found between the results of tests such as the OVMPT-Short-Term Memory and WAIS-Verbal Comprehension/Comprehension, which are similar among working groups, and thalamic areas. While there is a moderate positive correlation between OVMPT-Short-Term Memory scores and the right and left thalamic areas (r=0.390, r=0.397, respectively), a moderate positive correlation was detected between WAIS-Verbal Comprehension/Comprehension test scores and the right thalamic area (r=0.394).

4. Discussion

Cognitive dysfunction is observed in 35-60% of MS patients, and although this impairment is strongly correlated with disease progression, it is weakly correlated with disease duration and physical disability caused by the disease [23,24]. Studies have shown that 80% of patients with Clinical Isolated Syndrome (CIS) have deterioration in at least one cognitive area, and 57% have deterioration in two or more cognitive areas. These rates are similar to those of newly diagnosed (2-3 years) RRMS patients [25,26]. Recent studies have shown that cognitive impairment is seen in all forms of MS and is more pronounced and more common in progressive forms of MS. Consistent with this, it was found to be 20-25% in Radiological Isolated Syndrome (RIS), 30-45% in RRMS, and 50-75% in SPMS [27]. In a study by Amato et al., 45 MS patients with a mean disease duration of 1.5 years were followed for 10 years. While 74% of the cases were cognitively normal at baseline, this rate decreased to 51% at 4 years and to 44% at 10 years [28]. Recently, advanced imaging modalities have revealed that cognitive impairment in MS is closely related to cortical T2 demyelinating lesion volume and T1 hypointense lesion burden on MRI, and has a strong negative correlation with the brain parenchym-

Table 6

The relationship between MRI measurements and neuropsychological evaluation results of RRMS patients

RRMS patients (n=34)	Left thalamus area(cm^2) r	Right thalamus area(cm^2) r	Corpus Callosum area(cm^2) r	The width of third ventricle(cm) r
SMMSE	0,180	0,232	0,162	-0,161
DRT-Auditory Modality (s)	0,213	0,128	-0,010	-0,069
DRT- Visual Modality (s)	0,234	0,248	0,006	0,159
Digit Span Test	-0,119	-0,032	0,110	-0,033
Corsi Block Test	-0,201	-0,220	0,204	-0,320
OVMPT- Short Term Memory	*0,397**	*0,390**	0,038	-0,289
OVMPT- Long Term Memory/Recall	0,301	0,324	0,239	-0,272
OVMPT- Long Term Memory/Recognition	-0,122	-0,115	-0,184	0,171
OVMPT- Long Term Memory/Total Score	*0,414**	*0,471***	0,194	-0,281
WMS-VR- Short Term Memory	0,197	0,300	0,312	-0,286
WMS-VR- Long Term Memory/Recall	0,120	0,276	0,143	-0,223
WMS-VR- Long Term Memory/Recognition	0,223	0,104	0,316	-0,096
WMS-VR- Long Term Memory/Total Score	0,268	0,293	0,359	-0,246
WMS-LM- Short Term Memory	-0,064	-0,067	-0,029	0,076
WMS-LM- Long Term Memory/Total Score	0,059	0,038	0,052	0,064
PASAT	0,310	*0,395**	0,273	-0,065
Benton Facial Recognition Test	0,009	0,067	0,130	-0,156
Judgment of Line Orientation Test	-0,055	0,096	0,179	-0,141
Cube Drawing Test	-0,274	-0,167	-0,077	-0,100
Boston Naming Test	-0,136	-0,073	-0,043	-0,055
Clock Drawing Test	0,084	0,196	-0,093	0,246
Stroop Color and Word Test-1 (s)	0,181	0,163	-0,155	0,343
Stroop Color and Word Test-2 (s)	0,003	-0,049	-0,105	*0,372**
Stroop Color and Word Test-3 (s)	-0,064	-0,131	-0,217	0,225
Stroop Color and Word Test-4 (s)	0,057	0,044	0,071	-0,026
Trail Making Test-A (s)	-0,227	-0,277	-0,163	*0,423**
Trail Making Test-B (s)	*-0,500***	*-0,538***	-0,132	0,344
Categorical Verbal Fluency	0,083	0,091	0,076	0,025
Lexical Verbal Fluency	0,013	0,152	-0,184	0,057
Nine Hole Peg Test-Dominant Hand (s)	*-0,466***	*-0,476***	*-0,631***	0,243
Nine Hole Peg Test-Nondominant Hand (s)	-0,349	*-0,441**	*-0,534***	0,260
WAIS-Verbal Comprehension/Similarities	0,288	0,323	0,051	-0,037
WAiS-Verbal Comprehension/Comprehension	0,329	*0,394**	0,159	0,020
STMS- Calculation	0,292	0,289	0,310	0,096

*p<0,05; **p<0,01; r: Spearman Correlation Coefficient, During the Spearman Correlation analyses, demographic data that may affect the neuropsychological test results including age, gender, education duration, and Beck depression inventory results were kept under control with partial correlation analysis. SMMSE: Standardized Mini-Mental State Examination; DRT: Delphiforfun Reaction Time Test; OVMPT: Oktem Verbal Memory Processes Test; WMS-VR: Wechsler Memory Scale-Visual Reproduction; WMS-LM: Wechsler Memory Scale-Logical Memory; PASAT: Pacet Auditory Serial Addition Test; WAIS: Wechsler Adult Intelligence Scale; STMS: Short Test of Mental Status

-al fraction showing cortical atrophy [29]. It has been reported that cognitive impairment due to these pathologies is particularly evident in the areas of memory, processing speed and verbal fluency [29]. Furthermore, similar pathologies such as inflammation, demyelination, and neuronal loss in deep gray matter, particularly in the thalamus, have been linked to cognitive impairment in MS patients. For this purpose, we planned to investigate the relationship between cognitive impairment, which may be seen in early-stage RRMS patients, and thalamic and cortical cerebral atrophy. In this context, the fact that the patients in our study had a mean disease duration of 3.5 years and a median EDSS score of 2 indicates that the majority of the patients in our study were in the early-stages of RRMS. However, it has been shown in previous studies that EDSS is insufficient for assessing cognitive ability [30].

It has been reported previously that education period is one of the best indicators of cognitive reserve, which refers to the ability of the brain to tolerate underlying pathological processes associated with disease without manifesting symptoms or signs [31]. In a longitudinal study that determined the cutoff value of the education period for the cognitive reserve to be 9 years, a significant decline was observed in cognitive tests performed at regular intervals in MS patients with low cognitive reserve, while no significant changes were detected in MS patients with high cognitive reserve [32]. Based on this information, we determined the threshold value of education period, an indicator of cognitive reserve, to be 8 years, as compulsory education in our country lasts for 8 years. Therefore, individuals with an education period of 8 years or less are thought to have lower cognitive reserves. Similar demographic characteristics, including education period, among the study groups, have enabled a more objective evaluation of the neuropsychological test results in our study.

MS can affect all areas of cognition, and cognitive decline in MS typically manifests in the domains of episodic memory, information processing efficiency (processing speed and working memory), and executive functions [5].

In the PASAT, which is used to evaluate working memory, one of the most important functions of the dorsolateral prefrontal cortex with strong connections to the thalamic nuclei, deterioration was detected in approximately 20-25% of patients with CIS and early-stage RRMS [26]. In the studies conducted by Forn et al. [33] in 30 MS patients, Locatelli et al. [34] in 39 RRMS patients, and Deloire et al. [35] in 44 early-stage RRMS patients, significant deterioration was found in the PASAT and symbol digit modalities test (SDMT), which evaluate information processing speed and working memory, as well as in the

SCWT test, which evaluates attention and interference. Achiron et al. reported an average 10% decrease in PASAT 2 scores in MS patients 5 years after disease onset [36]. In this context, thalamic volume is associated with many tests that evaluate working memory such as PASAT and SDMT [37]. Barak et al. administered the clock drawing test, which is used to evaluate working memory as well as visuospatial construction, to 107 RRMS patients. The sensitivity of this test was found to be 93.4% and the specificity was 85.8%, and it was observed that most RRMS patients scored low on this test [38]. The SCWT, which primarily evaluates focused attention, information processing speed, and inhibition of inappropriate responses, among frontal executive functions, was applied to 25 MS patients by Macniven et al., [39] and a significant impairment was observed in this test in MS patients compared to healthy controls. In another study, an abnormality in SCWT was found in approximately 35% of early-stage MS patients [40]. In line with these findings, our study revealed an impairment in the frontal executive functions in early-stage RRMS patients compared to healthy individuals, as evidenced by the low scores on PASAT and prolonged durations of SCWT-2/3, TMT-A/B.

Long-term memory is one of the most affected parameters in the MS, like working memory. Accordingly, Duque et al. evaluated a group of 44 patients with all types of MS every 3 months for 2 years. Cognitive impairment, which was 31% at baseline, increased to 41% at the end of the 2nd year. It was determined that this impairment was most pronounced in verbal memory and information processing speed [41]. Janculjak et al stated that the impairment in long-term memory function in MS patients is in the stages of storing and recalling of information [42]. Besides the impairment in visual and verbal long-term memory, Litvan et al. also found a deterioration in short-term memory functions in MS patients [43]. In this context, the low long-term memory scores of OVMPT, WMS-VR, and WMS-LM, as well as the low short-term memory score of WMS-LM, identified in our study, provide evidence for the impairment of memory functions, especially long-term memory functions, in early-stage RRMS patients.

The main responsible regions for the praxis are the frontal and parietal cortical areas as well as the basal ganglia. Finally, in a study by Longstaff et al. evaluating fine motor skills, it was observed that patients with MS drew the spiral on the graphic tablet slower, applied less pressure to the pen, and deviated more from the ideal drawing on the spiral test [44]. In our study, fine motor skills of early-stage RRMS were evaluated with NHPT. In accordance with the literature, we detected that the completion duration of NHPT-Dominant/Nondominant hand was longer in patients with RRMS.

Thalamic axons carry information between subcortical and cortical areas. Damage to the thalamic nuclei and their connections causes a variety of symptoms, including cognitive impairment [14]. Although it has been observed that thalamic volume loss correlated with reduced brain parenchymal fraction in MS, thalamic atrophy is more prominent and selective in MS [45]. Demyelinating plaques causing secondary axonal damage in deep gray matter, the thalamic hypometabolism which occurs due to cerebral demyelinated plaques and axon loss, iron deposition in the thalamus leading to lipid peroxidation and oxidative stress have been reported among the reasons for this selective involvement of the thalamus [45]. Also, the decrease in these thalamic areas in MS patients can be attributed to neuronal loss secondary to diffuse macrophage/microglial activation, CD8 T lymphocyte-mediated cytotoxicity occurring in normal-appearing gray matter [46,47]. Furthermore, the relationship between thalamic hypometabolism and cognitive decline has been reported in a PET study [48]. The studies have revealed that volume loss in the thalamus is one of the earliest and most significant findings of subcortical gray matter pathology in CIS cases, and progressive atrophy of the thalamus is also observed in all other types of MS [49]. In an autopsy study involving 14 RRMS and SPMS patients, Vercellino et al. demonstrated that lesions affecting both the gray and white matter of the thalamus are predominantly located in the anterior and dorsomedial nuclei, which are associated with cognitive functions and form the periventricular surface of the thalamus [46]. Cifelli et al. reported a decrease in the volume of the total and dorsomedial nuclei of the thalamus due to decreased neuronal density distant from focal demyelinating lesions [50]. Despite studies reporting no correlation between cognitive deficits and thalamic volume loss, in line with several other studies, our study found a relationship between thalamic area, the width of the third ventricle with cognitive performance in MS patients. In our study, it was found that the areas of the right thalamus, left thalamus, and corpus callosum were lower, while the width of the third ventricle was higher in RRMS patients. Also, the cases with cerebral atrophy which was determined according to the width of the third ventricle were higher in the RRMS group (32.4% vs. 4.3%, p=0.019). In early-stage RRMS patients, this increase in the width of the third ventricle can be attributed to atrophy of the thalamus, especially the dorsomedial nucleus, which has tight connections with the prefrontal cortex, or specifically to a reduction in neocortical volume, particularly since this width is the linear marker that best correlates with the brain parenchymal fraction [51].

The decrease in thalamic volume in patients with MS is associated with a decline in scores of cognitive tests assessing information processing speed, verbal fluency, working memory, verbal and visuospatial memory, and executive functions [37,45]. A study that compared healthy controls to MS patients found that the increase in the width of the third ventricle was a strong predictor of impairment in information processing speed and memory tests [20]. Another study conducted by Papathanasiou et al. showed that cognitive functions such as long-term memory, reaction time, and executive functions assessed by the TMT A/B and lexical fluency, as well as all MRI parameters including third ventricle width, corpus callosum area, and thalamic area, were affected in patients with RRMS compared to healthy individuals. In this study, a strong positive correlation was observed between all atrophy measurements (corpus callosum area, thalamic area, and third ventricle width) and all cognitive indicators, and a mild to moderate correlation was found between total lesion volume and cognitive tests [52]. Tiemann et al. reported that parenchymal atrophy was the determinant of possible future cognitive impairment, and this atrophy showed a strong negative correlation with the width of the third ventricle, but did not correlate with lesion load [53]. Rimkus et al. have demonstrated that the lesion load of the corpus callosum and the whole brain were similar in diffusion tensor imaging examinations in MS patients with normal cognition and those with cognitive impairment, but the axonal loss in the corpus callosum was higher in patients with cognitive dysfunction. Additionally, this study reported significant impairments in attention, information processing speed, executive functions, and memory functions in MS patients with more microscopic corpus callosum lesions [54].

Our study investigated the influence of demographic data on all MRI parameters examined in both healthy individuals and RRMS patients. With the exception of a tendency towards greater third ventricle width in male populations in healthy individuals and a significant moderate positive correlation between third ventricle width and disease duration in RRMS patients, no demographic data was found to have an effect on MRI parameters. Furthermore, partial correlation analysis controlling for demographic data such as age, gender, education period, Beck Depression scale scores, and EDSS scores that could affect neuropsychological tests allowed for a more specific

examination of the relationship between MRI parameters and neuropsychological tests in RRMS patients.

In our study, in line with the literature, a moderate positive correlation was found between thalamic areas and executive functions evaluated with PASAT and TMT-B, and also between thalamic areas and long-term verbal memory evaluated with OVMPT. We found a negative, moderate correlation between the width of the third ventricle and executive functions evaluated with SCWT-2 and TMT-A. Additionally, our study demonstrated a moderate, positive correlation between fine motor skills evaluated by NHPT and the areas of the thalamus and corpus callosum. Also, as the duration of the disease increases, the deterioration in MRI parameters related to cognitive functions such as the increase in third ventricle width is consistent with the literature, and this condition suggests that cognitive functions worsen as disease duration increases in patients with RRMS. However, the lack of a significant correlation between EDSS and any of these MRI parameters suggests that EDSS may be inadequate in evaluating cognitive functions.

Finally, in our study, the correlation between thalamic areas and short-term memory evaluated by OVMPT and abstract conceptualization evaluated by WAIS-Verbal Comprehension test in early-stage RRMS patients has suggested that short-term memory and abstract conceptualization may deteriorate in the advanced stages of RRMS, because of the scores of these tests were similar among the study groups.

The relationship between thalamic atrophy and long-term memory, working memory, and executive functions in our study suggests that pathological processes associated with MS affect reciprocal innervation between the thalamic nuclei, particularly the dorsomedial and anterior nuclei, and the dorsolateral prefrontal cortex, orbitofrontal cortex, and limbic system. Our study demonstrates that thalamic atrophy is the best predictor of impaired memory, psychomotor speed, and executive functions in MS patients, and in line with the literature, it has shown a strong correlation with the width of the third ventricle [55].

Among the limitations of the study, it can be noted that the population of sample group is small size, and due to technical reasons, the volumes of the thalamus and corpus callosum cannot be measured. Additionally, although all MRIs were assessed by a neuroradiologist who was blinded to the individuals in the study groups, the manual execution of the area measurements due to technical reasons can also be considered as another limitation of the study.

5. Conclusions

Our study found that many cognitive domains, especially executive and memory functions, are affected even in the early stages of RRMS patients. Moreover, this study revealed that the cognitive deficits observed in early-stage RRMS patients are associated with subcortical gray matter changes, particularly thalamic atrophy, and the width of the third ventricle, which serves as an indicator of both cortical and thalamic atrophy. These MRI parameters, which are indicative of cognitive deficits that may develop in the future, are of great importance in predicting the prognosis of the disease and taking early precautions against potential cognitive dysfunction that may develop in the future.

Acknowledgements

None.

Statement of ethics

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Dumlupınar University, Faculty of Medicine, Clinical Research Ethics Committee (Date: 29.07.2016, No: 2015-KAEK-86/09-178).

Conflict of interest statement

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

Funding source

The authors declared that this study received no financial support.

Author contributions

All authors contributed to the study conception and design.

All authors read and approved the final manuscript.

Abbreviations

BDAE: Boston Diagnostic Aphasia Examination
BFRT: Benton Facial Recognition Test
BNT: Boston Naming Test
CBT: Corsi Block Test
CIS: Clinical Isolated Syndrome
CVFT: Categorical Verbal Fluency Test
DRT: Delphiforfun Reaction Time Test
DST: Digit Span Test
EDSS: Expanded Disability Status Scale
EHI: Edinburgh Handedness Inventory
JLOT: Judgment of Line Orientation Test
LVFT: Lexical Verbal Fluency Test
MRI: Magnetic Resonance Imaging
MS: Multiple Sclerosis
NHPT: Nine Hole Peg Test
OVMPT: Oktem Verbal Memory Processes Test
PASAT: Pacet Auditory Serial Addition Test
PPMS: Primary Progressive Multiple Sclerosis
RRMS: Relapsing-Remitting Multiple Sclerosis
SCWT: Stroop Color and Word Test
SMMSE: Standardized Mini-Mental State Examination
SPMS: Secondary Progressive Multiple Sclerosis
STMS: Short Test of Mental Status
TMT: Trail Making Test
WAIS-R: Wechsler Adult Intelligence Scale – Revised
WMS-VR: Wechsler Memory Scale-Visual Reproduction
WMS-LM: Wechsler Memory Scale-Logical Memory

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Comparison of Excisional Stapler Hemorrhoidopexy Method and Non-Excisional Arterial Detection Ligation Method; One Year Follow-Up

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Abstract

Aim: Hemorrhoidal disease is a chronic disease of the lower rectum and anus occurs due to increased pressure during straining. Millions of people in the world suffer from this disease. Since the stage of the disease and the symptoms of the patients do not show parallelism, we evaluated the results of two different surgical methods; arterial detection ligation (ADL) and stapler hemorrhoidopexy (SH).

Methods: A retrospective study among patients who were operated for hemorrhoids between 2021-2022.

Results: Adult patients with Grades II, III and IV were included. SH and ADL groups containing 60 patients were formed. Pain complaints (VAS) and normal daily activities (KATZ) of patients after surgery were examined. In this study, statistical analyzes were performed with NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. 50 of the patients were female and 70 were male. There was no difference between the age and gender distributions of the SH and ADL groups (p=0.231, p=0.711). On the 1st day VAS values in the SH group were found to be statistically significantly higher than the ADL group (p=0.003). When the daily activities of both groups were examined, the dressing (p=0.042) and toileting (p=0.012) activities in the SH group were lower. On the other hand, there was a statistically significant difference within the groups (SH; p= 0,0001, ADL; p=0,0001) related to the pain assessments.

Conclusions: When both methods were examined, the success rate of two techniques was similar and ADL least affects the anatomy of the anorectal region without serious complication risk.

Key words: *Hemorrhoids, treatment, Stapler hemorrhoidopexy (SH), Arterial detection ligation (ADL)*

1. Introduction

Hemorrhoidal disease is a chronic disease of the lower rectum and anus because of increased pressure during straining[1]. After the age of 30, more than half of the population develops hemorrhoidal disease. Millions of people around the world suffer from this disease. The incidence of hemorrhoidal disease worldwide is 4.4% [2]. There is no gender discrimination in the incidence of the disease. Despite technological advances in the treatment of hemorrhoidal disease, there is no single effective treatment. The reason for this is the location of the hemorrhoidal plexuses and especially the subjective sym-ptoms reported by the patients for example bleeding, and varying degrees of prolapse but there is no a good correlation between patients' symptoms and surgical treatment planning although the pathophysiology of the disease is well known. Goligher classification is used in the surgical treatment selection phase of hemorrhoidal disease[3]. Excision is the conventional method in the surgical treatment of hemorrhoids. With the development of new treatment techniques, the hemorrhoidectomy method is used less frequently because of significant pain and bleeding complaints in the postoperative period. In this study, we investigated the ADL technique and the SH method and the clinical outcomes of the patients to whom we applied these techniques retrospectively.

2. Materials and methods

This study was conducted from July 2021 to July 2022. Adult patients undergoing elective surgery for symptomatic hemorrhoidal disease (Grades II, III and IV) were included in the study. Only patients who had never been operated on for any reason on the anorectal region before were included in the study. A total of 120 patients were treated with SH and ADL, 60 patients for each method.

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Received: 25.06.2023, Accepted: 23.08.2023, Available Online Date: 31.08.2023
Cite this article as: Sakoglu N, Ocakoglu A. Comparison of Excisional Stapler Hemorrhoidopexy Method and Non-Excisional Arterial Detection Ligation Method; One Year Follow-Up. J Cukurova Anesth Surg. 2023; 6(2): 290-5.
doi: 10.36516/jocass.1319930

All patients were subjected to detailed preoperative evaluation including inspection during straining, digital rectal examination. Rectoscopy or colonoscopy was carried out selectively in those patients who had a positive family history of colon cancer. All cases were admitted on the morning of surgery. Before the surgical intervention, only fleet enema was applied to the patients. The procedures were explained to the patients and consent obtained. Similarly the Visual Analog Scale (VAS) for recording post-surgical pain and Katz Index Of Independence in Activities of Daily Living (Table 1) was explained to the patients.

Table 1
Katz Index of Independence in Activities of Daily Living

Activities Points (1 or 0)	Independence (1 Point) No supervision, direction or personal assistance	Dependence (0 Points) With supervision, direction, personal assistance or total care	Point
Bathing	Bathes self completely	Need help with bathing	
Dressing	Puts on clothes	Needs help with dressing	
Toileting	Goes to toilet without help.	Needs help transferring to the toilet	
Transferring	Moves in and out of bed.	Needs help in moving from bed to chair	
Continence	Exercises complete self-control over urination and defecation.	Is partially or totally incontinent of bowel or bladder	
Feeding	Gets food from plate into mouth without help.	Needs partial or total help with feeding or requires parenteral feeding.	
Score of 6 = High, Patient is independent. Score of 0 = Low, patient is very dependent.			Total Points

56 patients were operated under general anesthesia and 4 under spinal anesthesia in lithotomy position (Figure 1). The Proximate Hemorrhoidal Circular Stapler (HCS) manufactured by Ethicon Endo-surgery was used in 60 cases. First, we placed the circular anoscope inside the anal canal (Figure 2) then the purse string suture placed approximately 1-1.5 cm cephalad to the dentate line using a 2/0 polypropylene suture incorporating only the mucosa and submucosa to retract the anal cushions into their anatomical positions. Cushions do not recover sufficiently if the suture placed higher. After inserting the fully open stapler into the anal canal, it was closed in a controlled manner to avoid any complications and ring-shaped hemorrhoid tissue removed (Figure 3). Following operation dressings were applied and operative time and blood loss were assessed and recorded (Figure 4).

Of 60 patients who underwent ADL, 55 were operated on general anesthesia and 5 with spinal anesthesia in the lithotomy position. It is among the non-excisional treatment methods of hemorrhoid disease. It is based on the principle of determining the location of the hemorrhoidal arteries that supply blood to the hemorrhoidal pouches in the anal canal and distal rectum wall by Doppler USG and interrupting the arterial flow by suturing. After the induction of anesthesia, the anus and distal rectum are reevaluated and the LDL-2 is placed on the anal canal by applying gel to the tip of the proctoscope (Figure 5-6). After detecting the sound and images of the symptomatic hemorrhoidal arteries, the hemorrhoidal arteries with a depth of 6mm to a maximum of 12mm are ligated with a 5/8 needle with 2/0 absorbable sutures (Figure 7).

The peaks in the graph show the blood flow in the systolic phase and the flat points in the diastolic phase. We rechecked the arterial blood flow after ligation. After ligation, the amplitude of the pulse wave should decrease or disappear completely. Otherwise, resuture

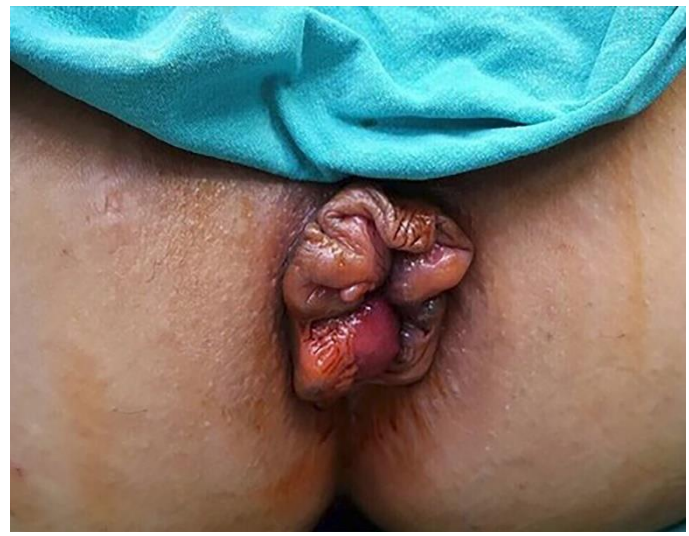

Figure 1
Lithotomy position

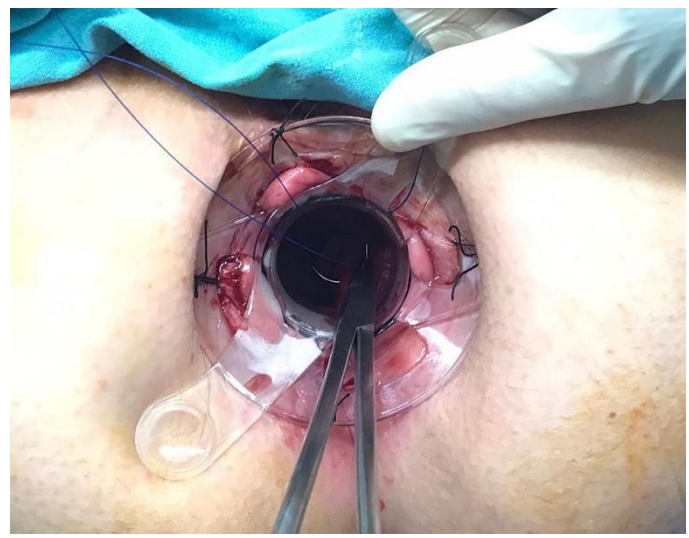

Figure 2
Circular anascope

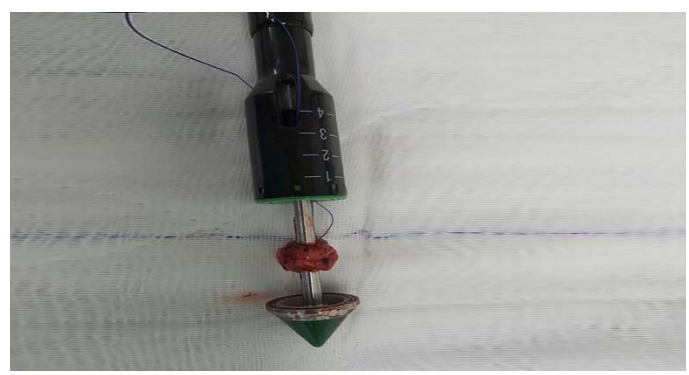

Figure 3
Ring-shaped tissue

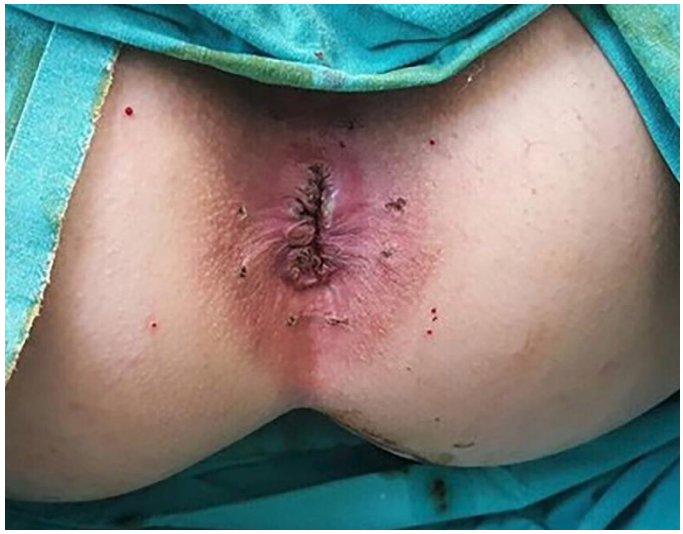

Figure 4
Post-operative image

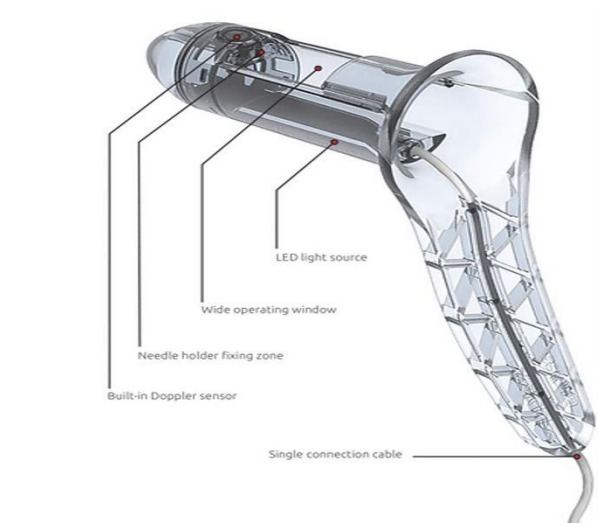

Figure 5
LDL-2 probe

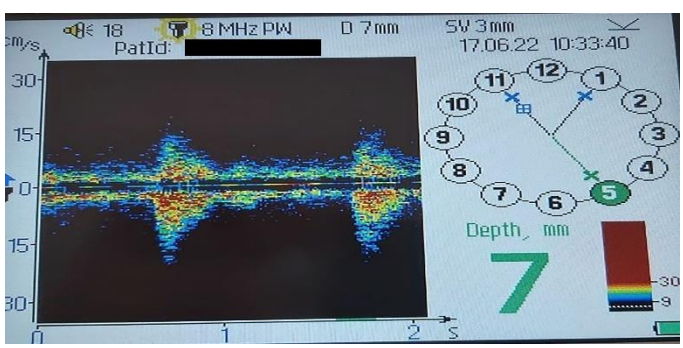

Figure 6
Detection of hemorrhoidal arteries

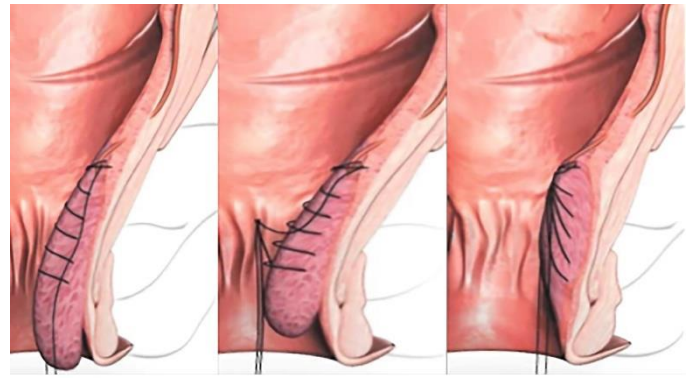

Figure 7
Ligation of hemorrhoidal arteries

is required. This process is repeated clockwise to include all arterial points. Almost 80% of the hemorrhoidal swellings recover immediately after the procedure and 100% within 1 week. If there is prolapsed hemorrhoid pouches, we applied the pexy process. As the dentate line gets closer, post-op pain can be severe. After controlling and recording bleeding we continued the post-op patient follow-up. To decrease post-surgery pain, pudendal nerve blok was done with marcaine.

All patients was permitted to take oral fluids after 4 h of surgery. In the post-operative period, the patient's pain assessment and analgesia requirement were recorded with the VAS. The criteria evaluated for the first 24 hours were the need and frequency of analgesics. Pain was assessed at 24 h, 1st week and 1st month postoperatively. Activities of Daily Living (ADLs); bathing, dressing, toilet, transfer, continence and feeding activities of the patients, which represent the processes of returning to normal daily life in the postoperative period measured with the KATZ index. Patients are scored Yes/No for independence in each of the six functions. A score of 6 indicates full function, 4 indicates moderate impairment, and 2 or less indicates severe functional impairment. Patients were also followed for presence of bleeding per rectum, post-operative urinary retention, incontinence to flatus/stool, presence of post-operative anal stenosis, and residual hemorrhoidal swelling at 1 week, 1 month, and 1 year after the surgery. The follow-up was done during visits and also by telephonic interview of the patients.

This study and all relevant procedures were performed in accordance with the Helsinki Declaration after obtaining the ethical board approval from the Ethics Committee of İstanbul Kanuni Sultan Suleyman Training and Research Hospital (KAEK/2022.06.149).

2.1 Statistical Analysis:

In this study, statistical analyzes were performed with NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. In addition to descriptive statistical methods (mean, standard deviation) in the evaluation of the data, the distribution of the variables was examined with the Shapiro-Wilk normality test, the independent t-test for the comparison of the normally distributed variables between the paired groups, the Mann Whitney U test for the comparison of the non-normally distributed variables between the paired groups, and the comparison of the qualitative data. Chi-square test was used. The results were evaluated at the significance level of $p<0.05$.

3. Results

A total of 120 patients, symptomatic with bleeding per rectum in-

cluded in this study. According to the Goligher Classification, of the patients who were operated with the ADL method, 13 had Grade II, 32 had Grade III, and 15 had Grade IV hemorrhoids. 24 of the patients were female and 36 were male. The mean age of the patients was 40,32±8,75. The patients who were operated with the SH method, 8 had Grade II, 39 had Grade III, and 13 had Grade IV hemorrhoids. 26 of the patients were female and 34 were male. The mean age of the patients was 42,17±8,707 (Table 2). No statistically significant difference was observed between the age and gender distributions of the SH and ADL groups (p=0.231, p=0.711). No statistically significant difference was observed between the HT and DM distributions of the SH and ADL groups respectively (p=0.191) (p=0.729) (Table 2).

Table 2
Clinical characteristics of our patients

		SH Group		ADL Group		p
Age		42.17±8.707		40.32±8.75		0.231*
Gender	Male	36	56.67%	36	60.00%	0.711+
	Female	24	43.33%	24	40.00%	
HT		11	18.33%	6	10.00%	0.191+
DM		5	8.33	4	6.67	0.729+

*Independent t test + Chi-square test. HT: Hypertension, DM: Diabetes mellitus

Table 3
Clinical characteristics of our patients

VAS	SH Group	ADL Group	p‡
1st Day AVG± SD	1.63±1.09	1.13±1.0	
1st Day Median(IQR)	1 (1-2)	1 (1-1)	0.003
1st Week AVG± SD	0.57±0.93	0.37±0.66	
1st Week Median(IQR)	0 (0-1)	0 (0-1)	0.365
1st Month AVG± SD	0±0	0±0	
1st Month Median(IQR)	0 (0-0)	0 (0-0)	
p†	0.0001†	0.0001†	

‡Mann Whitney U test †Friedman test

The ADL method was applied under general anesthesia in 55 of the patients and spinal anesthesia in 5 of them because of comorbidity. The mean operative time was 12±4. 57 of them were discharged at the post-op 4-5th hour. Only 3 patient discharged the day after the operation because of pain. Postoperatively, pudendal nerve block with 10 ml of marcaine was done to patients who were operated under general anesthesia. There was no blood loss during peroperative and postoperative period. Mean follow-up period was 1 year. The post-operative VAS score at 24h, 1st week, and 1st month shown in Table 3. In the post-operative period 3 doses of intramuscular pain reliever were administered to 5 patients with stage IV hemorrhoids who underwent pexy procedure. Other patients did not need painkillers.

SH was performed under general anesthesia in 56 patients and spinal anesthesia in 4 patients. The mean operative time was 20 ±6. Postoperatively, pudental nerve block was not applied to patients who were operated under spinal anesthesia. There was aproximately 10-15 ml blood loss during peroperative period. While 55 patients were discharged on the day of the surgical procedure, the remaining patients were discharged the next day.

On the 1st day 1 VAS values in the SH group were found to be statistically significantly higher than the ADL group (p=0.003) (Table 3). No statistically significant difference was observed between the VAS values of the SH and ADL groups at 1st week (p=0.365) and at the 1st month (p=1) (Table 3).

Table 4
Statistical Evaluation of Visual Analog Scale

Dunn's Multipl Comparison Test	SH Group	ADL Group
1ST Day/ 1st Week	0.0001	0.0001
1st Day/ 1st Month	0.0001	0.0001
1st Week/ 1st Month	0.0001	0.0001

A statistically significant difference was observed between the VAS values at 1stday, 1st week, and 1st month in the SH group (p=0.0001) (Table 4). 1st day VAS values were found to be statistically significantly higher than 1stweek and 1st month VAS values (p=0.0001). 1st week VAS values were statistically significantly higher than 1st month VAS values (p=0.0001). A statistically significant difference was observed between the VAS values at 1st day, 1st week 1, and 1st month in the ADL group (p=0.0001) (Table 4). 1st day VAS values were found to be statistically significantly higher than 1stweek and 1st month VAS values (p=0.0001). 1st week VAS values were statistically significantly higher than 1st month VAS values (p=0.0001) (Table 4**).** When both groups were examined in terms of pain in the first month after surgery, it was found that the VAS score was significantly lower in the patients who had the ADL method according to the SH group (Figure 8).

Table 5
Statistical Evaluation-KATZ Index of Independence in Activities of Daily Living

KATZ	SH Group		ADL Group		p
Bathing	57	95.0%	60	100.0%	0.079+
Dressing	56	93.3%	60	100.0%	0.042+
Toilet	54	90.0%	60	100.0%	0.012+
Transferring	56	93.3%	57	95.0%	0.697+
Continence	60	100.0%	60	100.0%	
Feeding	60	100.0%	60	100.0%	

+Ki Kare testi

The Katz Index scores of these patients shown in Table 5. Katz Index score in ADL group was 6 in 57 patients discharged on the same day. 3 patients with co-morbidities required assistance during the transferring discharged on the next day. Katz Index score was 6 in 47 patients in SH group. In this group 55 patients discharged on the day of surgery and 5 patients the next day. 3 of 13 patients who underwent stapled hemorrhoidopexy needed help in the bathroom, 6 in the toilet due to fear of pain, and 4 older patients needed help for transfer and dressing. No statistically significant difference was observed between the distribution of Bathing in the SH and ADL groups (p=0.079). Dressing and Toilet activities were significantly lower in the SH group than the ADL group (p=0.042) (p=0.012). No statistically significant difference was observed between the distribution of Transferring in the SH and ADL groups (p=0.697). Both groups did not need support during feeding There was no any problem related to continence in both groups.

4. Discussion

Hemorrhoids are vascular structures consisting of smooth muscle and connective tissue covered with anal canal epithelium that divided into internal and external according to the dentate line [4]. Venous cushions are a normal part of the anorectum. Internal hemorrhoids consist of three main cushions above the dentate line: left side, right anterior and right posterior. They do not usually cause pain, as there are no somatic sensory nerves that supply internal hemorrhoids [2].

Normal hemorrhoidal pads account for 15-20% of the resting anal pressure. Thus, they support solid, liquid and gas separation. Normal hemorrhoidal tissue becomes symptomatic when enlarged. The most common symptoms are bright red rectal bleeding from the arterial structures, mucus discharge and swelling. We decided to take the Goligher classification into consideration when deciding on surgery in symptomatic patients (Table 6).

Table 6
Goligher Classification

Goligher Classification	
Grade I	Prominent hemorrhoids, no prolapse
Grade II	Prolapse after a Valsalva maneuver, prolapse reduces spontaneously
Grade III	Prolapse after a Valsalva maneuver, prolapse needs manual reduction
Grade IV	Chronic prolapse, manual reduction of prolapse ineffective

In cases where local hygiene, appropriate diet, stool softeners are not effective, surgical method was considered in the treatment[4]. Since excisional hemorrhoidectomy applied in the treatment of hemorrhoidal disease is a very painful procedure[5], less painful methods have been developed. One of them is Stapler Hemorrhoidopexy, which was introduced by Sir Antonio Longo in 1997, has been widely applied for many years in the treatment of hemorrhoidal disease [6]. In this method, also known as rectal mucopexy, a circular mucosal tissue ring is removed from the anal canal above the dentate line. The blood flow to the hemorrhoid pads is reduced[7]. If the circular suture exceeds the mucosal layer, serious complications such as perforation, rectal stricture, recto-vaginal fistula, pelvic sepsis, gas-stool incontinence and hematoma may occur [8-12]. Pathological examination revealed true mucosectomy in 55 of our patients, and mucosa and submucosa in 5 of our patients. No complications similar to these were observed in my patients. In the post-operative period, we detected tenesm complaints in 4 of our patients. The patients stated that they went to the toilet as if they needed the toilet, but they could not do it. We found that this feeling decreased by 80% with the use of cortisone suppository that we started on the second post-operative day.

Unlike the excisional hemorrhoidectomy, the pain complaint is less common since the painless region is intervened through the anal canal and no intervention is made to the breech [4,13-16]. A statistically significant difference was observed between the VAS values at 1stday, 1st week, and 1st month in the SH group (p=0.0001) (Table 4). 1st day VAS values were found to be statistically significantly higher than 1stweek and 1st month (p=0.0001). We detected headache and urinary retention in 4 of our patients who were operated under spinal anesthesia. Urinary retention problem has been solved with hot application to groin areas. For headache, extra serum therapy was applied and caffeinated drinks recommended. In 47 patients, the KATZ index score was 6 in the post-operative period. 13 patients with additional co-morbidities achieved a score of 6 on the 3rd post-op day.

Cochrane analysis 2010 not accepted SH as a standard method in the treatment of internal hemorrhoids because of high rate of recurrence and prolapse symptoms in long-term follow-up [17]. No recurrence was observed in my patients at the first year after surgery.

ADL, a new less invasive surgical method, with less postoperative pain and complication risk, was developed by Morinaga [18-20]. In this method, terminal branches of the superior rectal artery (SRA) are selectively ligated [18,20]. To locate the hemorrhoidal arteries by Doppler ultrasound, a Comepa Angiodipine-Procto device and an LDL-2 proctoscope with a translucent window through which the ligation is performed and an internal Doppler probe distal to this window are used. With CW MOD, PW MOD, and M+PW MOD, location and depth of all arteries are displayed. While it is reducing the arterial inflow in the hemorrhoidal pack at the same time the direct fixative effect of the sutures and the inflammation cause fixation of the tissue [4,21].

The closer the pexy procedure is applied to the dentate line, the more pain complaints are seen in the patients. Pain complaints assessed by VAS were significantly higher in the SH group at 1 month postoperatively compared to the ADL group (Figure 8). The most common complaint we saw in patients with pexy was tenesm. We detected tenesm complaints in 10 of our patients (16.6 %) and is seen more prominently when vessels deeper than 12mm are ligated. Rotta et al reported a tenesmus rate of 85.7% in their study and they attributed this high rate to suturing and fixation of prolapsed hemorrhoids.

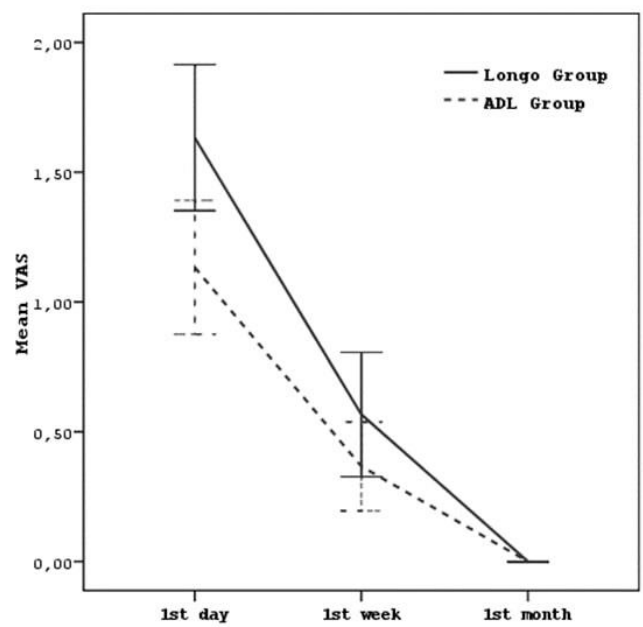

Figure 8
Post-operative pain-time graph

Bleeding after ADL procedure has been reported 2 to 29%[22-25] but there was no blood loss in our patients during peroperative and postoperative period.

When we examined both methods, the VAS score was measured higher in the SH group than in the ADL group within one month from the surgery. No pain was observed in the patients after one month. Return to daily life activities was earlier in the ADL group than in the SH group. At the end of one year, we detected recurrence in two

patients with Stage IV who underwent the ADL method. Patient satisfaction was 96%. There was no recurrence in the SH group, but 3 patients stated that they had difficulty recovering after surgery. They stated that they would not have surgery with this method again. Patient satisfaction rate was 95%.

Due to the difference in the severity of subjective symptoms such as bleeding, swelling and pain reported by the patients, there is no single effective treatment method in the treatment of hemorrhoidal disease. There is no good correlation between patients' symptoms and surgical treatment planning. It is based on the surgeon's experience to choose the appropriate surgical method that will minimize the risk of recurrence according to the stage of the disease.

5. Conclusions

We have seen that we had similar success rate. Since hemorrhoidal disease is a disease that can recur depending on the toilet habits and diet of the patients in some societies, it is necessary to choose the method that will least affect the anatomy of the anorectal region, considering that surgical intervention may be required again.

Acknowledgements

None.

Statement of ethics

This study and all relevant procedures were performed in accordance with the Helsinki Declaration after obtaining the ethical board approval from the Ethics Committee of İstanbul Kanuni Sultan Suleyman Training and Research Hospital (KAEK/2022.06.149).

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

All authors contributed to the study conception and design.

All authors read and approved the final manuscript.

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Effects of Pterygium Surgery on Holladay Equivalent Keratometry Readings

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Abstract

Aim: To investigate and compare the effects of pterygium surgery on the mean anterior surface Simulated Keratometry (SimK) and Holladay Equivalent Keratometry Readings-65 (EKR65) detail report.

Methods: For this prospective study, patients who underwent pterygium surgery between August 2022 and January 2023 were examined. All surgeries were performed under local anesthesia with conjunctival autograft method. Pentacam topography was performed after detailed ophthalmological examination before and 3 months after surgery. The mean anterior SimK, EKR65 report results in all zones, mean anterior corneal radius (rfront) and mean posterior corneal radius (rback) parameters were investigated preoperatively and at 3 months. In addition, postoperative change amounts (Δ) of SimK and EKR65 data were calculated.

Results: Twenty-four eyes of 24 patients were included in the study. The mean age of the patients was 51.50±9.48 (36-75) years. Mean anterior corneal surface SimK increased from 40.85±3.30 D, to 42.57±2.53 D at the postoperative 3rd month (p=0.003). Both rfront and rback values decreased significantly (8.30±0.66 mm vs. 7.95±0.49 mm, p=0.004, and 6.56±0.56 mm vs. 6.50±0.54 mm, p=0.001, respectively). A general increase in EKR65 report values was observed in the postoperative period. Increases in EKR65 values at 4.5, 5, 6 and 7 mm were significant (p<0.05 for all). Both ΔEKR65 at 2mm and ΔEKR65 at 3mm were found to correlate with ΔSimK (r=0.371, p=0.044 and r=0.347, p= 0.046, respectively).

Conclusions: Conventional keratometry calculations may be insufficient due to the irregularity of the cornea caused by pterygium surgery. For this purpose, the use of the results of the Holladay EKR65 detail report for irregular corneas can be considered.

Keywords: *Pterygium surgery, simulated keratometry, EKR65, corneal radius*

1. Introduction

In the Pentacam topography/tomography system with Scheimpflug camera technology, detailed and various analyzes of keratometry calculation are made. Simulated keratometry (SimK) and The Holladay Equivalent Keratometry Readings-65 (EKR65) detail report are some of them. For SimK measurement, the device calculates the anterior corneal radius and determines corneal power using the standard keratometric index (n=1.3375)[1,2]. As in other topography systems, posterior corneal curvature cannot be measured directly, and calculations are made by assuming a constant ratio of anterior and posterior curvature[1-3]. In the Holladay EKR65 detail report, posterior corneal curvature is also measured besides anterior corneal curvature[1,4,5]. It is argued that it gives more accurate results due to the change in the anterior/posterior curvature ratio in patients undergoing refractive surgery or other irregular corneas[2,3,6]. Pterygium occurs with the progression of the bulbar conjunctiva on to the cornea in the form of fibrovascular tissue[7,8]. It has been reported to cause significant changes in corneal shape and curvature[7-9]. The effects of corneal irregularity caused by pterygium and its surgery on curvature changes and keratometry calculations are a matter of curiosity. Therefore, in this study, it was aimed to examine and compare the effects of pterygium surgery on the SimK and EKR65 report. As far as we know, there is no study evaluating the effect of pterygium surgery on the results of the EKR65 report.

2. Materials and methods

For this prospective study, patients who underwent pterygium surgery between August 2022 and January 2023 were examined. Patients with nasal and primary pterygium were included. Patients

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Received: 31.07.2023, Accepted: 10.08.2023, Available Online Date: 31.08.2023, Cite this article as: Aydamirov SA, Kiziltas B, Ismayilov AS. Effects of Pterygium Surgery on Holladay Eqiuvalent Keratometry Readings. J Cukurova Anesth Surg. 2023; 6(1): 296-9. doi: 10.36516/jocass.1334962

with a previous history of ocular trauma or surgery, ocular infection or inflammation, corneal scarring, pseudopterygium, recurrent or temporal pterygium were excluded from the study. Pterygium are divided into 3 types according to their size. Small pterygium infiltrating the cornea less than 2 mm were classified as type 1, those infiltrating the cornea 2-4 mm were classified as type 2, and those infiltrating more than 4 mm were classified as type 3[10].This research adhered to the principles outlined in the Declaration of Helsinki and was approved by the local institutional ethics committee. Informed consent was obtained from each patient.

All surgeries were performed under local anesthesia with conjunctival autograft method. Pterygium borders marked. Subconjunctival lidocaine hydrochloride (1%) was applied for local anesthesia. The head of the pterygium was separated from the cornea by blunt dissection. Then, the pterygium body and subconjunctival fibrovascular tissue were excised. The dimensions of the exposed nasal sclera were measured. Upper conjunctival graft in required sizes was taken after local anesthesia. In the bare area, the graft was sutured to the conjunctiva approximately 1 mm behind the limbus. Absorbable interrupted 8.0 Vicryl (8-mm 0.5-c spatula double-armed violet braided; Ethicon) suture material was used for conjunctival sutures. In the postoperative period, drops containing a combination of 0.5% concentration of moxifloxacin and 0.1% concentration of dexamethasone to be used 5 times a day for 4 weeks were prescribed to all patients. In the postoperative period, follow-up was recommended for the patients on the 1st day, 1st week, 4th week, 3rd month and 6th month.

Pentacam topography was performed after detailed ophthalmological examination before and 3 months after surgery. The test was performed in a sitting position and in a dark room. Measurements were repeated until reproducible data were obtained. Only the measurements of patients who could meet the reliability parameter (Quality specification: Ok) were included.

The Holladay EKR 65 detail report divides the cornea into zones starting from the central 1 mm diameter up to 7 mm peripheral at 1 mm intervals. Total corneal power is calculated in all zones. The mean anterior SimK, EKR65 report results in all zones, mean anterior corneal radius (r_{front}) and mean posterior corneal radius (r_{back}) parameters were investigated preoperatively and at 3 months postoperatively. In addition, postoperative change amounts (Δ) of SimK and EKR65 data were calculated. The Δ value for the variables was found by subtracting the mean of the preoperative values from the mean of the postoperative values.

2.1 Statistical Analysis

Continuous variables were presented as mean±standard deviation. Data normality was confirmed using the Shapiro-Wilk test. Paired-sample t-test was used in dependent groups. The correlation between the variables was analyzed by Spearman analysis. SPSS (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) software was used for statistical analysis and a p value of <0.05 was considered statistically significant.

3. Results

Twenty-four eyes of 24 patients were included in the study. The mean age of the patients was 51.50±9.48 (36-75) years. Type 2 pterygium was present in 10 patients and type 3 pterygium in 14 patients. The demographic data of the patients are summarized in Table 1. Mean anterior corneal surface SimK increased from 40.85±3.30, to 42.57±2.53 at the postoperative 3rd month (p=0.003). The mean radius of curvature values on both anterior and posterior corneal surfaces decreased significantly (8.30±0.66 vs. 7.95±0.49, p=0.004, and 6.56±0.56 vs. 6.50±0.54, p=0.001, respectively).

Table 1

Demographic characteristics of patients

	n=24
Age (years)	51.50±9.48 (36-75)
Sex (female/male)	9/15
Laterality (right/left)	12/12
Pterygium type	
Type 1	-
Type 2	10
Type 3	14
Preoperative SE (D)	0.65±1.74 (-2-(+3))
Postoperative SE (D)	0.55±1.11 (-2-(+3.5)
Preoperative BCVA (Snellen)	0.73±0.21 (0.4-1)
Postoperative BCVA (Snellen)	0.8±0.14 (0.6-1)
Preoperative CA-front (D)	3.23±2.41 (0.76-6.4)
Postoperative CA-front (D)	1.81±1.29 (0.2-4.3)
Preoperative CA-back (D)	0.48±0.74 (0-2.3)
Postoperative CA- back (D)	0.33±0.33 (0.1-1.1)

SE: Spherical equivalent, BCVA: Best corrected visual acuity, CA: Corneal astigmatism, D: Diopter

Table 2

Comparison of mean anterior SimK, mean rfront, mean rback and EKR65 values in the preoperative and postoperative period

	Preoperative (Mean ± SD)	Postoperative 3rd month (Mean ± SD)	p
Mean anterior SimK (D)	40.85±3.30	42.57±2.53	0.003
Mean rfront (mm)	8.30±0.66	7.95±0.49	0.004
Mean rback (mm)	6.56±0.56	6.50±0.54	0.001
EKR65 at 1 mm (D)	42.26±3.31	42.24±2.39	0.951
EKR65 at 2 mm (D)	42.47±2.40	42.59±1.89	0.445
EKR65 at 3 mm (D)	42.64±2.11	42.84±1.90	0.066
EKR65 at 4 mm (D)	42.86±2.21	43.00±2.10	0.119
EKR65 at 4.5 mm (D)	42.86±2.23	43.06±2.12	0.036
EKR65 at 5 mm (D)	42.52±1.90	43.13±2.14	0.022
EKR65 at 6 mm (D)	43.10±2.10	43.26±2.17	0.006
EKR65 at 7 mm (D)	43.22±2.14	43.51±1.99	<0.001

*Paired samples t-test, p < 0.05 statistically significant. Results are denoted as mean ± standard deviation (SD). SimK: Simulated keratometry, rfront: radius of curvature at the front corneal surface, rback: radius of curvature at the back corneal surface, EKR: Equivalent keratometry reading

A general increase in EKR65 report values was observed in the postoperative period. Increases in EKR65 values at 4.5, 5, 6 and 7 mm were significant (p<0.05 for all) (Table 2).

The postoperative mean changes in SimK and EKR65 data are given in Table 3. ΔSimK and ΔEKR65 values were positive, denoting a postoperative mean increase in SimK and EKR65 values.

Both ΔEKR65 at 2mm and ΔEKR65 at 3mm were found to correlate with ΔSimK (r=0.371, p=0.044 and r=0.347, p= 0.046, respectively) (Table 4).

Table 3
Mean differences in SimK and EKR65 values

ΔSimK (D)	1.47±1.92 (-2-5.7)
ΔEKR65 at 1 mm (D)	0.30±1.54 (-2.56-2.74)
ΔEKR65 at 2 mm (D)	0.12±0.75 (-0.95-1.25)
ΔEKR65 at 3 mm (D)	0.20±0.50 (-0.43-1.18
ΔEKR65 at 4.5 mm (D)	0.20±0.45 (-0.73-0.73)
ΔEKR65 at 5 mm (D)	0.61±1.23 (-0.59-3.64)
ΔEKR65 at 6 mm (D)	0.16±0.26 (-0.17-0.59)
ΔEKR65 at 7 mm (D)	0.31±0.33 (-0.10-0.96)

Δ: Mean differences (Mean of the postoperative values- mean of the preoperative values), SimK: Simulated keratometry, EKR: Equivalent keratometry reading. Results are denoted as mean ± standard deviation.

Table 4
Correlation analysis results of ΔSimK and ΔEKR65 values

	ΔSimK
ΔEKR65 at 1 mm	r=0.218 p=0.306
ΔEKR65 at 2 mm	r=0.371 p=0.044
ΔEKR65 at 3 mm	r=0.347 p=0.046
ΔEKR65 at 4 mm	r=-0.024 p=0.912
ΔEKR65 at 4.5 mm	r=0.205 p=0.337
ΔEKR at 5mm	r=0.048 p=0.824
ΔEKR65 at 6 mm	r=-0.048 p=0.824
ΔEKR65 at 7 mm	r=0.084 p=0.697

Spearman Correlation Analysis, the cells contain the correlation coefficient and the corresponding P-value. Δ: Mean differences (Mean of the postoperative values- mean of the preoperative values), SimK: Simulated keratometry, EKR: Equivalent keratometry reading.

4. Discussion

In conventional topographic SimK, the central 3 mm of the cornea is used, it is assumed that there is a constant ratio between the anterior and posterior radius and the cornea consists of a single refractive surface[4, 5]. In the Holladay EKR65 report, posterior corneal curvature is also measured and the effect of the posterior cornea is taken into account[4, 5]. In this report, the cornea is divided into zones from central 1mm to 7mm. 65% of the mean of the keratometry values in each examined zone is calculated. For irregular corneas such as postrefactive, postkeratoplasty, and scarred corneas, this report makes it possible to obtain a mean K value from a larger surface[6, 11]. In addition, another advantage of EKR65 data is that it can be used directly in biometric measurements[4]. In the literature, it has been reported that EKR65 at 4.5 mm gives more accurate refractive results in cataract surgery than conventional SimK in eyes undergoing refractive surgery[2, 3]. Accurate measurement of keratometry is very important for optimum refractive results after cataract surgery. Considering that pterygium patients are generally elderly and have accompanying cataracts, accurate measurement of keratometry becomes very important in cataract surgery after pterygium excision. Therefore, in this study, it was aimed to compare the results of conventional SimK and EKR65 report in eyes with pterygium excision. There is no other study in the literature on the effect of pterygium surgery on the EKR65 report.

In this prospective study, mean anterior SimK increased significantly after pterygium surgery. There are other studies reporting significant steeping in the front cornea after pterygium surgery[12-17]. One of the hypotheses is that the meridian where the pterygium is located is flattened by the effect of its mechanical compression[14, 17, 18]. Another hypothesis is that the tear meniscus pooling between the corneal apex and the pterygium causes flatter results[14, 18]. In this study, postoperative increases were detected in the EKR65 report, similar to SimK. The increases were statistically significant in the 4.5 mm and above zones. From this result, it can be interpreted that the flattering effect of the pterygium is more dominant in the peripheral cornea close to the limbus.

Significant reductions in anterior and posterior corneal radius were detected in this study. There are studies in the literature showing that pterygium surgery causes anterior and posterior corneal radius changes[7, 8]. Based on these findings, it comes to the fore that the anterior/posterior radius ratio, which is assumed to be constant in SimK measurement, may change as a result of pterygium surgery and SimK may be insufficient in the calculation of intraocular lens power. Considering the EKR65 report in this group of patients may be more beneficial in this respect. However, there is a need for larger studies including the results of cataract surgery on this subject.

Holladay EKR65 detail report has been developed especially for intraocular lens calculation in corneas undergoing refractive surgery and with irregularities[1, 6, 19]. The comparison of conventional keratometry measurements with EKR65 report data has been made in the literature. Symes et al.[4]reported that EKR65 at 3 mm data was most compatible with Scheimpflug keratometry reading in terms of cataract surgery results in eyes that had not undergone refractive surgery. Holladay et al. [2] reported that the most accurate refractive results were obtained with EKR65 at 4.5 mm data in eyes undergoing corneal refractive surgery. Achiron et al.[20] examined EKR65 at 2mm data in terms of refractive prediction in irregular corneas and found that the results were similar to conventional keratometry but better than Scheimpflug keratometry reading.

It is a matter of curiosity which EKR65 measurement is best agreed with SimK. For this purpose, the correlations of postoperative change amounts were examined in this study. A weak correlation was found with the change in SimK and the change in the EKR65 report at 2 and 3 mm. The information that corneal central 3 mm was used in SimK measurement may support this result.

5. Conclusions

Keratometry measurements based on the conventional hypothesis may be insufficient in the calculation of intraocular lens power due to the distortion and irregularity of the cornea caused by the pterygium and its surgery. The use of the EKR65 report recommended for irregular corneas in this patient group may be considered. For this purpose, more comprehensive and long-term studies are needed.

Acknowledgements
None.

Statement of ethics
The study was compliant with the Declaration of Helsinki and additional approval was obtained from the Adana City Training and Research Hospital ethics committee (2022- 109, number of decision: 2030).

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

Funding source
The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions
ASA: Concept, design, surgical practice, data analysis, literature search, manuscript preparation and manuscript review. BK: Concept, design, surgical practice, data acquisition and manuscript review. ASI: Concept, design, statistical analysis, literature search and manuscript review.

All authors read and approved the final manuscript.

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Evaluation of Vancomycin Therapeutic Drug Monitoring in Intensive Care Units of a University Hospital

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Abstract

Aim: Therapeutic drug monitoring (TDM) of vancomycin aims to achieve an optimal response and minimize the risk of toxicity by keeping plasma levels within the therapeutic range. In this study, we aimed to evaluate the treatment and appropriateness of TDM in patients receiving vancomycin.

Methods: For this purpose, patients who received vancomycin in the ICUs of a university hospital during 8-month period between January and August 2022 were retrospectively evaluated. Demographic data, presence of renal dysfunction, length of stay, duration of treatment, dose, concomitant medications, presence of extracorporeal method, TDM, sampling time (trough and peak level) were collected.

Results: Within the scope of the study, 213 prescriptions of 202 patients were evaluated and it was revealed that TDM was performed in 18 (8%). A total of 26 trough (n=12) and peak (n=14) level were obtained. Three (25%) of the trough and eight (57%) of the peak samples were taken at the wrong time. 50% of the trough and 64% of the peak level results were outside the reference range. TDM was not performed in 174 patients taking nephrotoxic drugs concomitantly with vancomycin. There were 84 patients who developed acute kidney injury during treatment. TDM was performed in 10 (15%) of 65 patients with pretreatment renal dysfunction.

Conclusions: In order to minimize the risk of nephrotoxicity and to get the appropriate response, it is recommended that physicians should have a conscious approach, clinical pharmacists should take an active role and hospital pharmacists should make arrangements in the orders of patients who do not have TDM.

Keywords: *Vancomycin, TDM, intensive care unit, plasma level.*

1. Introduction

Critically ill patients in intensive care units (ICUs) receive polypharmacy for treatment and prophylaxis. Due to factors such as the variable condition of critically ill patients and polypharmacy, treatment is frequently reviewed and modified[1,2]. Therapeutic drug monitoring (TDM) enables narrow therapeutic range drugs to reach optimum therapeutic concentrations and individualization of doses to prevent/reduce potential toxicity. The availability of TDM in many hospitals plays an important role in personalized pharmacotherapy[3]. The aims of TDM are to inCrease drug efficacy and safety, minimize side effects and reduce drug costs. Vancomycin is a widely used antibiotic for the treatment of gram-positive bacterial infections, including *Methicillin-resistant Staphylococcus aureus* (MRSA)[4]. It is excreted from the kidneys largely unchanged. Vancomycin clearance is decreased in patients with reduced renal function. Therefore, doses should be reduced or dose intervals should be increased[5]. In addition, the dose should be adjusted due to the altered pharmacokinetics of the drug with the presence of obesity in patients.

The pharmacokinetic profile of vancomycin is characterized by pharmacokinetic/pharmacodynamic (PK/PD) properties that conform to a multicompartmental model (variable tissue penetration) showing that its efficacy and safety are multifactorial. The best PK/PD index to predict vancomycin activity is the ratio between area under the 24-hour concentration-time curve (AUC_{0-24}) and MIC (AUC/MIC), and a value above 400 is considered to indicate clinical and microbiological efficacy against serious infections. Therapeutic drug monitoring is recommended as a more practical alternative for monitoring the treatment, as calculating the AUC for monitoring the efficacy of vancomycin therapy requires the collection of multiple vancomycin serum concentrations and pharmacokinetic software that is not accessible in every institution. In order to reach the targeted AUC/MIC (>400) ratio, it is stated that the vancomycin trough level should be 15-20 µg/ml[6].

Optimal response is obtained when the plasma concentration of

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Received: 10.08.2023, Accepted: 21.08.2023, Available Online Date: 31.08.2023
Cite this article as: Surmelioglu N, Berber M. Evaluation of Vancomycin Therapeutic Drug Monitoring in Intensive Care Units of a University Hospital. J Cukurova Anesth Surg. 2023; 6(2): 300-3. doi: 10.36516/jocass.1341016

vancomycin is kept above the minimum inhibitory concentration values [5]. TDM of vancomycin is recommended both to ensure treatment efficacy and to prevent the development of acute kidney injury (AKI) [4]. This study aimed to evaluate the appropriateness of the TDM process and length of stay of patients receiving vancomycin treatment in adult ICUs of a university hospital.

2. Materials and methods

This retrospective and observational study was conducted at a university hospital. In this context, the files of patients who received vancomycin treatment in the hospital during the 8-month period between January 1, 2022 and August 31, 2022 were retrospectively analyzed. The study included;

- Patients treated in the adult intensive care units of x University Faculty of Medicine Hospital,
- On day one of vancomycin treatment between the specified dates,
- Received vancomycin treatment for at least 30 hours (time required to reach steady state),
- Patients aged 18 years and older were included.

Demographic characteristics of the included patients; gender, age, height/weight, body mass index, body surface area, APACHE II (Acute Physiology and Chronic Health Evaluation) and clinical data;

Pre-treatment renal dysfunction (GFR<50mL/min), duration of hospitalization, duration of vancomycin treatment, vancomycin dose information, concomitant medications, presence of extracorporeal method, plasma level monitoring process information [sampling time (trough and peak level), plasma level result] were scanned from the hospital information management system (Enlil HIS) and recorded in the data collection form used in the study.

Based on the information obtained, the appropriateness of the vancomycin dose was evaluated according to the patient's demographic characteristics and comorbidities (e.g. obesity and/or renal dysfunction and/or presence of extracorporeal method). For vancomycin plasma level monitoring, the accuracy of the sampling time and, if sampled, whether the trough or peak levels were within the reference range were examined by clinical pharmacist.

3. Results

Within the scope of the study, the vancomycin treatment process in 213 different hospitalizations of 202 patients who received vancomycin treatment and met the inclusion criteria was evaluated. Eleven of these patients were hospitalized in the specified ICUs in 2 different periods.

Renal dysfunction (GFR≤ 50 mL/min) was detected in 63 (31%) of 202 different patients who received vancomycin treatment in adult ICUs before vancomycin treatment. The median duration of hospitalization in the ICU was 18 days (2-92). The median duration of vancomycin treatment was 7 days (2-52). Descriptive statistical data of the patients are presented in Table 1.

In line with the findings obtained, it was determined that 43 of 174 patients whose body mass index was calculated were obese (Body mass index ≥ 30 kg/m^2) and the height and weight of 28 patients were not recorded. Vancomycin levels were measured in 6 of 43 obese patients. In 5 obese patients, it was determined that the vancomycin dose was not appropriate (low or high) during treatment. Of the 65 patients with renal dysfunction prior to vancomycin treatment, 29 patients had extracorporeal life support. There were 84 patients (39%) who developed AKI during vancomycin treatment. The mean number of drugs used in addition to vancomycin during hospitalization was 8.86 ± 2.68 and the mean number of nephrotoxic drugs was 1.44 ± 0.8 (0-4). TDM was not performed in 174 patients who used at least 1 nephrotoxic drug concomitantly with vancomycin. The number of patients using nephrotoxic drugs concomitantly with vancomycin is shown in Table 1. The sampling time of 6 of 15 samples taken from 11 patients who developed AKI and underwent TDM was incorrect. 4 vancomycin levels are within the reference range, 4 are in the supratherapeutic range and 1 are in the subtherapeutic range.

Vancomycin TDM was performed in 18 different patients from 213 vancomycin treatment courses evaluated within the scope of the study. A total of 12 trough levels and 14 peak levels were analyzed in these patients. Whether the trough and peak results were within the reference range was evaluated and given in Table 2. It was determined that dose adjustment was performed only in 4 out of these 18 patients after theevaluation of vancomycin plasma levels. The median duration of ICU stay of the 18 patients with vancomycin plasma levels was calculated as 13 days (3-44).

Timing of vancomycin samples taken, 3 out of 12 samples analyzed for trough level and 8 out of 14 samples analyzed for peak level were inappropriate. The distribution of trough and peak samples according to the time of collection is given in Table 3.

Plasma levels were monitored in 10 of 65 patients with renal dysfunction before vancomycin treatment. Also, plasma levels were monitored in 11 of 84 patients who developed AKI during vancomycin treatment. It was determined that no vancomycin TDM was performed in any patient included in the study in the neurosurgery ICU, neurology ICU, COVID-19 ICU. It was performed mainly in the medical ICU (7 of 85 patients), anesthesiology and reanimation ICU (7 of 39 patients), surgical ICU (3 of 22 patients), and coronary ICU (3 of 14 patients) (Table 4).

Table 1

Demographical Features of The Patients (n=202)

Demographics	
Female, n (%)	81 (40)
Age, years	58,90 ± 17,68
Patients with renal function pre-treatment, n (%)	65 (%31)
Length of stay (day), median (minimum-maximum)	18 (2-92)
Duration of vancomycin treatment (day), median (minimum-maximum)	7 (2-52)
Concomitant of Nephrotoxic Drugs, n (%)	
• 0	22 (%10)
• 1	94 (%44)
• 2	80 (%38)
• 3	16 (%7.5)
• 4	1 (%0.5)

Table 2

Distribution of Vancomycin Trough and Peak Levels

	Subtherapeutic Level (n)	Level Within Reference (n)	Supratherapeutic Level (n)	Total
Trough	2	6	4	12
Peak	5	5	4	14
Total	7	11	8	26

Table 3

Distribution of Vancomycin Sample Times

	Sampling Time	n
	Appropriate	
	After reaching steady state level	4
Trough Level	1-2 hours before the next dose	5
	Inappropriate	
	Without reaching a steady state level	1
	5-6 hours before the next dose	2
	Appropriate	
	1-2 hours after end of infusion	4
Peak Level	Inappropriate	
	Before distribution completed	8
	>2 hours after end of infusion	2

Table 4

Distribution of vancomycin plasma level monitoring according to intensive care

Intensive Care Unit	Number of Patients Receiving Vancomycin, n (%)	Number of Patients with Vancomycin Plasma Levels
Internal Medicine ICU	85 (%40)	7
Anesthesiology and Reanimation Unit	39 (%18)	7
Brain Surgery ICU	28 (%13)	0
General Surgery ICU	22 (%10)	3
Coronary ICU	14 (%7)	3
COVID-19 ICU	13 (%6)	0
Neurology ICU	12 (%6)	0

ICU: Intensive Care Unit

4. Discussion

In this study, we evaluated the appropriateness and outcomes of TDM of vancomycin in adult ICUs of a university hospital. For this purpose, the trough concentration of patients receiving vancomycin treatment should be monitored after the vancomycin serum level reaches steady state, i.e., 30-60 minutes before the 4th dose after at least three doses of vancomycin treatment every 12 hours by intravenous infusion. Vancomycin requires 5 half-lives to reach steady state. Elimination half-life is 6-12 hours in adults [7]. In this case, samples should be taken within 30-60 hours after vancomycin dosing to check the trough level. Therefore, patients who received vancomycin treatment for at least 30 hours were included in the study.

It has been reported that there is a continuous increase in the use of vancomycin, which is one of the most commonly prescribed antibiotics in hospitalized patients, in treatment and that this is mostly seen in ICUs [8,9]. Physiologic changes occurring during critical illness alter the pharmacokinetics of vancomycin and thus its plasma level. Therefore, TDM of vancomycin, which has a narrow therapeutic interval and is a hydrophilic drug, should be performed in appropriate indications in critically ill patients [10]. In the ICUs included in this study, 26 vancomycin concentrations were evaluated in only 18 (8%) different patients out of 213 vancomycin treatments and plasma levels were not monitored in 195 patients (92%).

Ye et al demonstrated that the clinical efficacy rate was higher and the risk of side effects was reduced in the group in which TDM of vancomycin was performed compared to the group in which it was not performed [11]. The retrospective evaluation of the data in our study and the low number of patients who underwent TDM (8%) limited the study and clinical efficacy, and safety comparisons could not be made between the two groups.

TDM should not be considered only as determining the drug level in the sample. When monitoring is performed, factors such as the purpose for which monitoring will be performed, when the sample is taken, and the method and time of administration of the drug should be taken into consideration [12]. Errors made in the timing of sampling are among the most important factors affecting the evaluation of the results [13]. Inaccurate evaluation of the results leads to inadequate response to treatment or toxicity [1]. In our study, in addition to the fact that the rate of vancomycin TDM was very low, it was found that 25% of the samples with trough levels and 57% of the samples with peak levels were taken at the wrong time.

Incorrect evaluation of plasma levels by physicians brings along problems such as increased treatment costs [1]. Darko and Gatta emphasized in their study that preventing the risk of vancomycin-related nephrotoxicity with TDM provides significant cost savings [14,15]. In the study by Ye et al., the duration of hospitalization in the TDM group was not found to be significantly shorter compared with the non-monitored group [11]. In our study, the median length of hospitalization of patients without plasma level monitoring during vancomycin treatment was 18 (2-92) days, while the median length of hospitalization of patients with plasma level monitoring decreased to 13 (3-44) days.

When determining the dose of vancomycin, the actual weight of the patient should be taken into account [16]. However, 43 of our patients were obese and it was observed that they did not receive appropriate doses when their doses were calculated based on their actual weight. In addition, it was determined that 37 of these patients did not receive TDM. In patients with impaired renal function and/or receiving extracorporeal therapy, dose assessment should be made according to the GFR value or the extracorporeal method used and the appropriateness of the dose should be evaluated with TDM at appropriate times [16]. Within the scope of the study, the dose of vancomycin treatment was evaluated by considering the mentioned factors and taking the guidelines as reference, and it was determined that the dose of 152 (71%), 25 (12%), and 7 (3%) patients were appropriate, high, and low, respectively, out of 213 patients. There were 29 (14%) patients whose vancomycin treatment dose was determined without evaluating the presence of obesity (without measuring height and weight). In a study by Carland et al., 42% of the vancomycin maintenance dose was found to be compatible with the guidelines, 34% was found to be low, and 24% was found to be high, and it was shown that 60% of subtherapeutics and 43% of supratherapeutics were not dose adjusted [4]. In our study, out of 26 plasma level results of 18 different patients, 15 plasma level results of 11 different patients were not in the therapeutic range. In 7 (64%) of these patients, no change was made in treatment. In 4 patients, the next dose was reduced and treatment was continued.

Vancomycin-induced AKI is defined as an increase of ≥ 0.5 mg/dL in serum creatinine level, a 50% increase compared to baseline or a 50% decrease in calculated creatinine clearance on two consecutive days compared to baseline. It has also been suggested that the risk of AKI increases when the trough concentration is above 15-20 mg/L [16]. In patients with renal dysfunction, vancomycin serum concentrations should be monitored and the dose should be repeated

after the plasma level reaches the target range [1]. In our study, vancomycin plasma concentrations were not monitored in 73 of 84 patients (87%) who developed vancomycin-induced AKI. In addition, trough level monitoring is recommended for all patients using nephrotoxic drugs concomitantly with vancomycin [17]. In this study, vancomycin plasma concentrations were not monitored in 174 (90%) of 191 patients who were found to use concomitant nephrotoxic drugs.

Although the retrospective nature of the study was a limiting factor, it led to objective results in line with the aim of the study, since the decisions of physicians in the treatment and therapeutic drug monitoring processes were not intervened. However, it also limited access to clinical efficacy and safety data. The fact that the study was conducted in the ICUs of a single university hospital and reflected a short period of 8 months brings along the necessity of conducting a larger study in our country.

5. Conclusions

In line with the findings, it has been determined that there is not enough TDM to ensure the efficacy and safety of vancomycin, one of the most commonly used antibiotics, in critically ill patients. Especially in critically ill patients, the pharmacokinetics and thus the effect of vancomycin changes with variable physiology and polypharmacy. In this study, it was revealed that the rate of TDM was very low in critically ill patients receiving vancomycin treatment despite the presence of risk factors such as concurrent nephrotoxic drug use, renal dysfunction and obesity. In addition, it was determined that in patients with TDM, samples were mostly taken at the wrong time. This situation caused physicians to misinterpret the results.

Previous studies and this study suggest that TDM, if performed at the right time and evaluated correctly, will both shorten the hospitalization period of the patient and would be also beneficial in minimization of treatment cost. Increased awareness of physicians and routine patient monitoring by clinical pharmacists will ensure the efficacy and safety of vancomycin treatment. In addition, it is recommended that hospital pharmacists should also monitor the vancomycin treatment process and new regulations should be introduced for the treatment approvals of critically ill patients whose vancomycin plasma levels are not monitored.

Acknowledgements

None.

Statement of ethics

This study was approved by Cukurova University Faculty of Medicine Ethics Committee for Animal Experimentation with the protocol number (134/62).

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

Conception: NS Design: NS Data collection: NS, MB Analysis and interpretation: NS, MB Writer: NS, MB Supervision: NS

All authors read and approved the final manuscript.

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https://doi.org/10.1086/600877

Investigation of the Efficacy Results of Atmospheric Cold Plasma Against Multi-Resistant Bacterial Strains

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Abstract

Aim: To investigate the efficacy of Atmospheric Cold Plasma (ACP)-treated phosphate buffered saline (PBS) against Gram positive and Gram negative multidrug resistant bacteria.

Methods: A total of 50 carbapenem-resistant *Klebsiella pneumoniae* and 10 vancomycin-resistant *Enterococcus faecium* strains were included in the study. 100 µl (1/2), 300 µl (3/4), 700 µl (7/8), 1500 µl (15/16), 3100 µl (31/32), 6300 µl of ACP-treated PBS was added to 100 µl of bacterial suspension (10^7 CFU/ml bacterial suspension). After pipetting, the suspension was incubated at room temperature for 30 minutes, inoculated onto sheep blood agar and incubated overnight (16-18 hours) at 37°C.

Results: All strains studied were inhibited by ACP-treated PBS solution. The dilutions given are those in which growth was completely inhibited. 45 of *K. pneumoniae* strains were completely inhibited by ACP-treated PBS solution at 3/4 concentration, while 5 of *K. pneumoniae* strains were completely inhibited by ACP-treated PBS solution at 7/8 concentration. Vancomycin-resistant *E. faecium* strains were inhibited by higher amounts of plasma than *K. pneumonia* strains. Three of *E. faecium* strains 15/16, three of *E. faecium* strains 31/32, four of *E. faecium* strains 63/64 were completely inhibited by ACP-treated PBS solution.

Conclusions: ACP-treated PBS solution was found to be effective against both Gram-positive and Gram-negative bacteria resistant to important antibiotics. A difference in the concentration of ACP-treated PBS required for inactivation was observed in the selected Gram-negative and Gram-positive bacteria. However, this method is hopeful as the available treatment options are limited day by day in both Gram-negative and Gram-positive infections. Future studies are needed for the use of ACP-treated PBS fluids as a treatment modality.

Keywords: *Plasma, multidrug resistance, efficacy, anti-bacterial agents*

1. Introduction

Gram-negative, multidrug-resistant bacteria from the Enterobacterales family are rapidly increasing in our country as well as throughout the world. These isolates may be resistant to antibiotics such as carbapenems, which are the last choice in the treatment of serious infections, and this resistance development may lead to treatment failures by limiting clinical treatment options[1]. Although enterococci, which are Gram-positive bacteria, are members of the intestinal and vaginal flora, they have developed high-level resistance to glycopeptide-derived antibiotics, especially beta-lactam and aminoglycoside groups, because of intensive and faulty antibiotic use in hospitals[2,3]. The decline in treatment options for both Gram-negative and Gram-positive infections has led to the search for other treatment modalities.

Atmospheric Cold Plasma (ACP) has gained increasing importance in recent years due to its strong antimicrobial activities on bacteria, viruses, fungi, and prions[4]. Reactive oxygen radicals (ROS), reactive nitrogen radicals (RNS) and other free radicals formed during the process play a role in the antimicrobial activity of ACP[5]. Recently, it was reported that ACP-treated phosphate buffered saline (PBS) solution gained antimicrobial activity and eventually became effective on multidrug resistant bacteria[6]. Joshi et al[4] demonstrated that a significant amount of ROS is produced by ACP and leads to antibacterial effect through lipid peroxidation and DNA damage in *Escherichia coli* strains. The efficacy of ACP-treated fluids in preventing bacterial infections has been demonstrated in animal studies, as in the study by Oztan et al[7]. It is thought to be a potential new treatment alternative

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Received: 14.08.2023, Accepted: 22.08.2023, Available Online Date: 31.08.2023
Cite this article as: Togay A, Tekin D, Irmak SE, et al. Investigation of the Efficacy Results of Atmospheric Cold Plasma Against Multi-Resistant Bacterial Strains. J Cukurova Anesth Surg. 2023; 6(2): 304-7.
doi: 10.36516/jocass.1342678

for the treatment of multidrug resistant bacteria, which have an important place in nosocomial infections. Therefore, it is important to demonstrate the efficacy of ACP-treated fluids against multidrug resistant bacteria. In this study, we aimed to investigate the efficacy of ACP against Gram positive and Gram negative multidrug resistant bacteria.

2. Materials and methods

2.1. Preparation of bacterial suspension:

Multidrug resistant *Klebsiella pneumoniae* and vancomycin-resistant enterococci (VRE) isolated from various clinical samples were revived from bacterial stocks in the Izmir Tepecik Training and Research Hospital Medical Microbiology Laboratory. bacterial strains were cultured on sheep blood agar and incubated overnight (16-18 hours) at 37°C. After incubation, colonies collected from the resuscitated strains were prepared in phosphate buffered saline (PBS) at a density of 0.5 McFarland (10^8 CFU/ ml) and diluted to 10^7 CFU/ml according to the recommendations of Oztan et al.[7]. Standard bacterial strains known as American Type Culture Collection (ATCC), *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *E. coli* ATCC 25922 were tested with ACP-treated PBS.

2.2. Preparation of ACP-treated PBS solution:

Atmospheric cold plasma was obtained from the Izmir Katip Çelebi University, Department of Biomedical Engineering Plasma Laboratory. Sterile PBS solution (0.9% NaCl) was processed under normal atmospheric pressure to flow through the set-up (see Figure 1). The setup consisted of a copper electrode whose surface is covered with a 1-mm glass act as dielectric barrier connected to a high voltage cable to obtain dielectric barrier discharge plasma. The microsecond alternating current (AC) power supply was operated at a peak-to-peak voltage of 24 kV, a discharge current of 3.5 mA and a frequency of 25 kHz, giving approximately 9 W in terms of power output. 3 ml of PBS was transferred into a petri dish made of glass with a diameter of 40 mm and treated for 5 min at a constant discharge gap of 1.5 mm. After ACP treatment, the PBS solution was collected and stored at +4°C.

Figure 1

Image of the plasma setup for the treatment of phosphate buffered saline solution.

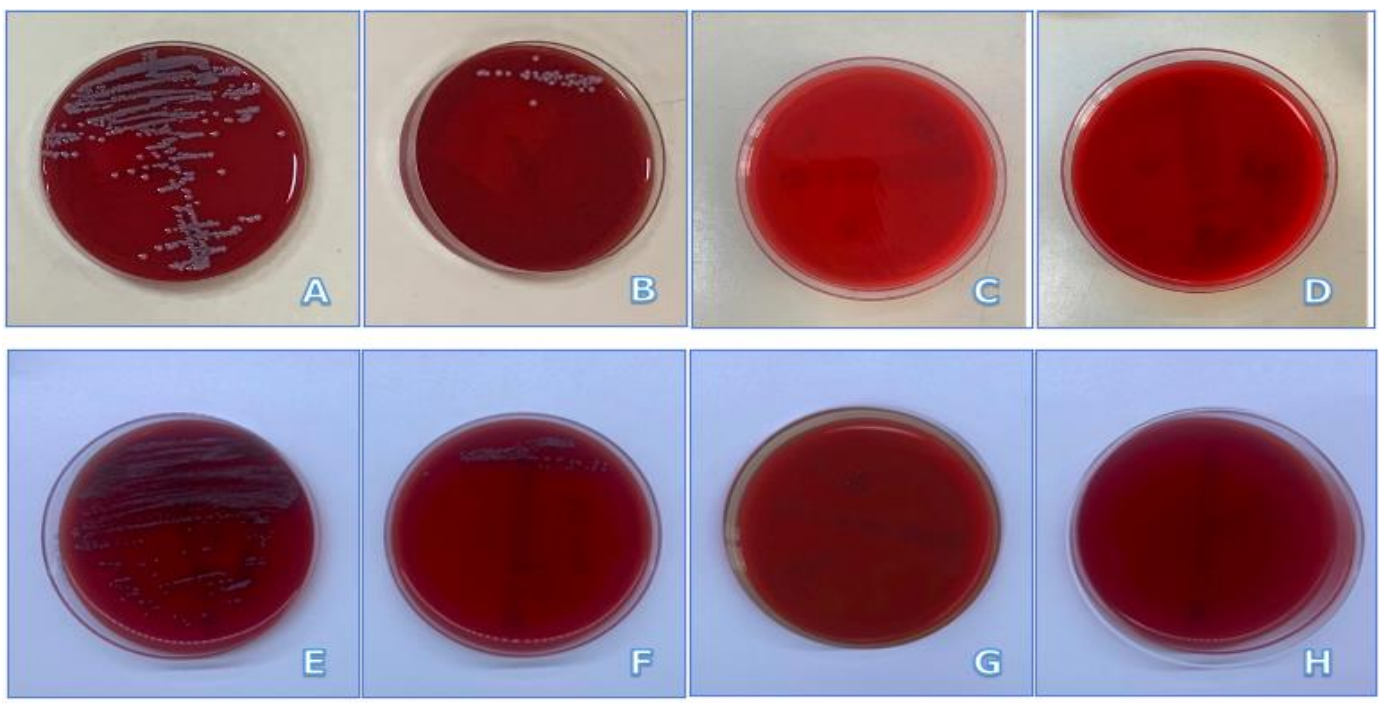

Figure 2

Efficacy samples of ACP-treated PBS solution at different concentrations. A, B, C, D figures are examples for K. pneumoniae; E, F, G, H figures are examples for E. faecium. A: Positive control for K. pneumoniae. B:100 bacterial suspension/100 ACP-treated PBS (1/2). C:100 bacterial suspension /300 ACP-treated PBS (3/4). D:100 bacterial suspension /700 ACP-treated PBS (7/8). E: Positive control for E. faecium. F: 100 bacterial suspension /300 ACP-treated PBS (1/4). G:100 bacterial suspension /700 ACP-treated PBS (7/8). H:100 bacterial suspension /1500 ACP-treated PBS (15/16).

2.3. Testing the effectiveness of ACP treated PBS solution:

Plasma treated PBS solution was not diluted since the plasma treated liquids lose their antimicrobial effect[7]. Therefore, 100 µl, 300 µl, 700 µl, 1500 µl, 3100 µl, 6300 µl of ACP-treated PBS was added to 100 µl of bacterial suspensions. The final solutions used contained ACP-treated PBS at a ratio of 1/2, 3/4, 7/8, 15/16, 31/32, 63/64 respectively. After pipetting, the suspension was incubated at room temperature for 30 minutes, inoculated on sheep blood agar with sterile loop (10 µl) and incubated overnight (16-18 hours) at 37°C. For the interpretation of efficacy, 10^7 CFU/ml was considered as the effective concentration inhibiting bacterial growth (Fig.2).

2.4. Statistical Analysis

Descriptive information will be obtained by giving distribution and frequency percentages in obtaining the data of the study.

3. Results

All strains studied were affected by ACP-treated PBS solution. The results of the efficacy of ACP-treated PBS solution against multidrug-resistant bacterial strains at different concentrations are given in Table 1. 45 of *K. pneumoniae* strains were completely inhibited by ACP-treated PBS solution at 3/4 concentration, while 5 of *K. pneumoniae* strains were completely inhibited by ACP-treated PBS solution at 7/8 concentration. Vancomycin-resistant *E. faecium* strains were inhibited by higher amounts of plasma than multidrug resistant *K. pneumonia* strains. 3 of *E. faecium* strains 15/16, 3 of *E. faecium* strains 31/32, 4 of *E. faecium* strains 63/64 were completely inhibited by ACP-treated PBS solution. The inhibition concentration for *E. coli* ATCC 25922 was inhibited with 3/4 ACP-treated PBS solution. On the other hand, the inhibition concentration for *E. faecalis* ATCC 29212 and *S. aureus* ATCC 29213 was 15/16. Thus, in the case of standard bacterial strains, higher amounts of inhibition by plasma were achieved in gram-positive as well as in the bacteria included in the study.

Table 1

The number of concentrations at which ACP-treated PBS is effective against multidrug-resistant bacterial strains.

Bacteria suspension	100µl	100µl	100µl	100µl	100µl	100µl
ACP treated PBS	100µl	300µl	700µl	1500µl	3100µl	6300µl
Bacteria strains	(1/2)	(3/4)	(7/8)	(15/16)	(31/32)	(63/64)
K. pneumoniae (n=50)	0	45	5	0	0	0
E. faecium (n=10)	0	0	0	3	3	4
S. aureus ATCC 29213 (n=1)	0	0	0	1	0	0
E. faecalis ATCC 29212 (n=1)	0	0	0	1	0	0
E. coli ATCC 25922 (n=1)	0	1	0	0	0	0

ACP, Atmospheric Cold Plasma; PBS, phosphate buffered saline; ATCC, American Type Culture Collection.

4. Discussion

In this study, the antimicrobial effect of ACP-treated PBS solution on carbapenem-resistant *K. pneumoniae* and vancomycin-resistant *E. faecium* was investigated. Antimicrobial resistance (AMD) is one of the most important items on the global health agenda in recent years due to both its public health problem and economic cost. According to surveillance studies, there is an increase in resistance in antibiotics used against *K. pneumoniae* and *E. faecium*, in addition to *Acinetobacter* species, which are resistant to many antibiotics in Turkey[8]. Therefore, the decrease in treatment options in infections caused by both Gram-positive and Gram-negative bacteria leads to the search for different treatment options. In 2017, the World Health Organization prepared a list of priority pathogens to guide and encourage research and development of new antibiotics. According to this list, carbapenem-resistant, extended spectrum beta-lactamases-producing *Enterobacterales* critical and vancomycin-resistant *E. faecium* are among the high priority bacteria[9].

In an era when it is becoming increasingly difficult to find new antimicrobial drugs against these resistant bacteria, it is important to understand how antimicrobial effects occur and their potential clinical implications. Various non-antibiotic agents exhibit antimicrobial activity through multiple and distinct mechanisms of action. Numerous studies have reported the antimicrobial activity of some non-steroidal anti-inflammatory drugs, local anesthetics, anti-psychotics, anti-depressants, antiplatelets and statins[8]. Non-traditional approaches are also being developed to combat antibiotic resistance with agents with antimicrobial effects such as antimicrobial peptides targeting the bacterial cell membrane, efflux pump inhibitors, phage therapies, antibodies with antibiotic effects and immunomodulators[10].

Physical plasma and plasma treated liquids have gained increasing importance in recent years due to its strong antimicrobial activities on bacteria, viruses, fungi, and prions[4]. Physical plasma is used especially in sterilization units under different temperatures and pressures. Apart from the studies in which it is applied directly to the skin, there are also studies in which ACP-treated liquids (such as N-acetylcysteine solution, PBS) were used for their antimicrobial properties[7,11]. In our study, we found ACP-treated PBS to be effective against 50 strains of *K. pneumonia* and 10 strains of *E. faecium*. The effect of ACP is mainly due to oxidative and nitrosative stress induced by ROS and RNS produced during its interaction[12,13]. ROS, RNS and free radicals are thought to cause damage to various cellular structures and eventually microbial inactivation[4,14,15,16].

In this study, the amount of ACP-treated PBS with complete inhibition was found to be different between Gram-positive and Gram-negative bacteria and more amount was needed in Gram-positive bacteria. This situation is similar to the study that use quality control bacteria for *E. coli* ATCC 12900 and S. aureus ATCC 25923[17]. According to this study, more plasma treated liquid was used for the inhibition of *Enterococcus faecalis* ATCC 29212 and *S. aureus* ATCC 25923 strains than for the inhibition of *E. coli* ATCC 12900 strains. The ROS produced by ACP damage the thin peptidoglycan and thicker lipopolysaccharide layer of the cell wall in Gram-negative bacteria but cause less DNA damage than in Gram-positive bacteria. In Gram-positive bacteria, serious damage to intracellular components such as DNA damage is more prominent, and the cell wall is intact[17]. Since cell wall structures are different in Gram-positive and Gram-negative bacteria, it was thought that this may be the reason for the difference in the need for ACP-treated PBS. In a study in which *E. coli* ATCC 25922 and *S. aureus* ATCC 25923 strains were used to model perforated appendicitis in rats, no significant bacterial inactivation was observed with ACP-treated PBS at 15 minutes, whereas no significant bacterial inactivation was observed at 30 minutes and 45 minutes of treatment with E. coli and S. aureus strains by approximately 3.5 log at 30 minutes and 7 log at 45 minutes, and these inactivation values demonstrated the in vivo efficacy of ACP-treated PBS[7]. On the other hand, this is the first study from Turkey to demonstrate the efficacy of ACP-treated PBS in resistant Gram-positive and Gram-negative bacteria in vitro.

As a result, ACP-treated PBS solution was found to be effective against both Gram-positive and Gram-negative bacteria resistant to important antibiotics. A difference in the concentration of ACP-treated PBS required for inactivation was observed in the selected Gram-negative and Gram-positive bacteria due to two possible inactivation mechanisms. These findings are critical for the successful development of plasma applications for in vivo experiments for treatment.

Acknowledgements
None.

Statement of ethics
This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Non-Interventional Clinical Research Ethics Committee of University of Health Sciences, Tepecik Training and Research Hospital (Date: 13.07.2023 and Decision no: 2023/06-58).

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

Funding source
None.

Author contributions
Concept and design: AT, UKE, NY
Analysis/Interpretation: AT, DT, NY
Data collection or processing: AT, DT, NY
Writing: AT, DT, NY
Review and correction: AT, UKE, DT, NY
Final approval: AT, UKE, DT, NY
All authors read and approved the final manuscript.

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Evaluation of Cystinosis Patients and Factors Associated with Chronic Kidney Disease

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Abstract

Aim: Cystinosis is a rare genetic, lysosomal storage disorder, leading to kidney involvement and other organs. The most critical factor determining the prognosis is its impact on the kidneys especially nephropathic cystinosis. This study aimed to evaluate cystinosis patients and identify factors associated with chronic kidney disease (CKD).

Methods: The medical records of 18 nephropathic cystinosis patients were retrospectively reviewed. Demographic and clinical features, prognosis were evaluated. Patients were classified according to their estimated glomerular filtration rate (eGFR) at last visit as eGFR<60 ml/min/1.73 m^2 and eGFR>60 ml/min/1.73 m^2, and were compared for CKD related factors.

Results: The mean age at diagnosis was 46.61±50.42 months. The most common allele was c. 451A>G. Polyuria, polydipsia, vomiting, growth retardation, and renal osteodystrophy were typical presenting symptoms. At diagnosis, the mean eGFR was 72.94±21.69 ml/min/1.73 m^2. After an average follow-up of 68.28±60.18 months, the mean eGFR was 63.97±23.59 ml/min/1.73 m^2, and CKD was observed in 44.4% of patients, and 5 (27.8%) underwent kidney replacement therapy (KRT). In patients with GFR<60 ml/min/1.73 m^2, the initial cysteamine dose was found to be significantly lower (p=0.03), while consanguinity (p=0.04) and family history presence (p=0.01), presence of renal osteodystrophy at diagnosis and the development of rickets (p=0.02), were statistically significantly higher.

Conclusions: **Conclusion:** This study highlights the importance of effective cystinosis management, focusing on early diagnosis and optimal cysteamine treatment to prevent complications especially CKD. Consanguinity and family history, accompanying rickets emerged as notable risk factors for CKD, underscoring the significance of genetic counseling and bone health monitoring.

Keywords: *Cystinosis, Kidney, Children*

1. Introduction

Cystinosis is a systemic disorder caused by mutations in the *CTNS* gene, which encodes the lysosomal cystine transporter protein, leading to intracellular cystine accumulation primarily affecting the kidneys, causing progressive organ damage[1]. The incidence of autosomal recessive cystinosis disease is 0.5-1/100.000[2]. So far, over 140 mutations have been found in cystinosis patients. The most common one is a significant 57-kb deletion that impacts the initial 9 exons of *CTNS* and a portion of exon 10[2,3]. However, it's worth noting that a Turkish patient group studied by Topaloglu et al. did not exhibit this particular 57-kb deletion[4].

There are three clinical forms of cystinosis based on age of onset and kidney involvement: infantile, juvenile, and adult (ocular non-nephropathic). Infantile nephropathic cystinosis is severe, often leading to end-stage kidney disease (ESKD). Juvenile form is less common, with diagnosis after age 10. Adult form is rare, causing photophobia due to corneal cystine accumulation[5].

Infantile nephropathic cystinosis presents with Fanconi syndrome around 6 months accompanying polyuria, growth issues, vomiting, dehydratation, and rickets[5,6]. Glomerular function declines, usually resulting in ESKD by the first decade, treated with kidney replacement therapy (KRT) include hemodialysis (HD), peritoneal dialysis (PD) or kidney transplantation. Since cystinosis patients do not experience recurrence after kidney transplantation, kidney transplantation is preferred for KRT[4]. However, early cysteamine therapy helps clear cystine, benefiting kidney function and delaying ESKD onset[7,8]. The prevention of progression to ESKD is of significant importance in terms of patients' prognosis and morbidity, as it enables the identification of other prognostic factors, in addition to the significance of early initiation and effectiveness of treatment. In a recent study, a high level of proteinuria at the time of diagnosis (spot urine protein/creatinine >6 mg/mg) was identified as a prognostic

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Received: 01.08.2023, Accepted: 22.08.2023, Available Online Date: 31.08.2023
Cite this article as: Avci B, Parmaksiz G. Evaluation of Cystinosis Patients and Factors Associated with Chronic Kidney Disease. J Cukurova Anesth Surg. 2023; 6(1): 308-12. doi: 10.36516/ jocass.1335966

factor affecting kidney survival[9].
This study aims to assess cystinosis, a rare condition with significant multisystem impact and potential complications, particularly kidney failure. By investigating clinical features, disease progression, and prognosis, we also aim to identify the factors like early treatment that relate to chronic kidney disease (CKD) and ESKD outcomes.

2. Materials and methods

We conducted a retrospective review of the medical records of cystinosis patients who were diagnosed and followed up at the Department of Pediatric Nephrology, Başkent University Adana Application and Research Center, from 2006 to 2023.

The study included patients diagnosed with cystinosis based on clinical and laboratory findings. Patients with accessible medical records and a follow-up period of at least 6 months were included. Cystinosis diagnosis was confirmed through the observation of corneal cystine crystals in slit lamp examinations, elevated leukocyte cystine levels (> 2 nmol ½ cystine per mg protein), and/or the presence of mutations in the *CTNS* gene identified through genetic testing.

The medical records of patients' age at diagnosis, consanguinity and family history, age of onset of symptoms, duration of diagnosis and follow-up, presenting clinical findings, and laboratory values at diagnosis and at the end of follow-up, leukocyte cystine level (nmol ½ cystine mg protein), cysteamine dose and supportive treatments were evaluated retrospectively. The eGFR was calculated with the Schwartz formula.[10]

Cysteamine was initiated orally at a dose of 60–90 mg/kg/day, which was initiated at a low dose and gradually increased, for all patients upon diagnosis. Additionally, topical cysteamine eye drops were prescribed for all patients upon detection of eye involvement.

At the end of the follow-up period, the patients were classified into five stages of CKD 1,2,3,4 and 5 according to the KDIGO classification. Then the patients were categorized into two groups based on their stages: patients with stage 3, 4 and 5 grouped as eGFR<60 ml/min/1.73 m^2 and with stage 1, 2 and without CKD grouped as eGFR>60 ml/min/1.73 m^2. Then, demographic, clinical, and laboratory data, along with treatment and disease-related complications, were statistically compared between these two groups to identify factors associated with CKD.

This study was approved by Başkent University Instutional Review Board. (Project no: KA23/253).

2.2 Statistical Analysis

Statistical analyses for this observational, descriptive, retrospective study were conducted using IBM® SPSS© 24 software. Categorical variables were presented as numbers and percentages. Normality of numerical variables was assessed using analytical methods such as Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics for normally distributed numeric variables were reported as mean and standard deviation. To compare continuous variables between groups, we used either Student's t-test for parametric values or Mann-Whitney U test for non-parametric values. Categorical variables between groups were analyzed using the chi-square test or Fisher's exact test. The threshold for statistical significance was set at $p<0.05$.

3. Results

3.1. Demographic and Clinical Findings

A total of 18 cystinosis patients, 7 males and 11 females, were followed up at our center, with a mean age at diagnosis of 46.61±50.42 months. The patient with the older age at diagnosis, he was at 174 months and had a homozygous c.451A>G p.Arg151Gly mutation. The other four patients with older age at diagnosis (minimum 43 months-maximum 126 months) also had the same mutation. The patient diagnosed at 53 months had a heterozygous mutation of c.864_842del p.Val279_Tyr281del/c.1015G>A p.Gly339Arg. Among the patients diagnosed at an early age (minimum 7 months, maximum 17 months), 5 had a homozygous c.681G>A p.Glu227Glu mutation, and the other 3 had a homozygous/heterozygous c.18-21del p.Thr7Phefs*7 mutation. The genetic analysis of a total of 15 patients revealed that the homozygous c.451A>G p.Arg151Gly, which was detected in six patients, was the most frequently observed mutation in our study. The mean diagnosis period was 4.33±7.64 months.

All patients presented with polyuria and polydipsia as their chief complaints, while vomiting (44.4%) and growth retardation (33.3%) were other commonly observed symptoms. While proteinuria was present in 17 (94.4%) patients, fanconi syndrome was observed in 12 (66.7%) patients. Eleven patients (61.1%) exhibited acidosis, while alkalosis was present in 2 patients (11.1%). One patient had acute kidney injury at presentation, which improved during follow-up. At the time of diagnosis, the mean eGFR of the patients was 72.94±21.69 mL/min/1.73m^2, and the mean spot urine protein/creatinine (Spot Up/cr) was 2.20±1.88 mg/mg. The mean leukocyte cystine level in all patients was 5.51±4.63 nmol ½ cystine per mg protein, while the initial treatment doses averaged at 27.22±8.61 mg/kg.Table-1 summarizes the demographic and clinical characteristics of the patients at the time of presentation.

Table 1

Demographic, clinical characteristics, and findings of the cystinosis patients at presentation and diagnosis

	Patients (n= 18)
Male, n (%)	7 (38.9%)
Consanguinity, n (%)	14 (77.8%)
Family history of Cystinosis, n (%)	4 (22.2%)
Age of diagnosis, months (mean±SD)	46.61±50.42
Diagnosis period, months (mean±SD)	4.33±7.64
Symptoms	
• Polyuria, n (%)	18 (100%)
• Polydipsia, n (%)	18 (100%)
• Vomiting, n (%)	8 (44.4%)
• Growth retardation, n (%)	6 (33.3%)
• Photophobia, n (%)	1 (5.6%)
• Tetany, n (%)	1 (5.6%)
Other findings	
• Proteinuria, n (%)	17 (94.4%)
• Corneal involvement, n (%)	14 (77.8%)
• Fanconi, n (%)	12 (66.7%)
• Acidosis, n (%)	11 (61.1%)
• Anemia, n (%)	9 (50.0%)
• Renal osteodystrophy, n (%)	6 (33.3%)
eGFR at (ml/min/1.73m2), mean±SD	72.94±21.69
Spot Urine protein/creatinine (mg/mg), mean±SD	2.20±1.88
Leukocyte cystine level (nmol half-cystine/mg protein), mean±SD	5.51±4.63
Cysteamine dose (mg/kg/day), mean±SD	27.22±8.61

eGFR: estimated Glomerular Filtration Rate

3.2. Prognosis

During an avarage follow-up of 68.28±60.18 months, rickets were observed in 9 cases (50.0%). At their last visit, patients had a mean eGFR 63.97±23.59 mL/min/1.73m^2. Among them, with 44.4% (8 patients) had an eGFR below 60 mL/min/1.73m^2, and 5 (27.8%) underwent KRT with three of them receiving kidney transplantation. Currently, 10 cystinosis patients are being actively monitored, with two having undergone kidney transplantation and one continuing PD. The prognosis is summarized in Table 2.

Among the 8 patients with eGFR<60 mL/min/1.73 m^2, 4 had the homozygous c.681G>A mutation and 1 had the homozygous c.18-21delGACT p.T7Ffs7 mutation (early-onset diagnosis), while 3 had the c.451>G p.Arg151Gly mutation (late-onset diagnosis). The mean age of ESKD development in the 5 patients with ESKD was 12.8±6.05 (ranging from 7 to 20 years) years. Among these, 3 patients with the homozygous c.681G>A mutation and 1 patient with the homozygous c.18-21delGACT p.T7Ffs7 mutation (early-onset diagnosis) had a mean age of ESKD development at 8.67±2.89 years. In siblings with late-onset c.451>G p.Arg151Gly mutation, the age of ESKD was 18 and 20 years.

3.3 CKD with GFR<60 mL/min/1.73 m2 associated factors

In patients with eGFR<60 mL/min/1.73 m^2, the presence of consanguinity (8/8 patients vs. 6/10, *p=0.04*) and family history (4/8 patients vs. 0/10, *p=0.01*), the presence of renal osteodystrophy at presentation (5/8 patients vs. 1/10, *p=0.02*), and the development of rickets (7/8 patients vs. 2/10, *p=0.02*) were statistically significantly higher. The initial cysteamine dose was found to be statistically significantly lower in patients with eGFR<60 mL/min/1.73 m^2 (22.50±8.45 vs. 31.0±6.99; *p=0.03*). The comparison between patients with eGFR<60 mL/min/1.73 m^2 and >60 mL/min/1.73 m^2 is shown in Table 3.

Table 2

Prognosis of the cystinosis patients

	Patients (n= 18)
eGFR at last visit (mL/min/1.73m2), mean±SD	63.97±23.59
Spot Urine protein/creatinine at last visit (mg/mg), mean±SD	2.59±2.32
Leukocyte cystine level at last visit (nmol half-cystine/mg protein), mean±SD	3.35±3.32
Cysteamine dose at last visit (mg/kg/day), mean±SD	53.3±14.45
Systemic findings	
• Rickets, n (%)	9 (50.0%)
• Hypothyroidism, n (%)	2 (11.1%)
• Gastrointestinal involvement, n (%)	2 (11.1%)
Chronic Kidney Disease with eGFR<60 mL/min/1.73m2, n (%)	8 (44.4%)
Kidney Replacement Therapy, n (%)	5 (27.8%)
• Kidney Transplantation, n (%)	3 (16.7%)
• Peritoneal Dialysis, n (%)	2 (11.1%)
Follow-up period (months), mean±SD	68.28±60.18
Follow-up situation at last visit	
• Follow-up	10 (55.6 %)
• Follow-up by adult	4 (22.2%)
• Unfollowed	4 (22.2%)

eGFR: estimated Glomerular Filtration Rate

Table 3

Demographic, clinical characteristics, and prognosis differences between cystinosis patients with eGFR<60 mL/min/1.73m^2 and eGFR>60 mL/min/1.73m^2

	eGFR<60	eGFR>60	p value
Number of patients, n (%)	8	10	
Gender (Male/Female)	5/3	2/8	0.06
Consanguinity, n	8	6	0.04
Family history of Cystinosis, n	4	-	0.01
Age of diagnosis, month (mean±SD)	42.13±50.24	50.20±52.97	0.74
Diagnosis period, month (mean±SD)	2.75±2.49	5.60±10.07	0.45
Growth retardation at diagnosis, n	2	4	0.50
Symptoms at diagnosis			
• Growth retardation, n	2	4	0.50
• Photophobia, n	0	1	0.36
• Vomiting, n	5	3	0.17
• Tetany, n	1	-	0.25
Other findings			
• Proteinuria, n	8	9	0.36
• Fanconi, n	6	6	0.50
• Renal osteodystrophy, n	5	1	0.02
• Acidosis, n	5	6	0.91
• Anemia, n	3	6	0.34
eGFR (ml/min/1.73m2) at diagnosis, mean±SD	80.13±23.47	67.94±19.43	0.22
Spot Urine protein/creatinin (mg/mg) at diagnosis, mean±SD	2.41±1.95	2.03±1.91	0.68
Leukocyte cystine level (nmol half-cystine/mg protein) at diagnosis, mean±SD	6.58±5.65	4.66±3.72	0.39
Initial dose of Cysteamine (mg/kg), mean±SD	22.50±8.45	31.0±6.99	0.03
Systemic findings			
• Rickets, n	7	2	0.02
• Hypothyroidism, n	2	-	0.09
• Gastrointestinal involvement, n	1	1	0.87
• Corneal involvement, n	7	7	0.38

Bold shows that p value is statistically significant, eGFR: estimated Glomerular Filtration Rate

4. Discussion

Cystinosis is a rare, autosomal recessive, multisystemic, lysosomal storage disorder. Although cysteamine treatment significantly improves the disease course, allowing for more widespread use of KRT, the development of ESKD and systemic symptoms are still commonly observed, particularly due to ongoing challenges in drug procurement and other social and economic difficulties in our country. Therefore, we evaluated cystinosis patients followed up at our center in terms of clinical manifestations, disease progression, and kidney involvement, aiming to identify factors associated with CKD and the development of ESKD.

In autosomal recessive hereditary diseases, consanguineous marriages increase the risk of being affected, and in our study, consanguineous marriage was found in 77.8% of cases, while family history was present in 22.2%. Similar rates have been reported in other studies conducted in our country, where the rate of consanguineous marriages is generally high in the general population[4,9,11,12]. In contrast to our population, Greco et al. reported the rate of consanguineous marriages as 8.6%[13]. Cystinosis, although considered a rare disease, is important in our country due to its relatively higher occurrence resulting from consanguineous marriages. Therefore, raising awareness about the condition is crucial to facilitate early diagnosis.

In our study, the average age at diagnosis (46.61±50.42 months)

was found to be higher compared to previous studies.[4,8,14] Among the patients with late-onset disease, six had the homozygous c.451A>G p.Arg151Gly mutation. On the other hand, among the patients diagnosed at an early age, five had the homozygous c.681G>A p.Glu227Glu mutation, and the other three had the homozygous/heterozygous c.18-21del p.Thr7Phefs*7 mutation. Likewise, a recent extensive cohort study conducted in Turkey revealed that the prevailing mutations were c.681G>A p.Glu227Glu and c.18-21del p.Thr7Phefs*7, both linked to early-onset disease and a more severe clinical progression.[4] In the study by Atmış et al[9], it was reported that patients with the c.451A>G mutation had older ages at diagnosis and longer follow-up periods compared to patients with other mutations. In our study, similar to the previously reported findings from the same region in our country, the homozygous c.451A>G p.Arg151Gly mutation was also found to be prevalent[9,15]. The higher proportion of patients with the homozygous c.451A>G p.Arg151Gly mutation, which was the initial description was provided by Topaloglu et al. in Turkey[16], in our study might have contributed to the higher average age at diagnosis compared to previous studies. Although we observed fewer patients with mutations detected at a young age, we would have expected a longer diagnosis period due to factors such as non-specific evaluation of symptoms in younger patients, insufficient awareness of the disease among primary care physicians, limited diagnostic methods, and the presence of corneal cystine crystals in examinations before the age of 1.5 years. However, the diagnosis period in our study was not very long. This may be attributed to pediatric physicians promptly referring suspicious patients to the nephrology department.

Consistent with previous research, our study also found that the most frequent initial symptoms were polyuria and polydipsia, followed by vomiting, growth retardation, and renal osteodystrophy.[4,8] At the time of diagnosis, renal osteodystrophy was observed in 33.3% of patients. Previous studies by Brodin et al.[8] and Topaloglu et al.[4] reported the occurrence of rickets in 41% and 44% of cases, respectively. Patients with rickets were found to have a younger age at diagnosis and to have the c.681G>A p.Glu227Glu and c.18-21del p.Thr7Phefs*7 mutations. Nevertheless, the research conducted by Topaloglu et al.[4] reported no notable distinction concerning the occurrence of rickets between individuals with these frequently observed mutations and those with other genetic mutations. While typical clinical presentation in cystinosis involves proximal renal tubular acidosis, our study and the others reported cases where patients presented with a hypokalemic, hypochloremic metabolic alkalosis pattern, resembling Bartter syndrome[12,17-20]. The exact cause of metabolic alkalosis is not fully understood. Nonetheless, it has been proposed that an abnormality in sodium-dependent transtubular transport contributes to heightened sodium reabsorption, leading to the depletion of potassium and hydrogen ions. Consequently, this process culminates in the development of metabolic alkalosis[18-20].

At the time of admission, the average eGFR of the patients was 72.94±21.69 ml/min/1.73 m2. One patient had acute kidney injury due to dehydration, with an eGFR of 32 ml/min/1.73 m2, which later improved to above 90 ml/min/1.73 m2 during follow-up. After an average follow-up of 68.28±60.18 months, the mean eGFR was 63.97±23.59 ml/min/1.73 m2, similar to the findings reported by Atmış et al.[9] with the most common C.451A>G mutation. At the end of the follow-up period, the prevalence of CKD (eGFR<60 mL/min/1.73m2) was 44.4%, and the rate of KRT was 27.8%. In a large-scale cohort study conducted in our country, the rate of KRT was reported as 36%,[4] while in the study by Atmis et al.[9], where the C.451A>G mutation was most commonly identified, the rate was 16.6%. Our study, in which the mean age of ESKD development was found to be 12.8 years, is consistent with a similar study where the most common C.451A>G mutation was identified, reporting an mean ESKD age of 122 months[9]. On the other hand, in a large cohort study by Topaloglu et al.[4], where the c.681G>A p.Glu227Glu and c.18-21del p.Thr7Phefs7 mutations were more prevalent, the average ESKD age was reported as 11 years. The later onset of ESKD in the study with a higher frequency of these mutations, which are more common and have a more severe course at a young age diagnosed, was attributed to the early initiation of cysteamine therapy (<2 years). In our study, cysteamine treatment was started before the age of 2 in patients, who developed ESKD, with the c.681G>A p.Glu227Glu and c.18-21del p.Thr7Phefs7 mutations.

In cystinosis patients, various factors affecting prognosis, such as the timing of cysteamine treatment initiation, and treatment dose, patient adherence to therapy, leukocyte cystine levels, and spot urine protein/creatinine ratios, have been evaluated in previous studies. It has been suggested that starting cysteamine treatment before the age of 2 delays the onset of ESKD[4,8,13], and that patient adherence and proper dosage usage also delay ESKD development.[8] Furthermore, it has been observed that patients with lower leukocyte cystine levels develop ESKD at a later stage,[8] and those with spot urine protein/creatinine ratios lower than 6 mg/mg have a better prognosis[9].

In our study, there were no significant differences in the age of cysteamine treatment initiation, leukocyte cystine levels, and spot urine protein/creatinine ratio between patients with eGFR<60 ml/min/1.73 m^2 and eGFR>60 ml/min/1.73 m^2. However, it was observed that the initial cysteamine treatment dose was lower in patients with eGFR<60 ml/min/1.73 m^2. This result is consistent with the poor adherence to cysteamine treatment is associated with early onset of ESKD detected in the previous studies[8]. Also, the most significant contributing factor to this situation in our country is the difficulties patients experience in obtaining drugs. These results are emphasizing the importance of starting treatment with higher doses or increasing doses promptly to ensure treatment adherence and achieve optimal outcomes. Compliance with medication and regular intake of prescribed drugs are of critical importance for cystinosis patients[21].

In our study, there was a statistically significant higher in consanguinity and family history among patients with CKD. Consanguinity and family history should be considered as risk factors for CKD development. In our country, where consanguineous marriages are observed at a high rate, patients should be evaluated for their family history and receive genetic counseling. Close monitoring, family education, and early diagnosis are crucial, and sibling screening is highly important for cystinosis patients.

In our study, the presence of renal osteodystrophy or the development of rickets during follow-up period was found to be significantly associated with CKD. Rickets, being a factor associated with ESKD, can have negative effects on patients' growth and bone health. Therefore, regular monitoring of bone health in cystinosis patients and the appropriate and adequate treatments, especially cysteamine and other supportive therapies, are crucial, as emphasized once again in this study.

The limitations of our study include its retrospective nature, small sample size, short follow-up period, and the lack of molecular genetic analysis performed in all patients. However, considering the importance of identifying factors that can impact the prognosis of this rare and preventable condition, the findings of this and other studies may be beneficial in planning larger-scale prospective studies in the future.

5. Conclusions

In conclusion, our study highlights crucial aspects of managing cysti-

nosis, including early diagnosis and appropriate treatment dosing to prevent complications and enhance patients' quality of life. Consanguinity and family history emerged as significant risk factors for CKD in cystinosis patients, underscoring the importance of assessing family history and providing genetic counseling, especially in regions with prevalent consanguineous marriages such as our country. The presence of renal osteodystrophy or rickets during follow-up was strongly linked to CKD, stressing the need for regular bone health monitoring and timely, suitable cysteamine therapy. Despite the study's limitations, these findings underscore the significance of further research involving larger patient cohorts to better comprehend cystinosis and CKD-related factors. This knowledge will ultimately lead to improved patient outcomes and a deeper understanding of the disease.

Acknowledgements

None.

Statement of ethics

This study was approved by was approved by Başkent University Instutional Review Board. (Project no: KA23/253).

Conflict of interest statement

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

Funding source

This study was approved by Baskent University Institutional Review Board (Project no: KA23/253) and supported by Baskent University Research Fund

Author contributions

All authors contributed to the study conception and design.

All authors read and approved the final manuscript.

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The Role of Prognostic Factors in Perioperative Adverse Events and Complications in Children with Cleft Palate Repair

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Abstract

Aim: Cleft lip and palate (CLP) deformity is the most common type of craniofacial malformation and is usually corrected surgically in infancy. Anesthetic management of children undergoing CLP repair has many challenges. In this study, it was aimed to evaluate the effect of prognostic factors on perioperative complications in children with cleft palate (CP) repair.

Methods: In this study, pediatric cases who underwent cleft palate surgery in a tertiary care hospital between 2015 and 2020 were analyzed retrospectively. The primary outcome measure was perioperative adverse outcomes rate.

Results: The incidence of all perioperative adverse events including airway, and respiratory complications, ICU admission, blood transfusion and re-operation requirement was determined as 40.7% (n=88) and the incidence of respiratory adverse events was found as 28.7% (n=62). Moreover, low body weight (OR 0.69, 95% CI 1.18-1.78, p<0.001), comorbidity, concomitant presence of syndrome (OR 7.19, 95% CI 2.02-25.60, p<0.001) and cleft lip (OR 2.73, 95% CI 1.10–6.73, p=0.030), and complete type of cleft palate (OR 0.33, 95% CI 1.22–7.46, p=0.017) were risk factors for perioperative adverse events.

Conclusions: In this study, a significant relationship was found between underweight, comorbidity, the presence of concomitant syndrome, cleft lip, complete type of cleft palate and the risk of developing perioperative adverse events in children with CP repair.

Keywords: *Cleft palate, cleft lip, difficult airway, perioperative complications, underweight*

1. Introduction

Craniofacial clefts are deformations of the face and skull as a result of development and/or fusion defects in bone and/or soft tissues along linear anatomical planes[1]. Oral clefts are the most common craniofacial malformations among all congenital anomalies, with three basic types: cleft lip (CL) alone, cleft palate (CP) alone, and cleft lift with cleft palate (CLP)[2]. Although the exact incidence of oral cleft is not known, it is estimated to occur at a rate of 14.5 per 10,000 live births[3]. Treatment for CP is surgical repair of the deformity under general anesthesia when the child reaches a minimum age of 10-12 months. Anesthesia management of these children presents challenges in many aspects. Conditions such as airway problems, accompanying syndromes and musculoskeletal, cardiovascular and central nervous system abnormalities, malnutrition and growth retardation contribute to anesthesia-related morbidity and mortality. Furthermore, recurrent respiratory infections and reactive airway are common in these children due to continuous aspiration and impairment of the protective properties of the airway[4]. This significantly increases the risk of airway and respiratory complications at all stages of anesthesia practice, including induction, maintenance, and recovery[5]. In addition to the anatomical defect, accompanying structural deformities, such as micrognathia, glossoptosis, and airway obstruction, as in the Pierre Robin sequence, increase the risk of encountering a difficult airway[6]. Moreover, children with CLP with maxillary or mandibular hypoplasia, macroglossia, or poor motor tone are at risk for obstructive sleep apnea, which further complicates anesthesia management[6]. Therefore, CP repair, which constitutes an important part of infant and childhood surgeries, is still associated with increased morbidity and mortality. While there are identified risk factors, more evidence is needed in this area that

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Received: 08.08.2023, Accepted: 29.08.2023, Available Online Date: 31.08.2023
Cite this article as: Ici EE, Laflı Tunay D. The Role of Prognostic Factors in Perioperative Adverse Events and Complications in Children with Cleft Palate Repair. J Cukurova Anesth Surg. 2023; 6(2): 313-7.
doi: 10.36516/jocass.1339300

could improve patient outcomes. Thus, this study aimed to investigate the prognostic factors affecting the incidence of perioperative adverse events and postoperative complications in pediatric patients undergoing cleft palate repair, and the primary outcome measure was perioperative adverse outcomes rate.

2. Materials and methods

This study was approved by the Institutional Investigation and Ethics Committee on November 6, 2020, with approval number: 105/16 and conducted at Cukurova University in Turkey.

2.1. Patients

For this retrospective cohort study, two hundred sixteen pediatric patients who underwent primary cleft palate repair by the Department of Plastic, Reconstructive and Aesthetic Surgery at Cukurova University Hospital between January 2015 and October 2020 were recruited. Re-operated patients and patients who were scheduled for palatal fistula repair were not included in the study. The sample size of the study consisted of all pediatric patients who had undergone cleft palate repair surgery within the five-year experience of our tertiary care hospital and met the inclusion criteria of the study. Power analysis was not used in the study.

2.2. Data collection

Electronic medical records, anesthesia records, preoperative evaluation records, nursing records, laboratory findings, and postoperative evaluation records and clinical outcomes were reviewed for all patients. All data were collected, recorded and checked by two different independent research assistants.

2.3. Outcomes

From the preoperative records, the demographic characteristics of the patients (age, gender, weight, height), American Society of Anesthesiologists (ASA) physical status classification, cleft palate classification whether being complete, incomplete or submucous cleft palate, concomitant diseases, syndromes, malformations and chromosomal abnormalities, and preoperative laboratory tests were recorded. From the records during the operation, the fluid, blood and blood product use, the presence of difficult airway, bronchospasm, hypercarbia, hypoxemia, and accidental extubation, and the duration of the operation were recorded. From the postoperative period records, the presence of stridor, rhonchi, hypoxemia, need for reintubation, and intensive care unit (ICU) admission and length of ICU stay, the amount of blood and blood products transfusion, need for reoperation, and length of hospital stay were documented.

Perioperative adverse events were defined as difficult mask ventilation, difficult laryngoscopy and intubation, intraoperative blood transfusion, bronchospasm, hypoxemia, hypercarbia, and accidental extubation, requirement of postoperative reintubation, need for ICU admission, blood transfusion, need for reoperation, postoperative respiratory distress and other complications.

2.4. Statistical analysis

IBM SPSS Statistics Version 25.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation (median and minimum-maximum where necessary). The conformity of the variables to the normal distribution was evaluated using histogram and probability graphs and Kolmogorov-Smirnov/Shapiro-Wilk tests. Pearson Chi-square test and Fisher's exact test were used to compare categorical variables. Student's t-test was used for groups with normal distribution in binary variables, and Man-Whitney U test was used for groups that did not fulfill normal distribution. One-way ANOVA tests were used for groups with normal distribution in multiple variables. Logistic regression analysis was performed to determine variables that were predictors of perioperative adverse outcomes. Statistical significance level was accepted as 0.05 in all tests.

3. Results

Two hundred and seventy-eight patients were evaluated for this study. A total of 62 patients were excluded from the study because 39 patients were scheduled for reoperation and 23 patients had palatal fistula repair. Thus, this study was conducted with two hundred sixteen pediatric patients obtained from a single center's 5-year cleft palate repair experience. The mean age of the children was 621.5±28.0 days. The demographic characteristics and the medical history of the patients were represented in Tables 1 and 2.

14 (6.5%) of the patients had a documented difficult airway. Respiratory complications such as bronchospasm, hypercapnia and hypoxemia were observed in 53 (24.5%) patients in the intraoperative period, while airway and respiratory complications were detected in 27 (12.5%) patients in the postoperative period (Table 3).

The overall rate of perioperative adverse events including difficult airway, intra- and postoperative airway and respiratory complications, intra- and postoperative blood transfusion, post-

Table 1

Patient Characteristics and Length of Hospital Stay

Number of patients	n=216
Age (day)*	621.5±28.0
Gender (M/F)†	115(53.2)/101(46.8)
Weight (kg)*	10.5±2.4
Weight percentile†	
• <25%	122(56.5)
• 25-75%	69(31.9)
• >75%	25(11.5)
ASA physical status†	
• I	178(82.4)
• II	38(17.6)
Type of cleft palate†	
• Complete	95(44.0)
• Incomplete	108(50.0)
• Submucous	13(6.0)
Indication for surgery†	
• Isolated CP	125(57.9)
• CLP	91(42.1)
Length of hospital stay‡	4(2-21)

Abbreviations: ASA, American Society of Anesthesiologists; CP, cleft palate; CLP, cleft lip and palate. *Values are given as mean±standard deviation. †Values are given as n (%). ‡Value is given median (min-max)

Table 2

Preoperative Concomitant Diseases, Anemia and Syndromes

Chromosomal abnormality	3(1.4)
Syndrome	16(7.4)
• Pierre-Robin	4(1.9)
• Others*	12(5.5)
Concomitant diseases	45(20.8)
• Congenital heart disease	24(11.1)
• CNS disease	7(3.2)
• Metabolic disease	3(1.4)
• Others**	11(5.1)
Preoperative anemia	58(26.9)

Abbreviations: CNS, central nervous system. Values are given as n (%). *Including Cat Eye, Dandy Walker, Sotos and Charge syndromes. **Including pulmonary, skeletal and renal abnormalities.

Table 3
Airway and Respiratory Complications

Difficult airway	14(6.5)
• Difficult mask ventilation	2(0.9)
• Difficult intubation	12(5.6)
Prolonged intubation	4(1.9)
Re-intubation	2(0.9)
Intraoperative respiratory complications	53(24.5)
• Bronchospasm	33(15.3)
• Hypercapnia	10(4.6)
• Hypoxemia	2(0.9)
Accidental extubation	8(3.7)
Postoperative respiratory complications	27(12.5)
• Stridor	12(5.6)
• Roncus	12(5.6)
• Hypoxemia	2(0.9)
• Pneumothorax	1(0.5)

Values are given as n (%).

Table 4
Perioperative Adverse Outcomes

Perioperative adverse events*	88(40.7)
Intraoperative blood transfusion	18(8.3)
Postoperative blood transfusion	23(10.6)
Postoperative ICU admission	20(9.3)
Re-operation	45(20.8)

Abbreviations: ICU, intensive care unit. *Including difficult airway, intra- and postoperative airway and respiratory complications, intra- and postoperative blood transfusion, postoperative ICU admission, and re-operation requirement. Values are given as n (%).

operative ICU admission, and re-operation requirement were 40.7% (n=88) (Table 4).

When the occurrence of perioperative adverse events and the prognostic factors of the patient were compared, a significant relationship was found between the ASA II physical status, the presence of complete type cleft palate and concomitant cleft lip, and adverse events (Table 5).

On the other hand, when only perioperative respiratory complications and prognostic factors were compared, a significant correlation was found between low body weight, concomitant syndrome and comorbidity, and respiratory complications (Table 6).

According to the Logistic Regression analysis, it was determined that weight, type of cleft palate, history of cleft lip operation, presence of concomitant syndrome are risk factors for intraoperative adverse respiratory events. According to this: each one kg decrease in body weight increases the risk of intraoperative adverse respiratory events by 1.45 times (OR 0.69, 95% CI 1.18-1.78, p<0.001); type of complete cleft palate increases the risk of intraoperative adverse respiratory events by 3.02 times (OR 0.33, 95% CI 1.22–7.46, p=0.017) compared to incomplete type; the presence of concomitant cleft lip increases the risk of intraoperative adverse respiratory events by 2.73 times (OR 2.73, 95% CI 1.10–6.73, p=0.030); the presence of the syndrome increases the risk of intraoperative adverse respiratory events by 7.19 times (OR 7.19, 95% CI 2.02-25.60, p<0.001) were determined (Table 7).

Furthermore, in the Logistic Regression analysis for the postoperative adverse event, only the length of hospital stay was determined as a risk factor, and it was observed that each 1-day increase in hospital stay increased the risk of postoperative adverse events by 1.6 times (OR 0.06, 95% CI 1.29-1.99, p<0.001) (Table 8).

4. Discussion

In this retrospective cohort study, in which pediatric cases with primary cleft palate repair were analyzed, the incidence of all perioperative adverse events including airway, and respiratory complications, ICU admission, blood transfusion and re-operation requirement was determined as 40.7% (n=88) and the incidence of respiratory adverse events was found as 28.7% (n=62). Moreover, low body weight, comorbidity, concomitant presence of syndrome and cleft lip, and complete type of cleft palate were risk factors for perioperative adverse events.

A difficult airway is more common in children with CLP repair than other surgical pediatric patients7. Developmental defect of the linear anatomical planes in the craniofacial area makes it difficult for mask ventilation and laryngoscopy in certain patients6,7. In addition, the accompanying syndromes or OSA, which are accepted as risk factors for difficult airway, increase this risk even more8. In this study, difficult airway was documented in 14 (6.5%) patients, the majority of whom were difficult intubation (5.6%) and two (0.9%) were unsuccessful intubation. The prevalence of difficult intubation has been reported as 1.3-3.0% in studies examining various types of pediatric surgical patients9,10. As expected, the rate of difficult intubation in children who underwent CLP repair was reported to be 2.4-4.8%, higher than the other pediatric population5,11-13. When the studies are examined individually, it is understood that the rate of difficult airway is proportional to the

Table 5
Relationship Between Perioperative Adverse Events and Prognostic Factors

	Perioperative adverse events		
	Yes (n=88)	No (n=128)	p value
ASA physical status			0.001*
• I	63(71.6)	115(89.8)	
• II	25(28.4)	13(10.2)	
Weight percentile			0.485
• < 50%	67(76.1)	92(71.9)	
• > 50%	21(23.9)	36(28.1)	
Type of cleft palate			0.003*
• Complete	50(56.8)	45(35.2)	
• Incomplete	36(40.9)	72(56.2)	
• Submucous	2(2.3)	11(8.6)	
Concomitant cleft lip			0.001*
• Yes	49(55.7)	42(32.8)	
• No	39(44.3)	86(67.2)	

Abbreviations: ASA, American Society of Anesthesiologists. Values are given as n (%). *These values indicate statistical significance (p<0.05).

Table 6

Relationship Between Perioperative Respiratory Complications and Prognostic Factors

	Perioperative respiratory complications		
	Yes (n=62)	No (n=154)	p value
Weight percentile			0.004*
• < 50%	54(87.0)	105(68.1)	
• > 50%	8(13.0)	49(31.9)	
Type of cleft palate			0.478
• Complete	24(38.7)	71(46.1)	
• Incomplete	35(46.5)	73(47.4)	
• Submucous	3(4.8)	10(6.5)	
Concomitant cleft lip			0.119
• Yes	21(33.9)	70(45.5)	
• No	41(66.1)	84(54.5)	
Concomitant disease			
• Yes	25(40.3)	20(13.0)	0.001*
• No	37(59.7)	134(87.0)	
Concomitant syndrome			
• Yes	11(17.7)	5(3.2)	0.001*
• No	51(82.3)	149(96.8)	

Values are given as n (%). *These values indicate statistical significance (p<0.05).

Table 7

Logistic Regression Analysis of the Association Between Intraoperative Adverse Events and Prognostic Factors

Variable	Coefficient	SE	OR	Adjusted OR (95% CI)	p value
Complete type of cleft palate†	-1.106	0.462	0.331	1.220-7.460	0.017*
Concomitant cleft lip	1.003	0.461	2.727	1.105-6.731	0.030*
Concomitant syndrome	1.973	0.648	7.190	2.020-25.599	0.002*
Weight (kg)	-0.373	0.106	0.689	1.180-1.780	0.001*

Abbreviations: OR, odds ratio; CI, confidence interval.†According to reference category of incomplete type of cleft palate.*These values indicate statistical significance (p<0.05).

Table 8

Logistic Regression Analysis of the Association Between Postoperative Adverse Events and Prognostic Factors

Variable	Coefficient	SE	OR	Adjusted OR (95% CI)	p value
Length of hospital stay (day)	-2.752	0.533	0.064	1.290-1.990	<0.001*

Abbreviations: OR, odds ratio; CI, confidence interval.
*These values indicate statistical significance (p<0.05).

number of concomitant syndromic pediatric patients in the study population. Since the hospital where the current study was conducted was a tertiary care level, complicated patients were included in this study at a higher rate, and the prevalence of difficult airway was found to be higher than expected.

The presence of a reactive airway, other accompanying structural anomalies, and the intersection of the airway and the surgical field are the main reasons that increase the frequency of perioperative respiratory complications in children who have undergone CLP[4-6,8]. In this study, the incidence of all perioperative respiratory complications, including bronchospasm, hypercapnia, hypoxia, laryngeal edema, and pneumothorax, was calculated as 28.7%, and intraoperative bronchospasm was the most common complication (15.3%). In a study of children undergoing CLP repair, it was noted that respiratory complications, most commonly desaturation, were more than twice as common in patients with CP (38.4%) compared to patients with CL alone (15.8%)[5]. In another study, 460 pediatric patients with CP were analyzed and the respiratory complication rate was 8.7%[11]. This rate, which is inconsistent with our results, was interpreted as the majority of the patients were in the 3-8 age group. Feeding problems are common in children with CLP, so they are at high risk of growth failure and developmental delay. Preoperative malnutrition is associated with higher rates of postoperative complications in various type of surgery as well as CLP repair[14,15]. It is well known that there is a significant increase in the incidence of anesthesia and surgical related complications such as airway difficulties, wound healing problems, re-operation requirement, and prolonged hospitalization, especially in infants with less than 10 kg body weight or underweight (less than 50% percentile)[14-16]. Similarly, in this study we obtained that underweight is an independent risk factor for perioperative complications in both univariate analysis and logistic regression model.

CLP is frequently accompanied by additional malformations, including syndromes and various organ system anomalies, which vary geographically and ethnically[6-8]. The most common syndrome accompanying CLP is Pierre-Robin syndrome and the most common organ system malformation is congenital heart disease[6,17,18]. Comparatively, in this study, the most common comorbidity was congenital heart disease and the most common associated syndrome was Pierre-Robin syndrome, and both were identified as independent risk factors for adverse outcomes in the analysis of the data.

It is known that the complete type of cleft palate is associated with difficult laryngoscopy, frequent recurrent infections and fistula formation[19-21]. In the results of the present study, it was determined that the complete type of cleft palate and presence of concomitant cleft lip are associated with increased perioperative adverse outcomes compared to the incomplete type.

The strength of this study is that it consists all cleft palate cases in the 5-year experience of a tertiary reference regional hospital. However, the present study had some limitations such as being a single-center retrospective study, insufficient number of patients to be able to make subgroup analyzes more reliable, and the insufficient level of some data records.

5. Conclusions

According to the results obtained from this study, low body weight, presence of comorbidities, especially congenital heart disease, concomitant syndrome or chromosomal abnormality, complete type of cleft palate and associated cleft lip increase the incidence of perioperative adverse events in pediatric patients who have undergone cleft palate repair surgery. However, further multicenter prospective studies that include more reliable analyzes of subgroups such as malformations, syndromes and chromosomal abnormalities associated with cleft palate are needed to determine the factors that will improve patient outcomes in the anesthesia management of the children with cleft palate repair.

Acknowledgements

The authors of this article would like to thank everyone who played a role in carrying out this research, and especially thanks to Prof. Dr. H. Murat Gündüz for his valuable contributions and guidance.

Statement of ethics

The study was registered at the Cukurova University Institutional Investigation and Ethics Committee on 6 November 2020 with the approval number: 105/16 and conducted at Cukurova University in Turkey following the most recent version of the Declaration of Helsinki.

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

EEI conducted the methodology, data collection and processing, writing, reviewing and editing processes.
DLT handled the conceptualization, design, supervision, literature review, conduction and writing - original draft preparation. All authors contributed to the final manuscript revisions and approved the final version.

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The Effect of Covid-19 Disease During Pregnancy on Newborn Screening ABR Results

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Abstract

Aim: In our study, it was aimed to compare the newborn screening ABR (Auditory Brainstem Responses, AABR) results of babies of mothers who had Covid-19 (Coronavirus disease-2019) during pregnancy and babies of mothers who did not have Covid-19.

Methods: Newborns who underwent hearing screening tests in Adana Hospital Audiology Unit between April 2019 and September 2021 were included in the study, and newborns whose mothers had Covid-19 disease during pregnancy were called Group 1, and those who did not have were called Group 2. Statistical difference was studied by comparing these two groups by their birth weight, week of birth, type of delivery, first hearing test result, and referral to a reference center.

Results: A total of 746 newborn babies, 472/746 (63.3%) female and 274/746 (36.7%) males, were included in our study. There were 202/746 (27.1%) newborns in Group 1 and 544/746 (72.9%) newborns in Group 2. There was no statistically significant difference between the two groups in terms of testing age (p>0.05). When the right and left ears were evaluated separately in two groups in terms of passing the first test; no statistically significant difference was found in terms of passing the hearing test for the right and left ears, respectively (p=0.234, p=0.15). There was no statistically significant difference between the two groups in terms of birth weight and referral to a reference center (p>0.05), (p=0.775).

Conclusions: The Covid-19 disease of the mother during pregnancy does not affect the newborn hearing screening results.

Keywords: *Auditory brainstem responses (ABR), Covid-19, hearing, neonatal, pregnancy*

1. Introduction

Congenital hearing loss is accepted as an important congenital pathology and its incidence is 1.64 per 1.000 live births[1]. Detection of hearing loss in newborn children in the first 3 months and appropriate intervention in the first 6 months are important[1-3]. Otherwise, delayed detection and intervention will affect the child's speech, language, and psychosocial development, resulting in a failure in school and social life[1]. Universal newborn hearing screenings is mandatory in most countries for the early diagnosis and treatment of children with moderate to severe hearing loss[2]. The tests used in screening are otoacoustic emission (OAE) and auditory brainstem response (ABR)[3]. Since these screening tests are reproducible and non-invasive, they are very easy to apply in newborns. In these tests, a *refer* result even in one ear may indicate possible hearing loss and therefore these newborns should be retested within 1 month. If the result is *refer* again, it should be evaluated with clinical ABR within 3 months[2].

Various viral diseases can cause congenital or acquired, unilateral or bilateral hearing loss. These viral agents can harm inner ear structures directly or activate inflammatory processes that causing hearing loss. Virus can cause direct destruction to inner ear structures, especially inner ear hair cells and organ of Corti, or via activation of host immune-mediation devastation[4].

In our study, it was aimed to compare the newborn screening ABR (Auditory Brainstem Responses, AABR) results of babies of mothers who had Covid-19 (Coronavirus disease-2019) disease during pregnancy and babies of mothers who did not have Covid-19 disease.

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Received: 17.06.2023, Accepted: 29.08.2023, Available Online Date: 31.08.2023
Cite this article as: Alagoz S, Arlier S, Delibas V, et al. The Effect of Covid-19 Disease During Pregnancy on Newborn Screening ABR Results. J Cukurova Anesth Surg. 2023; 6(2): 318-23.doi: 10.36516/jocass.1316031

2. Materials and methods

Data of newborns who were admitted to the ENT clinic audiology unit at Adana City Hospital between April 2019 and September 2021, and screening ABR test results were recorded retrospectively. Madsen Acuscreen brand AABR device was used. The AABR test was recorded by attaching electrodes to the forehead, right and left ears mastoids, and using a 35 dBnHL stimulus. In AABR tests, the result was shown as "pass" or "refer".

In accordance with the national newborn screening program, the first test was conducted within 72 hours of discharge in case the test fails then the second test was conducted within 7-15 days, and in case that test fails then the third test was conducted within 15-30 days. And the who failed the tests were referred to the reference center (Fig. 1).[5] Patients whose file data could not be accessed were excluded from the study. In addition, conditions with congenital hearing loss risk factors such as syndromic diseases, stay in the intensive care unit, use of ototoxic drugs, meningitis, sepsis, intrauterine infections, jaundice, cerebral diseases were accepted as exclusion criteria. Newborn of mothers with Covid-19 and newborn of mothers without Covid-19 were followed up with the same national hearing screening program. There is no difference in practice.

Vaccine information could not be accessed because the mothers' Covid-19 vaccination program and our national newborn screening program are not yet integrated.

Newborns whose mothers had Covid-19 disease during pregnancy were defined as Group 1, and those who did not have were defined as Group 2. Statistical difference was studied between Group 1 and Group 2; by newborns' birth weight, week of birth, type of delivery, first hearing test result, and referral to a reference center.

The diagnosis of Covid-19 was made according to the results of real time PCR test on the swabs taken from the nasopharynx.

Our study was approved by the University of Health Sciences, Adana City Training and Research Hospital clinical research ethics committee with decision number 89/1570 on 30 September 2021. The patient was informed in detail and her written consent was obtained.

2.1. Statistical analysis

Number (n) and percentage (%) as descriptive statistics for categorical variables obtained within the scope of the study and mean±standard deviation as descriptive statistics if parametric test assumptions are provided for numerical parameters, if not, median and minimum-maximum values are given. Normality control for numerical parameters was evaluated with the Shapiro-Wilk Normality test. Comparison of numerical variables in groups was analyzed using the "Student t Test" if parametric test assumptions were met, and "Mann Whitney U Test" if not. Pearson chi-square test was used to compare categorical variables between the two groups. Statistical analysis and SPSS 16.0 software for Windows (SPSS, Inc., Chicago, IL) were used for all statistical analyses, and $p<0.05$ was considered statistically significant.

3. Results

30.921 babies were born between April 2019 and September 2021 in our hospital. Screening ABR test was performed in 30.148 (97.5%) of these newborns. During this period, 1.537 (5.1%) newborns were referred to a reference hearing center. A total of 746 newborn babies, 472/746 (63.3%) females and 274/746 (36.7%) males, were included in our study.

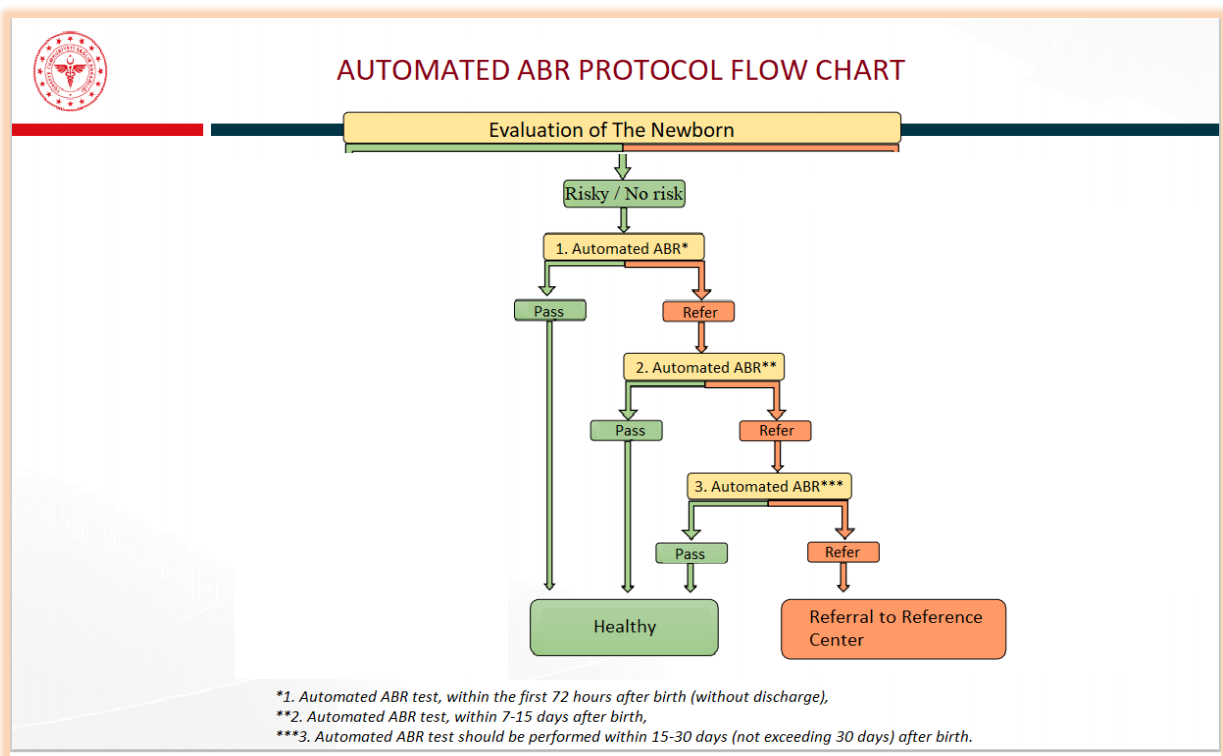

Figure 1
Automated ABR Protocol Flow Chart

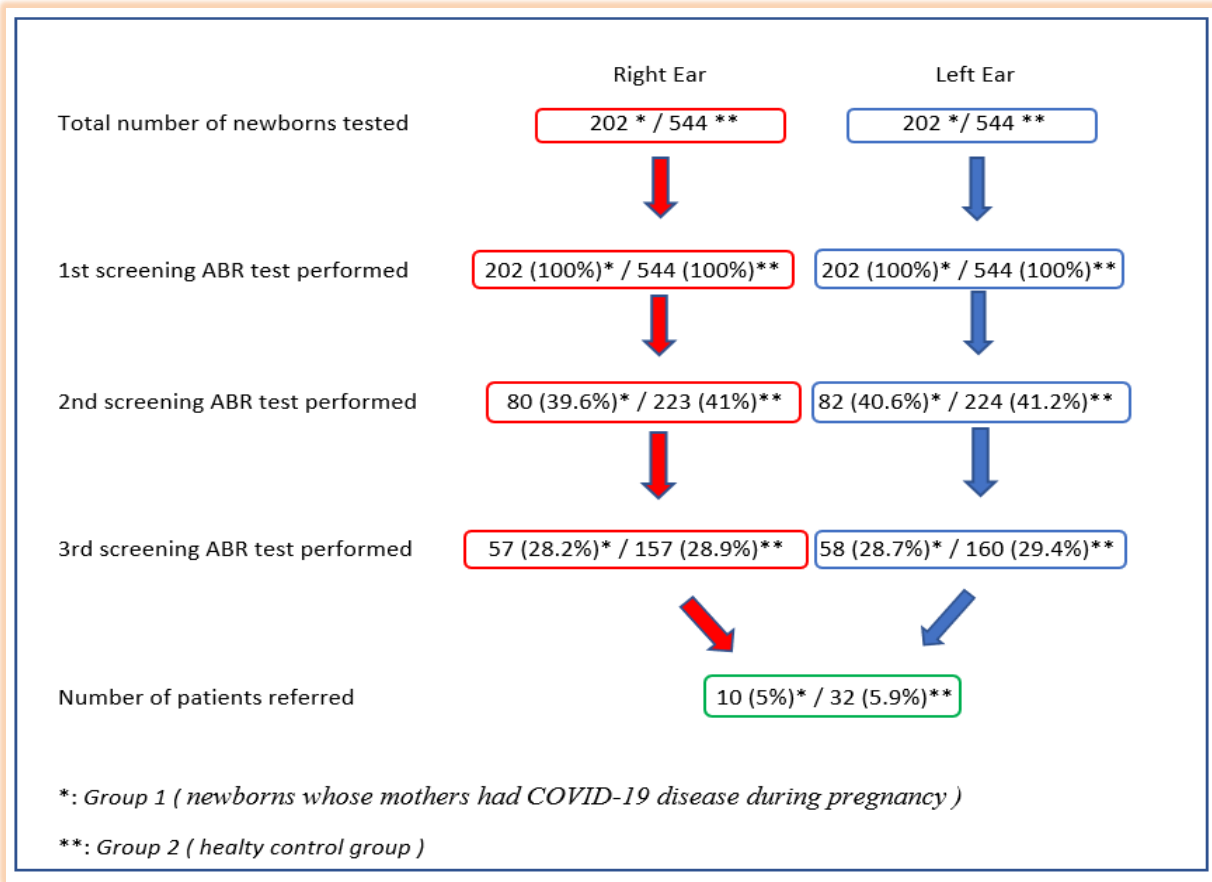

Figure 2
The numbers of passing and referral of newborn in group 1 and group 2

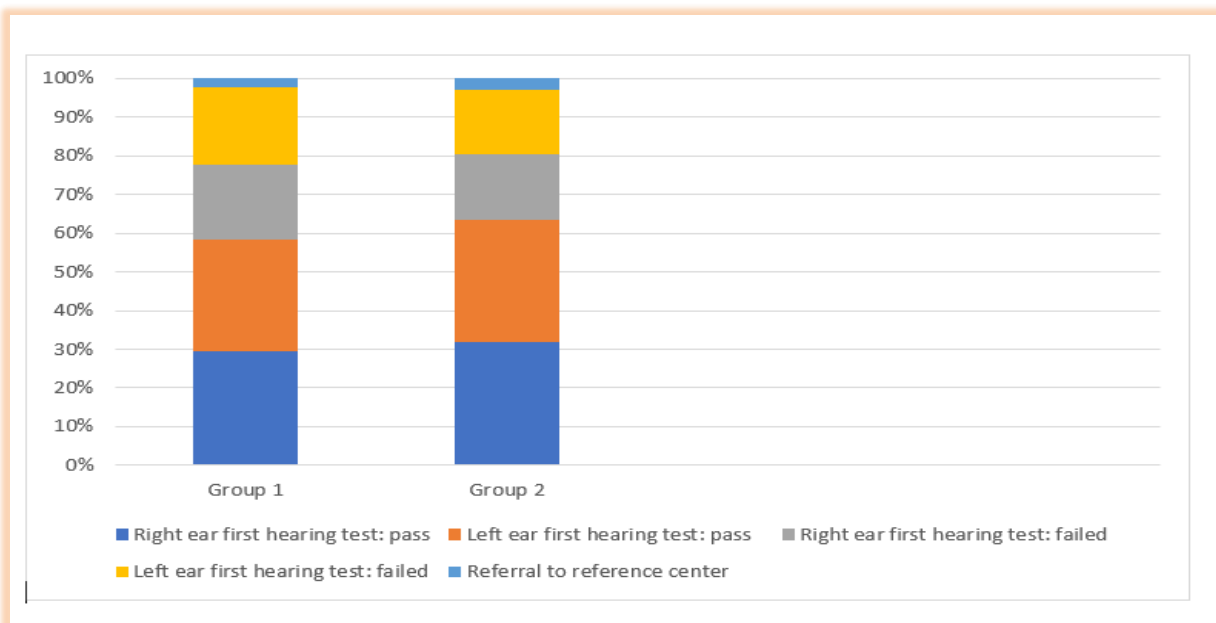

Figure 3
The Schematic view of the right and left ear first hearing test results and referral rates to the reference center between the two groups

Table 1
Categorical variables and screening results of newborns in group 1 and group 2

Variables		Group 1 (Covid-19 positive mothers) n=202	Group 2 (Covid-19 negative mothers) n=544	P value
Birthweight (gr)	min	1340	1180	
	max	5000	4500	
	25	2850	3000	0.746
Percentiles	50(Median)	3190	3100	
	75	3500	3450	
Gestational age (day)	min	0	1	
	max	200	158	
	25	1	2	0.105
Percentiles	50(Median)	5	2	
	75	18	3	
Delivery by C-section		135 (66.8%)	263 (48.3%)	<0.001
NICU stay		173 (85.6%)	462 (84.9%)	0.898
Referred on 1st screen		R=80 / L=82	R=223 / L=224	0.234
Referred on 2nd screen		R=57 / L=58	R=157 / L=160	0.150
Referred on 3rd screen		10	32	0.755

There were 202/746 (27.1%) newborns in Group 1 and 544/746 (72.9%) newborns in Group 2 (Fig. 2). Of all newborns, 398/746 (53.4%) were delivered by cesarean section and 348/746 (46.6%) were delivered by normal delivery. Birth weights are between 1.180 and 5.000 g; the mean was 3.108.1±538.6. There was no statistically significant difference between the two groups in terms of birth weight (p>0.05). Although the week of birth varied between 27 and 42; the mean was 39±1. There was a statistically significant relationship between the mother having Covid-19 during pregnancy and the delivery type of the newborn (p<0.001). While most of the mothers who did not have Covid-19 gave birth naturally 281/544 (51.7%), most of the mothers who had Covid-19 had a cesarean section 135/202 (66.8%). There was no statistically significant relationship between the mother's Covid-19 status and the need for intensive care of the newborn (p=0.898) (Table I). Their ages ranged from 1 to 200 days with a mean of 4.4±1.3. There was no statistically significant difference between the two groups in terms of testing age (p>0.05).

When the first test results of the newborns in Group 1, 80/202 (39.6%) right ears failed the test; 82/202 (%40.6) left ears failed the test. And in Group 2, 188/544 (34.6%) right and left ears failed the test equally. It was observed that a total of 42/746 (5.6%) newborns were referred to a reference center because they could not pass at least 1 of the AABR 3rd test results. There was no statistically significant difference between the two groups in terms of referral to a reference center (p=0.775) (Fig. 3).

4. Discussion

Bilateral permanent severe hearing loss in early childhood may interfere with children's speech, language, and cognitive development; and due to its increasing societal cost, it may cause negative effects on social, emotional, and academic development. However, children with mild or unilateral permanent hearing loss may have speech, language, educational, and psychosocial disorders[6]. Recognition of hearing loss in an infant by the family is generally not possible until the infant is 2-3 years old[3,7]. The ideal approach for the national newborn hearing screening program is to screen all infants before the first month after birth, to diagnose them at 3 months of age, and to provide an appropriate response (audiological, medical, and educational) until 6 months of age[6,8].

National newborn hearing screening is important in terms of reintegrating individuals with hearing loss into society through early rehabilitation and it is accepted as a mandatory screening in most countries.[2] In this screening program, which is also mandatory in our country, the screening is auditory brainstem responses (AABR)[3]. The screening program can be applied in different ways between countries and even in different regions within the same country. In some settings, the first screening occurs in the hospital. An out-patient screening enhances reliability of testing as fluid/vernix has likely resolved but also poses potential increases in losing infants in the follow-through of testing.

There are programs in which only OAE or ABR is used or in combination, and there are studies comparing these programs[6,9-11]. The response obtained in the measurements made with the scanning ABR is evaluated automatically and gives a result as passed or failed.[7] In the analysis performed by Cebulla et al.[10] in 2014, a 2-stage AABR screening program was applied and when the patients who got *passed* results were followed prospectively for 2 years, no permanent hearing loss was found in any of them. In this sense, the sensitivity of screening programs was found to be 100%. In the study conducted by Demir et al.[2] in 7.780 newborns in 2019, they adopted a 3-stage program as a hearing screening test. They used TEOAE in the first stage (on the first 3 days), TEOAE or DPOAE in the second stage (on the 15th day), and AABR in the third stage (1st month). In accordance with the literature, as the 3rd day approaches in the TEOAE test performed in the first 3 days, the infants' *passed* result rate had increased. At the end of the three stages, congenital hearing loss (47 bilateral, 3 unilateral) was detected in 50 newborns, and a ratio of 6/1.000 was obtained. They argued that the three-stage screening program had higher rates of detecting hearing loss in newborns than the other two-stage programs (in which TEOAE and AABR were used). In our study, T-ABR (Scan ABR/AABR) was used in accordance with the national newborn screening program. In our study, it was observed that the screening test of Group 1 and Group 2 babies was performed early enough and there was no difference between the test ages. This result reflects the importance given to the screening program despite all the negative aspects of the pandemic period in

terms of this mandatory testing service, among pregnant women with and without Covid-19.

In the study conducted by Sezer et al.[3] in 2017 with 253 newborns, they emphasized that cesarean section or normal vaginal delivery had no effect on hearing screening test results. In our study, the rate of cesarean section (66.8%) in Covid-19 positive mothers was high, but this did not cause a significant difference between the hearing screening test results in the two groups.

There is no single cause of congenital hearing loss, but it is a multifactorial condition that includes anatomical pathologies in the inner ear, mutations in inner ear endolymph hemostasis and conduction, mechanical-electrical conduction pathologies, and prenatal infections.[12] Cytomegalovirus, which is one of the prenatal infections, is the most common cause of non-genetic congenital hearing loss. Rubella virus, Toxoplasma, Syphilis, and Herpes simplex virus are also other pathogens[13]. The effect of Covid-19 disease, which causes many clinical spectrum and pandemic, during pregnancy on hearing in newborns is unknown.

The presence of ACE-2 receptors in cells belonging to the placenta was investigated in the immunochemical study conducted by Faure-Bardon et al.[14] in 2020 on 8 samples. This receptor was not observed in cytotrophoblasts and syncytioblasts before 7 weeks. There was no difference in ACE-2 receptor levels in the placenta of the Covid-19 positive mother and in the normal placenta, and it was detected at a minimal level. This finding may be compatible with the result of our study. The reason why we could not find a difference in hearing screening results in babies born to Covid-19 positive mothers in our study may be due to the fact that the fetus was not affected by Covid-19 in the intrauterine period. Also one potential protective mechanism suggesting fetuses may not be at greater risk for hearing loss due to maternal Covid-19 vaccine.

As new illnesses arise, it is important to understand if these need to be added to risk factors we consider as important to recognize a higher rate of hearing loss or late onset hearing loss. This data does not suggest that maternal Covid-19 during pregnancy confers a higher refer rate on hearing screening. As far as we searched the literature, there is no article similar to the results of our study. Çelik et al.[15] and Alan et al.[16] results different from our results.

In the study conducted by Çelik et al.[15] in 2021 with babies born to 37 Covid-19 positive pregnant women and 36 healthy (Covid-19 negative) pregnant women, a significant hearing loss in the babies born to Covid-19 positive pregnant women in cooperation with the other group was found. They found low TEOAE amplitudes in patients at high frequencies (3–4 kHz) and weak contralateral suppression activity of patients, especially at higher frequencies (2,3,4 kHz). They argued that there is an insufficiency in the medial olivocochlear efferent system in babies exposed to intrauterine SARS-CoV-2 and emphasized that cochlear functions should be examined in babies whose mothers had Covid-19.

In the study conducted by Alan et al.[16] in 2021 with babies born to 118 Covid-19 positive pregnant women and 118 healthy (Covid-19 negative) pregnant women, their hearing levels were compared with AABR results, and it was found that the number of referrals and hearing loss were statistically higher in babies of pregnant women who were positive for Covid-19 compared to the other group. Alan noted screening "in the first 2 weeks of age" with a rescreen in 2 weeks from the first test (potentially moving to an age of 1 month). But we described screening within 72 hours of discharge followed by a re-screen in 7-15 days. The differences between the results of our study and Alan's study may be due to the difference in scanning times.

In our study, when Group 1 and Group 2 were compared, we did not detect any difference in the amount of stay in the right and left ears in the first test results. In addition, there was no statistically significant difference in terms of referral. Although there is a need for further controlled studies to be conducted with the Clinical ABR test to investigate the effect of Covid-19 disease on hearing, our study did not detect a negative effect of having Covid-19 disease during pregnancy on AABR results.

4.1. Limitation

The limitations of this study are the lack of information about the trimester that mothers were exposed to covid-19 and the hearing status of the referred newborns.

5. Conclusion

It was observed that the Covid-19 disease of the mother during pregnancy does not affect the newborn hearing screening results. Our newborn national hearing screening program continued to be implemented without interruption during the Covid-19 pandemic. We think it would be good to need for more studies as well as some longitudinal data on children pre-natally exposed to maternal Covid-19 to help us ensure there is not a risk for late-onset hearing loss. Current protocols would suggest no further need for testing once the child has passed hearing screening/testing and this may in fact be true.

Acknowledgements

The authors of this article would like to thank everyone who played a role in carrying out this research, and especially thanks to Prof. Dr. H. Murat Gündüz for his valuable contributions and guidance.

Statement of ethics

The study approval was obtained from Adana City Hospital Clinical Research Ethics Committee. (Meeting Number: 89, Decision Number : 1570, Date: 09/30/2021),following the most recent version of the Declaration of Helsinki.

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

All authors conceptualization, design, supervision, literature review, conduction and writing- original draft preparation. All authors contributed to the final manuscript revisions and approved the final version.

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Robust Detection of Chronic Lymphocytic Leukemia with Support Vector Machines and Flow Cytometry

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Abstract

Aim: Our aim is to build a precise automatic tool for the diagnosis of CLL with the help of machine learning algorithms and flow cytometry immunophenotypic data.

Methods: We run experiments with two machine learning methods. First one is decision tree which was previously used in other similar works and second one is support vector machines which is considered to be a more robust classification method.

Results: Among the 40 CLL patients from the test set, the model correctly predicts 38 of them and among the 20 other B-CLPD patients, the model predicts 18 of them correctly. Its sensitivity, which is the fraction of true positive predictions among all positive samples, is 95% (38/40).

Conclusion: The model achieves very high accuracies on our leave out test set. This model can be a useful tool for automatic CLL diagnosis.

Keywords: *CLL, flow cytometry, machine learning*

1. Introduction

Chronic lymphocytic leukemia (CLL) is one of the most common types of adult leukemia in Western countries. It occurs more during or after middle age compared to childhood[1, 2]. Its diagnosis is based on parameters from blood counts, differential counts, a blood smear, and immunophenotyping[2].

Flow cytometry is used to assist the diagnosis and monitoring of malignant hematopoietic myeloid and lymphoid tumors. Furthermore, they are the most informative tests to confirm a diagnosis of CLL. In the diagnosis of CLL, CD5, CD19, CD20, CD23, and surface or cytoplasmic kappa and lambda light chains are regarded as essential markers. However, there are difficulties in differentiating the CLL diagnosis from the other B-cell chronic lymphoproliferative disorders (B-CLPD), because those markers can be seen in other B-CLPD as well[3]. For example, the CD5 expression can also be seen in other lymphoid malignancies, such as mantle cell lymphoma and the expression of CD23 can be observed in marginal zone lymphoma. In other words, those markers are not specific to CLL. Because of that, other markers, CD10, CD43, CD79b, CD81, FMC7 and CD200 can be useful in discriminating the CLL diagnosis from the other B-CLPD[3]. Scoring systems are also available to differentiate the CLL from the other B-CLPD and the most frequently used one is Matutes score[4]. The Matutes score system looks at the positivity of CD23 and CD5 and the absence or poor presence of CD79b (or CD22), FMC7 and SmIg. It converts those observations to a 0-5 numerical score. If the score ends up greater than 3, the subject is classified as a CLL patient [4]. However, this scoring system does not perfectly differentiate diagnosis between CLL and other B-CLPD [3]. B-CLPD neoplasms are challenging to diagnose due to their overlapping clinical features as mentioned before[3]. Machine learning algorithms have become useful tools in classification tasks. They learn from data and remove the need for hand-designed heuristics. As they find applications in many domains, healthcare providers also recognize their capabilities and use medical clinical decision algorithms based on a set of decision rules to improve diagnosis with reduced cost[5]. A machine learning approach to differentiate the CLL diagnosis from the other B-CLPD may reduce the cost, speed-up the diagnosis, and may even improve the accuracy of the correct diagnosis. Previous studies propose a decision tree in differential diagnosis of lymphoproliferative diseases[6].

In this study, we aim to develop an easy, precise, automatic tool for the diagnosis of CLL with the help of machine learning methods learned from flow cytometry immunophenotypic data.

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Received: 14.08.2023, Accepted: 22.08.2023, Available Online Date: 31.08.2023
Cite this article as: Boral B. Robust Detection of Chronic Lymphocytic Leukemia with Support Vector Machines and Flow Cytometry. J Cukurova Anesth Surg. 2023; 6(2): 324-6. doi: 10.36516/jocass.1342711

2. Materials and methods

2.1. Study Groups

The data of patients diagnosed with B lymphoproliferative disease between 2020-2023 were retrospectively analyzed. A total of 152 patients' data were analyzed. Among the analyzed patients, 108 patients were diagnosed with CLL and 44 patients with other B-CLPD. Among the patients diagnosed with other B-CLPD, 18 patients were diagnosed with mantle cell lymphoma, 14 patients with marginal zone lymphoma, 4 patients with splenic marginal zone lymphoma, 5 patients with hairy cell lymphoma, 2 patients with follicular lymphoma, and one patient with burkitt lymphoma.

The diagnosis of B-CLPD was made according to the most recent revision of the WHO classification of lymphoid neoplasms, released in 2022, based on clinical data and morphological, immunophenotypic, and genetic criteria[4].

2.2. Flow Cytometry

Peripheral blood samples were taken into tubes containing EDTA. Samples were prepared and analyzed with a flow cytometer immediately after collection. Then, immunophenotypic analysis was performed using monoclonal antibodies; CD19, CD5, CD23, CD81, FMC7, CD22, CD43, CD103, CD11c, CD123, HLA-DR, CD10, CD38, CD25, CD200, CD79b and CD20.

2.3. Machine Learning Set-up

We run experiments with two machine learning methods. First one is decision tree which was previously used in other similar works[6] and second one is support vector machines which is considered to be a robust classification method. Decision tree algorithm considers each attribute of the data to pick the best one that will result in branched out nodes with the most purity. We use the Gini index to measure the purity of the nodes. If a node is pure, that means all samples that fall into that node share the same class. They are considered unstable classifiers as new samples in the training set may cause the structure of the decision tree to change drastically.

On the other hand, support vector machines find a decision boundary between the positive and negative classes with the largest margin. Since the margin between the negative and positive samples are maximized, they are considered to be more stable and robust.

We use CLL as our positive class and other B-CLPD as our negative class for both of these methods and learn a model for this binary classification problem. Our dataset as mentioned in the Study Groups section includes 108 CLL patients and 44 other B-CLPD patients. We use 40 patients from CLL group and 20 other B-CLPD patients for our test set in which we evaluate our models. The rest of the data is used for the training. For each of these data points, we consider the 17 immunophenotypic attributes mentioned in the Flow Cytometry subsection.

For the decision tree and support vector machine algorithms, we use Scientific computing tools (version 1.2.3, SciPy.org) for Python (version 2.7.16, Python.org).

3. Results

In this section, we report our prediction results of the decision tree and support vector machine models. Firstly, the decision tree method serves as a baseline. It achieves 93.3% accuracy on the test set. Its confusion matrix is shown in Table 1. Among the 40 CLL patients from the test set, the model correctly predicts 38 of them and among the 20 other B-CLPD patients, the model predicts 18 of them correctly. Its sensitivity, which is the fraction of true positive predictions among all positive samples, is 95% (38/40). Its specificity, which is the fraction of true negative predictions among all negative samples, is 90% (18/20).

Next, we evaluate the support vector machine model which is considered to be a more powerful and robust method. It achieves 98.3% accuracy. Table 2 shows the confusion matrix of the model. The support vector machine model classifies all 20 other B-CLPD patients correctly and among the CLL patients the model correctly predicts 39 out of the 40 patients. The sensitivity of this model is 100% (39/39) and specificity is 95.23% (20/21).

Note that both models perfectly classify the training data they learn from as shown in Table 1 and 2.

Table 1

Confusion matrix of decision tree method on the training and test set.

		Train Dataset		Test Dataset	
		Ground Truth		Ground Truth	
		CLL	Other B-CLPD	CLL	Other B-CLPD
Predictions	CLL	68	0	38	2
	Other B-CLPD	0	24	2	18

Chronic lymphocytic leukemia (CLL), Other B-cell chronic lymphoproliferative disorders (B-CLPD).

Table 2

Confusion matrix of support vector machine method on the training and test set

		Train Dataset		Test Dataset	
		Ground Truth		Ground Truth	
		CLL	Other B-CLPD	CLL	Other B-CLPD
Predictions	CLL	68	0	39	0
	Other B-CLPD	0	24	1	20

Chronic lymphocytic leukemia (CLL), Other B-cell chronic lymphoproliferative disorders (B-CLPD).

4. Discussion

Flow cytometry tests are very important diagnostic tools in B-CLPD, especially in CLL[3]. The Matutes score that was mentioned in the introduction has been used for more than 20 years[4]. However, detecting CLL is not a solved task due to the ambiguous immunophenotypes[7]. To overcome this challenge Vergnolle et al[5] has developed a decision tree that enables the differentiation of CLL from non-CLL cases. Özdemir et. al.[8] also created a similar decision tree with sensitivity of 97.78% and specificity of 93.33%. We also set a decision tree model which achieved sensitivity of 95% and specificity of 90%. The results may differ because different datasets are used but these results serve as a baseline for our comparison. The support vector machine from our experiments has sensitivity of 100% and specificity of 95.23% and achieves better results than the decision tree baseline.

Decision tree models are interpretable. They are easily built and computationally efficient. However, they are simple models and considered to be not stable. In this work, we show that with support vector machine models, better results can be obtained. Those results show that automatic tools can be considered for the diagnosis of CLL.

Interpreting flow cytometry tests is a difficult task that requires experts in the field. Performing these tests by unauthorized persons may result in misdiagnoses and incorrect or unnecessary drug use. With these newly developed methods, it is aimed to prevent such errors.

In this study, we collect a dataset to learn a classification model of CLL and other B-CLPD classes using immunophenotyping with flow cytometry. We train a machine learning model specifically a Support Vector Machine which is a robust classification method. The model achieves very high accuracies on our leave out test set which shows that it can be a useful tool for automatic CLL diagnosis.

Acknowledgements

None.

Statement of ethics

This was a retrospective and single-center study which was approved by the Ankara Oncology Training and Research Hospital local Ethics Committee and was conducted in accordance with the Declaration of Helsinki. (AEŞH-EK1-2023-472)

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

Author read and approved the final manuscript.

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Hypomagnesemia and Calcineurin Inhibitors in Kidney Transplant Recipients

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Abstract

Aim: Post-transplant hypomagnesemia is a frequently encountered and significant electrolyte disorder and is more common in patients using calcineurin inhibitors (CNIs). This study aimed to evaluate the frequency of hypomagnesemia and accompanying conditions in the outpatient follow-up of renal transplant recipients.

Methods: This cross-sectional study included 236 renal transplant patients. Demographic characteristics of the patients and their biochemical values, including drug levels, were recorded.

Results: Of the patients, 69 (29.2%) were female, and 194 (82.3%) were living donor recipients. The mean age of the entire group was 43.1 years. The frequency of hypomagnesemia was 40% (10/25) in the first 12 months, 26.1% (23/88) between the 12th and 60th months, 26% (32/123) after 60 months, and 27.5% (65/236) in all patients. In patients with higher levels of tacrolimus compared to those with the target level, the frequency of hypomagnesemia increased in those with a posttransplant period of 12-60 months (40.9% vs. 20.8%, p: 0.018) and over 60 months (44% vs. 26%, p: 0.046). In addition, the magnesium (Mg+2) level was lower in patients using tacrolimus compared to those using cyclosporine (CsA) (1.80±0.18 vs 1.91±0.25, p: 0.003). The effect of hypomagnesemia on graft functions was statistically insignificant in all groups.

Conclusion: Hypomagnesemia is a common electrolyte disorder in the early and late periods after transplantation. In our study, hypomagnesemia did not differ according to proton pump inhibitor (PPI) use, gender, fasting blood glucose, and glomerular filtration rate. However, the frequency increased in patients using tacrolimus and those with above-target serum tacrolimus levels.

Keywords: *Hypomagnesemia, kidney transplant, calcineurin inhibitor, posttransplant electrolyte disorders*

1. Introduction

Mg^{+2} is the fourth most abundant cation in the body and the second most crucial intracellular cation[1,2]. Approximately half of the total body Mg^{+2} is found in bones, and the rest is found in skeletal muscles and soft tissues[2]. Mg^{+2} involves physiological processes such as nerve and muscle function, cardiac rhythm, and blood pressure regulation. Low serum Mg^{+2} level (hypomagnesemia) is an electrolyte disorder frequently seen after renal transplantation[3].

It may cause symptoms such as muscle cramps or spasms, arrhythmias, numbness or formication in the extremities, mood swings or nervousness, loss of appetite, nausea, and vomiting. Hypomagnesemia may develop due to diuretics, acid-base imbalances, or Mg^{+2} loss due to renal tubular damage or gastrointestinal disturbances such as diarrhea, nausea, or vomiting. It is diagnosed by measuring serum Mg^{+2} levels. Treatment is primarily provided by supplementing Mg^{+2}, and the dosage and administration route depends on the deficiency level and the patient's clinical condition. Regular monitoring of Mg^{+2} levels is of great importance to ensure the effectiveness of the treatment and maintain the appropriate Mg^{+2} balance. Hypomagnesemia becomes more of an issue, especially in patients using CNIs[4].

In our study, we aimed to observe the frequency of hypomagnesemia in short (<12 months), medium (12-60 months), and long-term (>60 months) after renal transplantation and its relationship with the use of CNIs and biochemical and demographic characteristics.

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Received: 21.06.2023, Accepted: 30.08.2023, Available Online Date: 31.08.2023
Cite this article as: Onan E, Paydas S, Balal M, et al. Hypomagnesemia and Calcineurin Inhibitors in Kidney Transplant Recipients. J Cukurova Anesth Surg. 2023; 6(2): 327-31. doi: 10.36516/jocass.1317894

2. Materials and methods

2.1. Patients:

A total of 370 kidney transplant patients were evaluated. Of these 370 patients, 236 kidney transplant patients aged over 18 who underwent kidney transplantation between 2000 and 2016, who did not have acute rejection or acute kidney injury, who had a glomerular filtration rate of (GFR) >30 ml/min, who did not have any gastrointestinal or other critical diseases, who did not use diuretics, and who did not have uncontrolled diabetes were included in the study. Power analysis was performed for identifying the number of participants in the study conducted between 2016 and 2019, and two hundred and twenty patients were targeted. In the study, the frequency of hypomagnesemia in the first 12 months, between the 12th and 60th months, and after 60 months and the estimated glomerular filtration rate (e-GFR/CKD-EPI 2021), CNI levels (Tacrolimus C0 and cyclosporine A C2 level), and laboratory parameters were compared. In the study in which hypermagnesemia was not observed, patients were divided into two groups according to the Mg^{+2} level: hypomagnesemia (below 1.8 mg/dL) and normomagnesemia. Tacrolimus therapeutic target range was accepted as 8-12 ng/mL in the first 12 months, 5-8 ng/mL between 12 and 60 months, and 3-5 ng/mL after 60 months; C2 target level in patients treated with cyclosporine A (CsA) was accepted as 1000-1200 ng/ml (0-3 months), 600-1000 ng/ml (3-12 months), and around 600-800 ng/ml (>12 months). The study was designed as a cross-sectional and retrospective study. The study was conducted on outpatient kidney transplant patients admitted to the nephrology outpatient clinic of Cukurova University Faculty of Medicine.

Ethics committee approval was taken from Cukurova University Ethics Committee (Dated: 4/3/2016, Decision Number: 24). Informed consent was taken from all patients.

2.2 Statistical Analysis:

SPSS 18.0 for Windows was used for statistical evaluation. As a descriptive value, minimum, maximum, mean, and standard deviation were used for quantitative data. In intergroup comparisons, Chi-square and Fisher's exact tests were used for categorical variables, and a t-test was used for paired group comparisons. In evaluation, $p<0.05$ was accepted as the significance level.

3. Results

Of the patients included in the study, 69 (29.2%) were female, and 194 patients (82.3%) were transplant recipients from a living-relative donor. The mean age of the entire group was 43.1. Post-transplant hypomagnesemia was observed in 65/236 (27.5%) patients. The frequency of hypomagnesemia was 40% (10/25) in the first 12 months, 26.1% (23/88) between the 12th and 60th months, and 26% (32/123) after 60 months. The primary kidney diseases of the patients, the immunosuppressive drugs they used, and their demographic data are presented in Table 1.

Serum calcium and potassium levels were statistically significantly lower in the hypomagnesemia patient group compared to the normomagnesemic group (9.31±0.78 mg/dL vs. 9.59±0.59 mg/dL, p=0.008 - 4.14±0.48 mmol/L vs. 4.3±0.51 mmol/L, p=0.028, respectively). There was no statistically significant difference between patients with and without hypomagnesemia regarding age, gender, follow-up periods, e-GFR levels, living or cadaveric transplantation, serum levels of sodium, glucose, CNI, and PPI use (Table 2).

In cases where tacrolimus was above the target level, hypomagnesemia was statistically significantly more frequent than normomagnesemia in both the patient groups with a posttransplant period of 12-60 months and >60 months (42.9% vs. 20.4%, p=0.048 / 44% vs. 22.6%, p=0.046, p=0.046, respectively), but there was no significant difference in terms of the frequency of hypomagnesemia in patients with a posttransplant period of <12 months (p=0.665) (Table 3).

Table 1

Demographic characteristics of patients

Variables	
Female/Male, n (%)	69(29.2)/167(70.8)
Female/Male Mean age±SD	40.52±12.3/44.17±12.37
The mean age ±SD of the entire group	43.10±12.42
Cadaveric/living donor n (%)	42(17.7)/194(82.3)
Number of patients using PPI, n (%)	71(30.1)
Number of patients using tacrolimus	186/236
Number of patients using cyclosporin	33/236
Number of patients using mTOR inhibitor	10/236
Other immunosuppressive drugs	7/236
Primary Kidney Disease	n(%)
Hypertension	75(32)
Diabetes mellitus	56(24)
Idiopathic	37(14)
Chronic glomerulonephritis	36(16)
Kidney stone	10(4)
Polycystic Kidney Disease	19(8)
Tubulointerstitial Nephritis	3(2)

Abbreviations: mTOR: Mammalian target of rapamycin, PPI: Proton pump inhibitor

Serum Mg^{+2} levels were significantly lower in patients using tacrolimus (n=186) than in patients using CsA (n=33) (1.80±0.18 mg/dL vs 1.91±0.25 mg/dL, p=0.003). Sodium levels were significantly lower in cyclosporine patients than those using tacrolimus (136.47±2.54 mmol/L vs 137.98±2.74 mmol/L, p=0.004) (Table 4).

There was no statistically significant difference between cadaveric and living transplantation regarding the demographic and laboratory parameters (Table 5).

4. Discussion

In immunosuppressive regimens using CNIs after kidney transplantation, hypomagnesemia is frequently observed due to increased urinary excretion of Mg+2. CsA and tacrolimus are most recommended for maintenance immunosuppressive therapy, and both have a magnesium-lowering effect. CNIs down-regulate renal expression of epidermal growth factor and distal collecting tubule of Transient Receptor Potential Melastatin 6 (TRPM6), which absorbs distal magnesium[5,6]. Hypomagnesemia was observed in 6.6% of patients receiving tacrolimus and 1.5% receiving CsA[7] It has been reported that hypomagnesemia frequently develops in the first few weeks after transplantation and that serum Mg is at the lowest level in the second month after transplantation[8]. A cohort study on 49 kidney transplant recipients reported that 22.4% of patients developed hypomagnesemia six years after transplantation and that posttransplant hypomagnesemia could persist for a long time[9]. In our study, according to the follow-up period, the frequency of hypomagnesemia after renal transplantation was 40% (10/25) in the first 12 months, 26.1% (23/88) in between the 12th and 60th months, and 26% (32/123) after 60 months. The frequency among all patients was 27.5% (65/236).

Our study found that serum calcium and potassium levels were statistically significantly lower in the hypomagnesemia patient group than in the normomagnesemic patient group.

Table 2

Comparison of renal transplant patients with low and normal magnesium levels in terms of the follow-up period, calcium level, phosphorus level, graft function during transplantation, age, sex, donor source, and drug level

Variables	Serum magnesium (<1.8 mg/dL) (n=65, 27.54%)	Magnesium level normal (>1.8 mg/dL) (n=171, 72.46%)	P
<12 months (n=25)	10 (40%)	15 (60%)	
12-60 months (n=88)	23 (26%)	65 (74%)	
>60 months (n=123)	32 (26%)	91 (74%)	
Calcium (mg/dL)	9.31±0.81	9.58±0.59	0.018
Phosphorus (mg/dL)	3.37±0.84	3.30±0.66	0.450
Calcium x phosphorus product	31.15±5.96	31.51±6.04	0.689
Sodium level (mmol/L)	137.5±3.42	137.8±2.46	0.530
Potassium level (mmol/L)	4.14±0.48	4.3±0.51	0.028
Glucose level (mg/dL)	103.12±48.54	106.74±56.98	0.671
12 months e-GFR (ml/min)	75.63±38.66	68.73±23.48	0.583
12-60 months e-GFR (ml/min)	84.16±28.73	75.78±24.32	0.179
>60 months e-GFR (ml/min)	76.67±31.97	70.95±26.92	0.328
Age (year)	42.70±12.34	43.26±12.51	0.760
Sex (Female/Male)	22(32%)/47(68%)	43(26%)/124(74%)	0.337
Cadaveric transplantation (n=42)	13(20%)	29(17%)	0.585
Living transplantation (n=194)	52(80%)	142(83%)	
Tacrolimus level (ng/dL) (n=186)	5.78±2.46	5.13±2.38	0.098
Cyclosporin level (C2 level, ng/mL), (n=33)	336.06±301.06	251.34±191.83	0.386
Use of proton pump inhibitor (Yes/No)	22(34.4%)/43(65.6%)	50(29.5%)/121(70.5%)	0.475

Table 3

The frequency of hypomagnesemia in patients with serum tacrolimus levels in the target range and above the target level

Posttransplant period	Magnesium level	Number of patients	Number of patients with a tacrolimus level above the target value*	P
<12 months	Hypomagnesemia	10	3/10 (30%)	0.665
(n=24)	Normomagnesemia	14	3/14 (21.4%)	
12-60 months	Hypomagnesemia	21	9/21 (42.9%)	0.048
(n=75)	Normomagnesemia	54	11/54 (20.4%)	
>60 months	Hypomagnesemia	25	11/25 (44%)	0.046
(n=87)	Normomagnesemia	62	14/62 (22.6%)	

* The therapeutic target range for tacrolimus was accepted as 8-12 ng/mL for <12 months, 5-8 ng/mL for 12-60 months, and 3-5 ng/mL for >60 months.

Table 4

Comparison of patients' serum magnesium, glucose, and calcium levels using tacrolimus and cyclosporine as maintenance immunosuppressive.

Variables	Patients using tacrolimus (n=186)	Patients using cyclosporin (n=33)	P
Patients with hypomagnesemia, n (%)	53(28.5%)	6(18.2%)	0.218
Serum magnesium (mg/dL)	1.80±0.18	1.91±0.25	0.003
Serum calcium (mg/dL)	9.51±0.69	9.44±0.56	0.579
Serum phosphorus (mg/dL)	3.31±0.70	3.38±0.66	0.568
CalciumxPhosphorus product	31.34±5.74	31.94±6.30	0.585
Serum glucose (mg/dL)	107.93±58.57	94.61±16.56	0.259
Serum potassium (mmol/L)	4.26±0.47	4.34±0.61	0.388
Serum sodium (mmol/L)	137.98±2.74	136.47±2.54	0.004

Table 5
Comparison of renal transplant recipients according to the donor

Variables	Cadaveric Transplantation	Living Transplantation	P
Female/Male, n (%)	19(45.2%)/23(54.8%)	50(25.8%)/144(74.2%)	0.012
Age (year)	43.81±14.03	42.96±12.11	0.689
Tacrolimus level (ng/dL)	5.46±2.75	5.28±2.33	0.682
Cyclosporin C2 level (ng/mL)	354.57±204.67	257.96±214.63	0.462
Patients using tacrolimus, n (%)	39(92.9%)	147(83.1%)	
Patients using cyclosporine, n (%)	3(7.1%)	30(16.9%)	0.110
<12 months, n (%)	6(14.3%)	19(9.8%)	
12-60 months, n (%)	21(50%)	67(34.5%)	0.064
>60 months, n (%)	15(35.7%)	108(55.7%)	
Glucose level (mg/dl)	122.44±92.26	101.73±40.36	0.178
Calcium (mg/dL)	9.42±0.78	9.53±0.64	0.343
Phosphorus (mg/dL)	3.40±0.66	3.30±0.72	0.404
Calcium x phosphorus product	32.04±5.63	31.28±6.09	0.467
Serum sodium (mmol/L)	138.17±3.01	137.61±2.70	0.242
Serum potassium (mmol/L)	4.25±0.46	4.26±0.52	0.903
Serum magnesium(mg/dL)	1.78±0.19	1.82±0.21	0.218
<12 months e-GFR (ml/min)	80.53±40.36	68.63±26.53	0.407
12-60 months e-GFR (ml/min)	80.58±23.32	77.16±26.45	0.597
>60 months e-GFR (ml/min)	72.38±26.31	72.45±28.67	0.993
Patients using proton pump inhibitor, n (%)	16(39%)	55(29.1%)	0.212

In the study conducted by Suh et al., it was shown that the parathormone response might be impaired in hypomagnesemia conditions, and it was stated proposed that although the parathormone level increases, this may not be enough to provide sufficient calcium level[10].

CsA and tacrolimus lead to a 2- to 3-fold and 1.6- to 1.8-fold increase in urinary calcium and magnesium excretion, respectively, whereas rapamycin has no effect on calcium but doubles urinary magnesium excretion[10].

Our study showed that the potassium levels were within normal limits in hypomagnesemia patients but statistically significantly lower than in normomagnesemic patients. CNI were also examined according to the donor source, but no difference was found in potassium levels in both comparison groups. In the literature, there is no data on lower potassium levels within the normal range of posttransplant hypomagnesemia in the case of immunosuppressant use or other clinical processes. The possible reason for this might be associated with the potassium secretion-increasing effect of hypomagnesemia from the distal tubules.

Serum sodium levels of patients using CsA were significantly lower than those using tacrolimus. Contrary to our study, Higgins et al.[12] stated that serum Na^+ levels were lower in patients using tacrolimus, which could be associated with high glucose levels. Our study found that the mean fasting blood glucose (FBG) was 107 mg/dL in patients using tacrolimus and 94 mg/dL in patients using CsA and that there was no statistical difference between the groups. There are many findings in the literature stating that there is no difference in serum Na^+ levels of patients using tacrolimus and CsA[12,13].

Kidney Disease Improving Global Outcomes (KDIGO) recommended the target tacrolimus level as 5–15 ng/mL in the early post-transplant period[14]. However, in their study, Richards et al.[14] reported that tacrolimus concentrations of >8 ng/mL are required to reduce the frequency of early rejection in the first year after transplantation. In our study, the therapeutic target range for tacrolimus was determined as 8-12 ng/mL for <12 months, 5-8 ng/mL for 12-60 months, 3-5 ng/mL for >60 months and the frequency of hypomagnesemia was found to be increased in patients with tacrolimus above the target value for 12-60 months and over 60 months (40.9% vs. 20.8%, p=0.018 and 44% vs. 26%, p=0.046, respectively). In addition, it is known that tacrolimus increases renal Mg^{+2} excretion, which is more common in patients with high drug levels[15]. Serum Mg^{+2} levels were significantly lower in patients using tacrolimus than those using CsA. This has been shown in studies on Type 2 DM, which is newly developing in the posttransplant period[16].

The limitations of our study were the relatively small number of cases, examination at different stages of the posttransplant period, and the study's cross-sectional design.

5. Conclusions

Hypomagnesemia is a common electrolyte disorder seen in the early post-transplant period and the late period after five years. Interestingly, gender, proton pump inhibitors use, blood glucose levels, and GFR values did not differ for hypomagnesemia in our study. It was determined that using tacrolimus and above-target tacrolimus levels after the 12th month increased the frequency of hypomagnesemia after transplantation. Due to the long-term persistence of hypomagnesemia, monitoring the serum Mg^{+2} levels in renal transplant recipients is crucial.

Acknowledgements
None.

Statement of ethics
This study was approved from Cukurova University Ethics Committee (Dated: 4/3/2016, Decision Number: 24). Informed consent was taken from all patients.

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

Funding source
None

Author contributions

EO, SP: concepts, design, data acquisition, statistical analysis, manuscript editing and manuscript review.
ET: definition of intellectual content, literature search, data analysis, manuscript preparation and manuscript review.
MB, NCG, İA: clinical studies, data acquisition, manuscript review.
All authors read and approved the final manuscript.

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Comparison of Noncontact Plating with Conventional Methods and Osteosynthesis Techniques in the Treatment of Pediatric Femoral Fractures

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Abstract

Aim: Studies on surgical options in pediatric femoral fractures have been continuing for many years. We aimed to compare the noncontact plating we applied with the other techniques.

Methods: Pediatric patients treated for femoral shaft fracture were included. The patients were evaluated in terms of fracture type, time until surgery, duration of surgery, time of union, complications, Flynn criteria, radiological findings. 21 were in the elastic nailing (group 1), 27 were in the conventional plating (group 2), 11 were in the noncontact plating (group 3).

Results: The mean age was 8.3±1.4 (6-11) in group 1, 10.2±2.2 (7-15) in group 2, and 9.7±2.8 (7-15) in group 3. The time of union was 8.0±2.2 weeks (6-16) in group 1, 9.7±2.7 weeks (7-20) in group 2, and 7.1±1.0 weeks in group 3 (6 -9). In group 1, one patient had delayed union, two patients had a valgus deformity, two patients had minor wound site infection, and four patients had shortening of less than 2 cm. In group 2, three patients had a valgus deformity. Moreover, one patient underwent revision due to plate fracture. In group 3, no delayed union or deformity was observed in any patient.

Conclusions: The fact that elastic nailing, which is the most frequently recommended method in pediatric femoral fractures. However, it is obvious that conditions such as the absence of splinting, better reduction, fewer deformity, early rehabilitation provide advantages over noncontact plating. While it is up to the surgeon's preference, noncontact plating can be applied safely and successfully.

Keywords: *Pediatric femoral fracture, elastic nailing, locked plating, noncontact plating*

1. Introduction

While pediatric femoral fractures are less common than clavicle and wrist fractures, they are the most common orthopedic injury requiring hospitalization[1,2]. Conservative treatment, elastic nailing, and plate-screw applications are commonly used in pediatric femoral fractures. There are studies indicating that conservative treatment has successful outcomes up to sixty-six months[3]. However, patient care provided by the family, hygiene, difficulties during patient handling, and non-adoption of plaster cast are challenges of conservative treatment. Surgery comes to the forefront after six years of age[4]. In this case, elastic nailing, plate-screw systems, and external fixator fixation are used.

The use of external fixators is limited in open fractures due to pin tract infection and the difficulty of using extracorporeal implants. Elastic nailing and plate-screw systems are commonly used in closed fractures. There are many studies on these two techniques[5,6]. Noncontact plating, which is the subject of this study, is fracture fixation in such a way that the plate never contacts the bone. We think that it supports the callus formation since it does not exert pressure on the periosteum and allows micromovement. There are successful studies on the use of noncontact plating to treat open fractures and pathological fractures due to osteomyelitis[7-10]. However, we could not find a study comparing the mentioned technique with conventional methods in pediatric femoral fractures. There are scarce studies on this technique in the literature. We aimed to demonstrate the effect of this technique, which does not disturb the periosteal circulation, on pediatric femoral fractures.

2. Materials and methods

The study was initiated by obtaining approval from the Ethics Committee of our hospital (06/05/2021 no:1390). Patients aged between 6-18 years who were admitted to the emergency department of our hospital and diagnosed with femoral fractures between Janu-

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Received: 17.08.2023, Accepted: 29.08.2023, Available Online Date: 31.08.2023
Cite this article as: Uluoz M, Kapukaya A. Comparison of Noncontact Plating with Conventional Methods and Osteosynthesis Techniques in the Treatment of Pediatric Femoral Fractures. J Cukurova Anesth Surg. 2023; 6(2): 332-7.
doi: 10.36516/jocass.1345285

ary 2018 and June 2021 were screened retrospectively. One hundred fifty-five patients were reached. When patients who had multiple fractures, metabolic disease, tumor-related pathological fractures, and a follow-up period of less than six months and who underwent interlocking intramedullary nailing were excluded from the study, 59 patients were included in the study. The patients were divided into three groups, those who underwent elastic nailing (GROUP 1), those who underwent plate-screw osteosynthesis with a conventional method (GROUP 2), and those who underwent locking plate-screw osteosynthesis with a noncontact method (GROUP 3).

2.1. Surgical technique:

All patients were operated in the supine position under general anesthesia. In group 1, a closed reduction was initiated; however, when the reduction was prolonged, an open reduction was performed, and the surgery was completed with a standard retrograde technique with two nails. The long leg arched at the hip was splinted. In group 2, a closed reduction was performed. After the plate length was planned with fluoroscopy and shaped according to the bone anatomy, a 5-cm incision was made on the distal lateral of the femur, and the plate was advanced submuscularly. A 5-cm incision was made on the proximal part of the plate, and the plate was placed lateral to the closed reduced bone. It was fixed with locking and non-locking screws according to the surgeon's preference. In group 3, the plate was placed through a 5-cm incision in the lateral distal without shaping. Three mm osteotomes were placed between the plate and the bone proximally and distally, and screwing was started. The fracture position was fixed with locking screws so that the plate did not contact the bone in the reduction position we desired. Since we could not perform a very rigid fixation, we aimed to ensure that it would allow both micromovement and the callus formation under the plate. Splint fixation was not performed in group 2 and group 3. In group 1, the splint was terminated at the end of 45 days, and loading was initiated. In the other groups, partial loading was initiated when the callus tissue was observed in the control on day 20. All patients were called for control at weeks 3, 6, and 12 and at month 6.

The patients' age, sex, fracture type, time until surgery, duration of surgery, technique used, presence of complications, clinical and radiological findings (alignment, shortness, callus), and Flynn criteria[11] were recorded. These results were evaluated statistically.

2.2 Statistical Analysis:

SPSS 23.0 package program was used for the statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, while continuous measurements were summarized as mean and standard deviation (median and minimum-maximum values where appropriate). The Shapiro-Wilk test was used to determine whether the parameters in the study were normally distributed. The Kruskal-Wallis test was used for non-normally distributed parameters. The post hoc Bonferroni method was used to examine the source of differences between the groups. The level of statistical significance was accepted as $p<0.05$ in all tests.

3. Results

As a result of the retrospective evaluation, 59 patients were included in the study. There were 21 patients in group 1, 27 patients in group 2, and 11 patients in group 3. Age, time until surgery, duration of surgery, time of union values, and the statistical comparison of these values are presented in Table 1. The sex distribution of the patients by groups, their fracture types, and the callus pattern of the union tissue are shown in Table 2.

Table 1

Comparison of age, time until surgery, duration of surgery, and time of union

	Group 1 (n=21) Mean±sd Med (Min-Max)	Group 2 (n=27) Mean±sd Med (Min-Max)	Group 3 (n=11) Mean±sd Med (Min-Max)	p1	p2
Age (years)	8.3±1.4 8 (6-11)	10.2±2.2 10 (7-15)	9.7±2.8 9 (7-15)	0.013*	Group2-1; p=0.007
Time until surgery (hours)	9.2±4.6 8 (4-24)	9.0±4.6 8 (4-24)	7.6±1.2 8 (6-10)	0.695	
Duration of surgery (min)	39.8±4.2 40 (30-48)	54.4±10.5 54 (38-98)	47.1±6.4 45 (40-60)	<0.001**	Group2-1; p<0.001 Group2-3; p=0.042
Time of union (weeks)	8.0±2.2 8 (6-16)	9.7±2.7 9 (7-20)	7.1±1.0 7 (6-9)	<0.001**	Group2-1; p=0.044 Group2-3; p=0.007

* p<0.05, **p<0.001, p1: Kruskal-Wallis test, p2: Post hoc Bonferroni test

Table 2

Sex, fracture type, callus pattern

	Sex F/M	Transverse fracture	Oblique fracture	Spiral fracture	Primary callus	Secondary callus
Group 1	8/13	13	3	5	0	21
Group 2	4/23	14	2	11	23	4
Group 3	2/9	5	3	3	0	11

Table 3

Evaluation of the groups according to the Flynn criteria

	Excellent	Good	Poor
Group 1	15	5	1
Group 2	17	8	2
Group 3	9	2	0

With regard to complications, two patients (10 and 17 degrees) in group 1 had union in the valgus. Two patients had minor wound site infection, and four patients had shortening of less than 2 cm; however, it did not affect their gait. In group 2, one patient underwent revision with a plate due to plate fracture in the second month, and three patients (11, 12, and 8 degrees) had union in the valgus. While four patients had minor wound site infection, there was no shortness in any of the patients. In group 3, two patients had minor wound site infection, while no shortening or deformity was present in any of the patients. Upon examining the Flynn criteria, in group 1, the excellent result was 15, the good result was 5, and the poor result was 1. In group 2, the excellent result was 17, the good result was 8, and the poor result was 2. In group 3, the excellent result was 9, the good result was 2, and the poor result was 0 (Table 3).

A significant difference ($p<0.05$) was found between the groups with the duration of surgery ($p<0.001$) and time of union ($p<0.001$) results of the patients. When the source of difference between the groups was examined, it was determined that the difference originated from the significantly longer duration of surgery and time of union of the patients in group 2 compared to the patients in group 1 and group 3 ($p<0.05$) (table 1), which revealed that the duration of

surgery and time of union in group 2 were significantly longer than the other groups.

It was found that the reason for the difference determined between the groups with the age results (p=0.013) was the higher mean age of the patients in group 2 compared to the patients in group 1 (p<0.05).

4. Discussion

The most significant strength of our study is the comparison of the noncontact plating technique with two known surgical techniques in pediatric femoral fractures. Casting, external fixation, elastic nailing, and plate-screw systems are used to treat femoral shaft fractures in children. There is no absolute consensus on these techniques among the authors. However, the North American Pediatric Orthopedic Society argues that surgical treatment should be performed after the age of six[12].

Nowadays, elastic nailing is one of the most commonly used methods. In the studies, successful outcomes of elastic nailing and rotational stability problems in transverse or comminuted fractures were observed[13,14]. Furthermore, the fact that unstable fractures such as spiral and comminuted fractures are not supported by splint fixation may lead to the development of shortening[14]. Although we used postoperative splints for all patients, we observed complications of shortening and union in the valgus in elastic nailing, similar to the literature. Nevertheless, noncontact with the periosteum in elastic nailing appears as a significant and obvious advantage over the plate-screw system. The external fixator fixation also has the same advantage. However, external fixators are not frequently preferred in closed fractures due to frequent complications such as patient compliance and pin tract problems[15,16]. In this case, while noncontact plating has advantages by working with the logic of an external fixator, it does not have the complications of an external fixator due to the absence of implants outside the skin. In our study, while there were patients who recovered with valgus deformity in groups 1-2, this deformity was not observed in group 3.

The closed reduction of the fracture line is also important for the preservation of the fracture hematoma. The closed reduction was planned in all three groups, and the case was started. However, the open reduction was performed in four patients with transverse fractures in group 1. In group 2 and group 3, the closed reduction was applied in all cases. The fact that closed reduction is attempted and open reduction is initiated in elastic nailing is also encountered in the literature. A study by Heffernan et al. emphasized that open reduction should be initiated in case of prolonged closed reduction in elastic nailing in pediatric femoral fractures. The researchers reported that they had difficulty in reduction, especially in overweight and elderly patients[17].

With the understanding of the importance of periosteal circulation in fracture union, the plates used were changed so that they would not prevent biological osteosynthesis. Instead of flat plates, LC-DCP (limited contact plate), point contact plates were produced[18,19]. The aim here is both the non-disturbance of the periosteal circulation and the advancement of callus tissue through spaces. We think that the noncontact of the plate placed as in group 3 with the bone will further contribute to biological recovery. The shorter time of union than in the conventional plating technique supports our opinion.

In group 1 and group 3, micromovement caused the callus tissue to be in the form of secondary osteosynthesis; however, the fact that the implants did not fully contact the periosteum paved the way for the placement of the callus tissue under the plate.

The positive effect of micromovement on union was also demonstrated by Ilizarov's studies conducted with external fixators. Successful outcomes were obtained in the treatment of fractures with an external fixator, and it was revealed that rigid fixation was not necessary in osteosynthesis[20]. Therefore, indirect (secondary) bone healing occurred in fixation, allowing micromovement obtained with nails and external fixators. Indirect bone healing is healing with apparent callus tissue, as in natural fracture healing. It has been known for a long time that micromovement in the fracture line increases callus formation[21]. In our study, we attributed the apparent callus appearance on x-rays to this micromovement, even in the 3rd-week controls (Figure 1). Furthermore, with the 3 mm osteotome we placed under the plate, we allowed the callus tissue to fill under the plate during the union period. No need for splinting provides comfort to the patient and convenience in rehabilitation.

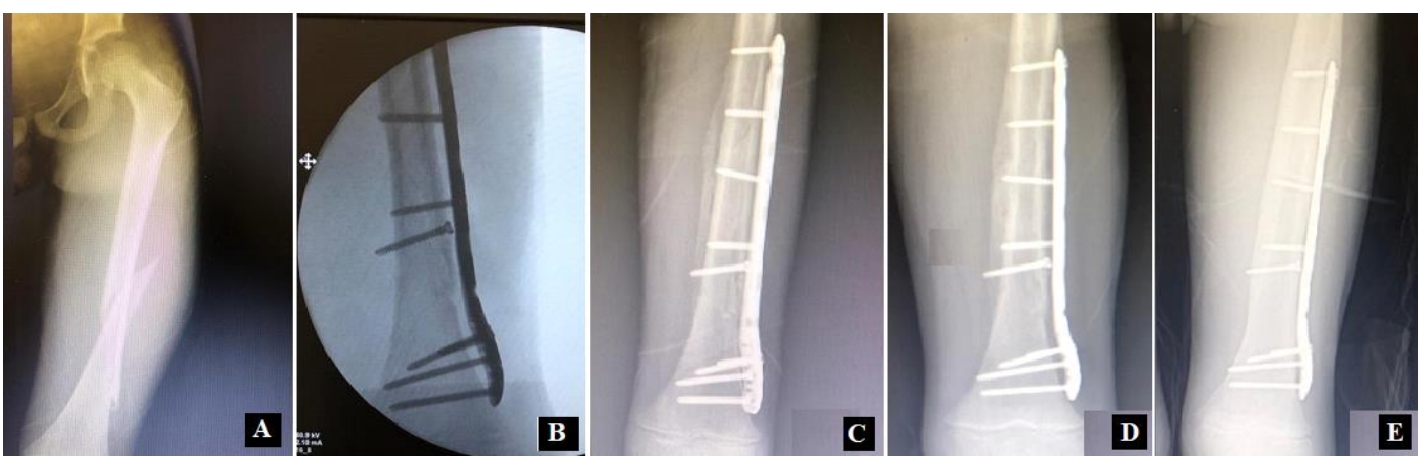

Figure 1

A) preoperative X-ray **B)** intraoperative X-ray **C)** postoperative 3. week X-ray **D)** postoperative 6. week X-ray **E)** postoperative 6. month X-ray

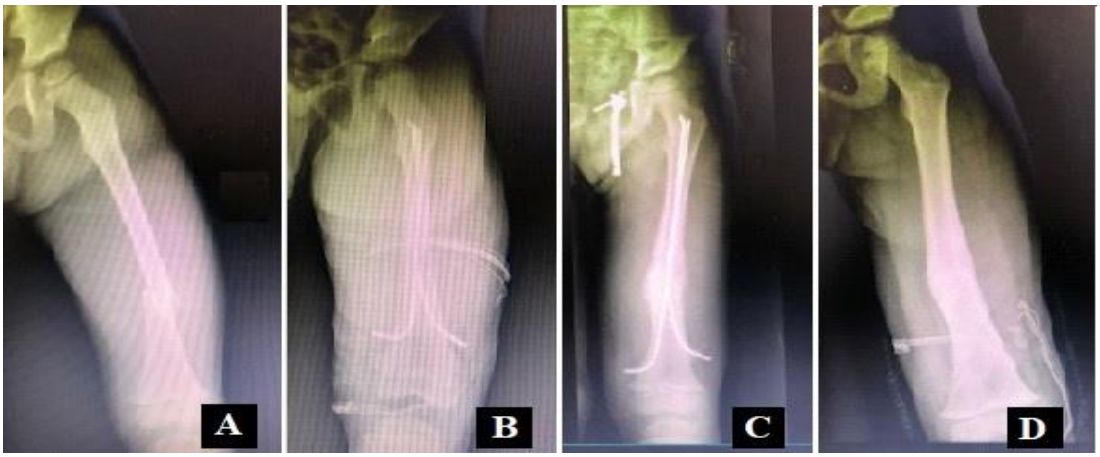

Figure 2

Group 1 A) preoperative X-ray **B)** postoperative 1.day X-Ray **C)** postoperative 6. week X-Ray **C)** postoperative 6. month X-Ray

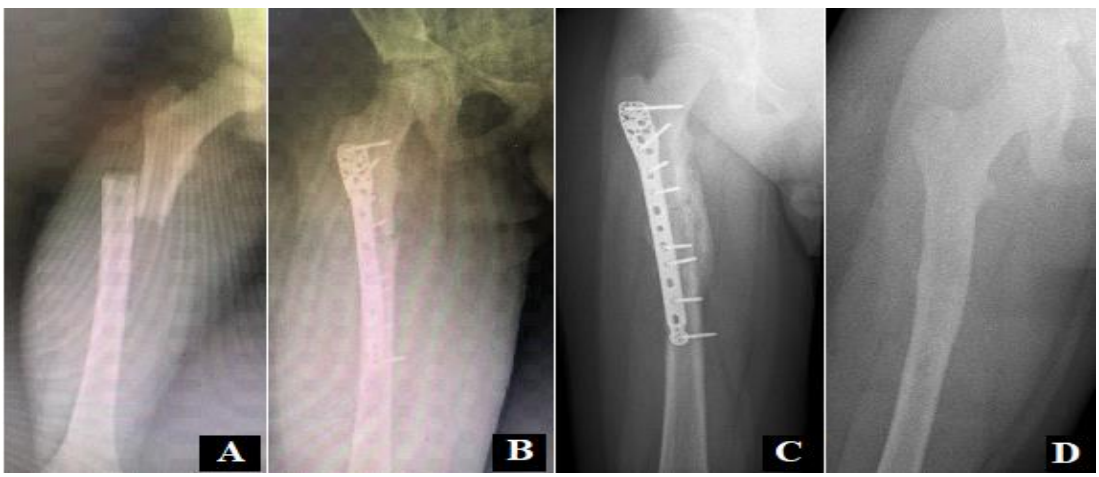

Figure 3

Group 2 A) preoperative X-Ray **B)** postoperative 1. day X-Ray **C)** postoperative 6. week X-Ray **D)** 1. year X-Ray

There are many studies reporting successful outcomes with elastic nailing in pediatric femoral fractures without causing a significant deformity[14,22]. Nevertheless, in a study conducted by Heybeli et al. in 2004 and evaluating the application of titanium elastic nails in femoral fractures, the researchers revealed that this technique was effective in a wide range of age groups, such as 5-15 years, and checked deformity with tomography. Rotation, which appeared normal on X-ray, was found to be significantly retroverted compared to the intact side on tomography[14]. We agree with the authors who reported poor outcomes in terms of loss of compliance and delayed union in patients over 49 kg and in comminuted fractures[23]. Furthermore, a study conducted in the 11-15 age group reported that plate-screw osteosynthesis should be considered an effective method due to stable and complete anatomical fixation[24].

When the time of union was evaluated, while no significant difference was found between group 1 and group 3, it was found to be significantly longer in group 2 compared to the other two groups. However, dense callus tissue due to secondary osteosynthesis, which was significantly observed in group 3, provides confidence in early rehabilitation and mobilization (Figure 1).

Although the intraoperative reduction is excellent in fixation with elastic nails, deterioration may occur in the follow-ups. In our study, the only case in group 1 who caused a poor outcome according to the Flynn criteria was completely reduced on the first postoperative x-ray and recovered in a 17-degree valgus in the final control (Figure 2). This patient was an 11-year-old male patient. In this technique, the compliance of the patient and the patient's relatives is very important. In this case, we estimated that reduction was impaired by the weight of the leg and the splint during the patient's transfer at home. According to the literature review, Anderson et al. should have suspected that rotation was impaired in the postoperative period. Therefore, they reported that the deformity defect could be prevented by applying an external fixator on the elastic nail[25]. While elastic nailing is the first choice in pediatric femoral shaft fractures, we recommend noncontact plating, especially in well-built patients over the age of 10.

Recovery with secondary callus tissue in groups 1 and 3 gave confidence to the surgeon in the follow-ups. The dense callus tissue, which is formed earlier, shares the load on the implant earlier. Here, the importance of micromovement emerges. We would like to mention a situation that caught our attention during the review. In group 2, while primary union was observed in two patients for whom two interfragmentary screws were used in spiral fractures with bridge plating, union with secondary callus was observed in patients for whom no interfragmentary screw was used or a single screw was used. While an interfragmentary single screw did not prevent micromovement, two screws may have prevented micromovement by causing more rigid fixation, which needs to be studied.

In group 2, the plate was tilted outside and placed inside. We observed that the attachment of the plate to the bone with non-locking screws during fracture fixation impaired reduction in three patients. An error that can be made while shaping the plate outside impairs the reduction with non-locking screws (Figure 3). In the noncontact plating that we recommend, the shape of the plate is unimportant after the reduction is achieved. The fracture is fixed with a locking plate that does not contact the bone in the reduced position.

The authors are aware of the study's limitations. Firstly, the study was conducted as retrospective. Secondly, although we used standard 3 mm for noncontact plating in our study, there is a need for future biomechanical studies for optimal distance. Finally, since noncontact plating is a new subject, it would be appropriate to increase the number of cases and conduct larger series of investigations.

5. Conclusions

In conclusion, the fact that elastic nailing, the most frequently recommended method in pediatric femoral fractures, is a less invasive method is still considered an advantage compared to noncontact plating. However, it is obvious that conditions such as the absence of splinting, better reduction, fewer deformity complications, early mobilization and rehabilitation provide advantages over noncontact plating. Based on this information, while it is up to the surgeon's preference, noncontact plating can be applied safely and successfully in appropriate patients.

Acknowledgements

None.

Statement of ethics

This study was approved from Adana City Training and Research Hospital Ethics Committee (Dated: 2021-80/380). Informed consent was taken from all patients.

Conflict of interest statement

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

Funding source

None

Author contributions

All authors conceptualization, design, supervision, literature review, conduction and writing- original draft preparation. All authors read and approved the final manuscript.

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Microsatellite Instability (MSI) and P16/P53 Protein Status in Different Subtypes of Endometrial Carcinoma: with Emphasis on Tumor Aggressiveness

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Abstract

Aim: We investigated microsatellite instability (MSI) in endometrial cancer (EC) and correlated results with traditional markers (p16, p53, Ki-67) to predict tumor aggressiveness.

Methods: Records of patients admitted with EC between 2010 and 2022 were reviewed, and the widest immunohistochemical (IHC) panel including (1) estrogen or progesterone receptors (ER, PR), (2) mismatch repair (MMR) proteins (MLH1, PMS2, MSH2, MSH6), (3) Ki-67, (4) p16 and (5) p53 proteins were recorded. Chi square test was used for statistical analysis.

Results: Total of 44 female patients with pathology reports containing all five IHC panel markers were included. Mean age was 64.1±12.51 years. Type I EC was the most common pathology (72%). ER or PR positivity were very prominent in type I tumors in comparison with non-endometrioid (type II) tumors (84% vs 16%, respectively; $p<0.05$). MSI was also more pronounced in type I than that of type II (46% vs 16%, respectively; $p<0.05$), but p16 and p53 expressions were more significant in patients with type II tumors ($p<0.05$). Pathological stage (pTNM) was seen to be significantly more advanced in type II and un/dedifferentiated cancers (each, 44% vs 18% in type I, $p<0.05$), and most of the tumors in these subtypes expressed Ki-67>10% ($p<0.05$).

Conclusions: A wider IHC panel including all MSI (MLH1, PMS2, MSH2, MSH6), ER, PR, p16, p53 and Ki-67 may help oncologic planning in patients with different subtypes of EC, since first three markers can be used for tumor differentiation and others indicate the necessity of aggressive treatment.

Keywords: *Endometrial cancer; microsatellite instability (MSI); mismatch repair (MMR); immunohistochemistry (IHC); p16; p53; Ki-67*

1. Introduction

Microsatellites are short segments of repetitive DNA sequences, and microsatellite instability (MSI) has emerged as one of the most important pathways in the development of endometrial carcinoma (EC)[1]. MSI results from inactivation of some intracellular proteins or cofactors that comprise the mismatch repair (MMR) system, and MLH1 hypermethylation is the most common inactivation, known as epigenetic silencing[2]. Genetic or somatic mutations of other MMR components, such as PMS2, MSH2 and MSH6, are also common in patients with MSI occurring ECs[1,2].

Endometrial endometrioid (type I) carcinomas are related to excessive estrogen exposure, and most of them are positive for estrogen or progesterone receptors (ER, PR)[3]. However, their expression can be variable in tumor tissue and this is not always explained by differences in grade of the tumor, suggesting that MMR changes may contribute to this variability. Immunohistochemistry (IHC) expression of MMR proteins can be classified in five groups: no loss of expression, isolated loss of MLH1, combined losses of MLH1/PMS2 or MSH2/MSH6, and loss of all antibodies[4].

IHC panel, other than MSI and hormone receptors, can serve as additional diagnostic markers including p16 and p53, for distinction of non-endometrioid (type II) EC (serous, papillary, mucinous, etc.) from type I carcinomas[5]. Diffuse expression of p16 and p53, and absence or focal staining of ER or PR in EC should prompt one to consider a serous carcinoma. Since the differentiation of subtypes from each other is not easy in every case and their tumoral behavior change, an advanced IHC panel including traditional proteins ER, PR, p16 and p53 enriched with MSI MMR can help clinicians in planning oncologic treatment.

Therefore, in the present study, we investigated the IHC panel in all subtypes of EC, and correlated the results with nuclear mitosis index

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Received: 17.08.2023, Accepted: 29.08.2023, Available Online Date: 31.08.2023
Cite this article as: Firat A. Microsatellite Instability (MSI) and P16/P53 Protein Status in Different Subtypes of Endometrial Carcinoma: with Emphasis on Tumor Aggressiveness. J Cukurova Anesth Surg. 2023; 6(2): 338-41. doi: 10.36516/jocass.1339847

subtypes of EC, and correlated the results with nuclear mitosis index (Ki-67) and pathological stage.

2. Materials and methods

After the approval of study by Ethics' Committee (University of Health Sciences, IEAH-06.05.2022/151), records of patients who were admitted with EC and underwent surgery between January 2010 and December 2022 were reviewed. Patients signed informed written consent allowing their data to be used in medical researches. All cases were biopsy proven preoperatively, and their postoperative pathology reports were investigated in detail. All data were recorded at Excel program (Microsoft 2017, Chicago, Illionis, US).

Patients with sarcomatoid lesions and with reports other than EC or not including any of the MSI/ER/PR/p16/p53/Ki-67 markers were excluded from the study. Patients with a history of neoadjuvant chemo- or radiotherapy were also excluded.

Demographics, menopausal status, types of final histopathology, IHC panel results including MSI, p16 and p53 status, and hormone receptor types (ER and/or PR), if any, were recorded. Pathologic subtypes were recorded as; 1. Endometrioid cancer (type I), 2. Non-endometrioid cancer (type II) as papillary serous, clear cell, mucinous and squamous cell, 3. Mixed type, and 4. Undifferentiated or dedifferentiated (together with low grade endometrioid carcinoma).

EC patients were also staged according to the guidelines of International Federation of Gynecology and Obstetrics (FIGO) as early disease (stages 1 and 2) and advanced disease (stages 3 and 4). Aggressiveness of tumor biology was also assessed with nuclear protein Ki-67 antigen. Ki-67>10% was regarded as aggressive biology.

2.1. Statistical Analysis

Statistical package for social sciences (Version 11, US) was used for the statistical analyses. Number (n) and median value with standard deviation (SD) were calculated for quantitative variables. Frequency and percentage (%) were evaluated for qualitative variables. Chi-square test was used to determine the probable associations. P <0.05 was taken as statistical significance value.

3. Results

EC patients with pathology reports containing all five IHC panel markers were included in the study. There were only 44 female patients, of whom 34 with early-stage EC (77.2%, mean age, 63.9±9.8), and 10 with advanced/metastatic carcinoma (22.7%, mean age, 64.7±12.7). The age difference between the groups was not statistically significant (p>0.05), and most of patients were in postmenopausal period (n=36, 81.8%).

The most common histopathology in EC was type I (endometrioid, 72% of all patients, Table 1). Hormone receptors (ER or PR) were positive in 84% and 66% of patients with type I and mixted type pathology, respectively (each, p<0.05, Table 1). Type II non-endometrioid EC showed scarce hormone receptors (only 16%). MSI was also more pronounced in type I patients than that of type II (46% vs 16%, respectively; p<0.05).

On the other hand, p16 and p53 expressions were more significant in patients with type II and un/dedifferentiated pathologies, and they were seen to be correlated with Ki-67 expressions above 10% (Table 1, each, p<0.05). The latter findings were seen to be in accordance with FIGO advanced pathological stages (44.4% in type II and undifferentiated EC vs 18.75% in type I EC, p<0.05).

4. Discussion

EC has traditionally been classified into type I and type II based on its clinical, histopathological, and molecular findings[1,6]. Type I mainly consists of endometrioid tumor that is considered to develop in an estrogen-dependent pattern[3]. It arises in atypical endometrial hyperplasia and mostly seen in perimenopausal women. This type is well-known for its more favorable prognosis, as well. Recently, in type I endometrial endometrioid carcinoma, dysfunction of DNA MMR genes have been shown to be associated with carcinogenesis of endometrium[2,4]. On the other hand, type II EC consists of serous carcinoma that is thought to be de novo carcinogenesis developing directly from the atrophic endometrium[5]. It occurs mostly in postmenopausal period, and is associated with worse prognosis[6].

Sporadic or germline mutation in at least one of the MMR enzymes (PMS2, MLH1, MSH2 or 6) and epigenetic silencing due to MLH1 gene promoter's hypermethylation can cause MSI in the DNA of tumor cells compared with normal cell DNA (4). Hashmi et al have suggested that MMR expression loss shown by IHC might be used as a possible marker for MSI[7]. MSI is usually found in endometrioid type of ECs[2]. On the other hand, non-endometrioid serous, papillary or mucinous types usually present genetic instability at chromosomal level due to primary defects in p16 and p53 genes, rather than microsatellite variations[5,8,9].

P53 plays a pivotal role in the regulation of cell proliferation, DNA repairment, apoptosis process and genomic stability, and it acts mainly as a transcriptional factor. Genetically, p53 mutation is more frequent in type II than type I EC[8]. Schultheis et al showed that p53 mutations were detected in their 64 patients (28%) of ECs[10]. In total of endometrioid and serous ECs, p53 mutation was seen in 15% and 88% of the patients, respectively[10]. In endometrioid ECs, the pattern of mutations was: frameshift, missense, and nonsense. Moreover, Netzer et al. have found p16 overexpression in 78% of patients with

Table 1

MSI, hormone receptors, p16, p53 and Ki-67 status in EC subtypes

Pathology	Total	ER/PR	MSI	p16	p53	Ki-67>10%
	n(%)					
Type I (endometrioid adenoca)	32(72.7)*	27(84.3)*	15(46.8)*	16(50)	15(46.8)	6(18.7)
Type II (non-endometrioid)	6(13.6)	1(16.6)	1(16.6)	5(83.3)*	6(100)*	5(83.3)*
Mixed type	3(6.8)	2(66.6)*	1(33.3)	2(66.6)*	1(33.3)	2(66.6)*
Un/dedifferentiated	3(6.8)	1(33.3)	2(66.6)	3(100)*	3(100)*	3(100)*

ER=estrogen receptor, PR=progesterone receptor MSI=microsatellite instability (MLH1/PMS2/MSH2/MSH6), Type II=Serous, papillary, mucinous, clear cell, non-endometrioid adenocarcinoma (adenoca), *p<0.05

serous papillary carcinomas versus that of only 36% of patients with endometrioid subtype[11]. In our study, we found similar ratios supporting the current literature. Overexpressions of p16 and p53 were evident in nearly half of the patients with type I EC, while these ratios reached up to 100% in type II.

High Ki-67 indices have long been known to be related to increased tumor proliferation, poor prognosis and shortened survival time[12-14]. Ki-67 protein, a nuclear monoclonal antibody, can be detected during all active phases of cell cycle (G1, G2, S and M), but is absent from the resting cells (G0). First, it has been shown as useful clinical marker for subtype classifications of breast cancer, its overall prognosis, and in the prediction of therapeutic response[15,16]. In a healthy mammary tissue, very low levels of Ki-67 (<3%) have been reported, and it is expressed exclusively in ER-negative cells[15]. Positive expressions of p16 and p53 are also associated with unfavorable outcomes in most kind of tumors[17-20], and this was confirmed in the present research, as well. Therefore, since the nuclear protein Ki-67 is a well-established prognostic and predictive indicator for the aggressiveness of tumor, higher ratios in our patients with type II pathology along with p16/p53 expression seems logical, as well.

MMR gene mutations have also been shown to cause a genetic predisposition to hereditary nonpolyposis colorectal cancer (HNPCC) syndrome known as Lynch' s disease[21]. These patients have an up to 80% life time risk of developing EC with MLH1 and MSH2 mutations[22]. MSI occurring after sporadic mutation or epigenetic silencing has been shown to occur in up to 20% of ECs; whereas, germline mutations account for lesser rates[7]. Our MSI results were similar, since it was found to be significantly higher in endometrioid EC than that of non-endometrioid EC.

Undifferentiated carcinoma, when associated with low-grade endometrioid carcinoma is termed as dedifferentiated carcinoma, is usually negative for hormone receptors, and commonly demonstrates loss of the expression of DNA mismatch repair proteins, as seen in our patients. Therefore, tumor biology in this subtype resembles type II EC.

The present study has some limitations like lack of the availability of recent molecular studies, such as PAX2, CK7, CK20, CD10, etc. in all histopathology reports. Furthermore, the number of patients with histopathology reports containing MSI MMR results was also very limited. Since only the available molecular markers mentioned in the pathology reports are taken into consideration, the data compared are limited. However, high ratios of MSI in endometrioid and p16 or p53 in non-endometrioid types are outstanding. The latter finding also reflects the wild type of tumor biology as proved with a higher rate of Ki67 expression and advanced pathologic stage.

5. Conclusions

In conclusion, wide IHC panel including all of the MSI MMRs (MLH1/PMS2/MSH2/MSH6), ER, PR, p16, p53 and Ki-67 may help decision-making in oncologic planning of patients with different subtypes of EC.

Acknowledgements

None.

Statement of ethics

The study was approved by the University of Health Sciences, Istanbul Education and Research Hospital Ethics Committee (IEAH-06.05.2022/151).

Conflict of interest statement

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

Funding source

The authors declared that this study received no financial support.

Author contributions

Concept: A.F., F.F.V.A.; Design: A.F., S.K.B.; Supervision: F.F.V.A.; Data Collection or Processing: A.F.; Analysis or Interpretation: A.F., S.K.B.; Literature Search: A.F.; Writing: A.F.; Critical review: F.F.V.A. All authors read and approved the final manuscript.

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Compressive Peripheral Nerve Injuries in Earthquake Victims in Kahramanmaraş Earthquake on February 6, Our Clinical Observations

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Abstract

Aim: Earthquakes are one of the most common causes of mortality and morbidity due to natural disasters. In particular soft tissue and musculoskeletal injuries are the most common types of injuries following earthquakes and the most common reason for hospital admission. Turkey is a region with a very high risk of earthquakes. Compression is one of the most common causes of mechanically induced peripheral nerve injuries. Peripheral nerve injuries cause long-term disruptions in daily life, professional development, and education. These injuries are the important causes of labor loss, especially in young adult patients. The purpose of our study is to emphasize the importance of early diagnosis and treatment for these injuries by sharing our observations on compressive peripheral nerve injuries seen in earthquake victims after the Kahramanmaraş earthquakes on February 6.

Methods: We included patients with peripheral nerve injury who were admitted to the physical therapy clinic of Adana City Hospital for three months starting from February 6, 2023.

Results: The mean age of the injured was 32.64±17.63 years. The median time of being pulled from the rubble was 24 hours. 95.5% were living in Hatay province. The most common sites of peripheral nerve injury were legs (43.3%), arms (17.9%) and forearms (16.4%). 31.3% of the injured had bone fractures. The most common complaints were weakness in the legs (31.3%), foot drops (29.9%), and wrist drops (20.9%).

Conclusions: Earthquake is a natural disaster that can cause blunt and penetrating injuries and serious peripheral nerve injuries. Thus, it should be kept in mind that these injuries, which significantly affect the quality of life, are quite common and may be overlooked during the acute phase after earthquakes.

Keywords: *Earthquake, Peripheral Nerve Injuries, 6 February 2023, Kahramanmaraş*

1. Introduction

On February 6, 2023, a devastating earthquake with a magnitude of 7.8 on the Richter moment magnitude scale (Mw) struck southern, southeastern, and central Turkey and northwestern Syria. This massive earthquake, with the epicenter in Kahramanmaraş, affected 10 cities with a population of 15 million (approximately 17.6% of Turkey's total population). Nine hours after the first earthquake, a second earthquake with a magnitude of 7.7 Mw occurred 95 km northeast of Kahramanmaraş province, causing an even more devastating picture. Although the numbers are not yet clear, tens of thousands of lives were lost, and the earthquake was described as the disaster of the century in terms of material losses[1]. The mainshock was the largest earthquake to hit Turkey since the 1939 Erzincan earthquake, the second most powerful earthquake in the country's history after the 1668 North Anatolian earthquake. It was followed by more than 10,000 aftershocks. It caused widespread damage over an area of approximately 350,000 km^2, which is almost equal to the size of Germany. As of March 30, more than 50,000 deaths and approximately 115,000 injuries were recorded in Türkiye[2]. In the first earthquake in Türkiye, people were asleep and could not escape. Thousands of buildings and even some hospitals in the affected cities collapsed. Thousands of people were trapped under the rubble for hours or even days. Because hospitals were also damaged, earthquake victims were transferred to hospitals in other provinces[3].

In particular, soft tissue and musculoskeletal injuries are the most common types of injuries that lead to hospital admission after earthquakes. Many patients with blunt and penetrating trauma and crush injuries have complications leading to additional morbidity and mortality[4]. Peripheral nerve injuries are quite common complications after earthquakes. Peripheral nerve injuries can be divided into subgroups as root injuries and peripheral nerve injuries. Compression is

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Received: 18.08.2023, Accepted: 30.08.2023, Available Online Date: 31.08.2023
Cite this article as: Bilecik NA, Kösehasanoğulları M. Compressive Peripheral Nerve Injuries in Earthquake Victims in Kahramanmaraş Earthquake on February 6, Our Clinical Observations. J Cukurova Anesth Surg. 2023; 6(2): 342-5. doi: 10.36516/jocass.1345699

one of the most common causes of mechanically induced peripheral nerve injuries. The primary mechanisms of action of compression include the inhibition of axonal transport and vascular flow. The literature shows that the increasing duration and severity of compression causes increasing nerve damage and prolonged recovery time, and nerve damage may be irreversible in continuous compression[5]. Peripheral nerve injuries cause long-term disruptions in daily life, professional development, and education[6]. Lumbar and sacral plexus, sciatic nerve, peroneal nerve, radial nerve, and radial nerve injuries are the major nerve injuries that cause severe loss of limb function, gait disturbance and loss of fine motor skills. These injuries are the important causes of labor loss, especially in young adult patients. These injuries can be treated with early diagnosis and correct rehabilitation techniques; thus, they should not be overlooked in disasters with serious mortality rates such as earthquakes. Lifestyle is dramatically affected after an earthquake due to the necessity of evacuation and relocation. It is reported that this situation results in a decrease in physical activity level[7]. Additionally, complications such as peripheral nerve damage may be overlooked in this process. Thus, earthquake victims in need of rehabilitation should be quickly identified and treated in safe physical therapy and rehabilitation centers. This study aims to examine earthquake victims with peripheral nerve injuries who were admitted to and treated in Adana City Training and Research Hospital, which shouldered nearly the entire burden of the region in the first three months after the earthquake. It is to emphasize peripheral nerve injuries in possible earthquakes that may occur later.

2. Materials and methods

We retrospectively analyzed the records of 67 earthquake survivors with peripheral nerve injuries, who were admitted to the Physical Therapy Clinic of Adana City Training and Research Hospital for 3 months as of February 6, 2023. We evaluated patients' demographic data, the duration of being under the rubble, fasciotomy and fracture history, level of injury, strength and sensory examinations, electromyography (EMG) results, if any, and VAS pain scores. We excluded patients with pre-existing peripheral nerve injury and those with peripheral nerve injury secondary to any trauma other than entrapment during or after the earthquake.

2.1. Statistical Analysis

Continuous variables mean ± standard deviation, median (min-max); categorical data number and expressed as a percentage.

3. Results

The mean age of the injured was 32.64±17.63 years (min=1-max=75). The median time of being pulled from the rubble was 24 hours (1-180 hours). The median VAS pain score was 5 (0-10). 61.2% of the injured were female. 95.5% were living in Hatay province. 50.7% of the injured had a history of surgery (31.3% fasciotomy, 19.4% fracture surgery). The most common sites of peripheral nerve injury were legs (43.3%), arms (17.9%) and forearms (16.4%). 31.3% of the injured had bone fractures. The most common complaints were weakness in the legs (31.3%), foot drops (29.9%), and wrist drops (20.9%). EMG results were available only for 44.8% of the injured (most commonly brachial plexus neuropathy/lesion with 12%, followed by sciatic neuropathy with 7.5%). 58.2% had crush syndrome. 79.1% had a loss of muscle strength ranging from 1 to 4 out of 5. 52.2% had hypoesthesia in the sensory examination. 81.8% had pain and 51.5% had numbness (Table 1).

4. Discussion

Earthquakes are devastating natural disasters that have caused the loss of more than a million lives over the past few decades[8-11]. Peripheral nerve injuries are one of the important causes of morbidity induced by compression for a long time after an earthquake. Acute compressions occur after a short-term compression, as seen in radial mononeuropathy. It is typically manifested by numbness, tingling, or severe loss of strength. The healing process can take weeks and even years[12].

Apart from the high number of people injured in earthquakes, damaged and unusable buildings of medical facilities that respond to these injured people cause the disruption of health services [13,14]. Additionally, post-earthquake chaos and the insufficient number of medical personnel due to injuries and deaths cause the disruption in the health service to deepen even more. The impact of the earthquake on medical personnel, the need to transport a large number of patients at the same time, traffic and logistics problems, as well as the disruption of the communication system between health centers and the damage to other administrative buildings in settlements cause the adverse effects of the earthquake to increase even more[13,14]. In this study, 95.5% of the patients were transported to Adana from Hatay, which is one of the provinces with the highest damage caused by the earthquake. Important causes of morbidity such as peripheral nerve injuries may have been ignored in this process in which life-threatening injuries were first treated.

Apart from mortality, long-term morbidity is also a devastating effect of earthquakes. In our study, we found that 31.3% of the patients had a loss of strength in the leg, 29.9% had foot drops, and 20.9% had wrist drops.

Peripheral nerve injuries may occur secondary to crushing, ischemia, bone fractures and compartment syndromes[15]. In persistent ischemic nerve conduction block, there is a slow progressive process such as an enlarging hematoma, bleeding in the compartment or scar formation. Nerve damage lasts for weeks or months[16]. In our study, 31.3% of the patients had a history of fasciotomy and 19.4% had a history of bone fracture.

Crush injuries are the most common type of peripheral nerve injuries. It is accepted that two mechanisms, namely mechanical crushes and ischemia, could be the primary factors in these injuries. In short-term ischemia, changes are usually reversible. According to the literature, as the duration and severity of compression increase, nerve damage increases and the time of recovery is prolonged, and nerve damage may be irreversible in cases of continuous compression[17].

However, in this study, we observed that the duration of being trapped under the rubble was quite variable and extended and ranged from 1 to 180 hours. We believe that the healing process of nerve injuries that may be due to crushing and ischemia that occur during this process may be long.

Electroneuromyography (ENMG) is an important technique to evaluate the neurophysiological condition of the peripheral nervous system. It is indispensable for determining the diagnosis and prognosis, deciding on treatment, and monitoring the effectiveness of the current treatment[18,19]. However, in our study, 55.2% of the patients did not have an ENMG. Brachial plexus injury was detected in 12% of the patients who underwent ENMG. Considering that the majority of the patients were young adults, this situation means a significant loss of labor force. The scarcity of similar studies in the literature requires attention. We believe that peripheral nerve injuries may have been overlooked in the acute period due to the high number of damaged buildings, including hospitals, and the high rate of life-threatening situations during the Kahramanmaraş earthquakes on February 6.

Table 1

Some Demographic and Clinical Characteristics of the Patient Group

		Patient Group (n=67)
Age (years) (Mean±Sd)		32.64±17.63
Time of being pulled from the rubble (hours) [median (min-max)]		24 (1-180)
Pain VAS [median (min-max)]		5 (0-10)
Sex (n, %)	Female	41 (61.2)
	Male	26 (38.8)
Province of the earthquake (n, %)	Hatay	64 (95.5)
	Kahramanaraş	3 (4.5)
History of surgery (n, %)	No	33 (49.3)
	Yes (fasciotomy)	21 (31.3)
	Yes (fracture surgery)	13 (19.4)
Location of peripheral nerve injury (n, %)	Ankle	1 (1.5)
	Leg	29 (43.3)
	Cruris	9 (13.4)
	Elbow	1 (1.5)
	Lower foot	1 (1.5)
	Lower hand	1 (1.5)
	Hip	1 (1.5)
	Arm	12 (17.9)
	Arm and leg	1 (1.5)
	Forearm	11 (16.4)
Bone Fracture (n, %)	No	46 (68.7)
	Acetabulum	1 (1.5)
	Femur	3 (4.5)
	Humerus	3 (4.5)
	Clavicle, Pubis	2 (3.0)
	Pelvis	1 (1.5)
	Pubis	4 (6.0)
	Radius	3 (4.5)
	Sacrum	1 (1.5)
	Tibia	3 (4.5)
Complaints (n, %)	Leg weakness	21 (31.3)
	Foot drop	20 (29.9)
	Wrist drop	14 (20.9)
	Hand weakness	1 (1.5)
	Arm and leg weakness	2 (3.0)
	Arm weakness	9 (13.4)
	N/A	37 (55.2)
EMG results (n, %)	Brachial plexus neuropathy/lesion	8 (12.0)
	Brachial plexus and lumbosacral plexus neuropathy	1 (1.5)
	Severe deep peroneal neuropathy	1 (1.5)
	Lumbosacral plexus damage	3 (4.5)
	Partial peroneal neuropathy	1 (1.5)
	Radial neuropathy	3 (4.5)
	Radial and ulnar neuropathy	1 (1.5)
	Sacral plexus neuropathy	3 (4.5)
	Sacral plexus neuropathy - sciatic neuropathy	1 (1.5)
	Sciatic neuropathy	5 (7.5)
	Sciatic and peroneal neuropathy	2 (3.0)
	Severe ulnar neuropathy	1 (1.5)
Crush (n, %)	No	28 (41.8)
	Yes	39 (58.2)
Muscle strength (n, %)	0/5	14 (20.9)
	1/5	15 (22.4)
	2/5	25 (37.3)
	3/5	9 (13.4)
	4/5	4 (6.0)
Sensory examination (n, %)	Normal	30 (44.8)
	Hypoesthesia	35 (52.2)
	Anesthesia	1 (1.5)
	Not assessed	1 (1.5)
Pain (n, %)	No	12 (18.2)
	Yes	54 (81.8)
Numbness (n, %)	No	32 (48.5)
	Yes	34 (51.5)

5. Conclusions

Hospitals are specialized facilities that must be designed to resist earthquakes and remain operational during and after a seismic event. To minimize the risk of damage and disruption, hospitals should be constructed to meet the standards of seismic safety. In addition to building designs, emergency response plans for earthquakes and other disasters should be prepared in advance. Mortality and morbidity can be reduced through the rapid and effective triage of patients and prompt identification and treatment of life-threatening conditions. The possibility of peripheral nerve injuries, which are important causes of morbidity, should be considered during patient follow-up.

Acknowledgements

None.

Statement of ethics

The study was approved by the University of Health Sciences, Adana Education and Research Hospital Ethics Committee (IEAH-2023-128-2631).

Conflict of interest statement

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

Funding source

The authors declared that this study received no financial support.

Author contributions

Concept: NAB,MK, Design: NAB,MK, Writing: NAB, Critical review: NAB,MK, All authors read and approved the final manuscript.

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Reconstruction of Complex Abdominal Wall Defects with Pedicled Anterolateral Thigh Flap

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Abstract
Aim: Traumatic abdominal injuries, surgical wound dehiscences, oncologic resections, transplant related complications or abdominal sepsis related visceral edema and abdominal compartment syndrome can cause enormous abdominal defects Abdominal defects are treated differently according to etiology and chronicity, size and thickness of the defect. ALT flap can be used pedicled or as a free flap for abdominal defect reconstruction.
Methods: Medical records of 8 patients who underwent pedicled ALT flap reconstruction of abdominal defects between August 2019 and November 2020 were retrospectively reviewed demographic data, flap size, perforator number, complications, hospital stay, use of alloplastic mesh for fascia repair were recorded.
Results: 50% of patients received only 1 reconstructive operation while other 50% received more than one (min:2, max:4) operations. Total flap loss was seen at 12.5%. 25% of patients were lost due to non-flap related complications. Mean (min/max) hospital stay was 33,1 (12/90) days.
Conclusions: The pedicled ALT flap is a reliable and reproducable flap for reconstruction of abdominal defects without need for microsurgical vessel anastomosis. It has low donor and recipient site morbidity and potential complications can be easily managed with minor secondary operations.
Keywords: *Anterolateral thigh flap, abdominal defect, reconstruction*

1. Introduction

Abdominal surgeries are classified as clean-contaminated or contaminated procedures, but under emergency circumstances the operation can be included contaminated or dirty wound category[1]. Abdominal defects are treated differently according to etiology and chronicity. Traumatic abdominal injuries, surgical wound dehiscences, oncologic resections, transplant related complications or abdominal sepsis related visceral edema and abdominal compartment syndrome can cause enormous abdominal defects[2].
Negative pressure wound therapy or Bogota Bag are used for temporary closure. Immediate reconstruction can be performed in acute injuries, after oncologic resections or dehiscence related defects. However, reconstruction should be delayed in the presence of sepsis, fasciitis or intestinal edema until the patient's hemodynamic stabilization and surgical debridements are completed[3].

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Received: 13.08.2023, Accepted: 22.08.2023, Available Online Date: 31.08.2023
Cite this article as: Kokacya O, Gencel D. Reconstruction of Complex Abdominal Wall Defects with Pedicled Anterolateral Thigh Flap. J Cukurova Anesth Surg. 2023; 6(2): 345-9. doi: 10.36516/jocass.1342375

The main purpose of reconstruction is providing fascia and soft tissue integrity. Flaps are commonly used as free or pedicled fashion for soft tissue coverage. Meshes or fascia are combined with them to reconstruct "like with like". Anterolateral thigh (ALT) flap is first described by Song as a free flap, then Wei and colleagues spread out his technique. Both free and pedicled ALT flaps are widely used as workhorse[4,5]. Here in this article is discussed using of pedicled ALT flap for full thickness abdominal wounds.

2. Materials and methods

2.1. Patients

This study was conducted in accordance with the Helsinki Declaration after the approval of the local ethics committee.

Eight patients who underwent surgical reconstruction of abdominal defects between August 2019 and November 2020 were retrospectively evaluated. Age, sex, etiology of defects, body mass index, comorbidities and smoking status were recorded.

2.2. Surgical technique

Patients were evaluated preoperatively for the anterolateral thigh flap perforators and any previous lower limb scar. Radiological imaging for the flap pedicle was not performed in any of the patients. Under general anesthesia in supine position skin perforators were identified using a handheld Doppler with 8 Mhz probes (Huntleigh Mini

Dopplex, Huntleigh Health Care Limited, Cardiff, UK). After flap elevation on descending branch of lateral circumflex femoral artery pedicle, it moved to the defect area either under a subcutaneous tunnel or by incising skin. Donor sites were closed primarily or with a skin graft. Patients were followed for 1 year or until the patient's death.

2.3. Perioperative patient management

A 50 year-old male patient was consulted for reconstruction of the defect that will occur after resection of recurrent epitheloid sarcoma on the left groin region. On physical examination, tumoral mass was palpable at left groin region under the incision scar that belongs to previous tumor resection operation (Figure 1).

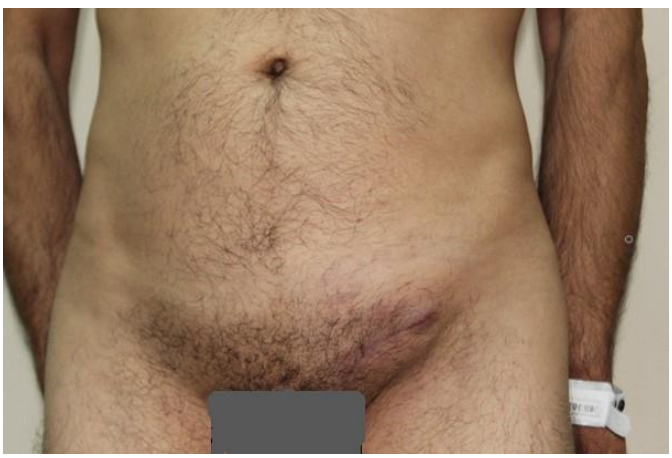

Figure 1
Previous tumor resection operation's incision scar on the left groin region.

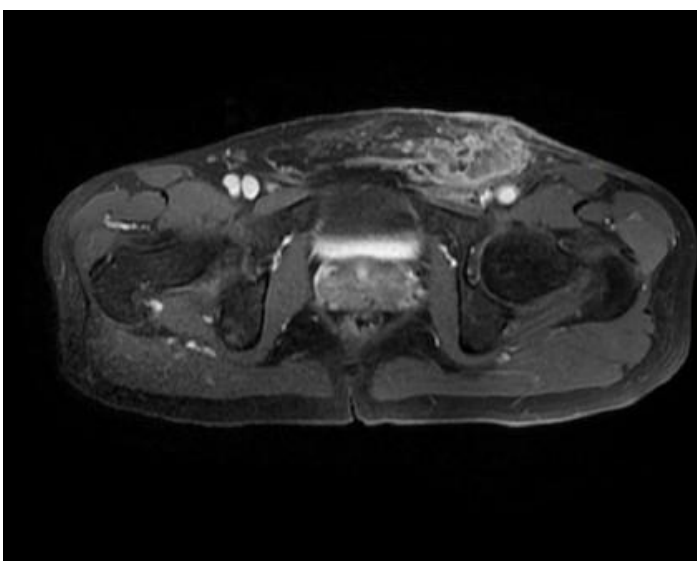

Figure 2
Computer tomographic view of mass located anteriorly to the left common femoral artery and vein.

6×5.5 cm size mass was located anteriorly to the left common femoral artery and vein (Figure 2). Tumor excision was performed by oncologic surgeon. Left inguinal ligament and sartorius muscle were resected, then dual polypropylene mesh was applied for fascia repair (Figure 3).

30×25 cm sized ALT flap was harvested on three perforators (Figure 4). There was no skin left between the flap and the defect to incise or prepare a subcutaneous tunnel. After flap was sutured to its new place (Figure 5), donor area was covered with split thickness skin graft. Scrotal edema and hyperemia were seen in early postoperative period. Symptoms revealed spontaneously and patient was discharged uneventfully (Figure 6).

Another 66-year-old male patient who underwent liver transplantation surgery due to Hepatitis C infection 9 years ago at our hospital applied with squamous cell carcinoma at the abdominal region. He had upper abdominal incision scars due to previous surgery and he had ventral herniation. Tumoral mass was resected with 60 cm bowel segment and anastomosis proceeded with insetting a dual polypropylene mesh. Defect was reconstructed with 32×15 cm sized ALT flap that was harvested on 2 perforators. Skin between the defect and flap donor area was incised to prevent pedicle compression.

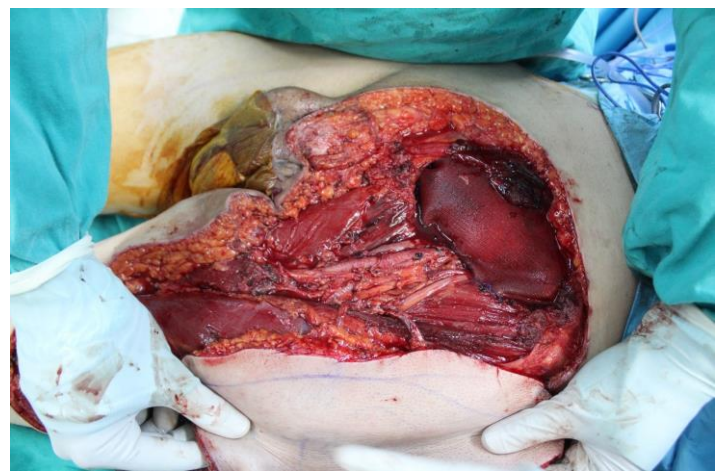

Figure 3
Fascia repaired with dual polypropylene mesh after tumor resection.

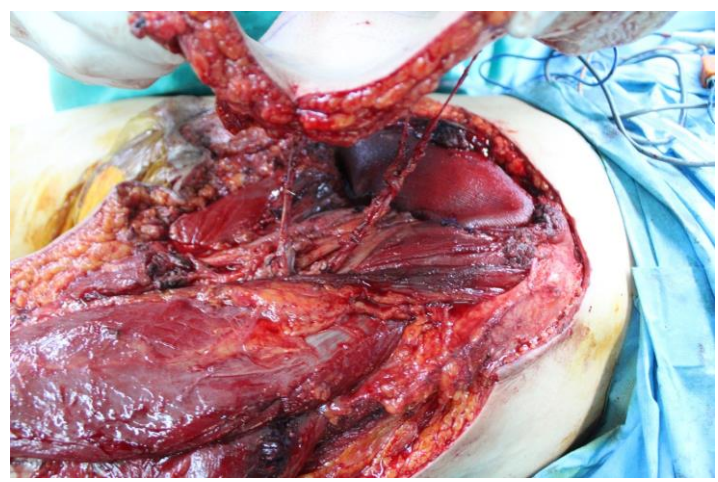

Figure 4
Anterolateral thigh flap harvested on 3 perforators..

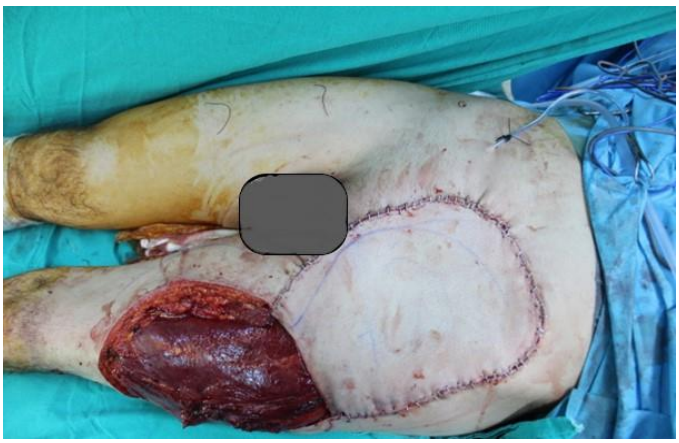

Figure 5
Flap inset

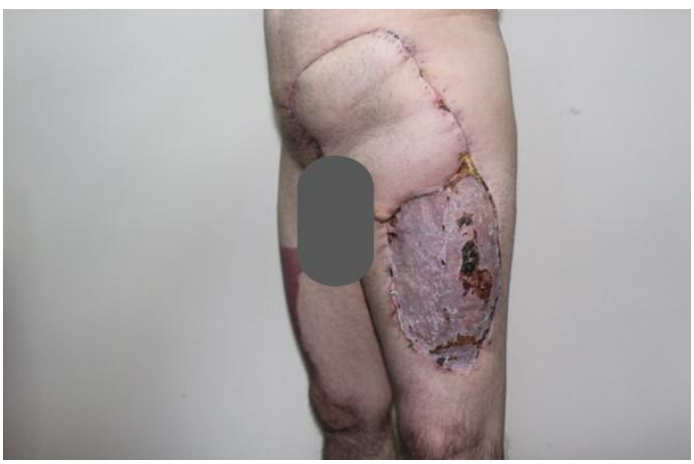

Figure 6
Early postoperative result at discharge

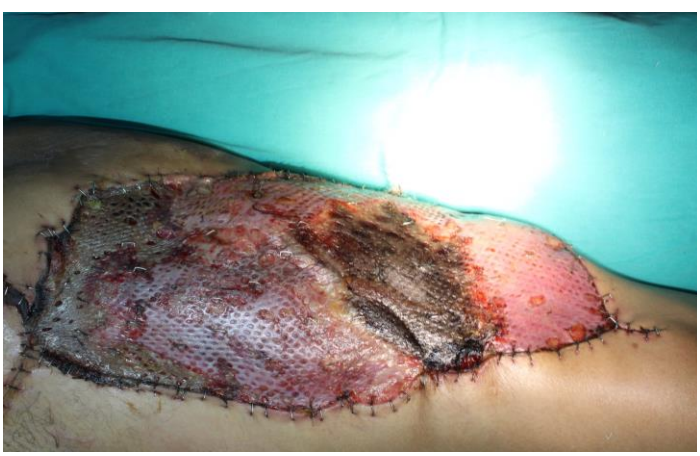

Figure 7
Superficial necrosis at vastus lasteralis muscle.

Donor areas was covered with split thickness skin graft but necrosis at the superficial part of vastus lateralis muscle was seen. (Figure 7). After debridement, defect was covered again with split thickness skin graft. Flap and donor area healed uneventfully (Figure 8).

3. Results

A total of thirteen surgeries were performed over a 16-month period in 8 patients who underwent ALT flaps in a tertiary level teaching hospital. Mean age of the patients was 60.8 years (range 48-72 years). Five (62.5%) of the patients were female and three (37.5%) were male. The mean BMI of the patients was 31.4 kg/cm2 (range 26-35 kg/cm2). Majority of the defect types were necrotizing fasciitis (37.5%) and tumor ablation defect (37.5%). There was any additional disease in 75% of the patients. Among comorbidities, the most common concomitant disease was diabetes mellitus (50%). The rate of smokers among the patients was 37.5% (Table 1).

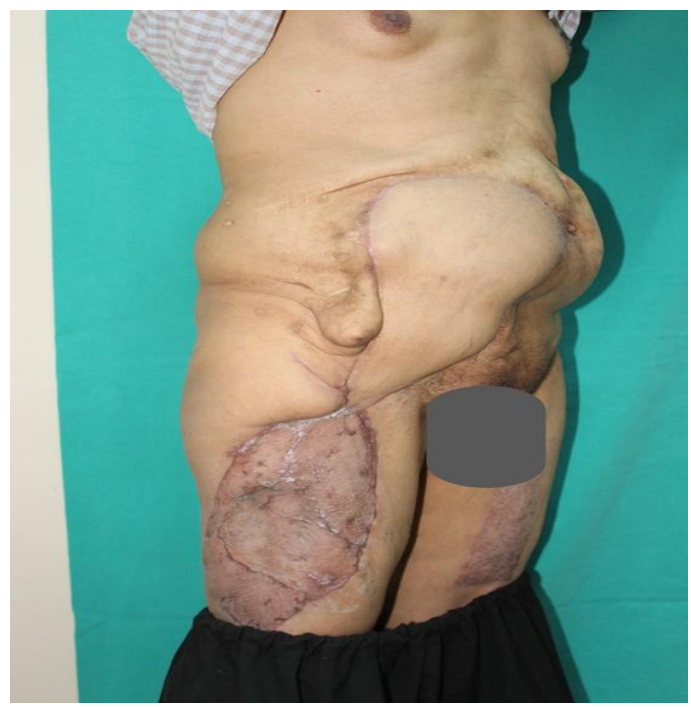

Figure 8
Postoperative view of flap and donor site.

Defect size, flap details, operative and follow-up data are shown in Table 2. The mean defect size was 325.1 cm2 (range 144-750 cm2). While 25% of the flap donor area was repaired with a split-thickness skin graft, the other 75% was closed primarily. The mean number of perforators were 1.6 (range 1-3 perforators). In 50% of the patients, the flap pedicle was passed under a skin tunnel, while an incision was made in the skin bridge between the flap and the recipient site in 50% of the patients. Fascia defect in the abdominal wall was repaired with an alloplastic surgical patch in 37.5% of the patients. While 50% of the patients had only one reconstructive operation, the other 50% had more than one operation (range 2-4 operations). The overall flap success rate was 87.5% (1 flap loss out of 8). 25% of the patients died due to non-flap complications. The mean length of hospital stay was 33.1 days (range 12-90 days).

Table 1
Patient characteristics and demographic data

Patient No	Age	Sex	Etiology	BMI (kg/cm^2)	Comorbidity	Smoking
1	50	M	Epithelioid Sarcoma	28	None	No
2	66	M	Squamous Cell Carcinoma	26	Liver Transplant Hepatitis C	Yes
3	64	F	Complication of Ventral Hernia Repair with Abdominoplasty	32	Diabetes Hypertension Cardiac Failure	No
4	60	F	Endometrium Adenocarcinoma	32	None	No
5	71	F	Necrotizing Fasciitis	34	Bladder carcinoma Hypertension	No
6	72	F	Perforated Ileus	33	Diabetes Hypertension Asthma	No
7	55	M	Necrotizing Fasciitis	35	Diabetes	Yes
8	48	F	Necrotizing Fasciitis	31	Diabetes Hypertension	Yes

Abbreviations: *M*, male; *F*, female; *BMI*, body mass index.

4. Discussion

Open abdominal wounds can be challenging for surgeon due to multilayered components of abdominal wall and inflammatory etiologies. Primary objective of reconstruction is repair like with like. Abdominal reconstruction includes skin and soft tissue defect repair, fulfilling the abdominal wall strength, and preventing incisional hernia[7]. There are different flaps and various techniques applied for abdominal reconstruction[5-10]. Versatility of anterolateral thigh flap is commonly analyzed for free tissue transfer, pedicled locoregional transfer, anterolateral thigh flap combined with fascia lata, vastus lateralis muscle, functional vastus lateralis[4,6,11].

In this study, we performed pedicled anterolateral thigh flap maintaining maximal pedicle length and safety while considering patients' hemodynamic status and comorbidities. Mobilization of the pedicle give a wide range of motion which lets the wound to be closed under minimal tension.

To perform defect coverage we harvest flaps on subfascial plane, larger than the actual defect size. Free latissimus dorsi or free ALT flap achieves excellent soft tissue coverage for abdominal defects but longer operation times are needed and employment of microvascular procedures makes the operation more complex.

Due to partial loss of abdominal fascia, appropriate synthetic materials are applied to prevent hernia in various cases. ALT flap ensures excellent soft tissue coverage of alloplastic materials used to reconstruct abdominal fascia. Primary closure of the donor site ensures good cosmetic result of the thigh.

5. Conclusions

With pedicled ALT flap the entire abdominal wall can be reliably and safely reconstructed. Its versatility offers satisfactory solutions to problems without need for microsurgical vessel anastomosis. The use of completely autologous tissue in a single stage offers a definite advantage. If alloplastic materials are used for fascia repair, ALT flap provides adequate soft tissue coverage. It has low donor and recipient site morbidity and potential complications can be easily managed with minor secondary operations.

Table 2
Operative and follow-up data

Patient No	Defect size (cm)	Donor area closure	Number of perforators	Skin tunnel or incision	Mesh use	Complications	Number of operations	Duration of hospitalization (day)	Postop follow-up time (month)
1	30x25	Skin graft	3	Incision	Yes	Scrotal edema	1	15	12
2	32x15	Skin graft	2	Incision	Yes	Partial superficial necrosis of vastus lateralis muscle	2	28	12
3	23x14	Primary	1	Incision	Yes	Total flap necrosis managed by other ALT flap	4	90	12
4	17x9	Primary	1	Incision	No	None	1	6	12
5	25x12	Primary	2	Tunnel	Yes	Colostomy related	2	54	Death at postop 54th day
6	20x15	Primary	1	Tunnel	Yes	None	1	42	Death at postop 42th day
7	19x8	Primary	1	Tunnel	No	None	1	12	12
8	16x9	Primary	2	Tunnel	No	None	1	18	12

Abbreviations: ALT, anterolateral thigh.

Acknowledgements

Some of the cases reported in this study were presented in a poster presentation at 43rd Annual Meeting of Turkish Society of Plastic Reconstructive and Aesthetics Surgery, November 10-14, Antalya, Turkey.

Statement of ethics

This was a retrospective and single-center study which was approved by the Cukurova University local Ethics Committee (protocol no: 2021-107-45 and was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Conflict of interest statement

The authors declare that they have no financial conflict of interest

with regard to the content of this report.

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

All authors read and approved the final manuscript.

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The Awareness Level of Pulmonary Rehabilitation and Compliance with Respiratory Exercises After COVID-19

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Abstract

Aim: Coronavirus Disease 2019 (COVID-19) is an infectious disease that can cause respiratory, physical, psychological, and generalized systemic dysfunction. COVID-19 can significantly impact the respiratory system. Pulmonary rehabilitation may be required for the appropriate person and at the appropriate time.

Methods: The study included 112 outpatients who were admitted to the Pulmonary Diseases and Physical Therapy and Rehabilitation Polyclinics after being diagnosed with COVID-19 between January 2021 and June 2021. The demographic data of the patients, their smoking behavior and duration, the Modified Charlson Comorbidity Index, clinical characteristics of the disease, the Modified Borg Scale were all assessed. The presence of information on respiratory exercises, the source of this information, and their compliance with the exercises were all evaluated.

Results: Of the patients, 30 (26,8%) of them reported that they have information on respiratory exercises. Only 11 (36,7%)'i of these patients were doing the respiratory exercises regularly. In the study, the history of hospitalization and high level of education were found positive correlated with the presence of information on pulmonary rehabilitation (p=0.001). Compliance with exercises was found low.

Conclusions: In the study, the history of hospitalization and high level of education were found to correlate with the presence of knowledge on pulmonary rehabilitation. Exercise compliance was found to be low. The number of awareness-raising activities for these patients and healthcare professionals should be increased to reduce their morbidity, mortality, and health expenditure.

Keywords: *Awareness, COViD-19, pulmonary rehabilitation, respiratory exercises*

1. Introduction

COVID-19, defined as coronavirus disease-2019 by the World Health Organization (WHO), is a respiratory tract infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The most apparent pathological alterations in early and later periods of COVID-19 are diffuse lung damage, and in some patients, additional fibrinous exudates in alveoli and pulmonary interstitial fibrosis were observed. These alterations contribute to all-body hypoxemia, and cardiopulmonary and organ dysfunctions[1,2].

Pulmonary rehabilitation during the acute management of COVID19 should be considered when possible and safe and may include nutrition, airway, posture, clearance technique, oxygen supplementation, breathing exercises, stretching, manual therapy, and physical activity.

The complications and dysfunctions can continue in discharged patients for up to 6 months and result in significant morbidity[3,4]. Fifty percent of the COVID-19 patients who were hospitalized required long-term care[4]. Because of lung fibrosis as a pneumonia sequela, especially among the patients suffering from severe COVID-19, with older age, obesity, multiple chronic illnesses and/or organ failures, respiratory deficiency or respiratory symptoms can persist, and pulmonary rehabilitation (PR) is required[1,5].

The long-term consequences of the disease in terms of damage and sequelae are not certain. For a suitable patient and an appropriate time will definitely arise for a pulmonary rehabilitation intervention[6].

This study aimed to evaluate the level of awareness of pulmonary rehabilitation and the compliance with respiratory exercises after COVID-19.

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Received: 14.06.2023, Accepted: 31.08.2023, Available Online Date: 31.08.2023
Cite this article as: Sen SB, Cetinkaya PD. The Awareness Level of Pulmonary Rehabilitation and Compliance with Respiratory Exercises After COVID-19. J Cukurova Anesth Surg. 2023; 6(2): 350-4. doi: 10.36516/jocass.1314769

2. Materials and methods

Between January and June 2021, the patients who were diagnosed COVID 19 with clinic, radiologic, and positive PCR (Polymerase Chain Reaction) test and applied to the Chest Diseases and Physical Medicine and Rehabilitation polyclinic within 1-4 months after the acute period were included the study. Patients under the age of 18 were excluded from the study. A cross-sectional study was performed and patients were selected consecutively.

A total of 112 consecutive patients (60 males and 52 females) over the age of 18 in the acute/chronic periods after COVID-19 were included in this study.

The age, gender, body mass index (BMI), education level, occupation, smoking habit, and smoking duration of the patients were evaluated. The clinical features of the disease (disease duration, hospitalization history, lung involvement on computed tomography (CT), presence of dyspnea), and respiratory functions were evaluated with the Modified Borg Scale. The Modified Borg Scale is one of the most reliable scales for determining the severity of dyspnea at rest and during exertion. It consists of 10 items describing the severity of dyspnea according to its degree. 0 means no dyspnea, and 10 means very severe dyspnea, and it evaluates the dyspnea of individuals in these two score ranges. It is a frequently used dyspnea evaluation parameter due to its ease of application and easy understanding by patients[7].

The comorbidity level was evaluated with the Modified Charlson Comorbidity Index. The Modified Charlson Comorbidity Index, which is calculated by the presence of comorbidities and is widely used to predict mortality, is an index valid all over the world. The index consists of 19 different items, and some of the same diseases have different ratings within these items. For example, mild liver disease has a score of 1, while the moderate or severe liver disease is a separate item and has a score of 3. These scores given to comorbid diseases are determined according to the relative risk values of the diseases, if " relative risk ≥1,2 " is taken into consideration, and if it is between 1.2 and 1.5, it is 1; 2 if it is between 1.5 and 2.5; Between 2.5 and 3.5, a score of 3 was given, and only two conditions (AIDS and 2nd homogeneous metastasis) were specifically given a score of 6 . A score is obtained by summing the scores of the patient's comorbid diseases and a score is added for the age of the patients. This age score is for patients older than 50; It is the increase of the age by one step in each decade, starting from 50, divided by decades, it is 1 for 50-59, 2 for 60-69, 3 for 70-79, 4 for 80-89 and 5 for 90-99 (8,9).

All patients were asked whether they knew about breathing exercises, the source of this information, and their compliance with the exercises.

Ethics committee approval for this study was received from Clinical Research Ethics Committee (dated 20.05.21 and numbered 1416). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent regarding the use of their personal information was obtained from all patients.

2.1. Statistical Analysis:

Continuous variables were expressed as mean ± standard deviation and categorical data as numbers and percentages. In the intergroup analysis of continuous variables, normality analyses were performed with the Kolmogorov-Smirnov Goodness of Fit Test. Analyses between the two groups were performed with the Student's T-Test when the data were in a normal distribution, and with the Mann-Whitney U Test when they did not. Chi-square Test and/or Fisher's Exact Test were used to compare categorical data. The linear relationship between the scales was tested using Spearman's rho correlation analysis. IBM SPSS version 22.0 (IBM Corporation, Armonk, NY, USA) was used for the analyses. Statistical significance level was accepted as $p<0.05$.

3. Results

One hundred and twelve patients in the post-acute period after COVID-19 were included in the study with a mean age of 52.8 ±15, 52 (46.4%) years of them female and 60 (53.6%) of them male. All demographic and clinical characteristics of the patients were summarized in Table 1.

A statistically significant relationship was present between the education level and the presence of knowledge on breathing exercises ($p<0.001$). There was a history of hospitalization in 59 (52.7%) of the patients, and the presence of knowledge about breathing exercises was statistically significantly higher in these patients than in those without a history of hospitalization ($p=0.046$). It was found that lung involvement on CT was higher in those with breathing exercise knowledge, but this elevation was not significant (90% vs. 78%; $p=0.182$). It was determined that the presence of dyspnea did not reveal a significant difference according to exercise knowledge ($p=0.820$) (Table 2). In addition there was not statistically significant correlation between respiratory exercise compliance and the clinical and demographic characteristics of the patients.

The mean age of patients with compliance to breathing (49.09±12.10 vs 53.06±15.33; $p=0.409$) and their BMI levels were lower (26.44±3.14 vs 28.29±5.51; $p=0.280$), but it was determined that these differences were not significant and the duration of illness was similar [60 (25-180) vs 60 (1-180); $p=0.673$]. It was observed that the Charlson index and Modified Borg values and the rates of lung involvement and dyspnea on CT did not reveal a significant difference according to exercise compliance ($p=0.233$, $p=0.212$, $p=0.525$, and $p=0.120$).

Thirty (26.8%) patients who participated in the study reported that they knew breathing exercises. However, only 11 (36.7%) of these patients were regularly doing these exercises (Table 3).

Of the patients who stated that they know breathing exercises, 63% answered the question on the source of knowledge as a health institution, and there was no significant difference in the distribution of answers to this question in terms of their education.

Table 1

Demographic and Clinic Characteristics

Age, (years), (Mean ± SD)	52.8 ± 15
Number of patients	112 (60M, 52F)
Body Mass Index (BMI) (kg/m²)	28.08 ± 5.3
Education Level, n (%)	
• Illiterate	15 (13.4)
• Primary School graduate	42 (37.5)
• High School graduate	26 (23.2)
• University graduate	29 (25.6)
Profession, n (%)	
• Currently Employed	48 (42.9)
• Retired	27 (24.1)
• Never employed	37 (33)
Modified Charlson Comorbidity Index	17.76 ± 1.86
Smoking, n (%)	
• Currently smoking	8 (7.1)
• Quit smoking	23 (20.5)
• Never smoked	81 (72.3)
Smoking duration (packages/year)	5.8 ± 11
Duration of illness (day)	74 ± 48.4
Hospitalization, n (%)	59 (52.7)
Pulmonary Involvement on Computerized Tomography (CT), n (%)	91 (81.3)
Dyspnea, n (%)	69 (61.3)
Modified Borg Scale	2.57 ± 2.4

SD: Standart deviation, n: number, %: percentage

Table 2

Comparison of patients with and without respiratory exercise knowledge according to some socio-demographic and clinical parameters

Socio-demographic and Clinical parameters	No breathin exercise information (n=82)	Has respiratory exercise knowledge (n=30)	p
Age (years) (Mean±SD)	54,28±15,93	48,83±11,73	0.090*
BMI (kg/m^2) (Mean±SD)	28,17±4,04	26,80±3,24	0.023*
Duration of illness (day) (Mean±SD)	50 (1-180)	95 (20-180)	0.006**
Modified Charlson Comorbidity İndex [median (min-max)]	1.5 (0-7)	0 (0-5)	0.017**
Modified Borg Scale [median (min-max)]	2 (0-8)	4 (0-7)	0.412**
Education Level (n ,%)			
Illiterate	12(14,6)	3(10)	
Primary School graduate	37(45,1)	5(16,7)	0.001***
High School graduate	20(24,4)	6(20)	
University graduate	13(15,9)	16(53,3)	
Dyspnea (n ,%)			
• No	32 (%39,0)	11 (%36,7)	0.820***
• Yes	50 (%61,0)	19 (%63,3)	
Hospitalization (n,%)			
• No	43(54,4)	39(47,6)	0.046***
• Yes	10(33)	20(66,7)	
Pulmonary Involvement on CT (n,%)			
• No	18 (%22,0)	3 (%10,0)	0.182****
• Yes	64 (%78,0)	27 (%90,0)	

SD: Standart deviation, n: number, %: percentage* Student's T Test** Mann Whitney U Test*** Chi-square Test**** Fisher's Exact Test

Table 3

The level of information on and compliance with pulmonary exercises

Has information on pulmonary exercises, yes, n (%)	30 (26.8)
Information sources for respiratory exercises, n (%)	
• Health institution	19 (17)
• Family-friend	3 (2.7)
• Social Media	8 (7.1)
Doing respiratory exercises regularly? , yes, n (%)	11 (9.8)

n: number, %: percentage

4. Discussion

In this study, pulmonary rehabilitation awareness levels and compliance with breathing exercises were evaluated in the follow-up of outpatients and inpatients after COVID-19. According to the results of the research, patients with a history of hospitalization after COVID-19 and with a high level of education knew breathing exercises. One of the most interesting results was that the level of exercise compliance was low in patients with breathing exercise knowledge.

Impediments to pulmonary rehabilitation in low- and middle-income countries include low awareness, limited resources, COVID-19, and patient access-related costs[10]. It has reported low awareness or recognition of PR in chronic respiratory diseases by the public, including healthcare professionals and governments. All individuals are less aware of physiotherapy services in their country, including PR. Low awareness of pulmonary rehabilitation results in decreased participation in PR in chronic respiratory diseases[11]. Also, this decrease in awareness and education has been observed in health professionals such as physicians who need to refer their patients to PR[12]. Our findings are also consistent with this study.

Despite its benefits in chronic obstructive pulmonary disease (COPD), studies have reported low participation rates in PR (pulmonary rehabilitation) programs by reporting barriers such as transportation problems, the severity of symptoms, acute exacerbations, lack of energy, and disruption of daily routines[13-16]. Indeed, PR continues to be underused worldwide, and growing evidence highlights that many patients have limited access to PR, and many do not complete rehabilitation programs. Spitzer et al.[17] reported that only 2.7% of their patients were referred to a PR program within 12 months of a COPD exacerbation. In another study, the PR compliance rate of patients with COPD was 76% (18), whereas, in other studies, compliance ranged between 56% and 88%[19-21]. Although there is a study showing that education level did not affect compliance with the PR program[22], the education level was found to be lower in patients who did not complete the PR program in many studies. Our findings are also consistent with those of these studies.

Smoking is considered one of the factors that negatively affect patients' compliance with the PR program[23]. According to a study on the consequences of those who quit the program, it was shown that the majority of smokers could not complete the program[24]. In our study, the rate of smoking was 7%.

It is not possible to change the education and income levels of the patients, but it is possible to increase participation rates by providing social support. It should be underlined that PR is a patient-specific program. Patients' sociodemographic and clinical characteristics should be considered when determining the type of program. Home programs and programs related to physical activity development strategies are needed for patients who cannot attend the program due to economic problems, transportation problems, or personal problems[25]. Physicians and other health practitioners have a great responsibility to improve the program compliance of COVID-19 patients.

The literature review based on the recent 40 publications emphasizes the importance of PR in COVID-19. However, rehabilitation associations, including the Turkish Society of Physical Medicine and Rehabilitation, have published PR recommendations that include diaphragmatic breathing, pursed lip breathing, and resistant breathing exercises in COVID-19 pneumonia with productive cough[26]. There are studies that show that the PR improved the exercise capacity, life quality, and respiratory functions of inpatients with post-COVID-19 symptoms[27]. The studies evaluating the changes in symptom severity and frequency after COVID-19 reported improvements in shortness of breath, fatigue, anxiety, and depression after PR[28].

The increase in opportunities with developed technologies makes rehabilitation programs more comprehensive. The important thing is that the physicians should first inform the patients and direct them to these programs. There are no studies in the literature to measure the level of pulmonary rehabilitation information and compliance with breathing exercises after COVID-19. Our work will be beneficial in terms of raising awareness about PR, especially in patients in the risk group after COVID-19, as well as raising awareness about PR that is not known enough by physicians and other healthcare professionals in primary care and directing patients in need to centers providing services in this regard[29].

A healthy control group should be included in this study and patients should be compared with this group. This is a limitation of the

current study. This is because even healthy individuals with the same education level in society may have limited knowledge about pulmonary rehabilitation.

5. Conclusions

In the study, the history of hospitalization and high level of education were found to correlate with the presence of knowledge on pulmonary rehabilitation. Exercise compliance was found to be low. The number of awareness-raising activities for these patients and healthcare professionals should be increased to reduce their morbidity, mortality, and health expenditure.

Acknowledgements

The summary of this article was presented as an oral presentation at the 20th National Family Medicine Congress on 11-14 November 2021.

Statement of ethics

Ethics committee approval for this study was received from Clinical Research Ethics Committee (dated 20.05.21 and numbered 1416). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent regarding the use of their personal information was obtained from all patients.

Conflict of interest statement

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

Funding source

None.

Author contributions

All authors contributed to the study conception and design.

All authors read and approved the final manuscript.

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Minimally Invasive Approach with Small-Bore Pleural Drainage Catheter (Easydren®) in Malignant Pleural Effusions

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Abstract

Aim: Treatment of malignant pleural effusion is drainage and chemical pleurodesis. Our aim in this study is to investigate the success and complications of the procedure in patients who underwent drainage with an 8F pleural drainage catheter due to malignant pleural effusion, according to the literature.

Methods: The study included 124 patients who underwent 8F pleural drainage catheter (Easydren®) for malignant pleural effusion between August 2020 and October 2022. Clinical, radiological and laboratory findings of all patients were obtained from the hospital automation system and archive files. Age, gender, etiology, number and duration of catheter drainage, complications and length of hospital stay of the patients were recorded.

Results: Of the124 patients, 67 (54.0%) were female and 57 (45.9%) were male. The mean age was 54 (range, 31-87). A total of 136 pleural drainage catheters were applied to 124 patients. Drainage and complete reexpansion of the lung were successful in 125 (91.9%) of 136 procedures. No acute surgical complications were observed during the application of pleural drainage catheters. The mean drainage time was 4.6 days (range, 3 – 11). The length of hospital stay was 5.7 days (range, 4-12).

Conclusions: Conclusions: We believe that small-bore pleural drainage catheters are as effective as conventional chest tubes for the drainage of malignant pleural effusion with greater patient comfort. Although they rarely have a disadvantage such as obstruction during follow-up, they are less invasive and have fewer complications compared to tube thoracostomy.

Keywords: *Malignant pleural effusion, small-bore catheter, drainage*

1. Introduction

Malignant pleural effusion is the accumulation of more than normal fluid in the pleural space due to any malignancy. Malignant pleural effusion is thought to occur as a result of direct tumor involvement of the pleura, increased permeability of pleural microvessels and obstruction of lymphatic drainage channels, resulting in decreased reabsorbed fluid[1]. The most common tumors metastasizing to the pleura are lung cancer in men and breast cancer in women. In addition, lymphoma, genitourinary or gastrointestinal system malignancies have an important role in etiology[2]. As in mesothelioma, the cause of pleural effusion may be the malignancy of the pleura itself.

The treatment of malignant pleural effusions is drainage and chemical pleurodesis. Traditionally, 24-28 F large diameter radiopaque drains were used for drainage until recently. This procedure is often painful and has the effect of limiting patient mobilization. In recent years, the use of small diameter drainage catheters has increased. It is argued that the pain and complication risk during placement and follow-up of these catheters are less3,4. Our aim in this study is to discuss the success and complications of the procedure in patients who underwent drainage with an 8F pleural drainage catheter for malignant pleural effusion in the light of the literature.

2. Materials and methods

The study included 124 patients who underwent 8F pleural drainage catheter (Easydren®) for malignant pleural effusion between August 2020 and October 2022. The study was planned as a retrospective cohort study. The study protocol was approved by the Institutional Ethics Committee. All patients with malignant effusion who were followed as inpatients in our Thoracic Surgery Clinic or Oncology Clinic were included in the study. Clinical, radiologic and laboratory findings of all patients were obtained from the hospital

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Received: 15.02.2023, Accepted: 07.07.2023, Available Online Date: 31.08.2023
Cite this article as: Esme H, Erdiril YE. Minimally Invasive Approach with Small Diameter Pleural Drainage Catheter (Easydren®) in Malignant Pleural Effusions. J Cukurova Anesth Surg. 2023; 6(2): 355-8. doi: 10.36516/jocass.1251766

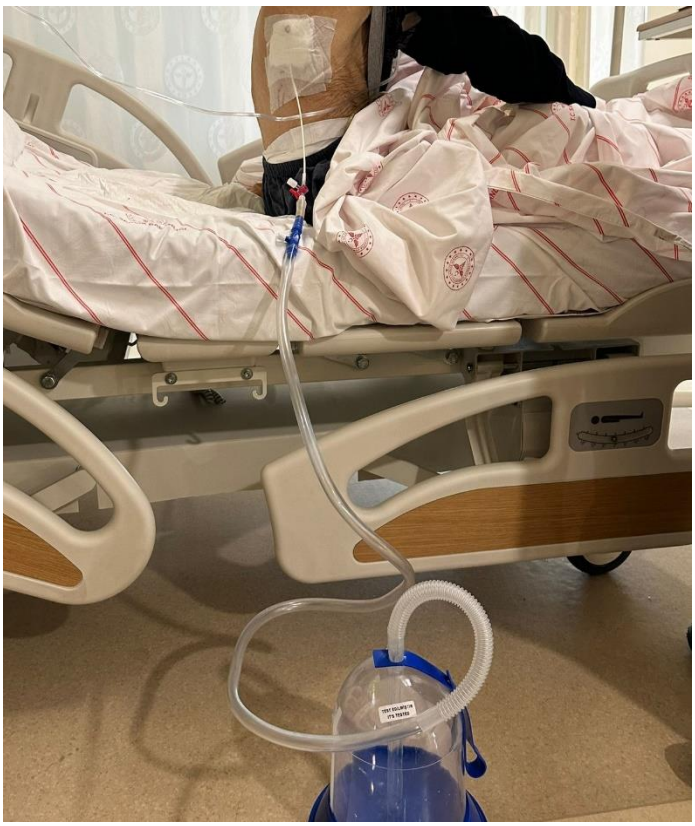

Figure 1
Connection of pleural catheter to underwater drainage system in a patient with incompletely expanded lung during drainage

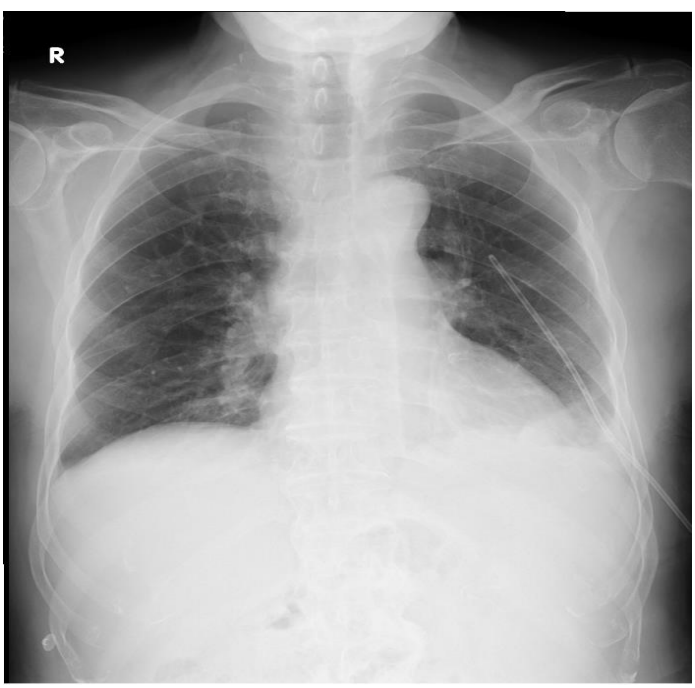

Figure 2
PA chest radiograph in a patient in whom pleural drainage was achieved

automation system and archive files. Direct chest radiography was seen in all patients. Thoracic computed tomography was performed in patients with suspected location and incomplete drainage. Thoracic ultrasonography was performed to determine the amount and localization of effusion in patients in whom thoracentesis failed. Before pleural drainage, thoracentesis was performed to determine the location of the catheter and to determine the nature of the pleural fluid. The pleural drainage catheter was inserted by the Seldinger method after asepsis was ensured and intercostal blockade was performed with local anesthetic. In patients with no location and free pleural fluid, an 8F drainage catheter was placed through the 5th or 6th intercostal space in the mid-axillary line. The pleural catheter was connected to the urine bag. In patients in whom the lung was not fully expanded during drainage, the pleural catheter was connected to an underwater drainage system (Figure 1). Chemical pleurodesis was performed with 4 mg talc in patients with an expanded lung and drainage below 300 ml. Drainage was terminated in patients with a drainage of 200 ml or less (Figure 2). Patients whose pleural catheter was terminated were discharged after chest radiographs 24 hours later showed that the lung was expanded.

3. Results

Of the patients, 67 (54.0%) were female and 57 (45.9%) were male. The mean age was 54 years (31-87). One hundred and twenty-four patients received a total of 136 pleural drainage catheters. Pleural drainage catheters were inserted 3 times in 3 patients, 2 times in 4 patients and bilaterally in 2 patients. The reason for multiple catheter placement was recurrence of pleural effusion or occlusion of the first catheter. Pleural effusion was exudate in 114 patients and transudate in 10 patients. The etiology of malignant pleural effusion was breast cancer in 54 (43.5%), lung cancer in 27 (21.7%), gastrointestinal system cancer in 19 (15.3%), lymphoma in 13 (10.4%), leukemia in 6 (4.8%) and other organ cancers in 5 (4.0%) patients. Cytology was sent for 3 days in patients with a history of primary malignancy. Effusions that were evaluated as malignant or suspected malignant on cytologic examination were accepted as malignant effusions.

No acute major surgical complications were observed during the application of pleural drainage catheters. Precautions against reexpension edema were taken by closing the catheter tap when the drainage volume reached 1500 ml. No reexpansion edema was observed in any of our patients. Drainage and complete lung reexpansion was successful in 125 of 136 procedures (91.9%). Expansion defect due to failure of lung expansion in the costodiaphragmatic sinus was detected in 3 patients. In these patients, the cavity was allowed to fill with fluid after the end of drainage. One patient developed significant pneumothorax after the procedure and underwater drainage was performed by tube thoracostomy with a 28 F radiopaque drain. Videothoracoscopic pleural drainage and decortication were performed in 2 patients aged 34 and 42 years with good general condition in whom septations developed after repeated drainage and drainage was not complete. In 4 patients with complete obstruction of the pleural drainage catheter, the catheter was replaced with a new one and drainage was achieved. In one patient, a portion of the pleural drainage catheter remained in the pleural space due to rupture of the catheter during termination. In this patient, the catheter was removed with the help of a videothoracoscope.

The mean duration of drainage was 4.6 days (3 - 11). During the follow-up of pleural drainage catheters, paracetamol was sufficient as analgesic except for 3 patients. In these patients, the addition of narcotic analgesics was sufficient to control pain if necessary. In addition, catheter obstruction occurred in 7 patients, but in these patients, 50 ml of isotonic fluid was administered through the

catheter via a syringe and flushing was performed. Catheter patency was achieved as a result of the application. No patient developed infection, bleeding or subcutaneous hematoma around the catheter. The mean duration of hospitalization was 5.7 days (4-12).

4. Discussion

Tube thoracostomy has been used as the primary tool for drainage of air or fluid in the pleural space resulting from different causes such as pleural effusion, empyema, hemothorax, chylothorax and pneumothorax. This procedure is performed with blunt dissection technique and usually requires hospitalization, limits patient mobilization and causes severe pain[5-7]. Tube thoracostomy has complications such as hemothorax, pneumothorax, organ perforation, diaphragmatic injury, empyema, pulmonary edema and horner syndrome[8,9]. In recent years, small bore pleural catheters have gained increasing popularity. Their safety and efficacy in managing different pleural pathologies have been the subject of several studies. In this study, we tried to determine the efficacy, advantages and disadvantages of small bore pleural drainage catheters used in patients with malignant pleural effusion.

Several clinical studies comparing large diameter chest tubes with small diameter catheters for malignant pleural effusion have shown that both procedures are equivalent in terms of both drainage and pleurodesis[10-12]. Different studies have measured the pain experienced by patients during the insertion of small diameter pleural catheters for malignant pleural effusion and reported that the pain experienced by patients was very mild and as a result, small diameter drainage catheters were well tolerated by patients[13,14]. In our patients, we found that there was much less pain and less need for analgesia during insertion of 8F catheters used for drainage of malignant pleural effusion compared to traditional tube thoracostomy.

We attributed this to the fact that unlike traditional chest tubes, small diameter catheters do not disrupt the anatomy of the intercostal space and do not compress neurovascular structures. Tube thoracostomy is a procedure that may cause pain in the intercostal space because it is performed with blunt dissection. It causes severe pain especially in obese patients as more dissection is required. Small diameter pleural drainage catheters are placed with the seldinger technique and cause less pain. The risk of diaphragmatic or intra-abdominal organ injury is lower compared to tube thoracostomy. Apart from this advantage, the risk of procedure-related bleeding or subcutaneous hematoma is lower in patients with bone marrow depression due to chemotherapy, coagulopathy due to impaired liver function, or high INR values due to anticoagulant use[2]. None of our patients experienced bleeding or subcutaneous hematoma due to the small diameter catheter.

Small diameter drainage catheters are more costly than radiopaque drains. However, several studies have reported that drainage and pleurodesis of malignant pleural effusion resulted in a shorter hospital stay compared to conventional tubes[15,16]. In addition, it has been reported that in recurrent malignant pleural effusions, small diameter pleural drainage catheters are connected to the urinary bladder and patients are called to outpatient clinic controls with close follow-up[17-19].

Some minor complications such as expansion defect or pneumothorax have been reported in the use of small diameter pleural drainage catheters. We observed lung expansion defect after drainage in three of our patients. We believe that the lung expansion defect was not due to the procedure itself, but to malignant infiltration of the visceral pleura or prolonged effusions causing thickened visceral pleura that prevented lung reexpansion. It is estimated that this complication occurs in 30% of malignant effusion cases[20]. In these patients, catheter drainage is not required for a long time and pleural fluid can be allowed to reaccumulate in the residual space over time[21,22]. Alternatively, as reported by some other authors, drainage can be provided for a longer period of time with the use of an indwelling pleural catheter[23]. In 3 of our patients, an expansive defect was detected in the costodiaphragmatic sinus due to failure of the lung to expand. In these patients, the cavity was allowed to fill with fluid after the catheter was terminated after decreased drainage.

Another common complication of small diameter pleural drainage catheters is frequent occlusion. In 4 of our patients, the catheter was completely occluded and we had to change the catheter for complete drainage. In addition, partial occlusion of the catheter occurred in 7 patients, but in these patients, 50 ml isotonic fluid was administered through the catheter via a syringe and flushing was performed. Catheter patency was achieved as a result of the application. Frequent flushing of the catheters with sterile isotonic may maintain drainage. There are also authors who recommend the use of fibrinolytics to facilitate drainage[24]. Rupture of a small diameter drainage catheter due to its thinness and intrapleural retention is a rare complication as we encountered in 1 patient. Patients should be warned that they should be careful not to get the catheter caught anywhere during mobilization.

5. Conclusions

In conclusion, we believe that small diameter pleural drainage catheters are as effective as conventional chest tubes for drainage of malignant pleural effusion with greater patient comfort. Although it has the disadvantage of rare obstruction during follow-up, it is less invasive and has fewer complications compared to tube thoracostomy.

Statement of ethics

Permission for the study was obtained from the local ethics committee of Health Sciences University Konya City Hospital (date: 02.02.2023, decision no: 2023/02-41).

Conflict of interest statement

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

Funding source

The authors declared that they received no financial support.

Author contributions

All authors contributed to the study conception and design.

All authors read and approved the final manuscript.

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The Impact of the COVID-19 Pandemic on Anesthesia Management and Clinical Outcomes in Cesarean Section Surgery

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Abstract

Aim: It is known that postoperative morbidity and mortality increased during the COVID-19 pandemic, even if there is no known COVID-19 infection in surgical patients. In this study, it was aimed to evaluate the effects of the pandemic period on anesthesia management and maternal and neonatal outcomes by considering pregnant women who had cesarean section (C/S) surgery between September 2019 and September 2020 in two different groups as pre-pandemic and pandemic.

Methods: In this study, pregnant women who underwent C/S surgery within the scope of one-year experience in a tertiary hospital were analyzed retrospectively in two different periods, before and during the COVID-19 pandemic. The primary outcome measure of the study was the rate of administration of regional anesthesia in C/S surgeries during the pandemic period.

Results: According to the results of this study, in which 1241 C/S cases were analyzed, maternal age, gestational age, gravida, pregnancy-related morbidities, neonatal data including APGAR score and indications for C/S surgery did not change during the early COVID-19 pandemic period. However, the rate of pre-existing maternal diseases including anemia, the rate of hospitalization in neonatal intensive care units and the length of hospital stay decreased in the pandemic period compared to pre-pandemic. it was also found that regional anesthesia practices and postoperative maternal complication rates increased during the pandemic.

Conclusions: In this study, it was observed that various changes occurred in the field of clinical practices of obstetric anesthesia and in patient outcomes with the initiation of the COVID-19 pandemic.

Keywords: *Cesarean section, COVID-19, obstetric anesthesia, pandemic.*

1. Introduction

The Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which continues today, albeit to a limited extent, is a global health problem that has caused approximately 770 million infections and 7 million deaths worldwide[1]. With the emergence of SARS-CoV-2 infection, coronavirus disease 2019 (COVID-19) rapidly spreads among pregnant women, as in all individuals.

Furthermore, with the declaration of the pandemic, lifestyle changes and infection measures in all areas of life took place as well as in the health system and in all interventional procedures, especially surgery and anesthesia practices. Similarly, in cesarean section (C/S) surgeries, with the belief that the risk of transmission due to aerosolization will be lower during airway management, the behavior of preferring neuraxial anesthesia to general anesthesia has developed and has come to the fore in obstetric anesthesia management during the COVID-19 pandemic[2,3]. However, general anesthesia for urgent C/S was preferred predominantly in pregnant women with pulmonary COVID-19 infection, and insufficient oxygen saturation (≤93%)[4]. In addition, it is known that postoperative morbidity and mortality increase during the pandemic, even if there is no known COVID-19 in surgical patients[5,6]. Therefore, with this study, it was aimed to evaluate the effects of the early pandemic period on anesthesia practice and maternal and neonatal outcomes, by considering the pregnant women who underwent cesarean section between September 2019 and September 2020 in two separate groups, as pre-pandemic and

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Received: 13.08.2023, Accepted: 26.08.2023, Available Online Date: 31.08.2023
Cite this article as: Babaoglan I, Laflı Tunay D, Ilgınel MT, et al. The Impact of the COVID-19 Pandemic on Anesthesia Management and Clinical Outcomes in Cesarean Section Surgery. J Cukurova Anesth Surg. 2023; 6(2): 359-65. doi: 10.36516/jocass.1342597

pandemic periods. The primary outcome measure was the incidence of regional anesthesia practice during COVID-19 pandemic, and secondary outcomes included the distribution of C/S indications, fetal, neonatal and maternal complications including intensive care unit (ICU) admission, bleeding, and mortality, and length of hospital stay.

2. Materials and methods

This study was approved by the Institutional Investigation and Ethics Committee on September 10, 2021, with approval number: 114/12 and conducted at Cukurova University in Turkey.

2.1. Patients

For this retrospective cohort study, 1241 pregnant women who underwent C/S surgery by the Department of Obstetrics at Cukurova University Hospital between September 2019 and September 2020 were recruited. The sample size of the study consisted of all pregnant women who had C/S surgery within one-year experience of our tertiary care hospital. Power analysis was not used in the study. Only two patients were excluded from the study because their perioperative records were not available.

2.2. Data collection

Electronic medical records, anesthesia records, preoperative evaluation records, nursing records, laboratory findings, and postoperative evaluation records and clinical outcomes were reviewed for all women and neonates. All data were collected, recorded and checked by two different independent research assistants.

2.3. Outcomes

From the preoperative records, the demographic characteristics of the women (age, weight, gestational age, gravida), American Society of Anesthesiologists (ASA) physical status classification, preexisting diseases, pregnancy associated comorbidities, history of COVID-19, indication of C/S, and preoperative laboratory tests were recorded. From the records during the operation, type of anesthesia, requirement of vasopressor, APGAR score, weight, height, sex, head circumference, and presenting part of neonate, and postoperative analgesia method were noted. From the postoperative period records, maternal and neonatal complications, postoperative laboratory tests and length of hospital stay were documented. Maternal complications were defined as excessive bleeding requiring blood transfusion, cardiovascular or respiratory complications, seizure, systemic inflammatory response syndrome (SIRS), wound infection, ICU admission, and mortality. Neonatal complications were ICU admission, SIRS, and mortality.

All data were compared with each other in two different periods, before and during the COVID-19 pandemic.

2.4. Statistical Analysis

Categorical measurements were expressed as numbers and percentages, and numerical measurements as mean and standard deviation (median and minimum-maximum where appropriate). The Chi-square test was used to compare categorical measures between groups. Whether the numerical measurements provided the assumption of normal distribution was tested with the Kolmogrov Smirnov test. In the comparison of numerical measurements between the groups, T-test was used in independent groups if the statistical hypotheses were met, and Mann Whitney U test was used if the statistical hypotheses were not met. Logistic Regression was used to identify risk factors for the variables of groups (pre-COVID vs. post-COVID). Variables that were significant at the $p<0.25$ level in univariate analysis were included in the logistic regression analysis. IBM SPSS Statistics Version 20.0 package program was used for statistical analysis of the data. Statistical significance level was accepted as 0.05 in all tests.

3. Results

In this study, a total of 1241 C/S cases within the one-year experience of a single tertiary hospital were analyzed in two different periods, just before the COVID-19 pandemic (n=621) and during the early COVID-19 pandemic (n=620) period. When the two groups were compared in terms of maternal age, gestational age, gravida and pregnancy-related comorbidities, the two groups were comparable, but preexisting diseases as well as preoperative anemia were significantly higher in the pre-pandemic group (Table 1). Neonatal data including sex, weight, head circumference, presenting part of fetus, and APGAR scores were comparable between groups (Table 2).

Operative characteristics and anesthetic data were presented in Table 3. During the pandemic period, the rate of regional anesthesia practice was significantly higher compared to general anesthesia (Table 3) (Figure 1). Moreover, in the pandemic, the rate of NSAID use in postpartum pain management decreased significantly and the rate of paracetamol use increased compared to the pre-pandemic (Table 3). While the incidence of maternal complications was found to be significantly higher in the pandemic, the rate of fetal complications mainly as ICU admission was significantly lower than in the pre-pandemic. In addition, the length of hospital stay was significantly reduced during the pandemic (Table 4). In the multivariate analysis model adjusted according to maternal age, gestational age, infant APGAR score, birth weight, urgency of surgery, preoperative hemoglobin level, preoperative white blood cell count, anesthesia type, intraoperative vasopressor requirement, postoperative complications, and length of hospital stay, it was shown that preoperative anemia and overall postoperative complications including both maternal and neonatal adverse events were significantly lower in pandemic. Similarly, in univariate analysis, preoperative anemia and the rate of general anesthesia practice (Figure 1) were significantly higher in pre-pandemic (Table 5).

4. Discussion

Although many changes in anesthesia practice, such as postponing elective cases, reconsidering urgency, have emerged with the COVID-19 pandemic, pregnancy-related procedures such as C/S surgery have not been interrupted[7]. Therefore, the best opportunity to observe the effects of the pandemic was obtained in these cases. During the COVID-19 pandemic, there were periodic differences in the SARS-COV-2 infection and the course of the disease, treatment and preventive modalities, and all clinical practices. In this context, in this retrospective study, in which 1241 C/S cases were analyzed, the effects of the COVID-19 pandemic on pregnancy, labor, patient outcomes and clinical practice in the initial period of the pandemic were evaluated. The current study reveals that, maternal age, gestational age, gravida, pregnancy-related morbidities, neonatal data including APGAR score, anthropometric measurements excluding height, and presenting part of neonate, and indications of C/S surgery were unchanged during the early COVID-19 pandemic. However, in the pandemic, pre-existing comorbidity, and anemia rate, NSAID use, neonatal ICU admission and length of stay in hospital decreased, on the other hand, regional anesthesia rate and maternal complications such as bleeding and infection increased. Although intrauterine bacterial infections are known as the main cause of spontaneous preterm birth, there is evidence that viral pathogens such as influenza, SARS and MERS also cause this adverse condition[8,9]. In this context, although there is a lot of evidence reporting the risk of preterm birth after COVID-19, this has not been clarified in all aspects[10,11].

Table 1

Maternal Characteristics, Concomitant Diseases and Preoperative Hemoglobin Values of Pre-pandemic and Pandemic Groups

Parameter	Pre-pandemic (n=621)	Pandemic (n=620)	p value
Maternal age (year) [a]	30.9±5.9	30.7±6.2	0.780
Gestational age (week) [a]	37.3±3.0	37.3±3.0	0.659
• <28 week[b]	12 (1.9)	11 (1.8)	
• 28-32 week[b]	36 (5.8)	34 (5.5)	0.991
• 33-37 week[b]	176 (28.3)	177 (28.5)	
• >37 week[b]	397 (63.9)	398 (64.2)	
Pre-existing disease[b]	244(39.3)	186(30)	0.001*
• Diabetes mellitus	26(4.2)	19(3,1)	
• Hypertension	31(5.0)	26(4.2)	
• Obesity	9(1.4)	6(1.0)	
• Asthma	18(2.9)	20(3.2)	
Gravida[b]			
• Primigravida	108(17.4)	121(19.5)	0.342
• Multigravida	513(82.6)	499(80.5)	
Pregnancy-related comorbiditiesb,[c]	282(45.4)	286(46.1)	0.068
Preoperative hemoglobin (g/dL)[a]			
• <11 g/dL	175 (28.2)	123 (19.8)	0.001*
• >11 g/dL	446 (71.8)	497 (80.2)	

[a] Values are given as mean±standard deviation. [b] Values are given as n (%).clncluding gestational diabetes mellitus and hypertension, preeclampsia, eclampsia, HELLP syndrome, oligohydramnios, anhydramnios, premature rupture of membranes or prolonged rupture of membranes, urinary tract infection etc. *These values indicate statistical significance (p<0.05).

Table 2

Comparison of Neonatal Data Between Study Groups

Parameter	Pre-pandemic (n=621)	Pandemic (n=620)	p value
Sex (Male/Female)a	314(50.6)/307(49.4)	322(51.9)/298(48.1)	0.629
APGAR score at 1 min[a]			
• 8-10	396(63.7)	355(57.3)	0.191
• 4-7	188(30.3)	229(36.9)	0.153
• <4	37(6.0)	36(5.8)	0.474
APGAR score at 5 min[a]			
• 8-10	536(86.3)	542(87.4)	0.604
• 4-7	72(11.6)	66(10.6)	0.738
• <4	13(2.1)	12(1.9)	0.932
Birth weight (g)b	2965.4±813.0	3008.9±771.4	0.300
• <2500 g	154(24.8)	130(21.0)	
• 2500-4200 g	448(72.1)	474(76.5)	0.221
• >4200 g	19(3.1)	16(2.5)	
Height (cm)[b]	46.7±4.7	47.2±4.5	0.009*
Head circumference (cm)[b]	33.5±2.8	33.7±3.0	0.406
Presenting parta			
• Head	505(81.3)	532(85.8)	
• Buttocks	79(12.7)	62(10.0)	0.193
• Transverse	28(4.5)	19(3.1)	
• Other (feet, face or oblique)	9(1.4)	7(1.1)	

[a] Values are given as n (%). [b] Values are given as mean±standard deviation. *This values indicates statistical significance (p<0.05).

Table 3

Comparison of Operative Characteristics and Anesthetic Data Between Study Groups

Parameter	Pre-pandemic (n=621)	Pandemic (n=620)	p value
Indication of C/S surgery			
• Fetal reasons	71(11.4)	51(8.2)	0.462
• Maternal reasons	246(39.6)	250(40.3)	
• Failed labor	40(6.4)	47(7.6)	
• Placental abnormality	22(3.5)	18(2.9)	
• Fetal and maternal reasons	60(9.7)	63(10.2)	
• Maternal and labor reasons	81(13.0)	76(12.3)	
• Fetal and labor reasons	60(9.7)	57(9.2)	
• Maternal and placental reasons	25(4.0)	38(6.1)	
• Patient request	16(2.6)	20(3.2)	
Type of surgery			
• Emergency surgery	284(45.7)	256(41.3)	0.114
• Elective surgery	337(54.3)	364(58.7)	
ASA status			
• II	615(99.0)	609(98.2)	0.221
• III	6(1.0)	11(1.8)	
Type of anesthesia			
• Regional	354(57.0)	402(64.8)	0.005*
• General	267(43.0)	218(35.2)	
Intraoperative vasopressor requirement			
• Yes	77(12.4)	64(10.3)	0.249
• No	544(87.6)	556(89.7)	
Postpartum pain management			
• Paracetamol	74(11.9)	112(18.1)	0.040*
• NSAID	241(38.8)	222(35.8)	
• Paracetamol+NSAID	238(38.3)	211(34.0)	
• Opioid	31(5.0)	36(5.8)	
• Opioid+Paracetamol	30(4.8)	34(5.5)	
• Epidural analgesia	7(1.1)	5(0.8)	

Abbreviations: C/S, cesarean section; ASA, American Society of Anesthesiologists; NSAID, Non-steroidal anti-inflammatory drug. Values are given as n (%). *This value indicates statistical significance ($p<0.05$).

In a large recent cohort, It has been reported that severe COVID-19 in late pregnancy triggers spontaneous preterm delivery, but mild and moderate, as well as early-term disease have a minimal effect on this risk[12]. Furthermore, in a systematic review and meta-analysis, it was concluded that preterm birth was not overall affected during the pandemic[13]. Consistent with this, in the present study, the gestational age distribution of pregnant women in the early COVID-19 pandemic was similar to that before the pandemic. Similarly, no increase in pregnancy-related comorbidities was observed during the pandemic. In contrast, in the large cohort study of Handley et al.[12], an increase in the rate of gestational diabetes and hypertension was reported during the outbreak period. This is a large database study analyzing 994,268 obstetric cases and covering the first one-year course of the COVID-19 pandemic, therefore it is inevitable being beyond our current study.

The association of preoperative anemia with adverse perioperative outcomes is well known[14]. Similarly, it has been shown that anemic pregnant women with COVID-19 have a higher risk of intensive care unit admission[15]. Interestingly, in the present study, the rate of cases with anemia before the pandemic was 28.2%, while it was 19.8% during the pandemic period. There could be numerous possible reasons for this situation. One of these may be due to the increasing intensity of pregnancy follow-up programs, and the improvement in preventive activities in primary health care. Another reason may be that the pregnant women's nutrition and healthy life habits improved and extra care has emerged, especially with the outbreak.

Researches evaluating C/S indications in the COVID-19 pandemic have reported that the incidence of fetal distress increased among all indications, and as well as elective surgery rates decreased[12,16,17]. Nonetheless, in our study, there was no difference between the COVID-19 pandemic and the C/S indications and elective surgery rates.

Table 4

Distribution of Postoperative Maternal and Neonatal Complications and Length of Hospital Stay in Study Groups

Parameter	Pre-pandemic (n=621)	Pandemic (n=620)	p value
Maternal complications[a]	36(5.8)	71(11.5)	0.001*
• Respiratory	2(0.3)	3(0.5)	
• Bleeding[b]	12(1.9)	25(4.0)	
• Systemic complications[c]	12 (1.9)	21 (3.4)	
• Wound infection	4 (0.6)	9 (1.4)	
• ICU admission	1(0.16)	2(0.32)	
• Thrombosis	0(0.0)	1(0.2)	
• COVID-19 PCR (+)	0(0.0)	8(1.3)	
• Other[d]	5(0.8)	2(0.3)	
Fetal complications[a]	66(10.6)	31(5.0)	0.001*
• Neonatal ICU admission	55(8.8)	20(3.2)	
• Neonatal mortality	11(1.8)	11(1.8)	
• Length of hospital stay[e]	2.1±0.9	1.8±1.5	0.001*

Abbreviations: ICU, intensive care unit; PCR, polymerase chain reaction.[a] Values are given as n (%).[b] Required blood transfusion or total abdominal hysterectomy.[c] Hemodynamic abnormality, arrythmia, impaired blood glucose, seizure, or fever. [d] Allergic reaction, ileus, and psychologic symptoms.[e] Value is given as mean±standard deviation. *These values indicate statistical significance (p<0.05).

Table 5

Univariate and Multivariate Analysis of the Potential Risk Factors in Pre-pandemic and Pandemic Groups

Parameter	Pre-pandemic n(%)	Pandemic n(%)	Univariate OR(95% CI)	p value	Multivariate aOR[a](95% CI)	p value
Preterm labor (<37 week)	224(36.1)	222(35.8)	1.01(0.80-1.27)	0.923	0.49(0.22-1.08)	0.077
Preoperative anemia (Hb<11 g/dL)	175(28.2)	123(19.8)	1.58(1.21-2.06)	0.001*	1.75(1.02-2.99)	0.039*
Maternal and neonatal complications	112(18.0)	104(16.7)	0.84(0.61-1.169	0.300	0.56(0.33-0.94)	0.029*
APGAR at 5 min <8	85(13.7)	78(12.6)	0.95(0.90-1.02)	0.186	-	-
Low birth weight (<2500 g)	154(24.8)	130(21.0)	0.80(0.36-1.76)	0.580	-	-
Emergency surgery	284(45.7)	256(41.3)	0.83(0.67-1.04)	0.115	-	-
Preoperative leukocytosis (WBC>11 103/mL)	389(62.6)	397(64.0)	1.00(0.78-1.28)	0.960	-	-
Type of anesthesia						
• RA	354(57.0)	402(64.8)	0.71(0.57-0.90)	0.005*	-	-
• GA	267(43.0)	218(35.2)				
Vasopressor requirement	77(12.4)	64(10.3)	0.81(0.57-1.15)	0.250	-	-
Length of hospital stay (mean±SD)	2.1±0.9	1.8±1.5	0.89(0.80-0.99)	0.390	-	-

Abbreviations: OR, odds ratio; aOR, adjusted OR; CI, confidence interval; Hb, hemoglobin; WBC, weight blood cell; RA, regional anesthesia; GA, general anesthesia. [a]aOR was adjusted according to maternal age, gestational age, infant APGAR score, birth weight, urgency of surgery, preoperative hemoglobin level, preoperative white blood cell count, anesthesia type, intraoperative vasopressor requirement, postoperative complications, and length of hospital stay. *These values indicate statistical significance (p<0.05).

It is obvious that great changes are observed in anesthesia practices during the COVID-19 pandemic period. Particularly in this period, there was a decrease in elective cases and a divergency from general anesthesia to limit airway interventions.[7,18] For that reason, regional anesthesia practices have arisen significantly in all procedures, as well as in C/S surgery[16,19]. In our study, it was shown that general anesthesia rates in C/S surgery decreased from 43% to 35% in the early pandemic period, consistent with the evidences.

In the early stages of the COVID-19 pandemic, many opinions have been suggested that the use of non-steroidal anti-inflammatory drugs may exacerbate COVID-19 and have serious side effects, and subsequently the World Health Organization (WHO) has published a statement on this issue. Therefore, clinicians have been relatively away from NSAIDs during the pandemic period.

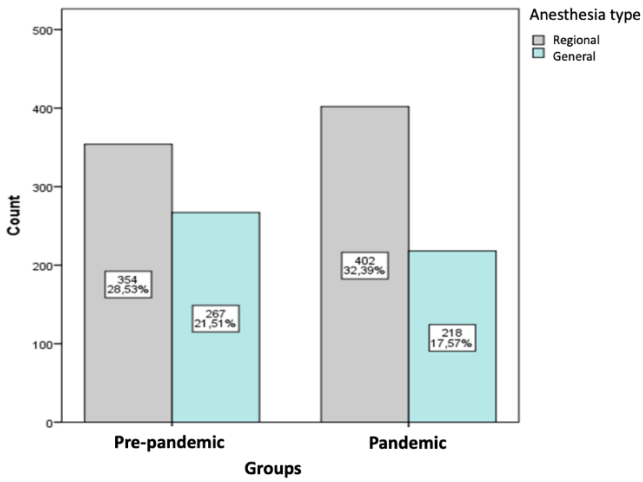

Figure 1

Comparison of the anesthesia types between the two study periods

Despite the lack of conclusive evidence and conflicting results, a decrease in NSAID use tendency has been observed. In the current study, a significant decrease in the rate of NSAID use in postpartum pain management was demonstrated statistically.

In a systematic review addressing the impact of the COVID-19 pandemic on maternal and perinatal outcomes at a global level, it was reported that maternal mortality, stillbirth, and ruptured ectopic pregnancies increased in the pandemic compared to pre-pandemic period. In contrast, preterm birth, maternal gestational morbidity, and neonatal outcomes including APGAR less than 7 at 5 minute, neonatal ICU admission, low birth weight, and mortality were unaffected[13]. It is understood from this that the COVID-19 pandemic does not seem to have directly affected the obstetric outcomes except maternal mortality and stillbirth. Mortality and stillbirth outcomes are probably due to pregnant women in the population with severe COVID-19 and reduced access to care. In our study, no difference was found between the two periods in terms of neonatal APGAR scores, birth weights, head circumferences, presenting part of neonate, and mortality. On the other hand, a significant decrease was observed in the neonatal ICU admission rate during the pandemic period. We interpreted this finding as neonatal ICU follow-up indications were revised and narrowed during the pandemic period.

In our study, a significant increase was found in postnatal maternal complications in C/S cases during the pandemic period. Eight patients had COVID-19 and one patient had thrombotic complications. However, in a way we could not explain, there was an increase in bleeding-related complications and systemic complications such as hemodynamic abnormality, arrhythmia, impaired blood glucose, seizure or fever in postnatal women during the pandemic.

While concerns about postpartum early discharge as a family-friendly and cost-effective approach have been on the agenda in recent years, this trend has accelerated during the COVID-19 pandemic period[12,19,20]. In the large database study mentioned above[12], it was observed that the length of hospital stay was significantly shortened in obstetric patients during the COVID-19 pandemic, and it did not cause any difference in re-admission to the hospital within postpartum 6 weeks. In the present study, we also found that the length of hospital stay was significantly shorter during the pandemic period.

The strength of the study is that it covers all C/S cases in our tertiary care hospital during the one-year period that includes just before and during the COVID-19 pandemic, thereby facilitating the comparability of the data and evaluation of the impacts of outcomes. The main limitation is the retrospective and single center design of the study by that limiting the generalization of the results. Another is that the pregnancy processes of the patients included in the study are not completely within these periods due to the long gestational duration.

5. Conclusions

In this study, which covers the immediate pre- and early period of the COVID-19 pandemic, the changes caused by the outbreak on health care delivery and patient outcomes were evaluated. Our findings suggest that C/S indications, gestational age, gestational comorbidities, and neonatal outcomes, including APGAR score, anthropometric measurements, and mortality, did not change during versus before the COVID-19 pandemic. Nevertheless, during the pandemic period, the rate of anemic pregnant women reduced, the use of regional anesthesia increased, the rate of postpartum NSAID use decreased, the neonatal ICU admission rate and length of hospital stay were shortened. We think that there is a need for large and homogeneous cohort studies at a global level that examine the longer-term effects of the COVID-19 pandemic on maternal and perinatal outcomes.

Acknowledgements

The authors of this article would like to thank everyone who played a role in carrying out this research.

Statement of ethics

The study was registered at the Cukurova University Institutional Investigation and Ethics Committee on 10 September 2021 with the approval number: 114/12 and conducted at Cukurova University in Turkey following the most recent version of the Declaration of Helsinki.

Conflict of interest statement

The authors declare no conflict of interest.

Funding source

The authors declared that this study received no financial support.

Author contributions

All authors contributed to the study conception and design.

All authors read and approved the final manuscript.

Informed Consent

Informed consent was obtained from all subjects or their relatives.

Availability of Data and Materials

The datasets analyzed in this study are available upon request to the corresponding author.

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Zor Hava Yoluna Neden Olabilen Pediyatrik Sendromlar

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Özet

Amaç: Pediyatrik yaş grubunda zor hava yoluna sebep olabilecek sendromlar çok daha fazla görülebilmektedir. Bu sendromlara bağlı gerek hava yolu ile ilgili gerekse diğer organ ve sistemlerle ilgili cerrahi geçirmeleri veya hava yolunun açılmasına yönelik girişimler endike olabilmektedir. Bu derlemede pediyatrik sendromların neden zor hava yoluna neden olabilecekleri sunulmaya çalışılmıştır.

Materyal ve Metot: Bu derlemede olgu sunumları, derlemeler ve kitaplarda bulunan literatür bilgileri bir araya getirilmiştir.

Bulgular: Özellikle maksillofasiyal anomaliler ve deposit sendromlara bağlı anatomik bozukluklar zor hava yoluna neden olabilmektedir. Ayrıca bu çocukların büyümesi ile anatomik anomaliler daha da artmakta ve böylece tekrarlayan cerrahiler geçirmek zorunda kalmaktadırlar. Cerrahi öncesi iyi bir fizik muayene ve görüntüleme yöntemlerinin kullanılması zor hava yolunun öngörülebilmesini sağlayabilir.

Sonuç: Sendromik çocuklardaki anatomik değişiklikler ve geçirilmiş cerrahiler zor hava yolu riskini artırmaktadır. Bu çocukların preoperatif değerlendirmesinin multidisipliner olması ve görüntüleme yöntemlerinin kullanılması ile hava yolu yönetimi daha kolay hale getirilebilir.

Anahtar Kelimeler: *Pediyatrik sendromlar, zor hava yolu, zor entübasyon, maksillofasiyal anomaliler*

1. Giriş

Pediyatrik havayolunda gelişebilecek olası komplikasyonlar erişkinlere oranla çok daha fazladır. Bunun nedeni sadece anatomik ve fizyolojik farklılıklar değil aynı zamanda pediyatrik yaş grubunda havayolunu etkileyebilecek sendromların daha fazla görülmesidir. Başın göreceli olarak büyük, oksiputun çıkık, boynun kısa, dilin büyük ve çenenin küçük olması hava yolu obstrüksiyonunu artırarak erişkine göre daha fazla zor havayoluna neden olabilecek pediyatrik anatomik değişikliklerdir. Pediyatrik hastalarda larinks sefale daha yakın yerleşimlidir. Yani erişkinde larinks C4-5 seviyesinde iken pediyatrik popülasyonda C3-4 seviyesindedir[1]. Çocukluk çağında eşlik eden sendromlar anatomik yapıları daha da bozarak havayolu obstrüksiyonu olasılığını artırabilmektedirler. Ayrıca pediyatrik yaş grubunda sık üst solunum yolu enfeksiyonu geçirilmesi hava yolunu daha reaktif hale getirecek dolayısıyla da bronkospazm, laringospazm gibi komplikasyonların olasılığını artıracaktır. Anatomik değişikliklere sekresyonların ve ödemin eşlik etmesi de havayolu yönetimini zorlaştıracaktır. Bu derlemede zor hava yoluna neden olan sendromların hangi anatomik veya klinik özelliğine bağlı olarak zor hava yoluna neden olabileceğini kısaca tanımlamayı amaçladık.

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Geliş tarihi: 10.02.2022, Kabul tarihi: 22.04.2022, Yayınlanma tarihi: 31.08.2023
Atıf: Biricik E. Zor Havayoluna Neden Olabilen Pediyatrik Sendromlar. J Cukurova Anesth Surg. 2023; 6(2): 366-74. Doi: 10.36516/jocass.1071305,

2. Tartışma

Sendromik çocuklar hem sendromlarına bağlı klinik sonuçlar nedeniyle hem de diğer çocuklarda görülebilen endikasyonlarla cerrahi operasyon geçirmek zorunda kalabilirler. Çoğu cerrahi de genel anestezi altında uygulandığından hava yolu güvenliği işin içine girmektedir. Pediyatrik sendromlar kraniyofasiyal veya nonkraniyofasiyal sendrom şeklinde sınıflandırılabilir.

1. Kraniyofasiyal Sendromlar

1.1. Mupopolisakkaridozlar (MPS)

MPS' ler lizozomal enzim sistemindeki defekte bağlı glikozaminoglikanların (GAG) anormal depolanması sonucu gelişen bir sendromdur. GAG' lar birçok organda bulunan, hücresel iletişimde etkin olan hücre ve ekstrasellüler matriksin yapımında rol oynayan polymerize şeker-protein molekülleridir. GAG ve GAG fragmanlarının birikmesi hücresel işlev bozukluğuna ve aşırı büyümeye neden olur. Enzim eksikliği tipi ve biriken GAG' a göre MPS' ler alt tiplere sınıflandırılmaktadırlar[2]. (Tablo 1)[2]

GAG birikimi ile birlikte yumuşak dokularda kalınlaşma, dilde büyüme gelişir. Dismorfik yüz görüntüsü vardır. Ağız büyüktür. Kısa hareketsiz boyun, servikal omurga ve temporomandibular eklemlerde hareket kısıtlılığı olur ve tüm bu anatomik değişiklikler maske ventilasyonu, laringoskopi ve entübasyonu zorlaştırır[3]. (Resim 1)[4] Ayrıca endotrakeal entübasyon faringeal duvarda bulunan GAG depozitlerini travmatize edebilir ve kanamaya neden olabilir.

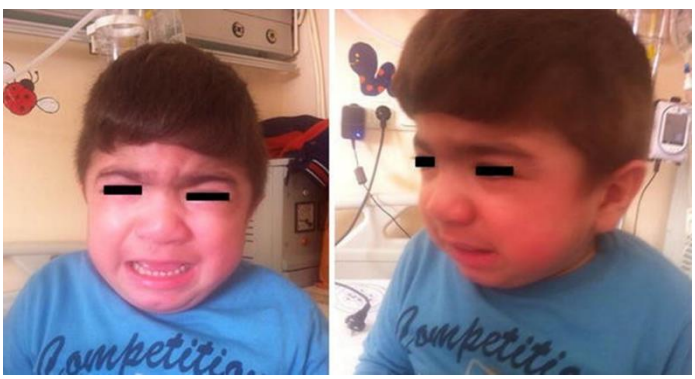
MPS Tip 1: Hurler, Tip 4: Morquio ve Tip 6: Maroteaux- Lamy' da atlantoaksiyal subluksasyon ve odontoid hipoplazi görülebilir bu da spinal kord kompresyonuna ve nörolojik defisit gelişmesine neden olabilir[5]. Mandibular hipoplazi, temporomandibular eklem problemleri de eşlik edebilir.

Tablo 1

Mukopolisakkaridoz Sınıflaması

Subtip	İsim	Enzim Eksikliği	GAG substratı	Klinik Özellikler
MPS IH	Hurler	Alpha-L-iduronidaz/ OR	Heparan sülfat Dermatan sülfat	Kaba yüz özellikleri, gelişme geriliği, ciddi çok seviyeli havayolu obstrüksiyonu, OSA, kardiyak defektler, hepatosplenomegali, korneal opasite ve iskelet deformitesi. Tedavi edilmezse adölesan döneme kadar yaşayabilir.
MPS HIS	Hurler-Scheie	Alpha-L-iduronidaz/ OR	Heparan sülfat Dermatan sülfat	Şiddeti veya başlangıç hızı farklılık göstermekle birlikte MPS IH' ye benzer özellikler. Normal zeka
MPS IS	Scheie	Alpha-L-iduronidaz/ OR	Heparan sülfat Dermatan sülfat	Hafif, geç başlangıçlı. Kardiyak kapak hastalığı, korneal opasite. Normal zeka
MPS II	Hunter	İduronidaz sülfat/ X'e bağlı genetik geçiş	Heparan sülfat Dermatan sülfat	SSS hastalıklarını da içeren geniş bir spectrum. MPS IH' ye benzer havayolu ve kardiyak problemler, gelişme geriliğ ve agresif davranışlar. Korneal opasite yok.
MPS III A-D	Sanflippo A-D	Her subgruba bağlı farklı enzim eksikliği/OR	Heparan sülfat	Agresif davranışlarla birlikte progresif nörokognitif gerilik. Kısa boy. MPS A en şiddetlisi
MPS IV A	Morquio A	N-asetilgalaktozamin-6-sülfataz/ OR	Keratan Sülfat	Sıklıkla boy kısalığı, kifoskolyoz ve dizostozis multipleks gibi kas iskelet hastalıkları görülür. Trakeal stenoz oldukça sıktır.
MPS IV B	Morquio B	Beta-galaktozidaz / OR	Keratan Sülfat	Morquio A' ya benzer ancak daha hafif şiddetlisidir.
MPS VI	Maroteaux-Lamy	N-asetilgalaktozamin-4-sülfataz/ OR	Dermatan sülfat	MPS IH' ye benzer hastalık spektrumu gözlenir ancak SSS tutulumu çok nadirdir.
MPS VII	Sly	B-glukuronidaz/OR	Heparan sülfat Dermatan sülfat	MPS I' e benzer ara bir klinik sergiler. Çok Nadirdir.

OR; Otozomal Resesif, MPS; Mukopolisakkaridoz,



Resim 1

Mukopolisakkaridoz tip 1[4]

MPS tanılı çocuklar obstrüktif uyku apnesi, tonsillektomi (sık üst solunum yolu enfeksiyonları), ileri derece iskelet deformitelerinin düzeltilmeleri gibi pek çok nedenle cerrahi operasyon geçirmek zorunda kalırlar. Odontoid hipoplazi ile birlikte subdural GAG depozitlerine bağlı spinal kompresyon varlığı havayolu yönetimini daha zor hale getirir ve bu durumdaki hastalarda nörolojik komplikasyon olasılığı da artmıştır[6]. Abdominal organlarda büyüme solunum işini artırmaktadır. Kaburgalardaki şekil değişikliği ve sertleşme toraksın ekspansiyonunu zorlaştıran bir başka faktördür ve trakeada torsiyositeye (bükülmeye) neden olur[7]. MPS tanılı çocuklar enzim replasman tedavisi (ERT) ve hemapoetik kök hücre transplantasyonu (HKHT) tedavisi almaktadırlar. Özellikle MPS I tanılı çocuklarda HKHT tedavisi üst ve alt havayolunda, miyokardiyumda GAG birikimini azaltmakta ve hepatosplenomegaliyi önleyebilmektedir[8,9].

1.2. Trizomi 21 (Down Sendromu)

Trizomi 21 21. Kromozom çiftinde genellikle ayrılmamaya bağlı fazladan 1 kromozumun bulunması sonucu gelişen otozomal genetik bir sendromdur. Karakteristik bir yüz şekli vardır. Karakteristik özellikler arasında geniş ve düz yüz, küçük burun, palpebral fissürlerin yakın olması, kalın ve uzun dil sayılabilir. Oksiput düz, burun kökü çökük, alın eğimli, kulaklar düzleşmiş kıvrımsız, gözler çekik epikantal kıvrımlı ve hipoteloriktir. Bu çocuklarda anatomik anomalilere yarık damak ve yarık dudak sıklıkla eşlik etmektedir. Trizomi 21' li çocukların mikrognattik, büyük dilli, kısa-kalın boyunlu olmaları ve faringeal kaslarındaki hipotoni havayolunu daraltan başlıca sebeplerdendir. Ayrıca bu çocuklarda adenoid ve tonsillerin hipertrofik olması, glossoptozis ve yüksek damak varlığı da havayolunu daha da daraltacak nedenlerdendir[10-12].

Laringomalazi 2 yaş altı, OSA da 2 yaş üzeri trizomi 21' li çocuklarda en sık görülen üst hava obstrüksiyonu nedenleridir[13]. Yaklaşık Trizomi 21' li çocukların %15' i atlantoaksiyal eklemde ligamentöz laksisiteye sahiptir[14].

Trakeomalazi, laringomalazi, laringeal kleft, trakeal stenoz Trizomi 21' de oldukça sık görülmektedir[15,16].

.

Resim 2

Pierre Robin Sendromu (PRS) [19]

1.3. Pierre Robin Sekansı (PRS)

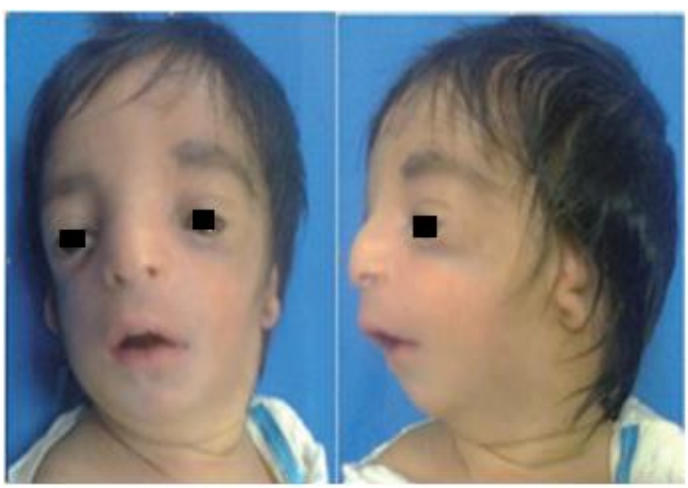
Mikrognatti (retrognatti), glossoptozis ve havayolu obstrüksiyonu ile karakterizedir[17]. Bazı otörler mikrognatti, glossopitozis ve yarık damak olarak tanımlasa da birçok infantta yarık damak olmamasına rağmen havayolu obstrüksiyonu mevcuttur[18]. (Resim 2)[19]

Ventriküler septal defekt (VSD), atriyal septal defekt (ASD), fallot tetralojisi ve patent duktus arteriosus (PDA) gibi kardiyak anomaliler %20 gibi büyük bir oranda eşlik etmektedir[20].

Stickler sendromu, velokardiyofasiyal (22q, 11.2 eksikliği), fetal alkol sendromu ve Treacher-Collins sendromu PRS ile ilişkisi gösterilmiş sendromlardır. PRS'nin en önemli semptomu havayolu obstrüksiyonudur ve hastalar beslenme güçlüğü, stridor, retraksiyonlar ve siyanoz ile başvurabilir. Mikrognatti ne kadar şiddetli ise epiglot ve dil kökü kollapsı ile havayolu obstrüksiyonu o kadar şiddetlidir. Beslenme güçlüğü ve reflü zamanla gelişme geriliğine neden olmaktadır. Havayolunu açmak için havayolu açma araçları ve pron pozisyon kullanılabilir. Pron pozisyon hastaların %70'inde havayolunu açmakta etkindir. Bazı hastalarda nasofaringeal airwayler, dil dudak adhesyonu, mandibular distraksiyon osteogenezisi ve trakeostomi gibi girişimler ile havayolu açılmaya çalışılmaktadır[21]. PRS' li hastalarda laringomalazi veya subglottik-trakeal patolojiler de görülebilmektedir.

1.4. Treacher Collins Sendromu (TCS)

İlk kez Edward Treacher Collins tarafından 1990' da tanımlanmıştır[22]. Mandibulofasiyal dizostozis, Franceschetti-Zwahlen-Klein sendromu veya TCS olarak da bilinmektedir. 'Treacle' nükleoler fosfoproteini kodlayan TCOF1genindeki mutasyon sonucu oluşur[23]. Maksiller, zigomatik ve mandibüler hipoplazi ile birlikte olan dar ağız açıklığı, mikrognatti, dış kulak anomalileri, işitme kaybı, yüksek arklı damak, kolobomlar (lens, iris veya retinadaki konjenital defektler) ve temporomandibüler eklem anormallikleri mevcuttur. Bu anatomik değişiklikler direk laringoskopi ve endotrakeal entübasyonda zorluklara neden olabilmektedir[24]. Orta yüzde hipoplazi vardır ve alt kirpikler tamamen veya kısmen yoktur. Tipik olarak çıkıntılı bir burun, küçük yüz ile kuş benzeri görünüm vardır[25]. (Resim 3)[13] Özellikle ağız açıklığının dar olması, posterior yerleşimli büyük dil, faringeal hipoplazi ve temporomandibüler eklem anomalileri zor hava yolu nedenidir.

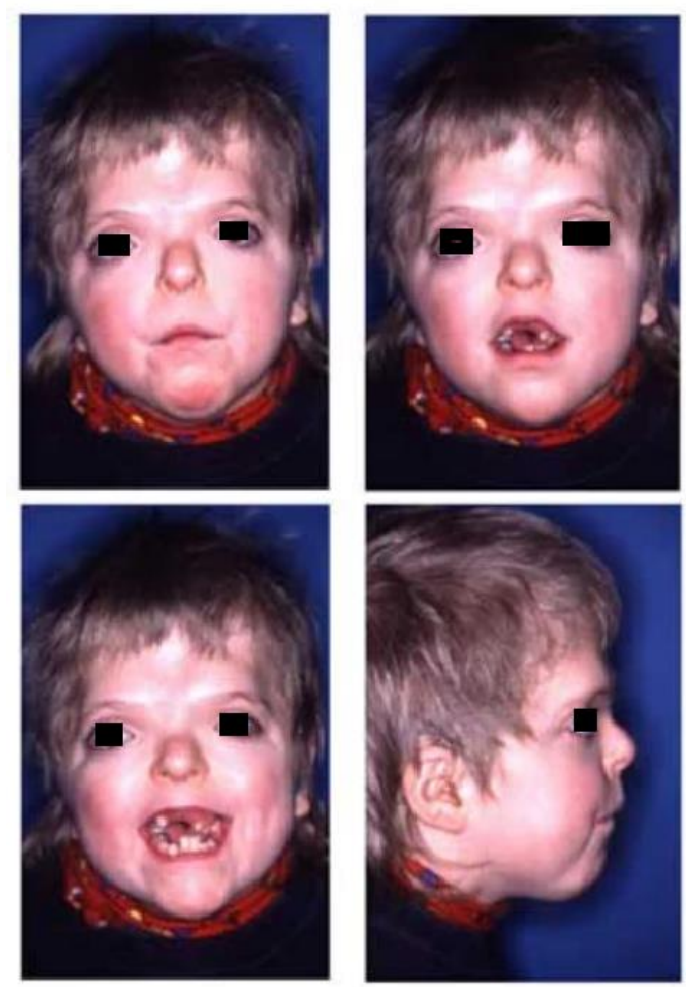


Resim 3
Treacher Collins Sendromu (TCS) [13]

1.5. Apert Sendromu

Apert, Crouzon and Pfeiffer sendromu kraniyosinositozis ile birlikte değişik oranlarda midfasiyal hipoplazinin, hipertelorizm ve propitozisin eşlik ettiği sendromlardır[26]. (Resim 4)[27]

Apert OD geçişli, FGFR2 (fibroblast growth factor) geninde mutasyonla karakterize bir sendromdur. Akrosefalosindaktili olarak tanımlanan sendrom, kraniyal süturlarının erken kapanması sonucu gelişen kraniosinositozis, fasiyal hipoplazi, el ve ayaklarda sindaktili ve kafa tabanında defekt ile karakterizedir. Makroglossi, mikrognatti, yarık damak, uvula bifida, koanal atrezi, özefagial atrezi, pilor stenozu, trakeaözefagial fissür gibi anomaliler eşlik edebilmektedir[28-30]. Servikal vertebra füzyonu özellikle C5-C6 seviyesinde gözlenmektedir[13]. Midfasiyal hipoplazinin şiddetine bağlı olarak bu hastalarda OSAS görülebilmektedir[31]. Zamanla orta hat hipoplazisi artmakta ve bu da havayolu obstrüksiyonunu artırmaktadır. Forte ve ark. Apert sendromlu hastalarda havayoluna ilişkin problemin nazal kaviteden çok farengeal bölgede olduğunu ve hipofarinkse doğru gidildikçe anteroposterior olarak daha fazla daraldığını göstermişlerdir[32]. Genel olarak da Apert sendromlu çocuklarda havayolu obstrüksiyon semptomları nazofaringeal alandan çok laringofaringeal alanla ilişkilidir[33].

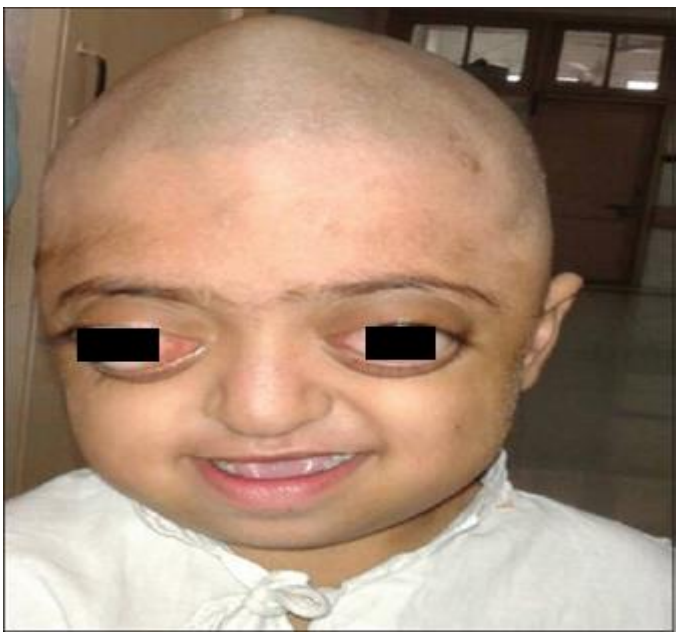


Resim 4
Apert Sendromu[27]

1.6. Crouzon Sendromu

Akrosefalosindaktili II olarak bilinen FGFR-2 geninde mutasyona bağlı gelişen OD bir sendromdur. Koronal, sajital ve bazen de lambdoidal süturlerde kraniosinositozis mevcuttur[28]. (Resim 5)[34]

C2-3 servikal vertebralarda füzyon, hipertelorizm, egzoftalmus, yüksek arklı damak, yarık damak, bifida uvula, koanal atrezi eşlik edebilmektedir. Maksiller hipoplazi maske ventilasyonunu zorlaştırır. Kraniosinositozise bağlı intrakraniyal basınç (İKB) artışı söz konusudur. İKB' nin artması cerrahiyi zorunlu kılar. Bu çocuklarda havayolu obstrüksiyonunun artması OSAS'ı da tetiklemektedir[35]. Özellikle 1 yaşın altında yapılan cerrahi düzeltmeler havayolu obstrüksiyonunu azaltmaktadır[36]. Crouzon sendromlu çocukların %55' inde işitme kaybı mevcuttur ancak bu çocuklar çoğunlukla mental olarak normaldirler[37].



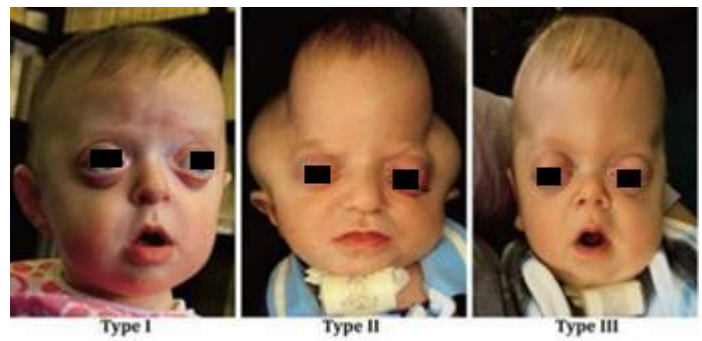
Resim 5

Crouzon Sendromu[34]

1.7. Pfeiffer Sendromu

Akrosefalosindaktili Type V olarak da bilinen Pfeiffer Sendromu, sagital kraniosinostozis, orta yüz hipoplazisi, ve yumuşak dokuda sindaktili ile karakterizedir. FGFR1 ve FGFR2 genlerindeki mutasyona bağlı gelişen çok nadir bir sendromdur. Cohen, Pfeiffer Sendromunu 3 grupta sınıflandırmıştır[38]. Tip I klasik bulguları içerirken, Tip II ve III' de orta yüz hipoplazisi ve oküler propitozis cok şiddetlidir ve nöral deformiteler daha fazla olduğundan yaşam beklentisi daha kısadır. Tip II' de yonca yaprağı (cloverleaf) kafatası deformitesi varken, III' te yoktur. (Resim 6)[13] Pfeiffer Sendromu

Koanal atrezi, yarık damak, makroglossi, laringomalazi, trakeomalazi ve bronkomalazi görülebilmektedir. Üst havayolundaki anormallikler beslenme güçlüğü ve ciddi uyku apne sendromuna neden olmaktadır. Mental retardasyon ve işitme kaybı birçok hastada mevcuttur. Trakeal kartilajinöz sleeve (uzantı) Pfieffer Sendromunda görülebilen bir diğer trakeal deformitedir. Subglottik alandan karinaya, hatta bronşlara kadar uzanabilen dairesel veya posterior membranöz septum şeklinde olabilmektedir[39]. Bu trakeada daralmaya dolayısıyla da entübasyon ve trakeostomi açılmasında zorluklara neden olmaktadır. Pfieffer Sendromlu hastalarda trakeada farklı seviyelerde granülasyon dokuları oluşmakta ve bu granülasyonlar havayolunu ciddi oranda daraltmaktadır. Ayrıca bu kıkırdak uzantıların sekresyonların atılmasını engellediği ve trakeal immüniteyi etkilediği düşünülmektedir[40]. Pfieffer Sendromlu çocuklarda maksiller ilerletme ve trakeal deformitenin düzeltilmesi için trakeal rezeksiyon gibi cerrahi girişimler gerekebilmektedir[41]. (Resim 6)[42]



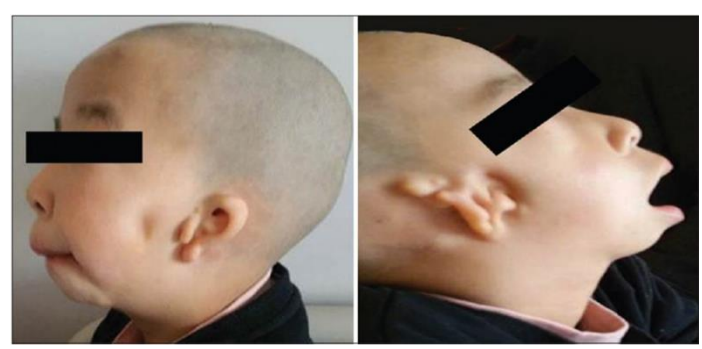
Resim 6

Pfieffer Sendromu[13,42]

1.8. Goldenhar Sendromu

Fasiyo-aurikülo-vertebral sendrom veya Okülo-Aurikülo-Vertebral sendrom olarak da adlandırılan Goldenhar sendromu göz, kulak, burun, yumuşak damak, mandibula kardiyak ve vertebral anomalileri içeren bir sendromdur[43].

İlk olarak 1952' de Dr. Maurice Goldenhar tarafından tanımlanmıştır. Kulakta; heliks gelişim anomalisi, dış kulak yolu atrezisi, iç kulak yolu anomalileri ve sağırlıktır, gözde; mikroftalmi, epibulber dermoid, göz kapağında kolobom, strabismus, vertebrada; servikal hemivertebra veya hipoplazi en sık görülen kraniyofasiyal anomalilerdir. Erkek cinsiyette daha fazla görülür (2/1), mandibular hipoplazi, hipoplastik zigomatik ark, mikrognatti, makrostomi gibi anomaliler zor hava yoluna neden olabilmektedir. Damaktaki yüksek ark ve yarık damak anomalileri de hava yolunu oldukça zorlaştırabilir. Servikal seviyedeki hemivertebra veya hipoplazi atlanto-oksipital eklemde sublüksasyona neden olabilir. Bu da baş-boyun hareketleri sırasında çok daha dikkatli olmamızı gerektirir. Aynı zamanda boyun hareketlerindeki ciddi kısıtlılık zor hava yolu ile sonuçlanabilmektedir. Hava yolu yönetimindeki zorluklar vertebral anomalilerin derecesinin artması ile ve ilerleyen yaşlarda daha da artmaktadır. Bilgisayarlı tomografi ile hava yolu anatomisinin incelenmesi birçok hastada endike olabilir[44]. (Resim 7)[45]

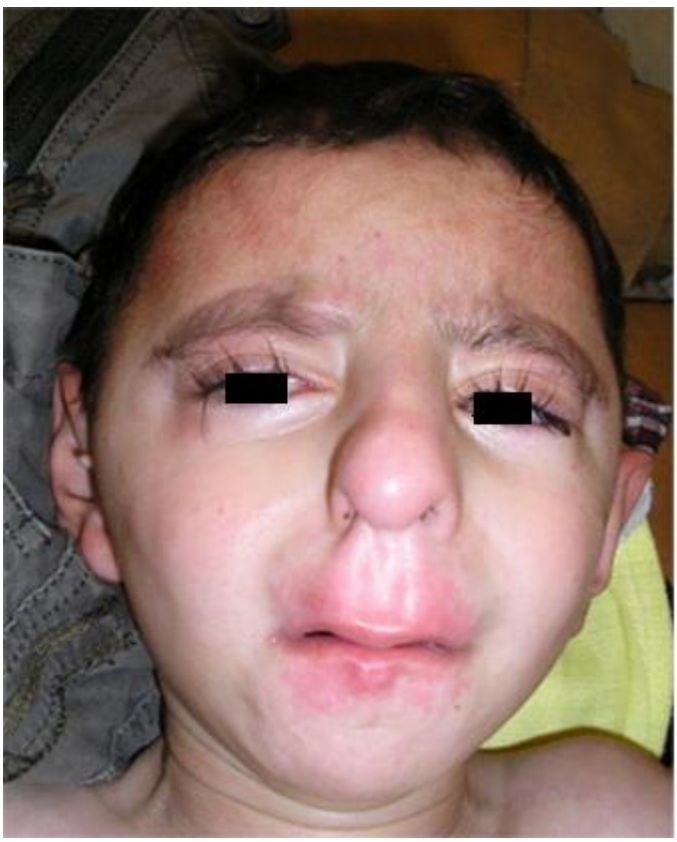


Resim 7

Goldenhar Sendromu[45]

1.9. Trikorinofalangeal Sendrom

TRPS1 genindeki mutasyon sonucu gelişen, kraniyofasiyal, iskelet ve saç anomalilerini içeren 3 subgruptan oluşan bir genetik bozukluktur. Geniş çıkıntılı büyük burun (armut şeklinde burun), çıkıntılı maksilla-üst dudak, anormal diş yapısı, hafif bir mikrognatti, mikrosefali ve kısa boy mevcuttur. Tipik üçgen yüz görünümü vardır ve çoğu hastada kliniğe mental retardasyon da eşlik edebilmektedir. Saçlar seyrek ve zayıftır. Çenede maloklüzyon görülebilir ve bu tüm dismorfik yüz değişiklikleri ve sık akciğer enfeksiyonları zor entübasyon, zor maske ventilasyonu ile havayolu yönetimi zor olabilir[46,47]. (Resim 8)[48]

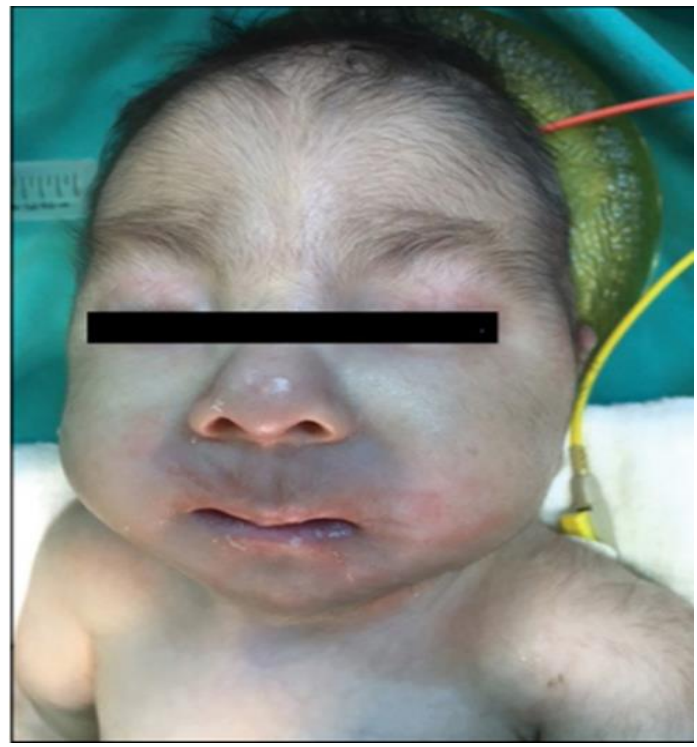


Resim 8
Trikorinofalangeal sendrom[48]

1.10. Trizomi 18 (Edwards Sendromu)

Otozomal trizomiler içinde ikinci sıklıkla görülen anomalidir. Bu sendromlularda %50'sinden fazlasında kraniofasiayal malformasyonlar mevcuttur. Mikrosefal, geniş oksiput, mikrognatti, yüksek arklı damak, yarık damak ve dudak, kısa boyun ve makroglossi sıklıkla eşlik etmektedir[49,50].

Ayrıca bu çocuklarda trakeomalazi ve obstrüktif uyku apnesi de görülebilmektedir. Birmingham ve ark 5 yıllık süre içerisinde kliniklerinde opere olan Trizomi 18 tanılı hastaları değerlendirdiklerinde en sık yaşanan komplikasyonlar olarak sırasıyla zor entübasyon, zor maske ventilasyonu ve zor intravenöz erişim olarak tespit etmişlerdir[51]. Kardiyak anomalilerin varlığı nedeniyle bu çocukların çoğunluğunda yaşam süresi 1 yılın altında olabilir. İki yaş ve üzerine kadar yaşayabilen çocuklarda ise kemik deformiteleri daha da ilerlemekte ve özellikle skolyoz gibi solunum fonksiyonlarını bozan anatomik değişiklikler gelişmekte dolayısıyla cerrahi endikasyonu doğmaktadır. Kettler ve ark Trisomi 18 tanılı çocuklarda maksiller hipoplaziyi % 38,1, dar ağız veya havayolunu % 33,3, hipotoniyi % 57,1, laringomalaziyi %14,3 oranında tespit etmişlerdir[52]. (Resim 9)[49]



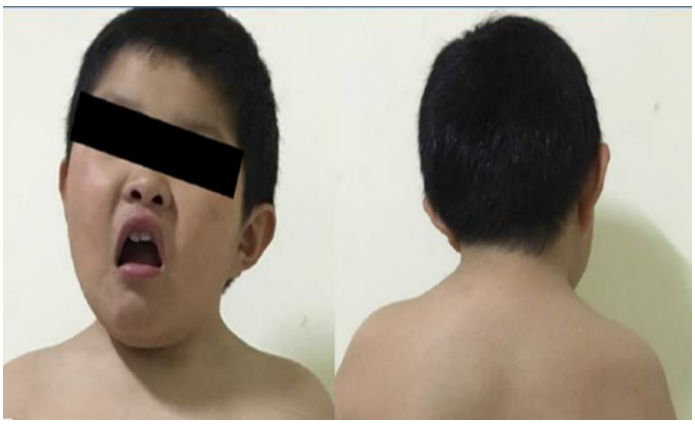
Resim 9
Trizomi 18 (Edwards Sendromu) [49]

1.11. Klippel Feil Sendromu

Klippel Feil Sendromu servikal vertebralarda eksiklik veya 2 ve daha fazla vertebranın füzyonuna bağlı aşırı kısa boyun, hareket kısıtlılığı olan boyun, ensede düşük saç cizgisi üçlü karakteristik bulgusu ile tanımlanan bir sendromdur. Otozomal dominant genetik bir sendromdur. İlk kez 1912 yılında tanımlanmıştır ve nadir görülen bir sendromdur[53]. Bu hastalara servikal kanal stenozu da eşlik edebilir. Hastaların %75'inde ilk servikal vertebrada füzyon mevcuttur[54]. Boyundaki hareket kısıtlılığı, kısa boyun ciddi hava yolu obstrüksiyonuna ve zor entübasyona neden olmaktadır. Ayrıca kısa boyun ve vertebral rotasyon ile tortikollis gelişebilmektedir. Tekrarlayan entübasyon girişimleri ile hava yolunda şişme ve hematom gelişebilir bu da zor ekstübasyona neden olabilir[55]. Oksipito-servikal dizilimin orofaringeal boşluk üzerinde önemli bir etkisi vardır. Bazı vaka sunumları, oksipito-servikal (O-C) füzyon açısının postoperatif üst hava yolu obstrüksiyonu için kritik olacağını ortaya koymuştur[56]. Oksiput-C2 açısı azaldıkça dispne ve disfajinin arttığı gösterilmiştir[57]. Bazı servikal füzyon cerrahileri sonrası da oksiputo-servikal açı azalabilir bu da hava yolu obstrüksiyonuna neden olabilir. Cerrahi sonrası ekstübasyon da zorlaşabilmektedir. Uzun süreli entübasyon ve zor entübasyona bağlı hava yolu daha da daralabilir ve ekstübasyon öncesi kaf kaçak testi de her zaman doğru sonuçlar vermeyebilir[58].

Klippel Feil sendromuna yarık damak, kraniosinistozis, mikrognatti ve laryngeal defektler de eşlik edebilir. Hiperlaksit servikal vertebralarla nörolojik defisit ve nörodejenerasyon sıklıkla görülebilir. Klippel Feil sendromlu çocukların hemen hemen çoğunda zor hava yolu mevcuttur. Atlanto-oksipital eklemin ekstansiyona izin vermemesi ile Sınıf 3 ve üzeri Cormack-Lehane görüntüleri mevcut-

tur. Klippel Feil sendromlu hastalarda preoperatif görüntüleme yöntemleri kullanılması önerilmektedir. (Resim 10)[59]

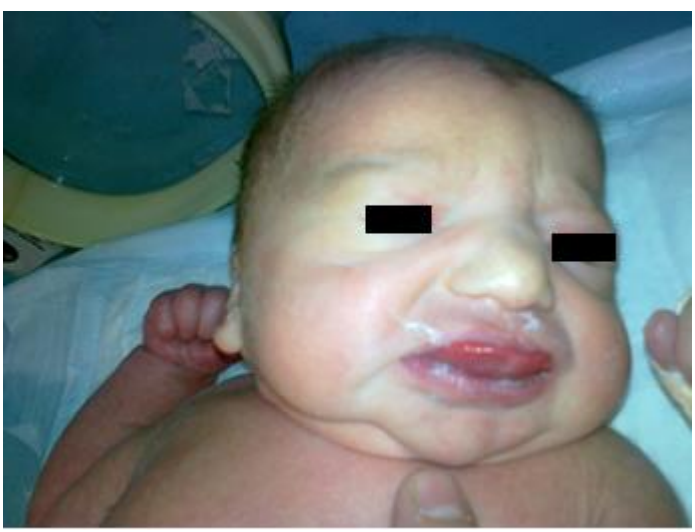


Resim 10
Klippel Feil Sendromu[59]

1.12. Beckwith-Wiedemann Sendromu

Kromozom 11p15 bölgesinde genetic değişiklik sonucu oluşan, 13700-15000' de 1 sıklıkla görülen bir sendromdur. Makroglossi, abdominal duvar defektleri (ör; omfalosel), hipoglisemi, makrozomi ve hepatoblastom ve Wilms tümörü gibi embriyonal tümörler ile karakterizedir. Beckwith-Wiedemann Sendromundaki en önemli zor hava yolu nedeni dilin aşırı büyük olmasıdır. Makroglossi, dil kas liflerinin aşırı büyümesinden kaynaklanır ve kraniyofasiyal anormalliklere yol açabilir[60].

Artmış mandibula uzunluğu ile prognatik bir görünüme neden olabilir. Ayrıca trakeal duvar anormallikleri de zor hava yoluna katkıda bulunur. Beckwith-Wiedemann sendromlu çocuklarda trakeal çap normalden daha küçük olabilmektedir[61]. Trakeomalazi görülebilir.



Resim 11
Beckwith-Wiedemann Sendromu[63]

Sequera-Ramos ve ark. Beckwith-Wiedemann sendromlu 122 hastayı yaşana hava yolu zorlukları açısından değerlendirmiş ve makroglossisi olan hastalarda daha yüksek oranlarda zor maske ventilasyonu, zor entübasyon, çoklu entübasyon girişimi yaşandığını göstermişlerdir[62].

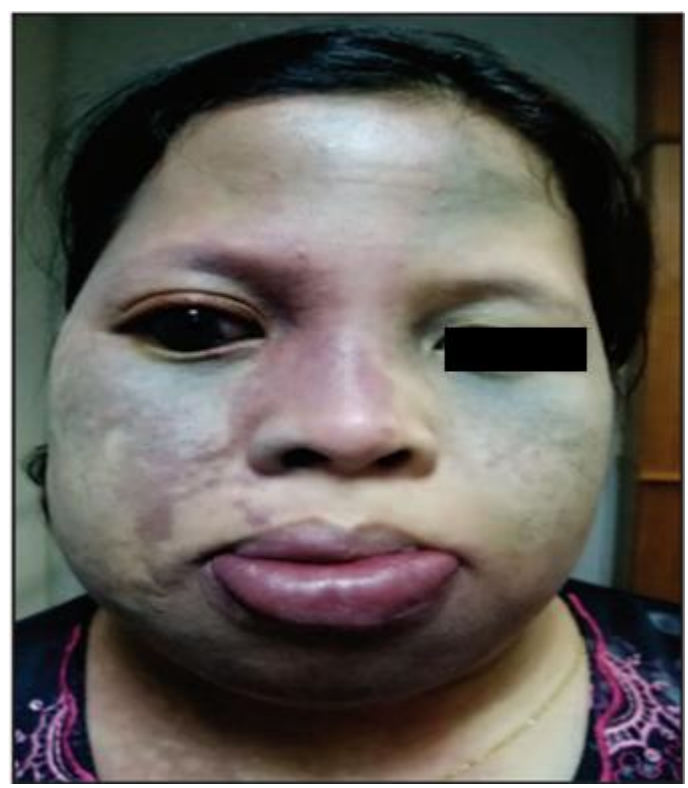
Ayrıca makroglossinin yanı sıra 1 yaş altı, düşük kilo, plastik/kraniofaciyal cerrahi, dil küçültme ameliyatı, OSA öyküsü ve endokrin komorbiditelerin de zor hava yolu ile ilgili olduğunu göstermişlerdir. Bu çocuklar en çok dil küçültme ve OSA cerrahilerine ihtiyaç duymaktadırlar. (Resim 11)[63]

2. Vasküler ve Kutanöz Anomalilerin Eşlik Ettiği Sendromlar

Baş boyun bölgesini etkileyen vasküler anomalilerin ve kutanöz tutulumun eşlik ettiği sendromlar da pediyatrik zor hava yoluna neden olabilmektedir. Bu sendromlar da bazen kitle oluşumu yaparak bazen hareket kısıtlılığı yaparak anatomiyi bozmaktadırlar. Hemanjiyomlar, lenfatik ve/veya lenfatikovenöz malformasyonlar (kistik higroma), arteriovenöz malformasyonlar şeklinde karşımıza çıkabilmektedir.

2.1.Sturge–Weber Sendromu

Ensefaloanjiomatöz anjiomatozis olarak da bilinen leptomeningeal angioma, fasiyal vasküler malformasyon (porto şarabı lekesi) ve gözde vasküler malformasyon triadı ile karakterize bir nörokutanöz sendromdur. Vasküler anomaliler ve anjiomlar havayolu ve orak kaviteyi de içine alacak şekilde olabilir. Burun, gingiva, damak, dili larinks ve trakeada yerleşmiş olabilir ve fasiyal hipertrofi uyku apne sendromuna neden olabilmektedir[64,65]. Sturge-Weber' li çocuklarda zor maske ventilasyonu ve zor laringoskopi görülebilmektedir[66].

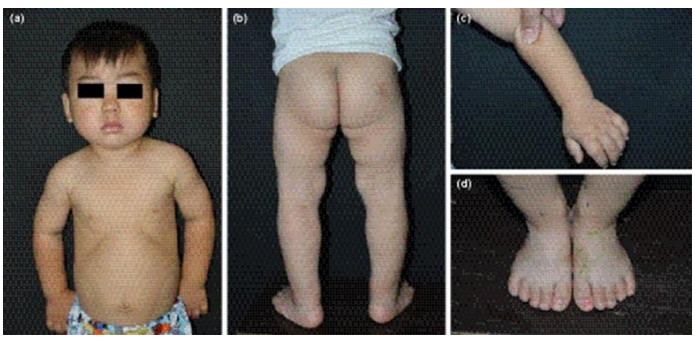


Resim 12
Sturge-Weber[67]

Ayrıca bu anjiomalar havayolu obstrükte etmekle birlikte kolaylıkla kanayabileceklerinden aspirasyona da neden olabilirler.
Entübasyon sırasında travmatize etmemek için kayganlaştırıcı jeller kullanılabilir ve aspirasyon sırasında dikkatli olmak gerekmektedir. (Resim 12)[67]

2.2. Sert Deri Sendromu (Stiff Skin Syndrome)

Konjenital fasiyal distrofi olarak da byline sert deri sendromu erken infant ve çocukluk döneminde yaygın sert ve gergin cilt varlığı ile karakterizedir[68]. Ciltteki gerginlik ve cilt elastikiyetinde azalma ağız açıklığında ve boyun hareketlerinde kısıtlılığa, göğüs ekspansiyonunda azalmaya, eklem kontraktürlerine, büyüme geriliğine neden olmaktadır. Genel olarak yüzden ziyade bacak, uyluk ve kalçalar daha ciddi olarak etkilenir. Ancak anelastik submental cilt nedeniyle boyun hareketleri kısıtlı ve mikrognatti varlığında ağız açıklığı daralmış olarak gözlenir. Ciltteki sertlik yaşla birlikte artmaktadır. Bu da daha ileri yaşlarda zor havayolu ile karşılaşma riskini artırmaktadır[69]. (Resim 13)[70]



Resim 13
Sert Deri Sendromu[70]

3. Sonuç

Bu derlemede pediyatrik dönem sendromlarının zor hava yoluna neden olan özellikleri sunulmak istenmiştir. Pediyatrik zor hava yoluna neden olan sendromlar cerrahi veya hava yolu girişimi öncesinde fizik muayene ve görüntüleme yöntemlerin de dahil edilmesi ile dikkatli bir şekilde değerlendirilmelidirler. İyi bir preoperatif hazırlık ile olası komplikasyonlar en aza indirilebilmektedir. Bu sendromlar, ağız açıklığını kısıtlayarak, tiromental mesafeyi kısaltarak, dili büyüterek, boyun hareketlerini kısıtlayarak, uyku apne sendromuna neden olarak vb. hava yolu obstrüksiyonuna neden olmaktadırlar. Tekrarlayan cerrahi girişimler ve çocuğun büyümesi ile anatomik değişiklikler de ilerleyecek ve hava yolu yönetimini zorlaştıracaktır. Bu nedenle birçok sendromik çocuk erken yaşlarda hava yolunun açılmasına yönelik cerrahileri geçirmelidir. Dolayısıyla sendromik çocuklar preoperatif dönemde daha dikkatli bir şekilde değerlendirilmelidir.

4. Telif

Yazar tüm resimlerde hasta vasisinin, kendisinin yazılı onamının olduğunu veya kaynaklarından izin alınarak yayınlandığını ve atıfladığını veya açık erişimli görselleri kullandığını beyan eder.

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The Postoperative Analgesic Effect of Transversus Abdominis Plane Block in Inguinal Hernia Repair: A Randomized Controlled Study

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Abstract

Aim: The objective of this study was to investigate the effect of preincisional (preemptive) Transversus Abdominis Plane (TAP) block on perioperative opioid consumption, hemodynamic parameters and postoperative rescue analgesic consumption in patients undergoing inguinal hernia repair.

Methods: 60 adult patients were included in this prospective randomized controlled study. The patients were divided into two groups: those who received conventional systemic analgesia (Group C) and those who received US-guided TAP block (Group TAP). By ultrasonography, normal saline (1 mL) was injected between the internal oblique and transverse abdominal muscles, and after separation was observed, 20 mL of 0.25% bupivacaine was administered. Postoperatively, 1mg/kg Tramadol HCl was given to all patients as a rescue analgesic. Perioperative hemodynamic data, perioperative total amount of remifentanil consumption amount, postoperative Visual Analogue Scale (VAS) scores, starting time and number of rescue analgesics were recorded.

Results: There was no difference in demographic data. Intraoperative remifentanil dose, VAS values at all times, need for rescue analgesics and the number of applications were significantly lower in Group TAP than in Group C ($p=0.012$, $p<0.05$, $p=0.047$). The number of patients who received rescue analgesics was significantly higher in Group C than in Group TAP ($p<0.05$). It was found that the first rescue analgesic administration time was needed later in Group TAP than in Group C ($p=0.032$). No difference was found in postoperative nausea and vomiting ($p>0.05$).

Conclusions: We concluded that preincisional TAP block is a safe and effective analgesia technique for postoperative pain control in patients undergoing unilateral inguinal hernia repair and our findings should be supported by advanced controlled randomized studies.

Keywords: *Hernia, Inguinal, transversus abdominis plane block, analgesia*

1. Introduction

More than 20 million people undergo inguinal hernia repair worldwide per year. In many countries, general or regional anesthesia is used in inguinal hernia surgery, while local anesthesia is less commonly preferred. In a study of 57,505 patients undergoing inguinal hernia repair, it was reported that 64% underwent general anesthesia, 18% underwent regional anesthesia and 18% underwent local anesthesia [1].

Pain of open inguinal hernia repair can be moderate-to-severe in intensity, with the most severe pain commonly experienced on the day of surgery[2]. Postoperative acute pain can cause immobilization, risk of respiratory failure, atelectasis, hypoxia and pneumonia. Daily life activities can be limited if inadequate analgesia is provided, and chronic pain can also impair quality of life[3]. Patients should be trained to be able to evaluate with Visual Analog Scale (VAS) or numerical rating system (NRS) to facilitate postoperative pain management[4].

Multimodal analgesia involves the simultaneous use of different pain control mechanisms to reduce the dose of a single agent, particularly opioids, while providing postoperative pain relief, augmenting analgesic efficacy and minimizing the risk of side effects[5]. This strategy attempts to avoid the use of opioids, or at least the enable the use of opioids at the lowest dose required, thus minimizing the risk of developing side effects that may even delay recovery[6].

TAP block is used in lower abdominal operations (cesarean section, inguinal hernia repair, appendectomy, abdominal hysterectomy, prostatectomy)[7]. TAP block decreases the perioperative opioid anal-

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e-mail: zelihalara@yahoo.com, Received: 25.02.2023, Accepted: 31.08.2023, Available Online Date: 31.08.2023 Cite this article as: Ilhan SC, Tuncel Z, Ozdemir M, et al. The Postoperative Analgesic Effect of Transversus Abdominis Plane Block in Inguinal Hernia Repair: A Randomized Controlled Study. J Cukurova Anesth Surg. 2023; 6(2): 375-81. doi: 10.36516/jocass.1268067

gesic requirement in inguinal hernia repair, provides hemodynamic stability, allows early recovery from anesthesia and reduces side effects[8,9]. TAP block provides analgesia by blocking the intercostal (T_7-T_{11}), subcostal (T_{12}) and ilioinguinal-iliohypogastric (L_1-L_2) nerves, and hydrodissecting between the internal oblique and the transversus abdominis muscles through the deposition of local anesthetics[10,11]. Analgesia lasting 24 hours is provided by blocking the T_6-L_1 nerves that pass through the fascial plane[12,13].
However, little is known about the timing of TAP block and its impact on postoperative pain control. While administration of the block prior to surgical incision can reduce opioid requirements, provide better pain control in the postoperative period[14].
This study tries to answer the question whether TAP performed before surgical incision (preemptive) would provide better analgesia than conventional systemic analgesia, by comparing effects on intraoperative opioid (remifentanil) consumption amount, hemodynamic parameters and postoperative rescue analgesic (Tramadol HCl) starting time in adult patients undergoing inguinal hernia repair under general anesthesia.

2. Materials and methods

The prospective, randomized and controlled clinical study was conducted between April 1, 2021, and October 1, 2021, after obtaining approval of the, Ümraniye Training and Research Hospital Ethics Committee with decision number 35 dated March 11, 2021, and the written informed consent of the patients. The study was designed in accordance with the Declaration of Helsinki defined in 2008. Written informed consent for trial was obtained from the patients.

A total of 60 adult patients 18 to 80 years, American Society of Anesthesiologists (ASA) 1-3 who underwent unilateral inguinal hernia repair were included in the study.

Exclusion criteria were inability to understand Turkish, neurocognitive dysfunction, relevant drug allergy, pregnancy, drug abuse, patients with organomegaly or coagulopathy, pain medications within 24 hours (h) before surgery and infection at the injection site.

The patients were divided into two groups using the sealed envelope method: those who received conventional systemic analgesia (Group C) and those who received US-guided TAP block (Group TAP). In group TAP, a unilateral TAP block was performed with ultrasound guidance using 20 mL of % 0.25 bupivacaine before the skin incision of surgical procedure following the induction of general anesthesia. The patients, the anesthesiologists and staff providing postoperative care were blinded to group assignments.

The primary outcome measure of the study was based on visual analogue scale (VAS) pain scores and rescue analgesic starting time postoperatively. The secondary outcome measures of the study were based on remifentanil consumption amount and hemodynamic parameters perioperatively.

2.1. Interventions

After non-invasive blood pressure, pulse oximeter (SpO_2), electrocardiogram (ECG) and bispectral index (BIS) monitorization all patients received intravenous (iv) propofol 2-2.5 mg/kg and fentanyl 1µg/kg for the induction of anesthesia. Rocuronium 0.6 mg/kg was administered, endotracheal intubation was performed and end-tidal carbon dioxide ($EtCO_2$) was monitored. The mechanical ventilation settings were adjusted to maintain an $EtCO_2$ of between 35 and 40 mmHg. Anesthesia was maintained through 1 minimum alveolar concentration (MAC) sevoflurane in 50% 0_2 + 50% air and remifentanil administered at a rate of 0.05–1 µg/kg/min. A mean arterial blood pressure (MAP) of less than 60 mmHg was considered hypotension, for which ephedrine hydrochloride 5 mg iv was administered.

After the anesthesia induction, a 38-mm linear array US probe (3-6 MHz) was dressed in a sterile cover and moved from the cephalic to the caudal direction to visualize the subcutaneous fat tissue, external oblique muscle, internal oblique muscle, transversus abdominis muscle, peritoneum and intraperitoneal cavity. Under ultrasound guidance, a 100-mm, 22-gauge TAP block needle was introduced anteriorly and inserted in plane under real-time US guidance to lie between the internal oblique and the transversus abdominis muscles.

After observing the hydrodissection of the transversus abdominis muscles and internal oblique through the injection of normal saline (1 mL) solution, 20 mL of % 0.25 bupivacaine solution was administered. The operation proceeded after the injection of local anesthetic with simultaneous visualization by ultrasound. Ondansetron 4 mg was administered intravenously as an antiemetic. No additional local anesthesia was administered by the surgeon. Group C patients was received conventional systemic analgesia paracetamol 1 gr and tenoxicam 20 mg and Group TAP was received paracetamol 1 gr for analgesic purposes 10 minutes before the end of surgery, and the patients were extubated following administration of atropine 0.03 mg/kg and neostigmine 0.05 mg/kg. Patients with an Aldrete score of 8 or greater after anesthesia were transferred to the recovery room.

After anesthesia, the patients were followed up in the recovery room for one hour and the VAS score was determined at 30 and 60 minutes. Tramadol HCl 1 mg/kg was administered iv if the VAS score was above 4. Patients with an Aldrete score of over 10 were transferred to a regular ward at the end of one hour. During postoperative follow-up, the patients were continued on iv paracetamol every six hours. Tramadol HCl 1 mg/kg was administered as a rescue analgesic if the VAS score was above 4.

2.2. Data collection

The demographic data of the patients, including age and gender were recorded. The MAP, HR, SpO_2 and BIS values were recorded at 0 min (baseline, before induction) and at 5, 15, 30, 45 and 60 minutes after induction, as well as at the end of surgery (120 minutes). Remifentanil consumption amount, at the end of surgery visual analogue scale (VAS) pain scores (4., 8., 12. and 24. h), rescue analgesic starting time, number of rescue analgesic administrations used and the presence of nausea and vomiting were recorded in 24 hours. Bowel sounds were followed up in the recovery room and the ward.

2.3. Statistical methods

The study data were analyzed using IBM SPSS Statistics (Version 25.0. Armonk, NY: IBM Corp.). A Kolmogorov-Smirnov test was used to check whether the variables were normally distributed. Along with descriptive statistics (mean, standard deviation, frequency) used for the analysis of the study data, the Student's t-test, a paired sample t-test and a Chi-square test were used for the evaluation of parametric data. A p-value of less than 0.05 was considered statistically significant.

3. Results

One hundred and twenty-seven patients were approached for participation in the study from April 2021 to October 2021. Sixty-six patients were recruited and randomly assigned to their treatment group. However, 6 patients were later excluded, resulting in 60 patients in the final analyses (The Consort Flow Diagram) (Figure 1).
There was no significant difference between the groups in terms of mean age, gender distribution and operation time ($p>0.05$) (Table 1).
Total intraoperative opioid (remifentanil 1 ml=50 µgr) consumption amount was significantly lower in Group TAP than in Group C ($p=0.012$) (Table 2). The VAS scores were lower in Group TAP than in Group C at all time points ($p<0.05$) (Table 3).
There was no statistically significant difference between the groups in terms of HR, MAP, BIS and SpO_2 values ($p>0.05$) (Table 4).

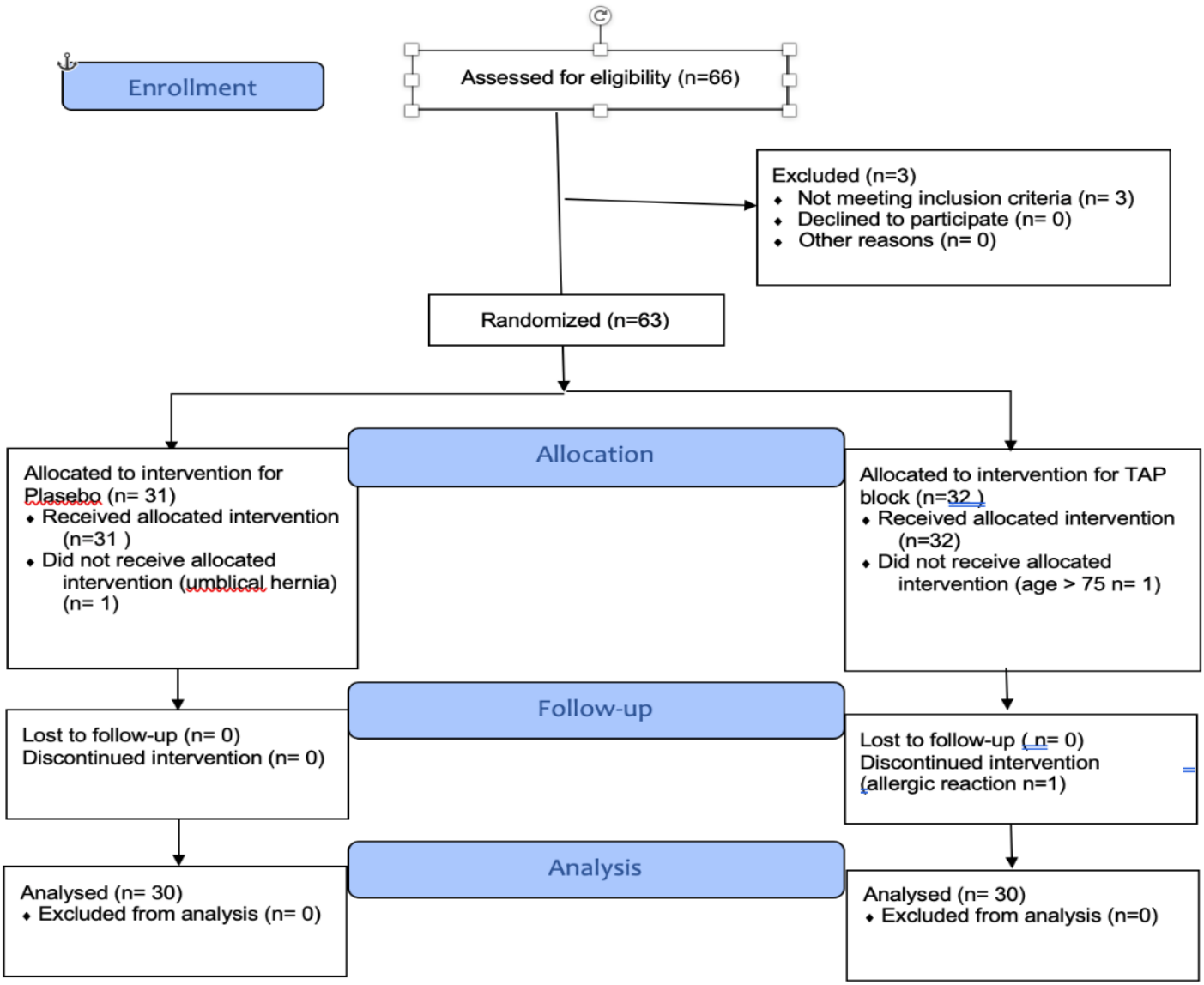

Figure 1
Consort Flow Diagram

Table 1
Demographic data

		Group C (n:30)	Group TAP (n:30)	p-value
Gender n (%)	Male	25 (83.3)	27 (90.0)	
	Female	5 (16.7)	3 (10)	b0.445
Age (year)	Mean±SD	52.27±16.03	54.40±13.85	
	Min-Max (Median)	20–72 (58)	30–79 (57)	a0.583
ASA (1/2/3)		10/15/5	7/18/5	b0.670
Operation	Mean±SD	58.77±24.09	60.50±14.28	
time (min)	Min-Max (Median)	20–115 (58)	35–100 (60)	a0.736

[a]Student's t-test [b]Chi-square test p<0.05 n=number of patients, Mean±SD Mean Standard Deviation, Min: Minimum, Max: Maximum, ASA: American Society of Anesthesiologists

Table 2
Total opioid (remifentanil) consumption in the groups

Remifentanil consumption amount (1ml=50µgr)	Group C	Group TAP	p
Mean±SD	4.56±1.66	3.25±2.23	0.012
Min-Max (Median)	1/8 (4)	1/7 (2)	

Remifentanil dose (50 mcg= 1ml)

Mean±SD Mean Standard Deviation Min: Minimum Max:Maximum

Table 3
Visual Analogue Scale (VAS) in the groups

Time		Group C	Group TAP	p-value
30. min	Mean±SD	3.77±1.50	2.87±1.38	0.019
	Min / Max (Median)	2.00/7.00 (3)	1.00/3.00(2)	
1. h	Mean±SD	4.10±1.42	2.83±1.09	< 0.05
	Min / Max(Median)	1.00/8.00 (5)	1.00/4.00 (3)	
4. h	Mean±SD	3.99±1.05	2.40±0.81	0.015
	Min / Max (Median)	2.00/8.00 (6)	1.00/5.00 (3)	
8. h	Mean±SD	4.7±1.31	1.80±0.81	0.01
	Min / Max (Median)	2.00/9.00 (6)	1.00/5.00 (2)	
12. h	Mean±SD	3.70±0.65	2.00±0.69	< 0.05
	Min / Max (Median)	2.00/6.00 (4)	1.00/5.00 (2)	
24. h	Mean±SD	2.20±0.61	1.00±0.67	< 0.05
	Min / Max (Median)	1.00/6.00 (3)	1.00/3.00 (1)	

Student's t-test p<0.05. Mean±SD Mean Standard Deviation, Min: Minimum, Max:Maximum, VAS: Visual Analogue Scale hr: hour. min:minute

The number of patients administered rescue analgesics was statistically significant lower in Group TAP than in Group C (p<0.05) (Tables 5). The rescue analgesic starting time was longer in Group TAP than in Group C (p=0.032) (Tables 6).

There was no significant difference in the number of patients experiencing postoperative nausea and vomiting (p>0.05) (Table 7). Bowel sounds were present in all patients. There was no sign suggestive of perforation.

4. Discussion

This prospective, randomized study investigated the analgesic efficacy of preincisional TAP block and its effects on hemodynamic parameters, and the intraoperative opioid comsumption amount and postoperative rescue analgesic starting time in patients undergoing unilateral inguinal hernia repair under general anesthesia.

In our study, intraoperative opioid requirement (total remifentanil dose consumed) and VAS scores were lower in the TAP block group at all measurement points. The need for rescue analgesics was higher in patients without non-TAP block. Similarly, we found that rescue analgesic starting time was longer in the TAP block group.

Postoperative pain is common among patients undergoing surgery, and approximately 70 percent of patients report pain intensity to be moderate or severe.[15] Pain management strategies employed before starting surgery with the aim of reducing the intensity of pain before and after surgery, and to prevent progression to the development of permanent chronic pain, are known as preemptive analgesia.[16] The most remarkable feature of preemptive analgesia is the initiation of antinociceptive therapy before surgical incision.[6] In the study by Çanakçı et al.[17], the TAP block applied for the purposes of preemptive analgesia was reported to provide effective intraoperative hemodynamic control and effective postoperative pain control, to decrease inflammation and surgical stress by decreasing the levels of proinflammatory cytokines TNF-α and IL-1β in the first postoperative 24 hours, and to exert immunomodulatory activity. The TAP block was performed before the surgical incision in the present study, and no difference was found in the hemodynamic data or BIS values of the groups.

In their study, Venkatraman et al.[18] reported that USG-guided TAP block provided adequate postoperative analgesia in patients undergoing inguinal hernia repair, while also decreasing the analgesic requirement and improving VAS scores, and. The procedure was also associated with fewer postoperative complications. Aveline et al.[19] reported ultrasound-guided TAP block to be superior to conventional iliohypogastric nerve blocks in the provision of pain relief and decreased opioid requirement. In their randomized study, however, Petersen et al.[20] reported that a unilateral TAP block performed in combination with a paracetamol or ibuprofen containing basic analgesic regimen in patients undergoing inguinal hernia repair showed no postoperative analgesic efficacy over a placebo or ilioinguinal nerve block with wound site infiltration.

Table 4

Perioperative BIS, HR, MAP and SpO2 values in the groups

Time		BIS			HR			MAP			SPO2		
		Group C	Group TAP	p	Group C	Group TAP	p	Group C	Group TAP	p	Group C	Group TAP	p
0.min	Mean±SD Min / Max (Median)	94.23±4.97 85/98 (97)	96.27±2.74 87/99 (98)	0.064	80.90±13.37 48/119 (80)	83.83±16.59 59/125 (78)	0.454	115.93±13.98 91/128 (104)	113.68±15.94 91/125 (111)	0.568	97.93±1.86 93/100 (98)	98.27±1.70 95/100 (99)	0.471
5. min	Mean±SD Min / Max (Median)	41.17±9.68 30/61 (37)	37.83±7.53 29/58 (36)	0.142	80.57±17.56 51/130 (80)	81.17±20.09 53/128 (79)	0.902	96.50±13.13 70/117 (95)	87.93±17.82 52/113 (91)	0.062	98.90±1.18 96/100 (99)	99.13±1.11 96/100 (100)	0.434
15.min	Mean±SD Min / Max (Median)	39.03±10.24 30/70 (37)	37.53±7.12 30/57 (38)	0.513	71.03±13.52 50/105 (70)	71.53±17.02 50/116 (63)	0.900	92.77±13.31 69/121 (92)	87.97±12.31 70/123 (86)	0.152	98.73±1.11 96/100 (99)	99.10±1.06 97/100 (99)	0.197
30. min	Mean±SD Min / Max (Median)	39.26±9.21 30/60 (39)	38.33±8.16 30/61 (37)	0.697	63.26±8.74 48/78 (63)	62.41±11.16 50/88 (60)	0.756	84.15±11.35 63/107 (84)	86.04±15.70 61/125 (81)	0.614	98.67±1.24 96/100 (99)	98.93±1.41 94/100 (99)	0.477
45. min	Mean±SD Min/Max (Median)	41.21±14.70 30/88 (39)	40.59±11.79 30/82 (40)	0.882	62.21±9.44 47/89 (63)	61.23±7.81 51/80 (61)	0.717	85.11±14.40 66/116 (83)	83.13±14.05 57/111 (85)	0.668	99.00±1.00 97/100 (99)	99.05±1.00 97/100 (99)	0.885
60. min	Mean±SD Min / Max (Median)	47.75±20.55 30/88 (41)	41.80±11.05 28/62 (40)	0.442	60.88±12.99 55/71 (65)	73.10±14.05 55/96 (68)	0.992	84.88±12.99 66/99 (87)	84.80±17.74 59/112 (85)	0.992	98.25±2.31 93/100 (99)	99.20±0.92 98/100 (99)	0.250
Cessation	Mean±SD Min / Max (Median)	88.23±4.95 81/98 (88)	88.63±3.68 81/95 (85)	0.161	77.00±13.82 49/107 (78)	88.60±26.26 49/118 (100)	0.932	111.87±16.10 78/123 (103)	88.60±26.26 49/118 (100)	0.991	98.40±1.40 94/100 (99)	98.90±1.37 94/100 (99)	0.169

Table 5
The number of rescue analgesic administrations according to time between groups.

Time		Group C	Group TAP	p-value
3. min	No	20 (67.7)	30 (100)	0.015
	Yes	10 (33.3)	0 (0.0)	
1. h	No	18 (60.0)	30 (100.0)	< 0.05
	Yes	12 (40.0)	0 (0.0)	
4. h	No	19 (63.3)	29 (97.7)	0.021
	Yes	11 (36.6)	1 (3.3)	
8. h	No	20 (66.7)	28 (93.3)	< 0.05
	Yes	10 (33.3)	2 (6.7)	
12. h	No	19 (63.3)	27 (90.0)	< 0.05
	Yes	11 (36.7)	3 (10.0)	
24. h	No	27 (90.0)	30 (100.0)	0.047
	Yes	3 (10.0)	0 (0.0)	

*Chi-square test *p<0.05. n=number of patients h: hours. min:minute

Table 6
Postoperative Rescue analgesic administration starting time in the groups

		Group C	Group TAP	p-value
Rescue analgesic starting time (h)	Mean±SD	2.15±2.59	4.45±2.51	0.032

Student's t-test p<0.05, Mean±SD Mean Standard Deviation

Table 7
Nausea and vomiting in the groups

Nausea and Vomiting (n)		Group C	Group TAP	p-value
30. min	No	29 (96.7)	30 (100)	0.313
	Yes	1 (3.3)	0 (0.0)	
1. h	No	29 (96.7)	30 (100.0)	0.236
	Yes	1 (3.3)	0 (0.0)	
4. h	No	29 (96.7)	30 (100.0)	0.313
	Yes	1 (3.3)	0 (0.0)	
8. h	No	30 (100.0)	30 (100.0)	
	Yes	0 (0.0)	0 (0.0)	-
12. h	No	30 (100.0)	30 (100.0)	
	Yes	0 (0.0)	0 (0.0)	-
24. h	No	30 (100.0)	30 (100.0)	-
	Yes	0 (0.0)	0 (0.0)	

*Chi-square test * p<0.05 n=number of patients h: hour. min:minute

There have been several meta-analyses reporting that paracetamol can reduce opioid consumption by 20 percent and to have fewer perioperative side effects.[6,21,22] There is also valuable evidence supporting the efficacy of the use of acetaminophen in combination with another non-opioid agent, such as a non-steroid anti-inflammatory drug or a COX-2 inhibitor, in an attempt to improve postoperative analgesia and reduce opioid consumption.[23] Similar to these reports, the patients in TAP block group in the present study received multimodal analgesia involving intravenous paracetamol infusion and tramadol where necessary for the treatment of postoperative acute pain, in addition to the preincisional TAP block. The number of tramadol HCl consumed in the group that underwent TAP block was lower and the rescue analgesic starting time was longer. In a study of 50 patients, Jain et al. [24] reported that the addition of a US-guided TAP block to the systemic administration of conventional analgesics resulted in a decrease in VAS scores and a rescue analgesic requirement. The authors also reported that early mobilization facilitated the early return of bowel sound, decreased the length of hospital stay and decreased the incidence of nausea and vomiting. They also reported a significant decrease in postoperative pain and opioid consumption in patients undergoing TAP block for laparoscopic intraperitoneal mesh repair. In their investigation of the effects of TAP block on sufentanil consumption and postoperative analgesia in patients undergoing laparoscopic cholecystectomy, El-Dawlaty et al.[25] administered 1 MAC sevoflurane and additional dose of sufentanil to patients in the two groups, based on hemodynamic data. They reported intraoperative sufentanil consumption to be significantly lower in the group that underwent the TAP block than in the non-TAP block group. Perioperative 1 MAC sevoflurane and remifentanil were used also in the present study. The total remifentanil dose was lower in the TAP block group than in the control group.

Undesired complications such as visceral perforation and pelvic hematoma can develop in rare cases during the delivery of TAP block[26,27]. No major complication was observed in the present study patients. The use of US guidance while performing the TAP block increases the safety of the procedure.

5. Conclusions

It was found in the present study that preincisional TAP block in patients undergoing unilateral inguinal hernia repair under general anesthesia reduced perioperative total opioid consumption amount and prolonged rescue analgesic starting time, while decreasing the number of administrations of rescue analgesic.

We concluded that preincisional TAP block is a safe and effective analgesia technique for postoperative pain control in patients undergoing unilateral inguinal hernia repair and our findings should be supported by advanced controlled randomized studies.

4.1. Limitations

The present study was limited by its short follow-up duration of only 24 hours and its disregard of operation times, recovery times, time to discharge, total rescue analgesic consumption and cost-effectiveness. In addition, only preincisional TAP block was examined, and so the efficacy of postincisional TAP block was not investigated.

Acknowledgements

None.

Statement of ethics

This study was approved by Ümraniye Training and Research Hospital with the protocol number (decision number 35 dated March 11, 2021)

Conflict of interest statement

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

Funding source

The authors declared that this study received no financial support.

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