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Interdiscip Med J 2024;15(53)

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Journal's History

Journal's Previous Name	Parallel Title	ISSN	Years
Mustafa Kemal Üniversitesi Tıp Fakültesi Dergisi	Medical Journal of Mustafa Kemal University	1308-7185	2010-2014
Mustafa Kemal Üniversitesi Tıp Dergisi	Medical Journal of Mustafa Kemal University	2149-3103	2015-2022

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Türkish Medline

Turkish Citation Index

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The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Council of Medical Journal Editors (ICMJE), The World Association of Medical Editors (WAME), The Council of Science Editors (CSE), The Committee on Publication Ethics (COPE), The European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (https://doaj.org/bestpractice).
In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with COPE guidelines.

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INTERDISCIPLINARY MEDICAL JOURNAL

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ABOUT

Interdisciplinary Medical Journal is an open access scientific journal, which publishes original contributions in clinical disciplines pertaining to human medicine. In this context, the Journal publishes original research, case reports and reviews based on clinical studies having interdisciplinary approach on medicine. The Journal is official publication of Hatay Mustafa Kemal University, Faculty of Medicine. The manuscript evaluation is based on the principles of blind peer-review process. It is published online three times a year on April, August, and December. The communication, review and publication language of the Journal is English. Manuscripts submitted for publication in the journal should be prepared in accordance with research and publication ethics. All manuscripts should be submitted by online system of the Journal. All manuscripts submitted to the Journal are screened in terms of originality.

Focus & Scope

Interdisciplinary medicine can be defined as "an interdisciplinary approach that relies on health professionals from different disciplines, along with the patient, working collaboratively as a team. The most effective teams share responsibilities and promote role interdependence while respecting individual members' experience and autonomy.

By supporting the interdisciplinary research on medicine, The Journal aims to;

Publish original contributions from different scientific disciplines through the advisory board covering a wide range of clinical medical disciplines,

Offer all its content freely available without charge to the user or his/her institution, to make research freely available to the public, and to support a greater global exchange of knowledge,

By permitting authors to enter into separate, additional contractual arrangements for the non-exclusive distribution of the journal's published version of the work (e.g., post it to an institutional repository or publish it in a book), to lead productive exchanges, as well as earlier and greater citation of published work.

Subject areas include, but are not restricted to the **clinical studies** of the following fields:

First Aid and Emergency Medicine

Family Medicine

Public Health and Preventive Medicine

Internal Diseases

General Surgery

Gynecology and Obstetrics

Ear, Nose and Throat Diseases

Eye Diseases

Orthopedics and Traumatology

Radiology and Radiodiagnostics

Anesthesia and Intensive Care Medicine

Adolescent Diseases

Childhood Diseases

Multisystem Diseases

Physical Medicine and Rehabilitation

Forensic Medicine

Mental Health and Diseases

Cardiovascular System Diseases

Nervous System Diseases

Neurosurgery

Respiratory System Diseases

Infectious Diseases

Occupational Diseases

Nuclear Medicine

Oncological Diseases

Sports Medicine

Genetic Diseases

Medical Pathology

The journal covers all relevant branches in **clinical medicine** specialties of the topics mentioned above.

Audience

Academicians, specialist physicians and research assistants in surgical and non-surgical medical disciplines and general practitioners.

Abstracting and Indexing

Interdisciplinary Medical Journal is indexed by TÜBITAK TR Index, Turkish Medline, Turkish Citation Index, and Index Copernicus World of Journals

Editorial Policy

The editorial and publication processes of the journal are shaped in accordance with the guidelines of The International Council of Medical Journal Editors (ICMJE), The World Association of Medical Editors (WAME), The Council of Science Editors (CSE), The Committee on Publication Ethics (COPE), The European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of

Transparency and Best Practice in Scholarly Publishing (https://doaj.org/bestpractice).

Peer-Review Policy

Initial Manuscript Evaluation

For consideration, all manuscripts should be submitted by online system of The Journal at https://dergipark.org.tr/en/pub/interdiscip. The whole editorial process of The Journal is done via online submission system and can be documented in case of a conflict or objection.

The suitability of papers for publication in The Journal is decided by the editorial policy of the editorial board.

Editor-in-Chief is fully authorized for reviewing process, which is processed in the order of submission to The Journal.

Editor-in-Chief assigns either one of the Co-Editors or himself in order to perform initial assessment. Then, the assignee conducts initial pre-refereeing checks to ensure the article is legible, complete, correctly formatted, original, within the scope of The Journal, in the style of a scientific article and written in clear language.

Ethical Declaration

The Journal is committed to practice the publication ethics and takes all possible measures against any publication malpractices.

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

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with COPE guidelines.Identifying information, including names, initials, or autopsy numbers of the patients/deceased should not be exposed in written descriptions or photographs in no ways. Identifying details should be omitted if they are not essential. Informed consent should be obtained in human studies and it should be stated in the manuscript.

Human and Animal Rights: For the experimental, clinical and drug human studies, approval by ethical committee and a statement on the adherence of the study protocol to the international agreements (World Medical Association Association of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended October 2013, www.wma.net) are required. In experimental animal studies, the authors should indicate that the procedures followed were by animal rights (Guide for the care and use of laboratory animals, https://nap.nationalacademies.org/catalog/5140/guide-for-the-care-and-use-of-laboratory-animals), and they should obtain animal ethics committee approval. The Ethics Committee approval document should be submitted to the The Bulletin of Legal Medicine together with the manuscript.

The approval of the ethics committee, statement on the adherence to international guidelines mentioned above and that the patient's informed consent is obtained should be indicated in the Method section and is required for case reports whenever data/media used could reveal the identity of the patient. The declaration of the conflict of interest between authors, institutions, acknowledgement of any financial or material support, aid is mandatory for authors submitting a manuscript, and the statement should appear at the end of the manuscript. Reviewers are required to report if any potential conflict of interest exists between the reviewer and authors, institutions.

For persons under 18 years of age, please provide a consent form that includes both parents' signatures or of the person's legal guardian or supervisor.

When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2013. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

Check for Plagiarism

The Journal is a member of Crosscheck, and all manuscripts are screened by Crosscheck in terms of originality. If serious issues are identified concerning the manuscript, the assignee will notify the corresponding author as part of our standard procedure. No action is required from you unless specifically requested for very serious concerns.

Any article that has problems with any of the above criteria may be rejected at this stage. Manuscripts rejected at this stage typically are not in line with the focus and scopes of the journal. Essays that pass through this stage are then entered into the peer review process.

Manuscript Files

This journal follows a double-blind reviewing procedure. Authors are therefore requested to submit; a blinded manuscript, and a separate title page file.

You may download full manuscript and blinded manuscript templates by following the links on Journal's homepage.

1) Blinded Manuscript File: This is the blinded manuscript file that will be presented to the reviewers. The main text of the article, beginning from Abstract till References (including tables, figures or diagrams) should be in this file. The file must not contain any mention of the authors' names or

initials or the institution at which the study was done, ethical committee or acknowledgements. Self-identifying citations and references in the article text should be avoided.

2) Title Page File: Only descriptive parts of the manuscript should be included in this file. General information about the article and authors is presented on the title page file and it should include the article title in English, author information, email address of each (all) author, ORCID iDs, any disclaimers, sources of support, conflict of interest declaration, ethical committee information, contact information of the corresponding author, acknowledgement and authorship contribution. This file will not be shared with reviewers.

The Journal adheres to a strict policy of double-blind, peer-review to ensure best practices in scholarly research and publication. In Double-blind model, the reviewers do not know the names of the authors, and the authors do not know who reviewed their manuscript. To ensure anonymity in the double-blind refereeing process, the author's name should not appear anywhere on the manuscript. If using Microsoft Word, the manuscript 'Summary', under the menu 'File/Properties/Summary', should also be erased. Once blinded, the assignee selects at least two members of the advisory board, and manuscripts are shared with these experts within the field for double-blind peer review, in which both the Reviewer and the Author remain anonymous throughout the process. A reviewer may not belong to the same institution as authors.

After assigned, the reviewers are invited to participate the review process via a notification email. The email invitation to reviewers will contain all necessary information about the manuscript. The reviewers are asked to log into the journal web site to indicate whether they will undertake the review or not, as well as to access the submission and to record their review and recommendation.

Automated email reminders are sent to the reviewer when the reviewer does not respond to a review request within 15 days. The typical period of time allowed for reviews is 4 weeks but note that it can be modified during the editorial process.

Peer Review Reports

Reviewers make one of the following recommendations to the Editors: accept submission, minor revision, major revision, decline submission. Additionally, reviewers are asked to provide significant commentary for authors and are also provided space to make comments intended solely for the editors. Reviewers are not asked or expected to make any copyediting comments.

If both reviewers agree on acceptance or rejection, the decision stands.

Occasionally, we receive contradicting Reviewers' reports and need to ask for a third reviewer, which does delay the process. When their opinions are poles apart, then the Associate Editor takes a further process to decide acceptance or rejection of that paper. For the further process, Associate Editors request an emergency review by another advisory board member. Associate Editors may take a further process for the manuscript of which reviewing process is overdue.

If a paper is not suitable for publication it will be returned to the author with a statement of reasons for rejection. The author may appeal if he or she believes an erroneous or unfair judgment has been made. A letter to the Editor-in-Chief presenting reasons why the decision should be reconsidered will be subjected to due consideration.

After review, the author is notified by email for revision in accord with suggestions made by the reviewers and the Editor.

At the completion of each round of the peer review process, the submitter receives a formal letter from the Editor that includes notes from the Peer Reviewers.

When authors make revisions to their article in response to the referees' comments, they are asked to submit a list of changes and any replies for transmission to the referees. The author must upload the revised manuscript to the online system within 4 weeks; otherwise, the author will be notified that the paper will be considered withdrawn.

The revised version is usually returned to at least one of the original referees who is then asked whether the revisions are satisfactory. If the referees remain dissatisfied, the paper can be referred to the advisory board of the journal for further consideration.

The assignee then, will check if the manuscript is revised as suggested by editorial members and proceed to the next step. If the assignee finds the revisions satisfying, then he or she will record the decision to accomplish the review process and reach final decision.

Decision Making Process

Based upon two or more reviewers' reports, the Co-Editors are responsible for making the decision regarding acceptance or rejection each essay and for communicating this decision to the submitter. At the completion of the peer review process, each submitter receives a formal letter from the Editors that includes notes from the Peer Reviewers.

The final decision by Editor-in-Chief is usually completed within 2 months from the time of the paper submission.

Authors are notified by e-mail when a manuscript has or has not been accepted for publication. Proofs of accepted manuscripts are sent to the author for correction within 4 weeks after acceptance. They should be proofread carefully according to the instructions attached and returned within the considered period. Authors will be charged for major corrections to their proofs.

For 2020, average days required to complete the review process is 120 days, whereas average days that pass till publication is 180 days.

Publication Frequency

Interdisciplinary Medical Journal publishes three issues online in April, August and December. The communication, review and publication language of the Journal is English.

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Author Guide

Dear author,

Thank you for your interest in submitting your manuscript to Interdisciplinary Medical Journal for editing and publication consideration. In order to facilitate preparation and submission of your manuscript, we have prepared this guideline explaining basic points that should be taken into account when preparing the paper.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. The text adheres to the stylistic and bibliographic requirements outlined in the Author Guidelines.

2. Where available, DOIs for the references list have been provided.

3. During the online submission, I undertake to enter the names of all the authors in the manuscript, their positions, ORCID ID*** information and the contact details of the responsible author.

*** The publication of ORCID ID information of all authors is mandatory by TUBITAK ULAKBIM Index.

4. By 2020, in accordance with the TR Directory Rules, the authors have to submit an official letter with an Ethical Commission report or equivalent for the works requiring ethics committee permission.

5. Blinded manuscript file to be sent to the reviewer,

6. Title page, A separate title page file containing article title; academic titles, areas of expertise, affiliations, and e-mail addresses each author; contact address of the corresponding author, disclaimer, financial resources of the study, information on whether there is a conflict of interest, article title, short title, thanks and authorship contribution.

7. The author agreement form has been signed by the corresponding author and prepared for submission.

Note: After filling the copyright and ethics form downloaded from the website of the journal with Adobe Reader program on the computer, the printout must be signed by the responsible author with a wet signature, as a picture file or as a pdf—the signed paper document can be photographed with a mobile phone or scanned with a scanner. It can be uploaded to the files section.

8. Blinded manuscript file and title page file are in the Microsoft Word file format.

Writing Rules

In order to prevent waste of effort and time, and to evaluate the manuscript drafts you send to Interdisciplinary Medical Journal, you must use Interdisciplinary Medical Journal templates, which you can download to your computer using the links on the journal homepage, and which contain explanations for the writing rules in the comments section.

The Journal is official publication of Hatay Mustafa Kemal University, Faculty of Medicine. It is an open access scientific journal, being published three times a year and peer reviewed. The Journal aims to publish original contributions based on clinical studies having interdisciplinary approach on medicine. The publication language of the journal is English.

Subject areas include, but are not restricted to the **clinical studies** of the following fields: first aid and emergency medicine, family medicine, public health and preventive medicine, internal diseases, general surgery, gynecology and obstetrics, ear, nose and throat diseases, eye diseases, orthopedics and traumatology, radiology and radiodiagnostics, anesthesia and intensive care medicine, adolescent diseases, childhood diseases, multisystem diseases, physical medicine and rehabilitation, forensic medicine, mental health and diseases, cardiovascular system diseases, nervous system diseases, neurosurgery, respiratory system diseases, infectious diseases, occupational diseases, nuclear medicine, oncological diseases, sports medicine, genetic diseases, medical pathology.

The journal covers all relevant branches in **clinical medicine** specialties of the topics mentioned above.

Audience

Academicians, specialist physicians and research assistants in surgical and non-surgical medical disciplines and general practitioners.

Manuscript Preparation

All manuscripts which will be published in the journal must be in accordance with research and publication ethics. All authors should have contributed to the article directly either academically or scientifically. Presentations at congresses or in symposia are accepted only if they were not published in whole in congress or symposium booklets and should be mentioned as a footnote.

Manuscripts are received with the explicit understanding that they have not been published in whole or in part elsewhere, that they are not under simultaneous consideration by any other publication. Direct quotations, tables, or illustrations that have appeared in copyrighted material must be accompanied by written permission for their use from the copyright owner and authors. All articles are subject to review by the editors and referees.

Process of Peer Review

The journal utilizes a standard online site (https://dergipark.org.tr/en/pub/interdiscip), supported by Tubitak Ulakbim, for the process of both manuscript submission and manuscript peer review. Upon receiving a manuscript submitted for consideration of publication to the journal, the journal manager and editorial staff review the submission to assure all required components as outlined in this Guide for Authors are included. The manuscript is then assigned to one of the co-editors (either the editor in chief or an associate editor) who directs and oversees the peer-review process. The co-editor then reviews the submission for relevance, content and quality. Those submissions deemed appropriate for consideration of publication are then assigned to at least two peer reviewers. In order for a manuscript to be considered for publication, it must be original and significant, providing a contribution to research and importance to field. In general, there should be no flaws in the specific procedures used in performance of the study, or in the logic used for the interpretation of the data. It is important that the results of the study support its conclusions, and that there are no errors in reference to prior work (or no exclusions of pertinent references). Where appropriate, confirmation of regulatory review (such as institutional review board approval) must be present. The validity of the statistics used (often including a justification of a sample size) to analyze data is necessary, and the data presented in the figures and tables should be reflective of the results presented and adequate to justify the study conclusions. In general, the manuscript length and quality of the writing are important to ensure its quality.

When the editor has a full complement of reviews completed, the editor reviews the comments and recommendations, and a decision regarding the suitability for publication of the manuscript is made. Acceptance is based on significance, and originality of the material submitted. If the article is accepted for publication, it may be subject to editorial revisions to aid clarity and understanding without changing the data presented.

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

About the scientific language to be used in writing your manuscript

In line with the recommendation of the international directories we applied to increase the scientific effectiveness of our journal and enrich its content, our Editorial Board has decided that the studies to be published in English. So, the manuscripts sent to our journal are subject to English language control and revision.

Our experience from previous articles has shown that most of the articles prepared in English need to be improved in terms of fluent readability and intelligibility, as well as scientific and technical examination. Most of the manuscripts should undergo a comprehensive review and revision process in terms of language, before they were included in the review stage.

Therefore, we recommend that you receive professional English editing and proofreading services before submitting your manuscript to our journal, although it is not mandatory.

Our journal does not have any commercial partnership with any translation or proofreading service company, and our authors are absolutely free to make their choices as they wish.

By uploading the revised English full text of your manuscript to our Journal system by ensuring that English Editing and Proofreading is carried out by a local or foreign professional, you may minimize the possibility of rejection due to translation errors.

Use of first person

In addition, it is necessary to make the necessary checks and revisions in terms of language of your work and to ensure integrity in terms of language and time use throughout the entire article.

Expressions such as ... "Our study, in our study, we, we did, we found, we aimed, I did, I found, I think ... etc." should be revised as follows;

- In this study, ... it was found/determined/... or
- In this study ... it was aimed to ...

Names made up of single word should not be abbreviated.

Instead of,

- Hypertension (HT) is one of the most ...

Throughout the manuscript, you should use;

- Hypertension is one of the most ...

Instead of,

- Rituximab (RTX) is an IgG1 kappa chimeric monoclonal

Throughout the manuscript, you should use;

• Rituximab is an ...

Numbers should always be used to indicate statistics, age and measurements (including time as in the 3 weeks example). In specifying the others, only the numbers one to nine should be written in letters. (Numbers between 1-10 should be written with letters, except for the date and number of cases)

For example;

• In 2 studies, ...

Should be replaced with;

• In two studies ...

For example;

• ... perivascular lymphotic infiltration in only 10 percent and fibrosis in 7 percent of the patients,

Should be replaced with;

• ... perivascular lymphotic infiltration in only 10% of patients ... in 7% of patients ...

Prejudiced expressions should be avoided in expressions other than classical textbook knowledge, which has been verified by dozens of studies and has become the industry standard in the literature.

• determined to be high

Should be replaced with;

• ... was found to be high.

Or throughout the entire manuscript;

• found to be significantly higher ...

If diametrically opposite findings are mentioned among the studies mentioned in the Discussion section, it should be stated as "... a significant relationship was found / observed / reported", rather than "a significant relationship was determined" etc.

• While no significant relationship was determined between blood pressure and disease severity (26,27), a strong relationship was determined in some studies (28,29).

Should be replaced with;

While no significant relationship was observed between blood pressure and disease severity (26,27), it was reported that a strong relationship was found in some studies (28,29).

General Principles

The text of articles reporting original research should be divided into Introduction, Method, Results, and Discussion sections. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection of the process of scientific discovery. Articles often need subheadings within these sections to further organize their content. Other types of articles, such as meta-analyses, may require different formats, while case reports, narrative reviews, and editorials may have less structured or unstructured formats.

Electronic formats have created opportunities for adding details or sections, layering information, cross-linking, or extracting portions of articles in electronic versions. Supplementary electronic-only material should be submitted and sent for peer review simultaneously with the primary manuscript.

Sections of the manuscript

Article title

The title provides a distilled description of the complete article and should include information that, along with the Abstract, will make electronic retrieval of the article sensitive and specific. Information about the study design could be a part of the title (particularly important for randomized trials and systematic reviews and meta-analyses). Please avoid capitalizing all letters of the title and capitalize only the capital letter of first word of the title, proper nouns, proper adjectives. Other words and conjunctions (e.g., and, but, both, or, either, neither, nor, besides, however, nevertheless, otherwise, so, therefore, still, yet, though etc.) should be in small letters. No abbreviations or acronyms should be used within the titles.

Short title

You should add a running title not exceeding 40 characters to be placed at the header of the inner pages.

Abstract

Original research, systematic reviews, and meta-analyses require structured abstracts. The abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study participants, settings, measurements, analytical method), main findings (giving specific effect sizes and their statistical and clinical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations, note important limitations, and not overinterpret findings. Please, do not cite figures, tables or references in the abstract.

Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to ensure that they accurately reflect the content of the article. All the articles submitted to the journal require to include abstract in English. Abstracts of original articles should not exceed 250 words.

Keywords

Three to six words or determinative groups of words should be written below the abstract. Abbreviations should not be used as keywords. Keywords in English should be chosen from MESH (Medical Subject Headings http://www.nlm.nih.gov/mesh) index. Abbreviations cannot be used as keywords, but instead they should be written explicitly. Letters that do not exist in Latin alphabet (e.g., alpha, beta, delta etc.) should be used with their pronunciation.

Examples: carbon monoxide, firearms, sexual abuse, oral mucosa

Introduction

Provide a context or background for the study (that is, the nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

Method

The guiding principle of the Method section should be clarity about how and why a study was done in a particular way. The Method section should aim to be sufficiently detailed such that others with access to the data would be able to reproduce the results.

The authors should clearly describe the selection of observational or experimental participants (healthy individuals or patients, including controls), autopsied persons, including eligibility and exclusion criteria and a description of the source population.

In general, the section should include only information that was available at the time the plan or protocol for the study was being written; all information obtained during the study belongs in the Results section. If an organization was paid or otherwise contracted to help conduct the research (examples include data collection and management), then this should be detailed in the method section.

The Method section should include a statement indicating that the research was approved or exempted from the need for review by the responsible review committee (institutional or national). If no formal ethics committee is available, a statement indicating that the research was conducted according to the principles of the Declaration of Helsinki should be included.

Identifying information, including names, initials, or autopsy numbers of the patients/deceased should not be exposed in written descriptions or photographs in no ways. Identifying details should be omitted if they are not essential.

Informed consent should be obtained in human studies, and it should be stated in the manuscript.

When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

Statistical Analysis

The authors should describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to judge its appropriateness for the study and to verify the reported results. They should define statistical terms, abbreviations, symbols and should specify the statistical software package(s) and versions used.

Results

You should present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Please, do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Method Section. Extra or supplementary materials and technical details can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

You should give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them, if any. You should restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Please, use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as “random” (which implies a randomizing device), “normal,” “significant,” “correlations,” and “sample.” Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

Discussion

It is useful to begin the discussion by briefly summarizing the main findings and explore possible mechanisms or explanations for these findings. Emphasize the new and important aspects of your study and put your findings in the context of the totality of the relevant evidence. State the limitations of your study and explore the implications of your findings for future research and for clinical practice or policy. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section.

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular,

distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted but label them clearly.

In-text Citations and References

Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. On the other hand, extensive lists of references to original work on a topic can use excessive space. Fewer references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently.

Do not use conference abstracts as references: they can be cited in the text, in parentheses, but not as page footnotes. References to papers accepted but not yet published should be designated as "in press". Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

Laws (e.g., penal code), statutes and regulations are not scientific writings. In addition to being published on the official gazette, since it is published on various internet sites, a reference number should not be given to laws, statutes and regulations. If it is to be cited within the text, the law could be cited by specifying the number of the law, the date and number of publications in the official gazette (e.g., A Review of Article 5 of the Turkish Criminal Penal Code No. 5237). They should not be numbered within the text, or in the reference list.

To minimize citation errors, references can be verified using either an electronic bibliographic source, such as PubMed, or print copies from original sources. Reference list should be numbered consecutively in the order in which they are first mentioned in the text. Roman numerals should be avoided. Identify references in text, tables, and legends by Arabic numerals (1, 2, 3 ... 9, 0) in parentheses. References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used for MEDLINE (www.ncbi.nlm.nih.gov/nlmcatalog/journals).

If you refer to a work more than once, use the first number also for the second and following references. References to more than one source in the same phrase may be entered like this: (2-4), i.e., references 2 through 4 in the reference list, and (2-4, 8), i.e. the references 2 through 4, plus reference no 8 in the list of references.

Sample for in-text citation:

In a clinical research in healthy individuals, Ellis (25) has studied the sciatic nerve excursion using ultrasound technique.

Wright and Ellis (10) has investigated the excursion of nerves around the elbow joint.

In another and similar cadaveric study by Wright et al (13), the radial nerve median excursion values were 4.1, 8.8, and 0.2, 0.1 mm with motions of shoulder, elbow, wrist and fingers respectively.

Suicide is a major public health problem and globally the second leading cause of death among young adults (1). Studies focusing on how mental health risk factors impact on youth suicidal behaviors suggest that psychopathological symptoms are associated with suicidal behavior (3,4). Adverse effects of H2S on human health vary from local irritation to immediate death depending on the form, concentration, duration and route of exposure (9, 13-15).

Reference Style

The Vancouver system, also known as Vancouver reference style or the author–number system, is a citation style that uses numbers within the text that refer to numbered entries in the reference list. Vancouver style is used by MEDLINE and PubMed. The names "Vancouver system" or "Vancouver style" have existed since 1978. The latest version of the latter is Citing Medicine, per the References > Style and Format section of the ICMJE Recommendations. In 1978, a committee of editors from various medical journals, the International Committee of Medical Journal Editors (ICMJE), met in Vancouver, BC, Canada to agree to a unified set of requirements for the articles of such journals. This meeting led to the establishment of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (URMs). Part of the URMs is the reference style, for which the ICMJE selected the long-established author–number principle.

Since the early to mid-2000s, the United States National Library of Medicine (which runs MEDLINE and PubMed) has hosted the ICMJE's "Sample References" pages. Around 2007, the NLM created Citing Medicine, its style guide for citation style, as a new home for the style's details. The ICMJE Recommendations now point to Citing Medicine as the home for the formatting details of Vancouver style.

Interdisciplinary Medical Journal, since the first day of its publication uses the PubMed/NLM reference style. Thus, references list should follow the standards summarized in the NLM's International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Samples of Formatted References for Authors of Journal Articles web page and detailed in the NLM's Citing Medicine, 2nd edition.

According to the Vancouver rules, you can only refer to the literature you have read yourself. If you find anything interesting in a text where it is referred to another text, you must read and refer to the original.

References List

The references list should be ordered numerically in the order in which the references appear in the text.

The journal's name may be abbreviated, according to the abbreviation rules for journal titles. Records retrieved from a search for the full journal title in the National Library of Medicine's search page include the abbreviated title.

Authors' names should be given as surname followed by initials. There should be a space between surname and initials. A maximum of two initials are allowed for each author, they should be entered without spaces or punctuation. Different authors should be separated by a space and a comma. A period (.) should follow the last author's name. If six or more authors, list the first six authors followed by et al.

Only capital letter of the first word of the title, proper nouns, proper adjectives, acronyms, and initialisms should be capitalized.

The most reliable method for calculating the impact factor of our journal and number of citations of articles published in our journal or calculating the number of times your own article is cited in a healthy way, is to add DOIs to the references section. In order to give the DOIs to the articles published in Interdisciplinary Medical Journal, the CrossRef membership application has been completed and all the research articles, case reports, and reviews are being assigned DOIs. For this reason, DOIs need to be added to the References section if available for those references. We hope that the Simple Text Query Form will be helpful in referencing articles published in our journal.

With the help of the Simple Text Query Form web page, which has a link in the full-text template, DOI records need to be added to the sources.

https://apps.crossref.org/SimpleTextQuery

Note: Please, **do not insert Pubmed ID (PMID) or Pubmed Central ID (PMCID) records** to the reference list since they are useless in determining the citation counts.

We place great importance to the addition of DOIs to the references list.

Sample for Journal Article without DOI

Dokgöz H, Kar H, Bilgin NG, Toros F. Forensic Approach to Teenage Mothers Concept: 3 Case Reports. Turkiye Klinikleri J Foren Med 2008;5(2):80-4

Kaufman DM, Mann KV, Miujtjens AM, Van der Vleuten CP. A comparison of standard setting procedures for an OSCE in undergraduate medical education. Academic Medicine 2000;75:267–71.

Sample for Journal Article with DOI

Koçak U, Alpaslan AH, Yağan M, Özer E. Suicide by Homemade Hydrogen Sulfide in Turkey a Case Report. Bull Leg Med. 2016;21(3):189-192. https://doi.org/10.17986/blm.2016323754

Article not in English

Kar H, Dokgöz H, Gamsız Bilgin N, Albayrak B, Kaya Tİ. Lazer Epilasyona Bağlı Cilt Lezyonlarının Malpraktis Açısından Değerlendirilmesi. Bull Leg Med. 2016;21(3):153-158. https://doi.org/10.17986/blm.2016323748

Books and Other Monographs

Personal author(s)

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

Editor(s), compiler(s) as author

Gilstrap LC 3rd, Cunningham FG, VanDorsten JP, editors. Operative obstetrics. 2nd ed. New York: McGraw-Hill; 2002.

Author(s) and editor(s)

Breedlove GK, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services; 2001.

Chapter in a book

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113

Emmerson BT. Gout and renal disease. In: Massry SG, Glassock RJ (Editors). Textbook of Nephrology 1. Baskı, Baltimore: Williams and Wilkins; 1989. p. 756–760.

Conference proceedings

Harnden P, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ Cell Tumour Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer; 2002.

Article published on the Internet ahead of the print version:

Yu WM, Hawley TS, Hawley RG, Qu CK. Immortalization of yolk sac-derived precursor cells. Blood. 2002 Nov 15;100(10):3828-31. Epub 2002 Jul 5.

Part of a homepage/Web site [Edited 28 Dec 2016]

American Medical Association [Internet]. Chicago: The Association; c1995-2016 [cited 2016 Dec 27]. Office of International Medicine; [about 2 screens]. Available from: https://www.ama-assn.org/about/office-international-medicine

Thesis

Skrtic L. Hydrogen sulfide, oil and gas, and people's health [Master's of Science Thesis]. Berkeley, CA: University of California; 2006.

Weisbaum LD. Human sexuality of children and adolescents: a comprehensive training guide for social work professionals [master's thesis]. Long Beach (CA): California State University; 2005. 200 p.

For the reference types not listed here, please visit Samples of Formatted References for Authors of Journal Articles available at Medline Web site (https://www.nlm.nih.gov/bsd/uniform_requirements.html).

Tables

Tables capture information concisely and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text.

It would be appropriate to place the tables at the end of the main text. Number tables consecutively in the order of their first citation in the text and supply a title for each. Titles in tables should be short but self-explanatory, containing information that allows readers to understand the table's content without having to go back to the text. Be sure that each table is cited in the text. Give each column a short or an abbreviated heading. In the tables, case counts (n) and percentages (%) should be specified in separate columns, not in the same cell.

Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes and use symbols to explain information if needed. Symbols may be as alphabet letters or such symbols as *, p t> T §). Please, identify statistical measures of variations, such as standard deviation and standard error of the mean.

Illustrations (Figures)

The lexical meaning of figure constitutes a number symbol (numeral, digit), a written or printed character, a diagram or pictorial illustration of textual matter, arithmetical calculation or digits representing an amount when plural. While definition of picture includes a design or representation made by various means (as painting, drawing, or photography), illustration means a picture or diagram that helps make something clear or attractive. Although these terms bear distinctive meanings, they are too often used interchangeably. Thus, we meant them in the same way without distinction.

Digital images

The 300 DPI Story

In the ancient times when digital cameras have not been invented, the photos taken by analogue cameras were used to be printed on photo papers. In order to transfer these photos to the digital environment, they had to be scanned by optical devices called scanners. On the same dates, desktop publishing and printing technology was far beyond the digital photography, and many years had passed since the invention of laser printing technology. Here, several technical terms should be explained to make the concept clearer. DPI is used to describe the resolution number of dots per inch in a digital print and the printing resolution of a hard copy print dot gain, which is the increase in the size of the halftone dots during printing. A dot matrix printer, for example, applies ink via tiny rods striking an ink ribbon, and has a relatively low resolution, typically in the range of 60 to 90 DPI (420 to 280 µm). An inkjet printer sprays ink through tiny nozzles and is typically capable of 300–720 DPI. A laser printer applies toner through a controlled electrostatic charge and may be in the range of 600 to 2,400 DPI. Along with the cheaper memory chips, 1200 dpi printers have been widely available in the consumer market since 2008. Monitors do not have dots but do have pixels. The closely related concept for monitors and images is pixels per inch or PPI. Old CRT type video displays were almost universally rated in dot pitch, which refers to the spacing between the sub-pixel red, green and blue dots which made up the pixels themselves. The DP measurement of a printer often needs to be considerably higher than the pixels per inch (PPI) measurement of a video display in order to produce similar-quality output. This dithered printing process could require a region of four to six dots (measured across each side) in order to faithfully reproduce the color in a single pixel. An image that is 100 pixels wide may need to be 400 to 600 dots in width in the printed output; if a 100×100-pixel image is to be printed in a one-inch square; the printer must be capable of 400 to 600 dots per inch to reproduce the image. The dpi of early model laser printers was 300 to 360, thus scanning images at 300 DPI was a common practice at that time.

In printing, DPI (dots per inch) refers to the output resolution of a printer or imagesetter, and PPI (pixels per inch) refers to the input resolution of a photograph or image. DPI refers to the physical dot density of an image when it is reproduced as a real physical entity, for example printed onto paper. A digitally stored image has no inherent physical dimensions, measured in inches or centimeters. Some digital file formats record a DPI value, or more commonly a PPI (pixels per inch) value, which is to be used when printing the image. This number lets the printer or software know the intended size of the image, or in the case of scanned images, the size of the original scanned object. For example, a bitmap image may measure 1,000 × 1,000 pixels, a resolution of 1 megapixel. If it is labeled as 250 PPI, that is an instruction to the printer to print it at a size of 4 × 4 inches. Changing the PPI to 100 in an image editing program would tell the printer to print it at a size of 10×10 inches. However, changing the PPI value would not change the size of the image in pixels which would still be 1,000 × 1,000. An image may also be resampled to change the number of pixels and therefore the size or resolution of the image, but this is quite different from simply setting a new PPI for the file.

Therefore, an image that is 2048 pixels in width and 1536 pixels in height has a total of 2048×1536 = 3,145,728 pixels or 3.1 megapixels. One could refer to it as 2048 by 1536 or a 3.1-megapixel image. Or you can think of it as a very low-quality image (72 ppi) if printed at about 28.5 inches wide, or a very good quality (300 ppi) image if printed at about 7 inches wide.

Since the 1980s, the Microsoft Windows operating system has set the default display "DPI" to 96 PPI, while Apple/Macintosh computers have used a default of 72 PPI. The choice of 72 PPI by Macintosh for their displays arose from the convenient fact that the official 72 points per inch mirrored the 72 pixels per inch that appeared on their display screens. (Points are a physical

unit of measure in typography, dating from the days of printing presses, where 1 point by the modern definition is 1/72 of the international inch (25.4 mm), which therefore makes 1 point approximately 0.0139 in or 352.8 µm). Thus, the 72 pixels per inch seen on the display had exactly the same physical dimensions as the 72 points per inch later seen on a printout, with 1 pt in printed text equal to 1 px on the display screen. As it is, the Macintosh 128K featured a screen measuring 512 pixels in width by 342 pixels in height, and this corresponded to the width of standard office paper (512 px ÷ 72 px/in ≈ 7.1 in, with a 0.7 in margin down each side when assuming 8.5 in × 11 in North American paper size (in Europe, it's 21 cm x 30 cm - called "A4")).

In computing, an image scanner—often abbreviated to just scanner, is a device that optically scans images, printed text, handwriting or an object and converts it to a digital image. Although the history of digital cameras dates back to the 1970s, they have become widely used in the 2000s. While the resolution of the first digital camera invented by Kodak was as low as 100 by 100 pixels (0.01 megapixels), the first commercially available digital camera, Fujix DS-1P had a resolution of 0.4 megapixels. On the other hand, modern scanners are considered the successors of early telephotography and fax input devices. The pantelegraph was an early form of facsimile machine transmitting over normal telegraph lines developed by Giovanni Caselli, used commercially in the 1860s, that was the first such device to enter practical service. The history of the first image scanner developed for use with a computer goes back to 1957. Color scanners typically read RGB (red-green-blue color) data from the array. This data is then processed with some proprietary algorithm to correct for different exposure conditions and sent to the computer via the device's input/output interface. Color depth varies depending on the scanning array characteristics but is usually at least 24 bits. High quality models have 36-48 bits of color depth. Another qualifying parameter for a scanner is its optical resolution, measured in pixels per inch (ppi), sometimes more accurately referred to as samples per inch (spi).

Images in web pages, video, and slide shows can be as low as 72 PPI for a static image or 150 PPI if we are going to focus in on the image. For printing, the DPI needs to be larger, with images scanned in at least 300 DPI. The DPI standard for and images to be printed within journals and books is 300 DPI and for museum exhibits, it's 600 DPI.

The most important factors determining image quality of digital images can be considered as pixel dimensions and color depth. Increasing the dpi value of an image by resampling in Photo Editors (e.g., Adobe Photoshop) has no improving effect on its quality, but it lets us to determine target printing size.

For vector images, there is no equivalent of resampling an image when it is resized, and there is no PPI in the file because it is resolution independent (prints equally well at all sizes). However, there is still a target printing size. Some image formats, such as Photoshop format, can contain both bitmap and vector data in the same file. Adjusting the PPI in a Photoshop file will change the intended printing size of the bitmap portion of the data and also change the intended printing size of the vector data to match. This way the vector and bitmap data maintain a consistent size relationship when the target printing size is changed. Text stored as outline fonts in bitmap image formats is handled in the same way. Other formats, such as PDF, are primarily vector formats which can contain images, potentially at a mixture of resolutions. In these formats the target PPI of the bitmaps is adjusted to match when the target print size of the file is changed. This is the converse of how it works in a primarily bitmap format like Photoshop but has exactly the same result of maintaining the relationship between the vector and bitmap portions of the data.

Long story short, it is not technically possible to talk about DPI value for images that were taken by digital cameras or any type of digital images that were transferred to the computer's storage media. The DPI value stored within exif information of images is just a virtual value just to guide the photo editing software and the graphic artist to determine the target printing size of that image.

Requirements for Digital Media

Figures and Figure Legends

Dear author, since the Journal has decision of publishing online, there is no need to upload the photos, pictures, drawings or shapes in the article as a separate file. However, to avoid blurring of images in the pdf of the article, you should add the photos or other images (X-ray, BT, MR etc.) in your Microsoft Word program as follows.

Insert menu - Pictures - Related image file in your computer

You must add the related image file on your computer and add the picture width to 16 cm. Since the need to upload each image (photo, X-ray, BT, MR or other images) is eliminated, please do not upload it to the system during submission. Place only at the end of full text and blind text.

Due to the reasons explained above, images should be taken by a digital camera of 5 megapixels or more in JPEG, RAW, or TIFF format, and should be inserted in their original form as JPEG, PNG or TIFF files.

Paper-printed images or documents should be scanned at 300 DPI resolution and should be inserted as TIFF, PNG or JPEG files.

Each vector graphic software has its own built-in settings and may have been preset at 72 dpi. So, the document should be created enough big to obtain the image in the desired dimensions. The vector graphics should be exported to a rasterized image format and inserted such as JPEG, PNG or TIFF files.

For X-ray films, CT scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, you should insert high-resolution photographic image files. Since blots are used as primary evidence in many scientific articles, we may require deposition of the original photographs of blots on the journal website.

Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication.

Figures should be made as self-explanatory as possible. Titles and detailed explanations belong in the legends— not on the illustrations themselves.

Figures should be numbered consecutively according to the order in which they have been cited in the text.

In the manuscript, legends for illustrations should be in Arabic numerals corresponding to the illustrations. Roman numerals should be avoided. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, you should identify and explain each one clearly in the legend.

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Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples.

Temperatures should be in degrees Celsius. Blood pressures should be in millimeters of mercury, unless other units are specifically required by the journal.

Authors must consult the International System of Units (SI).

Authors should add alternative or non-SI units, when SI units are not available for that particular measurement. Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

Abbreviations and Symbols

Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

Types of paper

Interdisciplinary Medical Journal publishes the following types of articles.

1. Original Articles: Original prospective or retrospective studies **clinical research** in areas relevant to medicine.

The manuscript should contain English abstract, a maximum of 250 words, and the structured abstract should contain the following sections: objective, method, results, and conclusion. Three to six words or determinative groups of words should be written as keywords below the abstract.

The text of articles reporting original research might contain up to 5000 words (excluding abstract, references list and tables) and should be divided into Introduction, Method, Results, and Discussion sections. References list should also be included so that their number does not exceed 50. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection of the process of scientific discovery. Articles need subheadings within these sections to further organize their content.

2. Review Articles: The authors may be invited to write or should be expert in that subject of review article.

The manuscript should contain English abstract, a maximum of 250 words, but a structured abstract is not required. The main text should include subtitles or related topics to further organize the content. The text of review articles might contain up to 5000 words (excluding Abstract, references list and Tables). Number of references list should not exceed 90.

3. Case Reports: Brief descriptions of a previously undocumented disease process, a unique unreported manifestation or treatment of a known disease process, or unique unreported complications of treatment regimens.

The manuscript should contain English abstract, a maximum of 250 words, but a structured abstract is not required. The main text should include titles or related topics to further organize the content. The manuscript could be of up to 2500 words (excluding references list and abstract) and could be supported with up to 25 references.

4. Editorial: Special articles are written by editor or editorial board members. An abstract is not usually included in editorials.

5. Letter to the Editor: These are letters which include different views, experiments and questions of the readers about the manuscript and should preferably be related to articles previously published in the Journal or views expressed in the journal. These should be short and decisive observations. They should not be preliminary observations that need a later paper for validation. The letter could have up to 1000 words and a maximum of 15 references.

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Conflict of Interest declaration. A conflict of interest can occur when you (or your employer or sponsor) have a financial, commercial, legal, or professional relationship with other organizations, or with the people working with them, that could influence your research.

Some authors claim, the influence of the pharmaceutical industry on medical research has been a major cause for concern. In contrast to this viewpoint, some authors emphasize the importance of pharmaceutical industry-physician interactions for the development of novel treatments and argued that moral outrage over industry malfeasance had unjustifiably led many to overemphasize the problems created by financial conflicts of interest.

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On behalf of all authors, I, as the corresponding author, accept and declare that; the authors whose names are listed immediately below report the following details of affiliation or involvement in an organization or entity with a financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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Acknowledgement

The Acknowledgements section immediately precedes the Reference list. All contributors who do not meet the criteria for authorship should be listed in an 'Acknowledgements' section. Additionally, if the article has been submitted on behalf of a consortium, all author names and affiliations should be listed at the end of the article in the Acknowledgements section. Authors should also disclose whether they had any writing assistance.

Authorship contribution: please indicate which part of the article each author contributed .

Article Format

The submitted file must be in Microsoft Word Document format.

The page size must be 210 mm × 297 mm (A4 size). All margins must be

set to 2.5 cm. If you are using Microsoft Word 2007 or later, you can easily set the margin by choosing "Normal" setting from Margins menu within Layout tab. The text layout should consist of single column.

Do not capitalize diseases or syndromes unless they include a name or proper noun. Note that the words "syndrome" and "disease" are never capitalized; for example, Down syndrome, Hodgkin disease.

The authors should turn off automatic hyphenation. Do not use hyphens with common prefixes unless the word looks confusing when closed up or unless the prefix precedes a proper noun, some other capitalized word, or an abbreviation. Common prefixes that should be "closed up" include ante, anti, hi, co, contra, counter, de, extra, infra, inter, intra, micro, mid, neo, non, over, post, pre, pro, pseudo, re, semi, sub, super, supra, trans, tri, ultra, un, and under.

Use italics sparingly for emphasis in the text.

Spell out Greek letters or use the "Insert, Symbol" feature in Microsoft Word. Do not create your own symbols.

Do not use italics for common expressions, such asin vivo, in utero, en face, aide-mémoire, or in situ.

Use bold type sparingly in text because it competes with headings for the reader's attention.

Always use numerals for statistics, ages, and measurements (including time, for example, 3 weeks). For other uses, spell out numbers from one to nine only.

Spell out abbreviations at first mention in the manuscript, with the abbreviation following in parentheses (except for units of measure, which are always abbreviated following numerals).

Manuscripts including tables, references list and figure legends, must be typewritten with a Unicode font (e.g., Times New Roman, Arial, etc.) that is available both for Windows and Mac Os operating systems. Please avoid using a mixture of fonts or non-Unicode fonts that do not support accented characters. The recommended font size is 12 points, but it may be adjusted for entries in a table. Authors should use true superscripts and subscripts and not "raised/lowered" characters. For symbols, please use the standard "Symbol" fonts on Windows or Macintosh.

Use the TAB key once for paragraph indents, not consecutive spaces. The pages should be numbered consecutively, beginning with the first page of the blinded article file. The pages should include title and abstract in English, the main text, tables, figures or diagrams-if exists- and reference list.

The title of the article should be centered at the top of the main text page, with the abstract below, and followed by Keywords. The capital letter of the first word of title should start with upper case letter. Please avoid capitalizing all letters of the title and conjunctions. The title, abstract, and keywords should be present in English and must be organized respectively. In order to start the Introduction section in a new page, a page break could be inserted at the end of Keywords.

While figure legends should be placed below the figures themselves, table captions should be placed above each table. Characters in figures, photographs, and tables should be uncapitalized in principal.

It would be appropriate to place the figures, tables and photographs at the end of the main text. Please, insert them at the end of main text at appropriate sizes, and order.

Figures and Figure Legends

Dear author, since the Journal has decision of publishing online, there is no need to upload the photos, pictures, drawings or shapes in the article as a separate file. However, to avoid blurring of images in the pdf of the article, you should add the photos or other images (X-ray, BT, MR etc.) in your Microsoft Word program as follows.

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INTERDISCIPLINARY MEDICAL JOURNAL
Interdiscip Med J 2024;15(53)

Reviewer Guide

Dear Reviewer,

Thank you for agreeing to conduct a peer review which will help us decide whether a manuscript is to be published in this journal.

Peer-review is a critical part of the functioning of the scientific community, of quality control, and the self-corrective nature of science. Participating in peer review of scientific publications can be viewed as a responsibility, a burden, and an opportunity all at the same time. Nonetheless, peer review remains a critical component of our profession that helps to ensure the quality, originality, and reliability of scientific findings and claims. Peer review is requested of a colleague with specific interest and expertise in the topic relevant to the manuscript submitted to The Journal. Yet despite the importance of this process in upholding rigorous scientific standards and the integrity of the journal, few if any reviewers receive any formal training or instruction in how to provide a quality manuscript review. This document serves to orient and guide individuals asked to provide peer review for This journal in the process and responsibilities of review and reviewer. In doing so, the hope is to increase scientific quality of the manuscripts and contribution to the medical scientific community.

Process of peer review in The Journal

The journal utilizes a standard online site https://dergipark.org.tr), supported by TUBİTAK, for the process of both manuscript submission and manuscript peer review. Upon receiving a manuscript submitted for consideration of publication to The Journal, the Journal Manager and editorial staff review the submission to assure all required components as outlined in the Guide for Authors are included. The manuscript is then assigned to one of the Co-Editors (either the Editor in Chief or an Associate) Editor who directs and oversees the peer-review process. The Co-Editor then reviews the submission for relevance, content and quality. Those submissions deemed appropriate for consideration of publication are then assigned to at least two peer reviewers. Selection of these reviewers is a key step in the peer review process, as this represents a critical component in ensuring quality of manuscript review and in the overall quality of the Journal. Specifically, the selection of a reviewer with expertise in the topic of the manuscript to be reviewed and without any conflict of interest improves both the timeliness and quality of the review. As such, the designation of an area of interest or expertise by the reviewer (entered at the time of registration into the system (and updated in the change details section of the website, in the subsection areas of expertise) is critical for this component of the process. Reviews are chosen to a great extent from members of the advisory board.

Once the reviewers are selected by the editor, an email is sent requesting the review; 30 days is provided to choose to review (or not review) the manuscript. A lack of response to this request leads to the reviewer being uninvited. Statistics on individual reviewers are maintained and reviewed by the journal editors, including the number of reviews requested (and those accepted, uninvited, and refused). These data help in the process of evaluating the overall quality of a reviewer and are used in the selection of future editorial board members.Before Accepting

Please consider the following:

Does the article you are being asked to review match your expertise?

If you receive a manuscript that covers a topic that does not sufficiently match your area of expertise, please notify the editor as soon as possible. Please feel free to recommend alternate reviewer.

Do you have time to review the paper?

Finished reviews of an article should be completed within four weeks. If you do not think you can complete the review within this time frame, please let the editor know and if possible, suggest an alternate reviewer. If you have agreed to review a paper but will no longer be able to finish the work before the deadline, please contact the editor as soon as possible.

Are there any potential conflicts of interests?

While conflicts of interest will not disqualify you from reviewing the manuscript, it is important to disclose all conflicts of interest to the editors before reviewing. If you have any questions about potential conflicts of interests, please do not hesitate to contact the receiving editorial office.

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Some resources;

https://violentmetaphors.com/2013/12/13/how-to-become-good-at-peer-review-a-guide-for-young-scientists/

https://www.theguardian.com/higher-education-network/blog/2013/sep/27/peer-review-10-tips-research-paper

https://www.degruyter.com/document/doi/10.7556/jaoa.2013.070/html

https://scholar.google.com.tr/scholar?hl=tr&q=good+peer+review&btnG=&lr=

(https://www.google.com.tr/search?num=50&btnG=Ara&q=how+to+write+a+good+peer+review).

Respond to the invitation as soon as you can – delay in your decision slows down the review process, whether you agree to review or not.

General criteria for a peer review

There are a number of general criteria that make for a quality review of a scientific manuscript, and a number of responsibilities that come with being a peer reviewer that further enhances the review process.

The peer reviewer is responsible for critically reading and evaluating a manuscript in their specialty field, and then providing respectful, constructive,

and honest feedback to authors about their submission. It is appropriate for the Peer Reviewer to discuss the strengths and weaknesses of the article, ways to improve the strength and quality of the work, and evaluate the relevance and originality of the manuscript.

Timely – Given the time sensitive nature of many scientific manuscripts, the rapid return of a solicited peer review minimizes the timeline between submission and decision (which helps the authors with resubmission if the manuscript is rejected and helps the journal with a shorter time from submission to publication if accepted). Thus, the reviewer plays a very important role in ensuring expeditious dissemination of data. Peer reviews that cannot be completed on time should not be accepted by the reviewer; every effort should be made to complete those accepted within the time allotted for review.

Fair – A reviewer has a responsibility to both The Journal and the author to provide a review that is thoughtful and complete. While the immediate goal of peer review is providing a decision regarding the suitability for publication in the journal, an additional goal is to provide the author comments that will ultimately improve the science and manuscript and providing it the best chance for publication in a peer-reviewed journal. For manuscripts eventually accepted for publication, quality peer review will ensure that the highest quality science is ultimately published (and will weed out unsound papers). Peer reviews requested in areas outside of the area of expertise of a reviewer should not be accepted; in that case, the review process is facilitated by the reviewer recommending those who could provide a quality review.

Collegial – It is rare for any manuscript to be reviewed without comments or criticisms. However, the responsibility of the reviewers is to provide these critiques constructively and objectively, and in a fashion, that is collegial and respectful. Consider each manuscript as one that was written by a valued colleague when drafting a peer review. Importantly, review the manuscript as you would like your own manuscript reviewed.

Clear – The goal of peer review is to provide an advisory recommendation to the editors as to the suitability of a manuscript for publication in The Journal. As such, the responsibility of the reviewer is to provide a clear signal to the editor regarding the appropriateness and priority for publication of a manuscript. The reviewer is expected to provide comments and criticisms to the editor that clearly justifies their recommendation for disposition of the manuscript. It is also critical that the comments to the editor are consistent with those made to the author (such that the comments of the reviewer justify the recommendation regarding the disposition of the manuscript).

Comprehensive – A quality review will include a number of considerations, and may be specific to the manuscript being reviewed. In order for a manuscript to be considered for publication, it must be original and significant, providing a contribution to research and importance to field. In general, there should be no flaws in the specific procedures used in performance of the study, or in the logic used for the interpretation of the data. It is important that the results of the study support its conclusions, and that there are no errors in reference to prior work (or no exclusions of pertinent references). Where appropriate, confirmation of regulatory review (such as institutional review board approval) must be present. A reviewer is expected to comment on the strengths and weaknesses or limitations of the study. The validity of the statistics used (often including a justification of a sample size) to analyze data is necessary, and the data presented in the figures and tables should be reflective of the results presented and adequate to justify the study conclusions. In general, the manuscript length and quality of the writing are important to ensure its quality.

Considerations for a quality peer review of a manuscript

Structure

Is the article clearly laid out? Are all the key elements present: abstract, introduction, methodology, results, conclusions?

Consider each element in turn:

Title: Does it clearly describe the article? This will be used for medical database searches, so it shouldn't try to be "cute".

Abstract: Does it reflect the content of the article? Are the data consistent with the results reported in the manuscript?

Introduction: Does it describe what the author hoped to achieve accurately, and clearly state the problem being investigated? Normally, the introduction is two or three paragraphs long. It should summarize relevant research to provide context, and explain what findings of others, if any, are being challenged or extended. It should describe the experiment, hypothesis; general experimental design or method.

Methodology: Does the author accurately explain how the data were collected? Is the design suitable for answering the question posed? Is there sufficient information present for you to replicate the research? Does the article identify the procedures followed? Are these ordered in a meaningful way? If the methods are new, are they explained in detail? Was the sampling appropriate? Have the equipment and materials been adequately described? Does the article make it clear what type of data was recorded; has the author been precise in describing measurements?

Results: This is where the author should explain in words, tables and figures what was discovered in the research. It should be clearly laid out and in a logical sequence. You will need to consider if the appropriate analysis been conducted. Are the statistics correct? If you are not comfortable with statistics, advise the editor when you submit your report and recommend review by a statistical editor. Any interpretation should not be included in this section.

Conclusion/Discussion: Are the claims in this section supported by the results, do they seem reasonable? Have the authors indicated how the results relate to expectations and to earlier research? Does the article support or contradict previous theories? Does the conclusion explain how the research has moved the body of scientific knowledge forward?

Language: If an article is poorly written due to grammatical errors, while it may make it more difficult to understand the science, you do not need to correct the language. You may wish to bring it to the attention of the editor, however, and we can refer the authors to an language editing service if you feel the paper may be worth publishing.

Finally, on balance, when considering the whole article, do the figures and tables inform the reader, are they an important part of the story? Do the figures describe the data accurately? Are they consistent (are the bars in the charts the same width, are the scales on the axis logical)? Are the legends appropriate?

Previous Research

If the article builds upon previous research, does it reference that work appropriately? Are there any important works that have been omitted? Are the references accurate and up to date?

Reviewer's Suggestions

Once accepted, the reviewer has 4 weeks to complete the review (details of the components of a review are described in more detail below), which is submitted through The Journal site. Failure to complete the review during this time period leads to a reminder email.

It is the responsibility of the reviewer to provide a recommendation to the editor for the disposition of the manuscript. Importantly, the recommendation of the reviewer is advisory to the editor, as it is ultimately the decision of the editor as to the final disposition of the manuscript.

When the editor has a full complement of reviews completed, the editor reviews the comments and recommendations, and a decision regarding the suitability for publication of the manuscript is made.

The recommendations can be categorized into 6 groups.

Accept Submission (without modification)

Minor Revision (Revisions Required): Accept with minor modification (but manuscript requires modifications to improve its quality)

Major Revision (Resubmit for Review): Major modifications required, manuscript is unique, but requires extensive revision and reevaluation prior to potential acceptance

Resubmit Elsewhere: manuscript is unique, but out of the journal scope.

Decline Submission: manuscript is of low quality or low interest to the readership)

The reviewer has two types of comments that can be provided – one to the authors, and one to the editors. It is strongly encouraged that the reviewer utilizes the comments to the editor to provide confidential comments regarding the manuscript under consideration. These comments help assure that the editor understands the true recommendation of the reviewer and provides key assistance to the Editor in determining a manuscript's ultimate disposition. In addition, completing the manuscript rating form is helpful in supporting a reviewer's recommendation for the disposition of a manuscript, and assists the Editor in justifying the final decision.

Review of the reviewer

The editor evaluates the quality of a review upon its receipt. Utilizing the criteria defining a quality review (timely, fair, collegial, clear, and comprehensive), a reviewer is evaluated and scored (from 0-5) on their review. This statistic, in combination with a separate statistic regarding the timeliness of the review, is helpful in assigning subsequent reviews to a reviewer. Reviewers with low scoring or late reviews are not considered highly for subsequent reviews.

Why be a reviewer?

Reviewing requires the investment of time and a certain skillset. Before you decide if you want to become a reviewer, we recommend that you read more about the peer review process and conducting a review.

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* Before all studies are sent to the reviewer, while they are in the pre-control stage, they are subjected to "Similarity Check" with iThenticate Crosscheck software and if they are above the tolerable level, the author is requested to make the necessary corrections.

* We ask the authors to use a dot as a decimal separator throughout the article, including the Turkish and English abstracts, so this is not an error.

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

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Individuals listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE - www.icmje.org).

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1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work;

2. Drafting the work or revising it critically for valuable intellectual content;

3. Final approval of the version to be published; AND

4. Agreement to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for

other specific parts of the work. Besides, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged on the title page of the manuscript.

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Ethical Responsibilities of The Reviewer

Given the sensitive nature of peer review, there are ethical responsibilities of the review and review process that are critical to ensure their validity. It is important for reviewers to identify potential conflicts of interest with the authors and the topic of the manuscript. The Journal requires that reviewers disclose potential and relevant conflicts of interest related to employment, consultancies, stock ownership, receipt of honoraria, patents, a professional relationship with, or direct competition in the field of the authors. The reviewer has a responsibility to review the conflict-of-interest forms submitted by the authors, which specifically document any relevant financial relationships.

Given the role of reviewer as an expert in the topic area of the manuscript, a reviewer is requested to report any known situations of duplicate submissions (a manuscript that may be under concurrent review at another journal), fraudulent data, or plagiarism in a manuscript. If identified, these comments should be conveyed to the editor (in the confidential comments to the editor section) so they can be addressed as appropriate. Since peer review of a manuscript allows a reviewer to view data that is not yet in the public domain, strict confidentiality is critical to ensure scientific integrity; destruction of documents and files related to peer review is also mandatory once the review is complete.

The Committee on Publication Ethics (COPE) is a group comprised of editors of academic journals and others interested in publication ethics. Members of COPE were provided with the Ethical Guidelines for Peer Review, describing the basic principles to which reviewers should adhere. These guidelines provide a broad ethical context in which the peer review process should be performed.

COPE Ethical Guidelines for Peer Reviewers

Peer review in all its form plays an important role in ensuring the integrity of the scholarly record. The process depends to a large extent on trust and requires that everyone involved behaves responsibly and ethically. Peer reviewers play a central and critical part in the peer-review process, but too often come to the role without any guidance and may be unaware of their ethical obligations. The COPE Ethical Guidelines for Peer Reviewers set out the basic principles and standards to which all peer reviewers should adhere during the peer-review process. It is hoped they will provide helpful guidance to researchers, be a reference for journals and editors in guiding their reviewers, and act as an educational resource for institutions in training their students and researchers.

Basic principles to which peer reviewers should adhere

Peer reviewers should:

• only agree to review manuscripts for which they have the subject expertise required to carry out a proper assessment and which they can assess in a timely manner

• respect the confidentiality of peer review and not reveal any details of a manuscript or its review, during or after the peer-review process, beyond those that are released by the journal

• not use information obtained during the peer-review process for their own or any other person's or organization's advantage, or to disadvantage or discredit others

• declare all potential conflicting interests, seeking advice from the journal if they are unsure whether something constitutes a relevant interest

• not allow their reviews to be influenced by the origins of a manuscript, by the nationality, religious or political beliefs, gender or other characteristics of the authors, or by commercial considerations

• be objective and constructive in their reviews, refraining from being hostile or inflammatory and from making libelous or derogatory personal comments

• acknowledge that peer review is largely a reciprocal endeavor and undertake to carry out their fair share of reviewing and in a timely manner

• provide journals with personal and professional information that is accurate and a true representation of their expertise

• recognize that impersonation of another individual during the review process is considered serious misconduct

INTERDISCIPLINARY MEDICAL JOURNAL

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ORIGINAL ARTICLE

ORIGINAL RESEARCH

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Molecular and cytogenetic evaluation of pediatric leukemias

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Abstract

Objective: This study was conducted to determine the rate of genetic changes that may be a risk factor in the treatment of our leukemia patients.

Method The study was conducted prospectively in 39 patients who were followed in department of pediatric hematology. Bone marrow or peripheral blood samples (with more than 30% blast invasion) evaluated for cytogenetics before the leukemia treatment. TEL/AML1 probe was applied to 18 of 20 acute lymphoblastic leukemia (ALL) patients and mixed lineage leukemia (MLL) probe was applied to 3 patients with infantile leukemia diagnosis.

Results: Chromosomal aberration was detected in 8(40%) of 20 patients with ALL diagnosis and in 6(60%) of 10 patients with acute myeloid leukemia (AML) diagnosis. Translocation involving the MLL gene region was detected cytogenetically in two of three patients with infantile leukemia while in the other patient, it was shown by Fluorescence In Situ Hybridization analysis. TEL/AML1 fusion was detected in 5(27.7%) of 18 patients with a diagnosis of B-precursor ALL. Amplification of the AML1 gene was defined in 7(38.8%) of 18 pediatric ALL patients.

Conclusion: Cytogenetic investigations should be continued in leukemia patients. The rate of chromosomal aberrations in ALL and AML patients was consistent with the literature. The rate of TEL/AML1 gene fusion which is a good prognostic factor in ALL patients, was consistent with the literature.

Keywords: Leukemia, cytogenetic analysis, prognosis

INTRODUCTION

Leukemia is the most common malignancy worldwide in children and is caused by the proliferation of hematopoietic cells that lead to impaired normal bone marrow function and bone marrow failure. Leukemias account for 27% of childhood cancers in the United States (1).

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, accounting for a quarter of all childhood cancers and three-quarters of all newly diagnosed acute leukemia patients. ALL is divided into B-cell and T-cell ALL subgroups. ALL is most common between the ages of 1 and 4. T-cell ALL is more common in males and in adolescents (2). Although the etiology of ALL is unknown in most of the cases, various genetic syndromes such as Down syndrome have been associated with an increased risk of leukemia (3). The survival rate in ALL patients reached 85.9% with multidisciplinary approaches (4).

Acute myeloid leukemia (AML) accounts for approximately 15-20% of leukemias in children. It can occur at any age, but its frequency is higher in adolescence. Although the results have improved in the last 10 years in AML patients, survival is around 70% (5). In chronic myeloid leukemia (CML), leukemia cells have not lost their ability to differentiate.

In childhood leukemias, age, leukocyte count, immunophenotyping, and “karyotyping” have an important diagnostic and prognostic value. Molecular analysis of chromosomal numerical or structural irregularities is also important in understanding the biology of the disease and elucidating the roles of these irregularities in leukomogenesis.

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Determination of these specific chromosomal abnormalities at the time of diagnosis and after treatment useful monitoring the disease, evaluating the response to therapeutic drugs, and monitoring minimal residual disease (6).

The aim of this study is to reveal chromosomal changes and chromosome rearrangement in leukemia patients.

METHOD

Patients

A total of 39 patients, 20 ALL, 10 AML, 8 mixed-lineage leukemia (MLL) and 1 CML patients, who were admitted to the Department of Pediatric Hematology at Ondokuz Mayıs University between 2005 and 2007, were included in the study. In the initial diagnosis, morphological examination of bone marrow, flow cytometry and genetic analyzes were performed. ALL BFM 2002 protocol, AML BFM 2004 protocol and AML or ALL protocol were applied according to the type of mixed leukemias.

The study protocol was accepted by Clinical Research Ethics Committee of Ondokuz Mayıs University Medical Faculty (Decision No: 2005/354) and informed consent was provided by the parents of the patients before the study.

Patients' demographic features such as age, gender, blood count at the time of diagnosis, blast rate in the bone marrow and peripheral blood and immunophenotyping results were recorded. Cytogenetics and Fluorescence In Situ Hybridization (FISH) technics were applied to bone marrow or peripheral blood samples (with more than 30% blast invasion) before the leukemia treatment. The identification of chromosomes in the study was made according to the "International System For Human Cytogenetic Nomenclature (ISCN) 2005" (7). Structural ≥2 and numerical ≥3 chromosomal aberration detection was considered clonal.

Cytogenetic and FISH Method

Karyotype analysis was carried out on lymphocyte culture of all patients using the conventional method. According to the standard protocols, four well spread G-banded metaphases were karyotyped and at least 20 metaphases were examined with a 450 bands resolution for each patient. FISH analysis with probes (Vysis Inc., Downer's Grove, IL, U.S.A) were performed on both metaphase spreads and interphase nuclei according to the guideline of manufacturer. Image analyses were evaluated using CytoVision software (version 3.93; Applied Imaging) with Olympus BX51 microscope equipped with Progressive Scan Video Camera. During the FISH analysis, at least 200 cells were counted from each patient slide. The positivity threshold value was taken as 3% for each probe. Positivities above this value were considered significant.

Identification of the probe

TEL/AML1 probe:

A normal nucleus hybridized with "LSI TEL/AML1 ES Dual Color Translocation Probe" (Vysis Inc., Downer's Grove, IL, U.S.A.) shows 2 red and 2 green signals. It is expected in a nucleus containing TEL/AML1 fusion that a green (TEL), a large red (AML1), a small red (residual red) and a yellow signal appear.

MLL Probe: With the "LSI MLL Break Apart Rearrangement Probe" (Vysis Inc., Downer's Grove, IL, U.S.A) used in FISH analysis, two red/green (yellow) fusion signal patterns are seen in the absence of MLL gene rearrangement in the cell. In the presence of MLL translocation, a red/green (yellow) fusion signal, a red signal and a green signal are expected.

Statistical Analysis

SPSS v21 IBM Corp, NY, USA software was used to analyze the data. First, distributed demographic characteristics (eg, age and gender) and clinical member descriptive statistics were evaluated. In this evaluation, frequencies and percentages were calculated for the data belonging to the categories. Since the number of patients was <30 in the study, non-parametric tests were preferred. Normal distribution data were expressed as median and interquartile range (IQR). Kruskal Wallis Test was used to compare numerical data between three independent groups, and Mann Whitney U test was used to compare subgroups. Chi-square test was used to compare categorical data. "In the analyses, a significance level of $p<0.05$ was considered statistically significant.

RESULTS

The study included 39 patients, 21 (53.8%) of were girls. The median age at admission was 56.5 months (IQR=60.5) in the ALL patient, 143.5 months (IQR=45) in the AML patient, 48 months (IQR= 53) in the mixed leukemia patient, and 155 months in the KML patient. The median leukocyte count was 24.7 $x10^9$ (IQR=83.6 $x10^9$) in the ALL patient, 11.2 $x10^9$ (IQR=11.9 $x10^9$) in the AML patient, 8.1 $x10^9$ (IQR=75.6 $x10^9$) in the mixed leukemia patient, and 171.0 $x10^9$ in the KML patient (Table 1). A significant relationship was detected between leukemia types and age at diagnosis with the Kruskal Wallis Test ($p=0.002$, $p<0.05$). A significant relationship was found between mixed and AML, and between AML and ALL by Mann Whitney U test ($p=0.013$, $p=0.003$, respectively). No significant relationship was detected between leukemia types and sex and leukocyte count with the Kruskal Wallis Test.

Chromosomal aberration was detected in 8 (40%) of 20 patients with ALL diagnosis by cytogenetic analysis. Aberration was detected in 6 (60%) of 10 patients with AML diagnosis and in 4 (50%) of 8 patients with mixed leukemia (Tables 2, 3 and 4). Metaphase was not detected in 1 patient each in the ALL, AML and mixed leukemia groups.

Table 1. Baseline patient characteristics

Immunphenotype	Number	Age in month Median (IQR)	Leukocyte count/L Median (IQR)	Follow-up time Median (IQR)
ALL	20	56.5 (60.5)	24.7 x10^9 (83.6 x10^9)	13 (7)
AML	10	143.5 (45)	11.2 x10^9 (11.9 x10^9)	12.5 (14)
MLL	8	48 (53)	8.1 x10^9 (75.6 x10^9)	9.5 (7.5)
CML	1	155	171.0 x10^9	7

Abbreviations: IQR, interquartile range; ALL, Acute lymphoblastic leukemia; AML, Acute myeloid leukemia; MLL, mixed-lineage leukemia CML, Chronic myeloid leukemia

MLL rearrangement probe was applied to 3 patients diagnosed with infantil leukemia. In 2 had B-precursor leukemia and 1 mixed type leukemia patients was detected. In one of the infantile leukemia patients MLL gene rearrangement was revealed by FISH analysis (Table 5).

TEL/AML1 probe was applied to 18 of 20 ALL patients. TEL/AML1 fusion positivity was detected in 5 of 18 (27.7%) patients with B-precursor ALL. Amplification of the AML1 gene was defined in 7 of 18 (38.8%) pediatric ALL patients. One patient with B-precursor immunophenotype had a TEL/AML1 gene fusion and TEL gene deletion (Table 2).

DISCUSSION

Leukemia is a common disease in recent years. In leukemia treatment, treatment schemes are selected according to risk classification. Chromosome and genetic research are the main elements of risk classification, especially in ALL and AML. In CML, diagnosis must be made based on genetic mutations. In some leukemia translocations and mutations, mutation-specific drugs have been discovered and put into routine use. In order for these drugs to be used in the patient, this mutation must be detected in molecular studies.

The use of mutation-specific drugs (For example: tyrosine kinase inhibitors in CML) changes the prognosis of patients.

Table 2. Results of cytogenetic and TEL/AML1 fluorescence in situ hybridization (FISH) analysis of acute lymphoblastic leukemia diagnosed patients

Karyotype	Number	Percentages (%)
Normal	11	55.0
High hyperdiploidy (51-67 chromosomes)	4	20
t(4;11)(q21;q23)	1	5
t(7;10)(q11;p11)	1	5
del(6)(q21q25)	1	5
inv(9)(p11;q12)	1	5
No metaphase	1	5
FISH	**Number**	**Percentages (%)**
TEL/AML1fusion	5	27.7
TEL/AML1 fusion and TEL deletion	1	5.5
AML1(>3copies gene)	7	38.8

Many mutation-specific drugs have been produced for other leukemias or phase studies are ongoing. For this reason, the importance of performing molecular genetic studies on patients is increasing. In this study, the genetic findings of patients treated at our university were examined. By examining these findings, it was investigated whether there were regional differences.

Although ALL is generally seen in previously healthy individuals, environmental risk factors and inherited genetic predisposition are thought to have an impact (8). Although approximately 80% of patients recover, some patients develop resistance to treatment and this worsens the prognosis in patients (9).

While 49.2% of chromosomal aberrations can be identified with the G-banding technique, 73.8% of the gene arrangements have been identified with the use of FISH analysis (10). Accordance with the literature, in this study, the frequency of chromosomal aberration was found in 8 (40%) of 20 ALL patients with cytogenetic results. When FISH analysis was added, it was observed that 55.5% of the gene arrangements were identified.

In a study of large series in which 371 AML patients were included, the rate of chromosomal aberration in AML was found to be 68-85% (11-13). In this study, the rate of chromosomal aberration in patients with AML was found to be 60.0%, consistent with the literature. All these differences are thought to be related to the methodological approaches used, especially the FISH method is believed to allow a higher rate of detection of cryptic changes. It is also conceivable that the differences may be due to geographical distribution and

racial genetic factors.

Recurrent chromosomal abnormalities such as t(12;21), t(9;22), 11q23 rearrangement, hypodiploidy, trisomy/polysomy 21 and der(21)t(21;21) duplication are observed in childhood ALL patients. Among these abnormalities, t (12;21) translocation, which is the most common abnormality among childhood ALL cases, is a good prognostic marker for the course of the disease (10,14). Translocation t (12;21) (p13;q22) resulting in the TEL-AML1 fusion gene is a chromosomal abnormality with a frequency of approximately 25% in childhood ALL patients (15). The non-translocated TEL allele t (12;21) is deleted in approximately 70% of ALL patients, and this subtype also has a good prognosis (16,17).

Table 3. Results of cytogenetic analysis of acute myeloid leukemia diagnosed patients

Karyotype	Number	Percentages (%)
Normal	3	30
Low hyperdiploidy (47-50 chromosome)	2	20
Hypodiploidy (<44 chromosome)	2	20
t(7;14)(p15;q32)	1	10
t(8;21)(q22;q22)	1	10
No metaphase	1	10

Table 4. Results of cytogenetic analysis of mixed leukemia and chronic myeloid leukemia

Mixed leukemia karyotype	Number	Percentages (%)
Normal	3	37.5
Low Hyperdiploidy (47-50 chromosome)	1	12.5
t(1;11)(p32;q23)	1	12.5
t(9;22)(q34;q11)	1	12.5
del(12)(p11p13)	1	12.5
No metaphase		12.5
Chronic myeloid leukemia karyotype	**Number**	**Percentages (%)**
t(9;22)(q34;q11)	1	100

Since the t(12;21) translocation is virtually undetectable by conventional cytogenetic procedures, the FISH method was used. In the study, TEL/AML1 fusion was detected with an incidence of 27.7% (5/18) in B precursor ALL patients. The frequency of TEL/AML1 fusion is in Scandinavian countries (25%) (18), USA (22%) (19) and India (7%) (20). It can be thought that frequency differences may be due to geographical distribution and racial genetic factors.

The incidence of additional abnormalities in TEL and AML1 genes in t (12; 21) positive ALL patients was determined as 20%. Previous studies have reported inconsistent results regarding the prognostic effects of additional genetic changes. Attarbaschi et al.(21) reported that in patients with TEL /AML1 fusion, TEL deletions, trisomy 21 and additional der (21) t (12;21) were detected with 55%, 14% and 15%, respectively, and also reported that the presence of TEL deletion in TEL/AML1 positive patients has a worse prognosis than those without.

In different study, TEL deletions in TEL/AML1 positive pediatric ALL patients are associated with better prognosis (22). For example, it was reported that there was no significant difference in clinical features and results according to the presence or absence of additional genetic changes (23).

It detected TEL deletion with TEL/AML1 fusion in 1 of the 18 B precursor ALL patients using TEL/AML1 probe. The patient remained in remission for 16 months.

Table 5. Results of FISH analysis performed with LSI MLL dual color, break apart rearrangement probe, relapse status and survival months of the infantil leukemia diagnosed patients

Age (in month)/ Sex	Leukemia type	Karyotype	MLL TR	Relapse (months)	Survival (months)
3.5 /Female	B-precursor	46,XX,t(4;11)(q21;q23)	+	NR	2 (death)
2/Female	B-precursor	46,XX	+	NR	2 (death)
6/Female	Mixed	46,XX,t(1;11)(p32;q23)	–	8	8

It detected three TEL/AML1 fusions in a patient with a cytogenetically normal karyotype. No relapse was observed in the patient during the 21-month follow-up.

In the literature, the rate of detecting three or more copies of the RUNX1 gene on chromosome 21 without polysomy was 21.4% (24). In this study, amplification of the AML1 gene was defined in 7 of 18 (38.8%) pediatric ALL patients. AML1 amplification was not observed in fusion carriers. Of these, 4 patients had three or more copies of the AML1 gene without chromosome 21 polysomy. Six AML1 copies were detected in 1 patient. He was in remission during the 15-month follow-up.

In this study, high hyperdiploid karyotype was detected in 2 of 19 patients (10.5%) with ALL diagnosis. High hyperdiploid karyotypes (chromosome number between 51-67) are numerical anomalies frequently (30%) seen in childhood B-cell ALL and are considered good prognosis markers. Trisomies and tetrazomies of 4,6,10,14,17,18, 21 and X chromosomes are frequently seen in hyperdiploid karyotypes (25). Similary, in this study, the most common chromosome gain was observed on 14, 20, 21 and X chromosomes. In hyperdiploid karyotype, it has been reported that especially trisomy 4 and trisomy 10 association is an indicator of low

relapse and better prognosis (26).

Combination of trisomy 4 and trisomy 10 was detected in 1 patient. It was observed that this patient remained in remission during the 23-month follow-up period.

KMT2A gene which was formerly known as the MLL gene is observed in 5% of child with ALL. However, when leukemia develops in infants, the frequency of KMT2A rearrangements increases to 70-80% (27).

Due to the term 'mixed' gene, MLL is rearranged with more than 80 different most frequently observed AF4, AF9, ELL, and ENL partner genes and have been shown to result in translocations (4; 11) (q21;q23), t (9; 11)(q22;q23), t (11;19) (q23; p13.1) and t (11;19) (q23; p13.3) respectively (28). The prognosis in infant ALL children with the 11q23 rearrangement is worse than in those without this rearrangement (29).

In this study, in 3 patients with infantile leukemia was detected the KMT2A rearrangement by cytogenetic and FISH analysis. A 3.5-month-old patient with B-precursor ALL presented with high leukocyte count (199 x10^9/L) and t(4;11) (q21;q23) was detected in peripheral blood cytogenetic examination. Infantile ALL induction therapy was initiated for the patient. Due to the development of sepsis during the course of the treatment, chemotherapy could not be completed and the patient died two months after the diagnosis. In a 6-month-old infantile leukemia patient with mixed immunophenotype, t(1;11)(p32;q23) was detected in bone marrow cytogenetic analysis. This translocations were not common translocations. Patient with t(1;11)(p32;q23) translocation developed a relapse eight months after relapsed despite intensive treatment.

Molecular cytogenetic techniques such as FISH are particularly valuable in patients where analyzable metaphase cells cannot be obtained or standard cytogenetic analysis cannot be performed in the presence of only a few low-quality cells. They are also required for cytogenetically identifying cryptic abnormalities

CONCLUSION

The genetic results found in this study contributed to the risk stratification of our patients. Molecular results were found in CML in the molecular therapies group. The rate of chromosomal aberrations in ALL and AML patients was consistent with the literature. TEL/AML1 gene fusion rate, which is a good prognostic factor in ALL patients, was consistent with the literature.

Limitations of the study

This study has limitations such as being a single-center with a limited sample size. Multicenter, prospective studies with larger sample sizes and longer follow-up times should be planned to validate the results.

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Peer-Review

Both externally and internally peer reviewed.

Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Thesis

This study was prepared by rearrangement of the specialty thesis by 2008, entitled as "Chromosome analyzes and fluorescent in situ hybridization studies in childhood leukemias".

Ethical Declaration

Ethical permission was obtained from the Ondokuz Mayıs University, Medical Faculty Clinical Research Ethics Committee for this study with date 12.28.2005 and number 354, and Helsinki Declaration rules were followed to conduct this study.

Athorship Contributions

Concept: MA, UA, Design: MA, UA, Supervising: UA, DA, Financing and equipment: MA, UA, DA, Data collection and entry: MA, Analysis and interpretation: MA, UA, DA, Literature search: MA, Writing: MA, Critical review: UA, DA

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ORIGINAL RESEARCH

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Effects of atropine used as eye drops on tears, pupil diameter and intraocular pressure in rabbits

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Abstract

Objective: It was aimed to determine the effects of using atropine as eye drops on tear amount (Schirmer tear test, STT), pupil diameter (PD), and intraocular pressure (IOP).
Method: STT, PD and IOP measurements were made before instillation of atropine and 30 minutes after instillation of single dose atropine for seven days in the six (6) male New Zealand Rabbits. Measurements were evaluated in Wilcoxon Signed Ranks Test.
Results: The STT, PD and IOP measurement values of both left and right eyes of the atropine group were statistically significantly different compared to those who did not receive atropine ($P<0.05$).
Conclusion: Atropine increase the PD values in the eye, decrease the STT values and increase the IOP values if it use in long-term.
Keywords: Atropine, Schirmer tear test, intraocular pressure, pupil diameter

INTRODUCTION

It is necessary to ensure adequate pupillary dilatation, especially in the examination of the lens, optic nerve and posterior segment (1). At the present time, there are many mydriatic agents such as tropicamide, phenylephrine, atropine, and cyclopentolate in routine use for pupil dilation (2, 3). It is important to ensure adequate pupillary dilation in fundus examinations, retinal laser photocoagulation, and cataract extractions in ophthalmic diseases because there may be a weak pupillary reaction to mydriatic drugs (4). This study is unique because it demonstrates the effects of mydriatic atropine usage on pupil diameter, intraocular pressure, and tear volume.

Clinical evaluation of tear production is performed with the Schirmer tear test (STT) (5). While Gelatt (6) reported the STT value in rabbits as 4.85 mm/min, the Schiötz tonometer intraocular pressure (IOP) value was not reported. There is no study examined the effect of atropine used in fundus examination on STT in the literature.

Mughannam et al. (7) used 1% atropine in horse eyes and reported that there was no significant IOP change. Wu et al. (8) reported that increasing atropine dose (0.1% and 1% doses) did not affect the treatment duration and IOP elevation. Liang et al. (9) revealed that topical atropine eye drops did not induce ocular hypertension and effectively slowed the progression of myopia. There are also studies reporting different results regarding the effects of atropine use on IOP. Instilling 1% atropine as eye drops may cause pupil dilation, stinging sensation, eye pain, photophobia, and blurred vision (10,11). Atropine causes increased intraocular pressure (IOP) due to pupil dilation (10). Atropine eye drops at a concentration of 0.01% have been reported not to cause an increase in IOP (7,8,12,13).

In this study, İt was aimed to determine the effects of eye drop atropine usage on STT, pupil diamater (PD) and IOP.

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METHOD

Ethics Committee permission was obtained for the study from Hatay Mustafa Kemal University, Experimental Animals Local Ethics Committee with the decision numbered 2023/03-03 and dated June 26, 2023. Six male New Zealand rabbits with a live weight of 550-650 grams were used in the study. The study was carried out in the Hatay Mustafa Kemal University Experimental Animal Laboratory between 09:00 and 11:00 in the morning. 0.1 milligram atropine sulfate solution (7,8) was topically administered as a single dose in the eye of each rabbit on seven day (14). STT, PD and IOP measurements were made before instillation of atropine and 30 minutes after instillation of atropine for seven days. PD was measured with a millimetric ruler, STT with strips, and IOP with Schiötz tonometer. The millimetric ruler was placed on the cornea, and the distance between the two irises was determined as PD in mm. STT strips were placed in the middle area of the lower eyelid and waited for one minute. At the end of one minute, the wetted amount on the strip was recorded as STT. For IOP measurement, the rabbit was laid on its back and its head was positioned appropriately. The Schiotz tonometer foot plate was placed on the cornea, and the value shown on the scale by the needle moving with the pressure applied by the plunger to the cornea was recorded. Since the Schiotz tonometer does not directly measure IOP, the scale values were converted to IOP values in mmHg using the conversion table provided with the device. These procedures were repeated for seven days.

Statistical Analysis

In this study, data were analyzed using SPSS 25 (Armonk, NY: IBM Corp.). Mean, standard deviation, minimum and maximum values were used for descriptive statistics. Wilcoxon signed-rank test, one of the non-parametric tests, was used in the statistical comparison of the measurements taken at two different times and situations of the dependent sample groups. Nonparametric Friedman's two-way analysis of variance was used for statistical comparison of measurement values on different days, meaning more than two dependent groups. The significance level for all tests was determined as $p<0.05$.

RESULTS

In this study, the effect of atropine used as eye drops on STT, PD and IOP was investigated; no systemic or ophthalmic symptoms or diseases were detected in the subjects. Atropine was used as eye drops for a week, and as a result of daily measurements, the seven-day average STT was 12.90±2.21 without atropine and 9.23±2.17 with atropine, respectively. The seven-day average PD was 0.26±0.06 without atropine and 0.71±0.15 with atropine, respectively. The seven-day average IOP was 13.95±1.60 without atropine and 17.60±2.25 with atropine, respectively.

In the daily statistical evaluation of daily measurements; There was a statistically significant difference in the STT measurement values of both left and right eyes of the atropine group compared to those who did not use atropine ($P<0.05$) (Table 1). Statistically significant differences were determined between the PD measurement values of both the left and right eyes of the groups with and without atropine ($P<0.05$) (Table 2).

In the IOP evaluation, although there was no statistically significant difference between the groups with and without atropine on days 2, 3, 4 and 5 regarding the left eyes ($P>0.05$), there was a significant difference on days 1, 6 and 7 regarding the left eyes. ($P<0.05$) (Table 3). In the IOP evaluation of the right eyes, there was a statistically significant difference between the groups with and without atropine on all days ($P<0.05$) (Table 3).

When the Friedmen test results were evaluated, in which we compared the days (comparing many dependent groups) in terms of relevant variables, no statistically significant difference was found between the days for the STT and PD measurement values of both left and right eyes without or with atropine ($P>0.05$).There was no statistically significant difference between the days in the IOP values of the right eyes with and without atropine ($P>0.05$). While there was no statistically significant difference between days in the IOP values of the left eyes with atropine ($P>0.05$), there was a significant difference between the days in the IOP values of the left eyes without atropine ($P<0.05$) (Table 4).

DISCUSSION

Atropine, an ophthalmic parasympatholytic drug, is widely used in both human and veterinary medicine. Mydriatic drugs are used for therapeutic purposes in a wide variety of ocular diseases and help prevent pupillary constriction (15). In this study, it was aimed to reveal the effect of atropine use for diagnostic purposes on the eye parameters STT, PD and IOP. The use of atropine as eye drops has complications such as pupil dilation, stinging sensation, eye pain, photophobia, and blurred vision (10,11). While STT, PD and IOP were evaluated in detail during the study, no other clinical symptoms such as pain or photophobia were observed. It has been reported that the use of atropine as eye drops has no effect on IOP (7, 8, 13). However, atropine or other anticholinergic agents may cause IOP elevation and are contraindicated in glaucoma

Table 1. Comparison of Schirmer tear test values (mm/min) of eyes with and without atropine administration*						
			Mean±Standart Deviation	Minimum-Maximum	Z	P
1st day	Left eye	Atropine	6.50±1.05	6-8	-2.214	0.027**
		Non-atropine	13.33±1.37	12-15		
	Right eye	Atropine	7.83±1.17	6-9	-2.201	0.028**
		Non-atropine	12.67±1.21	11-14		
2nd day	Left eye	Atropine	9.83±1.33	8-12	-2.264	0.024**
		Non-atropine	13.33±1.37	12-15		
	Right eye	Atropine	10.17±0.98	11-14	-2.041	0.041**
		Non-atropine	12.67±1.21	7-15		
3rd day	Left eye	Atropine	9±2.83	6-14	-1.892	0.058
		Non-atropine	12.00±3.10	9-11		
	Right eye	Atropine	8.67±2.34	5-11	-2.333	0.020**
		Non-atropine	11.17±2.71	7-14		
4th day	Left eye	Atropine	9.50±2.43	7-14	-2.023	0.043**
		Non-atropine	12.83±3.13	7-15		
	Right eye	Atropine	9.67±0.52	9-10	-2.207	0.027**
		Non-atropine	12.50±1.05	11-14		
5th day	Left eye	Atropine	8.67±2.16	6-12	-2.214	0.027**
		Non-atropine	13.33±1.86	11-15		
	Right eye	Atropine	10.17±0.98	9-11	-2.060	0.039**
		Non-atropine	12.50±1.05	11-14		
6th day	Left eye	Atropine	9±1.79	7-12	-2.214	0.027**
		Non-atropine	14.33±2.66	12-19		
	Right eye	Atropine	10.50±3.51	8-17	-2.207	0.027**
		Non-atropine	13.67±3.08	11-18		
7th day	Left eye	Atropine	10.17±1.94	7-12	-2.232	0.026**
		Non-atropine	14.00±1.55	12-15		
	Right eye	Atropine	9.67±2.16	7-11	-1826	0.068
		Non-atropine	12.33±1.03	11-14		
*Wilcoxon Signed Ranks Test. **p<0.05						

patients (16). Atropine used as eye drops may have a potential complication such as IOP elevation (10,11). Topical or intramuscular use of atropine sulfate increases IOP (17). On the other hand, other studies reported that atropine reduced IOP (15,16). The existence of different reports that atropine use has no effect on IOP, increases or decreases it, reveals the importance of this study. It is thought that these different notifications are related to the application times of atropine. It was reported that mydriasis lasted more than 14 days after administration of a single dose of 1% atropine sulfate ophthalmic solution to the normal horse eye (14). Therefore, it was thought that longer-term studies were needed to fully reveal the effect of atropine on IOP. In this study, atropine increased IOP. Although no difference was expected between the right and left eyes, there was an increase in IOP on all days in the right eye, while there was an increase on days 1, 6 and 7 in the left eye. More generalizable data may be obtained in repeated studies with larger sample sizes.

It has been reported that maximum PD occurs 30-60 minutes after topical atropine use in dogs, cats and cattle (17). In the literature review, pupillary dilation time was evaluated, yet no data on PD measurement were found. In this study, PD was determined as 0.26±0.06 without atropine and 0.71±0.15 with atropine.

Atropine has been reported to cause statistically significant

Table 2. Comparison of PD values (mm) of eyes with and without atropine administration*

			Mean±Standart Deviation	Minimum-Maximum	Z	P
1st day	Left eye	Atropine	0.65±0.10	0.5-0.8	-2.201	0.028**
		Non-atropine	0.32±0.11	0.2-0.4		
	Right eye	Atropine	0.63±0.08	0.5-0.7	-2.232	0.026**
		Non-atropine	0.28±0.04	0.2-0.3		
2nd day	Left eye	Atropine	0.65±0.10	0.5-0.8	-2.214	0.027**
		Non-atropine	0.27±0.05	0.2-0.3		
	Right eye	Atropine	0.63±0.08	0.5-0.7	-2.271	0.023**
		Non-atropine	0.27±0.05	0.2-0.3		
3rd day	Left eye	Atropine	0.57±0.08	0.5-0.7	-2.226	0.026**
		Non-atropine	0.23±0.05	0.2-0.3		
	Right eye	Atropine	0.83±0.24	0.5-1	-2.207	0.027**
		Non-atropine	0.23±0.05	0.2-0.3		
4th day	Left eye	Atropine	0.67±0.12	0.5-0.8	-2.226	0.026**
		Non-atropine	0.27±0.05	0.2-0.3		
	Right eye	Atropine	0.78±0.18	0.6-1.1	-2.201	0.028**
		Non-atropine	0.30±0.09	0.2-0.4		
5th day	Left eye	Atropine	0.68±0.18	0.5-1	-2.207	0.027**
		Atropinsiz	0.25±0.05	0.2-0.3		
	Right eye	Atropine	0.78±0.25	0.5-1.2	-2.214	0.027**
		Non-atropine	0.27±0.05	0.2-0.3		
6th day	Left eye	Atropine	0.70±0.14	0.5-0.9	-2.232	0.026**
		Non-atropine	0.25±0.05	0.2-0.3		
	Right eye	Atropine	0.83±0.19	0.6-1.1	-2.207	0.027**
		Non-atropine	0.23±0.05	0.2-0.3		
7th day	Left eye	Atropine	0.78±0.25	0.5-1.2	-2.207	0.027**
		Non-atropine	0.23±0.05	0.2-0.3		
	Right eye	Atropine	0.72±0.04	0.7-0.8	-2.233	0.020**
		Non-atropine	0.30±0.00	0.3-0.3		

*Wilcoxon Signed Ranks Test. **p<0.05

changes in various anterior segment parameters (13). It has been stated that the use of atropine inhibits aqueous humor flow in the Schlemm canal (16). It has been reported that atropine in dogs causes a statistically significant decrease in tear production in both eyes, and no statistically significant difference was detected in Schirmer tear test values between the left and right eyes (18). In this study, the mean STT value was determined as 12.90±2.21 without atropine and 9.23±2.17 with atropine. The effect of atropine, which is frequently used in veterinary medicine and human medicine, on ophthalmic parameters STT and PD was revealed with measurable values. It was determined that atropine use had an effect on eye parameters STT and PD with the first use, and its effect on IOP appeared after the fifth day.

Limitations of the study

There were some limitations in this study. The Schiötz tonometer and the Schimer tear test are accepted as the gold standard in eye studies. Nowadays, although tonopen studies have not become the gold standard for IOP measurements, they have become widespread. For IOP measurement, comparative studies with tonopen and the Schiötz tonometer and new studies to update the information can provide scientific contribution. Although STT measurement is considered to be the gold standard in pets, including humans, the routine reference parameters of the Schimer tear test in

experimental animals have not been fully established. It is understood that there is a need for studies to obtain both test paper and reference parameters for experimental animals.

Table 3. Comparison of IOP (mmHg) values of eyes with and without atropine administration*

			Mean±Standart Deviation	Minimum-Maximum	Z	P
1st day	Left eye	Atropine	16.95±2.22	14.6-20.6	-2.041	0.041**
		Non-atropine	12.60±0.98	12.2-14.6		
	Right eye	Atropine	20.82±7.08	14.6-34.5	-2.214	0.027**
		Non-atropine	13.40±1.31	12.2-14.6		
2nd day	Left eye	Atropine	17.95±2.30	14.6-20.6	-1.826	0.068
		Non-atropine	15.15±2.51	12.2-17.3		
	Right eye	Atropine	17.30±0.00	17.3-17.3	-2.041	0.041**
		Non-atropine	14.47±2.02	12.2-17.3		
3rd day	Left eye	Atropine	16.82±2.29	14.6-20.6	-0.756	0.450
		Non-atropine	16.10±1.64	14.6-17.6		
	Right eye	Atropine	17.32±1.43	14.6-18.9	-2.264	0.024**
		Non-atropine	12.60±0.98	12.2-14.6		
4th day	Left eye	Atropine	17.50±2.69	14.6-20.6	-1826	0.068
		Non-atropine	13.80±1.24	12.2-14.6		
	Right eye	Atropine	18.00±2.29	14.6-20.6	-2.214	0.027**
		Non-atropine	12.82±1.51	12.2-15.9		
5th day	Left eye	Atropine	17.05±2.25	14.6-20.6	-1.084	0.279
		Non-atropine	15.65±2.21	12.2-17.6		
	Right eye	Atropine	17.05±2.25	14.6-20.6	-2.214	0.027**
		Non-atropine	12.82±1.51	12.2-15.9		
6th day	Left eye	Atropine	17.72±2.45	14.6-20.6	-2.032	0.042**
		Non-atropine	14.30±2.00	12.2-17.6		
	Right eye	Atropine	18.15±1.24	17.3-20.6	-2.207	0.027**
		Non-atropine	13.40±1.31	12.2-14.6		
7th day	Left eye	Atropine	16.50±2.40	14.6-20.6	-2.041	0.041**
		Non-atropine	13.45±2.12	12.2-17.3		
	Right eye	Atropine	17.40±1.90	14.6-20.6	-1.992	0.046**
		Non-atropine	14.52±2.11	12.2-17.6		

*Wilcoxon Signed Ranks Test. **p<0.05

Table 4. Comparison of the difference between days in STT, PD and IOP values*

		P value		
		Schirmer tear test	Pupil diameter	Intraocular pressure
Left eye	Atropine	0.901	0.441	0.876
	Non-atropine	0.059	0437	0.017**
Right eye	Atropine	0.848	0.121	0.463
	Non-atropine	0.130	0.147	0.299

*Friedman's Two-Way Analysis of Variance. **p<0.05

CONCLUSION

In conclusion, it was determined that atropine decreased the STT value and increased the PD value in the eye, and increased the IOP value in long-term use. It is thought that longer-term studies are needed to fully reveal the effect of atropine on IOP.

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Peer-Review

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Ethics Committee permission was obtained for the study from Hatay Mustafa Kemal University, Experimental Animals Local Ethics Committee with the decision numbered 2023/03-03 and dated June 26, 2023. Thesis

Authorship Contributions

Concept: MSÇ, CTİ, Design: MSÇ, CTİ, Supervising: MSÇ, CTİ, Financing and equipment: MSÇ, CTİ, Data collection and entry: MSÇ, CTİ, Analysis and interpretation: MSÇ, CTİ, Literature search: MSÇ, CTİ, Writing: MSÇ, CTİ, Critical review: MSÇ

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ORIGINAL RESEARCH

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Analysis of laboratory parameters in non-traumatic epistaxis

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Abstract

Objective: The present study investigated the relationship between epistaxis and age, sex, hemogram and coagulation parameters and aimed to set a standard in the approach to epistaxis.

Method: Patients over the age of 18 who presented due to epistaxis between July 1, 2022, and July 1, 2023, were included in this study, and the files of these patients were examined retrospectively. Patients with trauma and chronic hypertension (HT), individuals with diseases that might predispose to bleeding and with a history of bleeding-related drug use such as coumadin derivatives or individuals with malignancy, those who were found to have active infection during the study, patients who were determined to be in the postoperative period, patients whose blood pressure was determined to be above 140/90 mmHg at the time of admission, and those who were found to have blood samples with hemolysis detected in the file records were excluded from the study.

Results: The data of a total of 100 patients, including 62 male and 38 female patients, who presented with complaints of epistaxis, were examined. It was found that more patients at older ages presented to emergency departments with complaints of epistaxis and the number of male patients with epistaxis was higher than female patients. It was concluded that headache is the most common early symptom before spontaneous bleeding in nosebleeds, which are more common in older adults, and platelet values, which are negatively correlated with age and positive correlated with activated partial thromboplastin time (aPTT) and hemoglobin (HGB) are an essential marker for nosebleeds. Furthermore, it was concluded that it is meaningless to check coagulation parameters in patients who are not coumadinized, while checking the hemogram remains important.

Conclusion: It should be kept in mind that headache is the most common early symptom before spontaneous bleeding in nosebleeds, which are more common in older adults, and that platelet values, which negatively correlate with age, are an essential marker for nosebleeds. Additionally, it was concluded that checking coagulation parameters is meaningless in patients who are not coumadinized, while checking the hemogram remains important.

Keywords: Nose bleed, hypertension, platelet, hemoglobin

INTRODUCTION

Epistaxis is a clinical condition that is frequently observed in emergency department admissions. Epistaxis, which has many different causes, can pose a life-threatening risk, although rare (1). Local factors such as trauma, foreign body, and inflammation may play a role in the etiology of epistaxis, as well as the use of some drugs, such as drugs for hypertension (HT), coagulation disorder, and anticoagulants. However, the rate of determining the exact causes is quite low (2). Various studies have investigated in which sex epistaxis occurs more commonly (3). Although epistaxis can occur in almost all age groups, it is observed more frequently at older ages (4). Epistaxis is a common clinical problem worldwide. However, since some attacks can resolve spontaneously or with self-treatment, it is difficult to determine their frequency precisely (5). Although most cases of epistaxis have mild symptoms and often resolve spontaneously, it can sometimes be life-threatening (6). Rarely, if uncontrolled, it can lead to life-threatening consequences, such as hypovolemia due to severe blood loss, cardiac failure, stroke, and aspiration (7,8). Causes of epistaxis can be local and systemic. The most common of local causes is trauma occurring through

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various mechanisms. Additionally, various infections, malignancies, and post-operative conditions may occur. Hypertension, bleeding disorders, cardiovascular diseases, and some drugs that cause bleeding may be systemic causes of nosebleeds. Digital trauma is the most common cause of local nosebleeds. Foreign objects, external trauma to the nose, and postoperative nosebleeds are the other sources of trauma (9,10).

This study investigated the relationship between epistaxis, which we frequently encounter in emergency departments, and age, sex, hemogram and coagulation parameters.

METHOD

Ethical permission was obtained from the Nigde Omer Halisdemir University, Non-Interventional Clinical Research Ethics Committee for this study with date December 12, 2023 and number 2023/127, and Helsinki Declaration rules were followed to conduct this study. Patients over the age of 18 who presented to the emergency department of Niğde Ömer Halisdemir Training and Research Hospital due to epistaxis between July 1, 2022, and July 1, 2023, were included in this study, and the files of these patients were examined retrospectively. Patients with trauma and chronic hypertension (HT), individuals with diseases that might predispose to bleeding and with a history of bleeding-related drug use such as coumadin derivatives or individuals with malignancy, those who were found to have active infection during the study, patients who were determined to be in the postoperative period, patients whose blood pressure was determined to be above 140/90 mmHg at the time of admission, and those who were found to have blood samples with hemolysis detected in the file records were excluded from the study. Laboratory tests were examined retrospectively from the file records. Hematocrit (HCT), platelet count (PLT), prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR) values were examined.

In the emergency department laboratory of our hospital: HCT normal value: 36-46%, PLT normal value: 150-450 10^3/(mcl), PT normal value:(Sec(50)) 8.40-10.6 seconds (sec), aPTT: 22.6-35.4 sec, INR: 0.93-1.16.

Statistical Analysis

All statistical analyses of the research data were performed using the IBM SPSS 22.0 program. The Kolmogorov-Smirnov analysis was performed to determine the suitability of the continuous (quantitative) variables to normal distribution indicated by measurement. Student's t-test was performed for comparison of means in continuous variables. Sperman correlation analysis was applied. P<0.05 was considered significant.

RESULTS

The 100 patients with complaints of epistaxis whose data were examined included 62 males and 38 females. In this study, the number of patients aged 18-59 was found to be 38 (%38), whereas the number of patients over the age of 60 was 62 (%62). It was observed that the mean age in male patients was (64.69±17.65) and the mean age in female patients was (61.92±13.58). In this study, the most common complaint at the time of admission was headache with 82%, the second most common complaint at the time of admission was dizziness with 17%, and 1% of the patients complained of fatigue. It was determined that male patients had higher values than female patients in terms of age, INR, HGB, and HCT values (p=0.4, p=0.13, p=0.09, p=0.09, respectively), and APTT, PTZ, INR, and platelet values were higher in female patients than male patients (p=0.22, p=0.01, 0.13, respectively). It is seen that only the PTZ value was statistically significant between sexes. All these relationships are presented in Table 1 and Figure 1.

Table 1. Relationships between parameters

Group		n	Mean±Standart Deviation	P value
Male	Age	62	64.69±17.65	0.40
Female		38	61.92±13.58	
Mean		100	63.64±16.21	
Male	APTT	62	26.45±3.81	0.22
Female		38	27.58±4.76	
Mean		100	26.88±4.21	
Male	PTT	62	10.43±0.92	**0.01**
Female		38	10.9±0.89	
Mean		100	10.61±0.93	
Male	INR	62	1.11±0.17	0.13
Female		38	1.07±0.1	
Mean		100	1.09±0.15	
Male	PLT	62	214.44±47.92	0.19
Female		38	226.55±43.2	
Mean		100	219.04±46.34	
Male	HGB	62	12.97±1.74	0.09
Female		38	12.38±1.64	
Mean		100	12.74±1.72	
Male	HTC	62	38.56±5.22	0.09
Female		38	36.76±5.19	
Mean		100	37.88±5.26	

Abbreviations: APTT, Activated partial thromboplastin time; PTT, Partial thromboplastin time; INR, International normalized ratio; PLT, Platelet count; HBG, Hemoglobin; HTC, Hematocrit

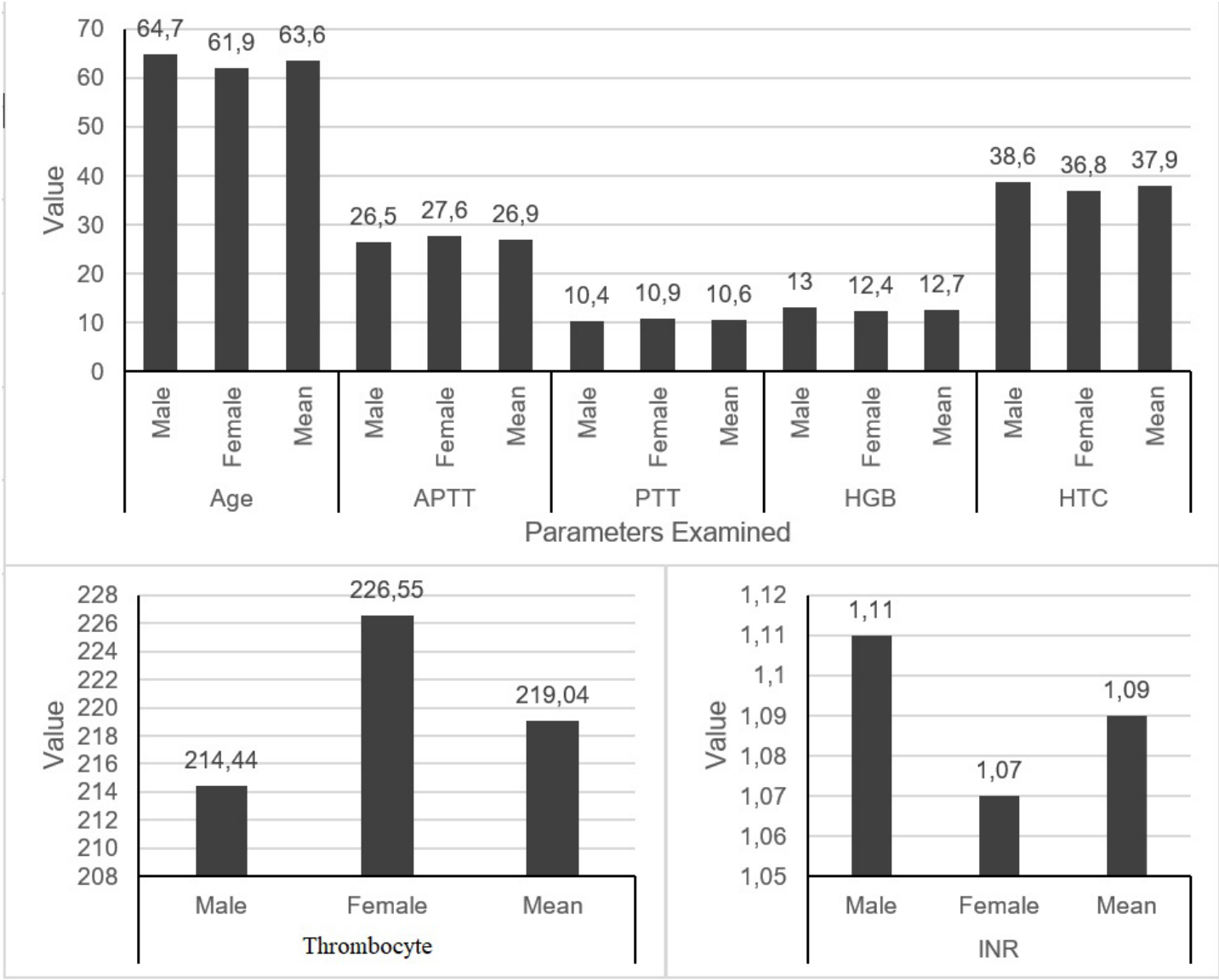

Figure 1. Relationship of laboratory parameters with age and gender.
Abbreviations: APTT, activated partial thromboplastin time; PTT, partial thromboplastin time; PLT, platelet count; HGB, hemoglobin; HTC, hematocrit; INR, International normalized ratio.

Pearson's correlation test was used to determine the correlation between quantitative data among all the parameters analyzed. The correlation analysis determined that age was negatively correlated with platelet value and platelet value was positively correlated with HGB and aPTT. Table 2 contains these correlations.

Table 2. Correlation of platelet and different parameters

Parameters		n	Correlation coefficient	P value*
Age	Platelet	100	-0.25	0.01
APTT			0.23	0.02
HGB			0.22	0.02

*Pearson correlation; APTT, activated partial thromboplastin time; HGB, hemoglobin.

DISCUSSION

One of the important findings of this study is that coagulation parameters (PT, PTZ, aPTT and INR) do not need to be routinely checked in non-coumadinized patients.

However, platelet counts are negatively correlated with age; in this context, the possibility of thrombocytopenia should not be ruled out in elderly patients presenting with epistaxis. In addition, there are various debates about the risk factors in patients with epistaxis presenting to the emergency department (7). Different studies have shown that age and sex may play a role in the etiology of epistaxis. Some studies have demonstrated that patients presenting to the hospital due to epistaxis can be of any age, but epistaxis is especially more common in individuals over the age of 50 and that the number of male patients presenting to the emergency department is usually higher than the number of female patients (11-13). In geriatric patients, systemic factors such as advanced age, bleeding disorders and hypertension are the most common causes of severe epistaxis (14). Likewise, in this study, the number of male patients (68) was higher than the number of female patients (32). However, patients with chronic diseases such as hypertension were not included in this study. On the other hand, this study had a higher proportion of elderly patients, and their coagulation values were high. In this study, the number of patients aged 18-59 was 38, whereas the number of patients over the age of 60 was 62.

Various studies investigating whether there is any correlation between nosebleeds and different blood parameters have been published recently. In a study by Ross et al. coagulapathy was found in approximately 17% of cases of epistaxis requiring intervention (15). In particular, complete blood count measurement has been used quite frequently. In contrast, some studies have reported no significant difference between hemoglobin, hematocrit, and platelet ratio and the frequency of epistaxis (16). Likewise, in the present study, we did not find a statistically significant correlation with hemoglobin, hematocrit, and platelet ratio in patients presenting with epistaxis. Various studies have also supported elevated PTZ and INR in epistaxis (17-19). However, study found coagulation markers to be within the normal range in the patient group. Furthermore, the INR value was higher in males, although it was within normal limits. Nevertheless, this difference was statistically insignificant. We think that the reason for this situation is that the study sample size was small. There are studies showing that epistaxis due to advanced age and thrombocytopenia is more common (20). Likewise, this study detected a negative correlation between age and platelet value. In this respect, this study is also compatible with the literature.

Some studies have stated that symptoms such as headache, tinnitus, and dizziness are observed due to epistaxis (21-22). This study also agrees with the literature. In the current study, the most common symptom was headache and, less frequently, dizziness and fatigue.

Limitations of the study

Undoubtedly, further studies on this subject will allow more data to be obtained. The limitation of this study is that the data were collected from a single hospital in the region. Moreover, since the study is retrospective, it limits the sample size of patients whose data cannot be accessed clearly.

CONCLUSION

It should be kept in mind that headache is the most common early symptom before spontaneous bleeding in nosebleeds, which are more common in older adults, and that platelet values, which negatively correlate with age, are an essential marker for nosebleeds. Additionally, it was concluded that checking coagulation parameters is meaningless in patients who are not coumadinized, while checking the hemogram remains important. We hope that this study will guide similar studies on the subject.

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The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Ethical permission was obtained from the Nigde Omer Halisdemir University, Non-Interventional Clinical Research Ethics Committee for this study with date December 12, 2023 and number 2023/127, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: ÖY, AV, TD, MOC, Design: ÖM, MCA, MÖ, Supervising: UA, DA, Financing and equipment: ÖY, TD, AV, Data collection and entry: ÖY, Analysis and interpretation: ÖY, AD, TD, Literature search: MCA, MÖ, Writing: ÖY, AD, TD, MD, MCA, MÖ, Critical review: ÖY.

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ORIGINAL RESEARCH

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Use of crystallized phenol in pilonidal sinus in the pediatric age group: a 5-year single surgeon experience

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Abstract

Objective: The Pilonidal Sinus (PS) is a pathology of the gluteal cleft that occurs with acute or chronic infection. This study aimed to report the evaluation of five-year experience with 50 patients' data outcomes of crystallized phenol in pilonidal sinus treatment (CP) pediatric age group.

Method: This retrospective study included 50 patients who underwent CP between 2017 and 2023 years. Patient demographics, operative data, follow-up findings, complications, and recurrence data were also evaluated.

Results: Fifty patients (female:31, male:19), mean of age 15,4 years. Hirsutism was diagnosed in 10 female patients (20%). Sixteen (32 %) patients had a family history of PS. Five patients had a smoking habit history (%10). The form of anesthesia was local anesthesia in eight patients (16%), sedation and local anesthesia in 27 patients (54%), and spinal anesthesia in 15 patients (30%). The average duration of the procedure was 13,8 min (10–22 minutes). The mean postoperative leakage time were 6,6 days. Complications were observed in five patients (10%). Recurrence was observed in three patients (6%). The overall cure rate is 94%.

Conclusion: The CP procedure should be used as the first choice, especially in adolescents, compared to the primary method in PS, such as total sinus excision, due to its minimally invasive, painless, low risk of recurrence, and very short postoperative recovery time.

Keywords: Pilonidal sinus, crystallized phenol, minimally invasive surgery, recurrence, complication

INTRODUCTION

Pilonidal sinus (PS) disease was firstly diagnosed by the finding of a characteristic epithelial tract situated in the skin of the natal cleft, a short distance behind the anus and generally containing hair by Hodges in 1880 (1). PS is an infectious and inflammatory disease frequently observed in young men. The disease is mostly seen in children who have hair on the gluteal sulcus, are obese, have poor hygiene, and spend most of their time sitting, like students (2). The incidence of PS is 0,26% (3). İn the pediatric age group incidence reported as 1,2-2/10,000 (4). The treatment of PS with primary and secondary flap methods is accompanied by local curettage, phenol application, electrocauterization, and total sinus excision. A treatment method with a shorter healing time, better cosmetic results, and lower recurrence rate has been discussed since the nineteenth century. In recent years, there has been a persistently high rate of recurrence and wound complications associated with PS, and there is still no universally agreed treatment. Crystallized phenol application is a minimally invasive treatment with no hospital stay and good cosmetic results (5).

In this study, we evaluated the minimally invasive treatment of PS with crystallized phenol in the pediatric population.

METHOD

This study included pediatric patients with PS who were treated with crystallized phenol. The patients' medical data were retrospectively analyzed. Written informed consent was obtained from the legal guardians of each child, and Ethical Committee Approval was obtained for the study (Ordu

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University Clinical Research Ethical Committee -2021/78).

Patients data

Fifty patients diagnosed with pilonidal sinus disease between 2017 and 2023 were retrospectively reviewed. No patient was excluded from the study among the 50 patients followed up. The reviewed parameters included patients' demographic data, age, sex, presence of hirsutism in female patients, additional chronic diseases, family history, history of smoking, form of anesthesia, duration of the procedure, postoperative leakage duration, complications, and recurrence data (Table 1).

Table 1. Patients' demographics and results

Gender (n (%))	**Female**	31 (62%)
	Male	19 (38%)
Mean of age (years)		15,44
Hirsutism (n (%)) (Mean of Ferriman-Gallwey Score)		10 (20%), 16,7
Family history (n (%))		16 (32%)
Smoking habit (n (%))		5 (10%)
Form of anesthesia (n(%))	Only local anesthesia	8 (16%)
	Sedation and local anesthesia	27 (54%)
	Spinal anesthesia	5 (30%)
Average duration of the procedure (minutes)		13,8
Mean of postoperative leakage time (days)		6,6
Complication (n (%)		5 (10%)
Recurrence (n (%)		3 (6%)
Time of recurrence (months)		5,6

All patients were admitted to our clinic with a history of wound leakage, abscesses, and severe pain. Patients who had sinuses with purulent discharge and inflammatory signs or abscess formation were considered to have acute pilonidal disease. Active infections or abscesses were treated with antibiotics three weeks before the procedure. All procedures were performed by the same surgeon with the same technique. The anesthesia type (only local, sedation and local, spinal) of the procedure was argued and decided by the anesthesiologist and patient together.

Preparation and application of crystallized phenol

Regional hair cleaning was performed before the procedure as part of both preoperative preparation and treatment because of regional hair growth, which is the most important Reason for PS. Before the procedure, a single dose of prophylactic antibiotics was administered.

The patient was placed in a prone position and cleaned with an antiseptic solution. Subsequently, local/sedation/spinal anesthesia was initiated. Prior to the procedure, a local anesthetic (2% lidocaine solution) was injecte subcutaneously into the cavity. The sinus orifices were widened using a mosquito clamp (BH-109 Aesculap®, Aescuplap Werke AG, Tutlingen, Germany).

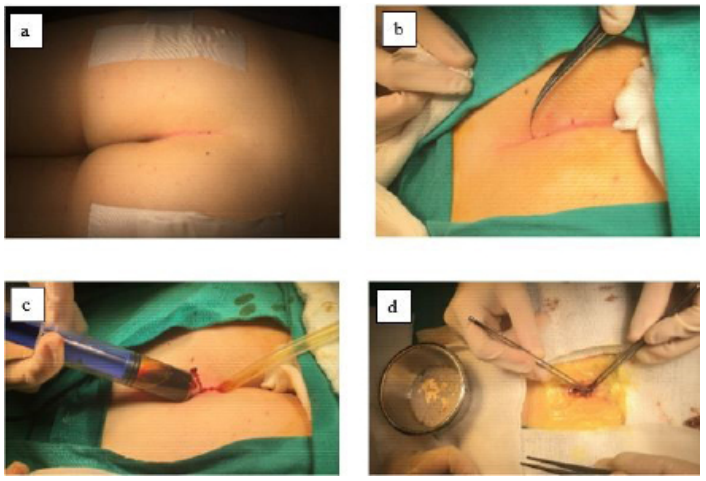

Figure 1. a, surgery field preparation, **b**, hair cleaning from inside the sinus. **c**, washing the sinus with povidone iodine. **d**, crystalline phenol application.

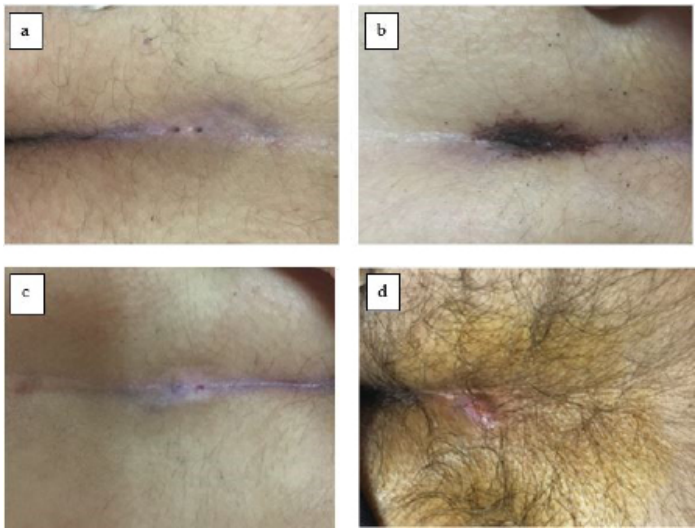

Fig.2. a, preoperative two fistula view. **b**, postoperative 1st day. **c**, postoperative 10th day. **d**, FG score-17, İdiopathic hirsutism patient.

If the sinus could not be dilated sufficiently, a vertical incision was made with clamp orientation. The hair materials in the cavity were cleaned with the help of the forceps and the sinus size was revealed. Povidone iodine and saline washes were performed using an anjiocath catheter. A barrier of skin was

formed with an oily pomade to prevent burns on the skin of the sinus circumference, and the anus was protected with sterile gauze.

Crystallized phenol (Phenol, Emprove®, Merck, Darmstadt, Germany) is a white crystalline solid substance that should be kept in glass bottles, and sunlight should be avoided. Owing to the serious properties of the substance, a face mask, eyeglasses, gloves, and a surgical gown with long sleeves should be worn during use. Crystallized phenol is solid at room temperature, but becomes liquid when applied to the skin.

Phenol was filled into the sinus with the help of Volkmann's spoon. During the procedure, liquid phenol flowing into the surrounding area was aspirated. Crystallized phenol reacts with the sinus and creates a blackish–dark brown color on the sinus surface. After the process, the area was closed with nitrofurantoin ointment (Furacin® Eczacıbası Ilaç San. ve Tic. A.S., Istanbul, Turkey) dressing. After the procedure, the patient was kept in a prone position for observation until oral feeding was initiated (Figure 1).

Preoperative and postoperative images of phenol applied patients were shown in Figure 2 and depicts a girl with hirsutism.

Postoperative follow-up and care

Oral intake was started one and half hours postoperatively. The need for analgesia was not observed, but anti-inflammatory use for one day was recommended for patients who underwent spinal anesthesia. The patient was discharged the same day. The dressing was removed on the first postoperative day. In the postoperative period, we recommended nitrofurantoin ointment twice a day and daily area cleaning with soap until the wound was dry.

Patients were evaluated on the first postoperative day, week, and month.

Statistical Analysis

SPSS® 10.05 for Windows (SPSS, Inc., Chicago, IL) computer program was used for statistical analysis, which was then evaluated by the descriptive statistics.

RESULTS

The average age of the 50 patients was 15.44 (10-17 years old). The female/male ratio of patients was 31/19. Ferriman-Gallwey (FG) score was measured in 10 (20%) female patients because of pathological hair growth, and further evaluation was performed to diagnose hirsutism. The mean FG score was 15.44. Three patients had polycystic ovary syndrome. In the operative evaluation, one fistula was observed in 37 patients, two was in 10 patients and three fistulas in 3 patients. One patient had a history of ureteropelvic junction obstruction and one patient had moderate mitral valve insufficiency. Sixteen patients (32%) had a positive family history of PS. Five patients had a smoking habit history (%10). The form of anesthesia was local anesthesia in eight patients (16%), sedation and local anesthesia in 27 patients (54%), and spinal anesthesia in 15 patients (30%). Average duration of the procedure was 13.8 min (10 to 22 min). Mean of postoperative leakage time was 6.6 days.

The patients were followed-up for an average of 13 months postoperatively. During the postoperative period, gluteal sulcus hair cleaning and the importance of personal hygiene were explained to the patients and their families.

Complications were observed in 5 patients. (10%). Three patients had prolonged leakage (2 weeks), which was diagnosed as a secondary infection and treated with oral antibiotics. Two patients had headaches secondary to spinal anesthesia. No recurrence was observed during the follow-up of these patients.

Recurrence was observed in 3 patients (6%). One male patient presented to the clinic three months postoperatively because of a sinus originating from a different location. This patient had a history of smoking. The patient was excluded from follow-up at his request. A female patient with hirsutism presented to the clinic with an abscess during the postoperative 1st year. The patient's hirsutism continued, and she did not undergo hair cleaning or laser hair removal. The patient was treated with antibiotic therapy, followed by drainage. After 3 weeks, the CP procedure was repeated. No recurrence was observed at postoperative 1-year follow-up. A male patient presented to the clinic with PS, which had the appearance of two fistulas. After the operation, protruding scar tissue developed at the orifice of one of the fistulas, and resistant leakage occurred. Two months after the operation, a secondary session was planned with excision of the scar tissue. No recurrence was observed in the postoperative 1-year follow-up. The overall cure rate was 94%.

DISCUSSION

As in the entire pediatric surgical approach, minimally invasive treatment protocols stand out in pilonidal sinus treatment. Pilonidal sinus surgery options have recently been used in pediatric surgeries, such as excision and primary closure, rhomboid excision and Limberg flap, marsupialization, and cleft lift procedures. Maurice and Greenwood first described local injection of liquid phenols in 1964 (6). This technics success rate was reported to be

between 59 and 93 percent (7, 8). The use of crystallized phenol was first published in the literature in 2004 by Dogru et al. (9), and its success rate was found to be much higher (95%) with crystallized phenol than with liquid injection. Reason why the crystallized phenol technique has been frequently preferred in recent years with no incision, no surgical procedure requiring suture, good pain control, easily accessible material, low cost, postoperative same-day return to active life, and recurrence rate is not different from open surgery.

Hirsutism is an important factor in the etiology of PS. Pilonidal disease often occurs after the onset of puberty when sex hormones stimulate pilosebaceous glands and body hair growth. Entrapped hair follicles become infected and require antibiotic treatment, with a recurrence rate of >30% (10). The American Society of Colon and Rectal Surgeons published in 2017 about pilonidal sinus in the literature; In order to prevent pilonidal diseases, it is recommended that hairs in the gluteal sulcus should be shaved or chemically depilated every 2-3 weeks until 30 years of age (11). In our study, 20% of the female patients were diagnosed with hirsutism. In the evaluation of this symptom, idiopathic results were determined and associated with ethnic and genetic factors. Gluteal sulcus hair removal was performed in 8 of the 10 patients with idiopathic hirsutism at the postoperative 3-year follow-up, and no recurrence was observed in any of these patients. Recurrence was observed in one patient because of not paying attention to hair cleaning and poor personal hygiene and was treated with the secondary CP method. No recurrence was observed during the 2-year follow-up. The recurrence rate was 10% in the patients diagnosed with idiopathic hirsutism.

It has been shown in the literature common PS risk factors such as gender, smoking, obesity, family history, excessive hairiness, diabetes mellitus, hair color, sweating, dermatological diseases and personal hygiene.

Family history was a risk factor for PS. Yildiz et al. published a risk factor for PS in teenagers, and 52% of the patients had a family history of PS disease (12). In our study, we found that family history posed a high risk (32%) of PS development.

In a study by Ates et al., excision, primary closure, and phenol application were compared. Complications (10.4% vs. 2.5%) and recurrence rates (13% vs. 2.5%) have also been reported (13). In Dogru et al.'s phenol application study of 41 patients, the recurrence rate was 17.1% (9). In our study, success and recurrence rates were 94% and 6 %, respectively. We would like to emphasize that the slightly higher complication rate in our study was due to the side effects of spinal anesthesia. As observed from the study data, we believe that spinal anesthesia is unnecessary in this group of patients. Additionally, in our study, a persistent discharge duration of longer than 2 weeks was considered a complication. However, in a similar series, this period was accepted as 30 days (14). Therefore, we believe that our complication rate is lower than that reported in the literature.

In this study, patients admitted to our clinic with PS were discharged on the same day. On the first postoperative day, the dressings were opened, and the patients were able to return to their active lives. We observed that patients who applied to our clinic with a diagnosis of PS preferred the CP procedure over other methods and were satisfied in the postoperative period.

Limitations of the study

The limitations of the study include the partially low number of patients and the fact that the study method was based on data from a single center and a single technique.

CONCLUSION

PS is frequently observed in adolescents. Although there are various treatment methods, a definitive treatment algorithm is not yet available. We believe that the crystallized phenol method should be used as the first choice, especially in adolescents, compared to primary methods such as total sinus excision because of its minimal invasiveness, painlessness, low risk of recurrence, and short postoperative recovery time.

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Conflict of Interest

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Ethical Declaration

Ethical permission was obtained from the Ordu University Clinical Research Ethics Committee for this study with date April 4, 2021 and number 78, and Helsinki Declaration rules were followed to conduct this study.

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ORIGINAL RESEARCH

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Cardiac and major vascular injuries due to chest trauma: insights from a five-year experience

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Abstract

Objective: In this study, it was aimed to determine the incidence, clinical presentation, diagnostic approaches and effective surgical treatment of penetrating thoracic injuries involving the heart and major vessels.
Method: One hundred and twenty-six patients, who had chest trauma between January 2015 and January 2019 were evaluated. The relationship between findings at the time of admission and postoperative patient status was attempted to be revealed.
Results: The mean age of patients included in this study was 27 ± 6.1 years. The stab injury was the most common mechanism of injury (n=76, 60.3%).The most commonly injured organ was found to be the heart with 56 patients (44.4%).The preoperative mean arterial pressure of patients transferred to the intensive care without mechanical support was 82 mmHg (range: 0–135 mmHg), while it was at 65 mmHg (range: 0–112 mmHg) for patients who died during the operation ($p < 0.001$).The hemoglobin values of patients who lived and died at admission were 6.9 mg/dl (range: 4.1–11 mg/dl) and 5.6 mg/dl (range: 2.8–10.1 mg/dl), respectively ($p<0.001$).
Conclusion: It is possible to predict mortality by evaluating complete blood count, systolic blood pressure, and site of injury at admission. Success can be achieved with accurate diagnosis, resuscitation, and early surgical interventions.
Keywords: Cardiac injury, chest trauma, vascular injury, thorax penetration

INTRODUCTION

Trauma has been identified as one of the leading causes of morbidity and mortality worldwide. Thoracic traumas account for 10%–15% of all trauma cases, and 75% of trauma-related deaths are associated with chest traumas [1]. Thoracic injuries can affect the chest wall, lungs, esophagus, heart, and large vessels. Blunt or penetrating thoracic traumas are two important causes of long-term hospitalization. They end up with a serious mortality rate at between 15% and 75% worldwide [2]. Penetrating thoracic traumas have been identified as significant causes of morbidity and mortality due to accompanying organ injuries. 30% of all chest traumas are identified as penetrating injuries which often lead to morbidity and mortality because of vital organ neighborhoods [3]. Approximately 10.4% of trauma patients requiring emergency surgery are chest injuries, and approximately 1% of these are heart injuries [4]. Only 6% of patients can reach the medical centers alive for treatment even though medical centers' experiences in treating trauma and much easier access to medical centers have increased the survival rates in recent years [5]. The injured organ may not be clearly evaluated just by looking at the location of the injury. There may be different injuries from intrathoracic organs under the anterior breast line. In the first evaluation, auxiliary diagnostic methods are life-saving in terms of detecting additional injuries that may be overlooked.

Increased penetrating chest injuries due to population in Turkey has become a particularly important factor in the death of the young population. Studies examining different factors of thoracic penetrating trauma are few [6].

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The incidence, clinical presentation, approaches for diagnosis, and treatment of penetrating thoracic injuries affecting the heart and its major vessels are revised in this study from the experiences of a high-volume trauma center in Istanbul that city having the highest population density in Türkiye.

METHOD

Ethical disclosure

This study has been done in accordance with the ethical guidelines set by the Helsinki Declaration and the International Association of Heart and Lung Transplantation (ISHLT). A retrospective study was made by obtaining signed documents and approvals from all patients for procedures, including the approval of the use of patient data in future retrospective studies. 2019/535 numbered, 12/04/2019 dated ethics committee permission from Istanbul University is available for this study.

Background and patients

Patients who had penetrating chest traumas admitted to our center between January 2015 and January 2019 were evaluated. This study was conducted in accordance with the 1964 Helsinki Declaration. Informed consent was obtained from all subjects, and all methods were carried out in accordance with the relevant guidelines and regulations. After explaining the interventions, including risks and benefits in detail as a policy of Turkish health system, informed consent was obtained either from the patient who was conscious or from their relatives before the procedure. All patients over the age of 16 with cardiac or major vascular injuries were included in the study. Patients who did not respond to resuscitation, who were operated due to isolated venous injury and who were treated with conservative or endovascular interventional methods were excluded from the study. Demographic characteristics, injury types, symptoms and comorbidities of the patients were included in the study. While angiographic computed tomography (CT) was applied to hemodynamically stable patients at the time of admission, focused assessment with sonography in trauma (FAST) or focused assessment with transthoracic echocardiography (FATE) methods were used to evaluate unstable patients (Figure 1.a).

The duration of stay in the postoperative intensive care unit and extubation, the amount of drainage and complications that developed were recorded. Thoracotomy or sternotomy was applied to all patients with penetrating cardiac or major vascular injuries due to bureaucratic difficulties in applying endovascular treatment in our medical center.

Statistical Analysis

The results were analyzed using SPSS version 15.0 (Statistical Package for the Social Sciences Inc, Chicago, USA). Numerical variables were expressed as the mean ± standard deviation or minimum and maximum, while categorical variables were presented as absolute values and percentages. For categorical variables, proportions were compared using Fisher's exact test or chi-squared test as appropriate. A p-value less than 0.05 with 95% confidence interval was considered statistically significant.

RESULTS

Over a 5-year period, 1128 penetrating chest trauma admitted to our center. 126 patients (98 males and 28 females) with cardiac and/or major vascular injuries were included in the study. The mean age of the patients was 27±6.1 years. The admission to emergency was made in an average of 24 minutes (6–41 min.) after the injury. Heart rate, mean arterial pressure (MAP) and hemoglobin (Hb) values at presentation were 87 bpm (0-164 bpm), 78 mmHg (0-135 mmHg), and 6.5 mg/dL (2.8–11 mg/dL), respectively. Preoperative MAP was 82 mmHg (0-135 mmHg) in rescued patients, while it was 65 mmHg (0-112 mmHg) in patients who died during surgery ($p<0.001$). Mean hemoglobin (Hb) values of surviving and deceased patients at admission were 6.9 mg/dL (4.1-11 mg/dL) and 5.6 mg/dL (2.8-10.1 mg/dL), respectively ($p<0.001$).

Injury types were determined as vehicle accident, gunshot injury, stab wounds, falling from heights and explosion injuries (Table 1). The most frequently injured organs were the heart, ascending aorta and aortic arch, pulmonary artery, descending aorta, and primary branches of the aortic arch (Table 1). In addition, data on accompanying bone and lung injuries are given in Table 1.

The diagnosis was made with clinical evaluation in 23 (18.25%) patients. While 98 patients (77.8%) were admitted with hypovolemic shock state, remaining 28 (22.2%) patients had a systolic blood pressure above 70 mmHg. While patients who entered hypovolemic shock were directly taken into operation, the remaining 28 patients with stable findings were evaluated with preoperative CT angiography and echocardiography (Figure 1).

Left thoracotomy was performed in 86 (68.25%) patients, sternotomy in 26 (20.6%), and right thoracotomy in 14 (11.1%). Data on cardiopulmonary bypass (CBP) and operation times are presented in Table 2. The primary goal in patients was to remove the tamponade clinic by opening the pericardium (Figure 2). The patients were taken under cardiopulmonary bypass (CPB) by determining the bleeding focus and applying direct heart massage according to the need for resuscitation. Of these patients, 11 had ascending aorta injury, three had

Table 1. Demographics and clinical characteristics of patients according to their survival status

		General	Survived	Not survived	P value
Age		27.1 ±6.1	27.4 ±5.5	25.9 ±7.1	0.203
Sex, n (%)	Men	98 (77.8)	75	23	
	Women	28 (22.2)	12	16	
Cause of injuries, n (%)	Stab injury	76 (60.3)	67	9	0.99
	Car accident (in the car)	19 (15.07)	11	8	0.45
	Gunshot	18 (14.28)	5	13	0.030
	Falling	7 (5.55)	2	5	0.035
	Car accident (out of the car)	4 (3.17)	1	3	0.032
	Explosion	2 (1.58)	1	1	0.052
Injured organs, n (%)	Heart*	56 (44.4)	39	17	0.70
	Ascending aorta & arch	26 (20.63)	12	14	0.048
	Pulmonary artery	22 (17.46)	19	3	0.84
	Descending. aorta	14 (11.1)	11	3	0.69
	Right subclavian artery	6 (4.76)	5	1	0.76
	Left subclavian artery	2 (1.58)	1	1	0.044
Bone Fractures, n (%)	Costa	50 (39.6)			
	Clavicula	4 (3.17)			
Lung injuries, n (%)		32 (25.39)	22	10	0.67
Clinical and laboratory parameters	Hemoglobin (Hb), median mg/dl (range)	6.5 (2.8-11)	6.9 (4.1-11)	5.6 (2.8-10.1)	0.044
	Systolic blood pressure, median mmHg (range)	78 (0-135)	62	38	0.002
	Heart rate median beats per minute (range)	87 (0-164)	94	13	0.016
Admission time		24 ±7.2	22 ±4	30 ±9.5	<0.001

*Heart injury; 24 right ventricle, 13 right atrium, 11 left ventricle, 7 left atrium , 1 vena cava

Table 2. Operation time according to cardiopulmonary bypass (CPB) done

	CPB (n=15)	None CPB (n=111)
Operation time, mean	98±16 (78-185)	72±21 (43-127)
Operation	3 patient dacron patch, 1 patient dacron greft side to side anastomosis	87 patients pericardial pledgets 24 patients - teflon pledgets repair

direct ventricular injury, and one had pulmonary arterial injury (Table 2). In three patients with ascending aortic injury, the Dacron patch was applied using by a large Satinsky clamp under CPB. A patient with serious damage to the main and right pulmonary artery was treated with Dacron graft (16 mm) interposition. After controlling of bleeding in 111 (88.1%) patients, pericardial (n = 87) or Teflon packs (n = 24) were used for primary repair (Figure 2). Three patients died before surgery due to multiple cardiac injuries (totally two of left ventricle and one of vena cava superior damage) and eight patients died due to ascending aortic root injuries. three patients were re-operated at the postoperative 1st hour due to hemorrhage.

Patients were evaluated with echocardiography within the first 24 hours postoperatively. Ventricular septal defect was found in two patients who underwent cardiac injury repair. In the postoperative period, 28 of 115 patients died of severe ARDS, multiple organ dysfunction syndrome or sepsis. The average hospital stays of discharged 87 (69.04%) patients was 12.1±3.7 days.

At the 1st month follow-up, the ejection fraction (EF) of 81 patients was 61±8.9% (48-83%). It was observed that ventricular septal defects due to heart injury closed spontaneously.

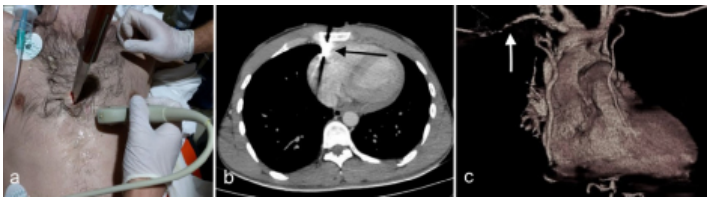

Figure 1. a) Evaluation with FATE in the emergency room, **b)** Right ventricular injury, CT angiography (black arrow), **c)** Right subclavian gunshot injury, CT angiography, 3D imaging (white arrow)

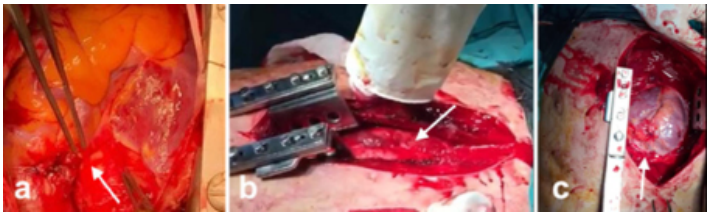

Figure 2. a) Pulmonary artery repair with pericardial plaget (white arrow), **b)** Penetrating left atrial injury, cardiac tamponade (white arrow), left thoracotomy, **c)** Pericardiectomy and resolution of cardiac tamponade (white arrow)

DISCUSSION

Penetrating chest trauma affects young male population more in rising communities [7]. It may cause serious socioeconomic problems due to its long hospitalization and permanent morbidity, but there is no defined treatment algorithm yet [8]. Penetrating thoracic injuries are less common than blunt thoracic injuries, and only less than 10% of patients can reach the hospital alive [9]. It is thought that 10% of deaths due to penetrating chest injuries are preventable. According to the literature, most of the patient group consists of young male population. Our patient group was also male in line with the literature, and the mean age was 27 (±6.1) [10].

Penetrating thoracic trauma often affects the lungs, heart, and great vessels [11]. 56 of our patients had cardiac injuries, 40 had aorta (26 ascending aorta, 14 descending aorta), 22 had pulmonary artery and eight had aortic arch injury (six right subclavian artery, two left subclavian artery). Additional bone fractures and parenchymal lung injuries were also detected in 54 and 32 patients, respectively.

Because this group of patients is generally not hemodynamically stable, the diagnosis is made by physical examination, history, and clinical findings, and there is no gold standard [12]. Chest radiography of only 25-50% of thoracic trauma cases is diagnostic. Findings such as air-fluid levels in the chest can guide the diagnosis. In a small number of patients who are hemodynamically stable, further examinations such as computed tomography can be performed to clearly visualize the injury [13]. The general algorithm recommends taking unstable patients directly into the operating room. X-ray imaging, CT angiography and FATE can be performed in stable patients. We took 23 patients directly to the operation room due to hemodynamic instability. CT angiography was performed in 28 stable patients, and FAST or FATE was performed immediately in the operating room for 75 patients.

In the literature, hypotension and heart rate at presentation have been defined as the main factors defining mortality [14]. Tachycardia in the presence of hypotension is the most prominent finding of hypovolemia. [12]. In line with the findings reported by Ceviker K. et al, our patient group also showed a significant difference in the MAP, heart rate, and Hb values at the time of admission between patients who died during the operation and those who survived.

There are studies showing that the most common cause of thoracic injuries is knife and gunshot injuries with 38.3% [13]. Particularly in gunshot injuries, the trajectory of the bullet can be very atypical. A remarkable example is presented by Ecevit A et al. in their case report where a bullet entered the left ventricle, then dropped into the ventricular cavity, and subsequently embolized to the right coronary artery, causing an inferior myocardial infarction [15]. The presence of cardiac or major vascular injury is the cause of serious mortality, but there are no studies showing the relationship between the type of injury and mortality [16]. In this study, nine (23.07%) patients with a sharp object, 11 (28.2%) patients due to a car accident, 13 (33.3%) patients with firearms, one (2.56%) patient with explosive materials, and the remaining five (12.8%) patients the patient was injured and died due to a fall from a height. Of the patients who survived, 67 (77%) were injured with a sharp object, 12 (13.79%) due to a car accident, five (5.74%) with a firearm, 2 (2.29%) falling from a height and one (1.14%) was injured by explosive materials.

Although endovascular treatment methods gradually manifest themselves in large vessel injuries, surgery is widely used in experienced cardiac surgery centers. Rarely, conservative follow-up can be performed in cases of minimal venous injury or minimal damage to the pulmonary artery [17]. The mortality rate reported in patients operated on in the literature ranges from 7% to 65% [18]. The medical center does not have the capability to perform endovascular treatment. In this study, 28 (24.3%) of 115 patients who were operated died due to various reasons mentioned above. In

line with this result, it was found that our mortality rate in cardiovascular trauma is relatively low.

Operation with CPB or extracorporeal membrane oxygenation (ECMO) may be preferred, especially in coronary artery injuries and heart valve injuries with myocardial injuries. ECMO has been recommended for trauma patients in recent years. The most common complication of ECMO is bleeding, and trauma patients have an increased risk of uncontrolled major bleeding. Therefore, experience is limited [19,20,21]. Only a few studies have found that ECMO support has a positive effect on the overall survival of patients who develop hemorrhagic shock from trauma and bleeding [22,23,24]. We did not use ECMO in our own patients since our intervention time to CBP was short enough.

Existing complications are an effective indicator of prognosis, which may affect the long-term survival of trauma patients. Bronchopleural fistula, empyema, and wound infections are identified as the most common complications. In this study, 3 (2.38%) patients were reoperated for hematoma in the first 24 hours. In elective thoracic surgical procedures, the reoperation rate has been found to be between 4 and 5%, and this rate has not been reported for emergency cases in the literature [25].

Limitations of the study

The limitations of this study include both the relatively small patient sample size and the exclusion of endovascular treatments. Addressing these limitations would require larger, more comprehensive studies that incorporate a broader range of treatment modalities. Such expanded research efforts would provide more robust data on the efficacy of various therapeutic approaches and offer clearer guidance for future clinical practice.

CONCLUSION

As a result, the ribcage often contains vital organs affected by penetrating injuries. Timely and correct intervention in these patients is lifesaving. It is possible to predict mortality by evaluating complete blood count, systolic blood pressure and injury site at presentation. However, patients who are hemodynamically unstable should be treated with FATE or FAST imaging without losing time. Additional examinations and imaging can be performed for more accurate intervention in patients who are hemodynamically stable. We anticipate that surgical methods other than hybrid or endovascular methods can be applied more easily and will be lifesaving in centers that are sufficiently experienced in terms of rapid and effective intervention. Emergency endovascular treatment may be beneficial in terms of mortality in centers with an adequate hybrid system. In addition, we think that the number of patients who need CBP is relatively low, as in our patient group. In case of necessity, we think that to provide hemodynamic stability and to stop bleeding, it is necessary to intervene with thoracotomy in the emergency room, and repair in operating room conditions after stabilization is achieved.

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Peer-Review

Both externally and internally peer reviewed.

Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Ethical permission was obtained from the Istanbul University Medical Faculty Clinical Research Ethical Committee for this study on April 4,2019 and number 2019/535 and Helsinki Declaration rules were followed to conduct this study.

Athorship Contributions

Concept: İD, Design: İD, Supervising: İD, DY, SÖ, Financing and equipment: İD, DY, SÖ, Data collection and entry: İD, DY, SÖ, Analysis and interpretation: İD, DY, SÖ, Writing: İD, Critical review: İD, DY, SÖ

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ORIGINAL RESEARCH

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A retrospective analysis of non-operating room anesthesia practices at a university hospital

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Abstract

Objective: The use of non-operating room anesthesia is increasing due to its advantages in procedure success and patient management. This study aims to retrospectively evaluate the complication rates and patient outcomes in non-operating room anesthesia practices at a university hospital over a two-year period.

Method: After obtaining ethical approval, the records of patients who underwent sedation-analgesia outside the operating room for diagnostic and therapeutic purposes between 2018 and 2020 were retrospectively analyzed. Recorded data included age, gender, weight, American Society of Anesthesiologists (ASA) physical status classification, comorbidities, types of procedures, anesthesia and recovery times, medications used, and complications.

Results: A total of 1199 patients were included in the study, with 759 (63.3%) adults and 440 (36.7%) pediatric patients. The patient group comprised 829 (69.1%) female and 370 (30.9%) male, with a mean age of 35.62 ± 28.69 years (0-98). Of the patients, 547 (46.1%) were in the ASA 2 risk group. The most common procedure was Magnetic Resonance Imaging (MRI) 541 (45.1%). The most frequently used anesthetic regimen was a combination of midazolam, propofol, and ketamine 840 (70.1%). Hypotension was the most common complication 44 (3.7%), followed by bradycardia 38 (3.2%). Hypertension was the most frequently 144 (12.0%) observed comorbidity.

Conclusion: The frequency of non-operating room anesthesia procedures is steadily increasing due to growing patient and surgeon satisfaction. Comprehensive preanesthetic evaluations, ensuring appropriate physical conditions and patient-specific drug selection are crucial for appropriate and rapid interventions for possible complications.

Keywords: Non-operating room anesthesia practices, pre-anesthetic evaluation, sedation, anesthetic agents, complications

INTRODUCTION

Providing sedation or general anesthesia to patients for painful or uncomfortable procedures outside the operating room is described as non-operating room anesthesia (NORA) (1). NORA procedures are increasingly preferred for both diagnostic and therapeutic purposes. Factors that play a role in choosing NORA include independence from hospital bed capacity, lower nosocomial infection rates, more efficient operations, and reduction of costs. Additionally, advancements in technology have enabled more complex and invasive interventions in NORA settings (2). Current research predicts that within the next decade, NORA practices will account for 50% or more of all anesthesia procedures (3). NORA is frequently applied in endoscopy suites, interventional cardiology labs, radiology settings, pain management procedures, intensive care units, electroconvulsive therapy, and dental offices (4). Anesthesia techniques in non-operating room areas vary from monitoring alone to general anesthesia. These methods reduce or completely eliminate the patient's anxiety and pain, ensure immobility, and increase the success of the procedure, especially in young children and uncooperative adults. However, inadequate sedation/analgesia may lead to patient distress or cardiac and respiratory depression. Despite its advantages, NORA faces several challenges, including environmental issues,

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insufficient or old equipment, inexperienced personnel, and distance from the operating rooms in case of emergency. These areas are often not optimized for anesthesia, leading to difficulties in accessing the patient. Additionally, electromagnetic devices and specially coated walls can block emergency communication via mobile phones (2).

The hypothesis of this study is that complication rates in NORA practices are low, and patient outcomes are generally favorable. Additionally, it is anticipated that the anesthetic agents used and the procedures performed may influence the risk of complications. Complication rates and patient outcomes in NORA applications were retrospectively evaluated in this syudy. Specifically, the aim to assess the effects of the anesthetic agents used and the procedures performed on the occurrence of complications.

METHOD

This study was conducted after obtaining approval from the Non-invasive Ethics Committee of Hatay Mustafa Kemal University Faculty of Medicine (Approval No: 26, dated 11.03.2021). The records of patients who underwent sedation-analgesia outside the operating room for diagnostic and therapeutic purposes between 2018 and 2020, were retrospectively analyzed. The data were obtained from forms in the anesthesia archive. These forms included pre-procedure consent, preoperative assessment, and anesthesia follow-up charts. This study aims to retrospectively evaluate the complication rates and patient outcomes in NORA practices.

Patients were evaluated in the anesthesia clinic before NORA procedures, with consultations with the relevant faculty member as needed. Sedation was administered by an anesthesiologist and anesthesia technician. Demographic data of the patients, including age, gender, weight, American Society of Anesthesiologists (ASA) physical status classification scores, comorbidities, surgical interventions, procedure, anesthesia and recovery times, anesthetic drugs used and any complications that developed were recorded. As hypothesized in this study, the selection of anesthetic agents and the procedures performed were recorded to assess their overall impact on complication rates. The choice of anesthetic drugs was left to the discretion of the anesthesiologist, based on the patient's comorbidities and the type of procedure. The most commonly used drugs were documented, and overall complication rates were analyzed, without directly assessing the association between specific drugs and complications.

In units where NORA is administered, there is an oxygen source, an aspirator, a laryngoscope, an ambu bag, and a monitor that can measure heart rate, non-invasive arterial blood pressure, and oxygen saturation. Additionally, there is an emergency cabinet containing resuscitation equipment, a defibrillator, and an anesthesia machine in some units. In all patients, vascular access was established after the required fasting period. In clinical practice, the most commonly used intravenous (iv) anesthetic agents during procedural sedation were midazolam (0.025-0.1 mg/kg), propofol (0.5-2 mg/kg) or ketamine (0.5-2 mg/kg). Additional doses of anesthetic agents were administered if patients experienced pain or discomfort. The Ramsay sedation score was used to assess the level of sedation, with a target sedation level of 4 or 5 (5). During the procedure, patients were monitored and given oxygen via nasal cannula or face mask.

Hypotension was defined as a decrease in systolic blood pressure below 90 mmHg or a decrease of more than 25% of the baseline value. Patients who developed hypotension were treated by administering 5-10 mg ephedrine intravenously. Bradycardia was defined as a decrease in heart rate below 50 beats/minute, and patients with this condition were administered 0.5-1 mg atropine intravenously. Respiratory depression was considered as spontaneous breathing falling below 12 per minute, and these patients were treated with maneuvers to stimulate breathing,changing head position, use of an airway, and oxygen support with a mask. Patients experiencing an allergic reaction were treated with intravenous antihistamines.

At the end of the procedure, patients were followed in the recovery area of the unit. Patients who were awake, oriented, cooperative, with stable vital signs, without risk of respiratory or cardiac depression, and with a modified Aldrete score ≥ 9 were transferred to the service (6). When complications developed and treatments did not provide a sufficient response, patients were transferred to the intensive care unit.

Statistical Analysis

The relationships between categorical variables were analyzed using Pearson's chi-square test and Fisher's exact test. Descriptive statistics for numerical variables were presented as mean ± standard deviation, median, and range (min-max), while categorical variables were summarized as frequencies and percentages. Data collected from the anesthesia archive were analyzed retrospectively to determine the complication rates and patient outcomes. While statistical analysis was conducted on the overall complication rates, no direct evaluation was made regarding the association between specific anesthetic agents and complication risk. Statistical analyses were performed using SPSS Windows version 24.0, with a p-value of <0.05 considered statistically significant.

RESULTS

The study included 1199 patients, of which 759 (63.3%) were adults and 440 (36.7%) were under 18 years of age. Among the patients, 829 (69.1%) were female, and 370 (30.9%) were male. The median age of the patients was 36 years (mean ± standard deviation: 35.62 ± 28.69 years), with a range from 0 to 98 years. The median weight was 65 kg (mean ± standard deviation: 51.93 ± 28.36 kg), ranging from 3 to 98 kg. The median procedure duration was 20 minutes (mean ± standard deviation: 21.99 ± 17.53 minutes), with a range from 2 to 250 minutes. The median anesthesia duration was 25 minutes (mean ± standard deviation: 27.63 ± 18.49 minutes), ranging from 2 to 265 minutes. The median recovery duration was 5 minutes (mean ± standard deviation: 6.73 ± 3.36 minutes), with a range from 0 to 25 minutes. Regarding interventions, 541 (45.1%) of the patients underwent Magnetic Resonance (MR) imaging, 534 (44.5%) underwent Endoscopic Retrograde Cholangiopancreatography (ERCP), and 124 (10.4%) underwent various other interventional procedures. According to the ASA physical status classification scores, 547 (46.1%) of the patients were ASA 2, 468 (39.5%) were ASA 1, 160 (13.5%) were ASA 3, and 11 (0.9%) were ASA 4 (Table 1).

Table 1. Distribution of general characteristics and American Society of Anesthesiologists scores (ASA=)

Gender	**n**	**%**	
Female	829	69.1	
Male	370	30.9	
	Median	**Mean±SD**	**Min-Max**
Age (year)	36	35.62±28.69	0-98
Weight (kg)	65	51.93±28.36	3-98
Procedure duration (min)	20	21.99±17.53	2-250
Anesthesia duration (min)	25	27.63±18.49	2-265
Recovery duration (min)	5	6.73±3.36	0-25
Procedures	**n**	**%**	
Magnetic Resonance	541	45.1	
Endoscopic Retrograde Cholangiopancreatography	534	44.5	
Interventional procedures	124	10.4	
ASA classification	**n**	**%**	
1	468	39.5	
2	547	46.1	
3	160	13.5	
4	11	0.9	

Table 2 shows the distribution of medications used among the patients. The most commonly used medication combination was Midazolam + Propofol + Ketamine, administered to 840 (70.1%) of the patients. This was followed by Midazolam + Ketamine, used in 259 (21.6%) of the patients. Propofol alone was administered to 52 (4.3%) of the patients, while the combination of Midazolam + Propofol was used in 48 (4.0%) of the patients.

Table 2. Medications administered

Medication	**n**	**%**
Midazolam + Propofol + Ketamine	840	70.1%
Midazolam + Ketamine	259	21.6%
Propofol	52	4.3%
Midazolam + Propofol	48	4.0%

As shown in Table 3, the most frequently observed complication was hypotension, occurring in 44 (3.7%) of the patients, with a significantly higher incidence in adults (40, 5.3%) compared to pediatric patients (4, 0.9%) ($p < 0.001$). Bradycardia was the second most common complication, observed in 38 (3.2%) of the patients, again with a higher frequency in adults (34, 4.5%) than in pediatric patients (4, 0.9%) ($p < 0.001$). Allergic reactions were observed in 10 (0.8%) of the patients, occurring more frequently in pediatric patients (7, 1.6%) than in adults (3, 0.4%) ($p = 0.033$). Respiratory depression affected 10 (0.8%) of the patients and was seen almost equally in both groups, with 6 (0.8%) in pediatric patients and 4 (0.9%) in adults, showing no significant difference ($p = 0.867$). The need for ICU admission was found in 13 (1.1%) of the patients, with higher rates in pediatric patients (6, 1.3%) compared to adults (7, 0.9%), although this difference was not statistically significant ($p = 0.514$). The need for intubation was observed in 8 (0.7%) of the patients, but it only occurred in adults (8, 1.1%) and not in pediatric patients (0%) ($p = 0.028$).

Table 4 shows the distribution of comorbidities among the patients. The most frequently observed comorbidity was hypertension (HT), seen in 144 (12.0%) of the patients. Diabetes Mellitus (DM) affected 125 (10.4%) of the patients. Other comorbidities, affecting 111 (9.3%) of the patients, included conditions such as anemia, malignancies, cerebrovascular diseases, smoking-related complications, and cerebral palsy. Coronary Artery Disease (CAD) was found in 84 (7.0%) of the patients, and epilepsy was noted in 58 (4.8%). Chronic Kidney Disease (CKD) and asthma were found in 40 (3.3%) and 38 (3.2%) of the patients, respectively, while hydrocephalus was observed in 11 (0.9%) of the patients.

DISCUSSION

This study aimed to retrospectively evaluate complication rates and patient outcomes in NORA procedures. The most frequently observed complications were hypotension and bradycardia, particularly in adults. These findings underscore

Table 3. Complications of the patients

Complication	Pediatric <18, n	Pediatric <18, %	Adult >18, n	Adult >18, %	Total, n	Total, %	P-value
Hypotension	4	0.9	40	5.3	44	3.7	<0.001
Bradycardia	4	0.9	34	4.5	38	3.2	<0.001
Allergic Reaction	7	1.6	3	0.4	10	0.8	0.033
Respiratory Depression	6	0.8	4	0.9	10	0.8	0.867
ICU Requirement	6	1.3	7	0.9	13	1.1	0.514
Intubation Requirement	0	0.0	8	1.1	8	0.7	0.028

Table 4. Comorbidities among patients

Comorbidities	n	%
Hypertension	144	12.0%
Diabetes Mellitus	125	10.4%
Other*	111	9.3%
Coronary Artery Disease	84	7.0%
Epilepsy	58	4.8%
Chronic Kidney Disease	40	3.3%
Asthma	38	3.2%
Hydrocephalus	11	0.9%

* Other includes anemia, malignancies, cerebrovascular diseases, smoking-related complications, and cerebral palsy.

the importance of careful monitoring during NORA procedures, as well as the need for appropriate drug selection based on patient characteristics and procedural requirements. The primary goal of NORA is to help patients tolerate invasive procedures by alleviating their anxiety and pain. This plays a critical role in improving the safety and effectiveness of anesthesia practices. There are ongoing discussions regarding the ideal drug combinations for procedural sedation. The selection and dosage of anesthetic drugs should be determined according to the purpose, duration and characteristics of the procedure (7). Drugs used in similar doses may not always provide the desired level of sedation, and this level of sedation may vary from patient to patient (8). Inadequate sedation can lead to significant patient discomfort. Adjusting sedative medications carefully can be particularly challenging for anesthesiologists.

Patients undergoing any interventional procedure outside the operating room should be prepared as if they might need general anesthesia at any moment. In an emergency, it may require transfer to the operating room. This plays an important role in determining the ideal anesthesia approach for each patient and procedure (9). The guidelines emphasize the minimal precautions that should be taken for NORA procedures and the need to create basic conditions to ensure patient safety. Patients should be evaluated and consent obtained before the procedure, and preparations should be made according to the fasting periods determined by the ASA (2). Similarly, Walls and Weiss emphasized that patient-specific comorbidities must be assessed before each NORA procedure, as these patients may be in critical condition and require emergency interventions (10). Karamnov et al. stated that complications developed in more than 5% of patients due to inadequate preoperative evaluation (11). Despite evaluating patients in the clinic, a complication rate of 10.3% was observed, likely linked to factors such as age, comorbidities, and the nature of the procedure.

In previous studies, it has been shown that more than half of NORA patients are female (12). Similarly in this study, 69.1% of the patients were female. The ASA classification is important for perioperative risk assessment in all anesthesia practices. NORA studies often report higher mean patient ages and a greater percentage of ASA Class III-V cases (3). However, Iyilikci et al. analyzed the records of 1622 patients who received NORAand found that 92.4% were ASA I, 5.6% were ASA II, and 4% were ASA III, with no patients in ASA IV (13). Similarly, in Turan et al.'s study, 48.2% of the patients were ASA I, 47.8% were ASA II, and 4% were ASA III (14). In this study, the mean age was determined to be 35.62±28.69 years, and the most common ASA class was found to be ASA II. This lower mean age may be due to the inclusion of pediatric patients in the study.

Studies indicate that medication selection in sedo-analgesia primarily depends on procedure duration and pain level, with propofol favored for its smooth induction, short recovery time, and low postprocedural nausea rates. Commonly used agents include propofol, ketamine, midazolam, dexmedetomidine, fentanyl and meperidine (2). Propofol and midazolam are often preferred, with ketamine frequently added for its analgesic effects. This combination provides effective sedation and quick recovery but may weaken airway reflexes, increasing the risk of aspiration. Continuous monitoring with pulse oximetry and, if available, capnography is vital for early detection of respiratory complications. Reversal agents (naloxone, flumazenil) should always be available to manage complications quickly (1,14-

17).

Hu et al. found that in their procedural sedation study comparing ketamine-propofol with ketamine alone, the ketamine-propofol group had significantly lower rates of cardiovascular side effects, nausea, vomiting, and respiratory complications compared to the ketamine-only group (18). In the study by Turan et al., midazolam, propofol, and ketamine were used as sedative agents. This combination is believed to allow for lower doses of anesthetic agents and to contribute to lower complication rates compared to those reported in the literature (14). In clinical practice, commonly used drug combinations include midazolam, propofol, and ketamine. This choice is made due to the practitioners' familiarity with these drugs and their effectiveness in addressing patient needs and various clinical conditions. Fortunately, reversal agents were not required for any patients. However, since capnography was not available, we could only monitor the patients' respiratory status with pulse oximetry.

The most common adverse effects in NORA patients are nausea and vomiting, inadequate pain control, hemodynamic changes, and respiratory depression (11). During their study conducted across 39 countries between 2010 and 2018, Mason et al. found oxygen desaturation as the most common adverse event, followed by airway obstruction and apnea. They also observed that ASA status above III and procedure duration were the most significant predictors of adverse events, with most events being resolved through minor interventions (19). In the study conducted by Karamnov et al., it was observed that the patient's gender played a role in the frequency of adverse events. In this study, it was noted that female patients experienced significantly more frequent hypotension and oversedation (11). Metzner et al. have indicated that respiratory events are more frequently observed as complications in NORA procedures (20). In this study, nausea or vomiting was not observed; the most frequently observed complication was hypotension. We believe the higher incidence of hypotension is due to older age and the presence of comorbidities, particularly cardiovascular conditions. In non-operating room procedures, just as in the operating room, post-anesthesia care should not be ignored. After the procedure, the absence of pain stimuli can increase the risk of deep sedation. Therefore, the patient should be closely monitored until they are fully recovered (21). All patients were monitored in the recovery room, with safe discharge or transfer to the relevant clinic ensured once their Aldrete score reached ≥ 9.

There are often difficulties in accessing medications and supplies for NORA procedures. Many NORA locations are not equipped with the standard anesthesia equipment and monitors that anesthesiologists are familiar with, and often contain older, unused ventilators. Patient-specific factors, such as age and comorbidities, were found to significantly contribute to the complication rates. This highlights the importance of ensuring adequate preoperative assessment and access to proper equipment in NORA settings. A successful NORA application relies on careful drug selection, preparation for potential complications and multidisciplinary team work. Prioritizing patient safety at every stage of anesthesia is essential to balancing the benefits and risks of sedation (22).

Limitations of the study

This study has a few limitations, including the retrospective data collection and small sample size. Conducted at a single center, the results may not be generalizable to the entire population. Capnography was not available; therefore, respiratory monitoring was conducted using pulse oximetry. The inclusion of pediatric patients impacted the age and ASA class distributions, and separating age groups within the study would have provided clearer insights. Long-term follow-up was not included, limiting the understanding of long-term outcomes. Future research should address these limitations to improve NORA procedure safety and efficacy.

CONCLUSION

In conclusion, patient-specific factors, such as age and comorbidities, were found to significantly influence complication rates in NORA procedures. It is recommended that clinicians focus on preoperative evaluations adapted to individual patient needs. Addressing these factors early can improve the safety and effectiveness of NORA procedures. Furthermore, although most adverse events in this study were minor, careful monitoring of sedation and the use of established drug combinations can enhance outcomes for both providers and patients.

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Peer-Review

Both externally and internally peer reviewed.

Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Ethical permission was obtained from the Hatay Mustafa Kemal University, Medical Faculty Non-interventional Clinical Research Ethics Committee for this study with date November 3, 2021 and number 26, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: SU, OK, MÇ, Design: SU, OK, MK, Supervising: SU, OK, MMÇ, MK, MÇ, ÇBÖA, Financing and equipment: SU, OK, MÇ, ÇBÖA, Data collection and entry: SU, OK, MÇ, Analysis and interpretation: SU, OK, MK, Literature search: SU, MMÇ, MÇ, OK, Writing:SU, OK, Critical review: SU, OK, MMÇ, MK, MÇ, ÇBÖA

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ORIGINAL RESEARCH

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Evaluation of hepatitis A, hepatitis B, hepatitis C, HIV, mumps, measles, rubella, and varicella immunity status of health sciences students

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Abstract

Objective: IIt is aimed to determine the immunity status of Hacettepe University health sciences faculty students against diseases specified in the Türkiye Ministry of Health's Health Personnel Screening Protocol for Communicable Diseases.

Method: The data of patients who were admitted to Hacettepe University Family Medicine outpatient clinics between 01.01.2018-31.12.2023, and were tested for at least one of the following tests: HAV antibody (anti-HAV IgG), Hepatitis B surface antigen (HBsAg), antibody against Hepatitis B surface antigen (anti-Hbs), HCV antibody (anti-HCV), HIV antibody (anti-HIV), measles antibody (Measles IgG), mumps antibody (Mumps IgG), rubella antibody (Rubella IgG), varicella antibody (VZV IgG), were retrospectively

Results: The median age of 9050 students was 22 (min=18, max=30, IQR=2), 6253 (69.10%) were female. While five (0.1%) students were HIV-positive, no HCV-positive students were found. The most immunized diseases were Rubella (97%), Varicella (93%), and Hepatitis B (80%); the least immunized disease was Measles (36.9%). AntiHbs and VZV IgG positivity were higher at younger ages ($p<0.001$).

Conclusions: As measles cases have begun to emerge in Türkiye, the low measles immunity identified in this study is concerning. It was found that the immunization rates among students at our university are generally lower than those among healthcare professionals in Türkiye. It is important to improve the implementation of the Ministry of Health's Protocol for Screening Healthcare Personnel for Infectious Diseases and to ensure that screening and immunization efforts reach all healthcare professionals and students in health sciences faculties effectively.

Keywords: Communicable diseases, health personnel, immunity, serologic tests

INTRODUCTION

Healthcare workers are at high risk of contracting infectious diseases because of their direct contact with patients. For these reasons, it is crucial to vaccinate healthcare workers. This helps prevent the spread of contagious diseases from healthcare workers to non-immune patients, reduces absences due to illness, and sets a positive example for society regarding vaccination (1). Healthcare workers are considered a special category by all institutions that set vaccination guidelines worldwide. The most recommended vaccines for healthcare workers globally are seasonal influenza and hepatitis B. In some countries, these vaccines are mandatory for employees without consent (2).

In Türkiye, the Ministry of Health has established specific infectious disease screening and vaccination programs for healthcare workers. The Ministry's Protocol for Screening Healthcare Personnel for Communicable Diseases outlines the evaluation of healthcare workers for tuberculosis, hepatitis B, measles, mumps, rubella, varicella, tetanus, diphtheria, and influenza. It also guides the immunization procedures for personnel who require vaccination. Students in medical, dental, nursing, midwifery, and other health-related schools are at a higher risk of being exposed to infectious diseases, similar to healthcare workers in medical institutions during

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their training. These students are also within the scope of screening and vaccination for infectious diseases (3). However, the vaccination program recommended for healthcare workers in Türkiye is not mandatory. Healthcare institutions advise that students undergo serology tests and receive any missing immunizations before their internship.

The objective of this study was to assess the vaccination status of students and research assistants at the University of Hacettepe Faculty of Medicine, Faculty of Dentistry, Faculty of Nursing, Faculty of Physical Therapy and Rehabilitation, and other faculties of Health Sciences for Hepatitis A, Hepatitis B, Hepatitis C, HIV, Mumps, Measles, Rubella, and Varicella.

METHOD

This study is a retrospective descriptive study. The necessary ethics committee permission was obtained from the Hacettepe University Health Sciences Research Ethics Committee with the date 05.12.2023 (Research Number: SBA 23/406) and decision number 2023/08-26.

Before starting their internships in hospitals, students from the Faculties of Medicine, Dentistry, Nursing and Midwifery, Physical Therapy and Rehabilitation, and other Health Sciences at our university are advised to undergo screening for Hepatitis A, Hepatitis B, Hepatitis C, HIV, Mumps, Measles, Rubella, and Varicella serologies at the Department of Family Medicine's outpatient clinics. If necessary, students receive vaccinations and follow-up care. This screening and vaccination program focusing on the health sciences faculty students is not mandatory. So all the students are not screened and vaccinated in our university. This study focused on students from health sciences faculties who visited the Family Medicine outpatient clinics for serology control.

The data of patients who were admitted to Hacettepe University Family Medicine outpatient clinics between 01.01.2018-31.12.2023, and were tested for at least one of the following tests: HAV antibody (anti-HAV IgG), Hepatitis B surface antigen (HBsAg), antibody against Hepatitis B surface antigen (anti-Hbs), HCV antibody (anti-HCV), HIV antibody (anti-HIV), measles antibody (Measles IgG), mumps antibody (Mumps IgG), rubella antibody (Rubella IgG), varicella antibody (VZV IgG), were retrospectively analyzed. Within the specified time interval, 9050 students from the health sciences faculty underwent at least one of the serology tests mentioned in this study in our outpatient clinics. Among them, 4398 students had all of the serologic tests mentioned in this study (Figure 1). The analyses included data from 9050 students at health sciences faculties who underwent at least one of the serological tests. For students with repeated test results, only the results from the initial test were considered.

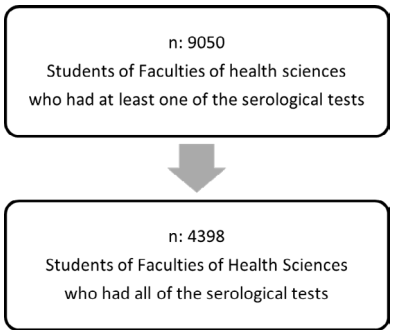

Figure1. Study population

Statistical analysis

The data obtained in the study were transferred to electronic media (data entry) and statistical analyses of the data were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp. Released 2015. Armonk, NY: IBM Corp) statistical computer package program licensed by Hacettepe University.

The data's adherence to a normal distribution was assessed through visual examinations (histogram and probability plots) and statistical analysis (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive statistics for non-normally distributed variables were presented using the median and interquartile range (IQR). The relationship between two categorical variables was examined using the chi-square test, and the relationship between nonparametric continuous variables and categorical variables was analyzed using the Mann-Whitney U test. A significance level of 0.05 was used.

RESULTS

The serologic testing data was gathered from 9050 students who had at least one of the serological tests. 48.59% (4398) of them had all of the serological tests mentioned in the study. The breakdown of serologic tests administered to the students can be found in Table 1.

The mean age of 9050 students included in this study was 21.95 years (median=22, min=18, max=30, 25p=21, 50p=22, 75p=23); 6253 (69.10%) were female. The mean age of the women was 21.90 years (median=22, min=18, max=30, 25p=21, 50p=22, 75p=23); the mean age of the men was 22.08 years (median=22, min=18, max=30, 25p=21, 50p=22, 75p=23). The mean age of males was statistically significantly higher ($p<0.001$).

The highest immunization rates were observed for Rubella (97%), Varicella (93%), and Hepatitis B (80%), while Measles had the lowest immunization rate at 36.9% (Table 1, Figure 2). None of the students tested positive for anti-HCV.

Table 1. Distribution of number of students who underwent serological tests and their serology results

	Students who had the test		Positive		Negative		Bord	
	n	%	n	%	n	%	n	%
Anti Hbs	8258	91.3	6605	80.0	1653	20.0	-	-
HbsAg	8052	89.0	50	0.6	7987	99.2	15	0.2
Anti HCV	7280	80.4	0	0.0	7233	99.4	47	0.6
Anti HIV	6575	72.7	5	0.1	6570	99.9	-	-
Anti HAV	7199	79.5	3066	42.6	4133	57.4	-	-
Measles IgG	6010	66.4	2215	36.9	2819	46.9	976	16.2
VZV IgG	5813	64.2	5460	93.9	280	4.8	73	1.3
Rubella IgG	5815	64.3	5640	97.0	83	1.4	92	1.6
Mumps IgG	5896	65.1	3949	67.0	1184	20.1	763	12.9

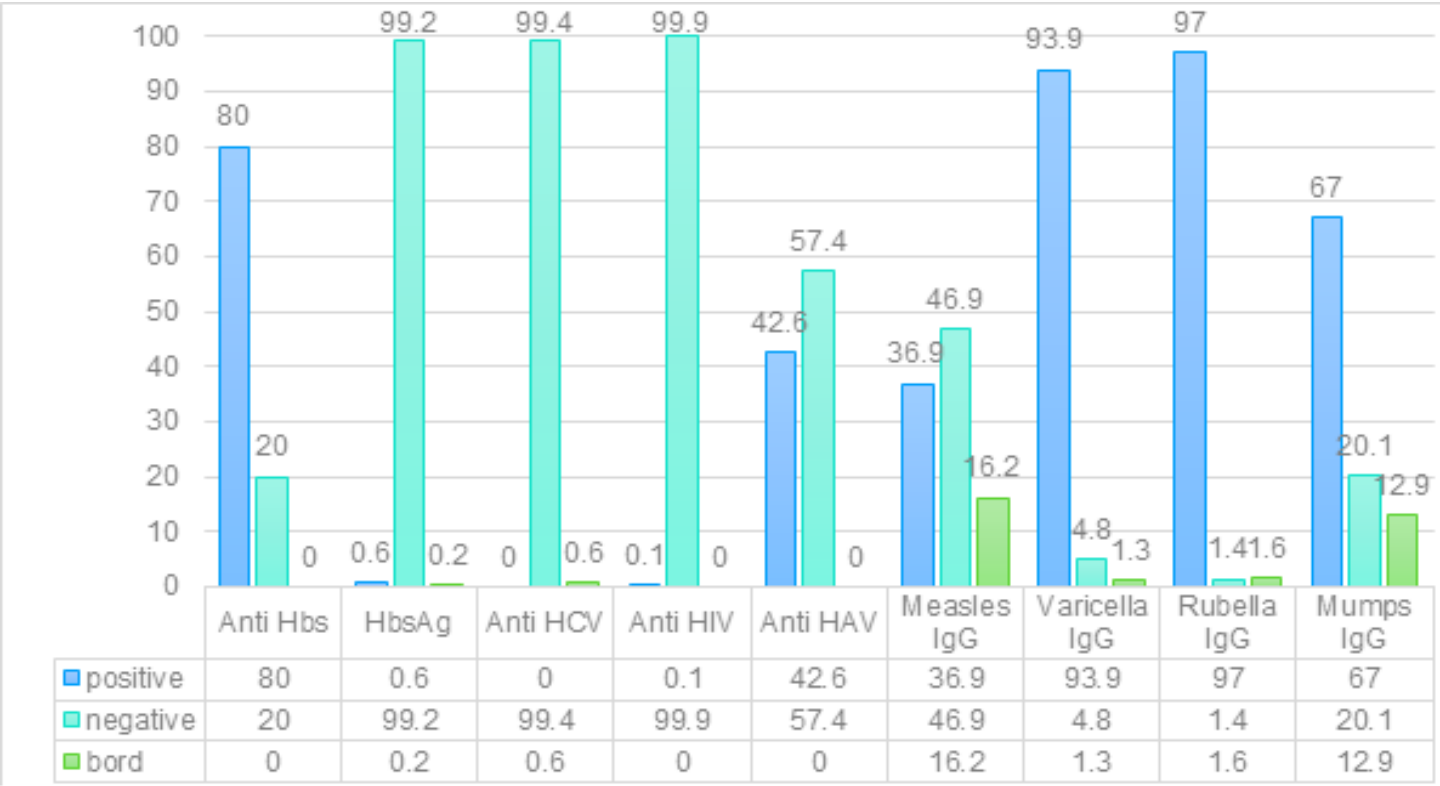

Figure 2. Percentage distribution of serology results

Upon analyzing the relationship between students' age and their serology results, it was observed that a higher prevalence of AntiHbs and VZV IgG positivity was evident among the younger age group. However, no statistically significant association was found between other serology results and age (Table 2).

Furthermore, gender-based analysis revealed no significant difference in the serology results (Table 3).

Table 2. Relation between serology results and students' ages

		Positive	Negative	p*
Anti Hbs	Mean	21.94	22.09	<0.001
	Median	22.00	22.00	
	IQR	2	2	
HbsAg	Mean	22.34	21.97	0.381
	Median	22.00	22.00	
	IQR	2	2	
Anti HCV	Mean	-		
	Median	-		
	IQR	-		
Anti HIV	Mean	20.50	21.91	0.183
	Median	21	22	
	IQR	3	2	
Anti HAV	Mean	21.81	22.01	0.164
	Median	22.00	22.00	
	IQR	2	2	
Measles IgG	Mean	21.85	21.92	0.679
	Median	22.00	22.00	
	IQR	2	2	
VZV IgG	Mean	21.86	22.55	<0.001
	Median	22.00	22.00	
	IQR	2	3	
Rubella IgG	Mean	21.88	22.10	0.872
	Median	22.00	22.00	
	IQR	2	3	
Mumps IgG	Mean	21.89	21.84	0.322
	Median	22.00	22.0	
	IQR	2	3	

*Mann-Whitney U test, IQR: interquartile range

Table 3. Distribution of serology results according to students' genders

		Female n (%)	Male n (%)	p*
Anti Hbs	Positive	4562 (69.1)	2043 (80.9)	0.515
	Negative	1128 (68.2)	525 (31.8)	
HbsAg	Positive	35 (70.0)	15 (30.0)	0.318
	Bord	13 (86.7)	2 (13.3)	
	Negative	5485 (68.7)	2502 (31.3)	
Anti HCV	Positive	-	-	-
	Negative			
Anti HIV	Positive	3 (60.0)	2 (40.0)	0.665
	Negative	4419 (67.3)	2151 (32.7)	
Anti HAV	Positive	2132 (69.5)	934 (30.5)	0.983
	Negative	2873 (69.5)	1260 (30.5)	
Measles IgG	Positive	1528 (69.0)	687 (31.0)	0.495
	Bord	655 (67.1)	321 (32.9)	
	Negative	1947 (69.1)	872 (30.9)	
VZV IgG	Positive	3733 (68.4)	1727 (31.6)	0.112
	Bord	58 (79.5)	15 (20.5)	
	Negative	3733 (68.4)	1727 (31.6)	
Rubella IgG	Positive	3883 (68.8)	1757 (31.2)	0.843
	Bord	61 (66.3)	31 (33.7)	
	Negative	56 (67.5)	27 (32.5)	
Mumps IgG	Positive	2735 (69.3)	1214 (30.7)	0.480
	Bord	525 (68.8)	238 (31.2)	
	Negative	798 (67.4)	386 (32.6)	

*Chi-square test

DISCUSSION

In this study, 48.59% of the health sciences students who were admitted to clinics for serology screening underwent all the serologic tests and successfully screened for all the diseases advised in the Türkiye Ministry of Health's Protocol for Screening Healthcare Personnel for Communicable Diseases.

The HBV and HCV serology tests were conducted in 90% and 80% of the students who were admitted for serology screening, respectively. Measles, mumps, varicella, and rubella IgG tests were performed in approximately 65% of the students who were admitted for serology screening. The higher frequency of HBV and HCV serology tests may be attributed to the necessity for testing following occupational accidents, such as needlestick injuries during patient care.

The results of this study indicate that the highest rates of immunization among students were for rubella (97%), varicella (93%), and hepatitis B (80%), while the lowest rates were for measles (36.9%) and hepatitis A (47%).

Although measles vaccination has been practiced in Türkiye since the 1970s, it wasn't widely adopted until the

1990s. As a result, there is a high rate of non-vaccination among individuals born between 1970 and 1991, especially for those born between 1980 and 1991 (4). Studies have shown varying immunization rates against measles among healthcare workers in different regions of Türkiye; 77.6% in a study conducted across Türkiye in 2020 (5); 99.1% in Elazığ Training and Research Hospital in 2016 (6); 75.8% in Izmir in 2023 (7); and 93.3% in Erciyes University in 2013 (8). In this study it was found that the measles seropositivity rate among health sciences faculty students who were admitted for serology screening is only 36.9%. This finding is concerning, particularly in light of the recent increase in measles cases in Türkiye. Additionally, it's worth noting that the age range of students included in the study was from 18 to 30, with the oldest participant being born in 1993.

Hepatitis B vaccine was added to the national vaccination schedule in 1998 (9). Additionally, the Hepatitis B vaccination program for healthcare workers has been in place in Türkiye since 1996 (10). In other studies conducted in Türkiye, the rate of anti-Hbs positivity among healthcare workers was found to range between 35-89% (11-14). Notably, it was reported to be 90.4% among younger healthcare workers (15). The 80% anti-Hbs positivity rate found in this study is consistent with the data from healthcare workers in Türkiye, underscoring the need for concerted efforts to raise this rate.

The prevalence of HBV carriage is 3.6% in the world and 2.6% in Türkiye (16). HBV carriage among healthcare workers in Türkiye has been reported at rates ranging between 0.3% and 1.8% (17-20). In this study, HbsAg positivity among screened health sciences students was found to be 0.6%. The mean age of HbsAg positive students was higher than that of negative students. This may suggest that HbsAg positivity rates may increase as the duration of occupational exposure of health workers increases, but it does not provide a clear result because the immunization status at the beginning of the faculty is not known.

It is generally accepted that immunity against hepatitis A varies according to socioeconomic level and hygiene conditions and that immunity increases with age. In Türkiye, seropositivity rates differ between the western and eastern regions (21-22). While 10% seropositivity was reported in some centers in the western regions, publications are reporting over 90% positivity in healthcare workers in the eastern regions (6, 23-24). Hepatitis A and varicella vaccines became part of the routine childhood vaccination schedule in 2013 (25). However, none of the students in this study had received these vaccines as they were not eligible based on their age. The 47% immunity rate against hepatitis A among screened students found in this study aligns with other research in the same age group. Nevertheless, this study did not observe the age-related increase in hepatitis A immunity reported in the literature (6).

The number of HIV positive patients is increasing in Türkiye and in the world. However, it has been reported that HIV positivity was not detected in studies conducted in healthcare workers in Türkiye (20,26,27). In this study, HIV positivity was found to be 0.1% among screened students.

Limitations of the study

The limitations of this study include the fact that it could not access the vaccination status of the students, whether they had the infectious diseases examined, and exposure information regarding these diseases. These limitations may have led errors in the analysis of serology results by age and gender. Furthermore, this study included only students who had at least one of the serologic tests, and not all 9050 students underwent all serologic tests. Additionally, as serologic screening at our university is voluntary, it was not possible to reach all students from faculties of health sciences who were doing internships at our hospitals. When there were repeated serologic tests from the same student, only the earliest dated test result was included in the analysis. Therefore, post-vaccination serology results of the students were not evaluated. In addition, since the number of cases in which immunity did not occur even though vaccination was completed was not known, each antibody negativity was considered as non-vaccination. Despite these limitations, it is important to highlight that the high number of evaluated results compared to other similar studies in the literature is a strength of this study.

CONCLUSION

In this study, the immunity status of the students in the faculties of health sciences at Hacettepe University against hepatitis A, hepatitis B, hepatitis C, HIV, mumps, measles, rubella, and varicella are evaluated. It was found that the students' immunity percentages were generally lower than those of healthcare professionals in Türkiye. It is important to implement the Ministry of Health's Protocol for Screening of Healthcare Personnel for Infectious Diseases more effectively and to reach all healthcare workers and students in health sciences faculties with screening and immunization studies. Lectures, activities, and brochures could be prepared to raise awareness among students on this issue. To ensure more consistent and accurate results nationwide, inspecting laboratories where serologic tests are performed more frequently is recommended.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Ethical permission was obtained from the Hacettepe University, Medical Faculty Clinical Research Ethics Committee for this study with University Health Sciences Research Ethics Committee with the date 05.12.2023 (Research Number: SBA 23/406) and decision number 2023/08-26., and Helsinki Declaration rules were followed to conduct this study.

Athorship Contributions

Concept: BB, İF, Design: BB, İF, Supervising: İF, DAB, Financing and equipment: HA, DAB, Data collection and entry: BB, İF, Analysis and interpretation: BB, İF, HA, DAB, Literature search: BB, İF, DAB, Writing: BB, Critical review: İF, HA, DAB

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ORIGINAL RESEARCH

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Acute cyanide poisoning and challenges in the diagnosis

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Abstract

Objective: Cyanide that is known may be cause poisoning for centuries by mankind is a poison that can cause fatal intoxications in minutes, even in very small doses. It was aimed to emphasize the importance of acute cyanide poisoning that may occur by consuming apricot kernels containing amygdalin, a cyanogenic glycoside.

Method: Between September 2016 and October 2018, the data of the patients exposed to cyanide poisoning due to apricot seeds were examined retrospectively.

Results: The mean age of the patients was 39 months (23-65 months). Nine of the patients were female and 12 patients were male. Ten of all patients were native Turkish citizens and 11 of the patients were foreign national. It was learned that the patients ate an average of 15 pieces (10-30) of raw apricots kernel in their anamnesis. The complaints of the cases begin on average 45 minutes (30-90 minutes) after eating apricot seeds.

Conclusion: However acute cyanide poisoning is rare, it has a high potential for mortality when being suspected of cyanide poisoning based on the anamnesis and clinical features of the cases; should be supported immediately and specific treatment should be started.

Keywords: Amygdalin, apricot kernel, cyanide poisoning

INTRODUCTION

Cyanide is called hydrocyanic acid or prussic acid and it has been firstly decomposed from Prussian Blue in 1782, it is one of the strongest and most deadly poisons. In fact, cyanide that is known may be cause poisoning for centuries by mankind is a poison that can cause fatal intoxications in minutes, even in very small doses (1, 2). Diagnosing of cyanide poisonings is difficult due to it has been nonspecific symptoms. Cyanide can be found as free molecules in nature as compounds of hydrogen, sodium, and potassium. Sodium or potassium compound of cyanide that it is called cyanide salts are white color and its solid form (1-4). Cyanide poisoning may occur with oral intake, inhalation, or direct skin transmission (2, 5, 6). Cyanogenic glycosides are found in more than one thousand plants. In the literature it has been reported that, Amygdalin is one of the cyanogenic glycosides also known as vitamin B17are found in almond, apple, apricot, cherry, peach, pear, quince, plum kernels, flaxseed, and legumes. Acute cyanide poisoning can occur in children even if they eat the foods containing cyanide glycosides due to it is released the cyanide result of hydrolysis of this cyanide glycosides (1, 2, 5, 6, 7). In acute cyanide poisoning, the use of oxygen of the cells has deteriorated, so it's seen hypoxia at the tissue level and metabolic acidosis occur. Clinical manifestations of cellular hypoxia due to cyanide poisoning are abdominal pain, general drowsiness, nausea, vomiting, headache, hypothermia, increased salivation, increased sweating, tachypnea, confusion and convulsion. These symptoms can be developed very rapidly within minutes. Even, respiratory failure and death may occur within minutes, if quickly not understood the cause of clinical symptoms (2-4, 7). The diagnosis of acute cyanide poisoning should be kept in mind in children who had the anamnesis of eating cyanogen fruit seed, the smell of bitter almond in the breath, and the gastric irrigation and increased metabolic acidosis in the laboratory test. It should not be forgotten that complete recovery of these patients may occur with early diagnosis and treatment. Management of cyanide poisoning is supportive and specific treatment. Supportive treatments include monitorization,

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oxygen therapy, fluid therapy, and intensive care when necessary. Cyanokit (hydroxocobalamin) and Nithiodote (sodium nitrite and sodium thiosulfate) are specific treatments against cyanide poisoning. In the treatment, despite sodium nitrite and sodium thiosulfate are the most common known antidote agents, due to the hydroxycobalamin and cobalt EDTA have faster and earlier effects, they are recommended use alone or in combination with these agents (1, 2, 8).

In this study, it was aimed to draw attention to acute cyanide poisoning which is may occur with the eating of apricot kernel including amygdalin as cyanogenic glycosides.

METHOD

Study Design

In this study, between September 2016 and October 2018 in the Hatay Mustafa Kemal University Faculty of Medicine, Department of Pediatrics, the data of the patients who were hospitalized and treated with a diagnosis of cyanide poisoning due to apricot seed were examined retrospectively. The diagnosis of the patients was made based on the development of clinical findings (fatigue, abdominal pain, sweating, drowsiness, nausea, saliva increase, vomiting, respiratory distress, loss of consciousness, convulsion etc.) approximately 1 hour after eating 15-20 apricot seeds according to their anamnesis. Ethical permission was obtained from the Hatay Mustafa Kemal University, Medical Faculty Clinical Research Ethics Committee for this study with date 2018 and number 06, and Helsinki Declaration rules were followed to conduct this study..

Data collection

Demographic data, clinical findings, the time to onset of symptoms from to eating the apricot seed, first intervention of families, time of admission to the health facility, hospitalization time, intensive care support requirements, blood gas analysis, liver and kidney function tests, coagulation parameters, diagnosis, and treatment algorithm of those patients were obtained from hospital records.

Laboratory analysis

Laboratory analyses including complete blood count (Mindray BC 6800 hematology analyzer), electrolyte values, liver, kidney function tests (Abbott, architect c 8000, USA); coagulation parameters, and also electrocardiography and echocardiography were evaluated.

Treatment

It was suspected from diagnosis cyanide poisoning with the careful anamnesis of patients, their clinical findings, and especially the smell of bitter almond in their breaths. Then, it was applied supportive treatment without losing time. During this time, blood gas analysis was evaluated. Due to there was no enough laboratory equipment, the serum cyanide levels of patients could not be measured. All patients were treated based on evidence-based medicine guidelines. After the first evaluations in the pediatric emergency department, the all of patients were done quickly monitoring, gastric lavage, oxygen therapy with the mask, and intravenous fluid therapy. Gastric lavage was applied to all of the patients especially patients with the smell of bitter almond in the breath. The parts of the apricot kernels were removed from their gastrointestinal tract with the repeated gastric lavage.

Patients with high liver and kidney function tests were treatment with N-acetylcysteine.

Patients with hypotension were treatment with positive inotropic agents (Dopamine, dobutamine).

Cases with prolonged coagulation parameters were given vitamin K and fresh frozen plasma. And also patients with respiratory failure were treatment mechanical ventilators (Figure 1).

Statistical analysis:

Data were analyzed using SPSS for Windows 18.0 version. (SPSS Inc., Chicago, IL, USA). The differences between the groups were examined by the student's t-test. Categorical variables were evaluated by the ki kare test. $P < 0.05$ was considered significant.

RESULTS

The mean age of the patients was 39 months (23-65 months). 12 of the patients were male and 9 were female. 10 of all patients were native Turkish citizens and 11 of the patients were Syrian refugees. In the anamnesis of the patients, it was learned that they ate an average of 15 pieces (10-30) of raw apricots kernel. It was learned that the complaints of cases started at an average of 45 minutes (30-90 minutes) after eating the apricot kernel. The first intervention of their families was drinking buttermilk, vomiting, washing their hands, and their mouth. The mean duration of admission to the health facility was 90 min (60-120 min). Clinical signs were fatigue (n=21, 100%), abdominal pain (n=21, 100%), pallor (n=21,100%) , sweating (n=21, 100%), drowsiness (n= 21, 100%), nausea (n=20, 95.23%), saliva increase (n=19, 90.47%), vomiting (n=17, 80.95%), respiratory distress (n= 17, 80.95%), loss of consciousness (n: 5, 23.80%) and convulsion (n: 2, 9.52%) (Table 1).

As a matter of fact, in this study, one of the patients was referred to our department with mimicking of encephalitis clinic because of suddenly developing respiratory failure.

In this study, it was found that patients had the smell of bitter almond in the breath of 17 patients and gastric lavage of all patients.

In this study, apricot kernels were detected during gastric lavage in 57.14% (n: 12) of the patients. The patients who it was learned they are healthy before their complaints were diagnosed cyanide poisoning with anamnesis of eating apricot kernel and clinical findings. However, apricot kernels were detected in the gastric lavage of the 4 patients who had a sudden loss of consciousness and respiratory failure but had no that anamnesis of eating apricot kernel, no pathological

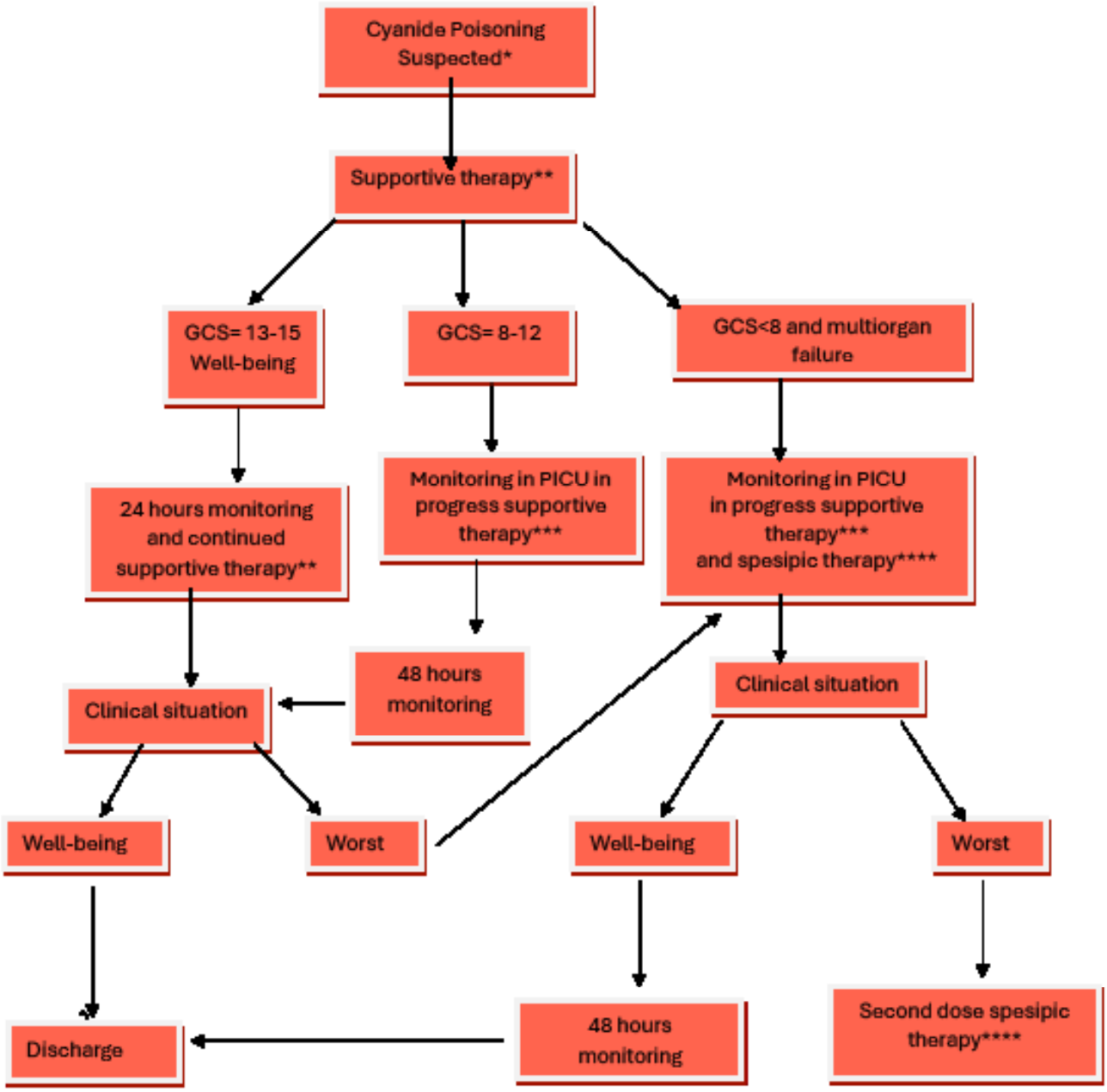

Figure 1: Algorithms in cyanide poisoning management
*It was suspected from diagnosis cyanide poisoning with the careful anamnesis of patients, their clinical findings and especially the smell of bitter almond in their breaths.
**The all of patients were done quickly monitorization, gastric lavage, oxygen therapy with mask and intravenous fluid therapy.
***Patients with high liver and kidney function tests were treatmented N-acetylcysteine and with hypotension was treatmented positive inotropic agents (Dopamin, dobutamin).
****Spesific teratment with hidroksikobalamin(Cyanokit: Pfizer)

In this study, it was detected that in the blood gas analysis high anion gap, metabolic acidosis, high lactate level, and other laboratory test parameters deteriorated similarly to the literature (Table 1).

Support treatment; in this study, the all of patients were done quickly monitoring, gastric lavage, oxygen therapy with the mask, and intravenous fluid therapy, as the first intervention. The parts of the apricot kernels were removed from their gastrointestinal tract with the repeated applications that gastric wash.

Diagnosis; in this study, it was suspected from diagnosis cyanide poisoning with the careful anamnesis of patients, their clinical findings, and especially the smell of bitter almond in their breaths. Then, it was applied supportive treatment without losing time. During this time, blood gas analyses resulted in metabolic acidosis with a high anion gap and normal PaO2 levels. Due to there was no enough laboratory equipment, the serum cyanide levels of patients could not be measured. In five of all patients who had severe poisoning symptoms (GCS <8, circulatory and respiratory failure) were applied specific treatment with hidroksikobalamin (cyanokit: Pfizer).

Four patients had leukocytosis and 3 patients had thrombocytopenia.

Five patients were detected high in the liver and kidney function tests.

In all patients, the mean base deficit in blood gases was -10.7 (-5.8 to -14.2), the mean pH level 7.14 (7.10-7.29), the mean lactate level 5.5 (4.5-7), and metabolic acidosis was detected (Table 1).

Four of all patients was detected sinus bradycardia.

Five patients who had liver and kidney high function tests were treatment NAC.

Five patients who had hypotension were treatment positive inotropic agents (Dopamine, dobutamine).

Four patients who had prolonged coagulation parameters were given vitamin K and fresh frozen plasma. Five patients who had respiratory failure were treatment mechanical ventilators.

In five of all patients who had severe poisoning symptoms (GCS <8, circulatory and respiratory failure) were applied specific treatment with hidroksikobalamin (cyanokit: Pfizer).

The mean duration of clinical response was 7.4 hours (5-18 hours).

Five patients who had intubation and mechanical ventilator support were extubated at the 13th hour (7-16).

Table 1: Clinical signs of patients

	n (Min-Max)	%
Demographic data		
Mean age of the patients (months)	39	
Gender		
Male	12	52.12
Female	9	47.88
Eating number of apricot kernel	15 (10-30)	
Average complaint start time	45 (30-90)	
Mean duration of admission to health facility (minutes)	90 (60-120)	
Clinical Signs		
Fatigue	21	100
Abdominal pain	21	100
Pallor	21	100
Sweating	21	100
Drowsiness	21	100
Nausea	20	95.23
Saliva increase	19	90.47
Vomiting	17	80.95
Respiratory distress	17	80.95
Loss of consciousness	5	23.80
Convulsion	2	9.52
Detected apricot kernels*	12	57.14
Base deficit(min-max)	-10.7 ((-5.8)-(-14.2))	
Mean pH level (min-max)	7.14 (7.10-7.29)	
Mean lactate level (min-max)	5.5 (4.5-7)	

*Number of patients with detected apricot kernels during gastric lavage

DISCUSSION

The amygdalin, a cyanogenic glycoside, was first isolated from bitter almonds by French biochemists Pierre-Jean Robiquet and Antoine Boutron-Charlard in 1830. After that, it was determined that bitter almond species have more 'amygdalin' content than sweet almond species. When the amygdalin is disintegrated with lysosomal enzymes occur cyanide. Therefore, acute cyanide poisoning may occur within minutes to hours, when the kernel of the apricot is eaten because it is containing amygdalin. As a matter of fact, it has been reported in the literature that it can cause mortality by releasing large amounts of cyanide, especially, when the apricot kernels were eaten. Although it is assumed that the deadly dose of cyanide in humans is normally 1.5

mg/kg, a case with lethal concentrations as low as 0.56 mg/kg has been reported (1, 2, 9). In the literature, it is stated that the cyanide content of the apricot kernel varies between 0.122 and 4.09 mg / g (1, 2).

In this study, the mean age of the patients was 39 months (23-65 months). Twelve of the patients were male and 9 were female. In the anamnesis of all of the patients, it was learned that they ate an average of 15 pieces (10-30) of raw apricots kernel. Ten of the patients were native Turkish citizens and 11 of the patients were Syrian refugees.

Clinical manifestations of oral cyanide poisoning occur in 2 to 4 hours after ingestion of apricot kernels in most poisoned cases (1, 2, 10, 11). Although it may be caused only induced salivary and tear secretion depending on irritation, as well as, it may be caused headache, dizziness, tinnitus, vomiting, confusion, dyspnea, tachycardia, non-cardiogenic pulmonary edema, mydriasis, change of consciousness, and even coma (2, 8, 12). Unfortunately, since the onset of clinical symptoms is non-specific general findings, the diagnosis of this poisoning is very difficult. The fact is that the main findings in acute cyanide poisoning are abdominal pain, general lethargy, nausea, vomiting, headache, and tachypnea as related to the lack of oxygen of cells. Especially, It should not be forgotten that symptoms can develop very quickly and death may occur with respiratory failure in 20 minutes or less (1, 2, 7).

In this study, it was learned that the complaints of cases started at an average of 45 minutes (30-90 minutes) after eating the apricot kernel. The most common complaints of patients who are healthy before poisoning were suddenly developing drowsiness, abdominal pain, and sweating (Table 1). And also, it was learned that the first intervention of their families was to drink ayran, vomit, washing their hands and their mouth. The mean duration of admission to the health facility was 90 min (60-120 min). In our study, the absence of mortal complications can be attributed to early admission.

Since the symptoms of cyanide poisoning are nonspecific may be confused with encephalitis or other intoxications, if not kept in mind (2). As a matter of fact, in this study, one of the patients was referred to our clinic with a misdiagnosis of encephalitis because of suddenly developing respiratory failure.

Remarkably, cyanide that it prevents generating energy from the oxygen of the cells thus it causes high-anion-gap metabolic acidosis and hypoxia without cyanosis. Because of there is not often enough time to wait for results of the blood cyanide level or other laboratory tests, in the diagnosis of cyanide poisoning, careful anamnesis and rapid evaluation of clinical findings are very important. For example, the bitter almond smell in the breath is an important finding that supports the diagnosis of cyanide poisoning. Therefore, cyanide poisoning should be kept in mind in patients who had suddenly mental status changes, especially metabolic acidosis with a high anion gap and normal PaO2 levels (1, 2, 7).

In acute cyanide poisoning, due to the deterioration of the using oxygen of the cells, occur hypoxia at all tissues and organs level. Therefore, it may be detected that deteriorated the parameters of blood gas analysis, hemogram analysis, coagulation, liver, and renal function tests. Therefore, cyanide poisoning should be kept in mind in patients who had suddenly mental status changes, especially the high anion gap metabolic acidosis and normal PaO2 levels (1,2).

In this study, it was determined that in the blood gas analysis high anion gap, metabolic acidosis, high lactate level, and other laboratory test parameters deteriorated similarly to the literature (Table-1).

The treatment of the patients with cyanide poisoning varies according to the taken cyanide dose and the severity of the patient's clinic. Unfortunately, due to insufficient anamnesis and laboratory equipment, cyanide dose may not always be determined. Although, Oxygen therapy and supportive treatment are sufficient in clinically mild cases further treatment require in clinically severe cases. In fact, the literature reported that a few cases where cyanide poisoning can be treated with only supportive treatment. However, it should be kept in mind that clinical findings may deteriorate rapidly, and these patients should be followed up in intensive care. Appropriate treatment with an early and accurate diagnosis is essential for the recovery of these patients. The basis of the treatment is a gastric wash, 100% oxygen therapy, cardiopulmonary support, fluid resuscitation, and specific antidote therapy, and, if necessary, mechanical ventilation support. 100% O2 therapy should be continued even if PaO2 pressure is normal (7). The other support treatments include the application of activated charcoal and hyperbaric oxygen therapy (8).

What if it is suspected that the cyanide poisoning, it must never lose time for to treatment by waiting for laboratory results and specific antidote therapy should be initiated as soon as possible. The literature reported that Sodium nitrite and sodium thiosulfate are the most common known as antidotes. Besides, hydroxocobalamin and cobalt EDTA, which have more rapid effects, are recommended for use alone or in combination with these antidotes in the literature (1, 2, 8, 11).

In this study, it was suspected from diagnosis cyanide poisoning with the careful anamnesis of patients, their clinical findings, and especially the smell of bitter almond in their breaths. Then, it was applied supportive treatment without losing time. During this time, blood gas analyses were resulted as metabolic acidosis with a high anion gap and normal PaO2 levels. Due to there was no enough laboratory equipment, the serum cyanide levels of patients could not be measured. In 5 of all patients who had severe poisoning symptoms (GCS <8, circulatory and respiratory failure) were applied specific treatment with hidroksikobalamin (cyanokit: Pfizer).4 patients had leukocytosis and 3 patients had thrombocytopenia. These patients who had hypotension and high liver and kidney function tests were treatment positive inotropic agents (Dopamine, dobutamine) and NAC. 4 of these patients was detected sinus bradycardia. 4 of these patients who had prolonged coagulation parameters were given vitamin K and fresh frozen plasma. Five patients who had respiratory failure were treatment mechanical ventilators. In 5 of all patients who had severe poisoning symptoms (GCS <8, circulatory and respiratory failure) were applied specific treatment with hidroksikobalamin (cyanokit: Pfizer). The mean duration of clinical response was 7.4 hours (5-18 hours). 5 patients who had intubation and mechanical ventilator support were extubated at the 13th hour (7-9).

In this study, in patients with cyanide poisoning who have high mortality potential was no mortality. This situation may be linked to which the timely diagnosis of patients and that were provided treatment of support and specific, without delay.

Limitations of the study

A limitation of this study is that although it would be ideal at diagnosing of cyanide poisining have laboratory confirmation of cyanide exposure, this was not possible due to there was no enough laboratory equipment. However, our study reflects worldwide clinical practice because cyanide levels are not currently used to guide clinical decisions.

CONCLUSION

It should be kept in mind that, acute cyanide poisoning is uncommon but it has a high potential for mortality, it may develop after eating foods included amygdalin. In addition, because of there is not enough time to waiting for results of the cyanide level or other laboratory parameters; when be suspected cyanide poisoning based on the anamnesis and clinical features in the cases; immediately supportly and specific treatment should be started. We think that, where consumption of apricot kernels is common, families should be warned that children should not consume apricot kernels, and family medicine centers and emergency units should be informed about this poisoning. This way, we believe that early diagnosis and treatment can be provided and mortality can be prevented.

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Peer-Review

Both externally and internally peer reviewed.

Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Previously presented

Some part of this study was presented as oral presentation at “4th International Agriculture Congress” held in Nevşehir city, entitled as “Cyanide poisoning linked to agricultural products”.

Ethical Declaration

Ethical permission was obtained from the Hatay Mustafa Kemal University, Medical Faculty Clinical Research Ethics Committee for this study with date 2018 and number 06, and Helsinki Declaration rules were followed to conduct this study.

Athorship Contributions

Concept: ÇE, Design: ÇE, Supervising: MEÇ, Financing and equipment: ÇE, Data collection and entry: MEÇ, Analysis and interpretation: MEÇ, Literature search: ÇE, Writing: MEÇ, ÇE, Critical review: MEÇ, ÇE.

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ORIGINAL RESEARCH

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Progression of cognitive impairment in hemodialysis patients

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Abstract

Objective: Cognitive impairment increases the risk of mortality in patients with chronic kidney disease. Progressive cognitive decline can be a serious issue for hemodialysis patients even if they are young with few comorbid conditions. This prospective study aims to evaluate hemodialysis patients using the Montreal Cognitive Assessment (MoCA) and search for the signs of cognitive decline using cognitive domain scores.

Method: Twenty-nine chronic hemodialysis patients were selected. All patients were tested with MoCA at baseline and after the two-year follow-up. Patients with heart failure, dementia, depression, visual disturbance, malignancy, active infections, and those with single-pool Kt/V<1.4 at baseline or during follow-up were excluded. Patients with MoCA global score <24/30 are considered to be cognitively impaired. MoCA and MoCA subscale scores were compared for differences in time.

Results: The number of patients with cognitive impairment at baseline increased from 18 (62%) to 22 (75.8%) after 2 years follow-up period. The mean total MoCA score after follow-up was significantly lower than that of the baseline (20.57±4.64<22.17±3.87; p=0.001). Analysis for MoCA subscale scores revealed that the mean scores for the attention and language cognitive domains were significantly lower in the follow-up measures compared to the baseline measures in hemodialysis patients (p=0.013 & p<0.001).

Conclusion: This study demonstrated that global cognitive scores in hemodialysis patients decrease over time. This cognitive decline was predominantly related to the differences in attention and language scores. Routine comprehensive evaluation of hemodialysis patients with cognitive batteries may be helpful in detecting the progression of cognitive function.

Keywords: Cognitive impairment, end stage renal disease, hemodialysis, attention, language

INTRODUCTION

Cognitive impairment (CI) describes the decline in cognitive abilities classified as executive function, language, attention, memory, and orientation. Major neurocognitive disorder (NCD) is described as a gradual decline in all cognitive domains that results in a decreased ability to function independently. Mild NCD is an early stage of cognitive deterioration beyond the expected decline of normal aging (1). Since NCD is an umbrella term, it is important to define the underlying neurological, neuropsychiatric, and/or medical disorders (2).

Chronic kidney disease (CKD) is one of the most common medical disorders that can lead to cognitive impairment which may result in major NCD. The incidence of cognitive impairment in CKD is nearly four times the general population (3). Pathophysiology of CKD-related cognitive impairment is mainly associated with atherosclerosis and small vessel cardiovascular disease (CVD). In patients with CKD, vascular aging, metabolic abnormalities, chronic inflammation, and comorbid conditions like diabetes mellitus (DM), and hypertension lead to occult cerebrovascular disease (4). The presence of low estimated Glomerular Filtration Rate (eGFR) and high albuminuria were shown to be independent risk factors for developing cognitive impairment in patients with CKD (5,6). In patients with advanced CKD increased uremic metabolites, vascular calcification, anemia, polypharmacy, intradialytic hypotension, and anticoagulant-associated cerebral microbleeds may contribute to cognitive impairment

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Progressive cognitive impairment would cause hemodialysis patients to be reckless and unaware of the risks of their medical condition. Even though it is known to be progressive and associated with increased mortality, cognitive impairment is usually overlooked, especially in chronic hemodialysis patients. The literature data about hemodialysis patients with CI indicates that vascular burden and intradialytic factors may affect the frontal brain (10). This kind of CI usually leads to a decline in the executive functions of the brain, without affecting praxis or memory. There are several types of cognitive tests used to assess NCD. Among them, the Montreal Cognitive Assessment (MoCA), is widely used in clinical practice and it is validated in patients with CKD (11,12). This prospective study aims to evaluate hemodialysis patients using MoCA and search for the signs of progressive cognitive decline using cognitive domain scores.

METHOD

Patient selection

This prospective time trend study was conducted in the hemodialysis unit of the Nephrology Department at Kahramanmaras Sutcu Imam University between April 2018 - May 2020. The study was approved by the Local Institutional Ethics Committee of the Faculty of Medicine at Kahramanmaras Sutcu Imam University (ethical approval ID: 2018/05 - 16). Participants were given information about the study and agreed by signing a consent form. The study followed the ethical standards of the Declaration of Helsinki.

Patients were selected according to the following criteria, inclusion; chronic hemodialysis patients between 18 and 65 years of age, exclusion; active infection, visual disturbance, thyroid dysfunction, severe anemia (hemoglobin < 9 g/dL), dialysis inadequacy (single-pool Kt/V value of the Daugirdas formula <1.4), diagnosis of heart failure, dementia, psychosis or cerebrovascular disease (13). The baseline study started with 34 adult patients who were on maintenance hemodialysis, three-times per week. During the two-year follow-up period, one patient passed away, one patient was diagnosed with cerebrovascular disease, and three patients moved to other cities. Therefore, we ended up with 29 participants who met the inclusion and exclusion criteria at baseline and after two years. These patients resided in the same region and continued their routine hemodialysis treatment within the same facility. Patients received hemodialysis treatment via their arteriovenous fistulas or tunneled/cuffed catheters. The duration of dialysis was 4 hours for each session with conventional heparinization and a blood flow rate of 250-400 mL/min. The known etiologies for CKD among the study subjects were; hypertension (37.9), DM (20.6%), glomerulonephritis (13.7%), polycystic kidney disease (10.3%), and amyloidosis (6.8). All patients were seen in the dialysis unit three times a week and any complaints that could affect their cognition were noted.

Cognitive assessment and data collection

All subjects were evaluated with the MoCA test (original version 7.1) at baseline and after a two-year follow-up period. Cognitive tests were performed in a separate room, just before a midweek hemodialysis treatment session (14,15). The total MoCA test score is calculated as 30 points. It includes variable cognitive domains, 5 points of visuospatial/executive, 3 points of naming, 6 points of attention, 3 points of language, 2 points of abstraction, 5 points of memory, and 6 points of orientation. Hemodialysis patients with MoCA global score <24/30 were considered cognitively impaired (15,16). The change in MoCA global and MoCA subgroup results before and after two years were analyzed comparatively. Comorbidities (DM, hypertension, & CVD), educational status (number of years), and body mass index (BMI-kg/m2) of all patients were recorded. Relatives and/or caregivers of the patients who scored below 24/30 were informed about the situation and adherence to their medical treatment was improved with the help of a dietitian and a social services specialist.

Statistical Analysis

IBM SPSS software, version 19.0 (IBM Corp., Armonk, NY) was used for the analysis of the data. Values were recorded as mean±SD or %. Chi-square and Fischer's exact tests were utilized for the analysis of categorical variables. The normality of distribution in continuous variables was evaluated with the Shapiro-Wilk test. Student's t-test and Mann-Whitney-U test for the comparison of continuous data.

RESULTS

Clinical data details

The study included 29 hemodialysis patients. The mean age at baseline was 43.79±11.6 years. The Mean education period was 8.72±3.83 years, and the mean MoCA global cognitive score at baseline was 22.17±4.00. In this initial cognitive evaluation, 18 patients (62.0%) had CI (MoCA score <24/30). The mean follow-up period of the patients was 25.17±1.28 months. Almost half of the patients had hypertension. The baseline demographics of the study population are shown (Table 1).

Comparative analysis of follow-up cognitive test scores

After the two-year follow-up, the number of patients with CI increased from 18 to 22 (75.8%). This increase in the

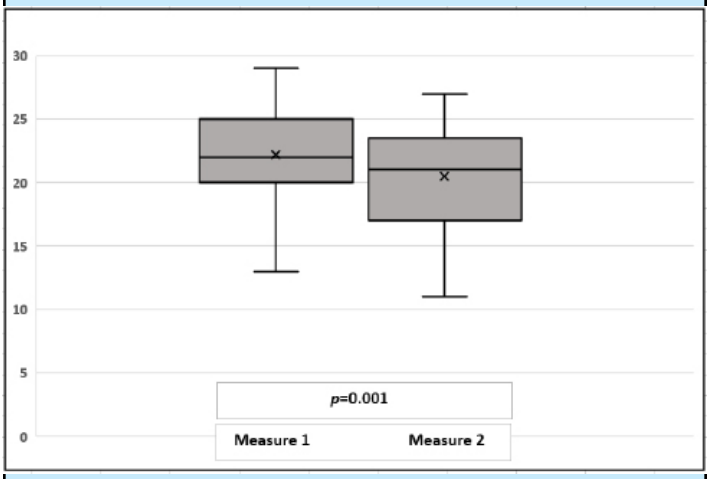

Figure 1. Comparison between baseline and two-year follow-up Montreal Cognitive Assessment global scores

Table 1. Baseline demographics of the study population

Variable	Hemodialysis patients (n = 29)
Age; years ±SD	43.79±11.06
Gender; male/female (%)	19 (65.5) / 10 (34.5)
BMI; kg/m² ±SD	23.10±3.21
Education; years ±SD	8.72±3.83
MoCA global score ±SD*	22.17±4.00
DM; n (%)	6 (20.7)
Hypertension; n (%)	14 (48.3)
CVD; n (%)	6 (20.7)
Hemodialysis vintage; months ±SD	55.34±47.20
Follow-up period; months ±SD	25.17±1.28

Abbreviations: BMI, Body mass index; MoCA, Montreal cognitive assessment; DM, Diabetes mellitus; CVD, Cardiovascular disease. *Baseline mean cognitive test score of the participants.

Table 2. Mean cognitive domain scores at baseline and after two-year follow-up (n=29)

Cognition (Max. score)	Measure 1	Measure 2	p value
MoCA global score (30)	22.17±4.00	20.57±4.03	0.001
Visuospatial / executive (5)	3.10±1.39	3.37±1.26	0.124
Naming (3)	2.76±0.43	2.62±0.56	0.157
Attention (6)	5.17±1.00	4.55±1.24	0.013
Language (3)	2.03±1.11	0.96±0.86	< 0.001
Abstraction (2)	1.34±0.76	1.00±0.80	0.072
Memory (5)	2.07±1.43	2.20±1.61	0.641
Orientation (6)	5.79±0.41	5.79±0.49	1.000

Abbreviation: MoCA, Montreal cognitive assessment

number of CI patients did not constitute a statistically significant impact (p=0.125). However, a statistically significant decline in the MoCA global score from 22.17±4.00 to 20.57±4.03 was observed after the follow-up period (p=0.001) (Figure 1).

After evaluating the MoCA global scores, the MoCA subscale domain scores of the hemodialysis patients were compared. This analysis revealed that the decline in MoCA global score over time was mostly associated with the declining scores for attention and language domains (p=0.013, p<0.001, respectively). The comparative scores of all MoCA domains at baseline and after follow-up in hemodialysis patients are shown in (Table 2).

DISCUSSION

Cognitive impairment is associated with all-cause mortality in patients with advanced CKD (17). Cognitive decline in hemodialysis patients is generally progressive. Early detection of cognitive decline may provide the time to prevent this progression to major NCD. In this study, it was shown that global cognitive scores decrease significantly over time in hemodialysis patients. More than that, the findings of this study indicated that language and attention domains of cognition may be impacted in young hemodialysis patients without evident cerebrovascular disease.

Evaluation of cognitive impairment is delving into the limitation of mental functions and abilities. We evaluated hemodialysis patients at baseline and after two years with MoCA, which is a sensitive testing tool (12,14,16). The percentage of patients with cognitive impairment increased after the follow-up period even if the difference was not significant. If the study sample size was larger, it would have been possible to demonstrate an increased number of patients with a MoCA cut-off value of < 24/30. We selected the 24-cut-off value instead of the standard 26, to prevent the overestimation of cognitive impairment in the hemodialysis population. This lower cut-off was validated in CKD patients for the evaluation of frontal and temporal lobe functions (15).

The important aspect of this study is that we recorded cognitive domain scores at baseline and after two years which was a suitable follow-up period considering the annual mortality rates in the hemodialysis population. Previous studies showed that executive, attention, language, and orientation domains of cognition may be adversely

affected in patients with advanced CKD (16-18). The results of this study revealed that attention and language subscale scores decreased significantly after follow-up, indicating a progressive cognitive decline. As we expected memory domain scores were similar to the baseline values. In previous studies, the memory function had the slowest rate of decline in CKD patients compared to other cognitive domains (17). Contrary to our expectations, executive cognitive scores did not decrease over time. This may be due to the low number of diabetic patients in our study sample.

Cognitive impairment increases with aging. Besides aging, prolonged hemodialysis vintage may be a contributor to CI in the hemodialysis population. The prevalence of CI in hemodialysis patients has been reported to range from 60% to 80% (18,19). We studied with young adults and the prevalence of CI observed in this study is consistent with the aforementioned findings. Although cognitive impairment is so common in the hemodialysis population, it is rarely diagnosed in young dialysis patients. Young patients and patients with high educational status tend to mask their cognitive deficits. Therefore, cognitive test tools are useful for uncovering occult cognitive dysfunction.

It should be noted that the CI associated with CKD differs from that associated with dementia and senility (2,20,21). The precise underlying mechanisms remain unclear but occult cerebrovascular disease is the main explanation. Other than vascular disease, a variety of risk factors have been identified that may contribute to the development of cognitive dysfunction in hemodialysis patients. Accumulation of uremic solutes, hypertension, intradialytic hypotension, fatigue, and anemia, may impair cognitive functions in hemodialysis patients (20,22,23). To avoid false measurements and confounding results, we designed the exclusion criteria to be comprehensive. For that, cognitive tests were implemented before a midweek hemodialysis session, and patients with heart failure, anemia, and dialysis inadequacy were not included. Our analysis did not reveal a significant correlation between the decrease in MoCA scores and the presence of comorbidity. Given our limited sample size, the likelihood of establishing such a connection was reduced. The strengths of this study are the implementation of detailed exclusion criteria, the inclusion of younger patients, and the comparison of follow-up data.

Limitations of the study

The main limitations of this study are that it is a single-center study and the sample size is rather small.

CONCLUSION

Hemodialysis patients are at risk for progressive cognitive impairment even at young ages. In this follow-up study, we evaluated young adult hemodialysis patients for cognitive performance. This study demonstrated that cognitive decline may affect attention and language domains generally preserving memory function. Routine evaluation for cognition may reveal occult cognitive impairments in hemodialysis patients. A multidisciplinary approach is necessary for the treatment of progressive cognitive decline.

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Peer-Review

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

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Authorship Contributions

Concept: EE, Design: EE, IO, Supervising: EE, NE, Financing and equipment: GA, NE, Data collection and entry: GA, NE, IO, Analysis and interpretation: EE, OA, Literature search: EE, GA, NE, IO, Writing: EE, NE, IO Critical review: EE, NE, OA.

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