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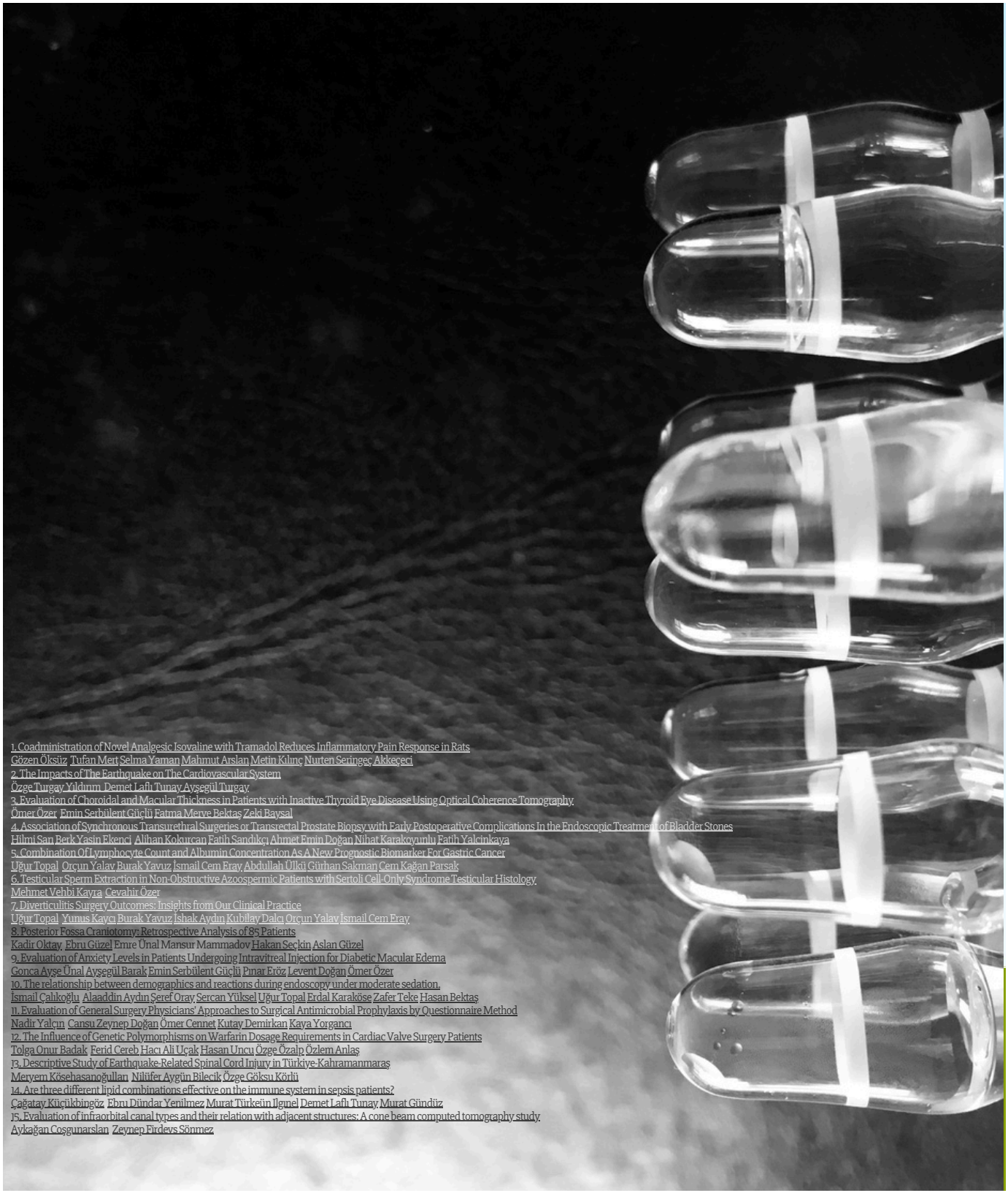

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ABSTRACTED & INDEXED

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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).
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• 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.

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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.
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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.
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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.

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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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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.
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- 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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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
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References should contain the full surnames of the authors and the first letters of their names.
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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
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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.
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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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CONTENTS

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Coadministration of Novel Analgesic Isovaline with Tramadol Reduces Inflammatory Pain Response in Rats

Gözen Öksüz[1], Tufan Mert[1], Selma Yaman,[1]
Mahmut Arslan[1], Metin KIlınç[1], Nurten Seringeç Akkeçeci[1]

1 Sütçü İmam University Medical Faculty, Department of Anesthesiology, Kahramanmaras, Türkiye

Abstract

Aim: Isovaline is a new and promising analgesic with an antinociceptive effect and, unlike μ-opioid agonists, interacts with aminobutyric acid receptors without causing sedation or respiratory depression. In this study we aimed to investigate whether subcutaneous application of isovaline alone has anti-hyperalgesic, anti-allodynic, and anti-edema effects on inflammatory pain experimentally induced using carrageenan.

Methods: In this study, isovaline, tramadol, and the combination of isovaline and tramadol were subcutaneously administered to rats with carrageenan-induced inflammation of the hind paws. Hyperalgesia in response to thermal stimuli and allodynia in response to mechanic stimuli were assessed by using a thermal plantar test and a dynamic plantar aesthesiometer, respectively.

Results: The administration of subcutaneous isovaline 400 mg/kg and tramadol 4 mg/kg combination effect was higher than the other groups on latencies and thresholds ($p<0.001$, $p<0.001$, respectively). Additionally, isovaline 400 mg/kg administration caused a statistical difference in latencies when compared with carrageenan, isovaline 200 mg/kg, and tramadol 2 mg/kg groups (($p<0.001$, $p<0.001$, $p<0.001$, respectively) and a statistical difference in thresholds when compared with carrageenan, tramadol 2 mg/kg and tramadol 4 mg/kg groups (($p<0.001$, $p<0.001$, $p=0.008$, respectively). When isovaline 200 mg/kg was used in combination with tramadol 2mg/kg, the latencies and thresholds were significantly higher than either treatment alone tramadol 2 mg/kg and carrageenan groups ($p\leq 0.001$, $p<0.001$, respectively).

Conclusions: The results of this study demonstrated that the subcutaneous administration of isovaline had analgesic efficacy and was effective in combination with tramadol when used for the treatment of inflammatory pain.

Keywords: *Inflammatory pain, isovaline, tramadol, paw edema*

1. Introduction

Tissue infection, trauma, and injury, which can cause the release of inflammatory mediators, often result in inflammatory pain[1,2]. Inflammatory mediators, such as potassium, serotonin, substance P, nitric oxide, bradykinin, and prostaglandins are responsible for the development of nociceptive hypersensitivity[3,4]. Analgesic medications allow us to control pain via the central or peripheral mechanisms[5,6]. The opioids currently used in the treatment of pain may result in complications during acute or chronic administration, such as sedation and respiratory depression[7,8].

Corresponding Author: Gözen Öksüz, gozencoskun@gmail.com, Received: 11.01.2023, Accepted: 26.06.2024, Available Online Date: 30.06.2024 Cite this article as: Öksüz G, Mert T, Yaman S, et al. Coadministration of Novel Analgesic Isovaline with Tramadol Reduces Inflammatory Pain Response in Rats. J Cukurova Anesth Surg. 2024; 7(2): 52-8. https://doi.org/10.36516/jocass.1232464

Tramadol hydrochloride ((1RS, 2RS)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol HCl) is a weak μ-opioid receptor agonist, which has both analgesic and adjuvant efficacies and is used commonly as multimodal analgesia for the treatment of postoperative pain. It inhibits the pre-synaptic reuptake of noradrenaline (NA) and serotonin (5-HT) while stimulating the release of 5-HT[9,10]. Studies have reported that the peripheral administration of tramadol has antinociceptive and anti-inflammatory effects[11-13]. As tramadol does not cause respiratory depression, these medications are preferred in treatments; however, their analgesic efficacies are dose-dependent. This has led to several challenges, particularly during attempts to cope with pain, and encouraged the search for new analgesics.

Isovaline (2-amino-2-methyl butanoic acid) is a new and promising non-proteinogenic amino acid that displayed analgesic efficacy and no respiratory depression or effects on the central nervous system

in animal experiments[14,15]. Whitehead et al. reported that the administration of isovaline with propofol was observed to be like fentanyl with propofol for anesthesia in mice[16]. Studies have shown that isovaline has an antinociceptive effect and unlike μ-opioid agonists, interacts with aminobutyric acid (GABA) receptors without sedation and respiratory depression. As isovaline activates GABA and group II metabotropic glutamate receptors, the coadministration of isovaline with an opioid may provide a stronger analgesic effect[17,18].

This study aimed to investigate whether subcutaneous application of isovaline alone has anti-hyperalgesic, anti-allodynic, and anti-edema effects on inflammatory pain experimentally induced using carrageenan.

2. Materials and methods

2.1. Animals

The Medical Sciences Experimental Research Centre of KSU provided male Wistar rats (240–260 g); six rats were used in each experimental group and handled for a minimum of 2 weeks before the experiments. The study was approved by the animal research committee of KSU (2016/06-04). All procedures were performed by the guidelines of the IASP (International Association for the Study of Pain) Committee for Research and Ethical Issues. Assessment of thermal latency and mechanic allodynia were accepted for primary outcomes.

The rats were housed in a sound-proofed room in regulated conditions (temperature, 22–24 °C; relative humidity, 40%–60%; 12 h (06:00–18:00) of light and 12 h of darkness) and fed with ad libitum water and food pellets. The air was changed 8 to 12 times every hour for the duration of the study. The number of animals used was kept to a minimum and each animal was used once.

2.2. Carrageenan-induced paw inflammation

Inflammation was induced by intraplantar injections of carrageenan (lambda carrageenan, Sigma-Aldrich Chemie GmbH, Munich, Germany) into the hind paws of rats. Carrageenan is ideal for the investigation of the indicators of inflammatory pain and anti-inflammatory factors and is often used as a medium for assaying inflammation during the development of new therapies. After collection of the baseline measurements, the rats were administered sevoflurane (1%–2% in oxygen) anesthetic. The right rear paw was administered an intraplantar injection of 0.1 mL of 2% (w/v) carrageenan by using a 26-gauge needle on a 1 mL syringe; for the control group, an equal volume of saline solution was administered via the same method.

2.3. Experimental Procedures and Drugs

As stress can skew measurements of the nociceptive threshold, the experiments were conducted by the same researcher in a quiet testing room close to the rat colony room to minimize the stress caused by the laboratory conditions. The rats were placed in the colony room 2 weeks before the experiments and were acclimatized to the experimental conditions for 1 week. The animals were handled by institutional guidelines. The researcher accustomed the rats to being handled by holding them a minimum of three times a day, for 20–30 s, for 3 days before the experiment so that on the day of the experiment, the rats did not react adversely to handling. The rats were acclimated to the experimental setup by the introduction of the rats to the experimental apparatus for a minimum period of 30 min, three times per day, for 3 days before the experiment. Once the rats were settled, baseline measurements were collected from all animals 1 h before the injection of the hind paw to allow sensor calibration.

As the experiment was conducted under blinded conditions, the measurements were all collected without the researchers' knowledge of the animal treatments.

2.4. Drugs

S-isovaline monohydrates were purchased from ACROS Organics (Geel, Belgium). The other drugs used in the experiments were purchased from Sigma-Aldrich (Munich, Germany). Isovaline or saline, in a total volume of 1 mL for subcutaneous (SC) was administered at 60 min after the carrageenan or saline injection. For the vehicle-only control groups, equal volumes of medium were injected subcutaneously. The pilot studies were used to determine the appropriate doses of drugs; S-isovaline monohydrates (200 mg/kg and 400 mg/kg SC) or tramadol (2 mg/kg and 4 mg/kg SC) were injected into the rats.

2.5. Sensory Testing Procedure

Sensory abnormalities, such as hyperalgesia in response to thermal stimuli and allodynia in response to mechanical stimuli, were assessed by using a thermal plantar test and a dynamic plantar aesthesiometer, respectively. For the daylight phase of the cycle, the tests were conducted on groups of six animals each in a quiet room kept at 23°C–25°C between 09:00 and 13:00.

2.6. Assessment of Thermal Latency

A system to measure delayed paw withdrawal in response to thermal stimulation (Commat, Ankara, Turkey) was used to detect if thermal hyperalgesia was present [19]. The rats were placed in separate boxes made of plexiglass measuring 10×20×24 cm. The boxes were set on a transparent glass base. After 15 min of acclimation, a radiant heat source attached to a moveable arm underneath a pane of glass was maneuvered into place to apply heat to the mid-plantar region of the rear paws. The idle intensity of the heat source was set to 1% of the maximum intensity. The purpose of the heat source was to concentrate the thermal stimulus on the correct part of the rear paw. Before any baseline latencies could be set, the light intensity was standardized, and it was maintained for the duration of the experiment. When set to deliver infrared stimulus at 25% of maximum intensity, the apparatus induced withdrawal of the paw after 10–12 s.

The mechanism was triggered by the withdrawal of the paw by the rat when the pain was felt. As the paw was pulled back, a beam of light was broken; this switched off the photocell and the infrared generator, and the timer, which measured the delay in withdrawal. This method for the measurement of paw withdrawal was accurate to 0.1 s. The thermal source automatically switched off after 25 s (cut-off delay) if the paw was not withdrawn to minimize animal suffering. Each rat had both rear paws tested three times for baseline determination and three times during an hour-long testing period. The tests on each rear paw were conducted 5 min apart and the average of three results was calculated. The values refer to the time before the paw was withdrawn.

2.7. Assessment of Mechanical Allodynia

The threshold before the rat withdrew its paw in response to mechanical stimulation was measured to determine mechanical allodynia. To measure the rat's sensitivity to benign, light touches of its paws, a dynamic plantar anesthesiometer was used. This is a mechanical version of the von Frey hair test (Ugo Basile, Comerio, Italy). Mechanical allodynia was considered present if there was a significant reduction in the threshold at which the rat withdrew its paw in response to mechanical stimulation [19].

The used rats were in separate plexiglass boxes measuring 10×20×24 cm placed on a steel mesh surface. Using a metal rod measuring 0.5 mm in diameter, force (increasing at 2.5 g/s) was constantly applied to the plantar region of the rear paw until the rat lifted its paw away, at which point the threshold for paw withdrawal (in grams) was recorded digitally. The mechanical stimulus automatically cut off at 50 g to prevent excessive tissue damage. Each paw was tested at least three times to establish a baseline and again over the 1-hour test period with a 5 min interval between each test.

The average for these tests was used for analysis. The values presented refer to the threshold for withdrawal of the paw.

2.8. Assessment of Paw Edema

After the sensor tests were completed, the mass of each paw was measured, and tissue samples were collected 210 min after the first injection was administered. The rats were then anesthetized with a light dose of sevoflurane and killed by decapitation. The paws were amputated at the ankle and measured to determine the mass in grams.

2.9. Statistical Analysis

The statistical analysis was conducted with SPSS 19 for Mac (IBM SPSS Statistics, Chicago, IL). The data are reported as mean group values ± SD (standard deviation). The results were assessed for normality with the Shapiro-Wilk test and equality of variance with the Mauchly test of sphericity and the Levene test. The data were analyzed by a repeated measure ANOVA followed by the Bonferroni test for between-group comparisons. We analyzed the interaction between 2 factors (the effects of time after drug administration and time by group interaction). When the Mauchly test was significant, normality and equality of variance were not violated in groups and the Greenhouse-Geisser adjustment was performed to determine the statistical significance of the factors (time after treatment and time group interaction). A p-value of <0.05 was considered statistically significant.

2.10. Sample Size

A priori sample size was estimated from paw edema. The pilot study results were analyzed by the One-Way ANOVA test. The sample size was determined based on the difference between paw edema in the carrageenan-induced inflammatory pain model. At one time point (240 minutes), the change in edema (Mean 45-77, SD: 12) in the number of 6 animals per group provided sufficient statistical power (1 - β ≥ 0.95). Study statistical power was confirmed via a sensitivity analysis performed with G*Power 3.1.9.2 software (University of Dusseldorf; http://www.gpower.hhu.de/en.html).

3. Results

3.1. Effects of Subcutaneous Administration of Isovaline on Latencies and Thresholds in a dose-dependent manner

Before the injections (Saline, Isovaline 200 mg/kg, and 400 mg/kg), no statistically significant differences were found between the basal latencies and thresholds. (p>0.05) We used a repeated measure ANOVA followed by Bonferroni's correction to analyze the significance of the data. There are statistically significant differences produced by time and by the time*group interactions (p<0.001) on latencies. Isovaline 200 mg/kg and 400mg/kg affected latencies in the first hour when compared with saline group latencies (p=0.003, p=0.001, respectively) (Figure.1a).

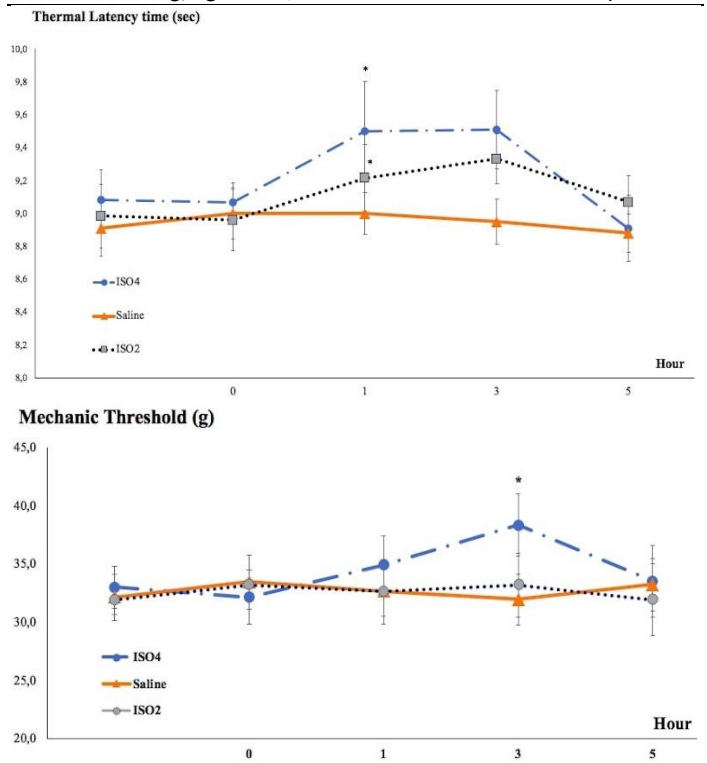
No significant differences were produced by time (p=0.116) however by time*group interaction is analyzed a significant difference was found (p=0.025) on thresholds. Isovaline 400mg/kg had a transient effect on the threshold at the third hour (p=0.010) (Figure.1b).

3.2. Effects of Subcutaneous Administration of Isovaline and Tramadol Combinations on Latencies in Carrageenan-Induced Inflammatory Pain

We used a repeated measure ANOVA test followed by Bonferroni's correction to analyze the significance of the data. Statistically significant differences were found in latencies produced by time and time*group interaction (p<0.001). When the post hoc test was used, the administration of isovaline 400 mg/kg and tramadol 4 mg/ kg combination effect was higher than the other groups (CARR, ISO4, TRA4, TRA2, TRA2ISO4) on latencies ((at 1. hour p<0.001, p<0.001, p<0.001, p<0.001, p<0.001, respectively; at 3. hour: p<0.001, p<0.001, p<0.001, p<0.001, p<0.001, respectively; at 5. hour: p<0.001, p=0.001, p<0.001, p<0.001, p<0.001, respectively).

Figure 1a-1b

Comparison of subcutaneous isovaline 200mg/kg (ISO2), isovaline 400mg/kg (ISO4), and Saline efficacies in healthy rats.



Dose-dependent changes in paw withdrawal latencies (a) and mechanical thresholds (b) Each point represents the mean value of six rats, and vertical bars indicate SD Statistical evaluation was performed by repeated measure ANOVA with Turkey multiple comparison post hoc test. The results were assessed for normality with the Shapiro-Wilk test and equality of variance with the Mauchly test of sphericity and Levene test. Statistical significance (P < 0.001 repeated measure ANOVA followed by Tukey HSD test) followed as determined by comparison with the curve of the control group*

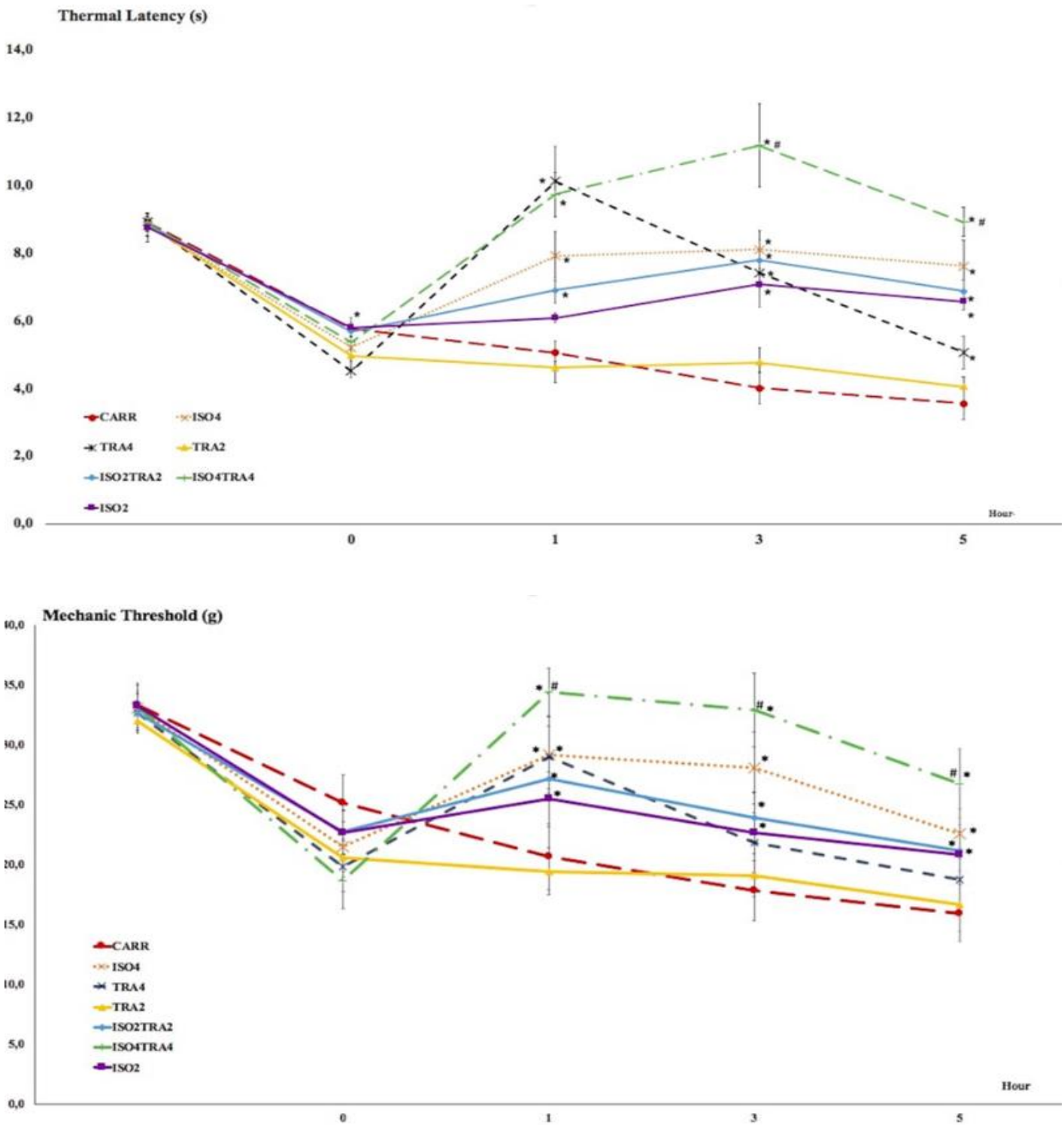
Additionally, isovaline 400 mg/kg administration caused a statistically significant difference in latencies when compared with carrageenan, isovaline 200 mg/kg, and tramadol 2 mg/kg groups. (p<0.001, p<0.001, p<0.001, respectively). When isovaline 200 mg/kg was used in combination with tramadol 2mg/kg, the latencies were significantly higher than either treatment alone tramadol 2mg/kg and carrageenan groups (p<0.001, p<0.001, respectively). There is no significant difference in the latencies between the administration of isovaline 200 mg/kg and tramadol 2 mg/kg combination and tramadol 4mg/kg alone or isovaline 400 mg/kg alone (p>0.05) (Figure.2a).

3.3. Effects of Subcutaneous Isovaline and Tramadol Combinations on Thresholds in Carrageenan-Induced Inflammatory Pain

We used a repeated measure ANOVA test followed by Bonferroni's correction to analyze the significance of the data. Statistically significant differences were found on thresholds produced by time and time*group interaction (p<0.001). When the post hoc test was used, the administration of isovaline 400 mg/kg and tramadol 4 mg/kg combination effect was higher than the other groups (CARR, ISO4, TRA4, TRA2, TRA2ISO4) on thresholds (at 1. hour p<0.001, p=0.011, p=0.007, p<0.001, p<0.001, respectively; at 3. hour: p<0.001, p=0.035, p<0.001, p<0.001, p<0.001, respectively; at 5. hour: p<0.001, p=0.046, p<0.001, p<0.001, p=0.002, respectively).

Figure 2a-2b

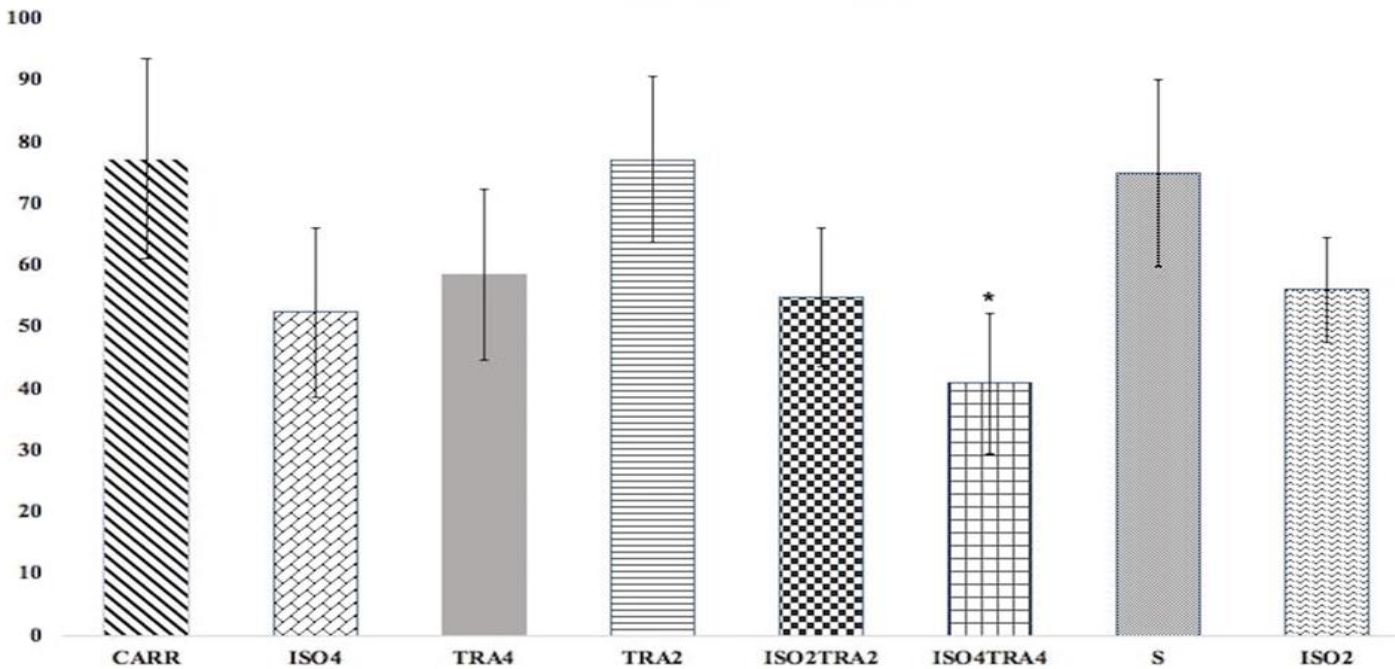
Time course of the paw withdrawal latencies



*Time course of the paw withdrawal latencies (a) and mechanical thresholds (b) of groups were administrated subcutaneous Isovaline 400 mg/kg (ISO4), TR4 (Tramadol 4mg/kg), TR2 (Tramadol 2mg/kg), Isovaline 200 mg/kg (ISO2), ISO2TR2 (Isovaline 200mg/kg coadministration with Tramadol 2mg/kg), ISO4TR4 (Isovaline 400mg/kg coadministration with Tramadol 4mg/kg) in Carrageenan (CARR) induced rats. Each point represents the mean value of six rats, and vertical bars indicate SD. Statistical evaluation was performed by repeated measure ANOVA with Turkey multiple comparison post hoc test. The results were assessed for normality with the Shapiro-Wilk test and equality of variance with the Mauchly test of sphericity and Levene test. Statistical significance (*P <0.05, repeated measure ANOVA followed by Tukey HSD test) followed as determined by comparison with the curve of the CARR group. #P <0.05 indicates significant differences as compared to all groups.*

Figure 3

Change in paw mass(%)



*One time point (240 minute after carrageenan injection) of the paw edema of groups were subcutaneous Isovaline 400 mg/kg (ISO4), TR4 (Tramadol 4mg/kg), TR2 (Tramadol 2mg/kg), Isovaline 200 mg/kg(ISO2), ISO2TR2 (Isovaline 200mg/kg coadministration with Tramadol 2mg/kg), ISO4TR4 (Isovaline 400mg/kg coadministration with Tramadol 4mg/kg), Saline (S) in Carrageenan (CARR) induced rats. Each point represents the mean value of six rats, and vertical bars indicate SD. Statistical significance (*P ≤ 0.001 one-way ANOVA followed by Tukey HSD test) followed as determined by comparison with the curve of the CARR group.*

Additionally, isovaline 400 mg/kg administration caused a statistically significant difference in thresholds when compared with carrageenan, tramadol 2 mg/kg, and tramadol 4 mg/kg groups (p<0.001, p<0.001, p=0.008, respectively). When isovaline 200mg/kg was used in combination with tramadol 2 mg/kg, the thresholds were significantly greater than treatment alone tramadol 2 mg/kg and carrageenan groups (p≤ 0.001, p<0.001, respectively). No significant difference was found on the threshold between the administration of isovaline 200 mg/kg tramadol 2 mg/kg combination and tramadol 4 mg/kg alone or isovaline 400 mg/kg and isovaline 200 mg/kg alone groups (p>0.05) (Figure.2b).

3.4. Effect of the Combination of Subcutaneous Isovaline and Tramadol on Carrageenan-Induced Paw Edema

Carrageenan injection caused paw edema in rats. One Way ANOVA test detected a significant difference in the carrageenan-injected paw mass after 240 min induction of inflammation between groups (p<0.001). Isovaline 400 mg/kg and tramadol 4 mg/kg combination produced a significant reduction of edema when compared with tramadol 2 mg/kg and saline treatment groups (the Tukey post hoc p=0.001; Figure 3).

4. Discussion

In this study, we found administration of isovaline 400 mg/kg alone and tramadol 4mg/kg alone effective on latencies and thresholds. The highest effect on latencies and thresholds was found when isovaline 400 mg/kg and tramadol 4mg/kg combination was administered. When isovaline 200 mg/kg was used in combination with tramadol 2 mg/kg, the latencies and thresholds were significantly higher than either treatment alone tramadol 2 mg/kg. The combined use of subcutaneous isovaline and tramadol enhanced the anti-hyperalgesic and anti-allodynic effects compared with the administration of the individual treatments.

Previous studies have suggested that isovaline may be a novel promising analgesic for anesthesia[20]. In an investigation of the anesthetic and analgesic efficacy of isovaline, the intravenous (IV) 50% effective dose (ED) was found to be 76 mg/kg and 500 mg/kg IV isovaline was found to significantly reduce total licking in the formalin test[15]. Whitehead et al. reported that the use of isovaline in combination with propofol for general anesthesia and “awake” sedation was safer than the propofol-fentanyl combination. This study concluded that isovaline was a suitable agent for total intravenous anesthesia and awake sedation. Isovaline alone or in combination with propofol did not cause respiratory suppression and propofol did not augment the effects on the central nervous system[16].

Both the R and S isomers of isovaline have anti-allodynic effects and neither shows acute toxicity[15]. It has been observed that no central nervous system depression was seen after the peripheral application of isovaline at a dose 10-fold higher than that applied for allodynia; even when a 20-fold higher dose was applied, no change in body temperature was observed. It was found to be safer than baclofen, which affects the GABAB receptor[21]. The tolerability of high doses of isovaline is an advantage, as it has a low potency; however, studies have been conducted on R-isovaline, S-isovaline, aminoisobutyric acid (AIB), the 1-amino-1-cyclobutane carboxylic acid (ACBC), which are isovaline molecules with different structures. Fung et al.[22] reported the antinociceptive effects of S-isovaline, the R-stereoenantiomer, and its cyclized isomer (ACBC) following

systemic administration. Both R-isovaline, S-isovaline, and ACBC decreased the response in phase II of the formalin foot assay without a loss of efficiency on the rotarod in mice.

As the potency of isovaline is low and because of the low side-effects such as respiratory depression and nausea and vomiting, it was thought that it could be more effective with an opioid, so in this study, the efficacy was evaluated of the combined use of isovaline and tramadol[16]. In addition to the efficacy of isovaline compared to the control group, when it was used together with tramadol, it was found to be more effective than either tramadol or isovaline used alone.

A previous study investigating the combined use of tramadol and baclofen found that baclofen enhanced tramadol's antinociceptive effect.[23] Like isovaline, baclofen affects the GABAB receptor[24]. Isovaline provides its analgesic efficacy through action on the GABAB receptors in the cutaneous tissue containing keratinocytes and nerve endings [21,25]. GABAB receptors on small primary afferent neurons with Aδ and C fibers regulate nociceptive transmission in the peripheral tissues and the spinal cord. GABAB receptors are G-protein coupled receptors and they have the capacity for presynaptic and post-synaptic inhibition[26]. Through the G-proteins, isovaline either increased the permeability to K^+ or suppressed voltage-gated Ca^{2+} channels [27].

Whitehead et al.[21] have reported that the subcutaneous application of isovaline was effective in the osteoarthritis (OA) model; however, the OA model was not inflammatory but had a degenerative status. The improvement in the degenerative OA model was attributable to the activation of the GABAB receptors present in the synovial fluid in the knee joint[28]. In this study, we prefer subcutaneous administration of isovaline and tramadol because subcutaneously administered substances are usually absorbed in a slower rate compared to other parenteral routes, and this provides a long-lasting effect. Although the exact absorption mechanism is not fully understood, it is considered that minimal lymphatic absorption occurs via the penetration of macromolecules to small capillaries in the subcutaneous tissue[29]. In addition, the effect of isovaline on GABAB receptors that are considered to be present in the subcutaneous tissue may explain the subcutaneous administration of isovaline effects[28].

The antinociceptive mechanism of tramadol results in μ-opioid receptor activation and inhibition of the reuptake of serotonin/noradrenalin via a non-opioid route. In studies made with tramadol, μ-opioid receptor activation and the inhibition of the reuptake of serotonin and noradrenalin resulted in a reduction in the development of hyperalgesia in carrageenan-induced inflammation[30,31].

In this study, the combination of isovaline and tramadol significantly reduced paw edema induced by carrageenan. The combination of the two treatments resulted in a greater reduction in paw edema than the use of either treatment individually. Therefore, it can be considered that the combination of isovaline and tramadol exerted anti-inflammatory efficacy through a different mechanism.

Further studies are planned to examine the combined use of isovaline with other analgesics. The current study may be limited as it was not possible to combine isovaline with different analgesic drugs such as opioids or NSAID.

5. Conclusion

In conclusion, the results obtained in this study demonstrated that the subcutaneous administration of isovaline alone had anti-hyperalgesic, anti-allodynic, and anti-edematous efficacy on inflammatory pain induced experimentally by using carrageenan. Furthermore, when isovaline was used together with tramadol, the anti-hyperalgesic and anti-allodynic effects were enhanced. Isovaline has been reported to have analgesic efficacy without causing respiratory depression; as a new drug, it may be effective in combination with tramadol, which is a weak opioid with few side effects when used for the treatment of inflammatory pain.

Statement of ethics

The study was approved by the animal research committee of KSU (2016/06-04).

Conflict of interest statement

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

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Author Contributions

All authors contributed equally to the article. All authors read and approved the final manuscript.

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The Impacts of The Earthquake on The Cardiovascular System

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Abstract

Aim: Various physiological and psychological effects of earthquakes can be seen on the human body, even without a direct physical impact from the earthquake. Both the experience of the earthquake process and the earthquake-related subsequent life changes cause stress through the activation of the sympathetic and parasympathetic systems in the body. This stress can affect various physiological processes, including the cardiovascular system. In this review, the effect of earthquakes on the cardiovascular system was aimed to be discussed in line with the available evidence.

Discussion: There are studies showing that natural events such as earthquakes increase the incidence of adverse cardiac events, such as myocardial infarction, heart failure, hypertension, and sudden cardiac death, or cause existing cardiac diseases to worsen during these periods. However, there are also some evidences with conflicting results. Therefore, the effect of earthquakes on cardiovascular diseases has not been clearly demonstrated yet.

Conclusions: Even survivors of earthquakes without physical injury are exposed to stress secondary to both internal and external factors. Studies indicate that individuals who are involved in the earthquake process may have adverse effects on cardiovascular health in the short and long term. Therefore, it is important to take necessary precautions and create appropriate conditions, especially in people with cardiovascular disease..

Keywords: *Earthquake, myocardial infarction, hypertension, sudden cardiac death.*

1. Introduction

The phenomenon of shaking the surface of the Earth through which the vibrations that occur suddenly due to fractures in the earth's crust spread as seismic waves is called an earthquake. Earthquake is an unavoidable natural event.[1] Since the formation of the world, earthquakes have occurred consecutively in seismically active regions, resulting in the destruction of millions of people and their shelters. Even if individuals who have experienced the earthquake process survive the process without physical injury, it is inevitable that there will be psychological effects. These individuals have to cope with the injuries and deaths of not only their families but also their friends and relatives, and they have to stay in emergency shelters and small-scale temporary housing or their relatives' homes for days or months.[2] For these reasons, individuals experiencing the earthquake process are exposed to acute and subacute psychological stress.[3]

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Stress affects the autonomic nervous system, hypothalamus-pituitary-adrenal axis by causing an allostatic load in the body in the long term and this causes effects on the cardiovascular, metabolic and immune systems. Being exposed to constant stress also causes less or more activation in the allostatic system, leading to disruptions in body regulation.[4] In other words, stress can harm the body by affecting the body physiology.[5] The magnitude of the threat, or the severity perceived by the individual, determines the magnitude of the individual's stress response to internal or external challenges.[4] Emotional or physical stress can affect acute and chronic diseases.[6-10] Unexpected natural events such as earthquakes can cause cardiovascular events by causing acute, subacute and chronic stress.[3] In this review, we aimed to compile the effects of the earthquake on the cardiovascular system.

1.1. Effect of earthquakes on acute coronary syndrome

Myocardial infarction is one of the most important causes of mortality and morbidity. In addition to well-known risk factors for myocardial infarction such as diabetes mellitus, hypertension, smoking, factors such as winter season, infections, physical exertion, insomnia and nervousness can also trigger myocardial infarction.[11-14] Studies draw attention to the fact that unexpected natural events can also trigger myocardial infarction.[15,16] There are conflicting

results in studies investigating the relationship between earthquakes and acute coronary syndrome.

The Great East Japan Earthquake with a magnitude of 9.0 and subsequent tsunami on March 11, 2011, severely damaged the region. During this period, the incidence of acute coronary syndrome in Fukushima Prefecture was studied. While no increase was observed in the incidence of acute coronary syndrome in all districts in this study, an increase was observed in the incidence only in Iwaki district in the subgroup analysis.[17] In a study conducted in patients with ST-elevation myocardial infarction in Iwate Prefecture, when the patients during the 2011 earthquake and the patients in the same time period in 2010 were examined, it was stated that there was no difference in the number of patients presenting with myocardial infarction, but the rate of percutaneous coronary intervention decreased and in-hospital mortality increased.[16] Another study conducted in Miyagi Prefecture showed that acute coronary syndromes increased in the early period but tended to decrease after 2-3 weeks.[18] Tanaka et al.[19] reported that the incidence of acute coronary syndrome increased in the first 4 weeks after the earthquake and then returned to its normal course. This study also examined the aftershocks of the main earthquake and the incidence of acute coronary syndrome during this period. As a result, it was seen that there is a positive correlation between seismic scale and admissions due to acute coronary syndrome.[19] In a single-center study by Nozaki et al.[20], it was stated that there was a significant increase in patients with acute coronary syndrome who applied to the emergency department when compared to previous years. Again, another study conducted in Iwate Prefecture compared the years 2009-2010 before the earthquake with the earthquake period and afterwards until 2014, and in this study, the areas affected by the earthquake and tsunami were divided into high impact zone and low impact zone. In this study, the number of non-fatal myocardial infarctions did not change according to years in both the high impact zone and the low-impact zone. The number of fatal myocardial infarctions did not change over the years in the low-impact zone. However, while fatal myocardial infarction increased significantly in the high impact zone compared to the predisaster period, this significant difference continued in the following 2012-2014 years.[21] In some studies conducted during the Hanshin-Awaji (1994), Athens (1981), The Noto Peninsula (2007) earthquakes, it was found that hospital admissions secondary to acute coronary syndrome increased after the earthquake.[22-24] When the relationship between the Newcastle earthquake (1989) and the incidence of myocardial infarction was examined, a statistically significant increase was not found in terms of fatal and non-fatal myocardial infarction, although there was a numerical increase.[25]

Brown et al.[26], in their study published with the hypothesis that the earthquake time and being awake or asleep may be important in acute coronary syndrome, compared the 1989 Loma Prieta and 1994 Northridge earthquakes; they suggested that the incidence of acute myocardial infarction when people were awake in the Loma Prieta earthquake at 05.04 pm was lower than the Northridge earthquake which occured at 04.31 am. A similar result was found in the Christchurch earthquakes. In the Christchurch earthquake, which happened at 4.36 am in 2010, the number of applications due to ST elevation myocardial infarction increased in the first two weeks, but a similar pattern was not found after the earthquake at 12.51 pm in 2011.[27]

The intense stress caused by earthquakes can activate the sympathetic system and the renin-angiotensin aldosterone axis, leading to myocardial damage and cardiac adverse outcomes. Sympathetic activity triggered by mental stress may trigger myocardial ischemia, especially in individuals with basal coronary artery disease.[13,28] In addition, interrupting antiischemic or antiaggregant treatment may lead to an increase in the incidence of acute coronary syndrome in the early post-earthquake period, as patients using drugs for coronary artery disease may have problems in accessing the drug after the earthquake. In the long term, it can be expected that there will be a chronic stress environment in earthquake survivors as they lose their relatives and accommodation opportunities. Studies have shown that there is an increase in waist circumference, body-mass index, weight, Hemoglobin A1c levels, decrease in HDL levels, deterioration in physical activity, mental health and socioeconomic status, especially in those who had to relocate after the earthquake.[2,29] Worsening of cardiovascular risk factors may also lead to increases in cardiovascular diseases in the long term.

1.2. Effect of earthquakes on congestive heart failure

When Nozaki et al.[20] compared the congestive heart failure patients admitted to the emergency department in the 3-week period following the 2011 Great East Japan Earthquake with the number of patients admitted in the same weeks in 2009 and 2010, they found a significant increase in the number of patients presenting with this diagnosis after the earthquake. In their study, Aoki et al.[18] showed that admissions to hospital with heart failure increased after the earthquake and that the applications entered a decreasing trend only in the 6th week of the event. Major events such as earthquakes can activate the sympathetic system and cause high blood pressure and heart rate.[30,31] In addition, during this period, the habits of patients such as eating and salt intake change due to unsuitable conditions.[18] In addition, during this period, it becomes difficult for patients with heart failure to access the drugs they regularly use. Apart from these, infectious diseases may increase due to the deterioration of accommodation opportunities, and the possibility of decompensation of heart failure patients increases with increasing infections.[32] For these reasons, hospital admissions of heart failure patients can be expected to increase after major natural disasters. After natural disasters, if suitable accommodation environments, proper nutrition, access to medicines, and hygienic environment are provided, worsening due to heart failure will be prevented.[33]

1.3. Effect of earthquakes on hypertension

Disasters are a serious source of stress for the body. With stress, physiological mechanisms are activated in the body, the sympathetic system and hypothalamic-pituitary-adrenal axis are activated, and the release of catecholamines and cortisol in the blood increases.[34] With this mechanism, an increase in blood pressure and an increase in hypertension and related cardiovascular events are expected in individuals under stress.[35]

In a study conducted during the Hanshin-Awaji earthquake, it was observed that hypertension patients with normally controlled blood pressure had high blood pressure in the 7-14 days after the earthquake, but regressed to the normal limits in the following 4-6 months.[36] Nishizawa also stated that blood pressure increase is transient after earthquakes and it mostly return to normal levels after the fourth week.[37] The post-earthquake elevation in blood pressure may be permanent in the elderly, those with chronic renal failure and microalbuminuria, metabolic syndrome or obese patients.[37-39]

In addition to the acute, subacute and chronic stress caused by the earthquake, dietary and salt intake habits may change, alcohol intake may increase, and weight gain may occur, which may cause metabolic disorders in the long term. This may lead to an increase in chronic diseases.[2,29,40] A study examining the incidence of post-earthquake hypertension in the long term was conducted by Ohira et al.[41] after the Great East Japan earthquake. When the individuals who were evacuated after the earthquake in Fukushima were examined in the 2-year follow-up, it was observed that the development of hypertension increased especially in males. Also Kobari et al.[40], in their 7-year follow-up study after the Great East Japan earthquake, stated that the development of hypertension increased in

earthquake victims. It has been determined that the reasons for this increase are the development of obesity in the affected individuals, the increase in alcohol consumption and evacuation from their settlements.

1.4. Effect of earthquakes on sudden cardiac death

The increase in cardiovascular-related deaths after major earthquakes has been discussed in previous studies.[23,25,42] When the 1994 Northridge earthquake was examined, it was determined that the incidence of sudden cardiac death in earthquake patients increased by 5 times on the day of the earthquake compared to previous years.[42] In the 1981 Athens earthquake, it was determined that sudden cardiac deaths increased in the first days after the earthquake.[43] In a similar study by Klooner et al.[44], it was determined that cardiac deaths increased within 14 days after the earthquake, and then decreased. During the Hanshin-Awaji earthquake, the incidence of cardiac death remained high for 4 months and then returned to normal limits.[45] In a study conducted in a single center in Iwake Prefecture during the Great East Japan earthquake, although an increase was found in the number of out-of-hospital cardiac arrests in the 3-week period after the earthquake, the difference was not statistically significant.[20]

It has been suggested that the mechanism underlying the increase in cardiac deaths after physical or emotional stress is the increased release of catecholamine and hypercoagulability factors after stress, which in turn may lead to coronary artery thrombosis by causing plaque rupture.[42,46-48] Emotional stress-induced myocardial ischemia and triggering of severe arrhythmias are likely to be the underlying mechanisms.[42]

2. Conclusion

Major natural events such as earthquakes cause serious loss of life and property, especially if the construction is not suitable for earthquakes. The survivors are exposed to life-threatening health problems, both secondary to trauma and organ damage. Survivors of the earthquake without physical injury are exposed to acute and chronic stress due to the earthquake, loss of life of their relatives, and having to leave their settlements. Studies have shown that there is an increase in cardiovascular diseases in the short and long term in individuals who have experienced earthquakes. The reasons for this increase may be the activation of the autonomic nervous system due to physical and mental stress, increase in blood pressure, inability to reach the medications they take routinely due to chronic diseases, and increase in salt intake as a result eating preserved food. In the light of this information, minimizing the post-earthquake stress and taking the necessary precautions for the continuation of appropriate health services, especially in individuals with underlying cardiovascular disease, will minimize the damage due to cardiovascular diseases.

Conflict of interest statement

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

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Evaluation of Choroidal and Macular Thickness in Patients with Inactive Thyroid Eye Disease Using Optical Coherence Tomography

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Abstract

Aim: In this study, we aimed to evaluate the choroidal and macular thicknesses according to clinical activity score in thyroid eye disease patients who were inactive period and to compare them with healthy controls.

Methods: For this purpose, 40 eyes of 40 thyroid eye disease patients and 40 healthy controls were included. Subfoveal, temporal, nasal, choroidal thickness measurements and central foveal thickness measurements were performed with spectral-domain optical coherence tomography (SD-OCT). Similar measurements were compared with an equal number of controls.

Results: The mean clinical activity score (CAS) of thyroid eye disease was 1.25 ± 0.47 and the mean Hertel exophthalmometer results were 21.6 ± 2.4 millimeters (mm). The mean central foveal thickness was 285.3 ± 15.2 µm, mean subfoveal choroidal thickness was 285.42 ± 81.3 µm, mean temporal choroidal thickness was 265.6 ± 57.5 µm, and mean nasal choroidal thickness was 232.1 ± 71.7 µm. There is a statistically significant difference between subfoveal and temporal choroidal thickness between both groups p=0.014 and p=0.008, respectively.

Conclusions: In conclusion, the central foveal thickness of patients with thyroid eye disease did not differ from healthy controls, whereas subfoveal and temporal choroidal thickness were higher than controls. There is a need for large-scale and long-term studies on the cause and long-term effects of these differences.

Keywords: *Choroid; Macula, ophthalmopathy, optical coherence tomography, thyroid*

1. Introduction

Thyroid eye disease (TED) is an autoimmune disease characterized orbital adipose tissue proliferation, inflammation of the orbital connective tissue and extraocular muscles enlargement resulting cause an enhancement in orbital tissue volume. TED is observed in roundly 30% of patients with Graves disease and 2% of patients is observed with thyroiditis.[1] Although most patients with TED have mild symptoms, about 3 to 5% patients may develop a more severe form. Clinical signs of TED include dry eye, exposure keratopathy, proptosis, diplopia and decreased visual acuity.[2-4] Some studies on retinal changes in TED patients have recently appeared, including publications on choroidal thickness and its association with macular degeneration.[5-9] TED patients were evaluated according to the Mourits et al. developed Clinical Activity Classification System (CAS) classified as active and inactive in 1989.

A total of seven parameters are queried in this evaluation system. In this scoring system, each parameter is assigned a score, and if the overall score is three or more, the disease is considered to be in the active phase. Criteria; 1) Spontaneous bulbar or retrobulbar pain for the last four weeks, 2) Pain with looking up or down, 3) Redness of the eyelids, 4) Redness of the conjunctiva, 5) Swelling in the caruncle or plica, 6) Swelling of the eyelids and 7) Conjunctival swelling.[10]

In this study, we aimed to estimate the choroidal and macular thickness (according to clinical activity score) in cases with TED who weren't in the active complaint period and to compare them with healthy controls.

2. Materials and methods

This retrospective study included 40 eyes of 40 patients (group 1) admitted to the Endocrinology and Ophthalmology Outpatient Mersin City Hospital between 01 February 2019 and 01 February 2022. Forty healthy controls (group 2) of similar age group were included. Written informed consent was obtained from all participants. This study approved from the Clinical Studies Ethics Committee of Mersin City Hospital (2021 / 799 – 29/12/2021). The

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study was conducted in agreement with the Declaration of Helsinki. Subfoveal, temporal, nasal, choroidal thickness evaluation and central foveal thickness evaluation of the right eyes of all participants were performed, independently, by an educated technician using Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) spectral-domain optical coherence tomography (SD-OCT). Similar measurements were compared with an equal number of controls.

Exclusion criteria: Greater than (- 5.00) diopters myopia (D) or greater than (+ 3.00) diopters (D) hyperopia, anomaly of optic disc, vitreoretinal interface disease, retinal vascular and degenerative diseases, corneal and lens opacity, previous ocular surgery, neurologic diseases, use of cardiovascular drugs, amblyopia, diplopia, uveitis, enlarged extraocular muscles confirmed by orbital magnetic resonance imaging (MRI) and keratitis. A detailed history was taken from all patients and comprehensive ophthalmologic examination with slit lamp biomicroscopy, intraocular pressure measurement and fundus examination was performed.

The level of proptosis was evaluated with Hertel exophthalmometer. All patients were also evaluated using orbital MRI to observe extraocular muscle involvement.

2.1. Statistical Analysis

Statistical analysis of this study data was performed with SPSS 24.0 package program (IBM Corp, Armonk, NY, USA). Categorical variables were epitomized as number, percentage and continuous variables as mean ± standard deviation (minimum – maximum). Normal distribution of continuous variables was checked by Shapiro-Wilk test. Student's t test, was used to compare the means of two independent groups for the variables that conformed to normal distribution. Connection between categorical variables were investigated by Chi-Square analysis. Statistical significance level was taken as $p < 0.05$ for all comparisons.

3. Results

In this study, the mean age of the 40 patients (group 1) was 52.1 ± 14.2 years (37–66 years), while the mean age of the 40 healthy controls (group 2) was 51.2 ± 13.4 years (37–66 years). Group 1 consisted of 17 males (42.5%) and 23 females (57.5%). Group 2 consisted of 21 males (52.5%) and 19 females (47.5%). Both groups were similar in terms of demographics (p=0.166 and p=0.371, respectively) (Table 1).

Table 1

Demographic data of study participants

	Group 1 (n=40)	Group 2 (n=40)	p
Age (years)	52.1 ± 14.2	51.2 ± 13.4	0.166
Male	17 (42.5%)	21 (52.5%)	0.371
Female	23 (57.5%)	19 (47.5%)	

The clinical profile of group 1 showed hyperthyroidism in 25 (62.5%), euthyroidism in 7 (17.5%) and hypothyroidism in 8 (20%) patients. In addition, thyroid function tests revealed a mean thyroid stimulating hormone (TSH) level of 3.3 ± 1.8 (1.5 - 5.1) mIU/L, a mean free thyroxine (T4) level of 1.6 ± 0.6 (1.0 - 2.2) ng/dl, and a mean free triiodothyronine (T3) level of 4.4 ± 1.2 (3.2 - 5.6) ng/dL. (Table 2)

The mean clinical activity score for group 1 was 1.25 ± 0.47 and the mean Hertel ophthalmometry was 21.6 ± 2.4 (19.2 - 24.0) millimeters. Mean intraocular pressure (IOP) was 16.3 ± 3.9 (12.4 – 20.2) mm Hg. The mean of IOP in the group 2 was 15.8 ± 3.1 (12.7 – 18.9) mm Hg. This difference was not statistically significant (p=0.253).

Table 2

Clinical profiles and thyroid function tests of the patients

Group 1 (n = 40)	
Hyperthyroid	25 (%62.5)
Euthyroid	8 (%20)
Hypothyroid	7 (%17.5)
TSH	3.3 ± 1.8 mIU/L
fT4	1.6 ± 0.6 ng/dL
fT3	4.4 ± 1.2 ng/dL

TSH: Thyroid Stimulating Hormone, T4: thyroxine, T3: triiodothyronine

In group 1, mean foveal thickness was 285.3 ± 15.2 (270.1 – 300.5) µm, mean subfoveal choroid thickness was 285.42 ± 81 (204.4 – 366.4) µm, mean temporal choroid thickness was 265.6 ± 57.5 (208.1 – 323.1) µm, mean nasal choroidal thickness was 232.1 ± 71.7 (160.4 – 302.8) µm.

In group 2, the mean foveal thickness was 288 ± 16.1 (272.1 – 304.1) µm, the mean subfoveal choroid thickness was 251.1 ± 57.4 (193.7 – 308.5) µm. The mean temporal choroid thickness was 233.7 ± 51.3 (182.4 – 285.0) µm, and the mean nasal choroid thickness was 221.1 ± 59.9 (172.2 – 281.0) µm. There is a statistically significant difference between subfoveal choroidal thickness and temporal choroidal thickness between both groups (p=0.014 and p=0.008, respectively). (Table 3)

Table 3

Central foveal and choroidal thickness of the participants

	Group 1 (n=40)	Group 2 (n=40)	p
Central FT (µm)	285.3 ± 15.2	288 ± 161	0.317
Subfoveal CT (µm)	285.4 ± 81.3	251.1 ± 57.4	0.014
Temporal CT (µm)	265.6 ± 57.5	233.7 ± 51.3	0.008
Nasal CT (µm)	232.1 ± 71.7	221.1 ± 59.9	0.106

FT: Foveal thickness CT: Choroidal thickness

4. Discussion

Thyroid eye disease is an autoimmune disease involving many factors. Inflammatory events occur more frequently during the active phase, whereas fibrosis of the orbital tissue predominates during the inactive phase [8]. Studies have shown that changes in choroidal thickness occur in orbital inflammatory and systemic diseases due to choroidal inflammatory cell infiltration, increased exudate, increased vascular leakage, and altered orbital blood flow.5-7 In TED patients, orbital fibroblasts overexpressing thyroid-

stimulating hormone receptors and insulin-like growth factor-1 receptors play an important role in orbital inflammation, extracellular matrix production, and adipocyte and myofibroblast differentiation. plays. Inflammatory cells normally infiltrate the orbital adipose tissue and extraocular muscles, and under the influence of inflammatory mediator cytokines, cause orbital stromal edema and extraocular muscle hypertrophy. It has been reported that orbital venous drainage is reduced in TED patients and that the reason for orbital venous flow reduction is elevated retroorbital pressure above normal venous pressure. It has been hypothesized that compression exerted by blood flow within the orbital space, restricted by reduced orbital venous outflow, may be associated with increased choroidal thickness.[14-16] We found that the intraocular pressure values in the patient group were higher than those in the control group. In the same study, foveal thickness was thinner in the patient group compared to the control group. In our study, the difference in intraocular pressure between patient and control groups was not significant.[11] In our study, foveal thickness and intraocular pressure were similar between patient and control groups. Elongation of the optic nerve and sclera, with or without muscle involvement, can increase the measured intraocular pressure when the thyroid gland is active or inactive. Macular thickness can be affected by changes in intraocular pressure. Ganglion cell damage in the macula was confirmed in a study by Wu et al. Demonstrated in patients with high intraocular pressure [13]. Macular thickness increases within a month due to the reduction in intraocular pressure after glaucoma filtration surgery. They hypothesized that this was due to the physiological response of the retina to a sudden drop in intraocular pressure. As no differences in intraocular pressure were observed in our study, there are no differences in foveal thickness.

Sen et al. the Graves' disease group was found to have higher intraocular pressure values than the control group (p=0.01).[12] Similarly, Wu et al. found higher intraocular pressure values in the patient group compared to the control group.[13] The reason the results differ from the literature is that the number of patients included in the study was relatively small and patients were inactive. In a study by Ozcan et al., subfoveal choroidal thickness was higher in the patient group than in the control group. Most patients in this patient group were clinically inactive, and it was reported that the increased subfoveal choroidal thickness may be due to the venous occlusion observed in the patient group.[8] In another study, Charshukan et al. They found that subfoveal choroidal thickness increases in active TED patients compared with controls, whereas subfoveal choroidal thickness does not change in non-active TED patients compared with controls.[2] In our study, similar to other literature studies, we found that the inactive TED group had higher subfoveal choroidal thickness than the healthy control group. Increased choroidal thickness in our study has been linked to venous occlusion, periorbital and retroorbital tissue inflammation, vascular macro- and microanatomical alterations due to proptosis, and consequent possible ischemic causes in the pathogenesis of TED. It is hypothesized that it is due to. Limitations of this study include the small number of patients, the lack of automation in the measurements of foveal and choroidal thickness, the lack of subgrouping of patients according to different clinical findings, and the lack of IOP and foveal thickness. and lack of correlation analysis with foveal thickness. It does not evaluate the best visual acuity.

5. Conclusion

In conclusion, foveal thickness in patients with thyroid eye disease did not differ from that in healthy controls, but subfoveal and temporal choroidal thicknesses were thicker than in healthy controls. Large-scale, long-term studies are needed on the causes and long-term effects of these differences.

Statement of ethics

This study approved from the Clinical Studies Ethics Committee of Mersin City Hospital (2021 / 799 – 29/12/2021).

Conflict of interest statement

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

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Author Contributions

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Association of Synchronous Transurethral Surgeries or Transrectal Prostate Biopsy with Early Postoperative Complications in the Endoscopic Treatment of Bladder Stones

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Abstract

Aim: To investigate the effect of synchronous transurethral surgeries or transrectal prostate biopsy on complications in endoscopic bladder stone treatment.

Methods: Between January 2016 and December 2021, 402 patient who aged 18 years and older, underwent endoscopic bladder stone surgery were retrospectively analyzed. 345 patients were included in the study, after the exclusion criteria were determined. Patients were divided into 2 groups according to the applied surgical treatments. Group 1(n=174) involved patients who underwent endoscopic bladder stone surgery alone and Group 2(n=171) who underwent TUR-P/TUIP/DVIU or TUR-BT or URS or TRUS-BX in the combination with endoscopic bladder stone treatment. Age, etiology, surgical treatments, operation times, hospitalization times and postoperative complications were compared.

Results: Mean age of the patients was 60 (SD=15, range=18-93) years. Mean (SD) stone size was measured as 3 (2.2) cm. There was no difference in patient age and stone size between the groups. Complications of both Clavien 2 and above, Clavien 3A and above were statistically significantly higher in Group 2 (p=0,019; p=0,030). There was no relationship between complications and comorbidities. Operation and hospitalization times were statistically significantly shorter in Group 1 (p= 0,033; p=0,020).

Conclusions: We observed an increase in early postoperative complications in TUR-BT or TRUS-BX surgeries performed synchronously with bladder stone treatment. Therefore, patients may need additional postoperative endoscopic procedures and may prolong hospitalization time.

Keywords: *Image-Guided Biopsy, postoperative complications, transurethral resection of prostate, urinary bladder calculi*

1. Introduction

Bladder stones contain 5% of all urinary tract stones[1]. Peak age is 61 years in adulthood and incidence is higher in developing countries[2,3]. In developed countries, bladder stones are responsible for 8% of deaths due to urolitiasis[4]. Removal of bladder stones by preferring invasive techniques has been widely adopted to reduce the risk of complications and shorten hospital stay.

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Therefore, transurethral cystolitotripsy (TUCL) and percutaneous cystolitotripsy are considered to be more preferred approaches than other methods. Although the main goal in the treatment process is the removal of stones; resolution of the predisposing disease is as important as preventing the formation of new stones in the bladder. Several procedures can be performed in a single session due to comorbidities, difficulties in anesthesia preparations, avoiding repetitive hospital stays and additional costs. However, doing several processes at the same time is not always innocent. In our study, we aimed to investigate the results of concomitant additional procedures performed with endoscopic surgical treatment of bladder stones.

2. Materials and methods

The study was started after the approval of the ethics committee (29/11/2021-125/04). Patients who underwent endoscopic bladder stone treatment were scanned between January 2016 and December 2021 retrospectively. Data from a total of 402 patients were accessed. The study was planned retrospectively and carried out in accordance with the Declaration of Helsinki. Patients who are younger than 18 years, who were not treated with TUCL and who used pneumatic lithotripter during cystolitotripsy were excluded from the study. At the conclusion, 345 patients were enrolled in the study. Etiology, comorbidities, demographic information, previous procedures, surgical techniques, bladder stone number and size, operation time, hospital stay, postoperative complications and laboratory results retrospectively reviewed from electronic medical records according to inpatient and outpatient history. Complications are classified as Clavien Dindo classification[5].

Operations were started by entering the external meatus with 20F cystoscopy. Patients who have urethral strictures were undergo internal urethrotomy. After that procedure, the operation was kept on using 20F cystoscopy again. In all patients, undergo transurethral laser lithotripsy after the evaluation of prosthetic urethra, bladder neck, ureteral orifices and bladder walls. A second synchronous procedure was applied after completion of a bladder stone, who would undergo transurethral prostatectomy (TUR-P), transurethral prostate incision (TUIP), transurethral resection of bladder tumor (TUR-BT), and retrograde intrarenal surgery (RIRS)/ urethrorenoscopy (URS).

Patients who undergo ultrasound guided transrectal prostate biopsy (TRUS-BX) were positioned in a lateral fetal position after TUCL was performed under general anesthesia. After the operation, all patients received a urethral catheter insertion. Additionally, patients who underwent synchronous RIRS/URS had a double J stent inserted. According to the treatments administered, the patients were partitioned into 2 groups. Group 1 includes patients who had undergone only TUCL (n=174) and group 2 included patients who had undergone synchronous endoscopic treatment with TUCL (Table-1.). Groups were compared for both Clavien 2 and above, Clavien 3A and the above complications. Operation times and hospital stay for groups and complications of the endoscopic treatment procedures were compared.

Statistical Analysis

Statistical analysis was conducted using Pearson chi-square and Fisher's exact test. A significance level of $p<0.05$ was considered statistically significant. The analysis was carried out using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Between 2016 and 2021, 345 patients who underwent TUCL for bladder stones were included in the study. Mean age of the patients was 60 (SD=15.00, range=18-93) years. The mean (SD) stone size was 3 (2.2) cm. When the etiology of the bladder stones were examined, it was found that 68.4% of the causes developed as obstructive, 8.1% as non-obstructive (neurogen) causes, 19.1% were secondary to migratory stones and 4.3% were secondary to a foreign body in the bladder. Patients underwent 5 different surgeries. The number of the patients who underwent TUCL, TUCL+ (TUR-P/IOU/TUIP), TUCL+TUR-BT, TUCL+(RIRS/URS), TUCL+TRUS-BX was 176, 109, 14, 22, 27 respectively (Table-1).

Table 1

Demographic data, the relationship of operation groups with length of hospital stay and duration of operation.

Patients				n:345
Age (year)				60 (SD=15, range=18-93)
Gender				329 M 16 F
Etiology				
• Obstructive				236 (68.4%)
• Non-obstructive (neurogenous)				28 (8.1%)
• Migratory stone				66 (19.1%)
• Foreign body				15 (4.3%)
Operation type				
Group 1	1: TUCL			174(0.4%)
Group 2	2: TUCL + (TUR-P/DVIU /TUIP)			108 (31.3%)
	3: TUCL + TUR-BT			14 (4.1%)
	4: TUCL + (RIRS/URS)			22 (6.4%)
	5: TUCL + TRUS-BX			27 (7.8%)
		Group 1	Group 2	p
Stone size (cm) (Mean [SD])		2.8 (2.1)	3.1 (2.3)	.216
Operation time (min) (Mean [SD])		51 (23)	81 (27)	.033
Hospital stay (day) (Mean [SD])		1.9 (1.9)	3.1 (2.8)	.020

M: Male, F: Female, TUCL: Transurethral cystolithotripsy, TUR-P: Transurethral resection of the prostate, DVIU: Direct vision internal optic urethrotomy TUIP: Transurethral incision of the prostate, TUR-BT: Transurethral resection of the bladder tumor, RIRS/URS: Retrograde intrarenal surgery/ Ureterorenoscopy TRUS-BX: Transrectal ultrasound guided prostate biopsy

Table 2

Association of operation groups with Clavien ≥2 complications

		Complications Clavien ≥2 (-)		Complications Clavien ≥2 (+)			p
Group 1	1:TUCL	156(45.2%)		18(5.2%)		174(50.5%)	
Group 2	2: TUCL +(TUR-P/ DVIU/ TUIP)	92	138(45%)	16(4.6%)	33(9.5%)	171(49.5%)	.019
	3: TUCL + TUR-BT	9		5(1.4%)			
	4: TUCL + (RIRS/URS)	20		2(0.5%)			
	5: TUCL + TRUS-BX	17		10(2.9%)			
Total		294(85.2%)		51(14.7%)		345(100%)	

TUCL: Transurethral cystolithotripsy, TUR-P: Transurethral resection of the prostate, DVIU: Direct vision internal optic urethrotomy
TUIP: Transurethral incision of the prostate, TUR-BT: Transurethral resection of the bladder tumor, RIRS/URS: Retrograde intrarenal surgery/ Ureterorenoscopy, TRUS-BX: Transrectal ultrasound guided prostate biopsy

Clavien 2 and above complication rates were 5.2% and 9.5% for group1 and group 2 respectively. Clavien 3A and above complication rates were 3.5% and 7.2% for group1 and group 2 respectively. Complication rates were significantly higher in group 2 (p=.019 ve p=.030) (Table-2,3).

When TUCL and TUCL+ (TUR-P/IOU/TUIP) were compared in subgroup analysis, no difference was observed between both Clavien 2 and above, Clavien 3A and the above complications respectively. When subgroups were examined in group 2, it was observed that Clavien 3A and the above complications were mostly caused by bladder perforation or impaired urinary drainage. It was observed that 5 of 9 patients who underwent TUCL + TUR-BT required additional endoscopic intervention due to hematuria (Table-3).

Clavien 3A and the above complications were detected in 6 of 21 patients who underwent TUCL + TRUS-BX. Following removal of the postoperative urinary catheter, a percutaneous cystostomy catheter was inserted in one patient due to the development of acute urinary retention. Cystoscopy was performed on five patients due to hematuria. Clavien 2 and the above complications were examined, it was observed that complication rates of the patients increased from 1.7% to 2.9% and hospital stay was prolonged due to the need for antibiotic treatment in 5 patients with post-procedure fever and urosepsis.

There was no difference in stone sizes between the groups (Table-1). The incidence of both Clavien 2 and above, Clavien 3A and the above complications, was significantly higher during the fracture of multiple stones compared to a single stone (p=.018; p=.011).

It was determined that both the operation time and the length of hospital stay were significantly longer in group 2 (p=.033; p=.020) (Table-1).

Table 3

Relation of operation groups with Clavien ≥3A complications.

		Complications Clavien ≥3A (-)		Complications Clavien ≥3A (+)			p
Group 1	1:TUCL	162 (46.9%)		12 (3.5%)		174 (50.5%)	
Group 2	2: TUCL +(TUR-P/DVIU/TUIP)	96 (27.8%)	146 (42.3%)	13 (3.7%)	25 (7.2%)	171 (49.5%)	.030
	3: TUCL + TUR-BT	9 (2.6%)		5 (1.4%)			
	4: TUCL + (RIRS/URS)	20 (5.8%)		1 (0.2%)			
	5: TUCL + TRUS-BX	21 (6.1%)		6 (1.7%)			
Total		308 (89.2%)		37 (10.7%)		345 (100%)	

TUCL: Transurethral cystolithotripsy, TUR-P: Transurethral resection of the prostate, DVIU: Direct vision internal optic urethrotomy
TUIP: Transurethral incision of the prostate, TUR-BT: Transurethral resection of the bladder tumor, RIRS/URS: Retrograde intrarenal surgery/ Ureterorenoscopy, TRUS-BX: Transrectal ultrasound guided prostate biopsy

4. Discussion

Bladder stones may occur primarily but often occur as a result of a concomitant predisposing disease. Bladder outlet obstruction, neurogenic lower urinary tract symptoms, foreign body, chronic bacteriuria and kidney stones were some of the reasons[6]. Bladder outlet obstruction in adults is the most common cause of bladder stone formation, accounting for 45-79% of bladder stones[7,8]. For this reason, bladder stones are often not treated alone. It is usually performed synchronously with TUR-P, IOU or an additional surgical procedure[9].

Cystolithotomy is the most effective method in the treatment of bladder stones. However, in this method, the duration of catheterization and hospital stay are longer compared to minimally invasive methods[10]. It is known that blood transfusion may be needed when open prostatectomy with cystolithotomy is performed. Hematuria and related complications may develop in the postoperative period. Amid advancing technology, minimally invasive techniques have gained widespread acceptance for their ability to mitigate the risk of complications, shorten hospital stays, and expedite recovery times.[11] In both adults and children, TUCL provides a high stone-free ratio, and appears to be safe with a very low risk of complications, major post-operative and late complications. Long-term urethral stricture development in transurethral interventions has not been reported with supporting evidence. In the literature, there are studies demonstrating that urethral stricture develops at a rate of 2.9% to 19.6%, respectively, at 12 to 24 months follow-up[11-13].

In our study, the incidence of both Clavien 2 and higher, Clavien 3A and higher complications of multiple stones were significantly higher compared to single stones. The literature lacks studies on the analysis of single or multiple stone processes. Due to limited data, it is difficult to advise an opinion on the complications caused by multiple stones for today. However, it is thought that the size of the multiple stones is larger than the single stone, and therefore complications due to the prolongation of the operation time are more common. The findings of the study must be corroborated by clinical investigations. Studies comparing the safety of BPH and bladder stone treatment in the same session and BPH treatment alone showed no difference in terms of major complications[12]. In synchronous procedures, no difference was found in complications, except for urinary tract infections which were more frequent[14-16]. An observational study compared 321 patients who underwent holmium laser enucleation of the prostate (HOLEP) and synchronous TUCL+HOLEP. There was no difference in terms of clinically significant perioperative and postoperative complications in patients who underwent synchronous intervention, except for postoperative early urinary incontinence and prolongation of operation times[17]. In our study, the complication rates of Clavien 2 and above, Clavien 3A and the above were found to be 5.2% and 3.5%, respectively, in patients who underwent TUCL, regardless of stone size. However, we found that when a synchronous interventional procedure is added to TUCL, complication rates increase, operation times and hospital stays are prolonged. When only TUCL and TUCL+ (TUR-P/IOU/TUIP) were compared in the subgroup analyzes, no difference was observed in terms of postoperative complications of both Clavien 2 and above, Clavien 3A and above, in line with the literature. We found that the complication rate of Clavien 3A and above in patients who underwent TUCL+(TUR-P/IOU/TUIP) was 3.7%, similar to TUCL alone. Although the results were similar, it is difficult to state that the complications and hospital stays in group 2 increased due to the synchronous procedure, since the subgroup patient distribution was not standardized in our study. However, it seems that TUR-BT or TRUS-BX synchronized with TUCL increases complications.

Complications occurred in 35% (5/14) of TUR-BT patients who were performed synchronously with TUCL. Patients in this group required additional endoscopic intervention, mostly secondary to impaired urinary drainage. The hypothesis for the increase in complications is that small stone fragments are missed, or the resection is not optimally performed as a result of loss of vision due to bleeding of the tumoral tissue as a result of stone breakage. The main reason for the need for additional intervention after the operation is the combination of small tissue and clot fragments with stone fragments and subsequent deterioration of urinary drainage. In these patients, it should be tried not to contact the tumor tissue with the laser during cystolitotripsy, and high negative pressure should be avoided during the collection of stones. Although the number of patients in the TUCL+TUR-BT group limits our comparison with other patient groups, it seems that caution should be exercised during a synchronous operation.

Clavien 3A and higher complications (6/27) were seen in 22% of TRUS-BX patients who were performed synchronously with TUCL, while the rate of Clavien 2 and higher complications was 37% (10/27). After the procedure, antibiotic treatments were changed in 5 patients due to fever and suspected urosepsis. We observed that the follow-up and hospitalization periods of the patients were prolonged after the revision of antibiotic therapy. In addition, we observed that in some patients who underwent TUCL+TRUS-BX, in the early period after discharge, the patients applied to the emergency room due to urinary infections and these patients needed hospitalization again. Early infection rates were higher in this patient group than in patients who underwent TUCL alone. Although the stone analysis results of the patients were not available, it can be concluded that simultaneous TRUS-BX increases the infective complications, considering that the stones in these patients develop as a result of bladder outlet obstruction and that this group of stones is mostly infection stones[18]. Although the small number of TUCL+TRUS-BX patients limits our comparison with other patient groups, it seems that synchronous operation increases the risk of urinary infection at an early period. Therefore, performing TUCL and TRUS-BX in different sessions in this group of patients may be beneficial in terms of both hospitals stay and early postoperative complications. However, these results need to be supported by prospective randomized clinical studies.

Antibiotic revision due to high fever was performed on only one patient who underwent RIRS/URS with TUCL, and the patient's hospitalization time was prolonged. One patient required repeated cystoscopy and additional endoscopic intervention due to hematuria.

The limitations of our study are that the stone size, surgical methods applied, and antibiotic prophylaxis are not standardized for each group. However, we believe that we found results that could be supported by prospective randomized clinical studies.

5. Conclusion

Considering the results of our study, TUCL is a reliable technique regardless of stone size. TUCL+(TUR-P/IOU/TUIP) has similar results with those who only had TUCL in terms of early postoperative complications. Synchronous TUCL+RIRS/URS can be done safely. Early postoperative complications increase in patients undergoing synchronous TUCL+TUR-BT. These patients may need additional postoperative endoscopic procedures and may prolong hospitalization. Early postoperative complications increase in patients undergoing synchronous TUCL+TRUS-BX. Infective complications may develop in the postoperative period and the duration of hospitalization may be prolonged accordingly.

Therefore, if possible, TUCL+TRUS-BX should be performed in different sessions.

Statement of ethics

The study was started after the approval of the Dışkapı Yıldırım Beyazıt E&R Hospital ethics committee (29/11/2021-125/04).

Conflict of interest statement

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

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Author Contributions

All authors contributed equally to the article. All authors read and approved the final manuscript.

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Combination of Lymphocyte Count and Albumin Concentration as a New Prognostic Biomarker for Gastric Cancer

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Abstract

Aim: This research links systemic inflammation and nutritional status with gastric cancer prognosis and postoperative outcomes.

Methods: Patients undergoing total gastrectomy for gastric adenocarcinoma (2015-2018) were categorized into two: Low Lymphocyte–Albumin(LA) score (Group 1) and High Lymphocyte-Albumin score (Group 2). Demographics, clinical data, operative outcomes, and survival rates were compared. The LA score's predictive ability for lymph node positivity was assessed.

Results: Using a cut-off value of 6069.7, Group 1 had 59 patients (low value) and Group 2 had 45 (high value). Hospital readmissions due to wound infections were higher in Group 1 (16.9% vs. 2.2%, p=0.041). Both groups had similar tumor localization and total lymph nodes removed, but Group 1 had more positive lymph nodes (4 vs. 2, p=0.026). Survival rates were comparable (32.59 vs. 31.32 months, p=0.390).

Conclusions: Low LA scores correlate with a higher number of positive lymph nodes, serving as a postoperative quality assessment indicator.

Keywords: *Gastric Cancer, prognosis, complication, albumin, lymphocyte count*

Main Points

·Gastric cancer is the fifth most prevalent cancer worldwide, with a low 5-year survival rate of 20-40%. Its prognosis largely depends on the disease stage at diagnosis.

·A composite index called LA, derived from lymphocytes and albumin levels, has emerged as a potential prognostic marker in other cancers, yet its relevance in gastric cancer remains unexplored.

·This retrospective study analyzed 82 patients who underwent gastrectomy for gastric cancer, assessing the predictive ability of the LA score for metastatic lymph nodes and overall prognosis.

·While the LA score did not directly correlate with survival rates in gastric cancer patients, a low LA score was associated with a higher number of positive lymph nodes.

·The LA score, though not a direct predictor of survival, can be a valuable marker in assessing lymph node metastasis in gastric cancer and warrants further research.

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1. Introduction

Gastric cancer is the fifth most common form of cancer worldwide, and the third leading cause of cancer-related death after lung and colorectal cancers. In 2018, 1.033.701 new cases were reported globally as well as 782.685 gastric cancer-related deaths.[1] Despite the use of multidisciplinary treatments, 5-year survival in gastric cancer is still low, reported in the range of 20–40%.[2]

While the prognosis of gastric cancer is determined based on such parameters as tumor localization, histological type, degree of differentiation and lymphovascular invasion, the leading prognostic factor is still disease stage at the time of diagnosis.[3,4] These parameters, however, remain insufficient for gastric cancer patients due to the search for individualized diagnosis and medical treatment. It is, therefore, necessary to identify prognostic markers that can accurately predict the prognosis of gastric cancer.

It would be erroneous to attribute the progression or metastasis of cancer solely to the behavior of tumor cells, as the nutritional and immune statuses of the host also play an important role, and can be assessed through a hematological examination.[5,6]

For instance, lymphocytes induce cytotoxic cell death and play an important defensive role against cancer by inhibiting the proliferation and migration of cancer cells.[7] Serum albumin level, one of the most used parameters for the prediction of nutritional status in patients, is also used for the assessment of cancer progression and prognosis – a decreased albumin level has been

linked to a shorter survival span in cancer patients.[8]

A recent research introduced the LA index, determined by the equation: (LA) = lymphocytes (/L) × albumin (g/L). This index was linked to lower survival rates in rectal cancer.[5] However, its correlation with gastric cancer hasn't been explored yet.

In the present study we assess the ability of a combined LA approach to predict the rate of metastatic lymph nodes and prognosis in gastric cancer patients who had undergone curative resection.

2. Materials and methods

The research encompassed 120 patients who received total gastrectomy for gastric cancer at the General Surgery Clinic of xxx University's Faculty of Medicine from January 2015 to December 2018. The Ethics Committee of xxx University Faculty of Medicine granted approval for this study. Informed consent was taken from all the patients. A database was created through a prospective review of patient files and hospital information system records, and this database was used to make a retrospective analysis of the patients. The study excluded patients who had palliative surgery, were diagnosed with Stage IV gastric cancer, were below 18 years old, were pregnant, had chronic inflammatory diseases like tuberculosis or sarcoidosis, suffered from autoimmune or hematological conditions, were on steroids for any purpose, or had unavailable records. Remaining 82 patients were included in the study.

The (LA) score was calculated using the formula of lymphocytes (/L) × albumin (g/L) using the blood samples collected when the patient was admitted for the operation. Based on the determined cut-off value using ROC curve, patients were categorized into two groups: Group 1 (Low LA) and Group 2 (High LA). The demographic characteristics, Body Mass Index (BMI), comorbidities, ASA score, neoadjuvant treatments, type and nature of the operation, tumor localization, and pathological stage of the tumor of the patients in both groups were recorded. The pathological tumor stage, total number of lymph nodes and the number of metastatic lymph nodes, duration of operation, mean blood loss, complications after surgery as classified by the Clavien-Dindo system.[9], rate of anastomotic leak, length of postoperative hospital stay, 30-day mortality, postoperative 30-day rate of unplanned hospital readmission and overall survival rate were recorded and compared between the two groups. The clinical value of the LA score in predicting postoperative lymph node positivity was calculated.

The tumor-node-metastasis (TNM) staging system 2016 was used for tumor staging.

An anastomotic leak was identified as a breach in the anastomotic connection, determined through a mix of clinical, radiological, and surgical methods.

The depth of tumor invasion was assessed preoperatively by endoscopic ultrasound in suspected cases. All patient records contained contrast-enhanced thoracic and upper and lower abdominal computed tomography imaging for staging purposes.

2.1.Statistical evaluation

IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA) package program has been used for statistical analysis of the data. While evaluating the study data, besides the descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum), Student's t test was used to compare quantitative data, and Mann Whitney U test was used to evaluate parameters that did not show normal distribution. Pearson's Chi-squared test and Fisher's Exact test have been used to compare qualitative data, Patients were divided into two groups according to the mortality, and roc analysis was performed according to these groups. Diagnostic accuracy was evaluated using receiver operating characteristic (ROC) curve analysis to assess the association of LA with gastric cancer overall survival, multivariate Cox's proportional hazard model was conducted to estimate Hazard ratios (HRs) and their 95% confidence intervals (CIs). Kaplan-Meier analysis and Log Rank test were used for survival analysis. The $p<0.05$ value was considered statistically significant in the results.

3. Results

A ROC analysis was performed, producing a ROC curve to set a threshold for the LA score, resulting in a 56.4% area under the curve. Based on the established LA cut-off value of ≤6069.7, patients were deemed to have positive lymph nodes, showing a sensitivity of 51.85% and a specificity of 68%. These findings are detailed in Table 1 and Figure 1.

Using the 6069.7 cut-off value, the patients were classified as lower and higher group. Group 1 comprised 59 patients (n = 59) and Group 2 comprised 45 patients (n =45).

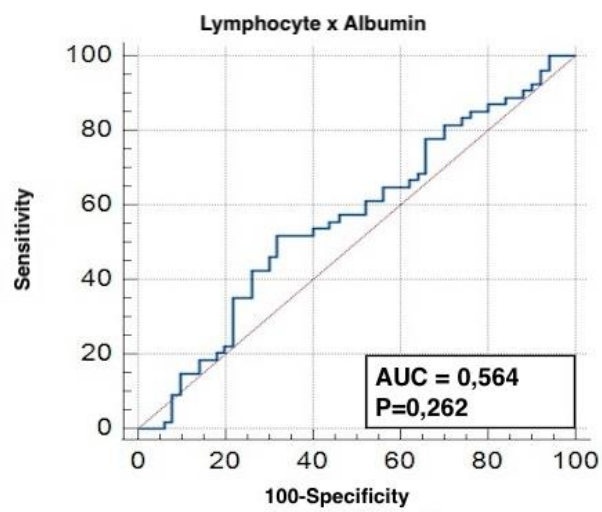
Table 1

Proposed cut-off values for significant parameters in lymph node positivity

	LA
AUC	0.564
95% CI (%)	0.463–0.661
Cut-off	>6069.7
Specificity	51.85
95% CI (%)	37.8–65.7
Sensitivity (%)	68.0
95% CI (%)	53.3–80.5
PPV	63.6
NPV	56.7
+LR	1.62
-LR	0.71
P	0.262

Figure 1

ROC analysis of LA analysis and positive lymph nodes



In comparing the groups, the average age (p=0.77), female proportion (p=0.313), and ASA score distribution (p=0.946) were consistent. However, Group 2 had a notably higher BMI (p=0.005). These findings are detailed in Table 2.

The rate of minimally invasive surgeries (p = 0.785), the distribution of complications in accordance with the Clavien-Dindo classification (p = 0.523), the rate of anastomotic leaks (p = 0.66) and the length of postoperative hospital stay (p = 0.080) were similar in the two groups (Table 3).

Table 2

Patient characteristics

		Group 1 Low LA	Group 2 High LA	p*
Age (mean ± SD)		61.3 ± 16.7	56.0 ± 11.8	0.077
Sex	Female	18 (30.5)	18 (40)	0.313
	Male	41 (69.5)	27 (60)	
ASA score	1	33 (55.9)	25 (55.6)	0.946
	2	17 (28.8)	14 (31.1)	
	3	9 (15.3)	6 (13.3)	
BMI (min–max)		23 (16–40.3)	25 (17.5–36)	0.050
Neoadjuvant CTx	Not received	42 (71.2)	33 (73.3)	0.829
	Received	17 (28.8)	12 (26.7)	

**p < 0.05 ASA- The American Society of Anesthesiologists CTx -Chemotherapy*

Table 3

Intraoperative and Postoperative Outcomes

		Group 1 Low LA	Group 2 High LA	p
Type of operation	Open	49 (83.1)	39 (86.7)	0.785
	Laparoscopic	10 (16.9)	6 (13.3)	
Duration of operation (min)		220 (170–500)	210 (160–480)	0.223
Complications (Clavien-Dindo)	1	10 (16.9)	8 (17.8)	0.523
	2	32 (54.2)	29 (64.4)	
	3A	10 (16.9)	6 (13.3)	
	3B	3 (5.1)	0 (0)	
	5	4 (6.8)	2 (4.4)	
Anastomotic leaks	None	53 (89.8)	40 (88.9)	0.666
	Stump leak	2 (3.4)	3 (6.7)	
	Esophagojejunostomy	4 (6.8)	2 (4.4)	
Length of postoperative hospital stay (days)		9 (4–46)	8 (2–40)	0.080
30-day hospital readmission	None	47 (79.7)	42 (93.3)	0.041
	Ileus	0 (0)	2 (4.4)	
	Impaired oral intake	1 (1.7)	0 (0)	
	Pneumonia	1 (1.7)	0 (0)	
	Wound site infection	10 (16.9)	1 (2.2)	

The two groups had a similar rate of neoadjuvant chemotherapy (p = 0.829); the most common tumor localization was the antrum in both groups (p = 0.607); the total number of lymph nodes removed, and the lymph node positivity rate were similar in the groups, while the number of positive lymph nodes was higher in Group 1 (p = 0.026). The most common pathological stage was Stage 2b in both groups (p = 0.084) (Table 4).

Group 1 saw a notably increased rate of readmissions to the hospital within 30 days (p=0.041). However, the overall survival rates between the groups were comparable (p=0.390), as illustrated in Table 5 and Figure 2.

Table 4

Tumor characteristics

		Group 1 Low LA	Group 2 High LA	p*
Tumor localization	Antrum	21 (35.6)	17 (37.8)	0.607
	Cardia	8 (13.6)	3 (6.7)	
	Corpus	19 (32.2)	14 (31.1)	
	Lesser curvature	5 (8.5)	8 (17.8)	
	Linitis Plastica	5 (8.5)	2 (4.4)	
	EGJ	1 (1.7)	1 (2.2)	
Total number of lymph nodes removed (mean) (min–max)		28 (3–63)	30 (7–60)	0.579
Number of positive lymph nodes (mean) (min–max)		4 (0–47)	2 (0–20)	0.026
Lymph node positivity	Negative	22 (37.3)	21 (46.7)	0.422
	Positive	37 (62.7)	24 (53.3)	
pSTAGE	1A	5 (8.5)	9 (20)	0.084
	1B	4 (6.8)	3 (6.7)	
	2A	0 (0)	5 (11.1)	
	2B	15 (25.4)	10 (22.2)	
	3A	7 (11.9)	4 (8.9)	
	3B	5 (8.5)	3 (6.7)	
	3C	23 (39)	11 (24.4)	
Pathological grade	Undifferentiated	7 (11.9)	11 (24.4)	0.342
	Poorly differentiated	24 (40.7)	18 (40.0)	
	Moderately differentiated	14 (23.7)	7 (15.6)	
	Well-differentiated	14 (23.7)	9 (20)	

**p < 0.05 EGJ Esophagogastric junction*

Figure 2

Comparison of overall survival rates between low and high LA groups

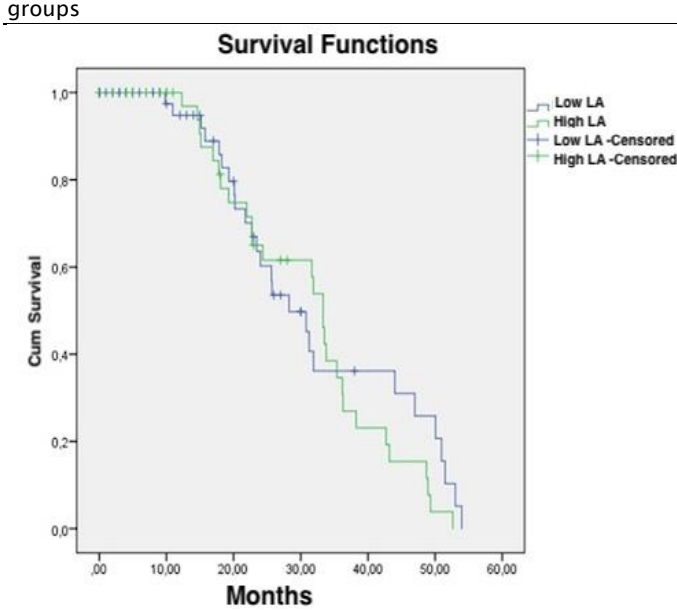


Table 5
Overall survival by LA groups

		Mean (Mean + SD (Min–Max))	Median (Mean + SD (Min–Max))	p
LA group	Low LA	32.59 ± 2.67	28.26 ± 3.13	0.390
	High LA	31.32 ± 2.18	33.32 ± 1.13	

4. Discussion

Although there are a growing number of studies highlighting the prognostic value of various inflammatory markers in different cancer types, the clinical significance of these markers remains unclear. Moreover, there is a lack of consensus on the cut-off values to be assigned to each marker. In the present study we assess the prognostic significance of the LA ratio – a combination of these inflammatory and nutritional parameters – in patients with gastric cancer, which is one of the gastrointestinal cancers.

Low preoperative serum albumin is known to be a strong predictor of postoperative morbidity and mortality.[10,11] In their study of gastric cancer patients, Ouyang et al. found a low albumin level to be associated with reduced survival[12], and it is important to note that an initial low albumin value may affect early surgical outcomes, regardless of albumin replacement.[10,11]

Preoperative serum albumin is also widely used to predict the lymph node metastasis of gastrointestinal tumors. Ouyang et al. found a low albumin level to be associated with reduced survival in gastric cancer[12]; Liu Q et al. detected more metastatic lymph nodes in patients with low albumin levels[13]; O Huamán et al. identified decreased albumin levels with increasing tumor stage in gastric cancer; while Kang et al. showed that low albumin levels were associated also with increased rates of postoperative complications in gastric cancer patients.[10,14]

The chronic inflammatory effect causes lymphocytes to enter the tumor, and consequently, the surrounding tissues, increasing the likelihood of metastasis. Lymphocyte plays an important role in tumor-related immunology, having a strong anti-tumor immune function that can inhibit tumor progression, while high lymphocyte levels have been reported to be associated with a favorable prognosis in various tumors.[15,16] Feng et al. reported a low lymphocyte count to be associated with poor prognosis in gastric cancer.[17] In their meta-analysis, Schroth found preoperative lymphopenia to be associated with more frequent mortality and complications, regardless of the type of surgery.[18] Xu et al. established that preoperative lymphocytopenia was associated with increased lymph node metastasis, increased stage, and serosal invasion (T3+T4) risk and poorer overall survival in gastric cancer.[19]

Building on this data, Yamamoto T and team analyzed 448 patients with stage II/III rectal cancer post-curative resection. They discovered that a diminished LA score was linked to both decreased overall and disease-free survival. The researchers suggested its potential use in pinpointing patients at greater risk of relapse and assisting in choosing post-surgery treatments to minimize recurrence chances.[5]

In the present study, we did not find LA score to be a survival-related factor in patients who had undergone curative resection for gastric cancer, but it was associated with the number of positive lymph nodes. In addition, a low LA score seems to increase the rate of unplanned hospital admissions, which is one of the postoperative quality indicators. We believe that our failure to identify any relationship with survival in our study could be related to the small patient population. Low LA increased the number of positive lymph nodes, as expected. Impaired nutritional status appeared to be an important parameter affecting the postoperative period.

Our research comes with certain limitations. Being a retrospective analysis with a limited sample size, there's potential for selection bias. To truly understand LA's clinical significance, more extended observation studies are necessary. Nonetheless, we believe that this work pioneers the exploration of this topic in the literature.

5. Conclusion

Our research indicates that the LA score by itself isn't a definitive predictor of survival for gastric cancer patients. However, a lower LA score does correlate with an increased count of positive lymph nodes. LA score can be used as a quality indicator for assessment in the postoperative period and is a new marker that can easily be calculated through routine blood tests, suggesting opportunities for further research.

Statement of ethics

The study was established, according to the ethical guidelines of the Helsinki Declaration and was approved by Institutional Review Board of the Çukurova University Faculty of Medicine 10.09.2021 114-37. Informed consent was obtained from all patients and/or their legal guardian(s).

Conflict of interest statement

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

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Author Contributions

OY,UT conceived and designed the study. OY,UT,İCE,AU,GS,CKP acquired data. OY and UT confirm the authenticity of all the raw data. UT,BY performed the statistical analysis. İCE,AU,GS,CKP,BY interpreted the results, analyzed the data and drafted the manuscript. All authors read and approved the final version of the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Originality Assertion

The authors have not submitted this article to another journal previously.

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Testicular Sperm Extraction in Non-Obstructive Azoospermic Patients with Sertoli Cell-Only Syndrome Testicular Histology

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Abstract

Aim: Sertoli cell-only syndrome (SCOS) is a prevalent cause of non-obstructive azoospermia (NOA) in males, where seminiferous tubules exclusively contain Sertoli cells, leading to minimal or absent spermatogenesis. Success rates for sperm retrieval in these cases vary significantly. We aimed to investigate the sperm retrieval rate with microdissection TESE (mTESE) in NOA patients with SCOS testicular histology and the factors that may affect it.

Methods: Patients who underwent mTESE due to NOA were retrospectively evaluated. Only patients with a histopathological diagnosis of SCOS were included in the study. Those with other histopathological diagnoses, those who underwent conventional TESE (cTESE) were excluded from the study. The sperm retrieval rate after mTESE was calculated for patients with a pathology result of SCOS. The age, testicular volume, and Follicle-Stimulating Hormone (FSH) level of the groups with and without sperm were compared.

Results: In our study, 186 patients with testicular histopathology diagnosed as SCOS were included. The rate of sperm retrieval after TESE in these patients was 28%. In patients with retrieved sperm, the mean age was 33.8 ± 5.4 years, the mean testicular volume was 11.1 ± 6.3 ml, and the mean FSH level was 22.5 ± 12.7 mIU/ml. In patients without retrieved sperm, the mean age was 33.8 ± 6.1 years, the mean testicular volume was 10.3 ± 6.1 ml, and the mean FSH level was 21.0 ± 9.8 mIU/ml. There was no significant difference observed in mean age, testicular volume, and FSH level between the group with retrieved sperm and the group without retrieved sperm (p=0.97, p=0.24, p=0.38, respectively).

Conclusions: The findings of our study can be used for counseling men with NOA. Obtaining intratesticular sperm is possible in the presence of NOA and a diagnosis of SCOS histology. Therefore, patients undergoing testicular biopsy with TESE for histological examination can simultaneously prepare for intracytoplasmic sperm injection if sperm is found.

Keywords: *Sertoli cell-only syndrome, non-obstructive azoospermia, infertility, testicular sperm extraction*

1. Introduction

Non-obstructive azoospermia (NOA) means the absence of spermatozoa in semen analysis.[1] Testicular failure is observed as a result of NOA in approximately 1% of all men and 10% of infertile men.[2] The primary treatment for NOA is testicular sperm extraction (TESE) followed by intracytoplasmic sperm injection (ICSI).[1] The testicular histopathology of NOA patients may include hypospermatogenesis, complete or incomplete maturation arrest, and Sertoli cell-only syndrome (SCOS). SCOS is a significant clinical condition where azoospermia and germ cells are not observed, and the success rate of TESE is low.[3]

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In studies, SCOS has been reported in 10.8-44% of infertile men with NOA.[3]

We aimed to investigate the sperm retrieval rate (SRR) in patients with SCOS testicular histology undergoing microdissection TESE (mTESE) and identify potential influencing factors.

2. Materials and methods

This study has been approved by the Başkent University Medical and Health Sciences Research Council (Project No: KA24/70) and conducted in accordance with the principles of the Helsinki Declaration. In our clinic, patients who underwent mTESE due to NOA were retrospectively evaluated. Only patients with a histopathological diagnosis of SCOS were included in the study. Individuals with other histopathological diagnoses, those who underwent conventional TESE (cTESE), and those with incomplete

data were excluded from the study. SRRafter mTESE was calculated for patients with a pathology result of SCOS. The age, testicular volume, and Follicle-Stimulating Hormone (FSH) level of the groups with and without sperm were compared.

2.1. Surgical Technique

With sedoanalgesia and/or local anesthesia combination, mTESE procedures were performed by applying approximately 2 cm vertical incision to the scrotum. The tunica albuginea of the unilateral testis was opened with a vertical incision. Subtunical vessels were identified and avoided under the surgical microscope. Direct examination of the testicular parenchyma was performed at magnifications of x20 to x40 using an operating microscope. Small samples were taken from large, opaque seminiferous tubules. The procedure was terminated when a sufficient volume of sperm was obtained for ICSI. In the instance no sperm was found in one testis, the same procedure was repeated on the contralateral testis. A small tissue sample obtained surgically during the same session was placed in Bouin's solution and sent to the histopathology laboratory.

2.2. Statistical Analysis

Statistical analysis was performed using the SPSS V 22.0 statistical package. Normality of each continuous variable was checked using Kolmogorov-Smirnov and Shapiro-Wilk tests, along with histograms. Between-group comparisons were conducted using the Mann-Whitney U test for non-normally distributed data. P-values less than 0.05 were considered statistically significant.

3. Results

In our study, 186 patients with testicular histopathology diagnosed as SCOS were included. SRR after mTESE in these patients was 28%. In patients with retrieved sperm, the mean age was 33.8 ± 5.4 years, the mean testicular volume was 11.1 ± 6.3 ml, and the mean FSH level was 22.5 ± 12.7 mIU/ml. In patients without retrieved sperm, the mean age was 33.8 ± 6.1 years, the mean testicular volume was 10.3 ± 6.1 ml, and the mean FSH level was 21.0 ± 9.8 mIU/ml. There was no significant difference observed in mean age, testicular volume, and FSH level between the group with retrieved sperm and the group without retrieved sperm (p=0.97, p=0.24, p=0.38, respectively). The parameters evaluated in the study are shown in Table 1.

Table 1

Comparison of clinical and laboratory data of patients in groups

Parameters	Group I*	Group II**	p
Age (year)	33.8 ± 5.4	33.8 ± 6.1	0.97
Testicular Volume (ml)	11.1 ± 6.3	10.3 ± 6.1	0.24
FSH (mIU/ml)	22.5 ± 12.7	21.0 ± 9.8	0.38

*FSH: Follicle-Stimulating Hormone *group with retrieved sperm **group without retrieved sperm*

4. Discussion

The most common histological diagnosis in patients with NOA is SCOS[1]. It is expected that in patients diagnosed with SCOS, there would be a lower SRR compared to other histological diagnoses[1]. However, due to the heterogeneity of testicular histology, it has been reported that spermatozoa can still be found in these patients as well[4]. In two different studies examining the success rate of sperm retrieval in patients with testicular histopathology diagnosed as SCOS, the success rate was found to be 27.6% and 23.6%, respectively[4,5]. In our study, this rate was 28%, which is consistent with these studies. However, in another study, an SRR of 14.8% was found[6]. The reason for this discrepancy may be attributed to the multicenter nature of the study, resulting in heterogeneous patients and TESE being performed by different surgeons.

Due to the emergence of accompanying diseases that negatively affect testicular perfusion and germ cell loss with age, theoretically, lower success rates in terms of SRR are expected in elderly patients[7]. It is known that age is one of the important factors affecting the SRR after TESE[8]. In a study involving a limited number of patients (n=64), the patient age was found to be similar between the groups with no sperm retrieved during TESE (36.4 years) and the groups with sperm retrieved (37.2 years), with slightly higher age observed in the TESE-positive group[7]. Similarly, Guneri et al.[9] also identified age as an important factor in their study (38 years versus 42 years). Okada et al.[10] also demonstrated that patient age is a factor influencing TESE outcomes, determining that the median age was significantly different between the unsuccessful and successful TESE groups (38 (28-43) and 31 (25-40) years, respectively). However, studies evaluating only SCOS patients have reported that age does not have an effect on the SRR[4,5]. In our study, it was also determined that age did not have an effect on the SRR, and we believe this is due to the selection of patients being homogeneous in terms of age.

It is known clinically that testicular volume correlates with spermatogenesis. Turunc et al.[11] found a positive correlation between testicular volume and SRR in patients with NOA, and determined that SRR was significantly lower in patients with testicular volume below 5 mL. However, in this study, distinction based on testicular histopathology was not made. In our study, it was found that testicular volume was not a determining factor for the presence or absence of sperm in the groups. This result differs from studies that only examined SCOS patients and reported lower SRR in men with smaller testicular volumes who underwent cTESE[12,13]. However, recent mTESE studies with large series of NOA patients have shown that testicular volume does not have any effect on SRR[6,14,15]. This suggests that performing mTESE or cTESE in SCOS patients may lead to different outcomes in terms of testicular volume.

There are studies suggesting that serum FSH levels can predict the presence of sperm retrievable by cTESE[16]. Conversely, it has also been reported that FSH has poor predictive value for sperm retrieval via TESE[13,17]. In addition to studies indicating that FSH levels are determinant for patients with testicular histopathology diagnosed as SCOS, there are also studies showing that it has no effect[4-6]. The discrepancy in the relationship between FSH levels and SRR success may stem from differing demographic characteristics across studies. A study by Silber et al.[18] demonstrated that FSH concentration is inversely proportional to the number of germ cells in the testis, yet it lacks correlation with more advanced stages of spermatogenesis. Additionally, it has been noted that FSH can only reflect the global function of spermatogenesis and cannot evaluate the function of an isolated region within the testis[18]. By allowing for more detailed examination of each part of the testis, the mTESE method increases the chance of finding spermatogenic areas[19]. Therefore, mTESE can increase the SRR rate even when the overall spermatogenesis function of the testis is very low[19]. This may explain why FSH cannot accurately predict the SRR of mTESE.

4.1. Limitation

Our study has two main limitations. The first of these is that it is a retrospective study. The other is that parameters related to ICSI and its outcomes, such as fertilization rate, implantation rate, clinical pregnancy rate, and live birth rate, were not evaluated. The high

number of patients in this special group is one of the strengths of our study.

5. Conclusion

The results of our study provide valuable insights for counseling men with NOA. Testicular sperm retrieval is feasible in cases of NOA with a SCOS histology. Consequently, patients undergoing testicular biopsy with TESE for histological assessment can concurrently consider preparation for ICSI if sperm is obtained.

Statement of ethics

This study has been approved by the Başkent University Medical and Health Sciences Research Council (Project No: KA24/70) and conducted in accordance with the principles of the Helsinki Declaration.

Conflict of interest statement

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

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Availability of data and materials

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Originality Assertion

The authors have not submitted this article to another journal previously.

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Diverticulitis Surgery Outcomes: Insights from Our Clinical Practice

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Abstract

Aim: To assess outcomes of diverticulitis surgery, focusing on various patient phases at a tertiary center and incorporating literature insights.

Methods: Analysis included diverticular disease surgeries at Cukurova University's General Surgery Clinic over five years, examining demographics, disease specifics, surgical details, stoma aspects, and complications. Patients were categorized into emergency and elective groups for comparison based on Hinchey scores and stoma status

Results: Of the patients, 72% were male, with an average age of 58.46. The sigmoid colon was predominantly affected (84%). Percutaneous drainage was used preoperatively in 44%, and 56% required a stoma, primarily Hartmann colostomies (36%). The median stoma closure time was 5 months, with 10 patients unable to have their stoma closed. Emergency surgeries were associated with higher Hinchey stages (III-IV) and an increased need for stoma creation (81% vs. 16% in elective surgeries).

Conclusions: The study indicates a median 5-month duration for stoma reversal, with sigmoid colon being the common site regardless of gender. Emergency surgeries showed a higher rate of stoma creation, suggesting elective surgeries could reduce stoma necessity. Further investigation is needed for broader applicability.

Keywords: *Diverticular disease, Hinchey classification, Hartmann procedure, complications, stoma closure*

1. Introduction

Diverticular disease of the colon is an acquired condition resulting from herniation of the mucosa through defects in the muscle layer. Colonic diverticular disease is a common aliment of the digestive system. Diverticulosis has become increasingly prevalent in industrialized societies over the last century. Particularly in Western countries, it is found in about 50% of individuals over the age of 60. Most patients with diverticular disease remain asymptomatic, but up to 25% of patients with diverticulosis will develop symptoms of diverticulitis such as abdominal pain, bloating, and changes in bowel habits over their lifetime. Complications such as abscess, fistula, obstruction, bleeding, or perforation will develop in up to 20% of patients with diverticular disease.[1-4]

Diverticular disease encompasses various stages of illness and, consequently, treatment strategies. While acute diverticular perforation is considered an absolute indication for emergency surgery, the surgical approach to acute diverticular disease, whether complicated or uncomplicated, largely depends on the stage and the patient.[5,6] Due to the challenges in the disease course and individual differences in management, numerous guidelines have been published.[6-8] Recently, the latest updated version of the German national guideline on sigmoid diverticular disease was published.[8] After a successful resolution of an acute diverticulitis episode, the purpose of proceeding with elective colon resection in patients is defined as the prevention of future hospitalizations, reducing the risk of needing emergency colon resection, and achieving long-term recovery without abdominal symptoms or recurrent diverticulitis, even though the literature does not fully support this recommendation.[9,10]

This study aims to present the findings related to the presentation, preoperative, perioperative, and postoperative periods of patients operated for diverticular disease of the colon at a tertiary center, alongside a review of the literature.

2. Materials and methods

After obtaining permission from the local ethics committee dated 08.12.2023 and numbered 139/37, patients who underwent surgery for diverticular disease of the colon at the General Surgery Clinic of Cukurova University in the last five years were included in

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our study. Patients with incomplete data or malignancy in pathology results were excluded. Data were retrospectively analyzed using the hospital's electronic medical records system.

Demographic data, history, and localization of diverticular disease, mode of presentation, type of operation, necessity for stoma creation, type of stoma, and timing of stoma closure, as well as perioperative complications, were analyzed. Additionally, patients were divided into emergency and elective groups, and these groups were analyzed based on their Hinchey scores and stoma statuses.

Patients in the diverticulitis group were divided into four stages according to the Hinchey classification based on abdominal CT findings.[11] Our institution considered the recommendations of the American Society of Colon and Rectal Surgeons for elective and emergency management of diverticular disease.[12]

2.1.Statistical evaluation

Statistical analysis was performed using SPSS 22.0 (IBM Corp) software. The normal distribution fit of numerical data was assessed with the Kolmogorov-Smirnov test. Numerical variables with normal distribution were presented as mean ± standard deviation; those without normal distribution were presented as median (minimum-maximum) values. Categorical data were expressed as numbers and percentages (%). Differences between categorical data were analyzed using the chi-square test. A p-value of less than 0.05 was considered statistically significant.

3. Results

Fifty patients were included in our study. The average age was 58.46. Male gender was predominant (72%). The average number of episodes was 2. The most common location was the sigmoid colon (84%), and percutaneous drainage was performed in 44% of the patients. The average duration of the disease was 12 months, with the most common Hinchey stage being 4 (42%). Demographic and clinical data are shown in Table 1.

Table 1

Demographic and clinical data

Variable		
Gender	Male	72% (n:36)
	Female	28% (n:14)
Age		58.46±14.38
Number of episodes		2 (1-4)
Smoking		60% (n:30)
Localization	Sigmoid Colon	84% (n:42)
	Ascending Colon	6% (n:3)
	Total Colon	6% (n:3)
Percutaneous Drainage		44% (n:22)
Disease length (month) Median(min-max)		12 (0.1-84)
Hinchey Score		
• I		24% (n:12)
• II		12% (n:6)
• III		22% (n:11)
• IV		42% (n:21)

Emergency presentations were frequent, with loop colostomy being the most common stoma type (36%), and 70% of patients had undergone open surgery. The most common complication was surgical site infection. Perioperative period data are shown in Table 2.

Emergency surgery patients had higher stages of Hinchey classification (III-IV) (p<0.001). Also, the study found a higher need for stoma in emergency cases (81% vs 16% p<0.001). Hartmann colostomy was the most common type of stoma in both emergency and elective cases (64% vs 67% p=0.927). Comparative analyses are shown in Table 3.

Table 2

Peroperative Period

Presentation Type	Emergency	64% (32)
	Elective	36% (18)
Stoma Requirement	End Colostomy	36% (18)
	Loop Ileostomy	20% (10)
Operation Type	Open	70% (35)
	Laparoscopic	30% (15)
Complications		%,n
Abscess		8% (n:4)
Anastomotic Leak		4%(n:2)
Incisional Hernia		6% (n:3)
Ileus		8% (n:4)
Surgical Site Infection		14% (n:7)
Stoma Closure	Closed	64.2% (n:18)
	Not Closed	35.7% (n:10)

Table 3

Comperative Analysis

		Emergency Surgery	Elective Surgery	P value
Hinchey Classification	IA	0[a]	66.7%(12)	<0.001
	II	3.1[a]%(1)	27.8%(5)	
	III	31.3%(10)	5.6%(1)	
	IV	65.6%(21)	0	
Stoma Requirement	Yes	81.3%(26)	16.7%(3)	<0.001
	No	18.8%(6)	83.3%(15)	
Stoma Type	Hartmann	64%(16)	66.7%(2)	0.927
	Loop Ileostomy	36%(9)	33.3%(1)	
Stoma Status	Closed	68%(17)	33.3%(1)	0.236
	Not Closed	32%(8)	66.7%(2)	
Stoma Closure Time				Median 5 (3-24)

Hinchey Classification	IA	II	III	IV	P value
Stoma Closure Failure	20%(2)	0	0	80%(8)	<0.05

4. Discussion

In this study, which presents the outcomes of surgical treatment for diverticular disease of the colon, we found that the most common site of diverticula was the sigmoid colon. The highest rate of presentation was at Hinchey stage 4. The majority of patients underwent conventional surgery under emergency conditions. There was a greater need for stoma in emergency presentations, with one-third of patients who had a stoma ending up with it being permanent. Patients with non-closable stomas were mostly classified as Hinchey 4 at the time of presentation.

The severity of diverticulitis is categorized using the modified Hinchey classification. Uncomplicated diverticulitis includes stage 0 (clinically mild diverticulitis) and stage Ia (pericolic inflammation), successfully treated non-surgically in 70 to 100% of cases. Complicated diverticulitis includes stage Ib (abscess near primary inflam-

mation <5 cm), stage II (intraperitoneal, pelvic, or retroperitoneal abscess, or abscess distant from primary inflammation), stage III (generalized purulent peritonitis), and stage IV (fecal peritonitis).[11-13] Evaluating our patient population, the high frequency of Hinchey 4 suggests a composition of complicated cases, which could explain the high rates of emergency surgery and stoma.

Historically, the Hartmann procedure was the gold standard for the surgical treatment of perforated diverticulitis. Its advantages include a relatively short operation time and avoidance of anastomosis; it was especially applied in unstable patients. However, current surgical practices are evolving, emphasizing adaptation to the Hinchey stage.[3] Laparoscopic lavage has emerged as an acceptable alternative to resection for patients presenting with generalized purulent peritonitis (Hinchey III disease). Three randomized clinical trials compared outcomes following laparoscopic lavage with the standard Hartmann procedure. Overall, results from all three trials were similar, suggesting that laparoscopic lavage may have lower mortality, fewer stoma and wound-related issues, but potentially higher postoperative interventions.[14-16] Primary sigmoid resection and anastomosis (PRA) have emerged as an alternative for perforated diverticulitis with purulent or feculent peritonitis (Hinchey III/IV). Various systematic reviews and meta-analyses have compared PRA with the Hartmann procedure (HP).[17,18] Ryan OK et al. included 12 studies with 918 patients in their meta-analysis and found no difference in 30-day mortality between groups, but overall mortality and major postoperative complications were lower after PRA. The initial and permanent stoma rates were also lower in the PRA group.[19] In our population, the rate of Hartmann procedure was 36%, and our stoma rate was 58%, with one-third of these being permanent. Our permanent stoma rate was associated with Hinchey 4 classification. We did not observe a relationship between the urgency of the operation (emergency or elective) and the permanence of the stoma.

The literature shows that patients experiencing more than two attacks do not have higher morbidity and mortality risks when compared to patients with fewer attacks. This suggests that the nature of this disease process is not progressive and that individuals presenting with complicated disease are likely to do so at their initial presentation. When discussing surgery with a patient, treatment should be individualized, and the surgeon should consider the patient's medical condition, the risks of surgery, the impact of recurrent attacks on the patient's lifestyle (occupational and personal), the possibility of undiagnosed carcinoma, the severity of the attacks, and chronic or persistent symptoms.[2,12] In our population, all patients were individually assessed when making decisions about elective colectomy. In our population with a median number of two attacks, 44% had a history of percutaneous drainage, and some had experienced four attacks; colectomies were planned with all these parameters in mind.

The main limitations of our study were its retrospective and single-center nature. The limited number of patients reduced the level of scientific evidence.

5. Conclusion

Diverticular disease represents a spectrum of clinical presentations ranging from mild, self-limiting diverticulitis to free colonic perforation requiring the resection of the diseased colon, with or without permanent colostomy. Surgical decision-making is increasingly based on a combination of individual patient and disease factors. Careful preoperative planning, intraoperative decisions, and technical considerations are crucial for successful postoperative outcomes in this patient population.

Statement of ethics

The study was established, according to the ethical guidelines of the Helsinki Declaration and was approved by Institutional Review Board of the Çukurova University Faculty of Medicine 08.12.2023 and numbered 139/37. Informed consent was obtained from all patients and/or their legal guardian(s).

Conflict of interest statement

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Author Contributions

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Originality Assertion

The authors have not submitted this article to another journal previously.

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Posterior Fossa Craniotomy: Retrospective Analysis of 85 Patients

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Abstract

Aim: Craniectomy procedures were traditionally performed in posterior fossa surgeries. However, craniotomy procedure has also been started to be performed routinely in recent years. In this study, we aimed to evaluate the patients who underwent posterior fossa craniotomy procedures.

Methods: The records of 85 patients who underwent posterior fossa craniotomy for various pathologies between 2016-2021 were retrospectively reviewed.

Results: The mean age of the patients was 36.1 (2-82 years interval). There were 43 female patients (50.5%) and 42 male patients (49.5%). The pathologies were tumoral in 63 patients and non-tumoral in 22 patients. The symptoms of the patients identified were headache (84.5%), cerebellar symptoms (68%), deterioration of consciousness (54%), nausea (48%), cranial nerve dysfunction (34%) and hemiparesis (18.5%). At admission, hydrocephaly was present in 22 patients. Ventriculoperitoneal shunt was applied to 12 of these patients. The duramater of the 68 patients were closed with primary suturation while 17 patients underwent duraplasty with fascia graft. Craniotomy flaps were fixed with only silk in 75 patients and miniplates in 10 patients. Two of the patients had pseudomeningocele and 1 had cerebrospinal fluid leak from the wound. The mortality rate was 3.5%. The mean duration of hospitalization was 7.6 days (2-54 days interval).

Conclusions: Posterior fossa craniotomy technique has recently become widespread and begun to replace traditional craniectomy technique. It was facilitated by using high-speed drill with the advancement in technology. Posterior fossa craniotomy is a prominent technique with the low complication rates and high patient comfort in the postoperative period.

Keywords: *Posterior fossa, craniotomy, tumor, microvascular decompression, complication*

1. Introduction

Posterior fossa surgery is one of the important applications of neurosurgical practice. It differentiates from other regions of the brain in terms of the path of intervention and comprises important anatomical and neurovascular structures. Posterior fossa surgery is a routine procedure in the surgeries such as tumor, hemorrhage, cystic lesions that are located in posterior fossa and microvascular decompression. Traditional craniectomy procedure was performed during posterior fossa surgery in the past while craniotomy procedure started to be routine procedure in the last three decades.

Preservation of the bone structure is useful in many ways for the patient. There are studies in the literature examining osteoblastic craniotomies performed in posterior fossa interventions and comparing craniotomy and craniectomy procedures.[1-4] Craniotomy is considered to be more advantageous. In this study, we aimed to evaluate 85 patients who underwent posterior fossa craniotomy for various pathologies.

2. Materials and methods

The records of 85 patients who underwent posterior fossa craniotomy for various pathologies between 2016-2021 were retrospectively reviewed. Patient records including age, gender, preoperative and postoperative neurological conditions, type and radiographic localization of their pathologies, applied surgical positions, closure methods of duramater, fixation methods of bone flaps, drain applications, hospitalization periods and postoperative complications were gathered.

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Figure 1

(a) Preoperative axial and sagittal contrast-enhanced magnetic resonance images of 17-year-old female patient with 4. ventricle localized cavernoma. **(b)** Postoperative axial and sagittal contrast-enhanced magnetic resonance images of the same patient revealing total resection of the lesion.

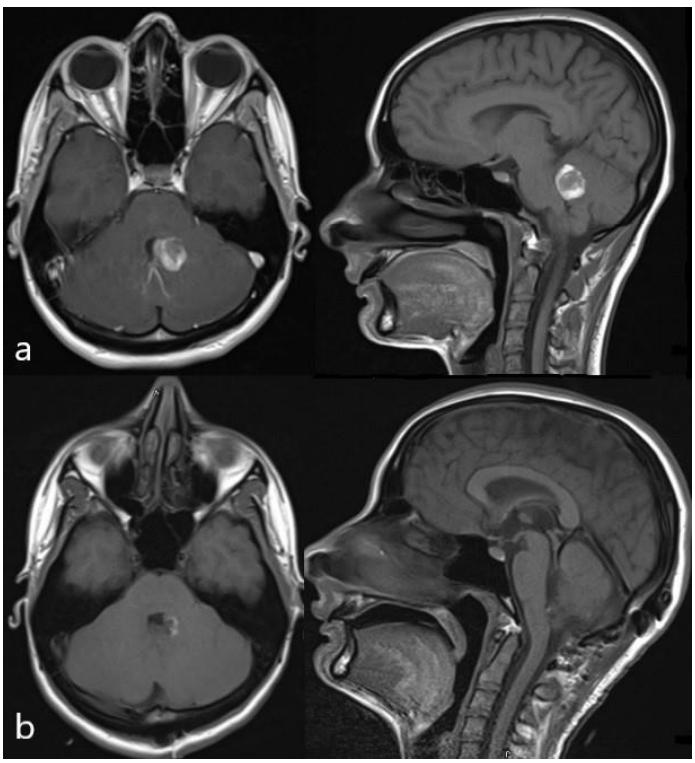
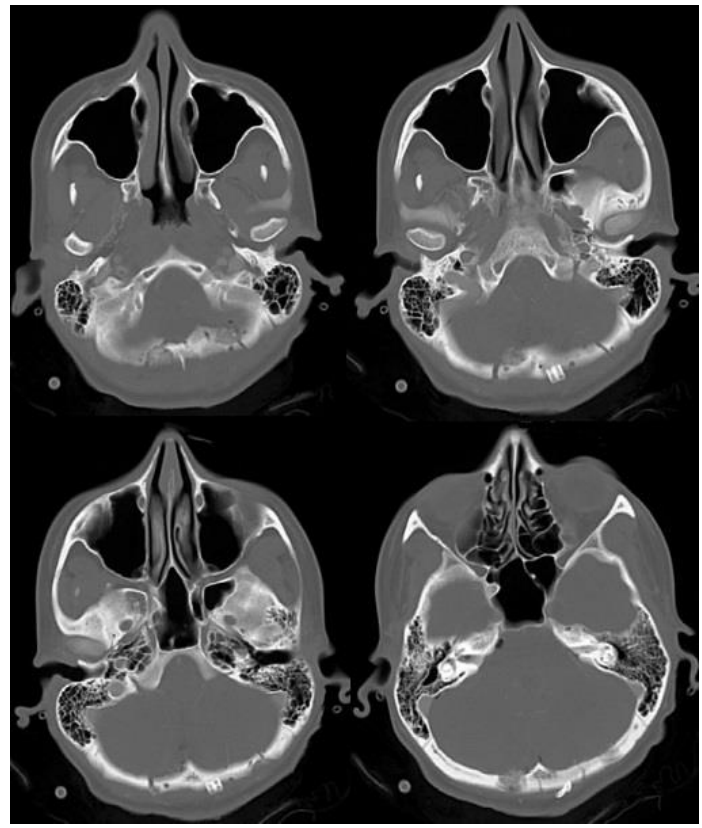


Figure 2

Postoperative axial cranial computed tomography images of the same patient demonstrating suboccipital craniotomy for posterior fossa cavernoma excision



Surgical planning was performed according to the location of the lesions. Contrast-enhanced magnetic resonance imaging of all of the patients was performed preoperatively (Figure 1). The patients were operated via sitting, prone and park bench positions. Duramater was closed with primary suturation in suitable patients while duraplasty with fascial graft was performed in inappropriate patients. However, watertight closure was ensured in all patients. Posterior fossa craniotomy procedures were applied to all patients (Figure 2). Craniotomy technique was applied to the patients with four burrholes from the safe areas and cutting with high-speed drill after dissection of the duramater under the bone. There was no dural or sinus injury in any of the patients except one. This patient had injury to the sigmoid sinus. However, the repair with the fascia graft and surgecell tamponade was performed and the patient was discharged without any problem. Bone flaps were fixed with silk in appropriate patients and by using miniplates in patients with defective or fragmented bone flaps. Jackson-pratt drains were placed in the required patients and drain was not placed in patients with good hemostasis. The patients were medicated with prophylactic antibiotherapy (ampicillin sulbactam) peroperatively and postoperatively for three days.

2.1. Statistical evaluation

SPSS software version 25.0 (IBM Corporation, Armonk, New York, USA) was used to analyze the variables. The Mann–Whitney U-test was applied with the Monte Carlo results to compare the categorical variables quantitatively. The quantitative variables were presented as the mean ± SD (standard deviation) and range (maximum-minimum) and the categorical variables as n (%). The variables were examined at a 95% confidence level, with $p < 0.05$ considered to indicate statistical significance.

3. Results

3.1. Patient Profile

A total of 85 patients were included in the study. The mean age of the patients was 36.1 (2-82 years interval). 43 patients (50.5%) were female and 42 patients (49.5%) were male. 24 patients were in pediatric age group and 61 were adult. 63 patients had tumoral and 22 patients had non-tumoral pathologies. Of these 22 patients, 17 had trigeminal neuralgia, 2 had cerebellar abscess, 1 had hydatid cyst and 2 had traumatic epidural hematoma. In the tumoral group, 19 patients had medulloblastoma, 11 patients had epidermoid tumor, 8 patients had meningioma, 7 patients had schwannoma, 3 patients had hemangioblastoma, 4 patients had low grade glial tumor, 2 patients had high grade glial tumor, 2 patients had ependymoma and 1 patient had cavernoma (Table 1).

3.2. Patient Symptoms

The most common symptom was headache (84.5%). Other symptoms identified were cerebellar symptoms (68%), deterioration of consciousness (54%), nause (48%), cranial nerve dysfunction (34%) and hemiparesis (18.5%), respectively (Table 2).

3.3. Neuroimaging

The pathologies were extra-axial in 66 patients and intra-axial in 19 patients. Localization of the pathologies were; right cerebellopontine angle in 23 patients, left cerebellopontine angle in 21 patients, fourth ventricle in 20 patients, left cerebellum in 13 patients, right cerebellum in 6 patients and brainstem in 2 patients. According to the neuroimaging of the patients, hydrocephaly was detected in 22 patients. All patients with hydrocephalus had tumoral pathologies.

Table 1

Demographic data of the patients in the study group

Characteristics		Study group n=85 (%)
Age (Mean)		36.1 ± 5.5 (2 -82 years)
Gender (Male/Female)		42/43
Pathology	Tumoral	63 (75%)
	· Medulloblastoma	19 (23%)
	· Epidermoid tumor	11 (14%)
	· Menengioma	8 (9%)
	· Schwannoma	6 (7%)
	· Metastasis	7 (8%)
	· Hemangioblastoma	3 (4%)
	· Low grade glial tumor	4 (5%)
	· High grade glial tumor	2 (2%)
	· Ependymoma	2 (2%)
	· Cavernoma	1 (1%)
	Non-tumoral	22 (25%)
	· Trigeminal neuralgia	17 (20%)
	· Cerebellar abcess	2 (2%)
	· Hydatid cyst	1 (1%)
	· Epidural hematoma	2 (2%)

Table 2

Clinical symptoms of the patients

Symptoms	Study group n=85 (%)
· Headache	84.5%
· Cerebellar signs	68%
· Consciousness deterioration	54%
· Nausea-vomitting	48%
· Cranial nerve deficit	34%
· Hemiparesis	18.5%

Table 3

Surgical procedures performed to the patients and postoperative complications

Characteristics		Study group n=85 (%)
Position	· Sitting	48 (56%)
	· Lateral park-bench	33 (39%)
	· Prone	4 (5%)
Dural closure	· Primary suturation	68 (80%)
	· Fascia graft	17 (20%)
Bone fixation	· Silk only	75 (88%)
	· Miniplates	10 (12%)
Jackson-Pratt drainage	· +	74 (87%)
	· -	11 (13%)
Hydrocephalus treatment	· External ventricular drainage	16 (19%)*
	· Ventriculoperitoneal shunt	12 (14%)**
Complications	· Pseudomeningocele (short term)	1 (1%)
	· Pseudomeningocele (long term)	1 (1%)
	· CSF leak + meningitis	1 (1%)
	· Hematoma	1 (1%)
	· Vegetative state	1 (1%)
	· Exitus	3 (3.5%)

CSF: Cerebrospinal fluid, Ventriculoperitoneal shunt was applied in 6 of these patients, 10 patient did not need ventriculoperitoneal shunt after tumor resection,*

*** Ventriculoperitoneal shunt was applied in 6 patients before the surgery and in 6 patients after external ventricular drainage.*

3.4. Surgery

Posterior fossa craniotomies were applied to all patients. The operations of 48 patients was performed in the sitting position, 33 patients in the park bench position and 4 patients in the prone position. All craniotomies were performed using high speed drill. The duramater of the 68 patients were closed by primary suturation and the rest of the 17 patients underwent duraplasty with the fascia graft. Watertight closure was ensured with valsalva maneuver in all patients. Craniotomy flaps were fixed using only silk in 75 patients (Figure 3-4). In 10 patients, bone flaps were fixed with miniplates because they were fragmented or defective. During closure, Jackson-Pratt drains were placed in 74 patients. 11 patients did not have a drain due to good hemostasis (Table 3). The mean duration of hospitalization was 7.6 days (2-54 days interval).

At admission, hydrocephaly was present in 22 patients. Ventriculoperitoneal shunt was applied in 6 of these patients before tumor resection. The remaining 16 patients underwent external ventricular drainage. In 6 of these patients, ventriculoperitoneal shunt was needed and shunt was inserted after tumor resection. A total of 12 patients underwent ventriculoperitoneal shunting (Table 3).

Figure 3

Peroperative images of the same patient revealing suboccipital craniotomy fixation with silk sutures.

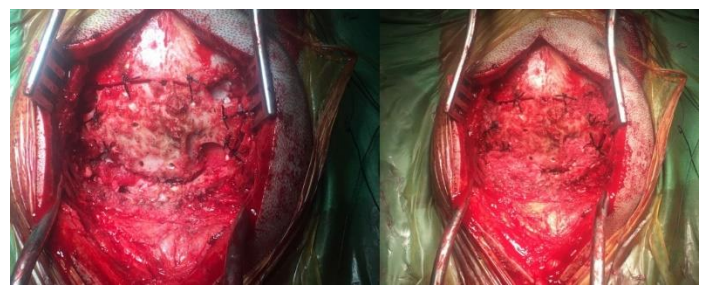
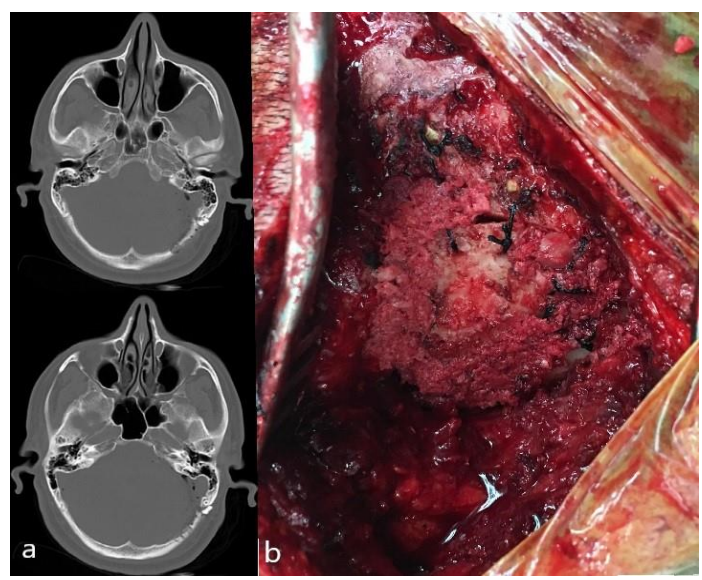


Figure 4

(a) Postoperative axial cranial computed tomography images of 32-year-old male patient who underwent microvascular decompression via left retrosigmoid craniotomy for trigeminal neuralgia. **(b)** Peroperative images of the same patient demonstrating left retrosigmoid craniotomy.



3.5. Complications

There were complications detected in 8 patients. During the follow-up, short term pseudomeningocele in 1 patient, long term pseudomeningocele in 1 patient, hematoma in 1 patient and co-existence of cerebrospinal fluid (CSF) leak from the wound and meningitis in 1 patient were detected. 3 patients died and 1 patient had vegetative status. The mortality rate was 3.5%. The patients who developed pseudomeningocele were treated with external lumbar subarachnoid drainage. The patient who developed hematoma in the operation region underwent re-operation and her hematoma was drained out. The patient who had co-existence of CSF leak from the wound and meningitis was treated with proper antibiotherapy and external lumbar subarachnoid drainage (Table 3).

4. Discussion

Traditionally, posterior fossa surgeries include craniectomy procedures. However, craniotomy procedures have been widely applied during the posterior fossa surgeries in the last three decades. This procedure was first described by Yaşargil and Fox[5] in 1974. This craniotomy procedure is a technique applied by several burrholes using gigli wires. Ogilvy and Ojemann[6] presented the craniotomy technique by using high-speed drill to the literature in 1993. In the following years, other techniques that have been modified using high-speed drill are also described in the literature[7-10]. This technique has been widely used in pediatric patients in previous periods and is currently used in both pediatric and adult age groups[3].

There are some advantages of osteoclastic craniectomy technique used in traditional posterior fossa interventions. It is a more familiar technique by neurosurgeons in terms of application, it is easier to apply and can provide a wide field of view and it is easier to preserve duramater and vital neurovascular structures such as transverse and sigmoid sinuses during the procedure[4]. However, anatomical plane is impaired after resection of the occipital bone and the vital neurovascular structures in the posterior fossa remain vulnerable as a result of this technique[1,4]. In addition, posterior fossa craniectomies have been associated with an increase in surgical complications in the literature[1-4].

Craniectomy procedures are thought to increase especially CSF leak in posterior fossa surgeries[1-4]. In cases where the skin integrity does not deteriorate, pseudomeningocele formation occurs, and in cases of deterioration, CSF leak and infections such as meningitis occur. In the study performed by Gnanalingham et al., three hypotheses were presented. The first one is the iatrogenic elimination of one of the anatomical layers to be breached before CSF can leak from the wound. The second is the bulging of the sutured duramater from the craniectomy defects with the increase in the intracranial pressure, such as coughs or strains, and dural sutures may tear out in these patients. The third is the formation of a dead space in the region where the muscles adhere together as a result of the resection of the bone, which is an adhesion area for the paravertebral muscles. Even in the small defects in the dura, this dead space is suitable for the formation of CSF collection and pseudomeningocele in the later stages[1].

CSF leak may also be seen after posterior fossa craniotomies. However, CSF leak rates were found to be much lower in craniotomies in the studies presented in the literature[1-4]. In the study performed by Legnani et al.[4], pseudomeningocele rates were 4% in craniotomy and 19.2% in craniectomy. CSF fistula rates were found to be 11.5% in craniectomy and 2% in craniotomy. Gnanalingham et al.[1] presented similar results. In the craniotomy group, the rate of pseudomeningocele was 9% and CSF leak rate was 4%, while these rates were 23% and 27% in the craniectomy group. Because of the high CSF leak rates, wound infection and meningitis rates also increased in the craniectomy patients. In the present study, the rates of CSF leak and pseudomeningocele were 1% and 2% in patients who underwent craniotomy. Meningitis occured in one patient who had risk factors including CSF leak from the wound and long-term stay in the intensive care unit. This patient was treated with appropriate antibiotherapy and external lumbar subarachnoid drainage application and discharged with no problem.

Severe headache is another problem that may occur after craniectomy procedures in posterior fossa surgery. It is thought that this situation is caused by adhesion of the paravertebral muscles to the duramater and traction of the duramater during neck movements[1,9,11]. In accordance with this, we did not observe severe headache in the present craniotomy cohort. Another advantage of craniotomy is the ease of reoperations in the long term. Since the anatomical plane is impaired in patients undergoing craniectomy, the risk of damage to the duramater and vital neurovascular structures increases in recurrent surgeries[1,4,9,12].

In previous periods, there was a thought that the craniectomy procedure would save the patients in emergency cases such as sudden brain swelling. However, it was found that this situation was not significant. No significant difference was found in the studies presented in the literature[2-4]. In order to avoid this situation, we think that total resection of the pathology in suitable patients, careful hemostasis, proper opening of subarachnoid cisterns and drainage of CSF should be performed.

In the literature, there are also publications in which the craniectomy defect is closed by using the autologous bone particles. Missori et al.[13] presented a technique in which autologous bone fragments were covered with Surgicel (Ethicon, Johnson & Johnson) and the suboccipital craniectomy defect was reconstructed. In the study performed by Sheikh et al.[10], reconstruction of the craniectomy defect was described by adding tissue glue to the autologous bone particles and covered with gel foam. There are also more studies about craniectomy defect reconstruction using tissue glue in the literature[14-16]. However, in such techniques, a certain fusion period is required for the bone flap and the strength of the bone in the early stages is not sufficient to be protective. In addition, we believe that craniotomy technique is more advantageous in terms of both susceptibility to infection and cost because it is applied without using a foreign body. Foreign material such as cranioplastic kit may cause artifacts in the neuroimaging of patients at later stages.

There are certain limitations of the present study. The most important limitation was the retrospective nature of the study. The absence of a craniectomy cohort in which we can compare the craniotomy group is another important limitation. The patient group was not classified as pediatric and adult, and a study group of total of 85 patients was composed.

5. Conclusion

Craniotomy procedure in posterior fossa surgery is a technique that has become widely used in recent years and replaces traditional craniectomy procedure. Although the application technique was thought to be more difficult in the early stages, it has been determined that the neurosurgeons could apply craniotomy procedure without damaging the patient with their modified techniques. It was difficult to apply with gigli wires in the past, but with the technology advancement, it was facilitated with the use of high-speed drill. It can be applied without any problem as a result of a certain learning period. In the present study, we present patients who underwent posterior fossa craniotomy with various pathologies. Posterior fossa craniotomy is a prominent technique with the low complica-

tion rates and high patient comfort in the postoperative period.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Cukurova University Clinical Research Ethics Committee (Date: 23/02/2024, decision number 22).

Conflict of interest statement

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

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Author Contributions

KO is the major contributor in writing the manuscript. KO, EG and AG are involved in the design and conception of the study. KO, EG, EU, MM, HS, and AG are involved in the collection of the data and the clinical follow-up of the patients. All authors read and approved the final version of the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Originality Assertion

The authors have not submitted this article to another journal previously.

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Evaluation of Anxiety Levels in Patients Undergoing Intravitreal Injection for Diabetic Macular Edema

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Abstract

Aim: In this study, we aimed to analyze the anxiety levels of patients regarding intravitreal injection (IVI) using the Amsterdam Preoperative Anxiety and Information Scale (APAIS) and to evaluate the effect of repeated injections on anxiety levels.

Methods: Between September 01, 2023 and January 10, 2024, 85 patients who underwent intravitreal anti-vascular endothelial growth factor injection for diabetic macular edema in our clinic were included in this study.

Results: According to APAIS scores, mean anesthesia anxiety was 5.4±2.6, surgical anxiety was 5.1±2.6 and total anxiety score was 10.5±3.7. Anesthesia information need was 2.7±0.95, surgical information need was 2.6±1.14 and total information need score was 5.3±1.50. There was no significant difference between genders in terms of total and subgroup scores (p>0.05, all). No significant correlation was found in the correlation analysis between age and number of injections and APAIS scores (subdimensions and total) (p>0.05, all).

Conclusions: In conclusion, the potential anxiety of patients before and during intravitreal injection should be considered. In addition, since IVI often involves repeated treatments, it is of great importance to identify modifiable factors that may reduce anxiety. Given the importance of compliance, premedication may be considered to reduce anxiety, especially in high-risk (high preoperative anxiety) patients. Comprehensive explanations about treatment and well-structured processes are crucial for long-term adherence to anti-VEGF therapy.

Keywords: *anti-VEGF; anxiety; diabetic retinopathy; intravitreal*

1. Introduction

Diabetic retinopathy (DR) is one of the most common microvascular complications of diabetes. For the treatment of DR, triamcinolone acetate, dexamethasone or anti-VEGF (vascular endothelial growth factor) containing solutions are given by intravitreal injection (IVI). Inhibition of VEGF leads to regression of neovascularization and prevents the development of neovascularization. In addition, it improves lipid and exudate leakage from existing vessels[1].

Due to the global aging population and increasing life expectancy, the number of intravitreal injections is increasing day by day. Anxiety disorders are common during the procedures. It is very important to determine the patient's level of anxiety and the causes of anxiety in determining appropriate interventions to relieve anxiety in the pre-procedure period. In this study, we aimed to analyze patients' anxiety levels about intravitreal injection using the Amsterdam Preoperative Anxiety and Information Scale (APAIS) and to evaluate the effect of repeated injections on anxiety levels.

2. Materials and methods

Written informed consent was obtained from all participants. The necessary permissions were obtained from the Toros University Scientific Research and Publication Ethics Committee (2023/155-21/12/2023). The study was conducted in accordance with the Declaration of Helsinki.

All patients who underwent IVI anti-VEGF for diabetic macular edema between September 01, 2023 and January 10, 2024 in our clinic were included in the study. The study population was between 30 and 85 years of age, communicable, literate, and not using any sedative and/or antidepressant medication. Age and gender data of all patients were noted. The number of previous intravitreal injections, if any, and the number of injected eyes were also recorded.

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Patients participating in the study were given verbal information about the procedure and the study by the ophthalmologist before the procedure. Participation in the study was voluntary. The Amsterdam Preoperative Anxiety and Information Scale was completed by the investigators (psychiatrists) at the bedside.

Amsterdam Preoperative Anxiety and Information Scale (APAIS) In 1996, the Moermann group in the Netherlands developed the Amsterdam Preoperative Anxiety and Information Scale. It is one of the tests used to assess anxiety in the preoperative period. The source of anxiety is divided into three in this test: anxiety about surgery, anxiety about anesthesia or anxiety about lack of information. It includes 6 statements for these three sources to assess anxiety. To objectify the questionnaire, each statement is given a numerical value based on a 5-point Likert scale according to severity. These severity values range from one to five; 1=none, 2=mild, 3=moderate, 4=severe, 5=extreme. Anesthesia anxiety is calculated with the scores given to questions 1 and 2, surgical anxiety is calculated with the scores given to questions 4 and 5, and the total anxiety score is calculated by summing both. The statements expressing the desire to obtain information about anesthesia and surgery are questions 3 and 6. The lowest score is 6 and the highest score is 302. The validity and reliability study in our country was conducted by Çetinkaya et al.[3]

Statistical analysis of the study data was performed with the SPSS 29.0.1 package program (IBM Corp, Armonk, NY, USA). Categorical variables were expressed as number (n) and percentage (%) and continuous variables were expressed as mean ± standard deviation. The normal distribution of continuous variables was checked by Shapiro-Wilk test. Student's t test was used to compare the means of the groups. The relationship between categorical variables was investigated by chi-square analysis. Statistical significance level was taken as $p<0.05$ for all comparisons.

3. Results

The mean age of the patients was 53.7±15.2 years. Forty-three (50.6%) of the patients were female. Fifty-two (61.2%) patients received injections in both eyes. The mean number of injections was 9.2±5.2. The mean age and number of injections did not differ between genders (p=0.154 and p=0.346 respectively) (Table 1).

Table 1

Demographic data, injection data and APAIS scores of the patients

		Overall	Gender		p
	N	85	Female 43	Male 42	
Age (years)		53.7±15.2	52.0±13.4	55.4±16.8	0.154
Laterality	Right (n,%)	18 (21.2)	10 (23.3)	8 (19.1)	0.642
	Left (n,%)	15 (17.6)	6 (13.9)	9 (21.4)	
	Bilateral (n,%)	52 (61.2)	27 (62.8)	25 (59.5)	
IVI number (n)		9.2±5.2	8.9±4.8	9.4±5.6	0.346
Anxiety	Anesthesia	5.4±2.6	5.7±2.6	5.1±2.5	0.112
	Surgery	5.1±2.6	4.8±2.5	5.5±2.6	0.096
	Total	10.5±3.7	10.5±3.7	10.6±3.8	0.471
Need for information	Anesthesia	2.7±0.95	2.7±1.00	2.7±0.90	0.398
	Surgery	2.6±1.14	2.5±1.20	2.7±1.07	0.208
	Total	5.3±1.50	5.23±1.56	5.38±1.45	0.325

IVI: intravitreal injection

According to APAIS scores, anesthesia anxiety was 5.4±2.6, surgical anxiety was 5.1±2.6 and total anxiety score was 10.5±3.7. Anesthesia information need was 2.7±0.95, surgical information need was 2.6±1.14 and total information need score was 5.3±1.50. There was no significant difference between genders in terms of total and subgroup scores (p>0.05, all) (Table 1).

No significant correlation was found in the correlation analysis between age and number of injections and APAIS scores (subgroup and total) (p>0.05, all) (Table 2).

Table 2

Correlation analysis between APAIS scores and age and number of injections

		Anxiety			Need for information		
		A	S	Total	A	S	Total
Age (years)	r	-0.031	0.164	0.092	0.040	-0.152	-0.090
	p	0.781	0.134	0.402	0.717	0.166	0.413
IVI number (n)	r	0.110	0.012	0.083	0.067	-0.048	0.006
	p	0.319	0.915	0.452	0.544	0.666	0.956

A: Anesthesia, S: Surgery

4. Discussion

Patients with long-term or poorly controlled diabetes have a higher risk of developing DR, which can lead to vision-threatening complications[4]. Currently, anti-VEGFs are widely used in the treatment of retinal disorders with exudation. Intravitreal injection of anti-VEGFs is a lengthy process involving regular follow-up in an ophthalmology clinic and frequent follow-up examinations. The decision to IVI and the uncertainties of the injection process may lead to increased anxiety in patients.

Thetford et al. showed that anxiety is most often present at the start of treatment, whereas another study found that anxiety was not related to the time since the start of treatment[5,6]. Anxiety is encountered before and during invasive procedures. Anti-VEGF injection therapies are a continuous process. Therefore, consecutive treatments may cause patient anxiety. This may affect the success of treatment. Anxiety may lead to complications related to sudden eye or head movement such as endophthalmitis, iatrogenic cataract and corneal abrasion[7].

Chaudhary et al. included 48 eyes of 48 patients with a mean age of 68.4 years. 62.5% of the patients were male. Severe anxiety and pain were seen in 10.4% and 12.5%, respectively. In addition, there was a significant correlation between visual analog scale scores for anxiety and pain (r=0.430, p=0.002) and no other pre-procedure parameter showed a significant relationship with VAS score[8].

In another study, high anxiety level in the pre-procedure period was found to be associated with higher pain sensation during the procedure[9]. Berger et al. included 201 patients (92 females and 109 males) with a mean age of 68 years in their study. The results showed that advanced age and high anxiety were associated with increased systolic blood pressure[10].

In a study of 300 patients undergoing IVI, 56% of patients reported anxiety related to anti-VEGF therapy and 17% of patients showed clinically significant anxiety. The main causes of anxiety included fear of blindness due to intravitreal injections and concerns about the efficacy of the treatment rather than pain. Anxiety levels were significantly higher in patients who received one or two injections compared to those who received three or more injections. However, no significant correlation was found between anxiety lev-

els and the number of injections[11].

In our study, no significant correlation was observed between age and number of injections and anxiety levels. However, patients need anesthesia and surgical information. When this finding and literature data are considered together, pre-procedure patient information should be detailed, explanatory and understandable. This may increase the comfort of patients at the time of the procedure and prevent unwanted iatrogenic trauma.

Many methods have been tried to reduce anxiety and increase patient comfort and compliance with the procedure. Wasser et al. included a total of 108 patients in their study and used two different techniques during IVI. As a result of the study, patients who were injected with the technique without a lid speculum had less anxiety and pain than those who used a lid speculum[12]. According to a study by Chen et al., playing classical music to patients before and during intravitreal injection decreases patient anxiety[13].

Anxiety was found to decrease in patients who received intravitreal injections after the respiratory relaxation session and 80% of the patients wanted the relaxation session to be repeated before the next injections[14]. According to the results of a study by Shaughnessy et al., 98% of the patients found it useful to hold hands during the injection and shown that hand holding provided a statistically significant decrease in patient anxiety[15].

In our study, all patients were informed about the injection and the study before the procedure. This may explain our lower anxiety rates compared to literature data. In addition, the relatively low average age of our patients may have led to lower anxiety related to anesthesia and surgery. Studies with large participation are needed to observe the effects and to evaluate them clearly.

5. Conclusion

In conclusion, the potential anxiety of patients before and during IVI should be considered. In addition, since IVI often involves repeated treatments, it is of great importance to identify modifiable factors that may reduce anxiety. Given the importance of compliance, premedication may be considered to reduce anxiety, especially in high-risk (high pre-procedure anxiety) patients. Comprehensive explanations about treatment and well-structured processes are crucial for long-term adherence to anti-VEGF therapy.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Toros University Scientific Research and Publication Ethics Committee (2023/155-21/12/2023).

Conflict of interest statement

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

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Originality Assertion

The authors have not submitted this article to another journal previously.

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The Relationship Between Demographics and Reactions During Endoscopy Under Moderate Sedation

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Abstract

Aim: Upper gastrointestinal (UGI) endoscopic procedures are performed under varying levels of anesthesia, with moderate sedation commonly utilized. However, some patients may exhibit reactions such as coughing, retching, and struggling, potentially affecting procedure quality. This study aims to investigate the relationship between patient characteristics and demographic variables and the occurrence of these reactions during UGI endoscopy under moderate sedation.

Methods: This prospective observational cohort study included patients scheduled for UGI endoscopy under moderate sedation. Patient reactions, including coughing, retching, and struggling, were documented during the procedure. Patients were categorized into two groups based on the presence or absence of reactions, and demographic characteristics were compared between groups. Institutional review board approval was obtained.

Results: Between December 2021 and May 2022, 79 patients (44 female, 35 male) were enrolled, with 51.9% experiencing reactions during UGI endoscopy. Coughing was the most common reaction (65%), followed by struggling with the scope (52.5%) and retching (47.5%). Procedure cancellation due to intolerance occurred in 12.2% of cases. No significant differences were observed between groups in terms of demographic variables or medical history. Additionally, no cardiac or pulmonary complications were reported.

Conclusions: Moderate sedation appears to be safe and effective for UGI endoscopy, facilitating adequate visualization of the UGI system while ensuring patient comfort. The occurrence of patient reactions during the procedure does not appear to be significantly influenced by demographic or clinical characteristics. Ensuring appropriate sedation levels remains essential for optimizing procedural quality and patient experience.

Keywords: *Endoscopy, sedation, moderate sedation, complication*

1. Introduction

Upper gastrointestinal (UGI) endoscopic procedures are routinely conducted under varying levels of anesthesia[1-3]. Sedation is employed to induce a controlled state of depression in consciousness, primarily aiming to alleviate patient anxiety and discomfort, enhance examination effectiveness, and minimize procedural recall. A range of sedative and analgesic agents are available to achieve the desired level of sedation for gastrointestinal endoscopy, contributing to decreased patient discomfort and improved procedural quality[4,5]. Nevertheless, some patients may exhibit adverse reactions during the procedure, such as coughing, retching, or resistance to the endoscope, occasionally necessitating procedure cancellation, particularly under moderate sedation.

Two hypotheses are postulated to explain such reactions. The first suggests that low socioeconomic and educational status may contribute to these occurrences, while the second posits that patients' comorbidities or medication usage could be influential factors. Although existing literature extensively discusses preprocedural assessments, anesthesia levels, drug options, and procedural complications, scant attention has been paid to these specific intra-procedural scenarios[1,2,6].

Therefore, this study aims to investigate potential associations between patient characteristics, demographic variables, and intra-procedural reactions during endoscopy conducted under moderate anesthesia in our endoscopy unit. By elucidating any correlations between patient factors and procedural responses, this research seeks to enhance our understanding of the underlying determinants of adverse reactions during UGI endoscopic procedures, thus facilitating the optimization of patient care and procedural outcomes.

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2. Materials and methods

This study adopts a prospective observational design, with institutional review board approval obtained from the local ethical committee under protocol number KAEK/2021.11.264. Prior to participation in the research, informed consent was obtained from all patients.

The study enrolled patients aged 18 and above who were referred to our endoscopy unit for screening or diagnostic upper gastrointestinal (UGI) endoscopy between December 2021 and May 2022. Eligible patients were required to present negative results from a COVID-19 polymerase chain reaction (PCR) test conducted prior to the procedure, and were admitted to the unit following an overnight fasting period.

Exclusion criteria encompassed patients with a known history of cancer or prior gastrointestinal surgery, individuals under the age of eighteen, pregnant women, patients diagnosed with chronic inflammatory (e.g., tuberculosis, sarcoidosis) or autoimmune diseases, hematological disorders, steroid users, and those with inaccessible medical records.

Demographic characteristics and medical histories were elicited from patients by the attending specialist physician and documented using a pre-designed form. Variables such as age, gender, educational background, occupation, weight, height, body mass index (BMI), personal medical history, known comorbidities, regular medication use, prior endoscopy history, and Mallampati score were recorded.

The endoscopy unit is officially acknowledged as a training unit by our national surgical association and all UGI endoscopies were done by educator level endoscopists. UGI endoscopy procedures were conducted using a Fujinon Eluxeo VP-7000 processor and EG-760R standard gastroscope. Prior to commencement of the procedure, vital signs including heart rate (beats/minute), systolic and diastolic blood pressure (mmHg), and pulse oxygen saturation (%) were recorded. Throat analgesia was administered using 10% lidocaine spray (Vem İlaç San. Tic. A.Ş., Istanbul, Turkey), followed by intravenous administration of midazolam (20 mcg) (Deva Holding A.Ş., Istanbul, Turkey) and pethidine hydrochloride (10 mcg) (G.L.Pharma GmbH, Lannach, Austria) by a registered nurse under the endoscopist supervision, with additional doses administered as necessary to achieve moderate sedation. Once sedation was achieved, the endoscopic examination was conducted. Vital signs were monitored throughout the procedure, with nasal oxygen support provided if pulse oxygen saturation levels decreased. Procedure duration and patient reactions were documented, while endoscopic findings were promptly recorded by the performing surgeon and stored in the database.

Patients were stratified into two groups based on their intra-procedural reactions. Group 1 comprised patients who exhibited coughing, retching, hiccups, significant decreases in oxygen saturation, or procedural intolerance, while Group 2 included patients who did not manifest any such reactions during the examination.

2.1. Statistical Analysis

The sample size was calculated with the G*Power Version 3.1.9.2 program. SPSS 23.0 for Windows program was used for statistical analysis. Descriptive statistics of evaluation results; numbers and percentages for categorical variables, mean, standard deviation, median, minimum and maximum for numerical variables. Independent student t-test, Oneway ANOVA and paired sample t-test were used for normally distributed parameters, Mann Whitney-U, Kruskall Wallis test and Wilcoxon signed-rank tests were used for non-normally distributed parameters. Differences between the ratios of categorical variables in independent groups were analyzed with Chi-Square and Fisher's exact tests. In all tests, the statistical significance level is considered as $p<0.05$.

3. Results

During the period between December 2021 to May 2022, a cohort of 79 patients (44 females, 35 males) was enrolled in this prospective study. Detailed patient characteristics and demographic data are outlined in Table 1.

Among the participants, 41 patients (51.9%) exhibited reactions during upper gastrointestinal (UGI) endoscopy, as delineated in Group 1. The most prevalent reaction within this group was coughing (65%), followed by struggling with the scope (52.5%) and retching (47.5%). Notably, 12.2% (5 out of 41) of patients in Group 1 required cancellation of the procedure due to intolerance, necessitating referral for administration under general anesthesia. Analysis revealed no significant differences between Group 1 and Group 2 with respect to age, gender, body mass index (BMI), educational level, comorbidities, medication usage, Mallampati score, history of surgery, or prior endoscopic procedures (Table 2).

Moreover, subgroup analysis indicated that obesity (BMI > 30 kg/m2) did not independently influence the occurrence of these reactions.

Two patients from Group 1 received additional sedative dosages, enabling the procedures to proceed without complication. Furthermore, oxygen support was provided to five patients in Group 1 due to significant decreases in oxygen saturation, with all patients spontaneously recovering. Mean blood pressure and oxygen saturation

Table 1

Distribution of the demographics and patient characteristics

	Group 1 (n=41) n(%)	Group 2 (n=38) n(%)	*p*
Gender			
Female	24 (58.5)	20 (52.6)	0.598
Male	17 (41.5)	18 (47.4)	
Age (Mean±SD)	45.6±14.4	45.1±15.8	0.877
BMI (kg/m2) (Mean±SD)	27.3±5.8	28.4±6.9	0.420
Educational level			
Primary or lower level	22 (53.7)	17 (44.7)	0.428
College or higher level	19 (46.3)	21 (55.3)	
Working status	22 (53.7)	24 (63.2)	0.392
Co-morbidities	13 (31.7)	12 (31.6)	0.990
Obesity	10 (24.4)	10 (26.3)	0.884
Operation history	19 (46.3)	17 (44.7)	0.886
Endoscopy history	12 (29.3)	14 (36.8)	0.474
Allergic history	5 (12.2)	2 (5.3)	0.279
Pill intake	17 (41.5)	14 (36.8)	0.674
Procedure			
UGI endoscopy	25 (61.0)	29 (76.3)	0.143
UGI endoscopy and colonoscopy	16 (39.0)	9 (23.7)	
Mallamopati score			
1	13 (31.7)	13 (34.2)	0.657
2	10 (24.4)	10 (26.3)	
3	7 (17.1)	9 (23.7)	
4	11 (26.8)	6 (15.8)	

UGI: Upper gastrointestinal, BMI: body mass index.

Table 2
Distribution of the procedural outcomes between two groups

	Group 1 (n=41) n(%)	Group 2 (n=38) n(%)	*p*
Retching	19 (47.5)	-	<0.001**
Desaturation	5 (12.5)	-	<0.001**
Struggling	21 (52.5)	-	<0.001**
Intolerance	5 (12.2)	-	<0.001**
Hiccups	1 (2.5)	-	<0.001**
Coughing	26 (65.0)	-	<0.001**
Biopsy	27 (67.5)	32 (84.2)	0.086
Chronic gastritis	25 (96.2)	29 (100)	0.286
Intestinal metaplasia	2 (7.7)	3 (10.3)	0.733
Helicobacter pylori status	16 (61.5)	19 (65.5)	0.759
	Group 1 (n=41) Mean±SD	Group 2 (n=38) Mean±SD	*p*
Heartrate (beat/min) Initial	85.2±13.4	83.6±12.3	0.586[b]
Middle of the procedure	105.8±18.2	99.1±15.3	0.092[b]
End of the procedure	95.2±16.2	88.8±11.5	0.053[b]
Maximum	111.8±18.2	103.5±14.9	0.057[c]
Blood pressure (mmHg)			
Initial systolic	122.4±12.3	129.6±18.8	0.068[b]
Initial diastolic	76.9±9.9	82.2±15.2	0.095[b]
Systolic (middle of the procedure)	128.1±16.1	134.8±24.3	0.271[b]
Diastolic (middle of the procedure)	86.6±15.4	84.9±15.2	0.665[c]
Systolic (end of the procedure)	122.3±13.6	125.0±18.0	0.542[b]
Diastolic (end of the procedure)	77.1±12.9	77.7±15.0	0.879[b]
Oxygen saturation (%) Initial (%)	98.9±1.3	98.8±1.2	0.687[c]
Middle of the procedure (%)	97.2±3.3	97.1±2.8	0.494[c]
End of the procedure (%)	97.8±2.2	97.9±1.8	0.938[c]
ΔHeartbeat	9.76±14.8	4.38±11.4	0.086[b]
ΔDiastolic	0.13±11.2	-1.82±14.8	0.589[b]
ΔSystolic	-0.55±12.2	-2.52±18.1	0.642[b]
ΔSaturation	-1.05±1.9	-0.77±1.6	0.600[c]

** p<0.05, **p<0.001, a:Chi-square and Fisher exact test, b: Independent T-test, c: Mann Whitney U test, Δ: Difference between the last and the initial value, UGI: Upper gastrointestinal, BMI: body mass index.*

levels, as well as changes observed at the conclusion of the procedure, are summarized in Table 2, indicating no discernible disparities between the two groups.

Of the study cohort, 25 patients underwent both UGI endoscopy and colonoscopy, with standard bowel cleansing performed prior to the procedures. All gastroscopies were done prior to the colonoscopy. Analysis revealed no significant variance in bowel cleansing status between the two groups ($p > 0.05$).

Endoscopy reports indicated that gastritis and mucosal erosion were the most frequently detected abnormalities, with no notable difference observed between the two groups. Biopsy samples were obtained from 59 patients (74.7%) in the cohort, with no significant differences noted between groups. Moreover, there were no disparities in the incidence of chronic gastritis or Helicobacter pylori positivity in the pathology samples (Table 2).

Notably, no cardiac or respiratory complications were observed during the early post-procedural period.

4. Discussion

Upper gastrointestinal (UGI) endoscopy, while considered an invasive procedure, is generally safe for patients when conducted under appropriate conditions. The primary goal of sedation during UGI endoscopy is to ensure procedural quality, minimize patient discomfort, and optimize examination outcomes[4,5,7]. A plethora of literature exists outlining recommendations for sedation levels and optimal drug combinations to achieve these objectives[1,8,9]. Sedation protocols may vary depending on the preferences of the endoscopist, the capabilities of the healthcare facility, and local legal considerations.

In settings where anesthesiologists are readily available, deep sedation is often the preferred choice for endoscopic procedures. Deep sedation offers maximal patient comfort and procedural efficacy. However, the availability of anesthesiologists may be limited, particularly in certain healthcare settings or during periods of high demand, such as the COVID-19 pandemic. In such cases, non-anesthesiologist-administered sedation protocols have been shown to be safe and feasible alternatives, providing effective sedation while minimizing procedural risks[1,2,9].

Guidelines suggest that endoscopists can safely administer propofol for deep sedation in the absence of an anesthesiologist[1,2,9]. Additionally, conscious sedation has been demonstrated to be both safe and cost-effective for outpatient procedures, offering a balance between patient comfort and procedural efficiency[10]. However, the decision to opt for superficial or moderate sedation in hospital settings may be influenced by local legal considerations and potential complications associated with deep sedation.

Our hospital, established during the COVID-19 pandemic, initially faced challenges due to a shortage of anesthesiologists, necessitating a preference for minimal or moderate sedation during endoscopic procedures. However, as the hospital has since adapted and acquired an anesthesiology team, there is now a shift towards performing endoscopic procedures under deep sedation, ensuring optimal patient comfort and procedural efficacy.

Common sedation-related issues during endoscopy often stem from inadequate measures to address patient discomfort or pain. Studies comparing the use of benzodiazepines alone versus in combination with analgesics like pethidine hydrochloride have demonstrated the efficacy of analgesic use in improving patient comfort[11,12]. However, the risk of sedative and analgesic overdose underscores the importance of continuous monitoring of respiratory conditions before and after drug administration to prevent complications such as upper airway obstruction and respiratory suppression[1,8].

While deep sedation offers optimal patient comfort, it may result in the loss of the gag reflex and compromised respiratory function, posing potential risks during the procedure[1,8]. Moderate sedation, on the other hand, allows for adequate airway maintenance but may lead to patient reactions such as coughing, retching, or struggling with the scope, impacting examination quality. Pre-procedural evaluation, including consideration of patient history, medications, and comorbidities, is crucial for assessing the risk of complications and tailoring sedation protocols accordingly. All patients were questioned about risk factors and underwent endoscopy but there was no relationship between these symptoms with patients' demographics and personal history. And also the patient's mallampati

score is not associated with these situations which was thought to be a possible major cause during the study design.

Despite existing literature on endoscopic complications, few studies have focused specifically on patient reactions and associated factors during procedures conducted under appropriate sedation. Our study aimed to fill this gap by observing patient reactions during UGI endoscopy performed under moderate sedation. Only hypoxemia and hypotension were mentioned in the literature with a rate of 6-9.9% and 3-7% respectively[9]. In our study hypoxemia rate was similar with 6.3%. The most common complication associated with the endoscopic procedures are cardiac and respiratory system problems. In contrast to belief, the cardiopulmonary complication rates were found to be similar when comparing propofol induced anesthesia and traditional anesthesia for endoscopic procedures in a systematic review[13]. No major cardiopulmonary complications were encountered in this study. Further research is warranted to explore optimal sedation practices and their impact on patient outcomes during UGI endoscopy.

Deep sedation is safe and more comfortable but potential legal issues and sedation-related malpractice claims, endoscopists are prone to apply moderate sedation during the endoscopy[14,15]. Hence, pre-evaluation of the characteristics of the patients can help to predict potential problems that may arise during the procedure, and in these cases, the depth of sedation can be increased by this way.

People subject to varying degrees of discrimination and prejudice in real world or healthcare services. Race, socioeconomic status and especially ageism has been revealed at different levels in the literature[16-20]. In parallel with this situation, it was thought that the reactions exhibited by the patients and the findings obtained during endoscopy under moderate sedation may be related to age groups, education level and socioeconomic status. When the obtained data were evaluated, it was observed that the reactions such as cough, retching, hiccups, and struggling with the scope during endoscopy were not associated with the demographic data, patient history, mallampati score of the patients, and variables such as age, gender, education level, and comorbidity were homogeneously distributed in both groups.

The study has some limitations. Firstly, this is a cohort study and need to be supported by a randomised trial. Second, groups are small but adequate for stastistical analysis. Finally, under moderate sedation, there may be additional factors yet to known to trigger these reactions.

5. Conclusion

In conclusion, the choice of sedation level during UGI endoscopy should be guided by considerations of patient comfort, procedural efficacy, local legal considerations, and available resources. Pre-procedural patient evaluation and continuous monitoring during the procedure are essential for ensuring patient safety and optimizing procedural outcomes.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Başakşehir Çam and Sakura City Hospital, Scientific Research and Publication protocol number KAEK/2021.11.264

Conflict of interest statement

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Availability of data and materials

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Originality Assertion

The authors have not submitted this article to another journal previously.

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Evaluation of General Surgery Physicians' Approaches to Surgical Antimicrobial Prophylaxis by Questionnaire Method

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Abstract

Aim: Surgical site infections (SSIs) are infections of the incision site, organ or cavity that occur after surgery, causing a significant burden in terms of morbidity, mortality and healthcare costs. SSIs are the most common healthcare-associated infections in low- and middle-income countries and may affect one-third of surgical patients. This study aimed to conduct a face-to-face survey to evaluate general surgeons' approaches and knowledge levels before and after the training seminar on the use of surgical antimicrobial prophylaxis (SAP).

Methods: An information-oriented questionnaire consisting of 10 questions was administered to a total of 18 surgeons working a General Surgery Department before and after the education meeting to evaluate their knowledge and attitudes towards the use of SAP. Data were presented as number, percentage, mean (standard deviation) and Fisher exact test was used to compare categorical data.

Results: All participants answered the question regarding the time of prophylactic antibiotic administration correctly in both surveys. According to the current American Society of Health-System Pharmacists (ASHP) guideline for cefazolin, 42.2% of the patients had the correct time of antibiotic administration. The proportion of patients whose cefazolin selection, dose and time of administration were appropriate was 14.6%. The number of physicians who thought that postoperative antibiotic prophylaxis was not significantly increased from 16 (88.8%) before the meeting to 18 (100%) after the meeting ($p>0.05$). In our study, the number of patients who continued to be given antibiotics unnecessarily postoperatively was 66 (16.4%).

Conclusions: In order to increase the rate of optimal application of the theoretical knowledge to patients in practice, it is important to organize routine trainings based on current literature and service data for surgeons with a high workload and to follow the reflection of these trainings to the clinic in order to improve SAP compliance rates.

Keywords: *Surgical antimicrobial prophylaxis, general surgery, survey, surgical site infection, guideline*

1. Introduction

Surgical antimicrobial prophylaxis (SAP) refers to the application of antimicrobial agents before exposure to contamination during surgery to prevent infectious complications.[1] Guidelines based on high-quality studies have stated that appropriate SAP is among effective measures to prevent surgical site infections (SSI). For optimal benefit, it is necessary to determine appropriate indications, select agents covering potential pathogens for wound contamination, and apply sufficient bactericidal concentrations throughout the period when the incision is open to the risk of bacterial contamination.[2] Treatment guidelines and antibiotic regimens have significantly evolved from aggressive and prolonged antibiotic prophylaxis regimens in the 1980s and 1990s to a more moderate practice today.[3] SAP guidelines are considered significant interventions for antimicrobial resistance. Compliance with guidelines is weak in many countries, leading to inappropriate and excessive antibiotic use. Creating awareness about the importance of rational antibiotic use and adherence to guidelines are crucial initiatives recommended for appropriate SAP use.[2]

Preoperative doses should be initiated within 60 minutes before surgical incision (120 minutes for fluoroquinolones and vancomycin). Pharmacokinetics of drugs may vary in obese patients, hence dose adjustments based on body weight may be necessary. In patients with impaired kidney and/or liver function, dose adjustments are often unnecessary in this patient group as antimicrobial

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prophylaxis is usually given as a single preoperative dose before surgical incision. In cases where the procedure duration exceeds twice the half-life of the drug, or there is excessive blood loss during the procedure, or in cases of extensive burns, intraoperative redosing is necessary in all patients to ensure adequate serum and tissue concentrations of the antimicrobial agent. New recommendations are provided for the shortened course of postoperative antimicrobials for single-dose or antimicrobials lasting less than 24 hours. Postoperative antimicrobial prophylaxis may not be necessary depending on the presence of permanent drains and intravascular catheters.[4]

In this study, a face-to-face survey (10 minutes) was planned to evaluate the approaches and knowledge levels of general surgeons before and after an educational seminar (approximately 1 hour) regarding the use of SAP.

2. Materials and methods

This study was a face-to-face questionnaire survey of physicians working in a department of general surgery of a university hospital who volunteered to participate in the study. The questionnaire questions were prepared in consensus with the senior surgeons involved in the study, taking into account the current literature and guidelines. On 4 January 2023, the head of the general surgery department provided an education on SAP to the faculty members and resident physicians of the general surgery department in accordance with the American Society of Health-System Pharmacists (ASHP) guidelines and current scientific literature. The questionnaire with the same questions was applied to the participating physicians right pre-education questionnaire phase (pre-EQP) and post-education questionnaire phase (post-EQP) with informed consent. In order to anonymize the physicians' answers, the number for coding written on the questionnaire before the education session was also asked to be written on the questionnaire applied after the education.

A questionnaire consisting of 10 questions was prepared according to the SAP compliance rate reports (obtained from the specialty thesis in which SAP compliance status and SSI development rates of 404 patients hospitalized and operated in the general surgery service between 24 January and 6 May 2022 were evaluated[4]) and the 2013 ASHP guideline.[5] The study was approved by local ethics committee.

There is a hospital protocol prepared in cooperation with the Department of General Surgery and the Department of Clinical Microbiology and Infectious Diseases within Hacettepe University. This protocol entered into force on 06.09.2021 and was made available to clinicians via the hospital information management system. Some of the recommendations in the SAP protocol are as follows:

- The recommended time is 30 minutes to an hour before surgery.
- If the operation lasts more than three hours and there is excessive fluid loss, an additional dose of antibiotics is recommended.
- Antibiotic prophylaxis started in the perioperative period should not be continued after surgery. The maximum duration of postoperative prophylaxis is 24 hours.
- Cefazolin should be administered as 2 g in patients weighing more than 80 kg and 3 g in patients weighing more than 120 kg.
- The team conducting CAE surveillance should include a senior surgeon, operating staff (anaesthetists and/or nurses) and infection control committee.

The data obtained from the research were analyzed using SPSS Version 23.0 statistical analysis software. As descriptive statistics, mean and standard deviation or median and minimum-maximum values for numerical variables and number and percentage values for categorical variables were given. In the comparison of numerical data, Student T Test was used for normally distributed data and Mann Whitney U test was used for non-normally distributed data. Chi-Square test was used to compare the ratios. In analyzing the change over time, the significance test of the difference between two pairs or Wilcoxon test was used. The relationship between numerical variables was analyzed using the appropriate correlation test (Pearson or Spearman). Mc Nemar test was used to determine whether there was a difference between two related groups on a dichotomous dependent variable. $p<0.05$ was considered statistically significant.

Table 1

Survey Questions & Answers

Q1. Which of the following is **incorrect** regarding the timing of preoperative and intraoperative antibiotic administration in adult patients?
A) The first dose should be started within 60 minutes before the surgical incision. B) The first dose of fluoroquinolones and vancomycin should be started within 120 minutes before the surgical incision. C) Intraoperative re-administration is necessary to ensure adequate serum and tissue concentrations of the antimicrobial in patients if the duration of the procedure exceeds the two half-lives of the drug. D) Corrected body weight is used to calculate the dose of aminoglycosides in patients with a body mass index ≥30 kg/m^2. **E) The first dose should be started immediately after surgical incision.**
Q2. Which of the following is **true** about **cefazolin**, which is frequently used for surgical prophylaxis?
A) Vancomycin is more effective than cefazolin in preventing Surgical Site Infections (SSIs) caused by *methicillin-sensitive Staphylococcus aureus* (MSSA). **B) Cefazolin is more effective than vancomycin in preventing CAIs caused by *methicillin-resistant Staphylococcus aureus* (MRSA).** C) The preoperative dose for adult patients is 2 g. For patients weighing ≥120 kg, it is 3 g. D) Because of its long half-life, intraoperative re-dosing is not required. E) If major blood loss (e.g., >1500 mL) occurs, a repeat dose should be administered before fluid resuscitation.
Q3. Which of the following statements is **incorrect**?
A) The Operation Start Time indicates the moment when the incision is made for a surgical procedure. B) End of Surgery Time refers to the time when all instrument counts have been completed and verified, all postoperative radiological studies to be performed in the operating room have been completed, all dressings and drains have been secured, and physicians/surgeons have completed all procedure-related activities on the patient. C) While current guidelines recommend a maximum duration of surgical antimicrobial prophylaxis of 24 hours, increasing evidence suggests that a single preoperative dose (and possible additional intraoperative doses) may have a similar effect. **D) Depending on the presence of indwelling drains and intravascular catheters, antimicrobial agents should be continued in the postoperative period.** E) Long-term antibiotic administration may increase the development of antibiotic resistance, antibiotic-specific side effects (e.g., acute kidney injury), fungal superinfections and the risk of *Clostridium difficile* infection.
Q4. Which of the following is **correct** to reduce the risk of SSI in adult patients undergoing elective colorectal surgery?
A) The oral antibiotic agent(s) used should only have anaerobic activity. B) Oral antibiotic agent(s) are administered before mechanical bowel preparation to reduce the microbiota load of the colon. C) Oral antibiotic + mechanical bowel preparation is not superior to mechanical bowel preparation alone without oral antibiotic administration. **D) Oral antibiotics are for preoperative use only and should not be continued postoperatively.** E) The risk of anastomotic leakage is much higher in patients undergoing mechanical bowel preparation.
Q5. Which of the following statements is **incorrect**?
A) Superficial incisional SSIs are only followed for a period of 30 days for all procedure types.

B) Breast surgery (BRST) and hernia repair (HER); deep incisional SSI and organ/space SSI are followed for a period of 90 days. **C) When calculating the surveillance period, the date of operation is recorded as Day 0.** D) Limiting the duration of antimicrobial prophylaxis to a single preoperative dose may reduce the risk of Clostridium difficile disease. E) Since the predominant organisms in SSIs after clean procedures are gram positive, the addition of vancomycin may be appropriate for a patient with a life-threatening allergy to β-lactam antimicrobials.
Q6. Which of the following is **not** the aim of the study titled 'Evaluation of Prophylactic Antibiotic Use in General Surgery Service' conducted in your clinic?
A) To evaluate the compliance of prophylactic antibiotic use in operated general surgery patients with the American Society of Health-System Pharmacists (ASHP) guidelines and hospital protocol B) To determine the level and rate of SSIs developed in patients within the surveillance period. C) Explaining the findings obtained to the residents and lecturers of the Department of General Surgery in accordance with the guidelines and conducting a pre- and post-training status assessment questionnaire. **D) To evaluate the attitudes and behaviors of operated general surgery patients about prescribing antibiotics to ward physicians.** E) To compare the changes, if any, in prophylactic antibiotic use before (x number of patients) and after (x number of patients) the training.
Q7. Which of the following do you think is **the most common comorbidity** according to ICD-11 diagnosis code in general surgery patients operated in our University Hospital?
A) Neoplasms B) Digestive system diseases C) Respiratory system diseases D) Endocrine, nutritional and metabolic diseases E) Circulatory system diseases
Q8. Which of the following do you think is **the most common type of surgery** performed in general surgery patients operated in our University Hospital?
A) Thyroid and/or parathyroid surgery B) Colon surgery C) Rectal surgery **D) Hernia repair** E) Gastric surgery
Q9. According to the ASHP guideline for **cefazolin** administered as prophylactic antibiotic in general surgery patients operated in our University Hospital, in what percentage (%) do you think the antibiotic selection was **correct**?
A) 90-100% **B) 80-90%** C) 70-80% D) 60-70% E) 50-60%
Q10. According to the American Society of Health-System Pharmacists Guidelines on Antimicrobial Prophylaxis in Surgery, for **cefazolin** administered as prophylactic antibiotic in general surgery patients operated in our University Hospital, in what percentage (%) of patients do you think antibiotic selection, antibiotic dose and antibiotic administration time were performed **correctly**?
A) 50-60% B) 40-50% C) 30-40% D) 20-30% **E) 10-20%**

3. Results

There are 25 surgeons in the general surgery department, 10 of whom are faculty members and 15 of whom are research assistants. A total of 23 (92%) surgeons attended the education session. However, 5 participants were excluded because of participation only in the pre-EQP and one participant was also excluded because of participation only in the post-EQP. Accordingly, the data of a total of 18 (72%) participants who participated in both phases were evaluated. Six of the participants (33.3%) were female, 5 (27.8%) had been working in general surgery for less than 6 months, 4 (22.2%) for 6-24 months, and 9 (50%) for more than 24 months. In addition, 15 (83.3%) of the physicians were residents, 2 (11.1%) were specialists and 1 (5.6%) was a faculty member. The answers given by the physicians to the questionnaire (Table 1) are given in Table 2. The median (min-max) number of correct answers given to the survey questions was 5 (2-6) in the pre-EQP and 7 (2-9) in the post-EQP (p=0.001).

SAP administration time was answered correctly by all participants in the pre-EQP. All participants correctly answered the time of SAP administration, the duration of SAP continuation and the most common type of surgery performed in the post-EQP. In the case of surveillance time calculation, all participants answered incorrectly in both periods. In the post-EQP, the best improvement in the correct response rate was in the question given to the most common disease group in patients.

Table 2

Comparison of the answers given to the questions

			After training		p
	Question no	Answer	Incorrect	Correct	
Before training	1	Incorrect	0	0	
		Correct	0	18	
	2	Incorrect	2	6	0.508
		Correct	3	7	
	3	Incorrect	0	2	0.500
		Correct	0	16	
	4	Incorrect	11	1	>0.05
		Correct	1	5	
	5	Incorrect	18	0	
		Correct	0	0	
	6	Incorrect	2	2	>0.05
		Correct	2	12	
	7	Incorrect	3	14	<0.001
		Correct	0	1	
	8	Incorrect	0	1	>0.05
		Correct	0	17	
	9	Incorrect	7	8	0.109
		Correct	2	1	
	10	Incorrect	10	7	0.016
		Correct	0	1	

According to the data in the thesis used to prepare the survey questions, among 404 patients evaluated for SAP compliance report, the proportion of patients with at least 1 comorbidity according to the International Classification of Disease (ICD) was found to be 91.3%. The most common disease were neoplasms. The most common types of surgery were hernia repair. The most preferred prophylactic antibiotic (404 patients) was cefazolin (352 patients, 87.1%). The number of patients whose cefazolin choice was appropriate according to ASHP guidelines was 315 (89.5%). The dose compliance rate of patients whose cefazolin choice was appropriate according to the ASHP guideline was 41%. The proportion of patients whose cefazolin selection was appropriate according to the ASHP guideline and whose time of administration was appropriate according to the ASHP guideline was 42.2%. The proportion of patients whose cefazolin selection, dose and time of administration were appropriate was 14.6%. Intraoperative repeat cefazolin administration was performed in 7 (50%) of a total of 14 patients who required intraoperative repeat cefazolin administration, and the time of administration was correct in 1 (14.3%) of these patients. The rate of preoperative oral antibiotic administration in patients undergoing elective colorectal surgery was 63.6% for oral ornidazole and 56.8% for oral cefuroxime.

However, when the time of mechanical bowel preparation (MBP) application was analyzed, it was noticed that it was usually

performed after oral antibiotic administration. When the patients who received antibiotics while hospitalized in the ward in the postoperative period were evaluated in terms of the presence or absence of infectious diseases specialist (IDS) approval and the presence or absence of indication, the number of patients who received antibiotics without indication was 66 (16.4%).[4]

4. Discussion

In this study, 10-question questionnaire was administered twice to surgeons' pre-EQP and post-EQP in order to evaluate their approaches and knowledge levels on SAP use. Not all physicians in the Department attended the meeting due to their workload in the operating rooms.

When the answers given by a total of 18 participants were evaluated, all participants answered the question about the time of prophylactic antibiotic administration correctly in both questionnaires. However, according to the data at the thesis data, it was found that the correct time of antibiotic administration according to the ASHP guideline for cefazolin was 42.2%. Intraoperative repeat cefazolin administration was performed in 7 (50%) of a total of 14 patients who required intraoperative repeat cefazolin administration, and the time of administration was correct in 1 (14.3%) of these patients. The number of patients who continued to be given antibiotics unnecessarily postoperatively was 66 (16.4%). The number of physicians who thought that there was no need to continue postoperative antibiotic prophylaxis increased from 16 (88.8%) before the meeting to 18 (100%) after the meeting ($p > 0.05$). Even though, surgeons are well-qualified in theoretical knowledge on the time of prophylactic antibiotic administration, application of this knowledge into their practice is lower.

In a survey study conducted to evaluate the use of SAP and compliance with ASHP guidelines among general surgeons in Turkey, the overall compliance rate of 317 participants with ASHP guidelines was found to be 26.8%. Although 96.5% of the participants correctly reported the time of SAP first dose administration, this rate decreased to 79.5% for intraoperative redosing of prophylaxis. The proportion of surgeons who continued antibiotic treatment of clean and clean-contaminated cases at discharge was 22.7% and 38.5%, respectively. As a result of this study, it has been shown that inappropriate SAP use is common in Turkey and antibiotics are continued to be prescribed at discharge.[6] According to our survey results, although 100% of the participants could correctly report the time of administration of the first dose of SAP, this rate decreased to 33.3% of those who reported that prophylaxis did not need to be continued in the postoperative period.

It is known that especially plastic surgeons lack knowledge and awareness about optimal SAP.[7] For this reason, it is recommended that SAP trainings for specific surgical branches should be given regularly. In a survey of Italian surgical (General, Cardiac, Thoracic, Plastic, Vascular, Orthopedics, Obstetrics, Gynecology, Urology, Otorhinolaryngology and Ophthalmology) and anesthesiology residents involving a total of 466 respondents, a total of 36.3% of respondents had an adequate knowledge score on SAP. General surgery residents were more likely than anesthesiology residents to agree that SAP should be performed within 60 minutes prior to surgical incision and to be aware of the existence of national guidelines on SAP. In addition, 14% of respondents were concerned about patients contracting SSIs during their hospitalization. It was concluded that organizing a training course on SAP, especially promoting educational intervention for surgical and anesthesiology residents, would be useful to improve correct antibiotic use and prevent healthcare-associated infections.[8]

In another survey study in which orthopedic surgeons were asked about the time of preoperative antibiotic administration, 47.4% of 395 surgeons stated that they administered preoperative antibiotics within 30 minutes before incision, 42.9% within 30 minutes to 1 hour before incision, and 8.2% within 1-3 hours before incision. Regarding the necessity of intraoperative redosing for prolonged surgical procedures, 77.8% of surgeons stated that redosing was necessary. In the postoperative period, 40.4% of the surgeons stated that they used antibiotics for 1 day, 44.4% for 2-7 days, 14.5% for 8-14 days, and 0.7% for more than 14 days.[9] In a questionnaire study in which the approach to prophylactic antibiotic use in hernia repair was evaluated with the participation of 81 surgeons who performed at least 75 hernia repairs per year, 44.4% of the participants used routine antibiotic prophylaxis, 49.4% used selective SAP, and 6.2% stated that they never used SAP. The lack of clear guidelines emphasizes that the surgeon bases prophylactic antibiotic use on perceived risk or SSI experience.[10]

In a questionnaire study conducted in England in which 97 surgeons performing elective colorectal surgery were included, all of the participants reported that they gave prophylactic antibiotics preoperatively; 24% continued antibiotics in the postoperative period; 62% performed oral antibiotics and MBP and 29% performed only MBP without oral antibiotics[11]. According to thesis data, the rate of preoperative oral antibiotic use in elective colorectal surgery was 63.6% for oral ornidazole and 56.8% for oral cefuroxime. The rate of MBP is 95.5%. In our survey study, 6 (33.3%) of the physicians gave the correct answer in accordance with the guideline regarding SAP application in elective colorectal surgery. The only shortcoming of MBP and oral antibiotic administration, which was higher compared to the other study, was observed in compliance with the timing of oral antibiotic administration.

The limitations of our single-center study are that not all faculty members and resident physicians were able to attend the educational meeting, the educational messages could not be conveyed in detail due to the insufficient duration of the meeting, and for this reason, the survey questions were simplified and as a result, we could not adequately measure the level of knowledge of physicians.

5. Conclusion

SSI is an undesirable situation that patients may frequently encounter in the postoperative period. Low compliance with SAP increases the risk of possible SSI development. In order to reduce preventable risk factors, the entire team in the operating theatre, especially the surgeons, and the personnel caring for patients in the ward should be informed about this issue and necessary precautions should be taken together. Providing education at regular intervals is beneficial for surgeons in order to improve their knowledge on rationale antibiotic use in SAP.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Hacettepe University Scientific Research and Publication protocol number 2022/17-11.

Conflict of interest statement

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

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Author Contributions

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Originality Assertion

The authors have not submitted this article to another journal previously.

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The Influence of Genetic Polymorphisms on Warfarin Dosage Requirements in Cardiac Valve Surgery Patients

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Abstract

Aim: Warfarin, a widely prescribed anticoagulant, exhibits considerable variability in patient response, making its clinical use challenging due to a narrow therapeutic window. This study aimed to evaluate the prevalence of CYP2C9 and VKORC1 gene polymorphisms in a cohort of 87 Turkish patients who underwent cardiac valve surgery and received warfarin therapy, as well as to assess their impact on warfarin dosage requirements.

Methods: The frequencies of CYP2C9 and VKORC1 polymorphisms were analyzed, and patients were stratified based on the presence or absence of mutations affecting warfarin dosing.

Results: Revealed that patients carrying at least one CYP2C9 or VKORC1 polymorphism required a significantly lower weekly warfarin dose to achieve the optimal international normalized ratio (INR).

Conclusions: This study highlights the critical role of genetic factors in determining warfarin dosage and supports the integration of pharmacogenetic testing into clinical practice to personalize warfarin therapy. Such an approach has the potential to enhance treatment outcomes and minimize the risk of adverse events. Further research involving larger sample sizes and diverse patient populations is warranted to validate these findings and refine the current understanding of the genetic determinants of warfarin dosing.

Keywords: *Warfarin, CYP2C9, VKORC1, genetic polymorphisms, cardiac valve surgery, Turkish population*

1. Introduction

Warfarin, a commonly prescribed anticoagulant worldwide, is administered to prevent and manage thromboembolic incidents. Roughly 0.5-1.5% of individuals are estimated to receive this medication.[1-3]

However, its clinical use is complicated by considerable individual variability in response, a narrow therapeutic window, and the risk of severe bleeding or stroke events, which are influenced by a myriad of environmental and genetic factors.[4-6] Although various models have been proposed for calculating warfarin dosage, incorporating both clinical and genetic markers (VKORC1 and CYP2C9 genotypes), their practical application in a clinical setting remains a subject of ongoing debate.[7,8]

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Variations in warfarin response among individuals can be traced back to genetic polymorphisms present in the CYP2C9 and VKORC1 genes.[9] Accounting for gene polymorphisms, age, and body surface area, daily dosage requirements for individuals can deviate by approximately 50%.[8,10] Warfarin is comprised of two enantiomers, S and R, with S-warfarin being the more potent enantiomer, contributing to 60-70% of the anticoagulant effect.[11]

Genetic variations in the CYP2C9 enzyme can affect drug metabolism by altering its ability to convert S-warfarin into inactive metabolites.[12] The gene responsible for encoding this enzyme is located on chromosome 10q24.2 in humans [13], and eight distinct single nucleotide polymorphisms (SNPs) have been identified within it, all of which reduce CYP2C9 activity levels.[14] Patients possessing the *2 or *3 variants of this gene require lower warfarin dosages due to their decreased enzymatic activity, resulting in less efficient S-warfarin metabolism overall.[15] Additionally, CYP2C9 polymorphisms *5, *6, *8, and *11 have been shown to significantly delay S-warfarin metabolism.[16]

The crucial role of the vitamin K cycle is fulfilled by the enzyme VKORC1, which facilitates the restoration of reduced vitamin K (KH2) and plays a vital part in clotting factor synthesis.[17] Warfarin exerts its anticoagulant effect by impeding the enzymatic function

of VKORC1, thereby obstructing the apt maturation process of vitamin K-dependent clotting factors.[18]

VKORC1 is located on chromosome 16p11.2 [19], and several genetic variants have been linked to altered warfarin metabolism.[20] The -1639G > A polymorphism is observed to decrease the expression of VKORC1, resulting in a reduction in both warfarin metabolism and coagulation factors. This phenomenon has been duly noted.[9]

This study aimed to investigate the occurrence rates of genetic variations in CYP2C9 and VKORC1 among patients who received warfarin treatment after undergoing surgery for heart valve disorders. Additionally, it sought to evaluate the potential influence of these gene variations along with pertinent clinical factors on the necessary dosage of warfarin.

2. Materials and methods

2.1 Study subjects

A total of 87 patients (41 females, 46 males) under warfarin maintenance therapy for cardiac valve operation in a tertiary state hospital between January 2018 and January 2022 were included in the study. The study was approved by local Clinical Research Committee. Written informed consent was obtained from all patients included in the study. Blood samples were taken from each patient and transferred to Department of Medical Genetics for genetic analysis. Clinicians were not aware of the patients' CYP2C9 and VKORC1 genotypes prior to anticoagulant therapy initiation. Beta adrenergic receptor blockers, statins and proton pump inhibitors were the frequent additional therapies used by the study population. Patients with liver and kidney dysfunction, malignancy, pregnancy and lactation, or those taking medications known to interfere with warfarin metabolism were excluded from the study.

2.2 Genotype analysis

Genomic DNA was extracted from peripheral blood sample using HiPure Blood DNA Mini Kit according to the manufacturer's protocol. Next Generation Sequencing (NGS) test was performed using Illumina MiSeq NGS platform (Illumina Inc., San Diego, CA, USA). The test platform screened targeted mutations on *CYP2C9* named 430C>T (haplotype CYP2C9*2), 1075A>C (haplotype CYP2C9 *3), 1076 T>C (haplotype CYP2C9 *4), 1080C>G haplotype (CYP2C9 *5), 817delA (haplotype CYP2C9 *6) and c.1003C>T (haplotype CYP2C9*11) and also mutations on VKORC1 gene named c.173+1000 (haplotype VKORC1*2), c.492+134 (haplotype VKORC1*3) and c.173+525 (haplotype VKORC1*4). The variants that passed through the filters were analyzed with Sequencing Analysis Viewer (SAV) Software, Illumina and The Integrative Genomics Viewer (IGV) according to the pathogenicity scores and *in-silico* prediction tools.

2.3 Statistical analysis

Descriptive statistics were used to present the baseline characteristics of the study population. The frequencies of CYP2C9 and VKORC1 polymorphisms were calculated, and the Hardy-Weinberg equilibrium was assessed. Patients were grouped according to the presence or absence of mutations requiring a reduction in warfarin dose. Comparisons of the median weekly warfarin doses for reaching the ideal INR between the two groups were performed using an independent samples t-test. The statistical significance was determined by a p-value lower than 0.05, with the aid of a commercially accessible software package used for all analyses.

3. Results

The study comprised 87 patients, consisting of 46 males, who had cardiac valve replacement between January 2018 – January 2022. Were included in the study. The baseline clinicopathological characteristics of the patients are listed in Table1. The mean age of the patients was 55±13 years (range: 19–80 years). The mean BMI of the patients was 28.5±4.5 (range: 19.1–42.3). Among the patients, 30 had hypertension (23%), 30 had diabetes (34.5%), 16 had atrial fibrillation (18.4%). Regarding the type of cardiac valve replacement surgery, 46 (52.9%) had aortic valve replacement (AVR), 32(36.8%) had mitral valve replacement (MVR), and 9 (12.3%) had both AVR and MVR.

Table 1

The distribution of clinicopathological characteristics of the study group.

Variables	n =87
Sex, Males (%)	46(52.9%)
Age (years)	55± 13 (19–80)
BMI (kg/m^2)	28.5± 4.5 (19.1–42.3)
Cigarette use, n (%)	33(37.9%)
INR	2.6± 0.5 (2.1–3.7)
Dose mg/month, n (%):	37.47± 17.1 (8.75–85)
Concomitant disease, n (%):	
· Hypertension	20(23%)
· Type 2 DM	30(34.5%)
· Atrial fibrillation	16(18.4%)
· MVR	32(36.8%)
· AVR	46(52.9%)
· AVR-MVR	9(12.3%)
Concomitant medications, n (%):	
· PPI	32(36.8%)
· Statins	46(52.9%)
· Metoprolol	55(65.2%)

INR: International normalization ratio of prothrombin time, AVR: aortic valve replacement, MVR: mitral valve replacement

Table 2

CYP2C9 and VKORC1 genotype frequencies of patients.

Genotype	Genotype frequency, n (%)
CYP2C genotype	
· *1/ *1	53(60.9%)
· *1/ *11	1(1.1%)
· *1/ *2	15(17.2%)
· *1/ *3	15(17.2%)
· *2/ *2	1(1.1%)
· *3/ *3	2(2.3%)
VKORC1 genotype	
· *1/ *3	2(2.3%)
· *1/ *4	2(2.3%)
· *2/ *2	22(25.3%)
· *2/ *3	27(31%)
· *2/ *4	8(9.2%)
· *3/ *3	5(5.7%)
· *3/ *4	17(19.5%)
· *4/ *4	4(4.6%)

The mean weakly warfarin dose for reaching ideal INR was 37.47±17.12 mg (range: 8.75-85 mg) CYP2C9 and VKORC1 gene

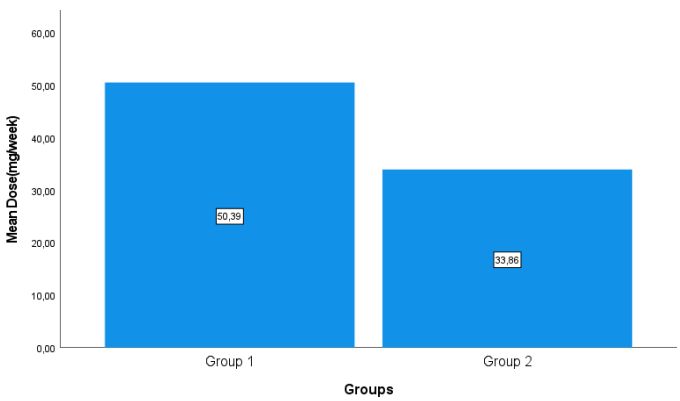
polymorphism frequencies for the whole study group are given in Table 2. The observed frequencies of CYP2C9 *1/*1, *1/*2, *1/*3, *2/*2, *3/*3 and *1/*11 genotypes were respectively as 60.9% (n = 53), 17.2% (n = 15), 17.2% (n = 15), 1.2% (n = 1), 2.3% (n=2) and 1.1% (n=1) (Table 2). VKORC1 frequencies were 25.3% (n=22) for *2/*2, 31% (n=27) for *2/*3, 19.5% (n=17) for *3/*4 (Table 2).

Normal coumadin dose is ordered for *1/*1 CYP2C9 mutation while decreased dose is ordered for other mutations. For VCORC1 mutations dose decrease is ordered for *2 mutations. So, patients were grouped according to dose requirements. 19 of the patients had mutations of both genes who did not need dose decrease while 23 patients had mutations in both genes requiring dose decrease.

Patients with and without mutations in any gene that required a reduction in warfarin dose were analyzed in two groups. 19 of the patients had none of the mutation (Group 1) while 68 of the patients had at least one mutation (Group 2). Median dose for reaching ideal INR was compared between two groups and it was 50.39±15.62 mg/week vs 33.86±15.81 mg/week: p=0.00 (Figure 1).

Figure 1

Mean weekly doses of groups.



4. Discussion

This study aimed to determine the frequencies of *CYP2C9* and *VKORC1* polymorphisms in patients who underwent cardiac valve surgery and received warfarin treatment, as well as to assess the potential effects of these genetic variants and clinical factors on the required warfarin dose. According to the findings, individuals with one *CYP2C9* or *VKORC1* polymorphism necessitated a notably lower weekly dose of warfarin to achieve the optimum INR. This underscores the criticality of factoring in genetic components when determining warfarin dosage.

In our cohort, the most frequent *CYP2C9* genotype was *1/*1, followed by *1/*2 and *1/*3. These findings are consistent with previous studies conducted in different populations, where the wild-type *CYP2C9* *1/*1 is the most common genotype, and *1/*2 and *1/*3 are the most frequent variants.[21] The VKORC1 genotype distribution in our study is also in line with previous research, which demonstrated a high prevalence of *VKORC1* *2/*2 and *2/*3 genotypes among patients taking warfarin.[22,23]

Our study found that patients with at least one *CYP2C9* or *VKORC1* polymorphism (Group 2) required a significantly lower weekly warfarin dose to achieve the target INR compared to patients without any mutations (Group 1). This observation is consistent with previous reports indicating that carriers of *CYP2C9* *2 and *3 alleles, as well as *VKORC1* variant alleles, have reduced enzyme activity and consequently require lower warfarin doses to avoid excessive anticoagulation and related complications.[24] Our findings underscore the importance of genotyping patients for *CYP2C9* and *VKORC1* polymorphisms to optimize warfarin dosing and minimize the risk of adverse events.

In addition to genetic factors, our study also considered clinical factors that could influence warfarin dosing, such as age, BMI, comorbidities, and type of cardiac valve replacement surgery. These factors have been reported to impact warfarin dose requirements and treatment outcomes in previous studies.[25] Further research is needed to elucidate the complex interplay between genetic and clinical factors in determining the optimal warfarin dose for individual patients.

There are some limitations to our study. First, the sample size was relatively small, which may have limited the statistical power to detect small differences in warfarin dose requirements among different genotype groups. Second, our study population was restricted to patients who underwent cardiac valve surgery, so the results may not be generalizable to other patient populations receiving warfarin therapy. Finally, other genetic polymorphisms not assessed in this study may also contribute to warfarin dose variability and warrant further investigation.

5. Conclusion

In conclusion, our study demonstrates the significant impact of *CYP2C9* and *VKORC1* polymorphisms on warfarin dose requirements in patients who have undergone cardiac valve surgery. These findings support the integration of pharmacogenetic testing into clinical practice to personalize warfarin therapy, thereby improving treatment outcomes and reducing the risk of adverse events. Further studies with larger sample sizes and diverse patient populations are warranted to validate our findings and refine the current understanding of the genetic determinants of warfarin dosing.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved *Adana City Training and Research Hospital* Scientific Research and Publication protocol number 2022/101-1835

Conflict of interest statement

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

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Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by T.O.B and O.O. The first draft of the manuscript was written by T.O.B and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Originality Assertion

The authors have not submitted this article to another journal previously.

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Descriptive Study of Earthquake-Related Spinal Cord Injury in Türkiye-Kahramanmaraş

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Abstract

Aim: Earthquakes are among the most common causes of mortality and morbidity due to natural disasters. In particular, soft tissue and musculoskeletal system injuries are the most common types of injuries reported after earthquakes and the most common reason for hospital admission. We aimed to review the epidemiological data of patients who were rescued from under the rubble in the Kahramanmaraş earthquakes on February 6 and developed earthquake-related spinal vertebral fractures.

Methods: Our study included 69 patients with spinal vertebral fractures and/or spinal cord injuries (SCIs) who were admitted to the Physical Medicine and Rehabilitation Clinic of Adana City Training and Research Hospital after the 6 February Kahramanmaraş Pazarcık and Elbistan earthquakes. Our study is a cross sectional-observational study. Patients with peripheral nerve damage or loss of muscle strength due to pelvic and extremity fractures were not included in the study.

Results: The mean age of the patients was 40.43±15.24 years (min=8-max=72). The median time of rescue from under the rubble was 15 (1-106) hours. The median visual analogue scale (VAS) pain score was 7 (0-10). 69.6% of the patients were female. Among the patients with a vertebral spinal injury, 72.5% had an incomplete SCI and 27.5% had a complete SCI. 84.5% of the patients underwent surgery, and posterior spinal instrumentation was performed in 56.5% of them.

Conclusions: There has been a significant increase in the number of SCI cases after the Kahramanmaraş earthquakes. Rehabilitation centers should be established, patients' access to these centers should be facilitated, and complications should thus be prevented or optimized. Injured people should be helped to return to their social lives

Keywords: *February 6th Kahramanmaraş, earthquake, spinal cord injury*

1. Introduction

Earthquakes are among the most common causes of mortality and morbidity due to natural disasters. In particular, soft tissue and musculoskeletal system injuries are the most common types of injuries reported after earthquakes and the most common reason for hospital admission[1]. Türkiye is a high-risk country for earthquakes; however, cities built on fault lines, unplanned urbanization, and non-earthquake-resistant and unsupervised structures increase the number of deaths and injuries. 100,000 people lost their lives due to earthquakes between 1908 and 1995. Poor disaster organization also increases earthquake-related losses[2,3]. Despite the developing technology, it is not possible to predict an earthquake.

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Because earthquakes frequently affect crowded urban areas with poor structural standards, they usually cause high mortality rates and mass casualties with many traumatic injuries.

A massive earthquake with a magnitude of 7.7 hit Türkiye with an epicentre of Pazarcık, Kahramanmaraş at 04.17 on February 6. A second earthquake measuring 7.6 occurred at 13.24 approximately nine hours later in Elbistan, Kahramanmaraş. These earthquakes affected 11 provinces as the most destructive earthquakes in the history of our country. After these two devastating earthquakes, thousands of aftershocks occurred, and thousands of people were killed and injured. Due to the collapse of thousands of structures and even hospitals, most of the injured were transferred to other cities.

Soft tissue and musculoskeletal system injuries are the most common types of injuries and the most common reason for hospital admission in earthquake victims stuck under the rubble for hours or even days. It is thought that most of the earthquake survivors have spinal vertebral fractures and/or SCIs.

The literature has very few studies on earthquake-related SCIs. Although the studies conducted after the 2005 Pakistan, 2008 China, 2010 Haiti, and 2015 Nepal earthquakes contributed significantly to

the literature on earthquake-related SCIs, the data are still insufficient[4–7]. Studies have shown an increased female rate, decreased cervical SCI and increased complications in earthquake-related SCIs compared to SCIs emerging from other causes[8].
Given the continuing risk of earthquakes, the approach to earthquake-related SCIs and patient management in the acute period and rehabilitation programs afterwards grow in importance.
In this study, we aimed to review the epidemiological data of patients who were admitted to our clinic with earthquake-related spinal fractures.

2. Materials and methods

Our study included 69 patients with spinal vertebral fractures and/or SCIs who were transferred from the earthquake-hit provinces to the Physical Medicine and Rehabilitation Clinic of ..... Training and Research Hospital or were later admitted to the clinic after the 6 February Kahramanmaraş Pazarcık and Elbistan earthquakes. Ethical approval was obtained for the study from the Clinical Research Ethics Committee of Adana City Training and Research Hospital (No:2633, Date: 08.06.2023). Our study is a cross sectional-observational study. Patients with peripheral nerve damage or loss of muscle strength due to pelvic and extremity fractures were not included in the study.

Table 1
Demographic Data and Clinical Characteristics

	n(69)
Age (year) (Median±Sd)	40,43±15,24
Time to get out of the rubble (hour) [median (min-max)]	15 (1-106)
Pain VAS [median (min-max)]	7 (0-10)
ASIA (n,%)	
· A	19 (27,5)
· C	7 (10,1)
· D	23 (33,3)
· E	20 (29,0)
Gender (n,%)	
· Female	48 (69,6)
· Male	21 (30,4)
Type(n,%)	
· Incomplete	50 (72,5)
· Complete	19 (27,5)
Surgery (n,%)	
· No	11 (15,9)
· Yes	58 (84,5)
Fixation (n,%)	
· No	30 (43,5)
· Yes	39 (56,5)
Crush İnjury (n,%)	
· No	42 (60,9)
· Yes	27 (39,1)
Pressure Ulcer (n,%)	
· No	65 (94,2)
· Yes	4 (5,8)
Urinary Catheter (n,%)	
· No	31 (44,9)
· Yes	31 (44,9)
· Spontaneus	7 (10,1)
Sensory Examination (n,%)	
· Normal	32 (46,4)
· Hypoesthesia	19 (27,5)
· Anesthesia	18 (26,1)

The demographic data of the patients (age and gender), the duration of being trapped under the rubble, the level of injury, the presence of a surgical operation and if present, the use of spinal instrumentation, the presence of crush injury, the use of a urinary catheter, and the history of urinary tract infection (UTI) were recorded. Pain intensity was measured with the VAS. Physical examinations were performed to determine the presence of an SCI, and if present, the American Spinal Injury Association (ASIA) impairment scale was used to determine injury levels.

Statistical analysis was performed using SPSS software. Continuous variables were expressed as mean ± standard deviation and median (min-max), while categorical data were expressed as numbers and percentages.

3. Results

The mean age of the patients was 40.43±15.24 years (min=8-max=72). The median time of rescue from under the rubble was 15 (1-106) hours. The median VAS pain score was 7 (0-10). 69.6% of the patients were female. Among the patients with a vertebral spinal injury, 72.5% had an incomplete SCI and 27.5% had a complete SCI. 84.5% of the patients underwent surgery, and posterior spinal instrumentation was performed in 56.5% of them. 39.1% of the patients had a crush injury, 5.8% had pressure ulcers, 44.9% had an indwelling catheter, and none of the patients developed a UTI.
Sensory examinations revealed hypoesthesia and anesthesia in 53.6% of the patients, pain in 98.6%, and numbness-tingling in 51.5% (Table 1).
94.2% of the patients had thoracolumbar vertebral fractures, especially in T12 (15.9%) and L1 (31.9%) vertebrae. Only four patients had a cervical injury.
Table 2 and Table 3 show patients' muscle strength grades and injury levels.

Table 2
Muscle Strength Grades

Muscle Strength	n	%
0/5	18	26.1
1	1	1.4
1/5	2	2.9
2+/5	1	1.4
3-/5	2	2.9
3/5	4	5.8
3+/5	2	2.9
4-/5	1	1.4
4/5	12	17.4
4+/5	2	2.9
5/5	21	30.4
(R)Lower extremity 1/5	1	1.4
(R)Upper extremity 2/5, (R)Lower extremity 1/5	1	1.4
Left Foot Dorsiflexion 1/5	1	1.4
Total	69	100.0

4. Discussion

Earthquakes are destructive natural disasters, and it is not possible to predict when and where an earthquake will occur[5]. Earthquakes cause greater losses in developing countries. SCIs due to post-earthquake trauma or compression are important causes of mortality and morbidity[5–8]. The epidemiology of SCIs in earthquakes is different from that of SCIs resulting from other traumatic

Table 3
Injury Levels

Level	n	%
C5	2	2.9
C6	2	2.9
L1	22	31.9
L1,L2	1	1.4
L1,L2,L3	1	1.4
L2	5	7.2
L3	3	4.3
L4	3	4.3
L4,L5	1	1.4
L5	1	1.4
T10	2	2.9
T11	1	1.4
T11-L4	1	1.4
T11,L1	1	1.4
T11,T12	3	4.3
T11,T12,L2,L3	1	1.4
T12	11	15.9
T12, L1-5	1	1.4
T12,L1	3	4.3
T4	1	1.4
T6	1	1.4
T9	2	2.9
Total	69	100.0

causes. Therefore, complications and rehabilitation processes are also different.

The search and rescue phase and early treatment are of vital importance for earthquake victims. There is a race against time to rescue as many people as possible; therefore, local people without search and rescue training also participate in rescue operations. In these cases, the injured are dragged out of the rubble piles without spinal immobilization, thereby resulting in SCIs. The posture of the victims at the time of the earthquake also plays a key role in the injury location[9,10].

Because the first earthquake in our country on 6 February occurred at 04.17 midnight, people were caught asleep by the earthquake. Most of the SCI patients woke up with a strong tremor and found themselves trapped under the rubble.

In our study, 69.6% of the patients were female. 94.2% of the patients had thoracolumbar vertebral fractures, especially in T12 (15.9%) and L1 (31.9%) vertebrae. Only four patients had a cervical injury. Although 21 (30.4%) patients had vertebral fractures, no neurological deficit was detected. 27.5% of the patients had a complete SCI, and 21.7% had a muscle strength score of 4/5. One patient had tetraplegia, one patient had monoplegia, and one patient had a drop foot.

Maruo et al.[10] found spinal fractures in 995 out of 1675 patients with bone injuries after the great earthquake that occurred in Japan in 1995. However, only 21 (2.1 %) had a SCI. Similar to our study, spinal fractures were found most commonly in the thoracolumbar region and T12 (29%) and L1 (29%) vertebrae. They attributed the low number of SCIs to the advanced search and rescue team and rapid rescue of the victims.

Tauqir et al.[11] assessed SCI cases after the 2005 earthquake in Pakistan. They found paraplegia in the majority of cases and observed cervical injury and tetraplegia in only four of 194 cases.

In another study conducted by Rathore et al[5] after the 2005 earthquake in Pakistan, paraplegia was found in 89.3% of the cases. The low number of cervical injuries and tetraplegic cases was attributed to the high mortality rate in cervical injuries and the lack of sufficient time to survive[5]. Likewise, in our study, cervical injury was observed in only four cases. We also believe that this may be associated with the high mortality rate in cervical injuries and victims died before they had the opportunity to be rescued.

Many studies have shown that traumatic SCI is observed more frequently in men in developing countries[12–14]. In the literature, the rate of women was found to be high in studies conducted in earthquake-related SCI cases. This rate was found to be 54% in Raissi et al[15], 74% in Tauqir et al[11], 70% in Maruo et al[10], and 56% in Groves et al[4]. Similarly, the rate of women (69.6%) was higher in our study. Social, behavioral, and occupational risk factors increase the risk of traumatic SCI in men, while in natural disasters, more people are at home in the early hours of the morning and women are more affected[9].

These major disasters in our country have once again demonstrated the importance of search and rescue activities, trained teams, rapid access to the rubble, and rehabilitation processes for survivors.

Limitations

Due to the high number of cases after the disaster, the hospital registration system was inadequate, and most of the cases were rapidly transferred to the surrounding provinces after they were stabilized. Only the cases admitted to our clinic could be evaluated; therefore, the number of cases in our study is insufficient. We believe that there are more SCI cases.

5. Conclusion

There has been a significant increase in the number of SCI cases after the Kahramanmaraş earthquakes. Spinal cord injury rehabilitation centers should be established under the leadership of physical medicine and rehabilitation physicians. Access to these centers should be facilitated to prevent and optimize complications. Patients should be followed up regularly. Injured people should be helped to return to their social lives as soon as possible.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved *Adana City Training and Research Hospital* Scientific Research and Publication protocol number 2633, Date: 08.06.2023.

Conflict of interest statement

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

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Author Contributions

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Originality Assertion

The authors have not submitted this article to another journal previously.

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Are Three Different Lipid Combinations Effective on The Immune System in Sepsis Patients?

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Abstract

Aim: We aimed to analyze the effect of the 3 different parenteral nutrition's (MCT/LCT (long and medium chain fatty acids), LCT with omega-9 (ω-9) and MCT/LCT with ω-3 and ω-9 on the inflammatory cytokine levels in sepsis patients. This is the first study from the Southern part of Turkey.

Methods: We included 30 patients, diagnosed with sepsis and took total parenteral nutrition in this study. Patients were divided into 3 randomized groups in terms of what parenteral nutrition have been taken. (Group A, B and C) Blood samples were taken and TNF-α, IL-1, IL-6 and IL-8 levels were evaluated. Adverse effects were recorded. TNF-α, IL-1β, IL-6, and IL-8 levels of were analyzed by ELISA method and each sample were studied in duplicate.

Results: The median age of the patients included in the study was 52 and 24 (80%) of them were male. The SOFA score was 5 in study group. We examined IL-1, IL-6, IL-8 and TNF-α distribution on the day of the first, third and fifth days depending on time. The inflammatory cytokine levels were not found statistically significant ($p > 0.05$) when we compared the study groups via 3 different parenteral nutrition's.

Conclusions: When we compare MCT/LCT, LCT/ω-9 and MCT/LCT, ω-3, ω-9 which are given as a component of total parenteral nutrition we concluded that there was no superiority to others in terms of proinflammatory cytokine levels in sepsis and they didn't increase proinflammatory cytokines. There is a need for more randomized controlled studies investigating the effect of lipids on the course of the disease in sepsis patients who cannot receive enteral nutrition and require TPN support.

Keywords: *Sepsis, lipid, cytokine*

1. Introduction

Sepsis is one of the most serious problems encountered in intensive care units; moreover, it causes hospitalization and is a complication occurring during hospitalization. Despite all supportive treatments and use of strong antibiotics, it results in 30%–70% mortality and significantly reduces the quality of life among sepsis survivors[1, 2]. Sepsis is defined as the uncontrolled systemic inflammatory response of the host to infection. Notably, it is caused when the causative microorganism interacts with the host's immune, inflammatory, and coagulation responses. In other words, both host response and causative microorganism are responsible for sepsis[3]. The physiopathological events occurring during sepsis are complex.

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Many antigenic structures and toxins in the bacterial cell wall trigger the release of several potent mediators from circulating mononuclear phagocytes, endothelial cells, and other cells. These mediators particularly include tumor necrosis factor alpha (TNF-α); interleukins 1, 2, 6, and 8 (IL-1, IL-2, IL-6, and IL-8); and platelet-activating factor (PAF)[4]. In patients with sepsis, total parenteral nutrition (TPN) is used to provide nutrition as well as to reduce the metabolic response to stress, positively control the immune system, and enhance clinical findings[5].

Intravenous lipid emulsion (IVFE)—a crucial element of TPN—is rich in essential fatty acids and is an energy-dense source of calories. Notably, lipid emulsions comprise many bioactive components, including fatty acids[6]. Further, various fatty acids can have different effects on several physiological processes, such as injury healing, metabolism, blood coagulation, oxidative stress, cell and organ functions and multiplication, inflammation, and immune response[7]. Conventionally, IVLE were composed of soybean oil (SO)[8, 9]. Nevertheless, SO is rich in ω-6 polyunsaturated long-chain triglycerides (LCT) which may contribute to immunosuppression in sepsis cases as relevant evidence has suggested. Moreover, SO may contribute to increased risk of complications by exacerbating the release of

proinflammatory cytokines and prostaglandin 2[10, 11]. Therefore, novel strategies have been developed to reduce the LCT content in parenteral nutrition lipid emulsions using other fats, such as medium-chain fatty acids (MCT), ω-9 containing olive oil (OO), or ω-3 containing fish oil (FO)[12].

This study aimed to compare three different lipid emulsions (those containing MCT/LCT; LCT and ω-9; or MCT/LCT, ω-3, and ω-9) in patients who diagnosed with sepsis,

These emulsions were employed in the TPN given to the patients to determine their effects on the levels of proinflammatory cytokines such TNF-, IL-1, IL-6, and IL-8 and to find out if any of them were better than the others.

2. Materials and methods

The present study was performed on patients in the intensive care unit (ICU) of Çukurova University School of Medicine Training and Research Hospital during a 13-month period between March 2015 and April 2016. This study received ethics approval from Çukurova University School of Medicine Ethics Committee (date: 19/03/2015; approval number: 39/11).

2.1. Selection of Patients

After ethics committee approval and informed consent from the patients or their caregivers were obtained, 37 patients (age > 18 years) who were diagnosed with sepsis and receiving TPN support were enrolled. Seven patients were excluded from the study: five patients in the experimental group were excluded owing to the transition to enteral nutrition, and two patients were excluded owing to the progress to septic shock. The diagnosis of sepsis was based on the focus of infection and the Sequential Organ Failure Assessment (SOFA > 2) criteria. Exclusion criteria were as follows: patients aged ≤18 years, those who were pregnant, those who had severe sepsis and septic shock, those who received corticosteroids (≥1 mg/kg) within the last 48 hours, those who were receiving major immunosuppressive drugs, those who tested positive for HIV, those who had a plasma triglyceride concentration of >200 mg/dL, those who had severe hyperglycemia (glucose >250 mg/dL), those who had acute kidney injury following the Kidney Disease Improving Outcomes guideline criteria, those who had fatal disease, and those who were able to receive enteral nutrition. The daily lipid profiles of the patients were followed and the patient was excluded from the study when the study limits were exceeded in triglyceride and other lipid values.

2.2. Nutritional Regiments Delivered to Patients

Participants were grouped into three in a random pattern, based on the parenteral nutrition composition using the website www.randomizer.org as follows:

Group A (n=10); TPN containing 1 g/kg MCT/LCT (Nutriflex®)

Group B (n=10); TPN containing 1 g/kg LCT and ω-9 (Oliclinomel N7®)

Group C (n=10); TPN containing 1 g/kg MCT/LCT, ω-3, and ω-9 (SMOF Kabiven®)

All patients were fed via a central venous catheter for 5 days. All groups received nutrition with 4 g/kg of glucose and 2 g/kg of protein administered as infusion for 24 hours. Based on the guidelines provided by the American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), we computed the required energy (total energy: 25–30 kcal/kg/day; protein: 1.2–2 g/kg/day)[13-15]. The target calorie intake was reached on day 4. The patients started receiving enteral nutrition in accordance with the hospital and enteral nutrition protocols based on daily examinations by the ICU physician and dietician.

2.3. Collection of Samples

The day the patients started to receive nutrition was defined as day 0. The age, gender, height, and weight of all patients were recorded (Table 1). Blood samples of the patients included in the study were collected between 08:00 and 10:00 in the morning on days 0, 3, and 5. Approximately 5 mL of whole blood from each patient was taken into gel separation tubes (BD Vacutainer® SST™ II Advance). The plasma of all samples was then separated by centrifugation at 1,500xg for 10 minutes at 4 °C and stored at –80 °C until experimental studies were performed. Allergic reactions, fever, and side effects were documented in all patients included in the study.

2.4. ELISA Assay

All samples were allowed to reach room temperature before the proinflammatory parameters were determined by ELISA and TNF-α, IL-1β, IL-6, and IL-8 levels of each sample were analyzed in dublicate.

IL-1β levels of the samples were obtained using ELISA kit (Human IL-1β; Catalogue number: KAP1211; DIAsource®, Belgium;) according to the manufacturer's instructions. The reference intervals of the Human IL-1β ELISA kit was 0-13.6 pg/mL, detection limit 0.35 pg/mL, intra-assay CV <2.3%, inter-assay CV <4.5%, and accuracy 90-97%.

IL-6 levels of the samples were obtained using ELISA kit (Human IL-6; Catalogue number: KAP1261; DIAsource®, Belgium;) according to the manufacturer's instructions. The reference intervals of the Human IL-6 ELISA kit was 0-17 pg/mL, detection limit 2 pg/mL, intra-assay CV <4.2%, inter-assay CV <4.4%, and accuracy 97-102%.

IL-8 levels of the samples were obtained using ELISA kit (Human IL-8; Catalogue number: KAP1301; DIAsource®, Belgium;) according to the manufacturer's instructions. The measurement range of the Human IL-8 ELISA kit was 0-50 pg/mL, detection limit 1.1 pg/mL, intra-assay CV <3.2%, inter-assay CV <8.6%, and accuracy 105-119%.

TNF-α levels of the samples were obtained using ELISA kit (Human TNF-α; Catalogue number: KAP1751; DIAsource®, Belgium;) according to the manufacturer's instructions. The reference intervals of the Human TNF-α ELISA kit was 4.6–12.4 pg/mL, detection limit 0.7 pg/mL, intra-assay CV <6.6%, inter-assay CV <4.5%, and accuracy 91–100%.

2.5. Statistical Method

We conducted the statistical analysis of all information through SPSS 17.0 software. Categorical variables were shown numerically and in ratio, whereas continuous variables were presented as mean ± standard deviation (minimum, maximum, and median if needed). We evaluated how the data is distributed when continuous variables are compared among the groups, and applied the Kruskal–Wallis and Mann–Whitney U tests because the prerequisite of parametric distribution was not met. The results of the time-dependent test were compared using the Wilcoxon test and repeated-measures ANOVA. Significance was met when p-value < 0.05 for all tests.

3. Results

3.1. Demographic Characteristics

The 30 participants have a median age of 52 (19–81) years; of these, 80% (n=24) patients were men. The mean body mass index (BMI) of the patients was 25.1±3.3 kg/cm^2. The median SOFA score was 5 (4–9). Demographic characteristics of the patient groups were similar. The three groups did not significantly differ regarding age, height, BMI, and SOFA scores (Table I).

3.2. IL-1β Measurements

The groups did not significantly change when analyzing the median IL-1β levels at baseline and on days 3 and 5. Moreover, time-dependent variations within the groups were not statistically

different (Table II). The measurement of IL-1β on day 0 revealed the median levels of 0.02 (0.01–7.76), 0.02 (0.01–2.94), and 0.45 (0.01–22.1) pg/mL in the three groups (A, B, and C), respectively (p >0.05). Similarly, the median IL-1β on day 3 were 0.02 (0.01–0.93), 0.11 (0.01–161.4), and 0.54 (0.01–72.2) pg/mL in the three groups, respectively (p >0.05). As for the levels on day 5, they were 0.03 (0.01–17.7), 0.02 (0.01–39.7), and 0.66 (0.01–16.7) pg/mL in the three groups, respectively (p >0.05).

Table 1

Distribution of Demographic Characteristics

	Group A Med (Min–Max)	Group B Med (Min–Max)	Group C Med (Min–Max)	p
Age (years)	49 (20–68)	53 (19–81)	54 (19–63)	>0.05
Weight (kg)	80 (50–92)	77 (49–82)	77 (57–87)	>0.05
Height (m)	1.75 (1.52–1.87)	1.72 (1.63–1.78)	1.73 (1.64–1.81)	>0.05
BMI (kg/m²)	26.4 (21.5–28.1)	25.5 (18–30.1)	25.8 (19.5–32.4)	>0.05
SOFA score	5 (4–8)	5 (4–9)	6 (4–9)	>0.05

Table 2

Distribution of IL-1β Levels

	Day	Group A Med (Min–Max)	Group B Med (Min–Max)	Group C Med (Min–Max)	p
IL-1β (pg/ml)	0	0.02 (0.01–7.76)	0.02 (0.01–2.94)	0.45 (0.01–22.1)	>0.05
	3	0.02 (0.01–0.93)	0.11 (0.01–161.4)	0.54 (0.01–77.2)	>0.05
	5	0.03 (0.01–17.7)	0.02 (0.01–39.7)	0.66 (0.01–16.7)	>0.05

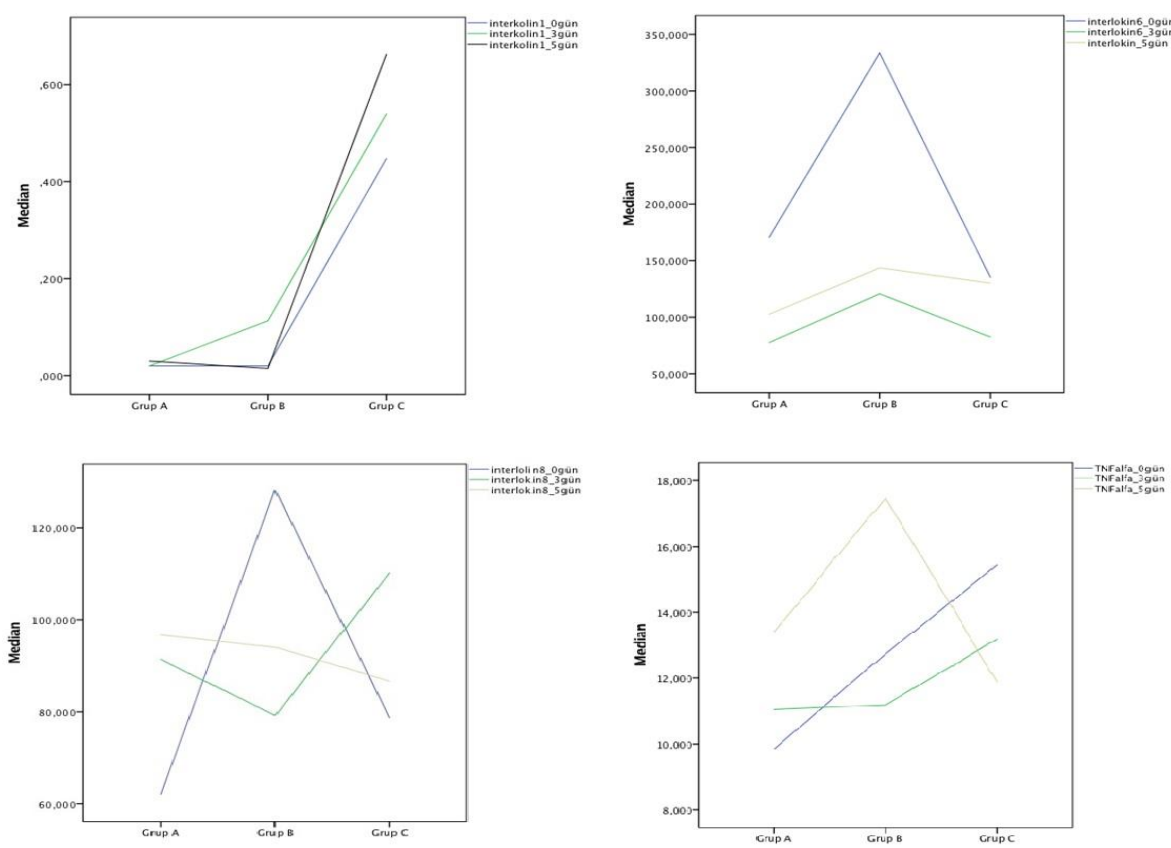
Figure 1 shows the distribution of IL-1β level at days 0, 3, and 5 as well as the time-dependent changes for each group. Although the levels comparatively increased and decreased in all three groups, the increase was most evident in the Group C, but the analysis of changes over time in terms of groups revealed no significant difference (Figure 1).

3.3. IL-6 Measurements

Analysis of median IL-6 levels at days 0, 3, and 5 did not significantly changed among the three groups. Moreover, time-dependent variations within the groups were not statistically different (Table III).

Figure 1

Comparison of proinflammatory cytokine levels of the groups



Median IL-6 levels on day 0 were 170.6 (15.5–546.7), 333.6 (46.4–1821.4), and 135.3 (50.1–761.2) pg/mL in the three groups (A, B, and C), respectively (p >0.05). The levels on day 3 were 77.6 (10.7–256.9), 120.7 (32.4–659.1), and 82.5 (26.9–942.3) pg/mL in the three groups, respectively (p >0.05). Further, the levels on day 5 were 102.6 (32.2–337.7), 143.6 (56.5–347.2), and 130.2 (37.6–1709) pg/mL in the three groups, respectively (p >0.05).

Table 3

Distribution of IL-6 Levels

	Day	Group A Med (Min–Max)	Group B Med (Min–Max)	Group C Med (Min–Max)	p
IL-6 (pg/mL)	0	170.6 (15.52–546.7)	333.6 (46.42–1821.4)	135.3 (50.13–761.2)	>0.05
	3	77.6 (10.75–256.9)	120.7 (32.4–659.1)	82.5 (26.94–942.3)	>0.05
	5	102.6 (32.18–337.7)	143.6 (56.49–347.2)	130.2 (37.6–1709)	>0.05

Figure 1 presents the distribution of IL-6 level at days 0, 3, and 5 as well as the time-dependent changes in terms of groups. None of the three groups demonstrated consistent increase or decrease in these levels. Moreover, the analysis of changes in measurements over time for these groups revealed no statistically significant difference (Figure 1).

3.4. IL-8 Measurements

Analysis of median IL-8 levels at days 0, 3, and 5 revealed a negative significant difference between the groups. Moreover, time-dependent changes within the groups showed no statistical difference (Table IV). Median IL-8 levels at baseline were 62.0 (32.8–664.6), 128.1 (37.8–913.1), and 78.7 (13.7–645.3) pg/mL in the three groups (A, B, and C), respectively (p >0.05). The levels on day 3 were 91.4 (46.8–280.3), 79.2 (40.5–1283.2), and 110.2 (48.2–865.4) pg/mL in the three groups, respectively (p >0.05). Further, the levels on day 5 was 96.8 (42.8–738.7), 94.1 (29.2–633.2), and 86.7 (42.3–1280.5) pg/mL in the three groups, respectively (p >0.05).

Table 4

Distribution of IL-8 Levels

	Day	Group A Med (Min–Max)	Group B Med (Min–Max)	Group C Med (Min–Max)	p
IL-8 (pg/mL)	0	62.0 (32.81–664.6)	128.1 (37.83–913.1)	78.7 (13.68–645.3)	>0.05
	3	91.4 (46.8–280.3)	79.2 (40.52–1283.2)	110.2 (48.2–865.4)	>0.05
	5	96.8 (42.76–738.7)	94.1 (29.25–633.2)	86.7 (42.31–1280.5)	>0.05

Figure 1 shows the distribution of IL-8 levels at days 0, 3, and 5 as well as the time-dependent changes in terms of groups. The Group A seemed to demonstrate a consistent increase in this level, whereas the other groups had both increases and decreases, but the analysis of changes in the measurements over time for these groups revealed no statistically significant difference (Figure 1).

3.5. TNF-α Measurements

The three groups did not significantly differ when testing the median TNF-α levels at days 0, 3, and 5. Moreover, time-dependent changes within the groups were not statistically significantly different (Table V). Median and range TNF-α levels at baseline were not significantly different between the three groups (9.8 (2.9-17.2), 12.7 (5.1-35.1), and 15.4 (4.0-102.6)) pg/mL, respectively] (p >0.05).Similar results between the groups were obtained at days 3 and 5 (11.1 (4.7–24.7), 11.2 (6.6–29.1), and 13.2 (6.0–51.9)) and (13.4 (5.5–27.8), 17.5 (4.0–30.5), and 11.9 (6.1–43.9)), respectively (p >0.05).

Table 5

Distribution of TNF-α Levels

	Day	Group A Med (Min–Max)	Group B Med (Min–Max)	Group C Med (Min–Max)	p
TNF-α	0	9.8 (2.92–17.2)	12.7 (5.11–35.1)	15.4 (4.04–102.6)	>0.05
	3	11.1 (4.72–24.7)	11.2 (6.60–29.1)	13.2 (6.02–51.87)	>0.05
	5	13.4 (5.47–27.8)	17.5 (4.0–30.5)	11.9 (6.13–43.93)	>0.05

Figure 1 shows the distribution of TNF-α levels at days 0, 3, and 5 as well as the time-dependent changes in terms of groups. Although there was a consistent increase these levels in the Group A and a consistent decrease in the Group C, analysis of the changes in measurements over time for these groups revealed no statistically significant difference; this may be attributed to the limited number of patients and randomized inclusion of the patients (Figure 1).

3.6. Adverse Effects

None of the groups experienced any allergic reaction to the nutritional mixtures.

4. Discussion

The lipid content of TPN in patients with sepsis has gained increased importance after it was reported to have effects on eicosanoid metabolism and the levels of proinflammatory cytokines. Recent studies have stated that the use of SO-based lipids may cause an increase in the levels of potentially harmful prostaglandins in sepsis owing to their ω-6 content[10, 11, 16, 17]. Briefly, it was found in this study that three different TPN mixtures, grouped MCT/LCT; LCT with ω-9; and MCT/LCT with ω-3 and ω-9, did not lead to any differences in proinflammatory cytokine levels in patients with sepsis. Since there hasn't been comparative research of these three lipid combinations, we believe that this is an important contribution to the field.

Dominique Granado et al. compared the effects of nutritional emulsions with SO- and OO-based lipid compositions on immune functions in human cells in vitro. They reported that SO-containing emulsions inhibit lymphocyte proliferation, whereas OO-containing emulsions do not. Moreover, both emulsions tended to inhibit the release of TNF-α and IL-1β to a similar extent[18]. In our study, we could not see any change in IL-1β level in group B containing FO, while an increase in TNF-α level was observed. In a double-blind randomized study of 32 infants undergoing open heart surgery, Larsen et al. compared pure SO-based lipids with emulsions containing 40% MCT, 50% LCT, and 10% FO. They evaluated TNF-α, IFN-γ, GM-CSF, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, and IL-10 levels at four days, i.e., at 2 hours before surgery as well as at 24 hours, 7 days, and 10 days after surgery. They found that TNF-α levels were

lower in the FO group at 24 hours after surgery[19]. In our study, we observed an increase in TNF-α level in group B containing FO. Owing to the randomized selection of patients and the complexity of the pathogenesis of sepsis, this conclusion can be attributed to the small number of patients. Further, Konstantin Mayer et al. investigated whether parenteral nutrition comprising ω-3 and ω-6 affected proinflammatory cytokine levels in 21 patients with sepsis. They found a decrease in cytokine levels in the ω-3 group, but there was a significant rise in proinflammatory cytokine levels in the ω-6 group[20]. However, in the present study, we did not use any SO-based emulsions containing ω-6 owing to their potentially harmful effects on proinflammatory cytokine levels in patients with sepsis. For this reason, we used TPN products containing other different lipid mixtures used to reduce LCT/ ω -6 level in our study.

Ming-Hsun Wu et al. investigated the effects of parenteral nutrition containing MCT/LCT, ω-3, and ω-9 and those containing only MCT/LCT on inflammatory markers in patients undergoing gastrointestinal surgery. They evaluated IL-6, CRP, TNF-α, and TGF-1β levels to be insignificantly changed between the two groups[21]. We could not find a statistically significant difference between the two groups in our findings. We attributed this to the difference between the pathogenesis of sepsis and the inflammatory response secondary to surgery. Maria Skouroliakou et al. studied the difference between the effects of parenteral emulsions containing MCT/LCT-, ω-3, and ω-9-based lipids with those of emulsions containing ω-6-based lipids alone on inflammatory cytokines in 60 infants. IL-6 and IL-8 levels were not significantly different between the two groups when compared to TNF-α levels, although they showed to be less in patients receiving mixed lipid content[22]. Stanislaw Klek et al. administered parenteral nutrition containing MCT, ω-6, ω-3, and ω-9 lipids as well as emulsions with SO-based lipids alone to 73 intestinal failure patients for 4 weeks and compared IL-6, sTNF-RII, and CRP levels between the two groups. The results of their clinical trial revealed no difference between the two groups[23]. Different results can be expected from the sepsis patient group in our study, since there is some impairment in lipid absorption, albeit at different rates, in patient groups with intestinal insufficiency. Veronique Donoghue et al. conducted a randomized controlled trial to investigate parenteral nutrition comprising MCT/LCT, ω-3, ω-9, and ω-6 in 68 patients. They reported that TNF-α concentrations declined from day 1 to day 6 in the groups that received parenteral nutrition emulsions containing MCT/LCT, ω-3, ω-9, and ω-6, whereas it increased in the group that received soy-based parenteral nutrition emulsions; however, the difference was not statistically significant[24]. The present study compared between parenteral nutrition containing MCT/LCT, ω-3, and ω-9 and only MCT/LCT; no significant difference was detected between the two groups in terms of proinflammatory cytokine levels. We attributed this result to the use of mixtures where the LCT content was similarly reduced to 50%.

In a clinical study of 32 patients, Gültekin et al. compared parenteral nutrition emulsions containing ω-9 lipids with those containing ω-3 lipids in patients with critical sepsis and septic shock. They evaluated IL-6 and TNF-α levels on days 1 and 6, but no significant difference between the two groups was detected[25]. Moreover, Jean-Marie Reiumund et al. investigated the effects of parenteral nutrition with LCT, MCT/LCT, and 80% OO-based lipids on inflammatory cytokine levels in vitro. They found that parenteral nutrition regimens containing OO-based lipids triggered the release of TNF-α and IL-1β to a lesser extent but did not lead to a significant difference in IL-6 and IL-8 concentrations[26]. In a randomized double-blind study of 100 patients at ICU, Umpierrez et al. administered emulsions containing pure SO-based and OO-based lipids for 28 days and evaluated TNF-α, CRP, and IL-6 levels in both groups. They found no significant difference between the two groups[27]. Agnieszka Gawechka et al. administered a parenteral nutrition emulsion containing SO-based lipids and a parenteral emulsion containing ω-9 lipids for 14 days to 38 premature infants and compared the emulsions in terms of their effects on inflammatory cytokines. However, their study failed to demonstrate any statistically significant change among the two groups regarding TNF-α, IL-6, and IL-10 levels[28]. Although we included only sepsis patients in our study, we could not find a similarly significant difference. Ulusoy et al. compared a parenteral emulsion containing ω-6 lipids with another parenteral emulsion containing ω-9 lipids administered for 10 days to 40 patients with sepsis and investigated the effects of these emulsions on inflammatory cytokines. They found a decrease in IL-1β, IL-6, IL-10, and TNF-α levels in all patients regardless of lipid solutions, but they failed to report any significant difference in terms of lipid content[29]. The present study reported that lipid emulsions containing ω-9 did not lead to a significant difference in proinflammatory cytokines in patients with sepsis compared to emulsions containing MCT/LCT lipids and those containing MCT/LCT, ω-3, and ω-9 lipids. We think that reducing the LCT ratio, which is the main source of proinflammatory cytokines, to 50% or less will lead to similar results.

In contrast to the present study, some previous reports have indicated that certain lipids alter proinflammatory cytokine levels. Hsiao et al. compared a parenteral emulsion containing MCT/LCT with a parenteral emulsion containing MCT/LCT, ω-3, and ω-9 (30%, 30%, 25%, 25%, 15%) used for 7 days in 60 premature infants and examined their effects on inflammatory cytokines. IL-1 and IL-6 levels were significantly reduced in the group that received the emulsion containing MCT/LCT, ω-3, and ω-9[30]. Our results may have been different because the lipid mixture ratios in the solution we used in our study were different from the mixture used here. Sungurtekin et al. administered a parenteral emulsion containing MCT/LCT lipids and another parenteral emulsion containing ω-3 lipids for 10 days in 40 patients with sepsis and SIRS. They found that TNF-α and IL-6 levels on day 7 were significantly higher in patients with sepsis who received the emulsion containing MCT/LCT lipids compared to those who received the emulsion containing ω-3 lipids. In contrast, IL-1 levels were found greater in the MCT/LCT group than in the ω-3 group on days 3, 7, and 10. Similarly, IL-10 levels in the ω-3 group were above the MCT/LCT group on days 3 and 7[31]. Since we ended our study on the 5th day, we did not find any significant difference between the groups. Barbosa et al. compared parenteral nutrition containing MCT/LCT (50%/50%) lipids with parenteral nutrition containing MCT/LCT/ω-3 (40%/50%10%) lipids in a study of 25 patients with sepsis and SIRS. Their clinical study compared IL-1β, IL-6, IL-10, and TNF-α levels between the two groups and found a significant decrease on day 5 in IL-6 and IL-10 levels in the group that received the emulsion containing FO[32]. Failure to find a significant difference in the three different lipids in this study might be attributed to the small sample of participants.
Consistent with the results of the present study, the current guidelines and reviews do not provide any recommendation on lipid selection. Additionally, the most recent guidelines published by the ASPEN do not recommend any particular formulation as there is no clear evidence of the superiority of any particular lipid in parenteral nutrition[33]. Similarly, the Metabolism and Nutrition Working Group of the Spanish Society of Intensive and Critical Care Medicine and Coronary Units recommend that the use of mixed formulas that lower the ω-6/ω-3 ratio for lipid selection is useful as a pharmacological strategy for artificial nutrition. However, they did not recommend a lipid of choice for critically ill patients[34]. A review by Abbasoglu et al. compared the effects of ω-3-containing parenteral nutrition emulsions with other lipid emulsions and reported different effects on inflammatory cytokines, but they did not report a significant superiority of any specific lipid over others[35].

This study has several limitations. First, patients could not be followed up after day 5. Second, the sample of participants was relatively small. Third, the total number of days during which the patients received TPN was not analyzed. These limitations warrant randomized controlled trials with greater number of patients and lengthier times of follow-up.

5. Conclusion

Most lipids that are used for nutritional purposes are immunoregulatory substrates with a major depressive effect. Sepsis is associated with high morbidity and affects the immune system as well as leads to excessive inflammatory responses. There are still not enough randomized controlled studies examining how lipids affect the course of the disease in sepsis patients who need TPN treatment but cannot obtain enteral nutrition.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved *Cukurova University* Scientific Research and Publication protocol number 2015-39/11

Conflict of interest statement

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

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Thesis number 435538
https://tez.yok.gov.tr/UlusalTezMerkezi/TezGoster?key=cbOXH84ZayrLjc0tI-QXKi75hCcgEI7Dj1ZmFUXXmCeP3V3YTq0LBgMmv8Qd2tKv

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Evaluation of infraorbital canal types and their relation with adjacent structures: A cone beam computed tomography study

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Abstract

Aim: This study aims to analyze infraorbital canal (IOC) types in patients with cone beam computed tomography (CBCT) scans and to investigate the potential relationship between the IOC types and mucosal thickening, as well as adjacent structure variations such as Haller cells, sinus septa, middle turbinate pneumatization (MTP) and IOC types.

Methods: Bilateral evaluation of 197 CBCT records was conducted to assess mucosal thickening, Haller cells, sinus septa, middle turbinate pneumatization (MTP), and IOC types. IOC types were categorized into three classes based on their extent of protrusion into the maxillary sinus: type 1, entirely within the sinus roof; type 2, located below and adjacent to the sinus roof; and type 3, suspended from the sinus roof and descending into the sinus cavity.

Results: The distribution of IOC types was as follows: 67.5% for type 1, 22.6% for type 2, and 9.9% for type 3. No significant correlation was observed between IOC types and MTP, mucosal thickening, or the presence of Haller cells. However, a significant relationship was noted between Type 3 IOC and the presence of septa. The occurrence of septa in the maxillary sinus was 8.3% for type 1 IOCs, 13.5% for type 2 IOCs, and 43.6% for type 3 IOCs. ($p<0.001$)

Conclusions: The protrusion of the IOC into the maxillary sinus is relatively uncommon but should not be overlooked. A significant relationship was detected between the presence of septa and the type 3 IOC. Examination of existing CBCT scans may offer valuable insights about IOC.

Keywords: *Infraorbital canal, maxillary sinus, cone beam computed tomography*

1. Introduction

The infraorbital canal (IOC) is located in the maxillary bone, anterior to the orbital floor. The IOC begins posteriorly as a continuation of the infraorbital groove and terminates at the infraorbital foramen. It includes the infraorbital branch of the maxillary nerve, the trigeminal nerve's second branch. Additionally, it includes the infraorbital artery and vein. The infraorbital nerve (ION) provides sensory innervation to the skin of the malar area between the lower eyelid and the upper lip, as well as to the upper incisor, canine, and associated gingiva via its superior alveolar branch[1,2].

Anesthesia of the ION may be required in various fields of study, including dentistry, otorhinolaryngology, and ophthalmology[3]. Additionally, during procedures such as rhinoplasty, endoscopic sinus surgery, Caldwell-Luc surgery, and tumor removal surgeries involving the nasal cavity and maxillary sinus, the position of the IOC could be quite crucial. It could also be significant due to traumatic events such as orbital floor fractures and zygomaticomaxillary complex (ZMC) fractures. Iatrogenic ION damage could occur during the procedures or fractures mentioned above, regarding the anatomical position of the IOC[1,4,5].

Cone beam computed tomography (CBCT) gained popularity in dentistry since the early 2000s. While CBCT scans offer a lower radiation dose compared to traditional computed tomography scans, they also provide superior spatial resolution[6]. Common applications include dental implant procedures, orthognathic surgeries, and pathological lesions affecting the maxilla and mandible. CBCT scans taken for these purposes provide clear visualization of the paranasal sinus region and neighboring structures and are considered adequate for their evaluation[7,8]. There are studies in the literature in which mucosal thickening and variations such as the presence of septa, the presence of Haller cells, and middle turbinate pneumatization (MTP) were successfully detected by CBCT[9,10].

It is crucial for clinicians performing ION anesthesia or surgical interventions in the area containing the IOC to possess knowledge about its anatomy, particularly its protrusion degree into the

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maxillary sinus. This knowledge plays a pivotal role in preventing nerve damage, as nerves protruding into the maxillary sinus are more prone to injury.

The classifications suggested to determine the degree of protrusion of the IOC divide the IOC morphology into three categories; completely within the orbital floor, inferior to the orbital floor, or completely within the maxillary sinus[1]. Studies in the literature have shown that the frequency of the IOC protruding into the maxillary sinus is not negligible and should not be overlooked[1,4,5,11-14]. Some studies found significant relationships between maxillary sinus variations, such as the presence of Haller cells or septa, and IOC protrusion, but the relationship between sinus variations and protrusion has not been sufficiently elucidated[4,11-13].

The aim of this study is to analyze IOC protrusion types in patients with CBCT scans for dental reasons and to investigate the possible relationship between IOC protrusion and mucosal thickening of the maxillary sinus as well as sinonasal variations including Haller cells, sinus septa, and MTP.

2. Materials and methods

This retrospective study was conducted by analyzing the medical and radiological records from the oral and maxillofacial radiology department of the faculty of dentistry. Ethics committee approval was obtained (number:2023/573) from the local ethics committee and the study was conducted in compliance with the Declaration of Helsinki.

The records have been scanned backward, thus 197 patients with CBCT scans encompassing the bilateral areas of the maxillary sinus, nasal cavity, and IOC in their field of view (FOV), and taken for various dental reasons between the years 2021 and 2022, were included in the study. The exclusion criteria are as follows: CBCT scans of insufficient diagnostic quality, lack of inclusion of the region of interest, patient age less than 20, having a history of maxillofacial trauma or surgery and presence of an odontologic or sinus-related pathological lesion in the region of interest.

All the included CBCT scans were obtained with the NewTom 5G CBCT machine (QR, Verona, Italy). All the scans were recorded at 110 kV and 3–5 mA, with a 0.16-mm voxel size, 18×16 field of view, and a typical exposure time of 5.4 s. The slice thickness of all the scans was 0.25 mm. Assessments were conducted using the built-in software (NNT) on a Dell Precision T5400 workstation (Dell, TX, USA), with a 32-inch Dell LCD screen having a resolution of 1280×1024 pixels, situated in a darkroom. Two researchers independently conducted the examinations, and in case of disagreement, a consensus was reached through discussion.

Classification of the IOC protrusion degree was made according to the study conducted by Ference et al[1]. According to their study, IOCs were categorized into three types based on the ION's course.

Type 1: The ION is situated entirely within the confines of the sinus roof, without extending beyond its boundaries.

Type 2: The ION is positioned below the sinus roof, yet maintains proximity to it, without penetrating the sinus cavity.

Type 3: The ION descends into the sinus cavity, suspended from the sinus roof within a septation or the lamella of the Haller cell. (Figure 1-2)

Figure 1

The coronal CBCT scans displaying the IOC protrusion types. A. Type 1. B. Type 2. C. Type 3,

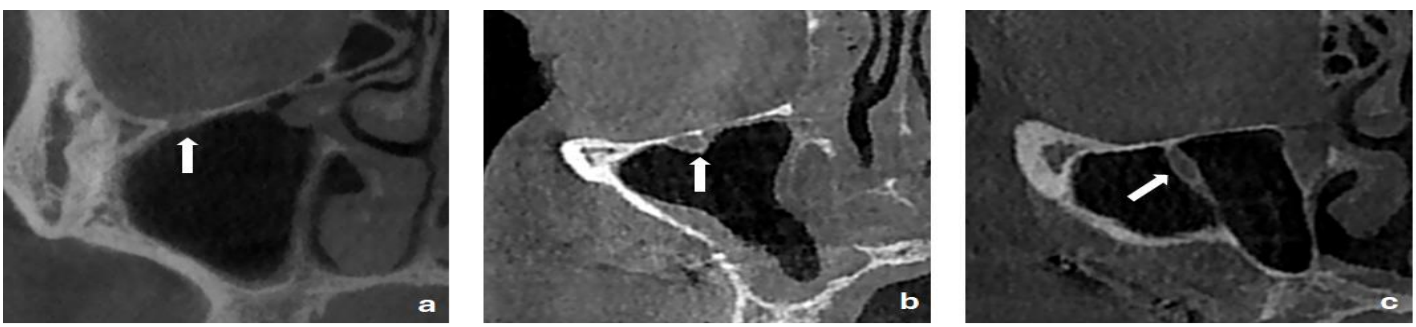
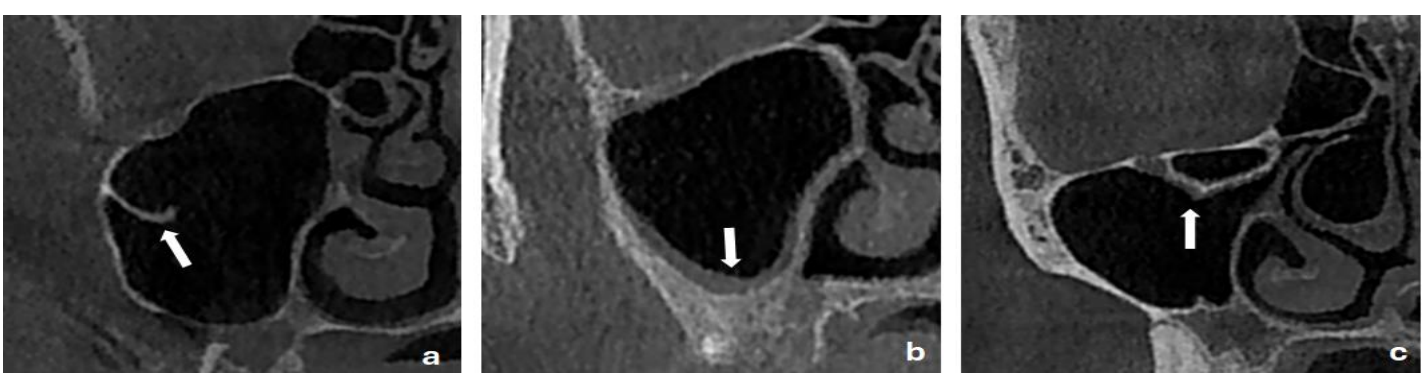


Figure 2

The coronal CBCT scans displaying the variations. A. Presence of septa in the maxillary sinus. B. Mucosal thickening. C. Presence of MTP and Haller cell



Additionally, CBCT scans were examined by two researchers for the presence of Haller cells, MTP, maxillary sinus septa, and mucosal thickening. The investigated variations were determined based on comparison features in the literature, taking into account the studies conducted[11-13]. Considering the studies in the literature, mucosal thickening was noted as present when the size of mucosal thickening was 3 mm or more[11,12].

Data analysis was performed using SPSS 24.0 software (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). The number and percentage distributions of categorical variables were calculated. The chi-square test was used to evaluate categorical variables, such as the distribution of variations in terms of infraorbital canal protrusion types and the distribution of infraorbital canal protrusion types and variations in terms of gender. The significance level was taken as $p<0.05$.

3. Results

394 IOCs and maxillary sinuses of 197 individuals (101 women (51.3%), 96 men (48.7%)) included in the study were examined. The mean age of the participants was 44.23±14.3 (20-68). The distribution of all examined IOC according to protrusion types was as follows: Type 1 (n=266) 67.5%, Type 2 (n=89) 22.6%, Type 3 (n=39) 9.9%. Mucosal thickening was observed in 48.2% of all individuals (n=190), MTP in 25.6% (n=101), sinus septa in 12.9% (n=51), and Haller cells in 6% (n=24). (Table 1)

Table 1

Distribution of descriptive parameters among participants.

	n	percent
Gender		
· Male	192	48.7%
· Female	202	51.3%
IOC Protrusion Type		
· 1	266	67.5%
· 2	89	22.6%
· 3	39	9.9%
Mucosal thickening		
· Present	190	48.2%
· Absent	204	51.8%
Middle turbinate pneumatization		
· Present	101	25.6%
· Absent	293	74.4%
Sinus Septa		
· Present	51	12.9%
· Absent	343	87.1%
Haller Cell		
· Present	24	6%
· Absent	370	94%

For the relationship between IOC protrusion types and variations, no significant correlation was found regarding mucosal thickening, MTP, or the presence of Haller cells. However, a significant correlation was observed between type 3 IOCs and the presence of septa. Specifically, the presence of septa in the maxillary sinus was 8.3% with type 1 IOCs, 13.5% with type 2 IOCs, and 43.6% with type 3 IOCs. ($p<0.001$) (Table 2)

No significant relationship was found between gender and the IOC types. (Table 3)

The presence of mucosal thickening was significantly more common in men than in women, whereas MTP was significantly more common in women than in men. ($p<0.001$ and $p<0.001$, respectively) (Table 4)

Table 2

Distribution of the relationship between IOC protrusion and mucosal thickening of the maxillary sinus as well as sinonasal variations.

	IOC Protrusion Type			p-value
n (%)	1 (n=266)	2 (n=89)	3 (n=39)	
Mucosal thickening	132 (49.6%)	41 (46.1%)	17 (43.5%)	0.701
Middle turbinate pneumatization	62 (23.3%)	26 (29.2%)	13 (33.3%)	0.277
Sinus Septa	22 (8.3%)	12 (13.5%)	17 (43.6%)	<0.001
Haller Cell	17 (6.4%)	6 (6.7%)	1 (2.6%)	0.62

Table 3

Distribution of IOC types between genders

Gender n (%)	IOC Protrusion Type			p-value
	1	2	3	
Male (n=192)	134 (69.8%)	40 (20.8%)	18 (9.4%)	0.637
Female (n=202)	132 (65.3%)	49 (24.3%)	21 (10.4%)	

Table 4

Distribution of variations between genders

	Gender		p-value
n (%)	Male (n=192)	Female (n=202)	
Mucosal thickening	112 (58.3%)	78 (38.6%)	<0.001
Middle turbinate pneumatization	34 (17.7%)	67 (33.2%)	<0.001
Sinus Septa	32 (16.6%)	19 (9.4%)	0.032
Haller Cell	16 (8.3%)	8 (4%)	0.07

4. Discussion

The infraorbital region is of paramount importance for anesthesia procedures, pain management, and surgical interventions, encompassing fields such as dentistry, otorhinolaryngology, neurology, and ophthalmology.

ZMC fractures are the second most frequently occurring facial fractures, following nasal fractures[15]. These fractures have the

potential to cause trauma to the ION through nerve compression, resulting in complications such as permanent paresthesia, sensory neuropathy, and hypoesthesia[16-18]. According to a study by Sakavicius et al.[19], sensory disorders of ION were detected in approximately 64% of patients with ZMC fractures, and authors reported that this rate increased up to 79.9% in displaced ZMC fractures. Apart from traumatic causes, iatrogenic damage to the ION can occur during tumor surgeries in the infraorbital area, orbital decompression surgeries, endoscopic interventions, Caldwell-Luc procedures, and Le Fort-type osteotomies. During these interventions, the ION can be stretched and exposed due to displacement of the orbital floor, thus facing the risk of injury[16,20,21]. In the literature, it has also been noted that the clinician who will perform an ION nerve block must have a comprehensive understanding of the position and anatomy of the IOC to avoid damaging the orbital structures and to administer anesthesia safely[3].

According to our findings, type 1 was the most common, while type 3 was the least common, with a rate of 9.9%. It can be inferred that although type 3, which protrudes completely into the maxillary sinus, is less common, its occurrence rate is notable. Similar rates have been reported in the literature. Among studies using CT scans, Ference et al.[1] emphasized that type 1 was the most prevalent, with a type 3 rate of 12.5%. Yenigün et al.[13] classified the type protruding completely into the maxillary sinus as type 1, reporting a rate of 12.3%. Açar et al.[5] identified a type 3 rate of 9.5%, although they utilized a different methodology by examining IOCs in four groups, including Type 4, located at the outer limit of the zygomatic recess. Only Haghnegahdar et al.[4] reported a relatively higher type 3 rate of 23.2%. Studies conducted with CBCT reported type 3 rates of 8.8%, 8%, and 7.9%, consistent with our findings[11,12,14].

According to our findings, there was no difference in IOC-type distribution between genders. Similarly, in the literature, the majority of studies did not find any difference in terms of IOC types between genders[11,12,14], but Haghnegahdar et al.[4] stated that the prevalence of type 1 was higher in females while the prevalence of type 2 was higher in males.

It was found that 43.6% of type 3 IOC types had septa in the maxillary sinus, and this relationship was statistically significant. Serindere et al.[12] also reported significant relationships between the presence of septa and IOC type for both the right and left sides; however, contrary to our findings, they noted an increase in the presence of septa in cases of type 1 IOC. Nevertheless, in agreement with our results, Yenigün et al.[13] identified a significant relationship between type 1, which completely protrudes into the maxillary sinus, and the presence of sinus septa. Their findings indicated that while the rate of type 1 was 9.8% in cases without maxillary sinus septa, this rate increased to 25% when maxillary sinus septa were present. One of the variations frequently associated with IOC types in the literature is the presence of Haller cells. Serindere et al.[12] reported a higher prevalence of Haller cell variation in individuals with type 1 IOC, while Haghnegahdar al. [4] and Kalabalık et al.[11] found it to be more common in type 2 and type 3 IOC. Ference et al.[1] noted a significant increase in the rate of IOC passing through the sinus in the presence of Haller cells. In contrast, Yenigün et al.[13] did not find a significant relationship between the presence of Haller cells and IOC types, consistent with our findings.

Only a few studies have assessed the relationship between IOC types and mucosal thickening. One study found a significant association between mucosal thickening and type 1 IOC on the left side only, while another study did not find any relationship, consistent with the findings of the present study[11,12]. The presence of numerous local and environmental factors that can cause mucosal thickening distinguishes it from other anatomical variations and makes its evaluation more challenging.

Similarly to mucosal thickening, MTP has also been addressed by a small number of studies, and consistent with our findings, the abovementioned studies have not detected a significant relationship between MTP and IOC types[12,13]. Inconsistencies in findings may be due to age and ethnic factors of the studied groups or due to differences in methodology.

In the individuals included in the study, mucosal thickening was observed in 48.2%, MTP in 25.6%, the presence of septa in 12.5%, and the presence of Haller cells in 6%. Mucosal thickness rates reported in the literature vary between 27.1% and 57.1%[11,12,22,23]. It is important to consider that mucosal thickening can be influenced by various environmental factors. MTP rates range from 18.2% to 76.4% according to a review[23], with the rate most similar to our study being 21.5%, as reported by Yenigün et al.[13] Similarly, the rate of septa presence varies between 5.3% and 36.9%, while the presence of Haller cells has been reported in ranges from 3.5% to 61.5%.[12,23,24] Yenigün et al.[13] also detected Haller cells at a rate of 4.9%, similar to our study's findings.

The limitations of our study include small sample size, the absence of separate evaluations for the right and left sides, and the lack of assessment of other sinonasal variations. As another limitation, there are certainly numerous factors that can contribute to mucosal thickening. Therefore, to accurately determine whether there is a true relationship between different types of IOC and mucosal thickening, it would be more appropriate to establish an isolated study group by excluding various conditions. Future studies should aim to include larger sample sizes, perform bilateral evaluations, and investigate a wider range of sinonasal variations to provide a more comprehensive understanding.

CBCT is becoming increasingly common in dentistry, particularly for cases involving maxillary pathology, missing teeth, or orthodontic concerns. As CBCT scans typically encompass the contents of the maxillary sinus and the IOC, oral radiologists must identify and report any variations in the maxillary sinus. This responsibility falls within their scope of practice[7]. When planning surgical interventions or ION anesthesia in the IOC area, it is advisable to review the patient's radiological records. If available, CBCT scans should be utilized as they are considered sufficient for evaluating the IOC.

5. Conclusion

Although the protrusion of the IOC into the maxillary sinus is relatively uncommon, it should not be overlooked. Additionally, a significant relationship was observed between sinus septa and the type of IOC protruding into the maxillary sinus. It is advisable to have a thorough understanding of its anatomy and degree of protrusion before undertaking procedures in the relevant area. CBCT scans offer valuable information in this regard.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved *Erciyes University* Scientific Research and Publication protocol number:2023/573

Conflict of interest statement

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

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Author Contributions

The authors confirm contribution to the paper as follows: study conception and design: Aykağan Çukurluoğlu; data collection: Zeynep Firdevs Sönmez; analysis and interpretation of results: Aykağan Çukurluoğlu, Zeynep Firdevs Sönmez; draft manuscript: Aykağan Çukurluoğlu, Zeynep Firdevs Sönmez. All authors reviewed the results and approved the final version of the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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