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CASE REPORTS

galenos yayınevi

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AIMS AND SCOPE

Namık Kemal Medical Journal is the scientific official journal of Tekirdağ Namık Kemal University School of Medicine. The journal is electronically publised tri-annualy (April, August, December). Articles accepted until one month before the month of publication are added to the relevant issue. The three issues form a volume.

Namık Kemal Medical Journal is an independent scientific medical journal that aims to reach its readers in electronic and open access free of charge. It is aimed to publish original articles, case reports and reviews that include the results of studies and research conducted in the fields of basic, internal and surgical medical sciences and medical nursing and passed through the peer review process.

The official publishing language of the Journal is both Turkish and English.

Namık Kemal Medical Journal (NKMJ) is indexed by **Turkish Index (TR DIZIN/ULAKBIM), EBSCO Host, Index Copernicus, TürkMedline, Ideal Online, J-Gate, Gale and CAB International (CABI).**

The Journal will not consider manuscripts any that have been published elsewhere, or manuscripts that are being considered for another publication, or are in press. Studies previously announced in the congresses are accepted if this condition is stated. If any part of a manuscript by the same author(s) contains any information that was previously published, a reprint or a copy of the previous article should be submitted to the Editorial Office with an explanation by the authors.

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All scientific responsibility for the articles belongs to the authors. The name order of the submitted articles should be a joint decision. The responsible author is considered to accept the author order in the name of all authors by signing the " Copyright Transfer Form". Anyone who does not meet the criteria for authoring but has contributed to the study can be listed in "Acknowledgements". The authors should declare in writing that the article is an original paper that has not been published before and that they will not attempt to publish it somewhere else during the evaluation process.

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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 (doaj.org/bestpractice).

Originality, high scientific quality, and citation potential are the most important criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts that have been submitted to another journal for evaluation and rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts that have been presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

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All submissions are screened by a similarity detection software (iThenticate by CrossCheck).

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.

Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors

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"Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" (2013, http://www.icmje.org/). The ICMJE recommends that authorship be based on the following 4 criteria:

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

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

3. Final approval of the version to be published;

4. Agreement to be accountable for all aspects of the work in 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 specific other parts of the work. In addition, 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 in the title page of the manuscript.

Namık Kemal Medical Journal requires and encourages the authors and the individuals involved in the evaluation process of submitted manuscripts to disclose any existing or potential conflicts of interests, including financial, consultant, and institutional, that might lead to potential bias or a conflict of interest. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board.

The Editorial Board of the journal handles all appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office regarding their appeals and complaints. When needed, an ombudsperson may be assigned to resolve cases that cannot be resolved internally. The Editor in Chief is the final authority in the decision-making process for all appeals and complaints.

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No fees are charged from authors for article submission, processing or publication.

Readers can download articles, case reports and reviews free of charge for academic / educational use. The journal is free for everyone at any time. In order to achieve this, the journal benefits from the financial resources of Tekirdağ Namık Kemal University and the ongoing voluntary efforts of the editors and referees.

Open Access Policy is based on rules of Budapest Open Access Initiative (BOAI) http://www.budapestopenaccessinitiative.org/.

By "open access" to [peer-reviewed research literature], we mean its free availability on the public internet, permitting any users to read, download, copy, distribute, print, search, or link to the full texts of these articles, crawl them for indexing, pass them as data to software, or use them for any other lawful purpose, without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. The only constraint on reproduction and distribution and the only role for copyright in this domain, is given to authors to retain control over the integrity of their work and the right to be properly acknowledged and cited.

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INSTRUCTIONS TO AUTHORS

Namık Kemal Medical Journal is the official journal of Tekirdağ Namık Kemal University Faculty of Medicine. Original articles, case reports, and short communications related to the either basic or extended clinical experience in medical sciences (i.e general medicine, basic medical sciences, surgical sciences) will be considered for publication. Review articles will be accepted upon request of the editorial board. The journal does not accept unsolicited review articles for consideration.

This is an open access journal which means that all content is freely available without charge to the user or his/her institution. Users are allowed to read, download, copy, distribute, print, search, or link to the full texts of the articles in this journal without asking prior permission from the publisher or the author. This is in accordance with the BOAI definition of open access.

The journal accepts articles written either in Turkish or English. The journal is currently published quarterly (four issues) comprising one volume per year.

Namık Kemal Medical Journal is a scientific journal that aims to reach all relevant national and international medical institutions and persons in print and electronic form free of charge.

Namık Kemal Medical Journal gives priority to publishing original research articles since it has the mission to announce and share the research to the international scientific circles in Turkey and to contribute to the promotion of Turkey in this context.

Namık Kemal Medical Journal, the Publisher, and the Editors assume no responsibility for the statements in the articles; authors carry the scientific and legal responsibilties of their own articles. The manuscript which is submitted to the journal must not contain previously published material or material under consideration for publication elsewhere. Accepted manuscripts become the property of Namık Kemal Medical Journal and may not be republished. All manuscripts will undergo peer review. A final review and a subsequent decision relative to publication will then be made by the editorial board of Namık Kemal Medical Journal.

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Publication Language

Articles are published in Turkish or English. In Turkish articles, the integrity of the Turkish language should be preserved and the Spelling Guide and Turkish Dictionary of the Turkish Language Association should be taken as basis.

In the use of medical terms, care should be taken to use “Turkish Science Terms” as much as possible. For this, the “Medical Terms Guide” of the Turkish Language Institution is the main source book, but when this book cannot be obtained, the “Country Medical Terms Dictionary” can be used. The authors are deemed to have accepted the changes to be made by the editor in Turkish articles, provided that no changes are made in the content.

English texts should be clear and accurate. In case the publication is accepted, the article is reviewed by the language editor of the journal.

Article Submission

All manuscripts should be submitted via https://jag.journalagent.com/nkmj/ online submission system.

Manuscript Evaluation

As a first step, manuscripts received are evaluated with regards to the instructions to authors. The approved articles are delivered to Editorial Board. The Editorial Board evaluates the context of articles and sends them to two referees in related fields. A final review and a subsequent decision relative to publication will then be made by the editor. The articles which are accepted by the Editorial Board, come in the list of publication and the authors of these articles are informed.

This journal uses double-blind peer review, which means that both the reviewer and author identities are concealed from the reviewers, and vice versa, throughout the review process. To facilitate this, authors need to ensure that their manuscripts are prepared in a way that does not give away their identity.

Manuscript Layout

Manuscripts sent to the editor to be published in the journal must be written on one side of the A4 page, in Arial, 10 pt, double spacing and 2.5 cm margins each. The abbreviations used should be written clearly in parentheses at the first mention in the text, and no special abbreviations should be made. Numerical data between 1-10 in the text should be indicated in writing (in both treatment groups, second day .....), with 10 and above numbers. However, numbers between 1-10, which have a descriptive tag, should be written in writing (.... 1 year) and the numbers at the beginning of the sentence (a fifteen-year-old female patient .....).

The title page, abstract, text, figures, tables and references of the article should be given in the same WORD file.

All visual elements except the table should be named as “Figure”. Table and Figure numbering (1,2,3 ..) should be made. The description text for the table should be placed above the table, below the figure for the figure. The abbreviations used in the table should be written clearly under the table.

The use of resources in the text should be indicated at the end of the quote and as superscript.

Title Page: On the title page; The title of the article in Turkish and English, the names and duties (academic titles) of the authors, the institution from which it was sent, if any, the institution supporting the study should be written. If the article has been communicated before in any congress, its place and date should be specified. In addition, the name, surname, addresses, telephone and fax numbers, e-mail address of the author to be corresponded and Ethics Committee Approval must be clearly written on this page.

Author’s name (Only the first letter is capital) surname (all text is capital) should be written clearly,

Abstracts: It should be prepared on a separate page in Turkish and English. The abstract should reflect the article, significant results should be given and their interpretation should be made. Abbreviations that are not explained in the abstract should not be used, and the source should not be shown. Abstracts should not exceed 250 words.

In research articles; Turkish and English abstracts should be divided and structured as follows:

Aim/Amaç, Materials and Methods/Gereç ve Yöntem, Results/Bulgular, Conclusion/Sonuç.

Structured abstract should not be used in reviews and case reports.

INSTRUCTIONS TO AUTHORS

Keywords: Turkish and English keywords should be found in accordance with the standards of "Index Medicus: Medical Subject Headings (MeSH)". (http://www.nlm.nih.gov/mesh/authors.html). Keywords should be given at least 3 and at most 5 on the page under the Turkish and English abstracts in all kinds of articles.

Sections: Original research articles should include Introduction, Materials and Methods, selection and description of the cases, technical information, Statistical Analysis, Results, Discussion, Study Limitations and Conclusion sections. Case reports should include Introduction, Case Report and Discussion sections.

After these chapters, "acknowledgements" can be written to those who contributed to the research or to the preparation of the article, if any. Acknowledgments are given at the end of the article before references. In this section, there are expressions of thanks for personal, technical and material assistance.

References

References should be numbered and listed according to the order in the text under the heading (References) at the end of the article. There should be no discrepancy between the list of references and the order they appear in the text.

References that have information obtained through another reference without the original appearance are not numbered, they are given in parentheses when necessary. Author (s) are responsible for the accuracy of the references. All references should be stated in the text.

The names of the journals are given in abbreviated form in accordance with Index Medicus. Journal names that are not included in the index are not abbreviated.

Examples for Writing Resources

For journals:

For the journal article in MEDLINE and abbreviated according to MEDLINE:

The first letters of the authors' surnames and names should be entered with a comma at the end without a full stop, and a period should be placed after the first name of the last author without passing to the title. If the authors are 6 authors and less, all of them should be written. If the authors are more than 6 authors, the first 6 should be written, then et al. should be used. Then the title of the article should be entered and a period should be placed at the end. The short name of the journal in MEDLINE is put at the end and a space is left after it is written; publication date semicolon; number in parenthesis, the starting number of the published pages are put in a colon, and the last page is written after the hyphen is inserted, but the numbers on the first page are not repeated on the last page.

Ozkan G, Ulusoy S, Guvercin B, Menteşe A, Karahan SC, Yavuz A. A new player in chronic kidney disease mineral and bone disorder: tenascin-C. Int J Artif Organs. 2015;38:481-7.

For books:

West JB: Respiratory Physiology (2nd ed). Baltimore: Williams and Wilkins, 1974; 72-5.

For chapters taken from the book:

Sagawa K: Analysis of the CNS ischemic feed back regulation of the circulation. In: Reeve EB, Guyton AC (eds), Physical Basis of Circulation Transport. Philadelphia: WB Saunders, 1967; 129-139.

For online articles:

Abood S: Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Webcast]. 2002 Jun [citation 12.08.2002]; 102 (6). Access: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm PMID: 12394070.

For the citations from the thesis:

Kulu A. Evaluation of Quality of Life After Surgical Interventions Applied to Patients with Bladder Tumors, Trakya University, Institute of Health Sciences, Department of Nursing. Master Thesis. 2010; Edirne.

For congress papers:

Felek S, Kılıç SS, Akbulut A, Yıldız M. A case of phylgellosis with visual hallucinations. XXVI. Turkish Microbiology Congress Abstract Book, 22-27 September 2000, Antalya, Mars Printing House, 1994, p.53-6.

In Turkish sources that are not included in Index Medicus, the above examples are followed, but journal names are written without abbreviation.

Tables and Figures

Tables and figures should be numbered according to the order of appearance in the text, and should be placed in the closest section with their explanations according to the place in the text. The information given in the table should not be repeated in the text, permission should be obtained for tables taken from other sources. Figures should be drawn professionally, photographed or presented as digital prints in photographic quality. The part of the photos and pictures to be printed should be at least 9x13 cm in size and 300 DPI resolution.

Symbols, arrows or letters should contrast with the background. The magnification rate and dyeing technique used should be specified in microscopic pictures.

If human photography is to be used, either they should not be identified from the photograph or written permission should be obtained (see Ethics section). Figures and pictures should be written at the bottom, together with (1, 2, 3, ..) numbers.

Publication Review Process

All articles (Original articles, Reviews, Case Reports and Letter to the Editor) are subject to the following process:

After the formal check, articles that comply with the journal's spelling rules are directed to the editor. All applications are evaluated by the responsible editor in terms of the journal's scope, purpose and compliance with the target audience. If the article sent to Namık Kemal Medical Journal is in conformity with the formal principles, the editor is directed to two independent reviewers by providing blindness between the reviewers and authors from Turkey and/or abroad.

If the reviewers deem necessary, they approve the publication after the changes requested in the article are made by the authors.

INSTRUCTIONS TO AUTHORS

Studies coming to the journal management system pass the pre-evaluation of the editor and the editorial board within 2 weeks at the latest;

Compliance with the scope and subject areas of the journal,

Compliance with the journal spelling rules (if any, article template, font, titles, submission and bibliography style, etc.)

Publication language (abstract, sufficiency of keywords, structured self-translation, etc.).

Studies that pass the pre-evaluation stage mentioned above by the editorial board are sent to at least 2 reviewers who are experts in their field, depending on the nature of the study.

Based on the nature of the work, the referees evaluate working on the standard evaluation form.

In addition, if the reviewers wish, they can submit notes on the full text, stating their suggestions and opinions, to the editorial board.

The deadline for reviewers evaluations is 6 weeks.

After the study is sent to the reviewer, it states to the editorial board whether it can be evaluated within 2 weeks at the latest. Rewievers who do not specify are removed from the study and a new reviewer assignment is made.

The reviewer opinions for the studies guide the editorial board to make the final decision. The final decision always belongs to the editorial board.

The reviewers can give opinions for the study in 4 ways;

- Publication is acceptable
- It can be accepted for publication after corrections (It is decided by the editorial board whether the corrections have been made or not)
- After revisions I would like to see it again (The work is taken into a second round evaluation after it is submitted by its authors)
- Unpublished (Rejection)

A 3rd or 4th reviewer can be appointed to work in line with the reviewer 's opinions, and this process works in the same way as the time specified above.

After the completion of the evaluation in line with the reviewer opinions, the reviewer opinions are reviewed by the editorial board (maximum 2 weeks). In this process, the aim is to adapt the articles of the authors to publication standards.

The editorial board makes the final decision in line with the reviewer opinions and suggestions and conveys the result to the study authors.

Accepted articles are sent to the correspondence author for proof control before the publication, and a reply must be given within 48 hours.

The responsibility of the ideas advocated in the articles belongs to the author.

The copyright of the published articles belongs to the journal and cannot be transferred, even partially, without the permission of the journal.

Plagiarism

Submitted articles are evaluated after plagiarism control. This evaluation contributes to the decision-making of the editorial group.

Final Checklist

1) Presentation page to editor
   a. Category of the article
   b. Information that it has not been sent to another journal
   c. Relationship with a sponsor or a commercial company (if any)
   d. Statistical control was made (for research articles)
   e. Checked in terms of English
2) Copyright transfer form
3) Permit certificate if previously printed material (text, picture, table) is used
4) Compliance with the principles of the Helsinki Declaration in the "material and method" section in the studies with human elements, the approval of the ethics committee from their institutions and the "informed consent" from the patients.
5) If the animal element is used, indicating its compliance with the principles of "Guide for the Care and Use of Laboratory Animals" in the "material and method" section.
6) Cover page
   a. The title of the article in Turkish and English (preferably one line each)
   b. Authors and their institutions
   c. Correspondence address, business phone number, GSM number, e-mail addresses of all authors
7) Abstracts: (Turkish and English)
8) Keywords: Between 3-5 (Turkish and English)
9) Acknowledgement
10) References

Ethic

Scientific Responsibility

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

All authors should have a direct academic and scientific contribution in the submitted article.

The name order of the authors should be a joint decision. All authors must indicate the author list on the copyright transfer form signed. The names of all authors should be included in the section under the title of the article.

All individuals who do not meet the sufficient criteria for authorship but contributed to the study can be listed in the "Acknowledgements/ Information" section. Written permission must be obtained from these individuals to be specified in the acknowledgment section.

Ethical Responsibility

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

Namık Kemal Medical Journal is a journal that has adopted the principle of complying with the ethical standards of the Human Experiments

INSTRUCTIONS TO AUTHORS

Committee (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/), which was revised in 2013 in the 1975 Helsinki Declaration. Therefore, in the articles sent for publication, it must be stated that the ethical standards of the specified committee are complied with. In addition, approval letters from local or national ethics committees should be sent with the letter.

In the material and method section of the article, the authors must state that they carried out the study in accordance with these principles, and that they received "informed consent" from the ethics committees of their institutions and the people who participated in the study.

If "animal" was used in the study, the authors stated that they protect animal rights in their studies in line with the principles of the "Guide for the Care and Use of Laboratory Animals" (www.nap.edu/catalog/5140.html) in the material and method section of the article and they have obtained approval from the ethics committees of their institutions. They must notify in writing whether they comply with institutional and national guidelines on the care and use of laboratory animals.

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In the studies requiring the permission of the Ethics Committee, the information about the permission (Name of the Committee, Date and Approval Number) should be included in the Method section and also in the first/last page of the article. This information should be included in the Title Page when submitting your article. At the same time, you must send the Ethics Committee Form of the article.

Confidentiality and Confidentiality of Patients and Study Participants

Privacy cannot be impaired without permission from patients. Descriptive information such as patients' names, initials or hospital numbers, photographs and family tree information, etc. They are not published unless absolutely necessary for scientific purposes and the patient (or parent, or guardian) gives written informed consent.

The informed consent should also be stated in the article.

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The works of the authors who do not submit the Copyright Transfer Form will definitely not be published.

International Study Design Guidelines

Preparation of research articles, systematic reviews and meta-analyses must comply with study design guidelines:

CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001; 285: 1987-91) (http://www.consort-statement.org/);

PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

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ORIGINAL ARTICLES

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ORIGINAL ARTICLE

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Mid-long Term Results of Dorsal Approach and Temporary Fixation Procedure in Overlooked Perilunate Carpal Dislocation

Gözden Kaçan Perilunat Karpal Dislokasyonda Dorsal Yaklaşım ve Geçici Tespit Prosedürünün Orta-Uzun Dönem Sonuçları

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ABSTRACT

Aim: Our aim in this study is to present our mid-long term functional and radiological results after open reduction with dorsal approach, K-wire application and scapholunate ligament repair in cases with perilunate dislocation.

Materials and Methods: Eleven patients who applied for perilunate dislocation between 2014 and 2018 and were followed up for at least 18 months were included in our study. The scapholunate angle, scapholunate gap, arthrosis, and avascular necrosis were evaluated in cases with isolated perilunate dislocations. The wrist flexion-extension and pronation-supination range of motion (ROM) of the patients were measured using a goniometer, and the wrist grip strength using a Jamar dynamometer. Functionally, the cases were evaluated according to the Disabilities of the Arm, Shoulder and Hand (DASH) scoring and the Herzberg clinical scoring system.

Results: The mean age was 41.1 (28-64) years, the mean follow-up time was 3.8 (1.5-6) years. The mean scapholunate angle was 49.1±8.7 (37.3-70.4) degrees, the mean scapholunate gap was 2.0±0.5 (1.2-2.8) mm, the mean flexion-extension ROM was 131±17.5 (90-155) degrees, and the mean pronation-supination ROM was 155.4±6.1 (140-160) degrees. Patients had a mean DASH score of 5.6±3.2 (0-10.9) and a mean Herzberg clinical score of 89.1±9.4 (70-100).

Conclusion: In perilunate dislocations, early and appropriate treatment is the main determinant of prognosis. Close follow-up of these injuries for at least 18 months is extremely important in terms of possible complications.

Keywords: Perilunate dislocation, carpal instability, arthrosis

ÖZ

Amaç: Çalışmadaki amacımız, perilunat çıkıklı olgularda dorsal yaklaşımla açık redüksiyon, K-teli uygulaması ve skafolunat ligaman tamiri sonrası orta-uzun dönem fonksiyonel ve radyolojik sonuçlarımızı sunmaktır.

Gereç ve Yöntem: 2014-2018 yılları arasında perilunat çıkık nedeniyle başvuran, en az 18 aylık takibi olan 11 hasta çalışmamıza dahil edildi. Bu olgularda, skafolunat açı, skafolunat gap, artroz ve avasküler nekroz varlığı değerlendirildi. Hastaların el bileği fleksiyon-ekstansiyon ve pronasyon-supinasyon hareket açıklığı gonyometre ile ölçüldü. Jamar dinamometresi ile el bileği kavrama gücü değerlendirildi. Olgular fonksiyonel olarak Kol, Omuz ve El Sorunları Anketi (DASH) skorlaması ve Herzberg klinik skorlama sistemine göre değerlendirildi.

Bulgular: Ortalama yaş 41,1 (28-64), ortalama takip süresi 3,8 (1,5-6) yıldı. Ortalama skafolunat açı 49,1±8,7 (37,3-70,4) derece, skafolunat interval 2,0±0,5 (1,2-2,8) mm, fleksiyon-ekstansiyon arkı 131±17,5 (90-155) derece, pronasyon-supinasyon arkı 155,4±6,1 (140-160) derece olarak ölçüldü. DASH skoru ortalama 5,6±3,2 (0-10,9), Herzberg klinik skoru ortalama 89,1±9,4 (70-100) olarak bulundu.

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Sonuç: Perilunat çıkıklarda tedavinin erken dönemde ve uygun şekilde yapılması prognozdaki ana belirleyicidir. Bu yaralanmaların olası komplikasyonlar açısından minimum 18 aylık yakın takibi son derece önemlidir.

Anahtar Kelimeler: Perilunat çıkık, karpal instabilite, artroz

INTRODUCTION

Carpal stability is defined as the preservation and maintenance of the static and dynamic balance of the joints under physiological loads and movements of the wrist. On the other hand, carpal instability is defined as disruption of this balance by bone and/or ligament injuries, resulting in disruption of articular anatomical integrity, biomechanical performance impairment, pain, and scapholunate advanced collapse (SLAC)[1].

Perilunate dislocations are rare, serious injuries. While approximately 65% of the cases are accompanied by scaphoid fractures, they are called major arch injuries and only ligamentous injuries are called minor arch injuries[2].

Among carpal injuries, dislocations are rare injuries. They constitute about 10% of carpal bone injuries. It is often caused by motor vehicle injuries and falling from height. Usually, young men are affected[3]. Characteristically, it presents as a dislocation of the joint between the capitate bone head and the distal lunate. Dislocation mostly develops dorsal and presents as a progressive form of bone and ligament damage[4].

Treatment modalities including closed reduction and immobilization with plaster, closed reduction and percutaneous fixation and open reduction, ligament repair and fixation are used in the treatment[5].

In the study, we aimed to present our mid-long term functional and radiological results after open reduction with dorsal approach, K-wire application and scapholunate ligament repair due to isolated perilunate injury (minor arch injury).

MATERIALS AND METHODS

Ethics committee approval was obtained for the study from Tekirdağ Namık Kemal University Faculty of Medicine Ethics Committee (29.12.2020/2020.263.12.08). The research was conducted in accordance with the principles of the Declaration of Helsinki. Twenty-two patients who presented with perilunate dislocation between 2014 and 2018 and had at least 18 months of follow-up were included in our study. Major arch injuries, chronic cases (>45 days), additional wrist injuries other than radius styloid fracture that might impair wrist functions, previous trauma and operation history affecting the same extremity, cases that remained conservative, cases with neurological and rheumatological diseases were not included in the study.

Eleven patients who did not meet the criteria were excluded from the study, one of them was chronic injury and lunate avascular necrosis developed (three-year trauma), 8 patients had perilunate injury accompanied by scaphoid fracture (major arch injury), and closed reduction was performed in 2 patients. A total of 11 patients with isolated perilunate dislocation were included in the study. The mean time between trauma and surgery in our patients was 7.4 (1-32) days. Two of these patients had accompanying radius styloid fractures, and in these cases, the fracture in the distal radius was fixed with a percutaneous K-wire (Figure 1A-E).

All of our patients included in our study underwent open reduction with a dorsal approach, ligament repair and percutaneous fixation. Scapholunate ligament repair was performed using remnants of the ligament with the aid of a rope anchor placed on the lunate bone. After open reduction, one or more of the scapholunate, lunotriquetral, lunocapitate or lunoradial temporary pins were applied to our patients with 1.2 mm thick K-wires, making a peroperative decision according to the condition of injury or stability (Figure 2A-D).

A splint was applied until the postoperative sutures were removed, and then a long arm cast was applied for 6-10 weeks. The controls of the cases were done with two weeks intervals in the early period after the sutures were removed. The cases were called for controls every 3 weeks between the 6th and 12th weeks and every 2 months in the following periods.

In cases where lunoradial K-wires were applied, they were removed at the 6th week, while the other wires were removed at the 10th week. Passive exercise was started on the same day, and active range of motion (ROM) exercises were started two weeks later, and axial loading was limited until the 6th month. At the last control of our patients, two-way radiographs (anteroposterior and lateral) were taken and the scapholunate angle and scapholunate gap, the presence of arthrosis in the joint, the presence of SLAC and avascular necrosis were evaluated (Figure 3A-F). Wrist flexion-extension arc and pronation-supination arc of the patients were measured with a goniometer. The cases were evaluated according to the wrist grip strength with a Jamar dynamometer, Disabilities of the Arm, Shoulder and Hand (DASH) scoring and the clinical scoring system defined by Herzberg for perilunate injuries[4].

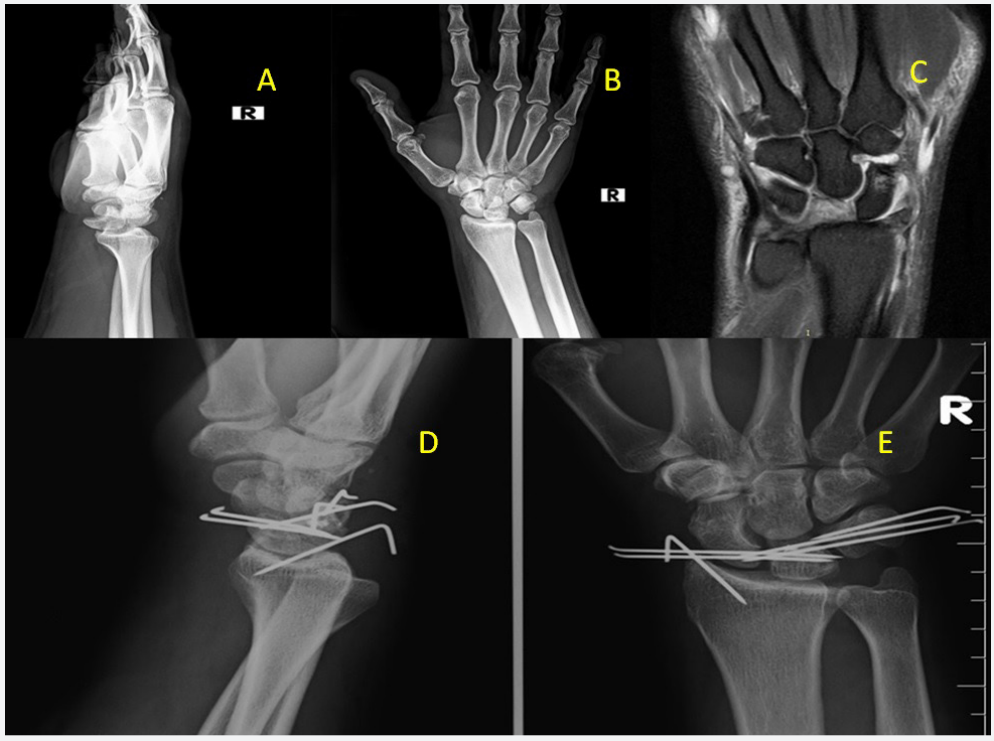

Figure 1. Preoperative and postoperative radiographs of the case with a styloid fracture of the radius. A) Perilunate dislocation and radial styloid process fracture lateral image, B) Anteroposterior image, C) Magnetic resonance image, D) Postoperative lateral image, E) Postoperative anteroposterior image

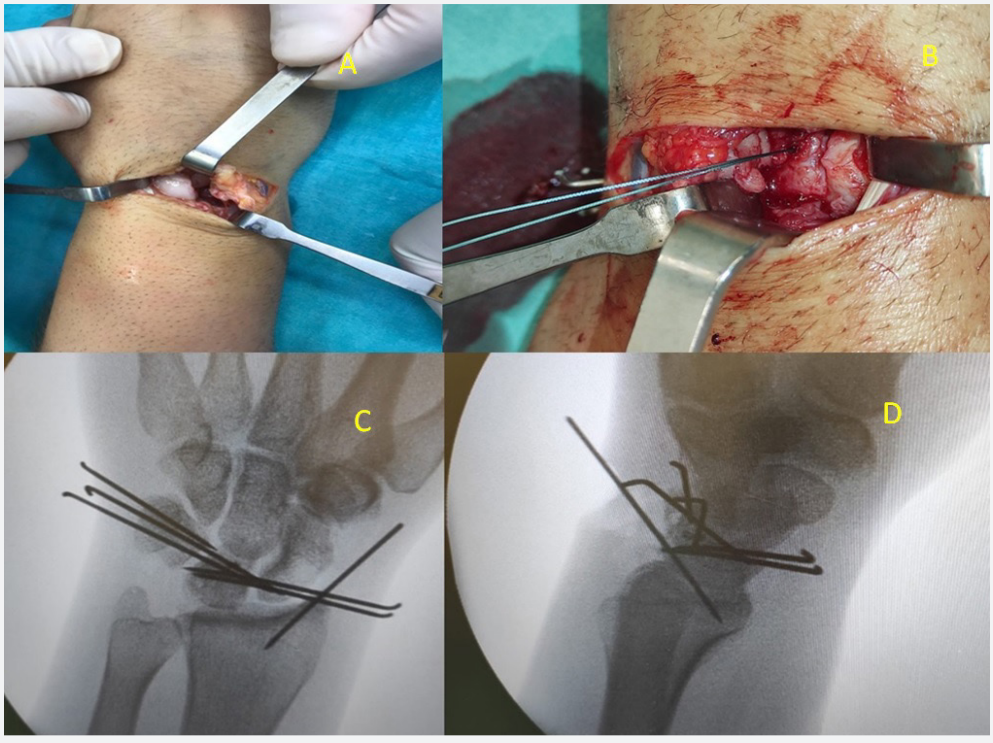

Figure 2. Peroperative evaluation of isolated perilunate dislocation and scapholunate ligament repair. A) Imaging of dorsal incision and perilunate dislocation, B) Repair of scapholunate ligament, C) Peroperative anteroposterior scopy image, D) Peroperative lateral scopy image

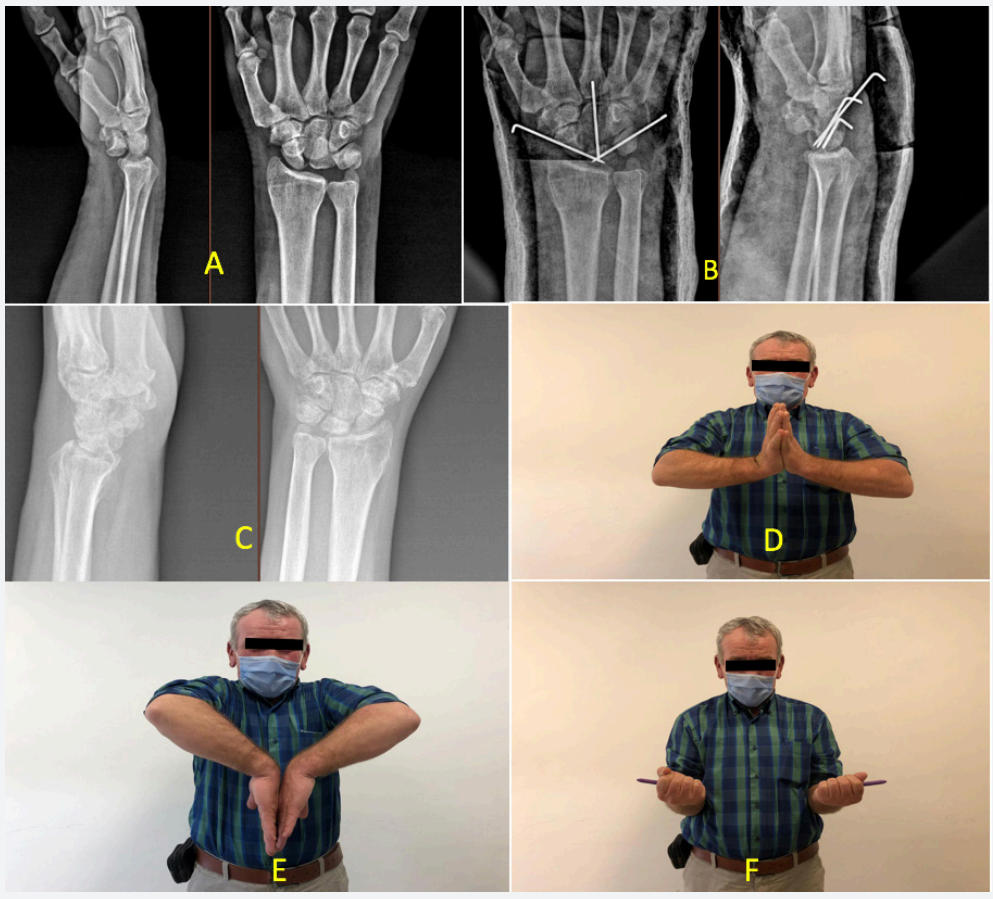

Figure 3. X-rays and functional results of the isolated perilunate dislocation case. A) Perilunate dislocation preoperative X-ray images, B) Fixation with scapholunate, lunotriquetral and capitolunate K-wires, C) Postoperative 3rd year X-ray images, D) Follow-up wrist joint dorsiflexion of the case, E) Follow-up wrist joint volar flexion of the case, F) Follow-up wrist joint rotation of the case

Statistical Analysis

Variables were given as percentage, mean (arithmetic mean) and standard deviation (minimum-maximum), and non-parametric tests were used for evaluation because the number of patients was relatively small and there was no comparison group.

RESULTS

All of our patients included in the study were male and the mean age was 41.1 (28-64) years. The mean follow-up period was 3.8 (1.5-6) years. The dominant side was affected in 7 (64%) of our patients. High-energy trauma was often present in the etiology (Table 1). SLAC or avascular necrosis was not observed in any of our cases. Wrist arthrosis findings were observed in only one case. In this case, the flexion-extension arc was relatively low, but there was no complaint of discomforting pain. The mean time between trauma and surgery in our patients was 7.4 (1-32) days.

The mean scapholunate angle was measured as 49.1±8.7 (37.3-70.4) degrees, we had only 1 patient above the normal range (30°-60°). The scapholunate interval was 2.0±0.5 (1.2-2.8) mm, and all of our patients were within normal interval (<3 mm) (Table 2).

The mean flexion-extension arc was 131±17.5 (90-155) degrees, and the mean pronation-supination arc was 155.4±6.1 (140-160) degrees (Table 2).

The mean DASH score was 5.6±3.2 (0-10.9), and the mean clinical score described by Herzberg was 89.1±9.4 (70-100). Excellent results were found in 5 patients, good results in 5 patients, and normal results in one patient (Table 2).

We observed that the ratio of the grip strength of the operated and healthy sides in our patients, whom we evaluated in terms of wrist grip strength, was between 65% and 100%.

Although none of our patients showed signs in favor of carpal tunnel syndrome at the last follow-up, in one of our

Table 1. Evaluation according to the etiology of injury

Occurrence mechanism	Number of cases	Percentage	Valid percentage	Cumulative percentage
Traffic accident	6	54.5	54.5	54.5
Falling from the height	4	36.4	36.4	90.9
Sports injury	1	9.1	9.1	100.0
Total	11	100.0	100.0	

Table 2. Descriptive statistical analysis of the cases

	N	Minimum	Maximum	Mean	Standard deviation
Age (year)	11	28.0	64.0	41.182	12.1476
Time for surgery (days)	11	1.00	32.00	7.3636	10.36603
Scapholunate angle (degrees)	11	37.30	70.40	49.1182	8.75326
Scapholunate gap (mm)	11	1.20	2.80	2.0545	0.53733
Flexion-extension arc (degrees)	11	90.00	15.00	130.9091	17.58098
Pronation-supination arc (degrees)	11	140.00	160.00	155.4545	6.10514
DASH	11	0.00	10.90	5.5909	3.25068
Herzberg score	11	70.00	100.00	89.0909	9.43880
Jamar operated (kg)	11	15.00	35.00	27.2727	6.31016
Jamar intact (kg)	11	16.00	46.00	29.9091	9.81279

DASH: Disabilities of the Arm, Shoulder and Hand

patients who presented late, findings in favor of carpal tunnel syndrome were detected in the preoperative evaluation. However, no additional intervention was needed in this case, and the symptoms of the case, which was followed closely, disappeared completely in the 6th month.

DISCUSSION

Carpal injuries are rare injuries, which complicates the classification and treatment of these injuries. The main factor affecting the outcome is the delay of treatment[6]. Herzberg divided these injuries into three according to the timing of treatment: Those treated in the first week; acute phase, delayed phase between eight and forty-five days; and chronic phase after 45 days[4]. The most common reason for delay in treatment is failure to diagnose in the early period. This condition is encountered in approximately 25% of cases[6]. In our practice, we have observed that the time between trauma and surgery can differ up to 3 years in these patients. Surgery was performed in the acute phase in 6 of our cases and in the delayed phase in the remaining 5 cases. Although the relatively small number of our patients did not provide clear statistical data, we observed a close relationship between functional scores and time of surgery. The functional results of our patients who underwent surgery in the acute phase were found to be better, but it is not possible to present a healthy result because other variables (scapholunate angle, gap, and presence of arthrosis) must be evaluated for this.

Although the palmar ligaments in the scaphoid proximal pole are theoretically important stabilizers, it is difficult to repair them by direct observation[7]. There are also publications showing that possible carpal tunnel syndrome can be treated in the same session by using the volar approach[8]. The reason why we prefer the dorsal approach in our practice is to have the chance to directly observe the scapholunate interval in addition to reduction with the dorsal approach and subsequent pin placement with direct observation.

In addition, the ability to easily repair the dorsal scapholunate ligament can be considered as another advantage of this approach. There was no difficulty in finding the ligament to be repaired in any of our cases, which might be related to the fact that our patients were not in the chronic period.

It is a known fact that persistence of the scapholunate gap above 3 mm adversely affects the results and causes instability[7]. In our study, we did not observe a gap exceeding 3 mm in any of our patients, and we did not observe any findings in favor of instability in any of our patients.

It has been reported in the literature that a scapholunate angle greater than 70° will lead to poor results[9]. In one case (9%), the scapholunate angle was above 60°. Although it did not present a healthy statistical datum due to the relatively small number of cases, the lower functional scores in this case than our other patients were considered in line with the literature.

Wrist grip strength was found to be at the rate of 65% compared to the healthy side. Although we think that this difference is due to the fact that the dominant side of the patients is affected and the difference between trauma and surgery time is effective, more patient numbers are needed to give healthy results. In a more comprehensive study, it was reported that the results of grip strength were approximately 65% compared to the intact extremity, and the factors that adversely affected the results were reported as affected dominant extremity, major arc injuries and isolated pinning[10]. We think that the reason why our results are relatively better is that our patients had isolated minor arch injuries and ligament repair.

While pain, stiffness and loss of strength are other known complications, it has been reported that wrist arthrosis develops at rates of up to 58% in 8-year follow-up[9]. In our study, we observed findings in favor of arthrosis only in 1 patient (9%).

Proper joint restoration is an important step in treatment because carpal malalignment has been recognized as a precursor of joint arthrosis. Even with excellent bone alignment and complete ligament healing, patients should not expect to have a normal wrist. The goal of proper treatment is a stable wrist with minimal pain and a functional ROM[11]. All these show that perilunate dislocations are injuries that are difficult to treat and prone to complications, no matter how meticulously every step in the treatment is performed. In the light of all this information, it should be kept in mind that perilunate injuries can leave a functionally limited extremity even if the treatment is very well done, and it should also be kept in mind that the damaged structures can be treated with maximum care and close follow-up.

Study Limitations

Our study includes some limitations. These are the retrospective evaluation of the cases, the relatively small number of patients, and the absence of a comparison group. Longer follow-up data are needed for late-stage arthrosis.

CONCLUSION

In conclusion, perilunate dislocations are rare cases, and both early diagnosis and surgery have extremely important effects on functional outcomes. Long-term close follow-up of these cases is needed in terms of possible complications.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained for the study from Tekirdağ Namık Kemal University Faculty of Medicine Ethics Committee (29.12.2020/2020.263.12.08).

Informed Consent: Retrospective study.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Ü.Ç., A.S., F.F., A.P., İ.B.Ö., Concept: M.Ü.Ç., F.F., Design: M.Ü.Ç., F.F., Data Collection or Processing: M.Ü.Ç., A.S., F.F., A.P., İ.B.Ö., Analysis or Interpretation: M.Ü.Ç., A.P., İ.B.Ö., Literature Search: M.Ü.Ç., A.S., Writing: M.Ü.Ç., A.S., İ.B.Ö.

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

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The Impacts of Intraoperative Ultrasonography Use on Revision Rate in Cases of Brain Tumor

Beyin Tümörü Olgularında İntraoperatif Ultrasonografi Kullanımının Rezeksiyon Oranına Etkisi

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ABSTRACT

Aim: Intraoperative ultrasonography is an accessible and cost-effective monitoring technique that provides a simultaneous view with minimum risk. Despite these advantages, it is still not in use. This study aimed to identify whether the ultrasonography technique would be advantageous for both surgeons in the preoperative period and patient in the postoperative period in cases where intraoperative ultrasonography was used.

Materials and Methods: This retrospective study included data of the cases (n=113) diagnosed with a brain tumor in Tekirdağ Namık Kemal University Hospital between January 01, 2015 and December 31, 2020. The cases operated without using ultrasonography (n=38) formed the control group (group 1), while the cases operated by using ultrasonography (n=75) formed the study group (group 2). In all cases selected randomly, the amount of bleeding during the operation, length of the operation and postoperative stay in the hospital, and residue tumor amount were compared. Data obtained were evaluated statistically. The results were presented in mean±standard deviation and/or percentage (frequency). The alpha significance value was accepted as <0.05 in intergroup comparisons of the data obtained by being evaluated in the 95% confidence interval.

Results: The average age of the cases in group 1 was 56.7±139 years while it was 57.7±13.2 in group 2. In intergroup comparisons, there was no statistically significant difference (p>0.05) between age (p=0.61), gender (p=0.74), and size of the tumor (p=0.27). It was observed that the average length of the operations of the cases in group 2 was shorter than that of group 1 (p=0.03), and this result was statistically significant (p<0.05). It was reported that the amount of bleeding of the cases in group 2 was also statistically significant (p<0.05) as against group 1. The gross total resection rate of cases in group 1 was calculated as 73.7% while it was 89.3% in group 2. It was understood that the amount of residue in group 2 compared to group 1 was statistically less (p<0.05) in a significant way (p=0.03). In addition to all these, it was found that the length of stay in group 2, which included cases operated with ultrasonography, was shorter than in group 1, which included cases operated without using ultrasonography (p=0.01).

Conclusion: The use of intraoperative ultrasonography helps the surgeon by identifying resection margin and revealing the relationship between surrounding neural and vascular structures, thus increasing surgical safety. At the same time, the use of ultrasonography decreases the length of operation, amount of bleeding, and length of stay in the hospital, and increases gross total resection rates.

Keywords: Brain tumors, intraoperative ultrasound, microsurgery

ÖZ

Amaç: İntraoperatif ultrasonografi eş zamanlı görüntü sağlayan, kolay erişilebilen, minimum riskli ve uygun maliyetli bir görüntüleme tekniğidir. Bu özelliklerine rağmen halen yaygın kullanılmamaktadır. Bu araştırmada intraoperatif ultrasonografi kullanılan olgularda, ultrasonografi tekniğinin hem preoperatif dönemde cerraha hem de postoperatif dönemde olguya faydasının olup olmayacağının araştırılması amaçlandı.

Gereç ve Yöntem: Bu retrospektif araştırmaya 01 Ocak 2015 ve 31 Aralık 2020 tarihleri arasında, Tekirdağ Namık Kemal Üniversite Hastanesi'nde beyin tümörü tanısı alan olgulara (n=113) ait veriler dahil edildi. Ultrasonografi kullanılmadan opere edilen olgular (n=38) kontrol grubunu (grup 1) oluşturuyorken, ultrasonografi kullanılarak opere edilen olgular (n=75) çalışma grubunu (grup 2) oluşturdu. Randomize olarak seçilen tüm olgularda, cerrahi esnasında gözlemlenen kanama miktarları, cerrahi süreleri ile postoperatif hastanede kalış süreleri ve rezidü tümör miktarları karşılaştırıldı. Elde edilen veriler istatistiksel olarak değerlendirildi. Sonuçlar ortalama±standart sapma ve/veya yüzde (frekans) cinsinden sunuldu. %95 güven aralığında değerlendirilerek elde edilen verilerin gruplar arası karşılaştırmalarında, alfa anlamlılık değeri <0,05 olarak kabul edildi.

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Bulgular: Grup 1'de yer alan olgulara ait yaş ortalaması 56,7±139 yıl iken grup 2'de bu ortalamanın 57,7±13,2 yıl olduğu görüldü. Gruplar arası karşılaştırmalarda yaş (p=0,61), cinsiyet (p=0,74) ve tümör büyüklükleri (p=0,27) açısından herhangi bir istatistiksel anlamlılık görülmedi (p>0,05). Grup 1'e oranla grup 2'de yer alan olguların cerrahi süre ortalamasının daha az olduğu (p=0,03) ve bu sonucun istatistiksel olarak anlamlı olduğu gözlemlendi (p<0,05). Grup 1'e oranla grup 2'de yer alan olgulara ait kanama miktarlarının da yine istatistiksel olarak anlamlı olduğu raporlandı (p<0,05). Grup 1'de yer alan olgularda gross total rezeksiyon oranı %73,7 olarak hesaplanırken grup 2'de bu oranın %89,3 olduğu görüldü. Grup 2'de rezidü miktarının grup 1'e oranla istatistiksel olarak anlamlı derecede (p=0,03) daha az olduğu anlaşıldı (p<0,05). Tüm bunlara ek olarak ultrasonografi kullanılan olguların yer aldığı grup 2'deki olguların hastanede kalış süresinin, ultrasonografi kullanılmayarak opere edilen grup 1'de yer alan olgulara oranla daha az sürede olduğu anlaşıldı (p=0,01).

Sonuç: İntraoperatif ultrasonografi kullanımı ile rezeksiyon sınırı belirleme, çevre nöral ve damarsal yapılarla ilişkiyi ortaya koyarak cerraha yardımcı olup, cerrahi güvenliği artırmaktadır. Aynı zamanda ultrasonografi kullanımı cerrahi süreyi, kanama miktarını, hastanede kalış sürelerini azaltmakta ve gross total rezeksiyon oranlarını artırmaktadır.

Anahtar Kelimeler: Beyin tümörleri, intraoperatif ultrason, mikrocerrahi

INTRODUCTION

Today, thanks to the widespread use of conventional imaging studies and the development of microsurgical methods, mortality and morbidity rates in neurosurgery operations have decreased significantly. With the use of computerized tomography (CT) and the development of magnetic resonance imaging (MRI) technology, the anatomical location and dimensions of the tumor have been revealed more clearly and tumor resection has begun to be performed at surgical margins[1].

The earliest use of diagnostic ultrasonography (USG) to detect brain tumors was in the 1930s by the Dussik brothers[2]. At similar times, the rate of development of intracranial imaging was slowed by the thought that ultrasound waves could damage tissue[2].

Leksell described midline encephalography in 1956 and used the shift in echo signals in midline structures to detect mass lesions such as hematomas[3]. Thus, intraoperative ultrasonography (IOUS) started to be used in the field of neurosurgery, but it did not become widespread. It is known that the factor that increases the disease-free survival the most in tumor surgery is gross total resection (GTR). GTR is one of the techniques based on the surgeon's ability to determine tumor tissue boundaries and features intraoperatively[4,5]. By providing real-time images, IOUS can be beneficial for the surgeon to plan or follow the tumor excision. IOUS may be more advantageous than navigation or intraoperative MRI in demonstrating certain features of central nervous system tumors due to many reasons such as inexpensiveness and ease of use, as well as repeatability and easy access during surgery.

These advantages have made IOUS the most important alternative in showing tumor resection margins and edges in adult and pediatric patients[6,7]. Neuronavigation systems sometimes do not allow obtaining real-time images due to changes in tumor and surrounding tissues during surgery[8,9].

From this point of view, iOUS can enable us to obtain real-time images superior to navigation with the right probe and experienced hands. IOUS is not a new technology. It has recently started to be used more widely with improved image quality and smaller ultrasonography probes[7,9].

The advantage of IOUS is to determine the location of the corticotomy after craniotomy and to minimize the risk of residue caused by brain shift[9].

Therefore, in this research, in order to demonstrate the effectiveness and benefits of using IOUS, it was aimed to compare the data of the patients who were operated without using IOUS in their surgery with the data of the cases who were operated using IOUS. In this way, we believe that the surgical experience on the use of IOUS can be transferred.

MATERIALS AND METHODS

Study Design

The data of the cases (n=113) diagnosed with brain tumor and operated by two different surgeons in the Neurosurgery Clinic of Tekirdağ Namık Kemal University Hospital between January 01, 2015 and December 31, 2020 were evaluated retrospectively.

In the archive files of the cases included in the study, it was understood that MRI examinations had a strength of 1.5 Tesla. The cases who were operated without using IOUS (Siemens Acuson X300 brand, Cat≠1547B05, Korea) formed the control group and were named group 1 (n=38). The cases operated using IOUS formed the study group and were named group 2 (n=75). Hospital files and archive images of the cases in both groups were examined. The numerical data obtained during the reporting were recorded in Microsoft Office program (version 10) Word and Excel lists.

The data of the cases whose preoperative and postoperative MRI examinations could not be reached were not included in

the study and were excluded from the study. For the cases in all groups, demographic data, duration of surgery, amount of bleeding, and length of hospital stay were recorded.

Preoperative brain MRI images and control contrast-enhanced brain MRI scans (Sectra Medical Systems™, IDS7) displayed within postoperative 24-72 hours of all operated cases were evaluated, and preoperative tumor sizes and postoperative residual tumor volumes were calculated (Figure 1).

Those with contrast enhancement below 0.175 cm^3 were considered as GTR, while those with contrast enhancement above 0.175 cm^3 were considered as subtotal resection (STR)[10].

IOUS Technique

In the use of IOUS, after craniotomy, before the dura is opened, the USG probe is prepared by putting gel in a sterile sheath. By wetting the dura with saline, the localization of the lesion is confirmed and its borders are determined by slow movements without pressing the USG probe in the craniotomy area, and the relationship with the surrounding vascular structures is confirmed with the Doppler USG function (Figure 2).

After tumor resection, an image is taken again with USG to see if there is any residue (Figure 3).

USG and surgical microscope images of the cases are stored in digital media. These images were evaluated retrospectively.

Statistical Analysis

Statistical Package for the Social Sciences (version 24) was used for statistical analysis. In the comparison between groups, the evaluation of whether two samples obtained from quantitative-scale observations came from the same distribution was carried out with the Mann-Whitney U test, which is a parametric test. The chi-square (χ^2) test was used for comparison of non-parametric testing and other categorical variables. Results were presented as number (n), mean ± standard deviation, and/or frequency (%). Alpha significance value was accepted as <0.05.

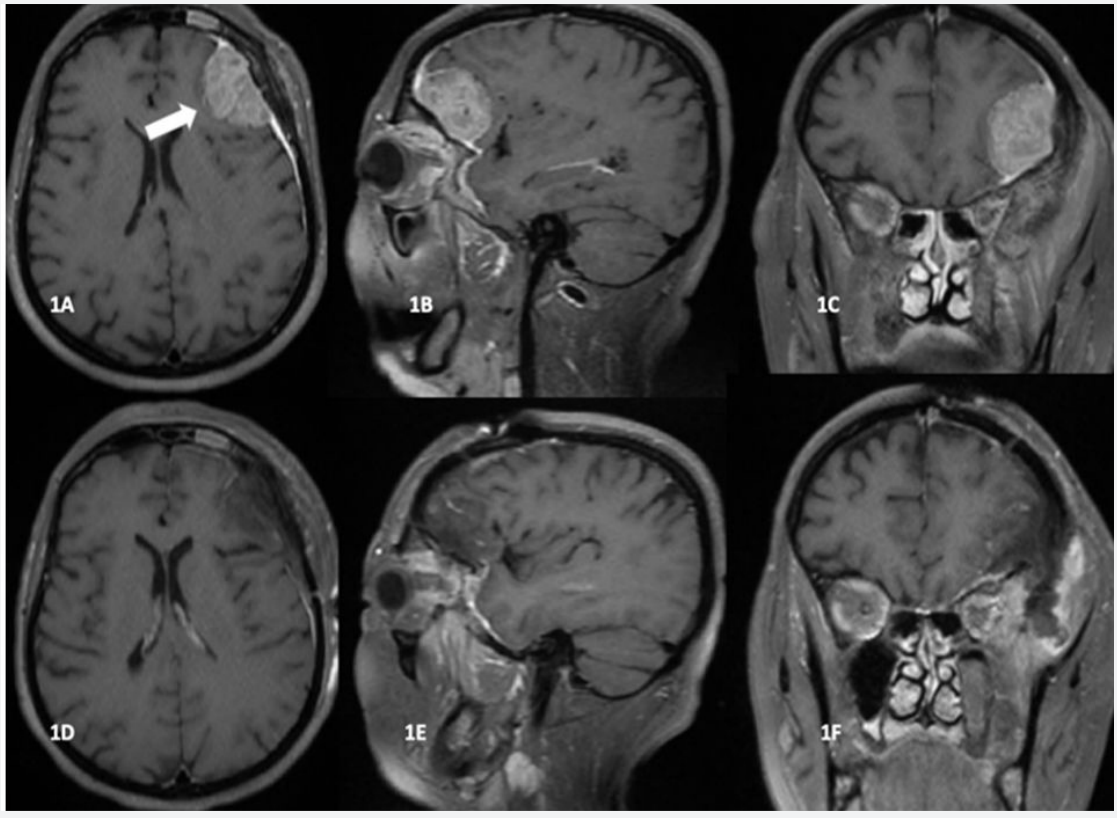

Figure 1. MRI; 1A: In contrast-enhanced T1-weighted sequence axial image, lesion consistent with meningioma with left frontal heterogeneous contrast enhancement (white arrow); 1B: T1-weighted sequence sagittal section shows that the mass is seated on the orbital roof. 1C: T1-weighted sequence, coronal section. 1D: In T1-weighted sequence axial image, it is understood that the mass is totally excised. 1E: T1-weighted sequence, sagittal section image of the same case. 1F: T1-weighted sequence, coronal section

MRI: Magnetic resonance imaging

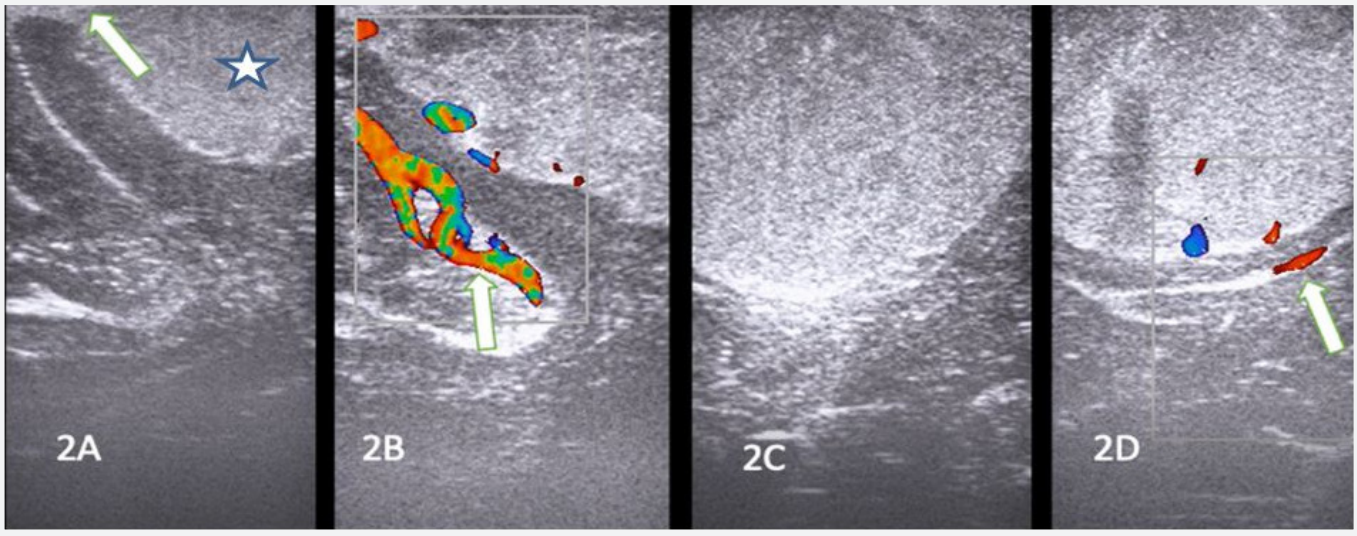

Figure 2. Transdural IOUS images of the same case after craniectomy. 2A: Dural thickening (white arrow), tumoral mass lesion image in the posterior (white star). 2B: In the USG of the same case, vascular structures adjacent to the tumor are observed in the intraoperative Doppler image (white arrow). 2C: Progression of the frontal part of the tumor pushing the brain parenchyma. 2D: Relationship with vascular structures in the frontal part

IOUS: Intraoperative ultrasonography, USG: Ultrasonography

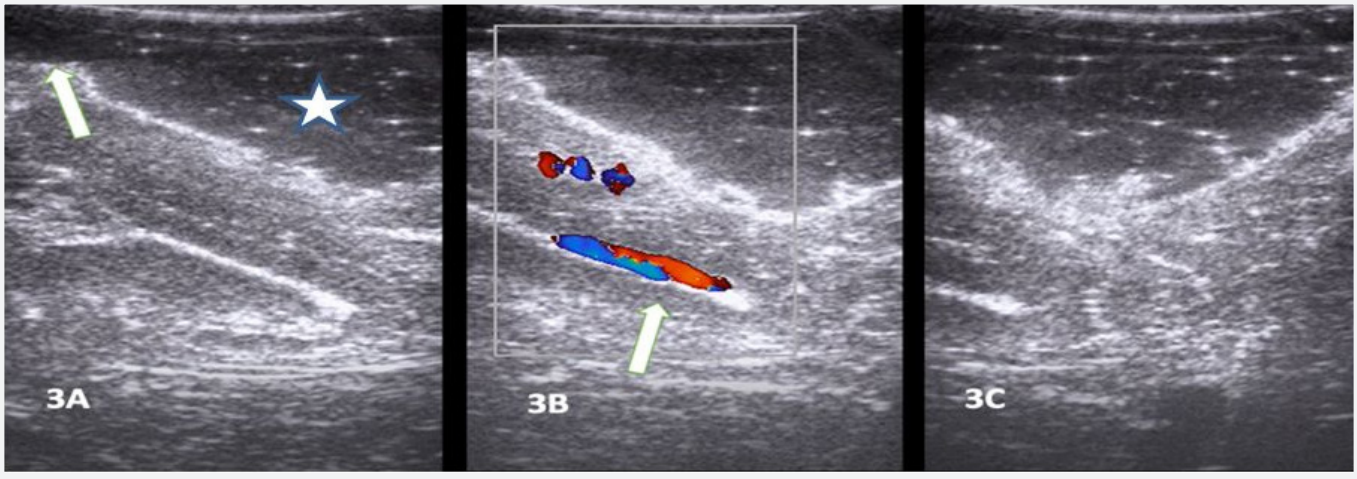

Figure 3. IOUS images after total excision of the tumor; 3A: Anechoic filled saline collection is observed in the extra axial area in the operation lodge (White star). No residual tumor lesion is observed in the images. Normal parenchyma is observed behind the fluid collection. 3B and 3C; Intraoperative Doppler examination reveals vascular structures in the parenchyma (white arrow)

IOUS: Intraoperative ultrasonography

RESULTS

Group 1 consisted of 18 male and 20 female cases and group 2 consisted of 38 male and 37 female cases. The data of 113 cases included in the study are summarized in Table 1.

While the median age of the cases was 59 years (minimum 20; maximum 86), the mean ages of the cases in group 1 (n=38) and group 2 (n=75) were 56.7±13.9 and 57.7±13.2 years, respectively.

There was no statistically significant difference between the groups in terms of age and gender (p=0.61; p=0.74). While the mean tumor size was 28.2±27.8 cm^3 in group 1, it was 34.3±107.4 cm^3 in group 2. Tumor sizes were found to be similar in both groups (p=0.273).

However, while USG was found to be beneficial in each case in the group using IOUS, it was found that one of the lesions could not be seen in one case. In the patient having lung cancer with multiple metastases, three metastases were found to be removed from the craniotomy area in the postoperative MRI sections. In the pre-closure control of the metastasis adjacent to the midline sagittal sinus, it was noted that the probe did not see the lesion under the bone tissue.

It was reported that the mean surgical time of the cases in group 2 was 276.8±76.4 minutes and this time was less than in group 1, whose mean surgery time was 300.4±75.9 minutes (p=0.03).

While the mean amount of bleeding was 482.1±149.1cc in group 1, it was 339.7±1208 cc in group 2. Compared to group 1, the amount of bleeding in group 2 was found to be statistically significantly less (p<0.05).

In addition to all these, GTR was detected in 28 cases and STR in 10 cases in group 1, while the rate of GTR was 73.7%. In group 2, 67 cases were evaluated as GTR and eight cases as STR, and the GTR rate was calculated as 89.3%. It was noted that the amount of residue in group 2 was significantly less than in group 1 (p=0.03).

The histopathological distribution of the cases between the groups is summarized in Table 2.

DISCUSSION

The purposes of using intraoperative imaging methods are to find the localization of the tumor accurately and precisely and

Table 1. Comparison of demographic, clinical and surgical data of the cases according to the groups with and without ultrasound usage

		Group 1 (USG-) (n=38)		Group 2 (USG1+) (n=75)		
		Mean±SD/n	Median	Mean±SD/n	Median	p*
Age (year)		56.7±13.9	56.5	57.7±13.2	60.0	0.61
Gender	Male	18 (47.3%)		38 (50.6%)		0.74
	Female	20 (52.7%)		37 (49.4%)		
GTR	Yes	28 (73.7%)		67 (89.3%)		0.03
	No	10 (26.3%)		8 (10.7%)		
Tumor size (cm^3)		28.2±27.8	17.8	34.3±107.4	13.0	0.27
Surgical duration (minutes)		300.4±75.9	295.0	276.8±76.4	255.0	0.03
Amount of bleeding (cc)		482.1±149.1	480.0	339.7±120.8	320.0	<0.05
Length of hospital stay (days)		15.4±9.4	13.5	11.4±8.6	9.0	0.05

GTR: Gross total resection, USG: Ultrasonography, SD: Standard deviation

Table 2. Histopathological distribution of the cases between groups

Pathology	Group 1	Group 2	Total number (n)	Frequency (%)
Pilocytic astrocytoma	1	0	1	0.9
Astrocytoma WHO Grade II	1	3	4	3.6
Anaplastic astrocytoma	1	3	4	3.5
GBM	8	19	27	23.9
Medulloblastoma	0	1	1	0.9
Atypical teratoid rhabdoid tm	0	1	1	0.9
Meningioma	9	16	25	22.1
Schwannoma	1	0	1	0.9
AC Ca metastasis	12	21	33	29.1
Breast Ca metastasis	3	5	8	7.1
GIS-originated metastasis	1	2	3	2.7
Clear cell Ca	0	1	1	0.9
Malignant melanoma	0	1	1	0.9
Epidermoid tumor	1	1	2	1.8
Lymphoma	0	1	1	0.9

WHO: World Health Organization, GBM: Glioblastoma, GIS: Gastrointestinal system

to distinguish important surrounding structures. USG has been used for diagnostic purposes in various branches for many years. USG, which was firstly used transcranially in the field of neurosurgery, has started to be used widely over time with the developing technology and the reduction in the size of USG probes. Although it is used in many pathologies such as abscess hematoma and hemangioma, its traditional use has been in the field of tumor resection[11].

On USG images, different pathologies have a diverse and characteristic appearance. Metastatic lesions, meningioma, craniopharyngeoma, hemangioma and acute hemorrhage are seen hyperechogenic. Most glial tumors and edema are seen moderately hyperechogenic. Cystic lesion, necrotic part of high-grade glioma (HGG), center of abscess, chronic hemorrhages and bone are seen hypoechogenic[2].

USG has been used for maximum safe brain tumor resection since the 1980s[12]. Resection margins affect patient survival in HGG, low-grade glioma (LGG), and high-grade meningiomas. Even experienced surgeons can sometimes make a mistake in assessing resection margins. Therefore, ancillary examinations are critical in reliably confirming the margins of intraoperative resection. USG is one of the promising examinations in terms of its providing flexibility and real-time information[13,14].

Serra et al.[15] evaluated resection with USG control before closure in a series of 22 high-grade tumors and reported that 95.5% total resection was achieved.

In the study of Woydt et al.[16] with 45 patients, 38 of whom had high grade, it was mentioned that the use of IOUS could detect residual tumor with high specificity and thus increase GTR.

Sweeney et al.[6], in their retrospective cohort analysis study in which they investigated the effect of using IOUS in brain tumor resection, showed that GTR was at the rate of 81% in cases with different pathologies. A strong correlation was found between IOUS interpretations and postoperative MRI. When the IOUS and postoperative MRI results of the patients who were thought to have STR were examined, they found a 100% correlation. When the false negative IOUS results in patients who were thought to have GTR were examined, it was seen that some of the cases were related to previous resection, chemotherapy and radiotherapy. They thought that these conditions affected the image resolution[6].

In this study, USG was found to be beneficial in each case in the case group for whom IOUS was used, but no lesion was observed in one case. In the patient having lung cancer with multiple metastases, three metastases were removed from the craniotomy area, but in the control before the closure of metastasis adjacent to the midline sagittal sinus, it was found that the probe missed the lesion under the bone tissue. Therefore, we think that craniotomy margins should be kept wide in the use of USG without navigation.

Intraoperative MR imaging, which is one of the intraoperative imaging methods such as USG, has been used in certain centers in recent years. In studies conducted with intraoperative MR, which could not become widespread due to its high cost, it has been stated that intraoperative MRI is superior to two-dimensional (2D) IOUS in capturing residues of 1 cm^3 and below[17,18].

However, in the literature, there are studies suggesting that there is a time loss of approximately 10 minutes in each intraoperative MRI and the cost is higher while the application in IOUS does not affect the surgical time[18].

Mahboob et al.[9], in their meta-analysis on the use of IOUS in the resection of gliomas, found the mean GTR to be 77%. They reported a compliance rate as 82% for postoperative MRI and IOUS, false positive IOUS rate as 9%, and false negative IOUS rate as 9%[9]. In the literature, there are many studies parallel to these results[13,14,18].

It is reported that the use of IOUS in LGG and HGG increases disease-free survival rates[9,19,20].

Especially in the surgery of glial tumors, which are intra-axial masses, the tumor is reached by entering through the cortical minimal incision and the tumor is removed through this opening. It can be quite difficult to control the tumor hidden under the cortex with a small cortical incision with standard surgical microscopes.

At this point, USG clears the confusion in the mind of the surgeon, gives important clues about the point where the incision will be made and which direction to go from the small cortical incision, and can provide residual control at the end of the surgery. Thanks to its fast and easy applicability and guidance, it can increase the speed of the surgeon.

In the series evaluated in this study, surgical times were significantly reduced in the group undergoing USG.

Significant decreases in the amount of bleeding and in the length of hospital stay were observed along with the duration of surgery. Making the separation of tumor and glial tissue easily and choosing the closest place to the tumor in the cortical incision reduce the amount of bleeding and glial tissue damage. Decreased blood loss during surgery can be interpreted as the continuation of brain perfusion within physiological limits.

This may reduce the length of hospital stay by causing the physical and cognitive functions of the cases evaluated in this study to improve in the early postoperative period.

Live mammal subjects can also be used in this type of research[21]. However, it is well known today that the sensitivity of animal-derived tissues and human tissue is different[22,23] and the results obtained from animals can be misleading[24,25]. Data obtained from humans were used in this study. Therefore, we believe that it can contribute to the literature.

Study Limitations

In the series evaluated in this study, it was observed that the GTR ratio increased significantly and we had results consistent with the literature. However, we think that larger series should be studied in tumors with the same histopathological character in order to reveal the survival rates. This is the first limitation of our study. The second limitation of our study was that the cases from whom the data were obtained were from the same race from a single center. We believe that the findings obtained from multiple centers and different races will be more effective.

CONCLUSION

In addition to micro-neurosurgical approaches in brain tumor surgery, the use of IOUS can lead to an increase in the GTR rate, a decrease in the surgical time, the amount of bleeding and the length of stay in the hospital, and can take its place among the low-cost, easy-to-use, safe and effective methods. In addition, a short learning curve may be sufficient for image interpretation and usage experience. In the near future, USG may progress to become one of the indispensable equipment of the neurosurgery operating room.

Ethics

Ethics Committee Approval: The study were approved by the Local Ethics Committee of the Tekirdağ Namık Kemal University (protocol number: 2021.04.01.04, date: 26.01.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.Ç., T.T., Concept: T.Ç., T.T., Design: T.Ç., T.T., Data Collection or Processing: T.Ç., T.T., Analysis or Interpretation: T.Ç., T.T., Literature Search: T.Ç., T.T., Writing: T.Ç., T.T.

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

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Accuracy and Reliability Study of the Simplified Nutritional Assessment Questionnaire (SNAQ) in Turkish Patients in Nutritional Evaluation

Nütrisyonel Değerlendirmede Basitleştirilmiş Beslenme ve İştah Anketinin (SNAQ) Türk Hastalarda Doğruluk ve Güvenilirlik Çalışması

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ABSTRACT

Aim: This study aims to reveal the accuracy and reliability of Simplified Nutritional Assessment Questionnaire (SNAQ), which is a test relatively simple and easy to apply, in the Turkish population.

Materials and Methods: This study was planned as monocentric and prospective. Patients who were hospitalized in the internal medicine ward and over 65 years old participated in the study. Since there is no SNAQ test in Turkish, its English version was translated into Turkish by a certified translator, and then translated back into English again for verification. The sample size of the study was determined as 200 patients. For each patient included in the study, Mini Nutritional Assessment, Nutritional Risk Screening-2002 and SNAQ tests were applied.

Results: Participants consisted of 51% female and 49% male. 55.5% were at the age between 65 and 74 years, 23.5% were between 75 and 84 years, and 21% were over 85 years old. The reliability coefficient of the SNAQ test was found as 0.86. This value satisfied the lower limit criterion of 0.60 proposed in the literature.

Conclusion: Turkish SNAQ was validated and proved to be reliable for the nutritional evaluation of the geriatric Turkish patient population.

Keywords: NRS-2002, MNA, SNAQ, Turkish validation, malnutrition

ÖZ

Amaç: Bu çalışmada oldukça basit ve kolay uygulanabilir bir nütrisyonel değerlendirme testi olan Basitleştirilmiş Beslenme ve İştah Anketi (SNAQ) testinin Türk popülasyonunda doğruluk ve güvenilirliği araştırıldı.

Gereç ve Yöntem: Çalışma tek merkezli prospektif bir çalışma olarak tasarlandı. İç hastalıkları kliniğimize yatan 65 yaş üstü hastalar çalışmaya dahil edildi. SNAQ testinin Türkçe formu bulunmadığından yeminli tercüman tarafından İngilizce'den Türkçe'ye çevrildi ve sağlamasını yapmak üzere Türkçe'den İngilizce'ye çevirisi yapıldı. Çalışmanın örneklem genişliği 200 hasta olarak tespit edildi. Çalışmaya alınan her hastada Mini Beslenme Değerlendirmesi, Nütrisyonel Risk Tarama Aracı-2002 ve SNAQ nütrisyonel değerlendirme testleri uygulandı.

Bulgular: Araştırmaya katılanların %51'i kadın, %49'u erkekti. Katılımcıların %55,5'i 65 ile 74, %23,5'i 75 ile 84 yaş aralığında ve %21'i ise 85 yaş ve üzerindeydi. Basitleştirilmiş beslenme ve iştah anketinin güvenilirlik katsayısının 0,86 olduğu görülmektedir. Bu değerin literatürde öngörülen 0,60 alt limit kriterini sağlamakta olduğu görüldü.

Sonuç: Türk geriatrik hasta popülasyonunun nütrisyonel açıdan değerlendirilmesinde Türkçe SNAQ doğruluk ve güvenilirliği ispatlanmıştır.

Anahtar Kelimeler: NRS-2002, MNA, SNAQ, Türkçe validasyon, malnütrisyon

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INTRODUCTION

More than 50% of hospitalized patients have varying degrees of malnutrition[1]. Studies have reported that there is a positive correlation between the length of hospital stay and the development of malnutrition[1]. Although there are various nutritional assessment tools to assess hospitalized patients for nutritional risk, there is still no ideal test that can be most recommended and agreed upon. An ideal nutritional risk assessment test should be simple and fast, sensitive and specific, easy to understand, and able to identify patients with moderate and severe malnutrition for early intervention.

The European Society of Parenteral and Enteral Nutrition recommends the Nutritional Risk Screening-2002 (NRS-2002) and Mini Nutritional Assessment (MNA) methods for nutritional assessment[2]. NRS-2002, the predictive validity of which has been demonstrated in many studies, is recommended for hospitalized adult patients[2]. MNA is considered the "gold standard" especially for the elderly patients, but has low efficacy. In addition to questions about diet, the existence of questions that address physical and mental status may explain the limited predictive capacity.

Moreover, there are studies reporting that nutritional risk tests, such as MNA and NRS-2002, which use body mass index as a criterion especially in the elderly patients, cannot be reliable tests.

The aim of this study was to determine the accuracy and reliability of the Simplified Nutritional Assessment Questionnaire (SNAQ) test, which is a very simple and easily applicable nutritional assessment test, in the Turkish population.

MATERIALS AND METHODS

Technical Information

This study was designed as a cross-sectional study and was approved by the Local Ethics Committee of Ümraniye Training and Research Hospital Clinical Research Ethics Committee (date: 16.06.2015; number: B.10.1.TKH.4.34.H.GP.0.01/28). For power analysis, the study of Kruizenga et al.[3] was taken as reference. For the SNAQ test, which included a four-question questionnaire, a minimum of 25 per question, type 1 error of 0.05, and the power of the study was calculated as 80%. A total of 200 patients were included in the study with a 20% loss.

All patients participating in the study were informed about the purpose and duration of the study, the type of applications to be carried out, the objectives, the study forms used, and the purpose for which they were used, and their consent was obtained.

Patients over the age of 65 years, who were admitted to the Internal Medicine Clinic of University of Health Sciences Turkey, Ümraniye Training and Research Hospital, were included in the study. This study was planned as a single-center prospective study. Since there is no Turkish version of the SNAQ test, it was translated from English to Turkish by a sworn translator and translated from Turkish to English for verification. The sample size of the study was determined as 200 patients, and it was planned to be performed in a single center for three months. MNA, NRS-2002 and SNAQ (Figure 1) nutritional assessment tests were applied to each patient included in the study. In the SNAQ test, patients were asked to complete the questionnaire by circling the correct answers. According to the answers given by the patients, they were scored as a=1, b=2, c=3, d=4 and e=5. The sum of the scores corresponding to the answers to the questions forms the SNAQ score. A SNAQ score of ≤14 indicates a significant risk of at least 5% weight loss within six months.

Name: ..... Gender: (please circle) Male - Female
Age: ..... Weight: ..... Height: .....
Date: .....

1. My appetite is
a. Very bad
b. Bad
c. Average
d. Good
e. Very good

2. When I eat
a. I feel full after eating just a few spoonfuls
b. I feel full after eating about a third of the meal
c. I feel full after eating more than half of the meal
d. I feel full after eating most of the food
e. I never feel full

3. Food tastes
a. Very bad
b. Bad
c. Average
d. Good
e. Very good

4. Normally, I eat
a. Less than one meal a day
b. One meal a day
c. Two meals a day
d. Three meals a day
e. More than three meals a day

Figure 1. Simplified Nutritional Assessment Questionnaire (SNAQ)

Statistical Analysis

The research findings were obtained as a result of the analyses performed on the data obtained from the participants, using the SPSS v23.0 package program.

The mean and standard deviation values, which are the descriptive findings of the data obtained, were analyzed and the results were presented in tables. While evaluating the findings, reliability analysis, difference analysis and multiple agreement analysis were applied, and the results were given in tables and graphics.

RESULTS

Of the participants, 51% were female and 49% were male. 55.5% of the participants were 65 to 74 years old, 23.5% were 75 to 84 years old, and 21% were 85 years old and over. The age of the participants ranged from 65 to 95 years. The mean age was 75.88 years and the standard deviation was 9,038. The general characteristics of the patients participating in the study are summarized in Table 1.

Before moving on to the descriptive values of the research variables and the analyses for the compatibility of the variables with each other, the questions whose grouping forms were finalized in the SNAQ were combined according to the results obtained and subjected to reliability analysis. In the reliability analysis, Cronbach's alpha coefficient was taken into account in measuring the internal consistency of the statements.

The reliability coefficient was found to be 0.86. This value provides the 0.60 lower limit criterion predicted in the literature[3,4]. The obtained values revealed a high degree of internal consistency of the statements on the (SNAQ) used in the study.

The NRS-2002 scale ranged from 0 to 6 points.

At the same time, its mean was 2.70 and its standard deviation was 1.707. When the MNA scale was examined, it was seen that the scale was scored between 1 and 30, with a mean of 16,563 and a standard deviation of 7.0890. It was observed that the scores of the SNAQ scale were between 4 and 20, with a mean of 12.01 and a standard deviation of 3,732 (Table 2).

When Table 3 is examined, it is seen that there is a 2-dimensional structure. The Cronbach's alpha value of the first dimension was 0.948 and the Cronbach's alpha value of the second dimension was 0.792, and reliability levels were found to be high. The first and second baseline inertia values were calculated as 0.763 and 0.445, respectively. While the first dimension explains 76.33% of the total inertia, the second dimension explains 31,809%. On the other hand, the eigenvalues obtained as a result of the analysis were found as λ_1=5,343 and λ_2=3,117. The eigenvalues obtained give an exact measure of the fit between the real graph and the resulting two-dimensional graph.

Accordingly, the fit value between the real graph and the two-dimensional graph obtained is 8,460.

Figure 2 shows the multiple fit analysis graph. When the graph obtained as a result of multiple coherence analysis is examined, it is determined that;

- The group without nutritional deficiencies in the SNAQ scale and those without nutritional deficiencies in the NRS-2002 scale were compatible,

- The nutritional deficiency group in the SNAQ scale was compatible with the nutritional deficiency group in the NRS-

Table 1. General characteristics of the individuals participating in the study

Groups	Frequency (n=200)	Percentage (%)
Gender		
Female	102	51
Male	98	49
Age		
Age range of 65-74 years	111	55.5
Age range of 75-84 years	47	23.5
Age 85 years and over	42	21

Table 2. Descriptive findings of all patients

Variables	N	Minimum	Maximum	Mean	Standard deviation
NRS-2002	200	0	6	2.7	1.707
MNA	200	1	30	16,563	7,089
SNAQ	200	4	20	12.01	3,732

NRS-2002: Nutritional risk screening, MNA: Mini Nutritional Assessment, SNAQ: Simplified Nutritional Assessment Questionnaire

Table 3. Multiple fit analysis values

Size	Cronbach's alpha	Eigenvalue	Inertia	Explanatory percentage
1	0.948	5,343	0.763	76,333
2	0.792	3,117	0.445	44,524

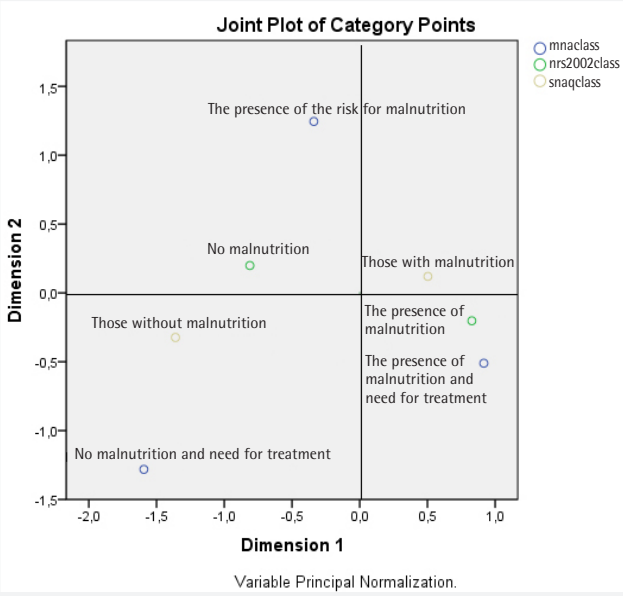

Figure 2. Multiple fit analysis graph

2002 scale and those in need of treatment for nutritional deficiency in the MNA scale,

- The group with the risk of nutritional deficiency in the MNA scale and those without nutritional deficiency and the need for treatment were not compatible with the other groups.

DISCUSSION

With this study, the accuracy and reliability of the Turkish SNAQ questionnaire has been proven in the nutritional evaluation of the hospitalized Turkish geriatric patient population.

Malnutrition is a condition that is not noticed by many clinicians, and even if it is diagnosed, its treatment is not dealt with much[4]. According to studies, early diagnosis and adequate and qualified treatment of malnutrition can prevent complications, accelerate recovery, and make an important contribution to the fight of the elderly in preserving their functionality and preventing the loss of their quality of life[5]. Therefore, early recognition and appropriate treatment of malnutrition are of great importance. Its prevalence can be found to be 23-62% in the elderly in the hospital and 85% in the patients staying in the nursing home[6].

In our study, similar results were obtained with other studies, and the NRS-2002, MNA and SNAQ scales showed a statistically significant difference according to age.

In a meta-analysis of 36 studies examining hospital malnutrition using MNA between 1997 and 2006 in different countries, it was seen that the mean malnutrition rate was 23% (1-74%) and the risk of malnutrition was 46% (8-63%)[7].

In another meta-analysis in which the nutritional status of hospitalized elderly individuals was questioned using various methods, malnutrition was found at rates ranging from 0.7% to 76.7%[8]. The reason for the different malnutrition rates found in malnutrition studies from the past to the present is not only the differences in geographical and medical practices, but also different societies and different malnutrition detection methods that are used[8].

Unfortunately, different definitions of malnutrition and different methods that are used prevent direct comparison of the obtained results regarding the risk of malnutrition in the hospital.

Elderly malnourished patients, on the other hand, have 2-20 times more complications, nearly 100% longer hospital stays, and increased hospital costs than individuals without malnutrition[9]. In addition, in elderly individuals, malnutrition is associated with time of re-admission to the hospital, infections, gait disturbances, falls, fractures, and delayed healing of wounds[10]. In a systematic review, it was stated that individuals with low MNA scores had longer hospital stays than those with high MNA scores[11]. Unlike these studies, some studies reported that no relationship was found between malnutrition and length of hospital stay[12,13].

In our study, it was determined that people between the ages of 65 and 74 years had lower MNA levels than those who were between the ages of 75 and 84 years and those aged 85 years and over.

In the SNAQ scale, people aged 65 to 74 years were found to have higher SNAQ levels than those aged 75 to 84 years and those aged 85 years and over.

Also, people aged 85 years and over had lower SNAQ levels than people aged 75 to 84 years.

In the study of Leistra et al.[14] involving heterogeneous patients followed up in the hospital, it was reported that the SNAQ test was a reliable, fast and easy-to-apply test in determining the nutritional risks of patients.

In our study, the NRS-2002 levels of people aged 75 to 84 years were higher than those aged 65 to 74 years. At the same time, people at the age of 85 years and over had higher NRS-2002 levels than people aged 65 to 74 years and 75 to 84 years.

MNA is a rapid, patient-friendly, inexpensive nutritional assessment method that does not require laboratory examinations and was developed for use in the evaluation of the nutritional status of the elderly in staying in clinics, nursing homes and hospitals or being defined as frail[15]. Recently, MNA has been widely used in the assessment of nutritional status[15]. The development of the MNA test began in 1989 due to a discussion at the meeting of the International Association of

Geriatrics and Gerontology, and the first article was published in 1994[16].

While the complex biological effects of aging accompanied by socio-economic factors affect the nutritional status of elderly individuals, weakness and physical dependence cause an increase in the prevalence of malnutrition[17].

In our study, 10% of the participants in the MNA scale who did not have nutritional deficiency and did not need treatment were female and 8% were male. Of the participants at risk of malnutrition, 18.5% were female and 18.5% were male. Of the participants with malnutrition and need for treatment, 22.5% were female and 22.5% were male. Of the participants, 18% did not have nutritional deficiency and did not need treatment, 37% were at risk of malnutrition, and 45% were malnourished and in need of treatment. In the SNAQ scale, 14% of the participants without nutritional deficiencies were female and 13% were male. 37% of the participants with malnutrition were female and 36% were male. While 27% of the participants were not malnourished, 73% had malnutrition. In the NRS-2002 scale, 25% of the participants without nutritional deficiencies were female and 25.5% were male. Of the participants with malnutrition, 26% were female and 23.5% were male. While 50.5% of the participants were not found to be malnourished, 49.5% had malnutrition.

In our study, in the light of these values, it was found that there was a difference among the averages of the NRS-2002, MNA and SNAQ scales according to gender; however, it was found that this difference was not statistically significant.

The number of studies on malnutrition in elderly individuals in Turkey is very few. In a multicenter study conducted by Korfali et al.[12], involving 29,139 people and 62 hospitals, 25.0% of 10,325 people over the age of 60 years were found to be at risk of malnutrition with NRS 2002. In another study including 140 individuals over the age of 65 years, who applied to the Gendarmerie Dispensary Internal Medicine Clinic of Karşıyaka District of İzmir Province, the rate of malnutrition and malnutrition risk with MNA was found to be 16.0%[13]. Four hundred and thirteen people who applied to the Internal Diseases Unit of Istanbul University Hospital within 1 year were evaluated with MNA, and 13.0% were found to have malnutrition and 31.0% were found to be at risk of malnutrition[18].

Rolland et al.[19] conducted a study on 175 people aged 65 years and over and they compared SNAQ and MNA in malnourished patients. They concluded that the SNAQ was a rather poor tool for predicting the elderly with abnormal MNA scores, but an abnormal SNAQ result might identify the elderly who would experience future weight loss earlier than MNA[19].

Sties et al.[20], in their study in which they tried to determine the clarity and validity of the SNAQ scale in Brazilian patients, observed that the Brazilian version of the SNAQ was valid and an important tool in the assessment of appetite.

Study Limitations

Our study had some limitations. Our study was a single-center cross-sectional analysis. In addition, the SNAQ scale was evaluated at a single time point.

CONCLUSION

SNAQ has proven its accuracy and reliability in detecting and treating malnourished patients in hospitalized patients, without the need to calculate weight loss or body mass index.

SNAQ is a practical tool that can be easily applied in all Turkish hospitals and all medical departments, without the need for specific details about the nutritional status of patients obtained by nurses or health personnel.

The Turkish version of the SNAQ test, which is a very practical test that has been studied in many countries, is a valid and reliable test in hospitalized patients over the age of 65 years.

Acknowledgement

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Ethics

Ethics Committee Approval: The study were approved by the Local Ethics Committee of the Umraniye Training and Research Hospital (date: 16.06.2015; no: B.10.1.TKH.4.34.H.GP.0.01/28).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.K.T., Concept: K.K.T., Design: K.K.T., S.U.B., Data Collection or Processing: R.S., Analysis or Interpretation: K.K.T., Literature Search: R.S., S.U.B., Writing: K.K.T., S.U.B.

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Analysis of Maxillofacial Traumas at Thrace Region amid COVID-19 Pandemic

COVID-19 Pandemisinin Birinci Yılında Trakya Bölgesi'ndeki Maksillofasyal Travmaların Analizi

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ABSTRACT

Aim: Pandemic caused by Coronavirus disease-2019 has created an unpredicted situation. Due to governmental regulations, a significant amount of health provider task force was relocated for pandemic management. This restrictions put forth a need for pragmatic solutions to cope with the demand of non-pandemic health management. Remote counselling was among these solutions. In this study, we aimed to share our remote counselling approach, also to analyze the maxillofacial trauma (MFT) patients operated during the first year of pandemic, and to compare these results with the results of the previous year.

Materials and Methods: Beginning from May 11th, 2020 to May 11th, 2021, MFT patients were evaluated retrospectively. For comparison, patients referred within the same dates of the previous year were also evaluated. Two groups were constituted as pre-pandemic and pandemic. Groups were compared for demographics, affected facial region, operation performed as emergency or elective, time spanned from referral to surgery, and operative complications. Statistical significance was set as $p<0.05$.

Results: The comparison for age, etiology, affected facial region, type of the operation and complication rates were insignificant among the groups ($p>0.05$). Time spanned from referral to surgery was significantly shorter for the pandemic group in which the remote counselling approach was utilized ($p<0.001$).

Conclusion: Remote counselling approach shortens the time spanned from referral to surgery among MFT patients referred during pandemic. Telemedicine may be used as a powerful tool for the management of MFT patients.

Keywords: Maxillofacial injuries, telemedicine, COVID-19

ÖZ

Amaç: Dünya Sağlık Örgütü tarafından 11 Mart 2020'de Koronavirüs hastalığı-2019 için pandemi ilan edilmesinin ardından, ülkemizde de sağlık hizmet sunumunda bazı değişlikler yaşandı. Bu değişiklikler, mevcut sağlık çalışanı sayısının ve ortaya koydukları iş gücünün, sağlık otoritesi tarafından pandeminin yönetiminde kullanılmak üzere başka alanlara kaydırılmasını da kapsamaktaydı. Bu koşullar beraberinde pandemi harici sağlık hizmetlerinin sunumunda bazı ihtiyaçları da doğurdu. Bu ihtiyaçlar için pratik çözümler ortaya çıktı. Bunların arasında uzaktan konsültasyon da yer almaktadır. Çalışmamızda pandemi sürecinde oluşturduğumuz uzaktan konsültasyon yaklaşımını paylaşmayı, pandeminin birinci yılındaki maksillofasyal travma (MFT) olgularını analiz etmeyi ve 1 yıl önceki MFT olguları ile karşılaştırmayı amaçladık.

Gereç ve Yöntem: On bir Mart 2020 tarihinden 11 Mart 2021 tarihine kadar olan süreçte, yönetilen MFT olguları ve tedavileri geriye dönük olarak değerlendirildi. Bir önceki yılın aynı tarihler arasındaki verileri ile kıyaslandı. Pandemi ve pandemi öncesi olmak üzere iki grup oluşturuldu. Gruplar, demografik özellikleri, travmanın etkilediği yüz bölgesi, uygulanan onarımın acil veya elektif olarak gerçekleştirilmesi, başvuru anından ameliyata kadar geçen süre, operasyon sonrası komplikasyonlar yönünden karşılaştırıldı. İstatistiksel olarak $p<0,05$ anlamlılık düzeyinde değerlendirildi.

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Presented in: This study was partially presented by the responsible author under the title of "Pandemi döneminde Maksillofasyal travmaların yönetiminde uzaktan konsültasyonun etkilerinin tek merkez kapsamında değerlendirilmesi" at the 10th International Trakya Aile Hekimleri Kongresi, in the oral presentations session on March 27, 2021 (09:00-10:30) presented as an oral report.

Bulgular: Gruplar arasında yaş, etiyoloji, etkilenen yüz bölgesi, onarımların acil-elektif dağılımı ve komplikasyonlar yönünden anlamlı fark saptanmadı (p>0,05). Uzaktan konsültasyon yaklaşımının kullanıldığı pandemi grubunda başvurudan ameliyata kadar geçen süre pandemi öncesi gruba göre kısaydı (p<0,001).

Sonuç: Uzaktan konsültasyon kapsamında yönetilen olgularda, hastanın başvuru anından ameliyata kadar geçen süresi anlamlı olarak kısalmıştır. Teletıp, MFT olgularını yönetiminde kolaylaştırıcı bir araç olarak kullanılabilir.

Anahtar Kelimeler: Maksillofasyal yaralanmalar, teletıp, COVID-19

INTRODUCTION

The disease caused by the new type of coronavirus, also known as Coronavirus disease-2019 (COVID-19), continues to be an important problem for public health. A pandemic was declared by the World Health Organization on March 11, 2020 for the new type of coronavirus[1]. On the same date, the health authority in our country announced the first case of COVID-19. After this date, there have been some changes in our professional practice as well as in our daily life. One of the main factors underlying these changes was the number of existing health workers and the shift of their workforce to other areas by the health authority to be used in the management of the pandemic. As a result of this orientation, healthcare organizations had to manage a workload approaching the pre-pandemic period with fewer employees. Different pragmatic solutions emerged under these challenging conditions. One of these was remote consultation (RC) with technology support.

Maxillofacial traumas (MFT) and their treatment is one of the important topics of plastic surgery practice[2]. It is a rule to use imaging methods in planning the treatment of MFT. Today, computed tomography is accepted as the gold standard in this planning process. Tomography series can be easily transferred to other computers or switchboards in digital environment with today's technology.

In this study, we wanted to evaluate the usability of these data in the management of emergency MFT within the scope of RC, based on the easy transfer of digital data. In this context, we aimed to share the RC approach that we created with the command and control center (CCC) of the health authority during the pandemic process in our clinic, which is the only center in the management of MFT in the Thrace region. As a primary inference, we determined to compare the patient data of the pre-pandemic period with the patient data of the pandemic period. As a secondary inference, we aimed to create an analysis of the MFT that occurred in our region in the specified time period.

MATERIALS AND METHODS

Selection and Definition of Cases

In the period from March 11, 2020, when the first COVID-19 case was diagnosed in our country, to March 11, 2021, MFT cases and treatments were evaluated retrospectively. Data from the previous year between the same dates were used for comparison. The cases were divided into two groups as "pre-pandemic" and "pandemic". As inclusion criteria for the study, cases in the adult age group consulted by CCC for patient referral or consultation were determined. Patients who applied to our hospital with their own means, patients with additional pathology other than MFT, and patients who were admitted to the hospital after 24 hours following trauma were not included in the study. The pediatric age group was not included in the study.

Technical Information

In order to facilitate communication with CCC, we were asked to send a video containing the patient's tomography, as well as verbally consulting the patient. The minimum features of the tomography standard were determined as follows: the tomographies taken should include the entire facial base starting from the frontal bone and including the lower border of the mandible, with 5 mm or thinner sections, and including at least one of the sections in the coronal or axial plane. It was requested to renew the tomographies that did not meet these technical specifications.

Within the scope of RC, videos containing maxillofacial tomographies of patients who applied during the pandemic period were sent to us using a cellular network (4G).

The included cases were evaluated in terms of demographic characteristics, facial area affected by trauma, emergency or elective repair, time from admission to surgery, and postoperative complications. These results were compared with the previous year's data.

Statistical Analysis

Within the scope of the study, demographic data of the cases were calculated using percentage and frequency from descriptive statistics. Relevant tests were performed using the mean and standard deviation for patient age and postoperative time. Before using the hypothesis tests, the Shapiro-Wilk test was used to examine whether the data showed normal distribution. Logarithmic variation was applied to the categories that did not show normal distribution. Parametric hypothesis tests were applied to the data after the variation. The Student's

t-test was used to compare two groups of quantitative data, and the chi-square test was used to compare qualitative data. IBM Statistical Package for the Social Sciences (SPSS) 19.0 package program (SPSS Inc., Chicago, IL, USA) was used in the analyses and $p<0.05$ was accepted as significance level.

RESULTS

Fifty-four cases were included in the study. Of the cases, 21 (38.8%) were in the pandemic group, and 33 (61.2%) were in the pre-pandemic group. The mean age was 39.9±8.4 years for the pandemic group and 40.9±11.5 years for the pre-pandemic group. There was a normal age distribution in both groups ($p>0.05$). The number of female patients was three (14.2%) in the pandemic group and five (15.1%) in the pre-pandemic group.

In the pandemic group, the most common etiology was in-vehicle traffic accidents (IVTA) with 10 (47.6%) cases. In the pre-pandemic group, the most common cause was IVTA with 18 (54.5%) cases. During the pandemic period, the rate of maxillofacial fracture cases developing after beating was 38.1%, and this rate was 30.3% in the pre-pandemic period.

Percentage changes in the frequencies of IVTA and beating were not statistically significant ($p>0.05$). Detailed data and comparison are given in Table 1.

The most frequently affected facial bone was the mandible in both groups. While this was 14 cases (66.6%) during the pandemic period, it was 19 (57.7%) cases before the pandemic. This percentage difference was not statistically significant ($p>0.05$) The affected facial region distributions are given in Figure 1.

Four (19%) cases were operated urgently in the pandemic group. In the pre-pandemic group, the number of patients who were operated urgently was three (9.1%). This increase during the pandemic period was not statistically significant ($p>0.05$). Cases that were operated urgently consisted of those whose tongue could cause airway obstruction due to mandibular fracture and cases that caused limitation of gaze in the orbita.

The mean time between admission and operation was 2.05±1.49 days for the pandemic group and 6.94±4.01 days for the pre-pandemic group. The time from admission to surgery was significantly shortened during the pandemic period ($p<0.001$).

Table 1. Prevalence of trauma etiologies in groups

Etiology	Pre-pandemic	Pandemic
IVTA	18 (54.5%)	10 (47.6%)
Beating	10 (30.3%)	8 (38.1%)
Work accident	5 (15.2%)	3 (14.3%)
Total	33 (100%)	21 (100%)

IVTA: In-vehicle traffic accident

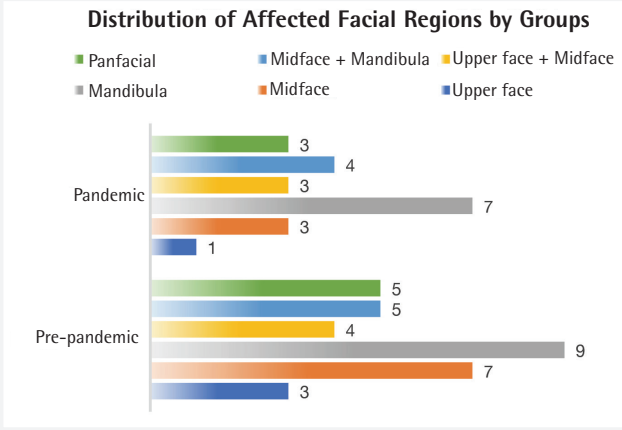

Figure 1. Distribution of affected facial regions by groups

Surgical site infection developed in two (9.5%) cases in the pandemic group, and in four (12%) cases in the pre-pandemic group. Surgical site infections were managed with local wound care and antibiotic therapy. No surgical procedure was performed.

DISCUSSION

With the beginning of the COVID-19 pandemic, certain order changes have occurred in both our social and professional lives. As a significant part of the healthcare staff's workforce was directed to combat the pandemic, there were some regressions in the healthcare services that healthcare institutions could offer to non-COVID patients. Different solutions emerged to compensate for these regressions. These include RC and rapid-transition protocols for surgical units[3-6].

Considering the results of the study, it is remarkable that the mean time from admission to surgery (2.05±1.49) of the patients who were evaluated with RC and admitted during the pandemic process was shorter than the mean time (6.94±4.01) in referrals without the use of RC ($p<0.001$). Maxillofacial tomographies of the patient are evaluated with RC before the patient is admitted by the team that will perform the possible surgery. Thus, whether the patient needs surgery or not is determined more clearly by evaluating the tomography as well as verbal data. For the same reason, the RC allows the doctor who will perform the surgery to create the surgery plan (like the possible duration of the surgery, the supply of internal fixation systems to be used) before the patient arrives. We think that this preparation process, which is carried out before the patient's admission, plays a major role in shortening the time from admission to surgery.

In addition, since only the patients who are accepted as candidates for surgery are hospitalized within the scope of the RC, the surgical preparation of the patients in the

pandemic group (such as taking a polymerase chain reaction test, preparations for general anesthesia) begins as soon as the patient is admitted to the service and hospitalized in the clinic.

In the pre-pandemic period, since patients were only consulted verbally, although there is the process of taking a tomography, the process of reporting this tomography and the process of consulting in the framework of emergency trauma behind the referral of the patient to us, additional processes such as evaluating the patient as a candidate for elective surgery and referring the patient to the outpatient clinic for surgical preparations are involved in the management of MFT patient.

We believe that elimination of these additional processes within the scope of RC also explains the shortness of the time from admission to surgery during the pandemic period.

During the pandemic process, our hospital served as the only reference center in the region for MFT. When the applications before and during the pandemic are examined in terms of etiology, IVTA is the most common cause of MFT in both groups, followed by beating. This situation is also compatible with the current literature[7,8]. When the distribution of these two etiology titles according to the groups is examined, it is seen that the rate of MFT due to physical attacks increased during the pandemic period (38.1% during the pandemic period and 30.3% during the pre-pandemic period) and the ratio of IVTA decreased (54.5% before the pandemic and 47.6% during the pandemic period). We could not show the statistical significance of this proportional change. We explain this by the small sample size of our sample. With the lockdowns during the pandemic process, the rates of major depression and domestic violence have increased in the society. We explain the proportional increase in MFT cases due to physical attack in our study with the secondary effects of restrictions in this pandemic period. Studies from different countries have also underlined this finding[9,10]. For the same reason, we explain the proportional decrease in MFT cases due to traffic accidents with the lockdowns in the pandemic process. The decrease in the number of vehicles in the traffic and the number of people on the street in a unit of time also reduced the number of accidents.

Compared to the pre-pandemic period, we explain the decrease in the total number of patients referred by CCC during the pandemic, with the restrictions imposed by the state authority (such as lockdowns at certain hours). In addition, as we mentioned, besides verbal consultation of the patients, the patient's tomographies were also directed to us during the pandemic process, and in the light of these data, only the patients who were accepted as candidates for surgery were included in this study. We believe that these two reasons explain the decrease in the number of cases despite our role as a single center during the pandemic process.

Remarkably, four patients underwent emergency surgery during the pandemic. Compared to the previous year, this number has increased proportionally. We explain this increase with the fact that we are the only center where these patients are referred during the pandemic process.

In accordance with the current literature, local infection was encountered most commonly in the early period in the postoperative follow-up of the patients.

Increasing local wound care and oral hygiene is the first step in the treatment of wound infections, which are especially common in segmental fractures of the midface and mandible[2]. With this treatment approach, all cases in our patient cohort who developed complications were treated with local wound care and complete healing was achieved.

Telemedicine and virtual consultation methods are also used successfully in orthopedics, which is a branch that frequently uses imaging methods in patient treatment[3,11]. In randomized controlled studies conducted within the scope of this branch, it has been shown that these methods can be used safely in selected patients[4,12]. In order to be used in a wider context, the success of this approach should also be demonstrated by economic and patient satisfaction-based studies.

These findings, which we shared, revealed the necessity of a more comprehensive study. However, in the light of these data involving the borders of the Thrace region, it can be supported that sharing patient images with the physician who will perform the surgery during the consultation is a facilitating factor in the decision of surgery and patient triage.

On the other hand, it is also important to examine patient data within the scope of the Law on the Protection of Personal Data (KVKK)[13]. Tomographs are considered as the patient's personal health data. All of the patients included in the study were patients consulted by us from external centers. As required by good medical practices, the necessity of informing and obtaining verbal consent before all procedures performed on the patient is also essential for obtaining patient photographs and other health data. However, in addition to patient consent in sending tomography videos, it does not create a conflict with the scope of KVKK, since the purpose is legitimate and the existing images are not stored and processed in a data recording system.

A non-cloud-based messaging program running on 4G infrastructure is used to transfer tomography data. This program has an end-to-end encipherment feature, and during the transmission of the message, no third party other than the receiving and transmitting party can access the content.

There is a digital system established by the Ministry of Health, called the Telemedicine System. The purpose of this system is

to report the images taken by different radiologists in order to balance the workload of radiologists between hospitals[14].

In this system, loading the tomographies into the system after they are taken can cause a certain delay, especially during non-working hours. If the center where the tomography has been taken does not have an agreement with the Ministry of Health, or if it is not integrated into this system, then the data will not be uploaded to the system. There is a need for arrangements to be made in this system, which is intellectually innovative.

Study Limitations

The fact that this study shares the results of a single center and its retrospective design are the limitations of this study. We could not find any similar study within the scope of the national literature that we could search. From this point of view, we believe that this descriptive study will have a high contribution to the literature.

CONCLUSION

The COVID-19 pandemic and state authority restrictions in this period have led to a decrease in MFT cases referred to our clinic. Although there is a difference in the etiology of the cases admitted during the pandemic, this could not be supported statistically. In the management of MFT patients in this period, sharing the tomography images of the cases within the scope of UK significantly shortened the patient's time from admission to the surgery. Telemedicine can be used as a facilitating tool in the management of MFT cases.

Ethics

Ethics Committee Approval: The study were approved by the Local Ethics Committee of the Trakya University (protocol number: 2021/267-12/23, date: 31.05.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.D., E.B., Concept: D.D., Design: D.D., E.B., Data Collection or Processing: D.D., Analysis or Interpretation: D.D., E.B., Literature Search: D.D., Writing: D.D., E.B.

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

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A Correlation Between Quantitative Measurement Parameters of Thorax Computed Tomography and Pulmonary Function Test: A Retrospective Study

Toraks Bilgisayarlı Tomografi Kantitatif Ölçüm Parametreleri ile Solunum Fonksiyon Testi Arasındaki Korelasyonun İncelenmesi: Retrospektif Çalışma

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ABSTRACT

Aim: Pulmonary functional and volumetric evaluation is routinely performed with pulmonary function test (PFT). However, volumetric evaluation is also possible in computed tomography (CT) imaging. The aim of this study is to examine the relationship between PFT and CT volumetric findings.

Materials and Methods: Between April 2017 and May 2020, a total of 69 patients (34 males, 35 females) having thorax CT (without any parenchymal disease) and PFT were studied retrospectively. The images and PFT examinations with an optimum quality were enrolled. In CT, the volume and density of both lungs as well as total lung volume (TLV) and total lung density (TLD) were calculated. Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio were recorded for the assessment with CT.

Results: In a total of 69 patients (34 male, 49.3%; 35 female, 50.7%), the mean age was 55±14.56 years, FEV1=2.12±0.87, FVC=2.92±1.05, FEV1/FVC ratio=72.19±13.07, right lung volume=2118.06±662.36, right lung density=-806.8±68.16, left lung volume=1755.35±605.02, left lung density=-774.80±248.98, TLV=3820±1272.35 and TLD=-1597.17±295.70. FEV1, FVC and FEV1/FVC ratio showed a positive correlation with bilateral (right and left) lung volume and density ($p<0.05$).

Conclusion: PFT provides important quantitative pulmonary functional data that can evaluate the severity and course of diseases causing respiratory symptoms. However, in cases where PFT cannot be performed (such as Coronavirus Disease-2019), CT quantitative pulmonary volumetric evaluation can be an alternative in the evaluation of main pulmonary functions.

Keywords: Lung volume measurements, computed tomography, respiratory function test

ÖZ

Amaç: Pulmoner fonksiyonel ve hacimsel değerlendirme rutin olarak solunum fonksiyon testi (SFT) ile yapılmaktadır. Ancak bilgisayarlı tomografi (BT) görüntülemede hacimsel değerlendirme de mümkündür. Bu çalışmanın amacı, SFT ile BT hacimsel bulguları arasındaki ilişkiyi incelemektir.

Gereç ve Yöntem: Nisan 2017 ile Mayıs 2020 tarihleri arasında toraks BT (parankimal hastalığı olmayan) ve SFT yapılan toplam 69 hasta (34 erkek, 35 kadın) retrospektif olarak incelendi. Optimum kalitede görüntüler ve PFT incelemeleri kaydedildi. BT'de, her iki akciğerin hacmi ve yoğunluğu ile toplam akciğer hacmi (TLV) ve toplam akciğer yoğunluğu (TLD) hesaplandı. BT ile değerlendirme için bir saniyedeki zorlu ekspiratuvar hacim (FEV1), zorlu vital kapasite (FVC), FEV1/FVC oranı kaydedildi.

Bulgular: Toplam 69 hastada (34 erkek, %49,3; 35 kadın, %50,7) ortalama yaş 55±14,56 yıl, FEV1=2.12±0,87, FVC=2,92±1,05, FEV1/FVC oranı=72,19±13,07 sağ akciğer hacmi=2118,06±662,36, sağ akciğer yoğunluğu=-806,8±68,16, sol akciğer hacmi=1755,35±605,02, sol akciğer yoğunluğu=-774,80±248,98, TLV=3820±1272,35 ve TLD=-1597,17±295,70 idi. FEV1, FVC ve FEV1/FVC oranı bilateral (sağ ve sol) akciğer hacmi ve yoğunluğu ile pozitif korelasyon gösterdi ($p<0,05$).

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Sonuç: SFT, solunum semptomlarına neden olan hastalıkların ciddiyetini ve seyrini değerlendirebilen önemli kantitatif pulmoner fonksiyonel veriler sağlar. Ancak, SFT'nin yapılamadığı durumlarda (koronavirüs hastalığı-19 gibi) BT kantitatif pulmoner hacimsel değerlendirme, ana pulmoner fonksiyonların değerlendirilmesinde alternatif bir yöntem olabilir.

Anahtar Kelimeler: Akciğer hacmi ölçümleri, bilgisayarlı tomografi, solunum fonksiyon testi

INTRODUCTION

The lung volumes are routinely evaluated by using pulmonary function tests (PFTs) in which total lung capacity (inspiratory volume), static expiratory volumes and dynamic volumes [absolute and relative forced expiratory volume in 1 second (FEV1)] can be assessed. However, the measurement of unilateral or regional lung volumes is difficult in PFT[1].

Lung volumes include tidal volume [(TV); the change in lung volume during normal breathing], inspiratory reserve volume (an extra volume that can be breathed in at the end of normal TV inspiration), expiratory reserve volume (an extra volume that can be breathed out at the end of normal TV expiration), and residual volume (a volume remaining in the lungs at the end of a maximum expiration). Vital capacity is the volume change between the end of a maximum inspiration and the end of a maximum expiration. Functional residual capacity is the volume remaining in the lungs at the end of normal expiration. Total lung capacity is the total volume in the lungs[2].

Computed tomography (CT) of thorax is a modality of choice which is widely used for the evaluation of either mediastinal or pulmonary parenchymal diseases, it provides indices reflecting regional density and it is capable to measure the density or volume of anatomical structures and lungs[1,3].

PFTs are used in combination with imaging in the follow-up of patients with diffuse lung disease. There are some studies in the literature investigating the correlation between PFT and CT in the patients with chronic obstructive pulmonary disease (COPD)[4-7], interstitial lung disease (ILD) or pulmonary fibrosis[8,9], lung transplantation[10], after bronchial valve treatment[11], rheumatoid arthritis[12], lung cancer[13] and in those with scoliosis[14].

In this paper, we aimed to evaluate PFT and CT volumetric results in normal population and whether CT volumetric values could be a good predictor for the assessment of PFT specially in extraordinary situations such as coronavirus disease-2019 (COVID-19), in which PFT is impossible to be performed.

MATERIALS AND METHODS

Study Population

Between April 2017 and May 2020, a total of 69 patients (34 male, 35 female) with any indication, who had thorax CT examination without any pulmonary disease and who had PFT, were scrutinized retrospectively.

Patients without a history of malignancy, chronic disease and lung parenchymal disease (infiltration, consolidation, tumor etc.), those CT images with good quality and inspiration, those at the age of 18 years or above, and those having PFT, were enrolled in the study.

Inclusion criterion was being subjects with normal spirometric values.

Exclusion criteria were as follows:

1) Subjects who had undergone thoracic surgery,

2) Subjects who had a CT finding of pneumothorax, pleural effusion, pneumonia, emphysema, ILD, chronic bronchitis, bronchiectasis, lung bullae, lung abscess, or lung mass, lung neoplasm,

3) Patients with insufficient breathing or CT image quality, having parenchymal disease, being less than 18 years old and those not having PFT were excluded from the study.

4) Active smokers and ex-smokers.

Patients' information was obtained from the hospital's data system.

CT images were achieved from picture archiving and communication system (PACS) and PFTs were obtained from the hospital data system.

This study was approved by the university/local human research ethics committee and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Tekirdağ Namık Kemal University, Non-Invasive Clinical Research Ethics Committee approved the study protocol (approval number: 2020.148.06.10).

Study Protocol

Non-enhanced CT examinations of 70 patients with any indication were included in the study. A 128-row multi-detector CT scanner (Aquilion™ Prime; Canon Medical Systems) was used for CT scanning. Field of view (FOV) of the whole

chest was scanned from the lung apex to the diaphragm with a single breath-hold. The patients were lying in supine position on the table of the device and the arms were above the head.

CT acquisition was done by the following parameters: the current of 100-250 mAs modulated by personal body mass index (BMI) dose; tube voltage of 100 140 kV and collimation of 0.5 mm x 80, gantry rotation time of 0.35 sec, pitch factor of 0.813, FOV: 20x20 cm, slice thickness 1 mm and slice interval 0.8 mm.

Imaging Assessment

Obtained CT images were transferred to PACS (Sectra 7.0, Sectra AB, Linköping, Sweden) and were analyzed at a workstation (Vitrea 2 workstation; Vital Images, Canon, Minnetonka, MN, USA). The assessment was done by an eight-year experienced radiologist.

By using semi-automated pixel-based image segmentation method (region growing algorithm) and manual drawing tools in the workstation, the volume and density of both lungs as well as total lung volume (TLV) and total lung density (TLD) were calculated. The range of density thresholds in semiautomatic segmentation were between -1062 HU and -138 HU (Figure 1).

PFT Assessment

PFT assessment was performed by using a device (MasterScreen PFT System; Jaeger, VIASYS Healthcare, Hoechberg, Germany) of spirograms having the largest FEV1 and forced vital capacity (FVC), selected from at least two technically acceptable spirometric measurements being used in the analysis.

PFT examinations with good quality and sufficiency were included. The values of FEV1, FVC, FEV1/FVC ratio were recorded for the assessment with CT. Also, the values of weight, height and BMI were noted. The median interval between PFT and CT was 1 day (range: 1-2 days). There was no therapeutic application or any applied procedure that might have affected the results.

Statistical Analysis

All data were analyzed using a statistical package program (SPSS version 17.0; SPSS, Inc., Chicago, IL, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods to determine whether they were normally or not normally distributed. Investigating the associations between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using the non-parametric test (Spearman correlation test). A 5% type-1 error level was used to infer statistical significance.

RESULTS

CT Volumetric Image

Obtained deep breath-hold CT images were evaluated at the workstation (Vitrea 2 workstation; Vital Images, Canon) in multi-plane reconstruction and three-dimensional view, calculating the volume and density in post-process analysis (Figure 1).

Descriptives of the Study

In a total of 69 patients (34 males, 49.3%; 35 females, 50.7%), the mean values of the calculated parameters were as follows: mean age=55±14.56 years (range: 18-86), FEV1=2.12±0.87 (range: 0.66-4.09), FVC=2.92±1.05 (range: 1.03-5.46), FEV1/FVC ratio=72.19±13.07 (range: 35.30-99.44), right lung volume (RLV)=2118.06±662.36 (range: 712.73-3668.26), right lung density=-806.8±68.16 (range: -904.20 to-574.70), left lung volume (LLV)=1755.35±605.02 (range: 357.06-3310.28), left lung density=-774.80±248.98 (range: -918.30 to 654.10), TLV=3820±1272.35 (range: 1378.95-6418.38) and TLD=-1597.17±295.70 (range: -1822.50 to 630.00).

FEV1, FVC and FEV1/FVC ratio showed a positive correlation with bilateral (right and left) lung volume and density ($p<0.05$), but there was no correlation with TLV and density ($p>0.05$). Demographic and laboratory data of the study population are shown in Table 1.

DISCUSSION

Results of the present study, which are compatible with the literature[10,11,13,15], suggest the positive correlation between

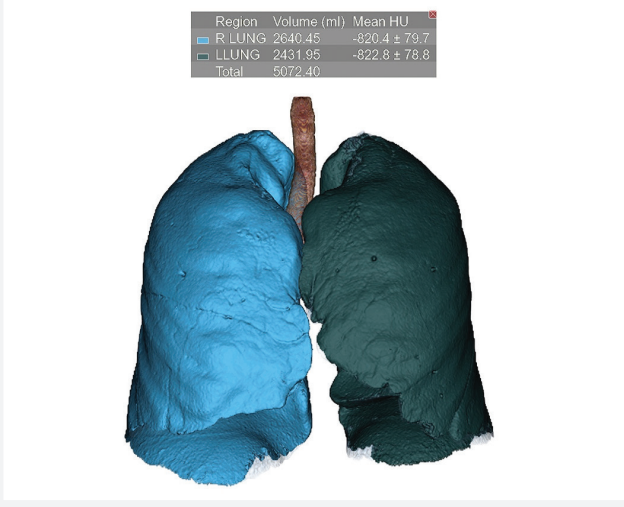

Figure 1. A 3D reconstructed CT image shows the volume and density of right and left lungs as well as total lung values

CT: Computed tomography

Table 1. Demographic and laboratory data of the study population

Parameters	Values
Age (mean)	55±14.56 years
Gender	Male: 49.3% (n=34) Female: 50.7% (n=35)
Smoking habits	None
FEV1	2.12±0.87
FVC	2.92±1.05
Right lung volume	2118.06±662.36 mL
Right lung density	-806.87±68.16 HU
Left lung volume	1755.35±605.02 mL
Left lung density	-774.80±248.98 HU
Total volume	3820±1272 mL
Total density	-1597.17±295.70 HU

FEV1: Forced expiratory volume in 1 second, FVC: Forced vital capacity

PFT (FEV1, FVC) and CT pulmonary volumetric and density parameters.

In the study by Kauczor et al.[1], the correlation of the total lung capacity (TLC) with the inspiratory CT volume was found to be higher (r=0.89) than with the expiratory CT volume (r=0.8). They underestimated TLC by 12% having a good correlation with static lung volumes (r=0.89). Using expiratory helical CT, they overestimated residual volume by 850 mL (r=0.77)[1].

Pelzer and Thomso.[16] studied the calculation of regressions for respiratory airflow conductance against age and height from measurements made by body plethysmography in 82 normal subjects aged 17-82 years. The mean coefficient of variation in plethysmographic thoracic gas volume in repetitive testings on the same day was found to be 3.8% and 10% in repeated testings on separate days[16].

Despite the highest image resolution and quantification facilities in CT, there are some pros and cons in assessment. The supine position in CT scans can result in an underestimation of the actual lung volume as compared to body plethysmography, which may be due to a submaximal inspiration in the supine position[17]. In the study by O'Donnell et al.[18], an average upright vs supine reduction in vital capacity was found to be less than 3%. Therefore, the results from the lung volumes measured by CT modality cannot be compared directly to those from other techniques. In addition, there is a radiation exposure for the patient in CT.

Similar to the current study, Tanabe et al.[7] investigated the associations of airway tree to lung volume ratio on CT with combination of PFT in 147 patients with COPD. The percentage ratio of the airway tree volume (AWV%) in the right lung lobes to RLV was calculated. In their study, the airway tree in the left lung was not included due to the fact that cardiac motion artefacts could affect the segmentation of this area. They found FEV1 to be 61%±20, FEV1/FVC=51%±13. AWV% decreased as the COPD spirometric grade increased. AWV% was more closely correlated with FEV1 and ratio of residual volume to TLC. Their study showed a correlation between RLV, RLV/predicted TLC (pTLC), AWV%, AWV/pTLC and FEV1, FEV1%, and RV/TLC. They concluded that AWV%, an easily measurable CT biomarker, could explain the clinical effects of airway-lung interaction in COPD patients[7].

In our study, there were similar correlation findings of PFT parameters with lung CT density-volumetry, compatible with the literature[5,7,11,19]. TLV and TLD in the current study were found to be 3820±1272.35 and -1597.17±295.70, respectively. In the literature, TLV was reported between 3380±1010 and 4668±1192 mL[10,19]. The difference in the volume values may be probably related to patient selection. Lung volumes decrease with age and gender. Since our patient group was relatively old, the values may have been low.

Density is also an important parameter in the evaluation and categorization of the pathologies [e.g. ILD, pulmonary infection, acute respiratory distress syndrome (ARDS)]. For ILD, the proportion of the lung volume with attenuation of -700-200 HU (a threshold of -700 HU)[20]; for the detection of ground-glass opacity, attenuation values from -800 to -500 HU[21]; for ARDS, lung proportion with attenuation between -1000 and -900 HU can be used. While a lung proportion with attenuation between -900 and -500 HU is defined as normally aerated, the lung attenuation above -500 HU is a poorly aerated or nonaerated area[22]. In our study, the densities of RLV, LLV and TLV, calculated by semi-automated algorithm in the workstation, were -806.8±68.16, -774.80±248.98, and -1597.17±295.70, respectively.

Study Limitations

There were some limitations of this study. Depending on the retrospective nature of the study, CT images were obtained only in deep breath phase (inspiration) in correlation with lung volumetric evaluation as pre-FEV1 volume and there were not expiratory phase images on CT examination. Therefore, in PFT evaluation, only some parameters including FVC, FEV1/FVC ratio were meaningful. In the current retrospective study, while CT was a static and PFT was a dynamic examination, total lung capacities were calculated in both of them and the correlation of both examinations (CT, PFT) was done. In the study population, diffusing capacity of the lung for carbon monoxide was not studied.

Conclusion

PFT provides important quantitative pulmonary functional data which are able to clarify pathologic conditions responsible for respiratory symptoms and to evaluate the severity and course of diseases. However, in the cases for which PFT cannot be done, such as COVID-19, CT quantitative pulmonary volumetric assessment can be an alternative in the evaluation of main pulmonary functions. Using the calculated volumes and densities, we need reference values that can be compared in order to make a decision about the patient. For this purpose, we can use the reference values of the spirometry.

Ethics

Ethics Committee Approval: Ethic permission was obtained from the Tekirdağ Namık Kemal University, Non-Invasive Clinical Research Ethics Committee (approval number: 2020.148.06.10).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.S., Design: H.S., L.C.M., Data Collection or Processing: H.S., L.C.M., Analysis or Interpretation: H.S., L.C.M., Literature Search: H.S., Writing: H.S., L.C.M.

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Conflict of Interest: The authors declared that there is no conflict of interests.

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Effectiveness and Safety of Autologous Stem Cell Mobilization with Granulocyte Colony Stimulating Factor in an Inpatient or Outpatient Setting

Yatarak veya Ayaktan Uygulanan Granülosit Koloni Uyarıcı Faktör ile Otolog Kök Hücre Mobilizasyonunun Etkinliği ve Güvenliği

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ABSTRACT

Aim: Autologous hematopoietic stem cell transplantation is the most frequently used treatment method in the treatment of lymphoma and myeloma patients. To apply this treatment method, first of all, a sufficient number of stem cells must be collected from the patient. With the development of apheresis methods and safe, effective mobilization methods, it is now possible to collect stem cells in an outpatient manner. In our study, we aimed to compare the efficacy and safety of outpatient based mobilization versus inpatient based mobilization of hematopoietic stem cells with granulocyte-colony stimulating factor (G-CSF) alone in patients with myeloma and lymphoma.

Materials and Methods: A total of 89 patients, including 54 patients who underwent outpatient and 35 patients who underwent inpatient based mobilization of stem cells with G-CSF alone were included in the study. Outpatient and inpatient based mobilization groups were compared in terms of efficacy and safety. Statistical analyses were performed with Jamovi 1.2.27 software. The Mann-Whitney U and chi-square tests were used to examine the differences. MANCOVA was used for univariate and multivariate statistical analysis of factors influencing mobilization.

Results: Three leukaphereses resulted in the collection of a mean $9.73x10^6$/kg (4.5-16.5) CD34+ cells in the outpatient based mobilization group and a mean $11.8x10^6$/kg (3.56-59) CD34+ cells in the inpatient based mobilization group (p=0.14). Life-threatening side effects were not observed in any of the patients. Grade 1, 2 side effects were observed and there was no significant statistical difference between the two groups.

Conclusion: In this study, we found no significant difference in terms of efficacy and safety between the outpatient and the inpatient based mobilization group patients with myeloma and lymphoma who were mobilized with G-CSF. The results of our study show that outpatient based mobilization can be effectively and safely performed with g-csf, especially in patients who need autologous transplantation and avoid hospitalization, as in the current Coronavirus disease-2019 pandemic.

Keywords: Mobilization, granulocyte-colony stimulating factor, G-CSF, filgrastim, autologous hematopoietic stem cell mobilization, apheresis, leukapheresis

ÖZ

Amaç: Otolog hematopoetik kök hücre nakli lenfoma ve miyeloma hastalarının tedavisinde günümüzde sık kullanılan bir tedavi yöntemidir. Bu tedavi yönteminin uygulanabilmesi için öncelikle hastadan yeterli sayıda kök hücrenin toplanması gerekmektedir. Aferez ile güvenli ve etkili mobilizasyon yöntemlerinin gelişimiyle birlikte, hastane dışında kök hücre mobilizasyonu olası durumdadır. Çalışmamızda, miyeloma ve lenfoma hastalarında tek başına granülosit-koloni stimüle edici faktör (G-CSF) ile ayaktan ve hastanede yatarak hematopoetik kök hücre mobilizasyonunun etkinlik ve güvenliğini karşılaştırmayı amaçladık.

Gereç ve Yöntem: Elli dördü evde mobilizasyon uygulanan, 35'i hastanede mobilizasyon uygulanan hasta olmak üzere toplam 89 hasta çalışmaya alındı. Ayaktan ve yatarak mobilizasyon grupları etkinlik ve güvenlik yönünden karşılaştırıldı. İstatistiksel analizler Jamovi 1.2.27 yazılımı ile yapıldı. Farklılıkların değerlendirilmesinde Mann-Whitney U ve ki-kare testleri kullanıldı. Mobilizasyonu etkileyen faktörlerin istatistiksel analizi için ise MANCOVA kullanıldı.

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Bulgular: Üç lökoferez işlemi sonrasında, evde mobilizasyon grubunda ortalama 9,73x10^6/kg (4,5-16,5) CD34+ hücre, hastanede mobilizasyon grubunda ortalama 11,8x10^6/kg (3,56-59) CD34+ hücre toplandı (p=0,14). Hiçbir hastada yaşamı tehdit edici bir yan etki gözlenmedi. Derece 1, 2 yan etkiler gözlendi, iki grup arasında anlamlı istatistiksel farklılık yoktu.

Sonuç: Bu çalışmada G-CSF ile evde ve hastanede mobilizasyon uygulanan miyeloma ve lenfomalı hasta grupları arasında etkinlik ve güvenlik yönünden anlamlı farklılık saptanmadı. Çalışmamızın sonuçları günümüzdeki Koronavirüs hastalığı-2019 pandemisinde olduğu gibi, otolog transplantasyona ihtiyaç duyan ve özellikle hastaneye yatıştan kaçınan hastalarda g-csf ile ayaktan hasta bazında mobilizasyonun etkin ve güvenli bir şekilde yapılabileceğini göstermektedir.

Anahtar Kelimeler: Mobilizasyon, granülosit-koloni uyarıcı faktör, G-CSF, filgrastim, otolog hematopoetik kök hücre mobilizasyonu, aferez, lökoferez

INTRODUCTION

High-dose chemotherapy with autologous hematopoietic stem cell transplantation is frequently used in the treatment of patients with multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), and Hodgkin's lymphoma (HL)[1-3]. The first requirement for this treatment is the collection of a sufficient number of hematopoietic stem cells (HSCs). HSCs can be collected in two ways. Historically, HSCs were collected via multiple bone marrow aspirations from bilateral iliac crests. This method is used for limited indications today. The other way is the collection by leukapheresis after mobilization of HSCs into the peripheral blood. With the development of apheresis methods and safe, effective mobilization methods towards the end of the 20th century, it is now possible to collect stem cells in an outpatient manner. Moreover, today, the Coronavirus disease-2019 (COVID-19) pandemic has made it clear that home remedies are necessary and may be needed in the future. In the setting of the COVID-19 pandemic, many patients avoid hospitalization. Therefore, outpatient based mobilization has become even more important.

In this retrospective study, we aimed to evaluate the effectiveness and safety of the HSC mobilization with granulocyte-colony stimulating factor (G-CSF) which was performed in the inpatient setting and in the outpatient setting for the patients who had hematological malignancies (MM, NHL, HL).

MATERIALS AND METHODS

Demographic and Baseline Characteristics

A total of 89 patients, including 54 patients who underwent HSCs outpatient based mobilization and 35 patients who underwent inpatient based mobilization with G-CSF alone, between 2012 and 2019, were included in the study. Our study objective was to evaluate the efficacy and safety of the HSC mobilization with G-CSF which was performed in the inpatient setting and in the outpatient setting for the patients who had hematological malignancies (MM, NHL, HL). In the outpatient based mobilization group, there were 39 patients with myeloma, 14 patients with NHL, (nine patients with diffuse large b-cell lymphoma (DLBCL), two patients with mantle cell lymphoma (MCL), two patients with follicular lymphoma, and one patient with MALT lymphoma), and one patient with HL.

The inpatient mobilization group included 24 patients with myeloma, five patients with NHL (two DLBCL, one MCL, one peripheral t-cell lymphoma, one Burkitt lymphoma), and six patients with HL.

The demographic and baseline characteristics, previous chemotherapy lines, HSC collection data of the patients are summarized in Table 1.

MM and lymphoma patients aged 18-75 years, mobilized only with G-CSF, were included in the study.

G-CSF (filgrastim) at a dose of 5 mcg/kg twice a day subcutaneously was administered as a mobilizing agent in all patients. Monitoring of peripheral blood CD34+ cells began on the fourth day of G-CSF administration and was performed daily. Leukapheresis was initiated if the CD34+ cell count had reached >10/μL in the peripheral blood.

Before harvesting, all lymphoma patients had complete remission and their bone marrow was normocellular without lymphoma infiltration. Patients with myeloma also had a complete response or very good partial response. None of them had received immunomodulatory drugs (imid) treatment prior to mobilization. The peripheral stem cell harvesting was performed with an Amicus Fenwal apheresis device and calcium infused to prevent citrate-related complications. Venous access was provided via a central venous catheter in all patients. Age, sex, body weight, diagnosis, time to stem cell collection, total mononuclear cell count, and CD34+ cell count at the beginning of the collection, time to reach the target CD34+ cell count, product CD34+ cell counts, adverse reactions and complications were recorded.

All patients gave written informed consent. Our study was approved by the Ethics Committee of Necmettin Erbakan University Medicine Faculty with the 2019/2079 consent number.

Statistical Analysis

Statistical analyses were performed with Jamovi 1.2.27 software. The Mann-Whitney U test was used to examine

the differences. A chi-square test was used to compare sex values between the groups. MANCOVA was used for univariate and multivariate statistical analysis of factors influencing mobilization. A p value of <0.05 was considered statistically significant.

Efficacy Outcomes

Minimal and target stem cell counts were considered ≥2x10^6 CD34+ cells/kg and ≥4x10^6 CD34+ cells/kg for lymphoma patients and ≥4x10^6 CD34+ cells/kg and ≥6x10^6 CD34+ cells/kg for myeloma patients.

The inability to achieve minimal CD34+ cell counts after 3 courses of apheresis was defined as "mobilization failure".

RESULTS

Two patients, who failed a first mobilization attempt using G-CSF in the outpatient based mobilization group, were identified. Three patients had mobilization failure in the inpatient based mobilization group. So, in a total of 84 patients, including 52 patients who underwent outpatient based mobilization and 32 patients who underwent inpatient based mobilization, HSCs were collected successfully.

The effect of baseline status on the mobilization of CD34+ cells is shown in Table 2.

The target CD34+ cell count was achieved in one leukapheresis procedure in 15 patients, two procedures in 34 patients, and three procedures in three patients who performed outpatient based mobilization. For the patients who were inpatient based mobilized of HSCs, the target CD34+ cell count was reached in one procedure in nine patients, in two procedures in 18 patients, and three procedures in five patients. There was no significant difference between the groups (p=0.39).

Total processed blood volume was 10,530+1,180 mL in the outpatient based mobilization group and 11220+1180 mL in the inpatient based mobilization group, and there was no statistically significant difference between the groups. Three leukaphereses resulted in the collection of a mean 9.73 (4.5-16.5)x10^6/kg CD34+cells in the outpatient based mobilization group and a mean 11.8 (3.56-59)x10^6/kg CD34+ cells in the inpatient based mobilization group (p=0.14) (Table 3).

Statistical analysis of factors influencing mobilization is presented in Table 4 and Figure 1.

Table 1. Characteristic data of two groups

Characteristics	Outpatient mobilization	Inpatient mobilization
Patients # (n)	54	35
Sex (M/F)	28/26	21/14
Median age (min-max)	60 (32-69)	57 (29-71)
Mean weight (kg) (min-max)	74.4 (44-102)	73.8 (51-120)
Diagnosis of patients (n)		
- MM	39	24
- NHL	14	5
- HL	1	6
Prior treatment lines, median (range)		
- MM patients	2 (1-4)	2 (1-2)
- NHL patients	2 (2-3)	2 (1-3)
- HL patients	2 (2)	2 (2-4)
Prior total chemotherapy cyclus, median (range)		
- MM patients	5 (2-18)	5 (3-9)
- NHL patients	10 (5-16)	8 (8-17)
- HL patients	8 (8)	8 (6-9)

M/F: Male/female, min-max: Minimum-maximum, MM: Multiple myeloma, NHL: Non-Hodgkin's lymphoma, HL: Hodgkin's lymphoma

Table 2. Effect of baseline status on the mobilization of CD34 cells

Baseline status	Home mobilization group	Hospital mobilization group	p value
Hb (g/dL) [median (min-max)]	12.5 (9.3-15)	11.4 (8.5-16.1)	0.50
Monocytes (/mcL) [median (min-max)]	3.31 (0.68-12)	2.57 (1.18-6.3)	0.35
Prior chemotherapy lines [median (min-max)]	2 (1-4)	2 (1-4)	0.68
Prior chemotherapy courses [median (min-max)]	6 (2-18)	5 (3-17)	0.60

Hb: Hemoglobin, min-max: Minimum-maximum

Table 3. Outcome of stem cell mobilization and harvesting

Outcome	Outpatient based mobilization group (n=54)	Inpatient based mobilization group (n=35)	p value
Mobilization failure (patients #)	2	3	0.76
Successful collections (patients #) 1st attempt (patients #) 2nd attempt (patients #) 3rd attempt (patients #)	52 15 34 3	32 9 18 5	0.39
Yield (mean, x10^6 CD34+ cells per kg body weight)	9.73 (4.5-16.5)	11.8 (3.56-59)	0.14
Mobilization duration (days, mean)	5.08 (4-7)	5 (4-7)	0.45

Table 4. Statistical analysis of factors influencing mobilization

MANCOVA, multivariate tests						Univariate tests						
	Value	F	df1	df2	p		Dependent variable	Sum of squares	df	Mean square	F	p
Pillai's Trace	0.0789	1.26	4	59	0.295	Groups	Monocytes (all)	6.991	1	6.991	1.7348	0.193
Wilks' Lambda	0.921	1.26	4	59	0.295		Hemoglobin (all patients)	2.622	1	2.622	1.0111	0.319
Hotelling's Trace	0.0857	1.26	4	59	0.295		ChemoLines (all)	0.172	1	0.172	0.4069	0.526
Roy's Largest Root	0.0857	1.26	4	59	0.295		Chemotherapy courses (all)	0.650	1	0.650	0.0563	0.813
						Residuals	Monocytes (all)	249.857	62	4.030		
							Hemoglobin (all patients)	160.762	62	2.593		
							ChemoLines (all)	26.265	62	0.424		
							Chemotherapy courses (all)	715.788	62	11.545		

Life-threatening side effects were not observed in any of the patients. Common terminology criteria for adverse events (CTCAE) Grade 1,2 side effects, including nausea, bone pain, fatigue, and fever, were observed and there was no statistically significant difference between the two groups.

DISCUSSION

HSC mobilization for autologous transplantation can be performed using chemotherapy plus G-CSF or G-CSF alone[4]. Stem cell mobilization with chemotherapy + G-CSF is usually performed in the inpatient group. In our country, too, G-CSF alone or chemotherapy + G-CSF is used as the first mobilization protocol. Although less than stem cell mobilization with chemotherapy + G-CSF, side effects are also seen in stem cell mobilization with G-CSF alone. Bone pain, chest pain, fatigue, back pain, fever, nausea, splenomegaly, and skin rash are relatively common adverse reactions of G-CSF. Rarely, life-threatening complications such as splenic rupture, stroke, myocardial infarction, anaphylaxis, aortitis, and capillary leak syndrome can occur, especially when used in high doses of G-CSF[5-7].

Spontaneous splenic rupture following the administration of G-CSF occurred very rarely both in autologous and allogeneic donors of peripheral stem cells. There are few case reports on this issue in the medical literature[5-8]. Inpatient based stem cell mobilization may be advantageous in terms of closely monitoring these side effects. However, life-threatening side effects are extremely rare. Patients should be informed about life-threatening side effects and their transportation facilities should be reviewed.

In the case report of Nuamah et al.[7] about spontaneous splenic rupture and review of the literature, a healthy female allogeneic peripheral stem cell donor, who was given 20 mcg/day G-CSF, developed a splenic rupture presenting with sudden sharp left upper quadrant pain, and emergent splenectomy was performed. In this publication, Nuamah et al.[7] recommended close monitoring of patients, informing patients and donors about potential fatal complications, and avoiding vigorous activities because of the possibility of damage to the fragile spleen even from minor traumas. Similarly, in six cases of spontaneous splenic rupture, previously published by Falzetti et al.[9], Dincer et al.[10], Balaguer et al.[11], Kasper et al.[12], O`Malley et al.[13], and Pitini et al.[14], the dose of G-CSF used in these cases was between 5 and 20 mcg/day. In the literature, most reported cases of splenic rupture had occurred within the days of apheresis and beyond. A definite correlation could not be established with the dose of G-CSF.

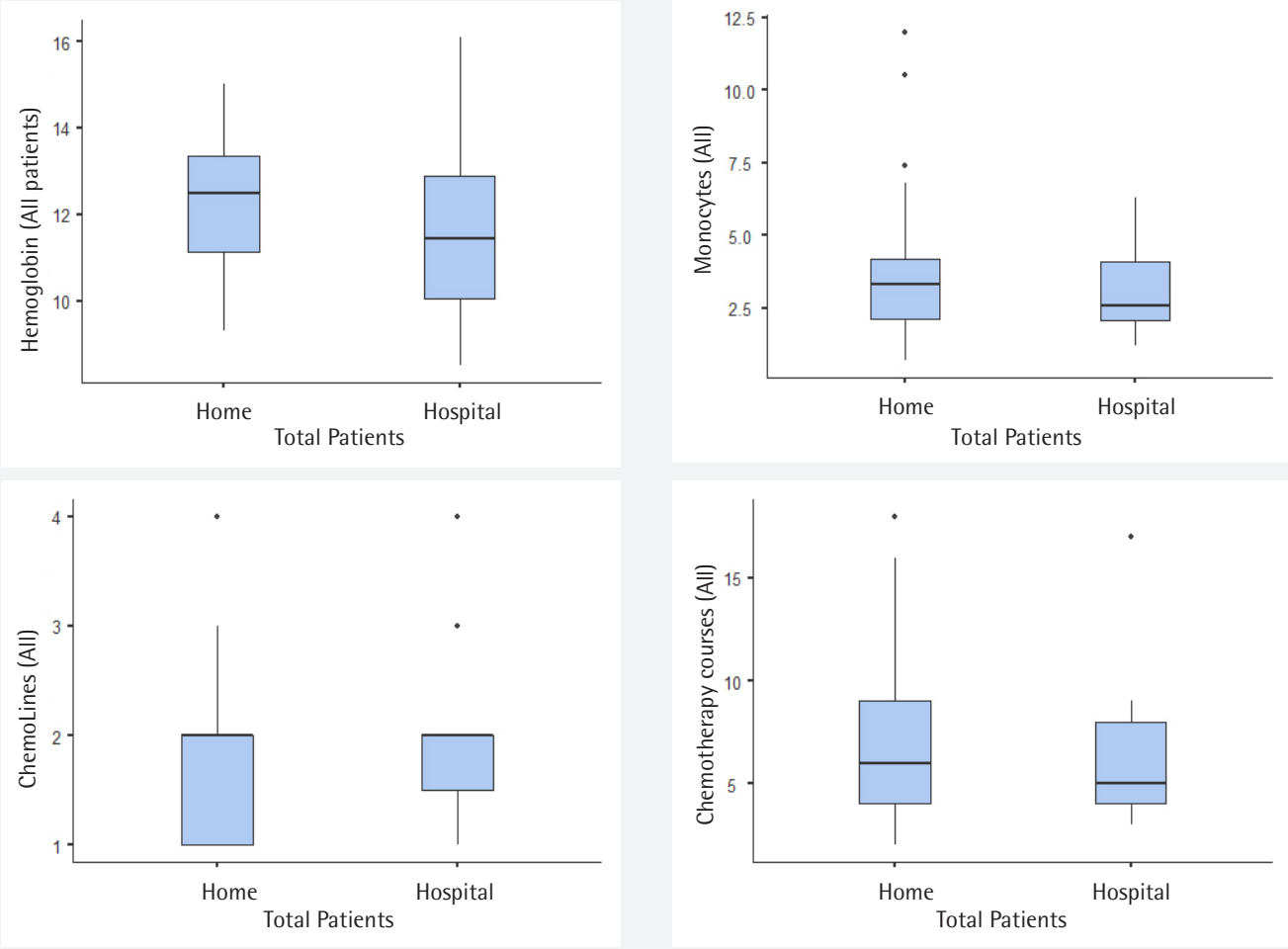

Figure 1. Plots graphics of mobilization influencing factors

Study Limitations

In our study, CTCAE Grade 1, 2 mild side effects were observed in both inpatient and outpatient mobilization patients (nausea, bone pain, fatigue, and fever). None of the rare life-threatening side effects were observed in our study.

Nevertheless, the fact that it is not a prospective study and the relatively small number of patients are the limitations of our study. It was revealed from this study that there was no difference between the two groups, but this is not enough to say that there is no difference in terms of security as a whole.

CONCLUSION

In this study, we found no significant difference in terms of efficacy and safety between the outpatient based mobilization group and the inpatient based mobilization group in patients with MM and lymphoma, who were mobilized with G-CSF. The results of our study show that outpatient based mobilization can be performed with G-CSF, especially in patients who need autologous transplantation and avoid hospitalization, as in the current COVID-19 pandemic. However, although extremely rare, patients should be informed about possible fatal complications and rapid access to the hospital should be evaluated individually. Prospective, randomized studies are needed for clearer data on this subject.

Ethics

Ethics Committee Approval: The study were approved by the Necmettin Erbakan University University of Ethics Committee (protocol number: 2019/2079).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.Ç., M.A.K., K.Ç., Concept: Ö.Ç., Design: Ö.Ç., Data Collection or Processing: Ö.Ç., M.A.K.,

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Hypogammaglobulinemia Prevelance in Children with Atopic Dermatitis and the Relationship Between Immunoglobulin Levels and Eczema Severity

Atopik Dermatitli Çocuklarda Hipogamaglobulinemi Sıklığı ve İmmünglobulin Düzeylerinin Egzama Şiddeti ile İlişkisi

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ABSTRACT

Aim: Atopic dermatitis (AD) is the most common chronic skin disease of childhood. Although eczema may be a prominent finding in some primary immune deficiencies, there are very few studies conducted on the frequency of hypogammaglobulinemia in patients with eczema. In our study, we aimed to determine the frequency of hypogammaglobulinemia in patients with AD and the relationship between immunoglobulin levels and eczema severity.

Materials and Methods: Patients between the ages of 0-18 years, who were diagnosed with AD between January 2015 and August 2018 in the Department Pediatrics Division of Pediatric Allergy and Immunology, Trakya University Faculty of Medicine, were included in the study. Hypogammaglobulinemia was defined as being less than -2 standard deviation of immunoglobulin A, M and G from normal values for age.

Results: The median age of 117 patients included in the study was 11 months [interquartile range (IQR): 6.7-33 months], the median age of eczema onset was 3.5 months (IQR: 2-6 months), the median SCORingAtopicDermatitis at presentation was 13.8 (IQR): 5-32]. Thirty-six (30.8%) patients had low levels in one of the immunoglobulin isotypes and decreased levels of immunoglobulin A (IgA), M and G were found in 21 (17.9%), 18 (15.5%) and 23 (19.7%) patients, respectively. While there was no difference between mild and moderate-severe eczema groups in terms of age at presentation, age of onset of eczema, family history of allergic diseases, smoking exposure, aeroallergen sensitivity, food allergy, the number of patients having hypogammaglobulinemia, and the levels of IgA, M and G, a male predominance and higher number of eosinophils were observed in the moderate-severe eczema group.

Conclusion: It is concluded that the evaluation of immunoglobulin levels independent of the severity of eczema is important for the distinction of primary immunodeficiency and the follow-up of patients in terms of transient hypogammaglobulinemia of infancy in patients with AD.

Keywords: Atopic dermatitis, eczema, hypogammaglobulinemia

ÖZ

Amaç: Atopik dermatit (AD) çocukluk çağının en sık görülen kronik deri hastalığıdır. Bazı primer immün yetmezliklerde egzama belirgin bir bulgu olarak karşımıza çıkabilmekle birlikte egzamalı hastalarda hipogamaglobülinemi sıklığı ile ilgili yapılmış çok az sayıda çalışma bulunmaktadır. Çalışmamızda AD'li hastalarda hipogamaglobülinemi sıklığının ve immünoglobulin düzeylerinin egzama şiddeti ile ilişkisinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Trakya Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk İmmünoloji ve Alerji Bölümü'nde Ocak 2015-Ağustos 2018 tarihleri arasında AD tanısı konulan 0-18 yaş arasındaki hastalar çalışmaya alınmıştır. Temel immünoglobulin izotiplerinden herhangi birisinde yaşa göre normal değerlerden -2 standart sapmadan fazla düşüklük olması hipogamaglobülinemi olarak tanımlanmıştır.

Bulgular: Çalışmaya alınan 117 hastanın başvuru yaşı ortanca 11 ay [çeyrekler arası aralık (IQR): 6,7-33 ay], egzama başlangıç yaşı ortanca 3,5 ay (IQR: 2-6 ay), başvuru anındaki SCORingAtopicDermatitis skoru ortanca: 13,8 (IQR): 5-32] idi. Otuz altı (%30,8) hastada immünoglobulin izotiplerinden

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en az birinde düşüklük olup immünoglobulin (Ig)-A, M ve G düşüklüğü sırasıyla; 21 (%17,9), 18 (%15,5) ve 23 (%19,7) hastada saptandı. Hafif ve orta-ağır egzama grupları arasında başvuru yaşı, egzama başlangıç yaşı, ailede alerjik hastalık öyküsü, sigara maruziyeti, aeroalerjen duyarlılığı, besin alerjisi, hipogamaglobülinemi saptanan hasta sayısı ve IgA, M ve G düzeyleri açısından bir fark bulunmazken, orta-ağır egzama grubunda erkeklerin daha fazla sayıda olduğu ve eozinofil yüksekliği saptandı.

Sonuç: AD hastalarında egzama şiddetinden bağımsız olarak immünoglobulin düzeylerinin değerlendirilmesinin primer immün yetmezlik ayrımının yapılması ve hastaların süt çocukluğunun geçici hipogamaglobulinemisi açısından takibi için önemli olduğu düşünülmüştür.

Anahtar Kelimeler: Atopik dermatit, egzama, hipogamaglobülinemi

INTRODUCTION

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease of the childhood. Its incidence in Turkey ranges from 9.6 to 17.1% in population screening studies[1,2]. In a recently published birth cohort study, it was found to be 12.8%[3]. Although the pathophysiology of the disease has not been clearly revealed, it is thought to occur as a result of a complex interaction between genetic, environmental, immunological and epidermal factors[4]. Factors exacerbating eczema include physical/chemical irritants, infections such as *Staphylococcus aureus* and *Herpes simplex virus*, aeroallergens and food allergens. Although AD-like skin rashes can be seen in immunodeficiencies such as Hyper IgE syndrome (HIES), Wiscott-Aldrich Syndrome and Omenn Syndrome, it has been reported that there is an increase in the frequency of AD in patients with selective immunoglobulin A (IgA) deficiency and common variable immunodeficiency[5]. Considering that transient hypogammaglobulinemia of infancy (THI) is a factor that aggravates eczema in AD patients, intravenous immunoglobulin (IVIG) treatment was given to 6 patients with hypogammaglobulinemia, who did not respond to standard treatment, by Breslin et al.[6], and clinical improvement was achieved in five of them. In our study, it was aimed to determine the frequency of hypogammaglobulinemia in patients with AD and to examine the relationship between eczema severity and immunoglobulin levels.

MATERIALS AND METHODS

Selection and Descrip0tion of Cases

The data of patients aged 0-18 years who were diagnosed with AD between January 2015 and August 2018 at Trakya University Faculty of Medicine, Department of Pediatric Allergy and Immunology were analyzed retrospectively. Ethics committee approval dated 25.02.2019 and numbered 107 was obtained from Trakya University Scientific Research Ethics Committee for the study.

The diagnosis of AD was made according to the diagnostic criteria of Hanifin and Rajka[7]. Demographic characteristics of the patients such as age, gender, age of onset of eczema, way of delivery, duration of breastfeed, history of formula feeding, smoking exposure and parental atopy history, hemogram, serum total IgG, IgA, IgM and IgE levels, peripheral blood eosinophil counts, skin prick test and nutrient challenge test results were evaluated. The SCORingAtopicDermatitis (SCORAD)[8] index was used to assess disease severity; AD was classified as <25 mild, 25-50 moderate, >50 severe AD.

Definition of Hypogammaglobulinemia

In the evaluation of serum immunoglobulin levels, the values determined by Bayram et al.[9] in healthy Turkish children were taken as reference. Hypogammaglobulinemia was defined as a decrease in any of the major immunoglobulin isotypes (IgG, IgA and IgM) by more than -2 standard deviations from the normal values for this age. Patients with primary immunodeficiency and those with diseases that might cause secondary hypogammaglobulinemia (nephrotic syndrome, intestinal lymphangiectasia, protein-losing enteropathy, malnutrition, Epstein-Barr virus infection, cytomegalovirus infection) or those taking medication (antiepileptic drugs, systemic corticosteroids) were excluded.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences version 25.0. Whether the data were normally distributed or not was evaluated with histogram and Kolmogorov-Smirnov test. The categorical data of the mild and moderate-severe AD groups were compared with the chi-square test, and the numerical data were compared with the Mann-Whitney U test. Correlation between immunoglobulin levels and SCORAD score was evaluated with the Spearman correlation test. In order to examine the factors affecting the severity of AD, variables that were found to be significant in univariate analyses and those that were thought to be clinically significant were included in the multiple logistic regression model. Cases with the p value below 0.05 were considered statistically significant.

RESULTS

During the study dates, a total of 327 patients were diagnosed as AD in our department, and 210 (64.2%) of these patients were excluded from the study due to lack of data. For 117

patients included in the study, the median age at presentation was 11 months [interquartile range (IQR): 6.7-33 months], the median age for the onset of eczema was 3.5 months (IQR: 2-6 months), the median SCORAD at admission was 13.8 (IQR: 5-32). Demographic and clinical characteristics of the patients are given in Table 1.

Thirty-six (30.8%) patients had a decrease in any of IgA, IgM and IgG isotypes, and decreased IgA, IgM and IgG were detected in 21 (17.9%), 18 (15.5%) and 23 (19.7%) patients, respectively. When mild and moderate-severe eczema groups were compared in terms of clinical and laboratory findings, no difference was found between these two groups in terms of age at admission, age of onset of eczema, family history of allergic disease, smoking exposure, aeroallergen sensitivity, number of patients with low immunoglobulin levels, and IgA, IgM and IgG values. No correlation was found between serum immunoglobulin levels and SCORAD (r=-0.113, p=0.269 for IgA, r=-0.175 for IgM and r=-0.168 for IgG, p=0.099). In the moderate-severe AD group, there were more males and the eosinophil count was significantly higher, while IgE levels and food sensitivity were found to be slightly higher. Fifty-one patients underwent 62 food challenge tests, mainly milk and egg, and no difference was found between the eczema severity groups in terms of food allergy (Table 2).

When gender, age of eczema onset, parental history of atopy, eosinophilia, high IgE, low IgG, and allergen sensitivity were included in the logistic regression model, male gender [Odds ratio (OR): 3.16, 95% confidence interval (CI): 0.98-10.12, p=0.050] and eosinophilia (OR: 3.26, 95% CI: 0.95-11.16, p=0.050) were found to be associated with eczema severity (Table 3).

DISCUSSION

In addition to being the primary barrier against microorganisms and allergens, the skin constitutes one of the most important elements of the natural immune system through the cells it contains[10]. In our study, immunoglobulin values were examined in order to evaluate immune functions in children with AD, and the frequency of hypogammaglobulinemia was found to be 30.8%. However, no correlation was found between the severity of eczema and immunoglobulin levels. Considering the literature, in the study of Celiksoy et al.[11] including 160 AD cases and 65 healthy controls, the frequency of hypogammaglobulinemia was found to be higher in the AD group than in the healthy controls (27.5% and 5%, respectively), and similar to our study, there was no correlation between immunoglobulin levels and eczama severity. In the study of Toyran et al.[12], the frequency of hypogmaglobulinemia was reported as 50%, no difference was found in the severity of eczema between patients with and without hypogammaglobulinemia, but a negative correlation was found between IgA and IgM levels and SCORAD score. In our study, the frequency of hypogammaglobulinemia in patients with AD was found similar to the literature.

In our study, it was observed that there were higher number of boys and the eosinophil count was higher in the moderate-severe AD group. In the study of Akan et al.[13] investigating the factors affecting the severity of AD, eosinophilia and allergen sensitization were found to be risk factors for severe eczema, but gender did not have any effect on the severity. In the study of Cansever and Oruç[14], it was found that early-onset AD, high eosinophil count, familial atopy history, and presence of food sensitization were associated with severe AD.

Table 1. Demographic and clinical characteristics of the patients

		n (%)
Patient age, month, median (IQR)		11 (6.7-33)
Gender	Female	47 (40.2)
	Male	70 (59.8)
SCORAD	Mild	70 (59.8)
	Moderate	36 (30.8)
	Severe	11 (9.4)
S. aureus colonization		4 (3.4)
Food allergen sensitization		19 (16.2)
Aeroallergen sensitization		11 (9.4)
Food allergy diagnosed by food challenge test		17 (14.5)
Concomitant allergic diseases	Asthma	24 (20.5)
	Allergic rhinitis	12 (10.2)
	Proctocolitis	6 (5.1)
Presence of allergic disease in parents		33 (28.2)

IQR: Interquartile range, SCORAD: SCORingAtopicDermatitis

Table 2. Clinical and laboratory findings associated with atopic dermatitis				
		Mild (n=72)	Moderate-severe (n=45)	p
Age (month)*		13.5 (7.1-30.8)	8 (6.5-38)	0.573
Age of onset of eczema (months)		3 (1.5-6)	4 (2-6)	0.230
Gender	Female	34	13	**0.049**
	Male	38	32	
Family history of allergic disease		18	15	0.641
Smoking exposure		20	13	0.990
Food allergen sensitivity		8	11	0.052
Aeroallergen sensitivity		4	7	0.127
Food allergy proven by food challenge test		7	10	0.164
IgA (<-2 SD)		14	7	0.594
IgM (<-2 SD)		12	6	0.627
IgG (<-2 SD)		18	5	0.066
IgA (mg/dL)*		30.3 (19.7-65.7)	37.3 (23.8-63.9)	0.482
IgM (mg/dL)*		81.7 (50.7-105.8)	83.9 (56.7-96.4)	0.691
IgG (mg/dL)*		601.5 (445.8-839.5)	615 (439.5-835.5)	0.640
IgE (IU/L)*		18.4 (7.5-73.4)	50 (9-206)	0.059
Eosinophil count (/mm^3)*		300 (200-400)	500 (300-610)	**<0.001**

*Median (IQR) values are given. Chi-square test was used for categorical variables and Mann-Whitney U test was used for numerical variables in the comparison of mild and moderate-severe atopic dermatitis groups.

IQR: Interquartile range, SCORAD: SCORingAtopicDermatitis, Ig: Immunoglobulin, SD: Standard deviation

Table 3. Factors associated with atopic dermatitis severity				
	p	OR	95% CI	
Gender	0.050	3.16	0.98	10.12
Age of onset of eczema (months)	0.919	1.00	0.97	1.02
Atopy history in the mother/father	0.483	1.53	0.46	5.09
Eosinophilia	0.050	3.26	0.95	11.16
Elevated IgE	0.476	1.58	0.44	5.66
Decreased IgG	0.127	0.33	0.08	1.36
Food/Aeroallergen sensitivity	0.354	0.55	0.15	1.93

The variables were put into the multiple logistic regression model.

CI: Confidence interval, OR: Odds ratio, Ig: Immunoglobulin

In a study that examined the relationship between eczema and gender, including 2,693 girls and 2.783 boys, eczema was found in 8.7% of the girls and 6.1% of the boys at the time of evaluation, and it was observed that the allergen sensitization was more in boys at the age of 5-7 years than in girls. In addition, only early-onset eczema was found to be associated with allergen sensitization in girls, while both early-onset and late-onset eczema were associated with allergen sensitization in boys[15]. Although the severity of eczema was not evaluated in this study, it can be indirectly assumed that the male gender has more severe course due to increased allergen sensitization due to skin barrier disorder in severe eczema.

Although the frequency of THI is not known precisely because it is a retrospective diagnosis, its incidence was reported as 23 per 1,000 live births in the largest series in the literature, and it was stated that 80% of the patients with THI had atopic disease or food allergy/intolerance[16]. Since eczematous skin lesions are frequently seen in primary immunodeficiencies such as selective IgA deficiency, common variable immunodeficiency, Wiskott-Aldrich Syndrome and HIES, primary immunodeficiency should be kept in mind in patients with severe AD[17]. In a study by Kasap et al.[18], while characteristic facial appearance, delayed eruption of primary teeth, skin abscesses, rash in the neonatal period, and pneumatocele STAT-3 were found to be predictors for HIES, mucocutaneous candidiasis and herpes infections were found to be more frequent in DOCK8 deficiency and these were rarely seen in patients with severe AD. Since none of the patients included in our study had clinical findings suggestive of primary immunodeficiency, the patients were evaluated as THI.

Sumikawa et al.[19] described two cases aged 4 and 6 months with eczema accompanied by THI. They reported that, despite topical and systemic corticosteroid treatment, resistant eczema started to improve in the 10th month when serum IgG levels started to increase and completely recovered about the 16th month when IgG levels returned to normal. In the study of Yasuno et al.[20], it was reported that 5 cases with hypogammaglobulinemia, whose eczema started at the age of 2 months, did not have exacerbation in their eczema after the immunoglobulin values returned to normal after the 12th month. It has been suggested that a possible mechanism for the coexistence of AD and hypogammaglobulinemia may be impaired skin barrier or loss of immunoglobulin from the GIS[16,21]. Moreover, it is also thought that THI may contribute to AD exacerbations due to inadequate response to secondary infections or fluctuations in inflammatory cytokines and CD4/CD8 ratio.[20] However, the relationship between THI and AD has not been clearly revealed yet. There are also studies showing that in patients with eczema associated with THI, the administration of IVIG treatment, provides clinical improvement and a decrease in IgE levels in addition to antibiotics, topical or oral corticosteroid treatments against pathogenic microorganisms, primarily *Staphylococcus aereus*[22,23].

Study Limitations

Although our study has limitations such as being retrospective and not having a control group, reference values according to age in healthy Turkish children were used for the definition of hypogammaglobulinemia. Thus, patients who fit the definition of hypogammaglobulinemia were correctly identified. The absence of primary immunodeficiency in any of the patients can also be considered as a strength of the study. Since primary immunodeficiencies accompanied by eczema were excluded, immunoglobulin levels in patients with isolated AD were evaluated in our study.

CONCLUSION

In conclusion, the frequency of hypogammaglobulinemia is quite high in AD patients, and it has been thought that the evaluation of immunoglobulin levels, regardless of the severity of eczema, is important for the differentiation of primary immunodeficiency and for the follow-up of the patients in terms of THI. Further studies with a larger number of patients are important in terms of revealing the relationship between THI and AD.

Ethics

Ethics Committee Approval: The study were approved by the Trakya University of Scientific Research Ethics Committee (no: 107, date: 25.02.2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.B., V.Ç., P.G.Ö., M.Y., Design: B.B., V.Ç., P.G.Ö., M.Y., Data Collection or Processing: B.B., Analysis or Interpretation: B.B., Literature Search: B.B., V.Ç., P.G.Ö., M.Y., Writing: B.B., V.Ç., P.G.Ö., M.Y.

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Effects of COVID-19 Pandemic on Diagnosis-treatment Process in Breast Cancer Patients Treated with Neoadjuvant Chemotherapy

Neoadjuvan Kemoterapi Alan Meme Kanseri Hastalarında COVID-19 Pandemisinin Tanı ve Tedavi Sürecine Etkileri

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ABSTRACT

Aim: In this study, we investigated the effect of pandemic on the diagnosis-treatment process in breast cancer patients receiving neoadjuvant chemotherapy.

Materials and Methods: The clinicopathological characteristics of the total patients who received neoadjuvant chemotherapy for one year during the Coronavirus disease-2019 (COVID-19) pandemic period and one year before the pandemic were compared. A total of 92 patients were analyzed retrospectively.

Results: The clinicopathological features in the pandemic and prepandemic periods were found to be similar. While the number of patients was 26 (28.3%) during the pandemic period, it was 66 (71.7%) in the prepandemic period. Pathology reporting time, chemotherapy administration time, preoperative preparation time and overall time from diagnosis to treatment were similar (p=0.305, p=0.171, p=0.104, p=0.061, respectively). Magnetic resonance reporting time was shorter during the pandemic period (p=0.005).

Conclusion: The diagnosis and treatment times of breast cancer in patients receiving neoadjuvant chemotherapy in the pandemic period are similar to those in the pre-pandemic period. Nevertheless, decision should be made on a patient-specific basis considering COVID-19 infection risk.

Keywords: COVID-19, pandemic, coronavirus, breast cancer, neoadjuvant

ÖZ

Amaç: Bu çalışmamızda neoadjuvan kemoterapi alan meme kanseri hastalarında pandeminin tanı-tedavi sürecine etkisini araştırdık.

Gereç ve Yöntem: Koronavirüs hastalığı-2019 (COVID-19) pandemisi dönemindeki bir yıl ile pandemi öncesindeki 1 yılda neoadjuvan kemoterapi alan hastaların klinikopatolojik özellikleri ile tanıdan operasyona kadar olan aşamaların süreleri karşılaştırıldı. Toplam 92 hasta retrospektif olarak analiz edildi.

Bulgular: Pandemi ve pandemi öncesi (prepandemik) dönemdeki hastaların klinikopatolojik özellikleri benzer bulundu. Pandemi dönemindeki hasta sayısı 26 (%28,3) iken pandemi öncesi dönemde 66 (%71,7) idi. Tanı-tedavi sürelerinden patoloji raporlanma süresi, kemoterapi uygulanma süresi ve preoperatif hazırlık dönemi ve total süre iki dönem arasında benzerdi (sırasıyla; p=0,305, p=0,171, p=0,104, p=0,061). Manyetik rezonans raporlanma süresi pandemi döneminde daha kısa saptandı (p=0,005).

Sonuç: Neoadjuvan kemoterapi alan hastalarda meme kanserinin tanı ve tedavi süreleri pandemi döneminde, pandemi öncesi dönemle benzerdir. Yine de COVID-19 enfeksiyon riski düşünülerek hasta özelinde karar verilmelidir.

Anahtar Kelimeler: COVID-19, pandemi, koronavirüs, meme kanseri, neoadjuvan

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Introduction

The Severe acute respiratory syndrome-Coronavirus-2 epidemic, which started in Wuhan, China in 2019, was declared as a COVID-19 pandemic by the World Health Organization (WHO) on March 11, 2020[1]. According to the latest WHO data, more than 125 million people were infected with COVID-19 and over 2.7 million people died[2]. Serious disruptions occurred in health systems that came to the point of collapse, and "stay at home" orders, travel restrictions, social isolation rules and lockdowns were implemented in many countries around the world[3,4]. In our country, the first case of COVID-19, which affected the whole World, was seen on March 11, 2020[5]. The first major measures for COVID-19 in Turkey were taken on March 21, 2020, for the purpose of precaution after rapid increase in cases[6]. Although the bans have been eased as of March 2021, lockdowns still continue in our country.

The coronavirus pandemic has led to sudden and complex changes in healthcare, including primary care[7,8]. Due to this situation, high-risk patients in terms of COVID-19 were determined in order to minimize disruptions, and this was led by patients diagnosed with cancer[9,10]. In the analysis performed by Saini et al.[11], the mortality rate in cancer patients was found to be 25.6%. As of 2021, new treatment, diagnosis and screening guidelines have been published in order to minimize the risk for breast cancer patients, which is the most common cancer worldwide[8,12-14].

With the pandemic, the normal working orders of the units except for the emergency health services were suspended, and oncology clinics were also affected. In this study, we examined the one year before the COVID-19 bans began to be implemented in our country, and one year in which COVID-19 measures and restrictions were applied, in breast cancer patients who were given neoadjuvant treatment. We aimed to investigate the effect of the COVID-19 pandemic on the clinicopathological changes of the patients diagnosed between two years, during the reporting period of radiology and pathology, during the chemotherapy process, and during the diagnosis-surgery periods. We aim to contribute to the literature on the effect of neoadjuvant chemotherapy applications and breast cancer diagnosis-treatment process during the pandemic period.

MATERIALS AND METHODS

The research was a retrospective comparative study and was conducted in the medical oncology department of the university hospital. The study was approved by the Ethics Committee of Tekirdağ Namık Kemal University Faculty of Medicine on 30.03.2021 (issue no: 2021.76.03.16) and by the T.R. Ministry of Health Scientific Research Platform. The research was conducted in accordance with the Declaration of Helsinki.

In our study, the data of patients, who were diagnosed with breast cancer in our hospital between March 21, 2019 and March 21, 2021, received neoadjuvant chemotherapy and were operated afterwards, were analyzed retrospectively. All of the patients included in the study consisted of patients who received either docetaxel (75 mg/m^2) every three weeks for four cycles or paclitaxel (80 mg/m^2) once a week for 12 cycles after four cycles of cyclophosphamide + epirubicin. Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography and magnetic resonance (MR) imaging performed before treatment were used for staging the patients.

Patients were put into two groups. Those diagnosed before March 21, 2020, when the COVID-19 restriction began to be implemented in our country, were evaluated as the pre-pandemic period (March 21, 2019-March 21, 2020) and those diagnosed after this date were evaluated as the pandemic period (March 21, 2020-March 21, 2021). In order to ensure complete reliability in the analysis of the data, patients who completed the entire period from diagnosis to operation in their own group were included in the study. Those with time deviations from the specified dates and groups were excluded from the study.

Pathology reporting time was accepted as the time between taking the tru-cut biopsy and reporting it, MR reporting time as the time from MR scan date to reporting for staging before neoadjuvant chemotherapy, chemotherapy time as the time between the first chemotherapy and the last chemotherapy (those who received weekly paclitaxel chemotherapy were evaluated as four cycles and the first day of the fourth cycle was taken as the end of chemotherapy). And the preoperative preparation time after chemotherapy was counted from this last chemotherapy date to the operation. As the total time, the time from the first biopsy date to the surgery was taken.

Clinicopathological and demographic characteristics, radiological examination and reporting dates, pathology acceptance and approval dates, chemotherapy durations and operation dates of the patients before the start of treatment were recorded from the hospital archive.

Statistical Analysis

Statistical Package for the Social Sciences for Windows 26.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation. The comparison of categorical measurements between groups was also done with the chi-square test. The Fisher's exact test was used when cells with frequencies less than five were present in the crosstab analysis. The normal distribution of the data was evaluated with the Kolmogorov-Smirnov test. Non-parametric tests

(Mann-Whitney U) were used to compare continuous variables that were not normally distributed, and parametric tests (independent sample t-test) were used to compare continuous variables that were normally distributed. The statistical significance limit "p" was accepted as 0.05.

RESULTS

A total of 102 patients' records were reached between March 21, 2019 and March 21, 2021. The examinations of 10 patients started in the pre-pandemic period but were extended to the pandemic period, and they were excluded from the study. 92 patients who met the criteria were included in the study. Of the patients, 26 (28.3%) were in the pandemic period, and 66 (71.7%) were in the pre-pandemic period. The median age was 47.14±10.48 (age range 24-79) years. All of the patients were female. It was determined that 2 (7.77%) of the patients in the pandemic group included in the study had COVID-19 infection within the specified period. When the clinicopathological features of pre-pandemic and pandemic patients were compared, no significant difference was found between the groups. The results were as in Table 1.

The mean total time from the first diagnosis to the operation of the patients included in the study was 220.91±28.85 (range 121-362) days. MR reporting time was 16.14±11.19 (range 2-51) days, pathology reporting time was 15±8.01 (range 6-36) days, chemotherapy time was 152.26±10.28 (range 131-189) days, and preoperative preparation time after chemotherapy was 35.94±9.02 (range was 20-61) days. When the prepandemic and pandemic periods were compared, a significant difference was found in the MR reporting period (p=0.005), and there was no statistically significant difference between the other periods. The results of the comparison of the two groups were presented in Table 2.

DISCUSSION

In our study, we aimed to investigate the effect of the COVID-19 pandemic, from breast cancer diagnosis to treatment, in breast cancer patients receiving neoadjuvant chemotherapy. It was planned to compare the year before the beginning of the restrictions on the COVID-19 pandemic in our country with the year in the pandemic process, and 92 patients who met the criteria were analyzed retrospectively. In the first year of the pandemic, the number of patients receiving neoadjuvant chemotherapy was found to have decreased significantly compared to the pre-pandemic period. In our study, there was no difference between the clinicopathological features of the patients admitted during the pre-pandemic period and the pandemic period. While there was a significant decrease in MR reporting time, there was no difference in the comparison of the other diagnosis-treatment stages.

In our study, a significant decrease was observed in the number of breast cancer patients receiving neoadjuvant chemotherapy in the pandemic period compared to the pre-pandemic period. The decrease in the number of patients might have resulted from the decrease in hospital access due to restrictions or patient's hesitation due to the pandemic[15-17]. The detection of a correlation between anxiety and female gender in studies on the COVID-19 pandemic conducted in our country and abroad suggests that patient's hesitation plays an important role in the decrease in the number of patients in addition to pandemic restrictions[18-20].

Studies reporting that there are similar reductions and disruptions in the diagnoses of new diseases in 2020, not only in our country but all over the world, are consistent with our study[16,21-23].

According to the American Society of Clinical Oncology and the European Society of Medical Oncology, one of the neoadjuvant chemotherapy regimens recommended for the COVID-19 pandemic is AC-T (± anti-HER-2 therapy), that is, the combination of cyclophosphamide and anthracycline. This regimen is the chemotherapy regimen that we included in our study and that is frequently used in our center. While delaying surgery is not recommended in the triple-negative and HER-2-positive groups in the guidelines, it is suggested that 6-12 months of neoadjuvant therapy may be continued in hormone-positive/HER-2-negative subtypes, depending on the risk status[24]. In our study, the durations in accordance with the guidelines were considered and there was no difference in chemotherapy duration between the pre-pandemic period and the pandemic period (p=0.171).

In our study, a significantly shorter MR reporting time was observed during the pandemic period compared to the pre-pandemic period (p=0.005). This may be a reflection of the decrease in the number of patient admissions to the workload. However, the similarity of the total times from diagnosis to operation may be due to the prolongation of the chemotherapy duration and preoperative preparation time, which did not reach statistical significance but showed a numerical increase. In addition, the delay in the treatment of 2 patients due to the diagnosis of COVID-19 during the pandemic period also contributed to this situation. However, the times determined in our study are within the times recommended in the guidelines[25,26].

In the current COVID-19 pandemic period, while healthcare institutions are trying to provide the highest level and complete service in diseases such as cancer, for which the treatment and diagnosis process is unlikely to be delayed, on the other hand, they have to make decisions according to the conditions of the day, taking into account the health of the employees and the patient. Recommendations about chemotherapy

Table 1. Clinicopathological characteristics of the patients and their distribution according to the pandemic period				
	Total	**Pre-pandemic period (n=66)**	**Pandemic period (n=26)**	**p**
Age				
<40 (young adult)	26 (28.3%)	20 (76.9%)	6 (23.1%)	0.488
≥40	66 (71.7%)	46 (69.7%)	20 (30.3%)	
Menopausal status				
Premenopause	38 (41.3%)	27 (71.1%)	11 (28.9%)	0.902
Postmenopause	54 (58.7%)	39 (72.2%)	15 (27.8%)	
Histological type				
Ductal type	73 (79.3%)	52 (71.2%)	21 (28.8%)	0.832
Others	19 (20.7%)	14 (73.7%)	5 (26.3%)	
Progesterone receptor				
Negative	42 (45.7%)	29 (69.0%)	13 (31.0%)	0.599
Positive	50 (54.3%)	37 (74.0%)	13 (26.0%)	
Estrogen receptor				
Negative	28 (30.4%)	18 (64.3%)	10 (35.7%)	0.293
Positive	64 (69.6%)	48 (75.0%)	16 (25.0%)	
HER-2 receptor				
Negative	55 (59.8%)	39 (70.9%)	16 (29.1%)	0.829
Positive	37 (40.2%)	27 (73.0%)	10 (27.0%)	
Grade				
Grade 1	4 (4.3%)	3 (75.0%)	1 (25.0%)	0.479
Grade 2	51 (55.4%)	34 (66.7%)	17 (33.3%)	
Grade 3	37 (40.2%)	29 (78.4%)	8 (21.6%)	
Clinical T stage				
T1	24 (26.1%)	16 (66.7%)	8 (33.3%)	0.777
T2	59 (64.1%)	43 (72.9.8%)	16 (27.1%)	
T3-T4	9 (9.8%)	7 (77.8%)	2 (22.2%)	
Clinical N stage				
N0	30 (32.6%)	26 (86.7%)	4 (13.3%)	0.099
N1	35 (38.0%)	23 (65.7%)	12 (34.3%)	
N2	17 (18.5%)	12 (70.6%)	5 (29.4%)	
N3	10 (10.9%)	5 (50.0%)	5 (50.0%)	
Status of receiving RT				
Received	86 (93.5%)	61 (70.9%)	25 (29.1%)	0.672
Not received	6 (6.5%)	5 (83.3%)	1 (16.7%)	
Surgery type				
Breast protective	75 (81.5%)	51 (68.0%)	24 (32.0%)	0.094
Others	17 (18.5%)	12 (88.2%)	2 (11.8%)	
Chemotherapy type				
CE+ weekly paclitaxel	38 (41.3%)	29 (76.3%)	9 (23.7%)	0.413
(±HER-2 blockade)	54 (58.7%)	37 (68.5%)	17 (31.5%)	

HER-2: Human epidermal growth factor receptor 2, RT: Radiotherapy, CE: Cyclophosphamide-epirubicin chemotherapy regimen

Table 2. Comparison of the characteristics of the time spent in the diagnosis and treatment stages according to the pandemic periods

	Pre-pandemic period (n=66)		Pandemic period (n=26)		
	Mean±SD	Median	Mean±SD	Median	p
Pathology reporting time	15.71±8.59	13.0	13.19±6.05	10.5	0.305
MR reporting time	18.30±11.8	18.0	10.65±7.05	8.0	**0.005**
Chemotherapy duration	150.48±8.12	149.0	156.76±13.55	150.5	0.171
Preop preparation time after chemotherapy	34.98±9.22	34.50	38.38±8.17	37.5	0.104
Total time	218.40±31.37	217.0	227.26±20.33	222.0	0.061

Statistically significant p values are shown in bold font.
SD: Standard deviation, MR: Magnetic resonance

regimens, patient follow-up, surgical preparation times and even operation options have been reported in guidelines and previous studies[8,24,25]. However, there are also publications stating that the same treatment cannot be applied to everyone during the pandemic period[27].

Study Limitations

The limitation of our study is that it was performed in a single center, the number of cases was limited, and it was retrospective. Imaging, reporting and other investigated times may differ in centers other than our hospital. This is another limiting factor of our study. Although studies examining the effects of the COVID-19 pandemic on diagnosis-treatment stages in breast cancer are limited in the literature, our study, which was conducted using the same center data, is important in that it is the first in this regard.

CONCLUSION

In conclusion, in our study, we have found that, in the pandemic period, the current diagnosis and treatment stages can be applied in the same way as in the pre-pandemic period for patients, and that disruptions are acceptable periods of time. However, considering our patients who caught COVID-19 during treatment, the risk of COVID-19 infection should be taken into account when making a treatment decision and cooperation with the patient should be made. Since the duration and continuity of the COVID-19 pandemic are unknown, multicenter, prospective studies with large numbers of patients are needed for effective treatment evaluations.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Tekirdağ Namık Kemal University Faculty of Medicine on 30.03.2021 (issue no: 2021.76.03.16) and by the T.R. Ministry of Health Scientific Research Platform.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.Ç., K.K., O.A., E.S.Ş., Design: E.Ç., Y.İ., O.A., E.S.Ş., Data Collection or Processing: E.Ç., Y.İ., K.K., O.A., E.S.Ş., Analysis or Interpretation: E.Ç., Y.İ., K.K., O.A., E.S.Ş., Literature Search: E.Ç., O.A., E.S.Ş., Writing: E.Ç.

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Factors Affecting the Survival Rate of Patients with Pulmonary Thromboembolism

Pulmoner Tromboembolili Hastalarda Sağkalımı Etkileyen Faktörlerin Belirlenmesi

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ABSTRACT

Aim: It is aimed to investigate the factors affecting the survival rate and complications that may arise throughout the treatment process from admission to the end of the 6-month period after discharge, the inpatient treatment of individuals with pulmonary thromboembolism, by monitoring these patients.

Materials and Methods: The study included adult patients who were followed up in the pulmonology clinic between 01.01.2017 and 01.12.2019 and who had at least segmental thrombus on computed tomography pulmonary angiography.

Results: The mean age of 210 patients enrolled into the study was 71.27±13.26 years and 55 (26%) of these patients were male and 155 (74%) of them were female. Pulse rate, Modified Geneva and Wells scores, pulmonary embolism severity index (PESI) and simplified PESI scores of the non-survivors were higher than in the patients who survived. In non-survivors, both red cell distribution width (RDW) and mean corpuscular volume on day 1 and 5, as well as the level of hematocrits were lower. Non-survivors had higher number of platelets but lower levels of total protein and albumin in blood on days 1 and 5. High alkaline phosphatase (ALP), total bilirubin and C-reactive protein (CRP) values on the 1st day were found to be associated with the mortality rate on the 5th day.

Conclusion: In our study, high PESI scores; low levels of hemoglobin, total protein, albumin as checked on day 1 and day 5; high RDW levels, high ALP; WBC, CRP and total bilirubin checked on day 5 remaining high were determined to be associated with mortality.

Keywords: Modified Geneva score, mortality, pulmonary thromboembolism, Wells score

ÖZ

Amaç: Bu çalışmada pulmoner tromboembolizmi olan bireylerin yatarak tedavisi, taburcu olduktan sonraki 6 aylık dönemin sonuna kadar olan tedavi süreci boyunca ortaya çıkabilecek komplikasyonlar ve sağkalım oranını etkileyen faktörlerin araştırılması amaçlanmaktadır.

Gereç ve Yöntem: Çalışmaya 01.01.2017-01.12.2019 tarihleri arasında göğüs hastalıkları kliniğinde izlenen ve bilgisayarlı tomografi pulmoner anjiyografisinde en az segmental seviyede trombüs saptanan yetişkin hastalar dahil edildi.

Bulgular: Çalışmaya alınan 210 hastanın yaş ortalaması 71,27±13,26 yıldı ve bu hastaların 55'i (%26) erkek, 155'i (%74) kadındı. Eksitus olan hastaların nabız hızı, Modifiye Cenevre ve Wells skorları, pulmoner emboli şiddet indeksi (PESI) ve basitleştirilmiş PESI skorları hayatta kalan hastalarınkinden daha yüksekti. Hayatını kaybeden hastalarda 1. ve 5. günlerde hem kırmızı hücre dağılım genişliği (RDW) hem de ortalama korpüsküler hacim ve hematokrit seviyeleri daha düşüktü. Hayatını kaybeden hastalar, 1. ve 5. günlerde daha yüksek sayıda trombosit ancak kanda daha düşük total protein ve albümin seviyelerine sahiplerdi. Birinci günde yüksek olan alkalen fosfataz (ALP), total bilirubin ve C-reaktif protein (CRP) değerlerinin, 5. günde olan ölüm oranı ile ilişkili olduğu saptandı.

Sonuç: Çalışmamızda yüksek PESI skorları 1. gün ve 5. günde düşük seviyelerde izlenen hemoglobin, total protein ve albüminle ilişkiliyken, yüksek seviyelerde izlenen RDW ve ALP ile ilişkiliydi. Beşinci günde yüksek olan beyaz kan hücresi, CRP ve total bilirubinin mortalite ile ilişkili olduğu belirlendi.

Anahtar Kelimeler: Modifiye Cenevre skoru, mortalite, pulmoner tromboembolizm, Wells skoru

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INTRODUCTION

Pulmonary thromboembolism (PTE) is a treatable disease with high mortality and morbidity rates, whose diagnosis can sometimes be difficult. Annual incidence is 1/1000 and it increases with age[1,2]. It should be known that common symptoms and physical examination findings such as dyspnea, tachypnea, tachycardia and chest pain in patients with pulmonary embolism are not unique to this disease. Clinical findings can range from an asymptomatic picture to sudden death as a result of a massive attack. Clinical diagnosis is much more difficult and unreliable in trauma or intensive care patients. Sudden onset of dyspnea and tachypnea are the most common symptoms and signs in patients with no previous cardiopulmonary problem in pulmonary embolism. Pleuritic pain with dyspnea and tachypnea is present in more than half of the cases. Hemoptysis is seen in less than 10% of cases. Clinical symptoms and findings may vary depending on the size, number (single/multiple) of the embolism, its location, the development of an infarction, the resolution rate, whether it is recurrent, the age of the patient and the reserve of cardiopulmonary functions[2,3]. Approximately 10% of patients undergoing deep vein thrombosis (DVT) develop PTE afterwards and nearly 10% of these patients lose their lives. Death rates within the first 3 months following the acute incident were determined as 15% in the prospective study on PTE diagnosis (Prospective Investigation of Pulmonary Embolism Diagnosis) and 17.5% in the study on international collection of PTE records (International Cooperative Pulmonary Embolism Registry)[3,4]. PTE is responsible for 5-15% of all hospital deaths. Approximately 2/3 of the patients undergoing or experiencing PTE are not accurately diagnosed and the mortality rates of these patients reach 30%. When PTE is accurately diagnosed and the proper treatment is administered, this rate can decrease to as low as 3%[3]. While hospital mortality increases up to 30% due to undiagnosed PTE, hospital mortality decreases to around 8% in diagnosed cases[4].

In this study, it is aimed to investigate the factors affecting the survival rate and complications that may arise throughout the treatment process from admission to the end of the 6-month period after discharge, the inpatient treatment of individuals with PTE.

MATERIALS AND METHODS

The study was carried out with adult patients being followed up with a diagnosis of pulmonary embolism in two separate pulmonology clinics. A total of 210 patients, including 55 males and 155 females, who had at least segmental thrombus in the pulmonary artery on computed tomography (CT) pulmonary angiography between 01.01.2017 and 01.12.2019 were included in the study.

The study was planned as a retrospective study and the inclusion criteria were the confirmation of the diagnosis with CT angiography, being hospitalized for at least 7 days and surviving this period, having undergone echocardiography (ECHO) and venous Doppler ultrasonography (USG) for DVT, having been reached by phone on the 6-month follow-up and completing outpatient clinic visits. Patients who died within the first 7 days of admission, pregnant women, patients whose follow-ups/analyses in the database were not complete, patients who did not visit the clinic after discharge, and patients on whom CT angiography was not performed due to high levels of creatinine were excluded.

In this period, a total of 290 patients were admitted to the service with PTE diagnosis. Fifteen patients on whom CT angiography was not performed for various reasons, 15 patients, whose ECHO data on admission were inaccessible, 10 patients who died within the first 7 days of admission, 25 patients whose day 1 and 7 laboratory findings were incomplete, and 15 patients who did not attend the follow-up visits and were unavailable when called by phone were not included in the study. The study was conducted with 210 patients who fulfilled all of the criteria (Figure 1).

The demographic characteristics of the cases (age, sex, body mass index, smoking history), comorbidities (chronic obstructive pulmonary disease, bronchiectasis, immunosuppression, diabetes mellitus, hypertension, coronary arterial disease, congestive heart failure, cerebrovascular accident, chronic renal failure, malignancy), risk factors (recent surgical, travel history, obesity, use of oral contraceptives, immobility), duration of admission, costs and mortalities were recorded. Respiratory rate (RR), arterial blood pressure, body temperature, heart rate, consciousness, and % saturation O_2 values obtained from the

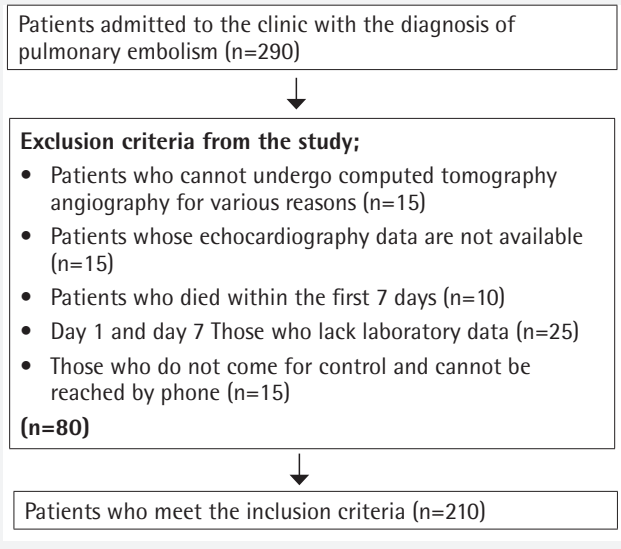

Figure 1. Flowchart of study

findings of the physical examination carried out at admission were included in the data. For cases, on whom ABG analyses were performed, PO_2, pCO_2, % saturation O_2 value and pH results were noted. The findings of the ECHO performed at the emergency unit and on day 7, as well as the results of bilateral lower extremity venous Doppler USG, were noted. % Saturation O_2 levels measured on days 1-6 in room atmosphere with pulse oximetry were recorded. Hemogram, coagulation, troponin, T, D-dimer, C-reactive protein (CRP), sedimentation, fibrinogen and overall biochemistry parameters at the time of arrival to emergency unit and outpatient clinic and on day 1 and 5 of admission were noted. Posteroanterior chest radiography and thorax computerized tomography findings at the time of arrival were noted. Wells and Geneva clinical probability scores and Wells bleeding risk scores, pulmonary embolism severity index (PESI) and simplified PESI (sPESI) scores measured within the first 24 hours of admission were recorded. The patients were called on the phone at Month 6 for obtaining information and were monitored with outpatient clinic follow up visits. The study was approved by the Bezmialem Vakıf University Non-Invasive Ethics Committee with the decision number: 03/20, date: 05.02.2020, and all patients participating in the study filled the informed consent form. Moreover, academic study permission was obtained. The work described was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Statistical Analysis

Statistical Package for the Social Sciences 22 statistics software was used for statistical analysis. For the assessment of data, continuous variables were indicated as mean±standard deviation and categorical variables were indicated in %. For comparing the two groups, Student's t-test or Mann-Whitney U tests were used. The correlations between the variables were studied using the Pearson or Spearman's correlation analysis. For the comparison of categorical variables, the chi-square testing was utilized. $P<0.05$ value was regarded as statistically significant.

RESULTS

A total of 210 patients were enrolled into the study. The mean age of the patients was 71.27±13.26 years. The demographical characteristics, comorbidities and risk factors of patients are shown in Table 1. When the correlation of vital signs with mortality at the time of admission was evaluated, only a significant correlation was found between high average heart rate and mortality (p=0.041). No statistically significant correlation was observed between the symptoms of the patients at the time of admission and mortality. Although the cost of admission was significantly higher for non-survivors than for the survivors, it was observed that this difference was not statistically significant (p=0.270).

The average modified Geneva scores and Wells PTE clinical prediction scores were higher in non-survivors; however, this difference was not statistically significant. The correlation of PESI and SPESI scores of patients, as calculated in the emergency unit, and mortality were studied. PESI score was 109.90±34.93 on average for non-survivors and 96.59±29.78 for survivors, and it was observed to be higher in non-survivors. However, the difference between non-survivors and survivors in terms of PESI scores was not statistically significant (p=0.139).

Table 1. Demographic characteristics, comorbidities and risk factors of patients

Sex patients	**(n) %**
Male	55 (26.19)
Female	155 (73.80)
Comorbidities	
Diabetes mellitus	36 (17.14)
Cerebrovascular accident	24 (11.42)
Hypertension	144 (68.57)
Coronary arterial disease	43 (20.47)
Congestive heart failure	24 (11.42)
Malignancy	34 (16.19)
Liver diseases	17 (8.09)
Immune suppression	19 (09.04)
Risk factors	
Recent surgery	43 (20.47)
Travel history	19 (9.04)
Obesity	60 (28.57)
Oral contraceptive use	48 (22.87)
Major surgery	43 (20.47)
Immobility	84 (40.00)
Other	108 (51.42)

Table 2. Correlation of mortality with PESI and sPESI scores

Non-survivors (n=42) (mean±SD)		**Survivors (n=168) (mean±SD)**	**p**
PESI	1109.90±34.93	96.59±29.78	0.139
sPESI	2.20±1.17	1.20±1.12	**0.013**
Geneva	6.1±1.7	4.7±1.6	0.07
Wells	4.8±1.8	4.2±2.1	0.09

PESI: Pulmonary Embolism Severity Index, sPESI: Simplified Pulmonary Embolism Severity Index, SD: Standard deviation

sPESI score was 2.20±1.17 on average for non-survivors and 1.20±1.12 for survivors, and this difference was found to be statistically significant (p=0.013) (Table 2).

When the correlation of the arterial blood gas (ABG) parameters at admission and mortality were studied, no statistically significant difference was observed between non-survivors and survivors.

Average WBC on day 1 was lower in non-survivors, and average WBC on day 5 was significantly higher in non-survivors and was found to be correlated with mortality (p=0.602 and p=0.039, respectively). Average platelet count on days 1 and 5 were higher in non-survivors; however, this difference was not found to be statistically significant (p=0.449 and p=0.729, respectively). Average levels of hemoglobin on days 1 and 5 were lower in non-survivors and this was determined to be correlated with mortality (p=0.002 and p=0.008, respectively). Average MCV on days 1 and 5 and hematocrit levels on days 1 and 5 were found to be lower in non-survivors; however, this was not significantly correlated with mortality (p=0.289, p=0.071, p=0.060 and p=0.141, respectively). Average levels of red cell distribution width (RDW) on days 1 and 5 were higher

Table 3. Correlation of day 1 and 5 hemogram parameters with mortality

	Non-survivors (n=42) (mean±SD)	Survivors (n=168) (mean±SD)	p*
WBC-1 (hc/uL)	8520±3048	9188±3418	0.586
WBC-5 (hc/uL)	8105±3896	5874±2824	**0.041**
PLT-1 (hc/uL)	241030±121678	198385±71322	0.452
PLT-5 (hc/uL)	253900±107365	243300±81682	0.734
Hb-1 (g/dl)	10.89±1.91	12.85±1.51	**0.003**
Hb-5 (g/dl)	10.79±1.41	11.95±1.52	**0.009**
MCV-1 (fl)	83.95±6.61	87.63±4.96	0.302
MCV-5 (fl)	81.71±5.18	85.87±5.64	0.071
HCT-1	35.12±5.94	39.04±4.28	0.059
HCT-5	32.93±3.41	35.74±4.34	0.143
RDW-1 (%)	14.96±2.85	12.18±1.23	**0.021**
RDW-5 (%)	15.94±2.85	12.74±1.36	**0.003**

The numbers 1 and 5 next to the laboratory parameters indicate the values on day 1 and day 5. Bold characters indicate statistical significance.

*Student's t-test.

WBC: White blood cell, PLT: Platelet, Hb: Haemoglobin, MCV: Mean corpuscular volume, HCT: Hematocrit, RDW: Red cell distribution width, SD: Standard deviation

Table 4. The comparison of the parameters obtained in repeated tests in died and surviving patient groups

	Survivors (n=168)			Non-survivors (n=42)		
	Day 1	Day 5	p	Day 1	Day 5	p
D-dimer	15192±24	3286±48	**<0.001**	7643±88	3234±18	0.121
Troponin	0.41±0.49	0.05±0.12	**0.002**	0.61±1.11	0.10±0.11	0.171
Leukocyte	9188±3418	54968±32	**<0.001**	8520±30	8105±3896	0.536
Platelet	198385±713	243300±81	**0.004**	253900±10	253900±107	0.264
Hemoglobin	12.8±1.51	12.2±1.49	**<0.001**	10.8±1.9	10.8±1.4	0.106
RDW	12.21±1.17	12.68±1.24	**<0.001**	15.0±3	16.0±2.7	**0.016**
ALP	81±39	83±47	0.692	141±11	106±80	0.449
Total protein	7.0±0.6	6.4±0.6	**<0.001**	6.2±0.7	5.9±0.4	0.224
Albumin	3.8±0.4	3.4±0.4	**<0.001**	3.0±0.6	2.7±0.5	0.081
Total bilirubin	0.87±0.45	0.45±0.22	**<0.001**	0.93±0.61	0.77±0.39	0.249
Direct bilirubin	0.30±0.16	0.18±0.08	**<0.001**	0.44±0.38	0.34±0.25	0.174
CRP	4.78±6.21	3.63±6.37	0.186	6.97±4.72	9.14±6.40	0.085
Fibrinogen	391±16	447±188	**0.020**	472±16	535±157	**0.033**
Sedimentation	33±28	34±26	0.577	49±35	58±38	**0.014**
LDH	454±64	311±114	0.163	413±295	339±142	0.343

The numbers 1 and 5 next to the laboratory parameters indicate the values on day 1 and day 5. Bold characters indicate statistical significance.

RDW: Red cell distribution width, ALP: Alkaline phosphatase, CRP: C-reactive protein, LDH: Lactate dehydrogenase

in non-survivors and this was determined to be correlated with mortality (p=0.003 and p=0.008, respectively) (Table 3). The comparison of day 1 and day 5 laboratory parameters of non-survivors and survivors are shown in Table 4.

As measured on day 1 and day 5, average levels of total protein (p=0.001 and p=0.002, respectively) and albumin (p=0.041 and p=0.001, respectively) were found to be lower in non-survivors, pointing to a correlation with mortality. Average alkaline phosphatase levels on both day 1 and day 5 were higher in non-survivors; however, only the difference on day 1 was found to be correlated with mortality (p=0.008 and p=0.251, respectively). As measured on day 1 and day 5, average total bilirubin (p=0.761 and p=0.001, respectively) and direct bilirubin (p=0.259 and p=0.081, respectively) were higher in non-survivors; however, only the difference in average total bilirubin on day 5 was determined to be correlated with mortality. As measured at admission (day 1), average levels of glucose, urea, creatinine, sodium, chlorine and uric acid were higher in non-survivors, and average levels of potassium, phosphorus, magnesium, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase were lower, but these were not found to be correlated with mortality (Table 5).

Average CRP levels of patients on both day 1 and day 5 were higher in non-survivors, and the difference on day 5 was found to be correlated with mortality (p=0.234 and p=0.018, respectively). Additionally, average sedimentation, fibrinogen and troponin 1 levels on days 1 and 5 were higher, and d-dimer levels were lower in non-survivors, but no significant correlation with mortality was detected (Table 6).

4 out of 21 patients (19%) with DVT in at least one extremity died and this was not found to be statistically correlated with mortality.

The correlation between certain ECHO parameters and mortality was examined. Two out of 4 patients (50%), whose ejection fraction was low, 2 out of 10 patients (20%) with large right spaces with no concomitant D-septum, and 2 out of 15 patients with D-septum died. No statistical correlation with mortality was observed in these results.

In our study, no complications such as bleeding due to the treatment used, medication side effects etc. were observed both during the inpatient treatment period and during the 6-month follow-up period.

Table 5. Correlation of mortality with biochemical parameters on day 1 and 5

	Non-survivors (n=42) (mean±SD)	Survivors (n=168) (mean±SD)	p*
Total protein-1 (g/dL)	6.21±0.72	7.11±0.59	0.001
Total protein-5 (g/dL)	5.89±0.41	6.39±0.71	**0.003**
Albumin-1 (g/dL)	3.23±0.61	3.83±0.42	**0.038**
Albumin-5 (g/dL)	2.69±0.49	3.39±0.38	**<0.001**
ALP-1 (U/L)	139.25±121.13	79.63±40.24	**0.009**
ALP-5 (U/L)	105.75±79.32	84.73±51.54	0.248
Total bilirubin-1 (mg/dL)	0.94±0.59	0.86±0.51	0.805
Total bilirubin-5 (mg/dL)	0.81±0.41	0.51±0.18	**0.003**
Direct bilirubin-1 (mg/dL)	0.39±0.42	0.31±0.21	0.261
Direct bilirubin-5 (mg/dL)	0.36±0.19	0.19±0.11	0.076
Urea (mg/dL)	61.18±29.83	51.87±19.84	0.468
Creatinine (mg/dL)	0.96±0.28	0.79±0.38	0.644
Na (mEq/L)	138.23±3.78	135.89±3.01	0.886
K (mEq/L)	3.87±0.58	4.31±0.48	0.204
CL (mg/dL)	105.10±6.44	104.64±16.47	0.876
P (mg/dL)	3.29±0.81	3.51±0.79	0.704
Mg (mg/dL)	1.89±0.32	1.94±0.28	0.889
ALT (U/L)	28.30±28.60	49.20±158.50	0.643
AST (U/L)	40.70±41.30	92.50±374.40	0.701
Uric acid (mg/dL)	7.4±4.12	6.12±3.11	0.204
CK (U/L)	78.00±89.76	106.32±172.68	0.654
LDH (U/L)	422±301	461±638	0.914

The numbers 1 and 5 next to the laboratory parameters indicate the values on day 1. and day 5. Bold characters indicate statistical significance. *Student's t-test.

ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CK: Creatine kinase, LDH: Lactate dehydrogenase, SD: Standard deviation

Table 6. Correlation of mortality with certain parameters on day 1 and day 5			
	Non-survivors (n=42) (mean±SD)	Survivors (n=168) (mean±SD)	p
CRP-1 (mg/dL)	7.14±5.13	5.06±7.04	0.306
CRP-5 (mg/dL)	10.21±7.56	3.54±7.44	**0.021**
SEDIM-1 (mm/h)	51.80±34.80	29.96±27.26	0.128
SEDIM -5 (mm/h)	58.84±41.82	36.84±28.28	0.088
D-dimer-1 (ng/mL)	7965±9743	138994±16912	0.276
D-dimer-5 (ng/mL)	2980±1896	3412±5139	0.838
Fibrinogen-1 (mg/dL)	504±208	403±214	0.181
Fibrinogen-5 (mg/dL)	541±162	454±204	0.208
Troponin 1-1	0.61±1.14	0.41±0.48	0.289
Troponin 1-5	0.07±0.09	0.04±0.06	0.161
The numbers 1 and 5 next to the laboratory parameters indicate the values on day 1. and day 5. Bold characters indicate statistical significance. *Student's t-test. CRP: C-reactive protein, SD: Standard deviation, SEDIM: Sedimentation			

DISCUSSION

In our study, high PESI scores, low levels of hemoglobin, total protein, and albumin as checked on day 1 and day 5, high RDW levels, high ALP, and WBC, CRP and total bilirubin checked on day 5 remaining high were determined to be associated with mortality.

The incidence of pulmonary embolism is typically equal in both sexes[4,5]. The mortality rate of PTE in non-treated cases is approximately 30%; however, in treated cases, the rate of mortality can decrease to below 8%[6,7]. Mortality typically has a linear relationship with malignancy, chronic cardiopulmonary comorbidities and advanced age[7,8].

74% of the cases enrolled into our study were female and the incidence of PTE was found to be higher in females in this study, in contrary to the literature. Additionally, in female patients, the rate of mortality was higher although the difference was not found to be statistically significant (24.32% and 7.69%, respectively). In a study carried out by Obradović et al.[9], which had a large population, it was reported that the mortality rate of pulmonary embolism was higher in females. The average age of the patients in our study was 71.27±13.26 years. Although all our cases were treated, the mortality rate observed (20%) was higher than the rate in the literature. The average age of non-survivors was higher than survivors.

While the average body temperatures of non-survivors and survivors in our study were similar, average systolic blood pressure and diastolic blood pressure levels were lower and RR values were higher. Additionally, high heartbeat per minute at arrival was correlated with mortality. The literature review did not review any studies mentioning the relevance of average heartbeat at arrival and mortality.

In many studies carried out, it has been shown that sPESI is as efficient as PESI in predicting mortality[10-12]. In our study, although the difference was not statistically significant, average PESI score of non-survivors weas higher, and average sPESI score was significantly higher in non-survivors. Our study also supports that sPESI score is as efficient as PESI score in determining mortality. For that reason, this score should definitely be taken into consideration in patients diagnosed with pulmonary embolism, as it is a determining factor in mortality.

When measuring ABGs, hypoxia, hypocarbia and respiratory alkalosis are expected in PTE patients. However, it can be detected as normal in 35% of the patients[13]. In the study carried out by Kohyama et al.[14] on 207 normotensive patients diagnosed with PTE, it was shown that hypoxia was positively correlated with the weight of the patient, although it was also common in the diseases for the differential diagnosis of PTE and was not always present in patients with PTE. Our study did not reveal any significant differences between average ABG values and mortality; we believe that this may be due to the fact that the sample size was small.

RDW, which is a parameter checked during routine blood tests, is a recently defined marker indicating the heterogenicity of red blood cells (anisocytosis). The increase in RDW in some cases and some studies stating that it is correlated with mortality is probably due to the fact that it increases in inflammatory conditions[15,16]. In the study on 136 acute PTE patients, published by Zorlu et al.[17] in 2012, RDW >14.6% was found to be significant in indicating mortality with a precision of 95.2% and specificity of 53%. In the retrospective study of Zhang et al.[18], which included 1,539 PTE patients, patients were divided into two groups according to the values determined with ROC analysis: RDW >14.8% and ≤14.8%. In the multivariate model, RDW was found to be significant in indicating mortality as an independent variable. The increase in RDW was explained more in relation to the inflammatory response mechanism against oxidative stress. In line with the literature, in our

study, low levels of average hemoglobin on days 1 and 5 were regarded to be significantly correlated with 180-day mortality. Additionally, the average WBC on day 5 was higher in non-survivors and was correlated with 180-day mortality. Similarly, in our study, average RDW on days 1 and 5 was higher in non-survivors and this was found to be correlated with 180-day mortality, and this is also in line with the literature.

ALT and AST increases with hepatocellular damage, and bilirubin in cases of cholestasis as well as hepatocellular damage. Level of albumin and prothrombin activity are the tests that reflect the synthesis capacity of the liver[19]. The morbidity and mortality in hypoalbuminemic patients are higher than in patients with normal levels of serum albumin[20]. The increase in bilirubin is dependent on the breakdown of erythrocytes in the infarct area. Unless there is a severe problem with the liver, ALT and AST levels do not increase significantly in cases of pulmonary embolism. However, if hypoxemia is severe, these enzymes may increase depending on liver damage[21,22]. In our study, average levels of ALT and AST were determined to be lower in non-survivors both on days 1 and 5. Despite the fact that the level of serum bilirubin was higher in non-survivors, this was not found to be correlated with mortality.

Albumin is the negative acute phase reactant. Serum levels decrease in many acute infective and inflammatory diseases. Low levels of albumin are correlated with poor prognosis and increased mortality in some diseases. The literature review has revealed studies emphasizing that low levels of serum total protein and albumin in critical diseases are correlated with mortality[23]. In line with the literature, our study also showed a significant decrease in average levels of serum total protein and albumin on days 1 and 5 in non-survivors.

High CRP is reported to be correlated with venous thromboembolism risk[24]. Our review of the literature revealed a few studies emphasizing the correlation of high CRP with prognosis of PTE. In the study conducted by Abul et al.[25] on 56 patients diagnosed with acute PTE, 36-month follow-up after discharge revealed higher mortality levels in patients with high levels of CRP and troponin T. Cardiac enzymes are known to be specific and sensitive markers indicating myocardium damage, released from the myocardium due to the overload on the right ventricle, reflecting left ventricle dysfunction. The mortality levels of patients, whose troponin levels were determined to be high in several meta-analyses, were significantly higher than patients with normal troponin levels[26]. Although the average level of CRP was higher in non-survivors on day 1, it was not significantly correlated with mortality; however, the high levels of CRP on day 5 were correlated with mortality, in line with the literature. Additionally, in contrary to the literature, no significant correlation was detected between average level of serum troponin T on days 1 and 5 and mortality.

Study Limitations

There are some limitations of this study that should be mentioned. The first limitation is that the data are based on hospital records since it is a retrospective study; and the second limitation may be that patients do not have longer follow-up. Another limitation is that the study may not reflect the general population due to the low number of patients included in the study.

CONCLUSION

In conclusion, PTE is a disease with high mortality and morbidity despite the advances in diagnosis and treatment. Routine, easily applicable physical examination and laboratory findings may help in predicting mortality.

Ethics

Ethics Committee Approval: The study were approved by the Bezmialem Vakıf University Non-Invasive Ethics Committee (decision number: 03/20, date: 05.02.2020).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.Ç., G.İ.D., Concept: H.Ç., Design: G.İ.D., Data Collection or Processing: H.Ç., G.İ.D., Analysis or Interpretation: H.Ç., Literature Search: G.İ.D., Writing: H.Ç.

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ORIGINAL ARTICLE

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Comparison of Post-transplant Cyclophosphamide Containing Immunosuppressive Regimen with Standard Immunosuppressive Regimen in Allogeneic Stem Cell Transplantation from Matched Sibling Donor

Tam Uyumlu Kardeş Donörden Yapılan Nakillerde Post-transplant Siklofosfamid İçeren İmmünosüpresif Rejimin Standart İmmünosüpresif Rejimle Karşılaştırılması

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ABSTRACT

Aim: Allogeneic stem cell transplantation (ASCT) is the only treatment that can cure most of malignant hematological diseases with the risk of some serious complications such as graft-versus-host disease (GVHD). GVHD can be got under control with post-transplant cyclophosphamide even in patients with haploidentical stem cell transplants. Here, we aimed to compare the effectiveness of post-transplant cyclophosphamide on GVHD with standard immunosuppressive therapy.

Materials and Methods: Patients with high-risk hematologic malignancies, who received ASCT from human leukocyte antigen-matched sibling donors, were studied. Patients in the post-transplant cyclophosphamide group also used tacrolimus and mycophenolate mofetil; on the other side, standard immunosuppressive treatment with cyclosporine and methotrexate was used. The primary endpoint of the study was to compare the severe acute GVHD rate between the groups.

Results: A total of 40 patients were included in the study. While severe (grade 3-4) GVHD was seen in three patients in the methotrexate-cyclosporin group, it was not seen in any patient in the post-transplant cyclophosphamide group. Also, 10th-month progress-free survival and overall survivals were 78.8% and 93.3% vs 56% and 72% in the post-transplant cyclophosphamide group and methotrexate-cyclosporin group, respectively.

Conclusion: Cyclophosphamide can be the cheapest, most applicable, and clinically effective treatment in GVHD prophylaxis.

Keywords: Allogeneic stem cell transplant, graft-versus-host disease, cyclophosphamide

ÖZ

Amaç: Allojenik kök hücre nakli (AKHN), birçok hematolojik malignite için, graft-versus-host hastalığı (GVHH) gibi bazı hayatı tehdit edici risklerine rağmen halen tek küratif tedavi yöntemidir. GVHH post-transplant siklofosfamid uygulamasıyla birlikte haploidentik kök hücre nakli yapılan hastalarda dahi kontrol altına alınabilmektedir. Çalışmamızın amacı da tam uyumlu kardeş donörden yapılan nakillerde post-transplant siklofosfamid kullanımının GVHH üzerine olan etkinliğini standart immünosüpresif tedaviyle karşılaştırmaktır.

Gereç ve Yöntem: Yüksek riskli hematolojik malignite tanısı olup tam uyumlu kardeş donörden AKHN yapılan hastalar çalışmaya alındı. Post-transplant siklofosfamid tedavisi alan hastalar, immünosüpresif tedavi olarak ayrıca takrolimus ve mikofenolat mofetil aldı; diğer kolda ise hastalar metotreksat ve siklosporin ile standart immünosüpresif tedavi aldı. Çalışmanın primer sonlanım noktası şiddetli akut GVHH gelişimi sıklığı olarak belirlendi.

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Bulgular: Çalışmaya toplam 40 hasta alındı. Standart immünosüpresif kolunda yalnızca 3 hastada şiddetli (grade 3-4) GVHH görülürken, post-transplant siklofosfamid alan grupta hiç görülmedi. Hastaların 1 yıllık progresyonsuz sağkalım ve genel sağkalım oranları standart immünosüpresif tedavi alanlar için %54 ve %62, post-transplant siklofosfamid alan hastalar için %78,8 ve %93,3 olarak izlendi.

Sonuç: Post-transplant siklofosfamid, ucuz, kullanılabilir ve klinik olarak etkili bir GVHH profilaksi ajanı olarak kök hücre naklinde kullanılabilir.

Anahtar Kelimeler: Allojenik kök hücre nakli, graft-versus host disease, siklofosfamid

INTRODUCTION

Allogeneic stem cell transplantation (ASCT) continues to be the only treatment modality that can cure most malignant hematological disorders even with high rates of complications such as acute and chronic graft-versus-host disease (GVHD). Some investigational manipulations, such as *in vitro/in vivo* T-cell depletion before transplant, T-cell repletion with cyclophosphamide (Cy) after transplant or long-term immunosuppression with cyclosporine A (CysA), mycophenolate mofetil (MMF), methotrexate (MTX), or anti-thymocyte globuline, can be used to maintain graft survival possibility and also decrease GVHD.

In vivo/In vitro T-cell depletion before ASCT is not a viable strategy in most transplantation centers due to technical and financial difficulties. For the first time in 2008, a group of experienced researchers from John Hopkins University reported that they successfully used post-transplant cyclophosphamide (PTCy) in haploidentical ASCT for T-cell repletion[1]. Especially the decrease in the frequency of severe acute and chronic GVHD (cGVHD) (grade 3-4) and the increase in GVHD free survival rates (HOVON96)[2] obtained with post-transplant high dose Cy (50 mg/kg/d, on days +3 and +4), which is widely applied in human leukocyte antigen (HLA) haploidentical stem cell transplantation (SCT) cases, paved the way for the application of PTCy in HLA-matched ASCTs.

In this study, we aimed to show the results of prophylactic PTCy use on GVHD in patients who underwent ASCT from HLA full-matched related donors (MRD), and to compare these results with conventional IST.

MATERIALS AND METHODS

This is a cross-sectional cohort study and designed from information obtained from electronic/hard-copy files of patients followed up in a single SCT center. For all patients in the study, ASCT was performed from a related donor with full compatibility of HLA-A, -B, -C, -DRB1, and -DQB1 alleles. The primary endpoint of the study was to show the rate of severe (grade 3-4) acute GVHD (aGVHD) defined by the International Bone Marrow Transplant Registry criteria[3]. Secondary endpoints were transplant-related mortality (TRM), graft failure (primary or secondary), progression-free survival (PFS), overall survival (OS), cytomegalovirus (CMV) reactivation, opportunistic infections, and cGVHD defined by National Institutes of Health (NIH) consensus criteria.

The study was approved by the Local Institutional Review Board and Ethics Committee and was conducted in accordance with the Helsinki Declaration of 1975. Approval for the study was obtained from the Local Ethics Committee of İstanbul Medeniyet University (decision no: 2021/0018, date: 13.01.2021).

Conditioning Regimens and Immunosuppressive Treatment

Fludarabine and busulfan-based conditioning regimens were used for myeloid malignancies, while fludarabine-TBI-based regimens were used in lymphoid malignancies.

GVHD prophylaxis regimens were as follows: for patients who received PTCy, it was given at 50 mg/kg/day iv on day +3 and +4 with MESNA. Tacrolimus at a dose of 0.03 mg/kg/day 24 h infusion was started on day +5, targeting through the plasma levels between 5 and 15 ng/mL and changed to oral form on day +14 and continued at least for 3 months. MMF at a dose of 15 mg/kg three times a day (total 45 mg/kg/day) was also started on day +5 and continued till +28th day. For patients who used MTX and CysA as prophylaxis, MTX was given at a dose of 15 mg/m^2/day on day +1 and at a dose of 10 mg/m^2/day on days +3, +6, and +11. Calcium folinate was administered on days +2, +4, +7, and +12 especially to prevent mucositis and renal

Table 1. Immunosuppressive regimens

Post-transplant cyclophosphamide	MTX-CysA
Cyclophosphamide 50 mg/kg/day +3, +4 with MESNA	15 mg/m^2/day on day +1, 10 mg/m^2/day on day +3, +6, and +11
Tacrolimus 0.03 mg/kg/day +5, targeting level 5-15 ng/mL, for three months	Calcium folinate on day +2, +4, +7, and +12
MMF 45 mg/kg/day, between +5 and +28 days	Cyclosporin A 1.8 mg/kg/day started on day +5, till at least six months, targeting level 200-400 ng/mL

MTX: Methotrexate, MMF: Mycophenolate mofetil, GVHD: Graft-versus-host disease, CysA: Cyclosporine A

toxicities of MTX. CysA was started at a dose of 1.8 mg/kg/day in two daily doses intravenously on day +5, targeting through the CysA plasma level of 200-400 ng/mL and continued as oral therapy for at least six months after transplantation (Table 1).

Supportive Care

Ganciclovir and valaciclovir were given to all patients for CMV prophylaxis. CMV DNA polymerase chain reaction analysis follow-up was performed according to related guidelines and CMV activation was defined as copy number of over 1,000 copies/mL or more in two consecutive measurements.

All patients received prophylaxis for bacterial and fungal infections as well as for *Pneumocystis jirovecii* according to related guidelines. Time to neutrophil engraftment was defined as the first of three consecutive days with an absolute neutrophil count >0.5x10^9/L after transplant, and time to platelet engraftment was defined as a platelet count of 20x10^3/L with no transfusion need during the preceding 7 days.

Lymphocyte recovery was defined as the day that absolute lymphocyte count was ≥0.4x10^9/L. While full chimerism was defined as 95% of blood CD3+ cells are of donor origin, mixed chimerism was defined as 66-94% of CD3+ cells are of donor origin, and non-chimerism was defined as < 65% of CD3+ cells are of donor origin in the host blood sample.

Statistical Analysis

The study population was described using frequencies with associated percentages for qualitative data and using median and range for quantitative data. The difference in blood levels in the two groups was compared using the Mann-Whitney U test comparing continuous data. The chi-square tests and Fisher's exact tests were used to compare categorical variables. OS and PFS were started from donor CD34+ stem cell infusion. Time elapsed between the day of transplantation and death or last contact was used to estimate OS. PFS was calculated as the time from the first day of the transplantation to progression, death of any cause, or last contact. The Kaplan-Meier curves were generated for survival analyses and the Breslow tests were used to assess differences in OS and PFS between study groups. A p value ≤0.05 was considered statistically significant. The IBM Statistical Package for the Social Sciences system version 25 was used for all analyses.

RESULTS

Demographic Data

Between 2016 and 2020, we enrolled 15 patients in the PTCy group and 25 patients in the MTX-CysA group. There was no difference between the two groups in terms of age, gender, and disease distribution, or treatment preferences. Characteristics of the patients are given in Table 2.

Engraftment and Immune Reconstitution

The median time to neutrophil engraftment for the PTCy and the MTX-CysA groups were 14 days and 15 days, respectively (p=0.94). The median time to platelet engraftment was 21 days for the PTCy group and 20 days for the MTX-CysA group

Table 2. Patients characteristics

Variable	All	Post-transplant Cy	MTX-CysA
Number	40	15	25
Age, median (range), years	47 (19-68)	51 (25-68)	44 (19-65)
Male, n (%)	23 (57.5)	8 (53)	15 (60)
Diagnosis, n (%)			
Acute myeloid leukemia	20 (50)	8 (53.3)	12 (48)
Acute lymphoblastic leukemia	11 (27.5)	4 (26.7)	7 (28)
Myelodysplastic syndrome	2 (5)	2 (13.3)	-
Non-Hodgkin's lymphoma	2 (5)	-	2 (8)
Multiple myeloma	4 (10)	1 (6.7)	3 (12)
Chronic neutrophilic disease	1 (2.5)	-	1 (4)
Remission status, n (%)			
CR1 and beyond	37 (92.5)	14 (93.3)	23 (92)
Progressive disease	3 (7.5)	1 (6.7)	2 (8)
Conditioning, n (%)			
MAC	27 (67.5)	9 (60)	18 (72)
RIC	13 (32.5)	6 (40)	7 (28)
Transfused CD34+ cells, median	5.5x10^6	5.5x10^6	5.5x10^6

CR: Complete remission, MAC: Myeloablative conditioning, RIC: Reduced-intensity conditioning, Cy: Cyclophosphamide, CysA: Cyclosporine A, MTX: Methotrexate

(p=0.99). Lymphocyte recovery time was 29.5 days and 20 days, respectively (p<0.001). Primary graft failure was seen only in one patient in the PTCy group (6.7%), and in five patients (20%) in the MTX-CysA group (p=0.381); secondary graft failure was observed in three patients and four patients, respectively (p=0.618). Donor chimerism could not be assessed in one patient in the MTX-CysA group due to early mortality. Full donor chimerism was achieved in all except one patient in the PTCy group (93.3%), and 21 patients (87.5%) in the MTX-CysA group at day +30 (p=1). Three patients in the MTX-CysA group, who had full-chimerism at day +30, lost full chimerism in long-term follow-up (Table 3).

Infections and Complications

Febrile neutropenia was observed in five patients (33.3%) and 15 patients (60%) in the PTCy group and the MTX-CysA group, respectively (p=0.191). All patients were treated with appropriate antibiotics and complete control of infection was achieved, but one patient in the MTX-CysA group died from sepsis on day +29. Both patients and donors had positive CMV serology before ASCT. CMV reactivation was seen in four patients (26.7%) and 15 patients (60%) for the PTCy group and the MTX-CysA group, respectively (p=0.06). In all patients, pre-emptive therapy with ganciclovir was successful. Frequency of hemorrhagic cystitis in both groups was similar (Table 4).

Graft-Versus-Host Disease

Grade 2-4 aGVHD was observed in two (13.3%) and seven (28%) of the patients in the PTCy and MTX-CysA groups, respectively. In terms of the primary endpoint of the study, there was no statistical difference between the groups. Grade 3-4 GVHD was not seen in any patient in the PTCy group and was seen in three patients in the MTX-CysA group (12%) (p=0.279). In the PTCy group, one patient had grade 1 skin and one patient had grade 1 liver GVHD, and one patient had grade 2 liver GVHD. In the MTX-CysA group, one patient had grade 1, four patients had grade 2, and one patient had grade 3 skin GVHD; one patient had both grade 3 skin and liver GVHD, one patient had both grade 3 skin and gut GVHD.

cGVHD was not evaluated in patients who progressed or died within the first 100 days of ASCT. It was seen in three patients (21.4%) in the PTCy group and five patients (25%) in the MTX-CysA group (p=1) (Table 4).

Survival Outcomes

The median follow-up period for the entire population was 10.6 months. PFS on the 100th day of the ASCT to evaluate early recurrence was 93.3% in the PTCy group and 80% in the MTX-CysA group; PFS on the 10th month of the ASCT was 78.8% in the PTCy group but 56% in the MTX-CysA group (p=0.18) (Figure 1). OS on the 100th day of the ASCT to evaluate

Table 3. Transplant outcomes

Variable	Post-transplant Cy	MTX-CysA	p
Neutrophil recovery, median (range), days	14 (11-28)	15 (9-41)	0.94
Platelet recovery, median (range) days	21 (14-42)	20 (12-141)	0.99
Lymphocyte recovery, median (range) days	29.5 (17-42)	20 (11-36)	**<0.001**
Full donor chimerism on day 90, n (%)	14 (93.3)	21 (87.5)	1
1-year PFS, %	78.8	52	0.18
1-year OS, %	93.3	64	0.2
Median follow-up (range), months	9.8 (5-17.3)	22.6 (0.97-84.8)	0.12

OS: Overall survival, PFS: Progress-free survival, Cy: Cyclophosphamide, CysA: Cyclosporine A

Table 4. Transplant complications

Variable	Post-transplant Cy	MTX-CysA	p
Number	15	25	
aGVHD 2-4, n (%)	2 (13.3)	7 (28)	0.44
aGVHD 3-4, n (%)	0	3 (12)	0.28
cGVHD 2-4, n (%)	3 (21.4)	5 (25)	1
Hemorrhagic cystitis, n (%)	1 (6.7)	3 (12)	1
CMV reactivation, n (%)	4 (26.7)	15 (60)	0.06
Incidence of poor graft function, n (%)	1 (16.7)	5 (20)	0.38
Treatment-related mortality, n (%)	0 (0)	4 (16)	0.28

aGVHD: Acute graft-versus-host disease, cGHVD: Chronic graft-versus-host disease, CMV: Cytomegalovirus, CysA: Cyclosporine A

early mortality was 100% in the PTCy group and 88% in the MTX-CysA group; OS on the 10th month of the ASCT was 93.3% in the PTCy group and 72% in the MTX-CysA group (p=0.2) (Figure 2). Treatment-related mortality was not seen in the PTCy group and was seen in four patients (16%) in the MTX-CysA group (p=0.28) (Table 4).

DISCUSSION

In this retrospective cross-sectional study, we aimed to compare the clinical results of patients who received high-dose Cy after allograft infusion and those who received MTX-CysA, with particular emphasis on GVHD. The use of tacrolimus for 3 months with PTCy is easier than the use of an immunosuppressive with a wide side effect profile such as cyclosporine for 6 months. As far as we know, this is the only study that compares patients who use PTCy and MTX-CysA for GVHD prophylaxis in HLA-matched sibling donors.

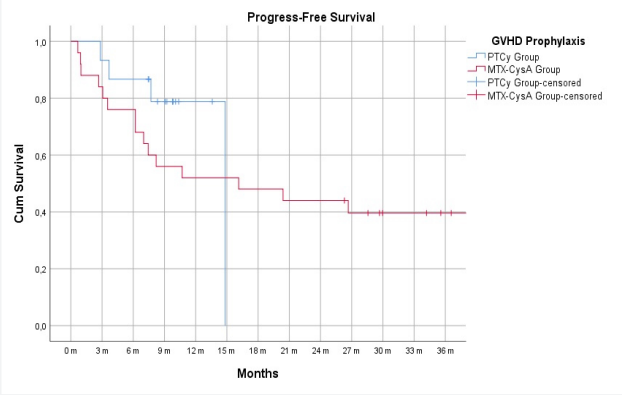

Figure 1. Comparison of progress-free survival of patients between the PTCy group and MTX-CysA group

MTX: Methotrexate, GVHD: Graft-versus-host disease, CysA: , PTCy:

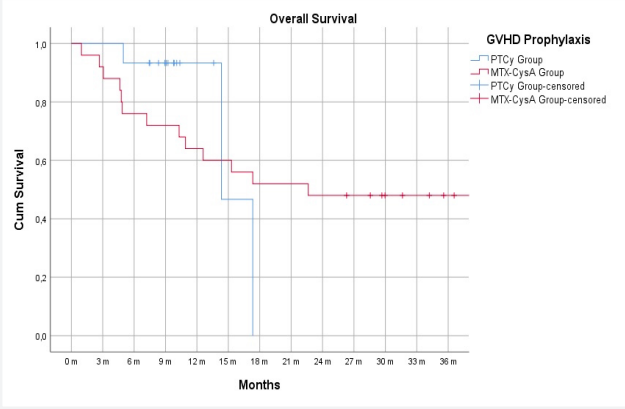

Figure 2. Comparison of overall survival of patients between the PTCy group and MTX-CysA group

MTX: Methotrexate, GVHD: Graft-versus-host disease, CysA: , PTCy:

aGVHD was seen in two patients (13.3%) in the PTCy group, while grade 3-4 aGVHD was not observed in any patient. In the MTX-CysA group, aGVHD was observed in 10 (40%) patients (p=0.44), while three of them (12%) had grade 3-4 aGVHD (p=0.27). Mielcarek et al.[4] performed a study, in which characteristics of the study population were quite similar to those of our study, which they used Cy plus cyclosporin for GVHD prophylaxis. The rates of grade 2-4 and grade 3-4 aGVHD were 77% and 0%, respectively. It has been shown that alloreactive T lymphocytes can be inhibited more with calcineurin inhibitors added to the PTCy; this explains why the frequency of aGVHD was lower in our study[5]. In the studies of Luznik et al.[6] and Kanakry et al.[7], the frequency of grade 3-4 aGVHD was found 10-15% in ASCT patients with HLA-matched related and unrelated donors receiving PTCy. It is slightly more than that of our study probably because we had fewer patients and we only included patients who underwent ASCT from HLA-matched sibling donors.

In a study conducted by Luznik et al.[1] in 2008, after HLA haploidentical donor SCT, the frequency of cGVHD was reduced to 25% with the administration of a single dose of Cy, and decreased to 5% with two doses of Cy. After the successful results of this study, both Luznik and et al.[6] applied PTCy after HLA-matched donor-derived allogeneic transplant in 2010 and observed the rate of cGVHD as 10%.

In our study, the frequency of cGVHD diagnosed according to the NIH criteria was 21.4% (n=3) in the patients in the PTCy group and 25% (n=5) in the MTX-CysA group.

In two large studies[8,9] using the same PTCy regimen that we used for GVHD prophylaxis, they found aGVHD (grade 2-4 and grade 3-4) rates similar to our study (27%, 19% grade 2-4 and 2%, 4% grade 3-4 aGVHD, respectively). cGVHD rates were about 16%, which was also similar to our study. The incidence of cGVHD in our study was higher than other reported studies due to the use of RIC regimen in 40% of patients in the PTCy group and the use of stem cells mobilized from peripheral blood[8,10].

Graft failure at day +30 post-transplant was observed in only one (6.7%) patient in the PTCy group but in five patients in the MTX-CysA group (20%) (p=0.38). Secondary engraftment failure was detected in three (20.1%) patients in the PTCy group, usually due to the use of cytotoxic agents such as ganciclovir or linezolid. We thought that the main causes of primary engraftment failure in a patient in the PTCy group were patients' diagnosis (myelodysplastic syndrome) and RIC regimen. Graft failure was observed in only one out of 35 patients who received PTCy-MMF-TAC in the study of

Carnevale-Schianca et al.[11] which was due to *P. aeruginosa* septicemia. It was also found in one of 28 patients (3.6%) in the study conducted by El Fakih et al.[12]. Full-chimerism rates were 93.3% for the PTCy group and 87.5% for the MTX-CysA group, which are similar to the aforementioned studies of Carnevale-Schianca et al.[11] and Mielcarek et al.[4].

In our study, times to neutrophil and platelet engraftment were found to be similar in the PTCy and MTX-CysA groups (neutrophil recovery time 14 days and 15 days, p value=0.94, platelet recovery time 21 days and 20 days, p value=0.98, respectively). Similar results were found for neutrophil and platelet recovery times in the study by Mielcarek et al.[4] (neutrophil recovery time 14 days and platelet recovery time 19 days).

In our study, lymphocyte recovery time after transplantation was 20 days in the MTX-CysA group and 29.5 days in the PTCy group (p<0.0001). Leo et al.[13] also showed that the absolute lymphocyte count was found as 440/microliter on the 30th day after transplantation and >700/microliter on the 60th day, similar to our study. In addition, protection of the immune reconstitution and immune-defense mechanism against bacterial agents with PTCy was also observed in our study. The frequency of febrile neutropenia was 33.3% (n=5) in the PTCy group and 60% (n=15) in the MTX-CysA group (p=0.191).

CMV reactivation was observed in 26.7% (n=4) in the PTCy group and 60% (n=15) in the MTX-CysA group (p=0.08). No CMV infection or end-organ damage developed in any of the patients in either group. The rate of CMV reactivation was 32% in patients who received PTCy in a study by Leo et al.[13], which is consistent with the data in our study. Although there was no statistically significant result in terms of CMV reactivation between the PTCy and MTX-CysA groups, a clinically significant decrease was observed in the PTCy group. The difference in CMV reactivation may gain statistical significance with the prolongation of the follow-up period.

In our study, the median follow-up time for all patients was 10.6 months (9.8 months vs 22.6 months). As of the 100th day; OS rate was 100% and PFS rate was 93.3% in the PTCy group, and OS rate was 88% and PFS rate was 80% in the MTX-CysA group. In the 10th month, while OS continued at the rate of 93.3% and PFS was 78.8% in the PTCy group, they were found to be 72% and 56% in the MTX-CysA group (p=0.2 and p=0.18), respectively. TRM was not observed in the PTCy group (0%) during the observation period, while this rate was 16% (n=4) in the MTX-CysA group (p=0.278). Luznik et al.[6] examined patients who received high dose Cy after MRD/MUD ASCT, they found OS 55%, EFS 39%, and TRM 17% at the end of the second year. In a cohort study on 1,479 patients with acute leukemia (acute myeloid leukemia and acute lymphocytic leukemia) and patients transplanted from an HLA-matched sibling/unrelated donor, the rates of two-year OS, PFS, relapse rate, and TRM were found 62%, 57%, 28%, and 14%, respectively, with PTCy plus two immunosuppressive agents as GVHD prophylaxis[14]. In the previous studies, the two most important factors related to superior OS in patients who received PTCy for GVHD prophylaxis were the disease status (complete remission) at the time of transplant (p<0.0001) and the addition of two immunosuppressive agents to Cy (p=0.02)[14]. Although the median follow-up period of our study has not reached the second year, it seems to be similar or better than the results of other studies.

Study Limitations

Our study had many limitations. The design of our study was retrospective, with an inadequate number of patients in both groups and the shorter median follow-up period of the patients in the PTCy group compared to the other. Also, the distribution of conditioning regimens or disease subgroups was not same in both groups. So, we could not compare the difference between myeloablative and non-myeloablative regimens. The patients in our study will be followed for a minimum of two years and the results obtained will be added to the literature in light of current information.

CONCLUSION

High-dose PTCy, which has been used successfully in GVHD prophylaxis in HLA haploidentical ASCT patients for many years, can be even used successfully in GVHD prophylaxis after HLA matched (sibling/non-sibling) ASCT. In addition to its success in GVHD prophylaxis, it has been shown that it allows the discontinuation of other immunosuppressive therapies in the early period, contributes to the continuation of the graft-versus-disease effect, causes a possible decrease in CMV reactivation and febrile neutropenia, and thus has positive effects on PFS and OS. PTCy, compared to other GVHD prophylaxis, can be said to be the cheapest, most applicable, and most clinically effective one.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Local Ethics Committee of İstanbul Medeniyet University (decision no: 2021/0018, date: 13.01.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.K., Concept: O.K., T.E., Design: O.K., T.E., Data Collection or Processing: O.K., Analysis or

Interpretation: O.K., T.E., Literature Search: O.K., T.E., Writing: O.K., T.E.

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

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The Investigation of the Effects of Melatonin on Electrocardiografic Findings in Rats Undergoing Acute Intense Exercise

Akut Yorucu Egzersiz Yaptırılan Sıçanlarda Melatoninin Elektrokardiyografik Veriler Üzerindeki Etkilerinin Araştırılması

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ABSTRACT

Aim: Acute intense exercise causes an additional strain on cardiovascular system. Melatonin has been known as a hormone with cardiovascular protective effects. The aim of this study is to investigate the protective effects of melatonin on cardiovascular changes in rats undergoing acute intense exercise, considering electrocardiogram (ECG) results.

Materials and Methods: The 3-5-month-old 28 Wistar albino rats were used in this study and they were divided into 4 groups. The vehicle injection was applied in the control group without any exercise procedure. The groups of exercise, exercise+melatonin (intraperitoneal injection of melatonin at the dose of 10 mg/kg before exercise) and exercise+melatonin+luzindole (intraperitoneal injection of luzindole at the dose of 0.4 mg/kg and melatonin at the dose of 10 mg/kg before exercise) were run on treadmill until they were tired. ECG recording was performed at the end of the exercise.

Results: A significant increase in heart rate was observed in both exercise groups. The decreasing effect of melatonin on QT and QTc prolongation in the exercise group was reported; however, this effect did not occur in the luzindol administrated group. Melatonin also decreased corticositerone levels, which increased with exercise, independent of receptor. White blood cell and neutrophile counts of the melatonin administrated group were observed to be close to that of the control group.

Conclusion: These results indicate that melatonin can be used as an agent that may decrease unfavorable effects of exercise and improve the quality of exercise.

Keywords: Exercise, melatonin, QT duration, corticosterone

ÖZ

Amaç: Akut yorucu egzersiz kardiyovasküler sistem (KVS) için ilave bir yük oluşturmaktadır. Melatonin ise KVS üzerine koruyucu etkileri olduğu bilinen bir hormondur. Bu çalışma ile akut yorucu egzersiz uygulanan sıçanlarda KVS'de meydana gelen değişikliklerin elektrokardiyografi (EKG) verileri üzerinden değerlendirilmesi ve melatoninin koruyucu etkilerinin araştırılması amaçlandı.

Gereç ve Yöntem: Çalışma 3-5 aylık 28 adet Wistar Albino sıçan üzerinde yürütüldü ve 4 ayrı grup oluşturuldu. Kontrol grubuna sadece taşıyıcı çözelti uygulandı ve herhangi bir egzersiz yapılmadı. Egzersiz, egzersiz+melatonin (egzersizden önce 10 mg/kg intraperitonal melatonin enjeksiyonu) ve egzersiz+melatonin+luzindole (egzersizden önce intraperitonal 0,4 mg/kg dozda luzindol ve 10 mg/kg melatonin enjeksiyonu) grupları 5-25 m/dk hızda koşu bandında yoruluncaya kadar koşturuldu. Egzersiz sonrasında EKG verileri kaydedildi.

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Bulgular: EKG verilerine göre, her iki egzersiz grubunda kalp hızının anlamlı düzeyde arttığı belirlendi. Melatonin uygulamasının egzersiz grubunda anlamlı düzeyde artan QT ve QTc süresi uzamalarını kısalttığı, luzindol verilen grupta ise melatoninin bu etkisinin ortaya çıkmadığı belirlendi. Melatonin aynı zamanda egzersizle artan kortikosteron seviyelerini reseptör bağımsız bir şekilde azalttı. Egzersizle artan akyuvar sayısı ve nötrofil düzeyleri melatonin grubunda kontrol grubuna yakın düzeyde belirlendi.

Sonuç: Bu sonuçlar melatoninin, egzersizde ortaya çıkabilecek istenmeyen etkileri azaltıcı ve egzersiz kalitesini artırıcı bir ajan olarak kullanılabileceğini göstermektedir.

Anahtar Kelimeler: Egzersiz, melatonin, QT süresi, kortikosteron

INTRODUCTION

It is known that regular physical activity is extremely beneficial for health. However, high-intensity exercise or exhausting exercise can lead to the formation of reactive oxygen species, causing organ and tissue damage, especially liver and kidney[1-3]. The relationship between exercise and cardiovascular system (CVS) is very important compared to other tissue and organ systems, and many studies have been performed on this subject. It is accepted that regular physical exercise has a reducing effect on the development of atherosclerosis and coronary artery diseases[4]. However, sudden cardiac deaths due to exercise have been reported and the most common underlying hereditary factors have been described as; long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, hypertrophic cardiomyopathy, and arrhythmiogenic right ventricular cardiomyopathy[5]. Therefore, the exercise-QT relationship has attracted the attention of researchers.

The QT interval reflects the total duration of depolarization and repolarization of the ventricular myocardium and varies inversely with heart rate. An increase in heart rate (tachycardia) causes a shortening of the QT interval, while a decrease in rate (bradycardia) causes QT prolongation. Therefore, heart rate should be calculated and corrected QT (QTc) time should be determined to say that the QT duration is within the expected values or is abnormally prolonged. Today, prolongation of the QTc duration is accepted as an age-independent risk factor for sudden death[6]. Exercise can cause arrhythmias by prolonging the QT duration. It is stated that this effect of exercise is associated with cardiac hypertrophy and oxidative damage. Therefore, protective agents are needed against the QT prolonging effect of exercise[7]. Melatonin is one of the candidate molecules that can be used for this purpose.

Melatonin is the most important hormone synthesized from the pineal gland, especially in the dark photoperiod. Although there are many factors affecting the synthesis and release of melatonin, the most important factor is light[8]. Melatonin exerts its effects through high-affinity G-protein coupled receptors of MT1 and MT2. Melatonin receptors have been isolated in various peripheral tissues, including the central nervous system and blood vessels[9]. Luzindole (N-0774), (N-acetyl-2-benzyltryptamine) is a pharmacological agent used in scientific research to investigate the role of melatonin in the body and acts as a selective melatonin receptor antagonist. It has approximately 11-25 times greater affinity for the MT2 receptor than for MT1. In animal studies, it was observed that the circadian rhythm related to melatonin was disrupted as a result of giving luzindole to the subjects[10,11].

In our study, it was planned to investigate the effects of melatonin, a powerful anti-inflammatory and antioxidant known to have protective effects on the cardiovascular system, due to the prolongation of QT duration, activation of inflammatory processes and the emergence of oxidative damage in strenuous exercise.

MATERIALS AND METHODS

Experimental Animals

This study was carried out on 28 rats of 3-5 months old Wistar Albino breed at Çanakkale Onsekiz Mart University (ÇOMÜ) Experimental Research Application and Research Center with the permission of ÇOMÜ Animal Experiments Local Ethics Committee, with the number of 2017-04-14. The rats were fed and water ad libitum and housed at 21-22 °C room temperature throughout the experiment.

Groups

1. Control Group (C, n=7): The rats in this group were injected with saline as the carrier solution of both solutions during the hours when melatonin and luzindole were administered to the other groups. No exercise protocol was applied. They were only kept still on the treadmill for 30 minutes and then electrocardiogram (ECG) measurements were made for 5 minutes under anesthesia and blood samples were taken.

2. Exercise Group (EGZ, n=7): The rats in this group were run on a treadmill set at a speed of 5-25 m/min until they got tired. When the running time was over, the rats were anesthetized at the sedative level and ECG measurements were made for 5 minutes and blood samples were taken.

3. Exercisez+Melatonin Group (MEL): The rats in this group were injected intraperitoneally with 10 mg/kg of melatonin 15 minutes before the exercise. For exercise, rats were run on a treadmill set at a speed of 5-25 m/min until they got tired. As

soon as the exercise was finished, the rats were anesthetized at the sedative level and ECG measurements were made for 5 minutes and blood samples were taken.

4. Exercise+Melatonin+Luzindole Group (LUZ+MEL, n=7): The rats in this group were intraperitoneally injected first with luzindole at a dose of 0.4 mg/kg and then, 15 minutes later, with melatonin at a dose of 10 mg/kg. 15 minutes after the melatonin injection, the animals were run on a treadmill set at a speed of 5-25 m/min until they got tired. When the running time was over, the rats were anesthetized at the sedative level and ECG measurements were made for 5 minutes and blood samples were taken.

Preparation of Solutions

Melatonin was prepared fresh daily to be administered intraperitoneally. For this purpose, melatonin solution was prepared by dissolving the solution containing 2% ethanol (Absolute GR for analysis, MERCK, Germany) in 1.5 mL of physiological saline solution[12].

Luzindole was injected to the rats at a dose of 0.4 mg/kg. For this purpose, luzindole was given daily by dissolving it in physiological saline.

Exercise Protocol

The rats placed on the treadmill were first run at a speed of 5 m/min. The speed was gradually increased to 25 m/min. After the speed of the treadmill reached 25 m/min, the rats were run until they got tired. When the rats showed signs of fatigue and did not want to run, they were stimulated to run with a mild electrical stimulus. The exercise protocol was terminated for rats that could not run despite the stimulation.

Sedation

The sedation procedure was performed by intramuscular administration of 40 mg/kg ketamine HCl and 4 mg/kg xylazine for ECG recording only. For this purpose, it was considered sufficient for the rats to remain in light sedation for about 5 minutes.

ECG Recording

As soon as the rats were removed from the treadmill, sedation was applied and ECG recording was started. From the rats, I, II and III extremity derivations and increased unipolar extremity derivations of aVR, aVL, and aVF were recorded. ECG recordings were performed non-invasively (Poly-Spectrum 12 channel ECG-System, Poly-Spectrum-8, Neurosoft, 5, Voronin str., Ivanovo, Rusia). ECG recordings were taken as 1 mV=20 mm, velocity 75 mm/sec and using a filter (35 Hz). The rats were sedated 5 minutes before the ECG recordings were taken. ECG recordings were taken uninterruptedly for 5 minutes at the same time in all groups. After evaluating the ECG data in general, heart rate, RR duration and QT duration were calculated. In ECG samples 2. RR and QT durations were calculated considering the derivation II and aVR recordings. Calculations were made by determining 3 consecutive RR intervals from each ECG recording. QTc times at the level of milliseconds (ms) were calculated from the determined QT and RR values. The following formulas were used for QTc calculations[13].

Bazett (QTcB): QT Interval / $\sqrt{RR}$

Fridericia (QTcF): QT Interval/ 3 $\sqrt{RR}$

Anesthesia

The rats whose ECGs were performed were administered general anesthesia. For this purpose, rats were given general anesthesia using ketamine (60-80 mg/kg) and xylazine (5 mg/kg). Introduction to anesthesia of rats was determined by making reflex control.

Collecting Blood Samples

Blood samples were taken from rats under anesthesia by cardiac puncture method. Two different blood samples were taken in the study. One of them was used for complete blood count. For this purpose, blood samples were taken into tubes containing EDTA to prevent coagulation and blood count was started without waiting. During this time, the blood samples were kept at +4 °C. Blood samples taken for corticosterone measurement were taken into serum tubes. These blood samples were centrifuged at 4,000 RPM for 10 minutes in a refrigerated centrifuge at +4 °C and the serum part was separated. Serum samples were transferred to eppendorf tubes and placed in storage boxes. And they were stored in a deep freezer at -80 °C until analysis.

Obtaining Hematological Data

Blood count was performed manually using a Thoma slide. For this purpose, the total leukocyte count was determined. Peripheral smear was also made from the blood samples taken, and the neutrophil percentage values were calculated.

Corticosterone Measurement

The samples were analyzed with the ELISA kit developed to measure corticosterone in rat plasma[14]. Corticosterone measurements were carried out in the Laboratory of İnönü University Faculty of Medicine, Department of Physiology.

Statistical Analysis

Obtained data were expressed as mean±standard error.

Statistical significance levels of the data were determined using the Statistical Package for the Social Sciences for Windows version 16 (Chicago, IL, USA) program. Multiple group comparisons were made using the Kruskal-Wallis test. The Mann-Whitney U test was used to compare the two groups. All the results obtained and the differences obtained as a result of this comparison were analyzed at $p<0.05$ significance level.

RESULTS

Duration of Exercise

In our study, the most dramatic changes were seen in tirelessness durations. While the duration of tirelessness in the exercise group was 14.2±0.6 minutes, this value reached 22.5±0.8 minutes in the melatonin group ($p<0.001$). Tirelessness duration decreased to the lowest value of 10.1±1.1 in the group administered with luzindole and showed a significant difference with both exercise ($p<0.01$) and melatonin groups ($p<0.001$).

ECG Data

Findings of Heart Rates

Data showing the heart rate values of all groups are presented in Figure 1. It is seen that the heart rate in the groups varies between 300-405 beats/min. The heart rate value of the MEL+LUZ group was statistically significantly higher than all other groups ($p\leq0.001$).

QTc Values

QTcB Results According to Bazett's Formula

When QTc values are calculated using Bazett's formula, it is seen that the values of all groups vary in the range of 101-213 ms. The QTcB value, which was 101 ms in the control group, reached 159 ms in the exercise group. In the group administered melatonin, the QTcB value decreased up to 128 ms and approached the control group value. On the other hand, the MEL+LUZ group showed the highest QTcB value with a value of 213 ms (Figure 2).

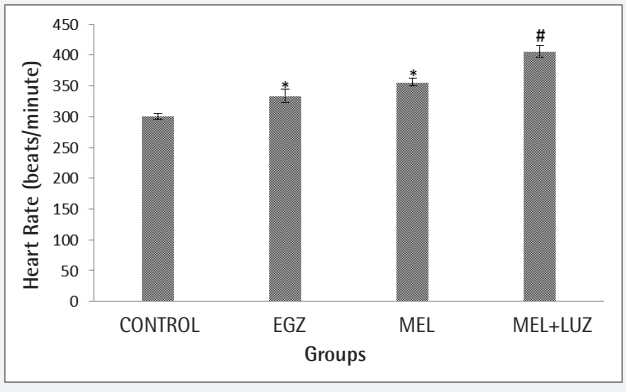

Figure 1. Showing heart rate changes of all groups (*: $p<0.05$ according to CONTROL and MEL+LUZ groups, #: $p\leq0.001$ according to CONTROL, EGZ and MEL groups)

QTc Results According to Fridericia Formula

It was observed that the change in the QTcF values calculated according to the Fridericia formula was similar to the QTcB values. Similarly, the lowest value occurred in the control group (77.6 ms), the QTcF value increased (119.8 ms) in the exercise group, melatonin administration caused a decrease in QTcF duration (95.6) and the highest QTcF value in the luzindole group (155.2) was determined (Figure 3).

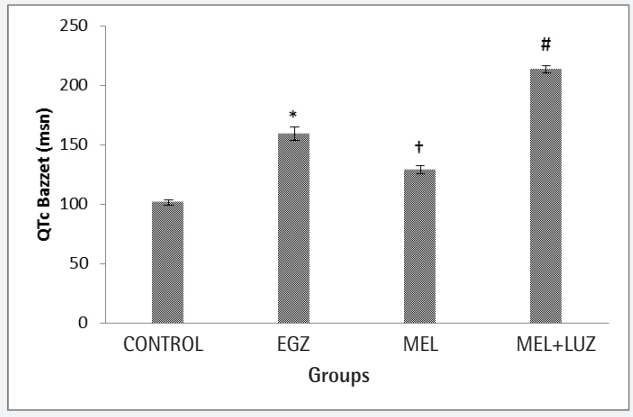

Figure 2. Graphical presentation of QTc values calculated according to the Bazett's formula for all groups (*: $p<0.001$ according to CONTROL, MEL and MEL+LUZ groups, †: $p<0.001$, according to CONTROL, EGZ and MEL+LUZ groups, #: $p<0.001$ according to CONTROL, EGZ and MEL groups)

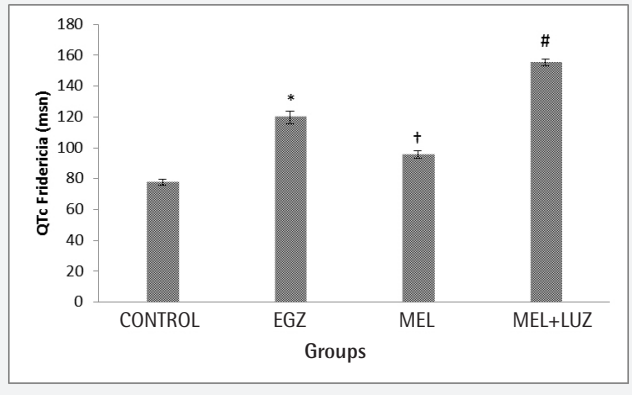

Figure 3. Graphical presentation of QTc values calculated according to the Fridericia formula for all groups (*: $p<0.001$ according to CONTROL, MEL and MEL+LUZ groups, †: $p<0.001$ according to CONTROL, EGZ and MEL+LUZ groups, #: $p<0.001$ according to CONTROL, EGZ and MEL groups)

Corticosterone Values

Corticosterone values were observed to vary between 249 and 451 ng/mL in all groups. While the lowest value (249 ng/mL) was observed in the control group, this value was found to be in the range of 405-451 ng/mL in all exercised groups (Figure 4).

White Blood Cell Count

The changes in the white blood cell count values of all groups and the markings showing the statistical significance levels are presented in Figure 5.

Neutrophil Count

The changes in the neutrophil count values of all groups and the markings showing the statistical significance levels are presented in Figure 6.

DISCUSSION

In this study, it was revealed that giving melatonin before exercise to rats subjected to acute intense exercise; (a) it reduced prolongations in QTc duration, (b) prevented the increase in white blood cell count (c) but did not cause significant changes in corticosterone levels and heart rate, (d) the QTc and white blood cell count reducing effects of melatonin were blocked by luzindole.

In our study, significant findings were observed in terms of exercise duration. While the rats in the group given melatonin were able to exercise for an average of 22.5 min, this value decreased to 14.2 min in the group not given melatonin, and to 10.1 min in the group given luzindole. Thus, it was understood that the rats in the group given melatonin were able to exercise without getting tired for about 2 times longer than the groups that were not given melatonin. This suggests that melatonin increases exercise duration and its effects on exercise duration are receptor dependent. There are reports that melatonin has effects that increase exercise performance. It is stated that the performance of athletes who take melatonin for a long time increases and this is due to the sleep quality-enhancing effect of melatonin[15]. In addition, it has also been demonstrated that taking melatonin before competitions improves athletic performance[16].

Changes in white blood cell and neutrophil counts were found to be significant in the melatonin group. Both parameters increased significantly in the exercise group compared to the control group, and melatonin administration reduced these values to the same level with the control group. However, it was observed that white blood cell and neutrophil counts reached higher levels when luzindole was given before melatonin administration, even compared to the exercise group. As in

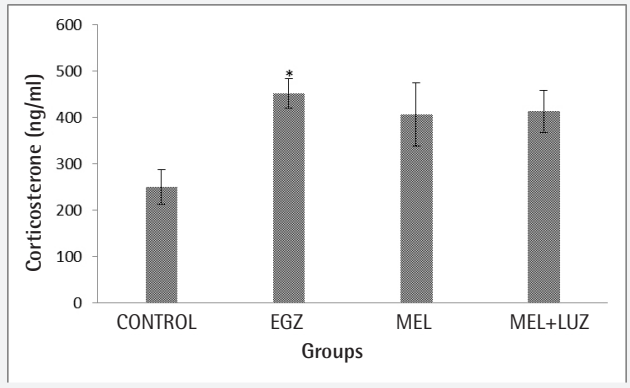

Figure 4. Showing corticosterone values of all groups (*: p<0.05 according to CONTROL group)

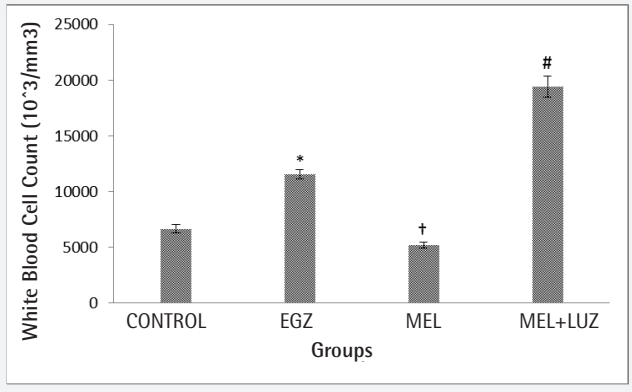

Figure 5. Showing white blood cell count of all groups (*: p<0.001 according to CONTROL, MEL and MEL+LUZ groups, †: p<0.001, according to EGZ and MEL+LUZ groups, #: p<0.001 according to CONTROL, EGZ and MEL groups)

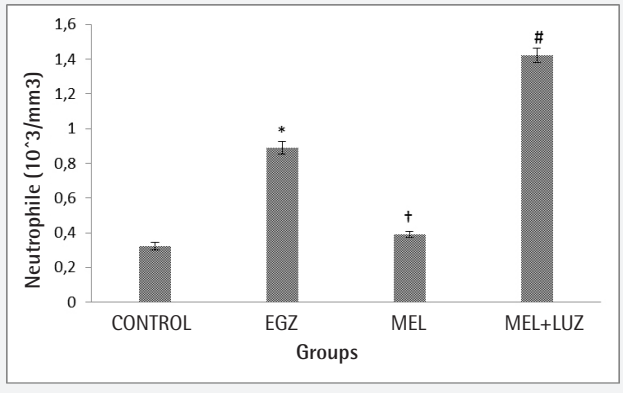

Figure 6. Showing neutrophil counts of all groups (*: p<0.001 according to CONTROL, MEL and MEL+LUZ groups, †: p<0.001 according to EGZ and MEL+LUZ groups, #: p<0.001 according to CONTROL, EGZ and MEL groups)

the exercise duration value, the effects of melatonin on white blood cell and neutrophil counts were thought to be receptor dependent. It is known that intense exercises disrupt the heart rhythm, stimulate apoptosis, increase oxidative damage, and ultimately cause heart damage[17]. During exercise, the need of the heart and muscle tissue for blood flow increases considerably, so muscle flow changes[18]. Intense exercise causes the aerobic state in the tissues and heart to become anaerobic[19]. In such a situation, the ischemic heart causes an increase in reactive oxygen species, and it is stated that this is the most important factor causing heart damage[20]. Melatonin is known as a very powerful antioxidant. It also has powerful anti-inflammatory effects. Therefore, depending on these effects, it may have prevented the increase in white blood cell and neutrophil counts during intense exercise and may have produced a protective effect against tissue and organ damage.

In our study, corticosterone values measured after exercise were found to be significantly higher in the exercise group than in the control group. There was no significant difference in the melatonin and luzindole groups compared to the exercise and control groups. It is known that exercise is a stress factor and causes the release of corticosterone[21]. Melatonin, on the other hand, has a stress reducing feature as well as many known effects[22]. Therefore, in our study, we planned to investigate the effects of melatonin on corticosterone levels. However, although we determined lower corticosterone levels in the melatonin group, this decrease was not statistically significant. At the same time, we observed that the application of luzindole had no effect. The fact that our study included a one-time acute exercise stress may have caused this result.

Sudden cardiac deaths are seen in young or amateur athletes due to hereditary, structural or electrical characteristics of the heart. ECG data are widely used to investigate and prevent some of these heart-related deaths. ECG findings are especially important in asymptomatic athletes. Another factor that makes ECG data important in athletes is the adaptation of the heart to long-term exercise because, in long-term exercises, an increase in vagal tone occurs with the growth of the heart muscle[23]. T wave inversion, ST segment depression and pathological Q waves may occur, especially in left ventricular hypertrophy[24]. Another common ECG finding in athletes is early repolarization characterized by elevation of the QRS-ST segment (ST segment)[25]. Other findings that occur in athletes and can be detected by ECG are abnormal T wave inversion, ST segment depression and left bundle branch block[26-28]. We did not find any of the above ECG findings in our study. The reason for this can be that the ECG findings obtained in these studies were obtained from athletes who exercised for a long time and whose cardiovascular systems were adapted to it because our study was not planned as a chronic exercise study.

In our study, heart rate, QT and QTc times were also determined from the ECG data. It was determined that the number of heart beats increased in all three groups that exercised. However, a significant increase was observed in the exercise and melatonin groups compared to the control group, while the heart rate reached 405.9 beats/min in the luzindole administered group, which shows a significant increase compared to all groups. In the QT and QTc data, unlike the heart rate, both parameters in the group given melatonin were at the levels of the control group. On the other hand, the highest values were reached in the group given luzindole. This suggests that the effect of melatonin on QT and QTc times is again receptor dependent.

In the ECG recordings made during exercise, especially the changes related to the ST segment are important. However, it is stated that changes in QT duration are important and even more informative than ST duration[29]. QT duration reflects the ventricular repolarization and depolarization time. It is calculated by measuring the time from the beginning of the QRS to the point where the T wave descends to the isoelectric line. Many factors can affect QT duration, and the most important of them is heart rate. For this reason, the QTc duration according to the heart rate is taken into account instead of the QT duration. Various formulas have been developed for this purpose, and the most common one is the Bazett's formula[30]. However, since the Bazett's formula does not give healthy results at very high and very low heart rates, other formulas have also been developed. Therefore, in our study, QTc times were also calculated according to the Fridericia formula. It was observed that the results obtained in both formulas were similar to each other. Another factor affecting QT duration is gender, and QT duration is higher in females than in males[31]. In order to prevent the gender difference from affecting the results, male rats were used in our study.

The effects of exercise on QT duration are highly variable and in particular, the association of post-exercise cardiac deaths with changes in QT duration have been focused[32,33]. Prolongations in QTc durations after exercise have been reported in other studies[34,35]. Prolongation of the QT duration is very important because it causes dangerous and fatal arrhythmias of the torsade de pointes type. Therefore, agents that can prevent QT prolongation are needed. In our study, melatonin was administered for this purpose and it was found to be effective. It was determined that these effects of melatonin did not occur when luzindole was used as a receptor antagonist. Therefore, it can be said that melatonin has an effect on QT duration and this effect is receptor dependent.

Study Limitations

In our study, the lack of blood pressure values to support ECG data and the absence of molecular analyses to show possible changes in the heart muscle can be considered as the limitations of the study.

CONCLUSION

As a result, melatonin administration reduced the increased stress after exercise, decreased white blood cell and neutrophil levels, prolonged exercise duration, and prevented prolongation in QT and QTc durations. These results show that melatonin can be used as an agent that reduces the side effects that may occur in exercise and increases the quality of exercise.

Ethics

Ethics Committee Approval: This study was approved by Çanakkale Onsekiz Mart University Local Ethics Committee (decision no: 2017/04-14, date: 27.03.2017).

Informed Consent: It is an animal study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.U., Concept: M.U., Design: M.U., Data Collection or Processing: M.U., P.Ç., Analysis or Interpretation: M.U., P.Ç., Literature Search: M.U., P.Ç., Writing: M.U.

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

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The Effect of Pulmonary Sarcoidosis on Cardiac Autonomic Dysfunction

Akciğer Tutulumu Olan Sarkoidozun Kardiyak Otonom Disfonksiyon Üzerine Etkisi

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ABSTRACT

Aim: The assessment of heart rate variability (HRV) has been considered as an important non-invasive method to evaluate cardiac autonomic function. Concerning recent evidence on the relationship between impaired autonomic dysfunction and sarcoidosis, we aimed to investigate the effect of pulmonary sarcoidosis on cardiac autonomic dysfunction.

Materials and Methods: This prospective study comprised of 36 participants, including 18 patients diagnosed with pulmonary sarcoidosis and 18 age-matched healthy volunteers. All participants underwent echocardiographic examination, 12-channel electrocardiography and 24-h Holter monitoring. HRV parameters were determined and compared between the groups.

Results: In time domain analyses, RMSDD values significantly decreased in the patient group compared to the control group (p=0.043). The low-frequency power in frequency domain analyses between sarcoidosis patients and controls demonstrated a statistically significant difference (p=0.045). In the correlation analysis, PR duration was negatively correlated with all-time domain and frequency domain parameters as SDNN, SDANN and high-frequency values, which had a statistically significant difference (p=0.009, p=0.003, p=0.047 respectively). Corrected QT (QTc) duration was negatively correlated with all-time domain and frequency domain parameters as well. The low-frequency/high-frequency ratio was positively correlated with QTc duration.

Conclusion: The patients with pulmonary sarcoidosis displayed a decrease in all HRV values reflecting diminished parasympathetic tone or blunted cardiac response to vagal modulation. This may cause cardiac outcomes such as atrioventricular conduction abnormalities, proarrhythmic tendency, ventricular arrhythmias and sudden death.

Keywords: Heart rate variability, sarcoidosis, autonomic dysfunction

ÖZ

Amaç: Kalp hızı değişkenliği (KHD), kardiyak otonom fonksiyonun değerlendirilmesinde kullanılan non-invaziv bir yöntemdir. Çalışmamızda akciğer tutulumu olan sarkoidoz hastalarında KHD ölçüm sonuçları değerlendirilerek, kardiyak otonom fonksiyon üzerine etkisinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya 18 akciğer tutulumlu sarkoidoz hastası ile yaş ve cinsiyet uyumlu 18 sağlıklı gönüllü bireyden oluşan kontrol grubu olmak üzere toplamda 36 kişi dahil edildi. Tüm hastalara transtorasik ekokardiyografi, elektrokardiyografi (EKG) ve 24-saat EKG Holter uygulandı. Holterde saptanan KHD parametreleri kullanılarak gruplar karşılaştırıldı.

Bulgular: Zaman alan analizinde RMSDD ölçüm değerleri ve frekans alan analizinde düşük frekans değerleri sarkoidoz grubunda kontrol grubuna kıyasla anlamlı ölçüde düşük bulundu (p=0,043 ve p=0,045). Ayrıca korelasyon analizinde, PR süresi ile zaman alan parametrelerinden SDNN ve SDANN, frekans alan parametrelerinden yüksek frekans arasında istatistiksel olarak anlamlı negatif bir korelasyon saptandı (p=0,009, p=0,003, p=0,047 sırasıyla). Düşük frekans/yüksek frekans oranı, düzeltilmiş QT süresi ile pozitif korelasyon gösterdi.

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Sonuç: Akciğer tutulumlu sarkoidoz hastalarında KHD parametrelerinde saptanan değişiklikler, azalmış parasempatik tonus ve vagal düzenlemeye bozulmuş kardiyak yanıt ile ilişkili olup, bu durum kardiyak aritmilere yatkınlık, ani kardiyak ölüm ve atriyoventiküler iletim bozukluğuna sebep olabilir.

Anahtar Kelimeler: Kalp hızı değişkenliği, sarkoidoz, otonom disfonksiyon

INTRODUCTION

Sarcoidosis is a chronic systemic disease of unknown cause characterized by the presence of noncaseating granulomas[1]. Although the lung and the lymphatic system are the most commonly involved, it affects multiple body systems and frequently young and middle-aged adults[2]. Clinical cardiac sarcoidosis can manifest with ventricular arrhythmias, conduction abnormalities, heart failure, and sudden death[3]. Heart rate (HR) varies as a result of respiration, thermoregulation, blood pressure regulation, the renin-angiotensin system, circadian rhythms, and other factors[4]. Also, the intervals of each heart beats depend on some unique physiologic mechanisms which are altered by the autonomic nervous system (ANS) via efferent vagal and sympathetic nerve impulses[5].

Dysfunction of the ANS is highly associated with increased risk of mortality in individuals with diabetes, heart failure, after myocardial infarction and in some systemic diseases[6-9]. Deterioration of autonomic function in the presence of cardiovascular disease has been strongly implicated in the pathophysiology of arrhythmogenesis and sudden cardiac death which have been associated with an adverse prognosis[10].

The assessment of cardiac autonomic function is carried out by the evaluation of HR variability (HRV) which has been considered as an important non-invasive method. This method supplies indirect information about cardiac autonomic modulation with oscillation in the interval between consecutive heart beats resulting from rhythmic changes in sympathetic and parasympathetic activity[11,12].

A high variability in HR suggests good adaptability, indicating a healthy individual with well-functioning autonomic control mechanism. Inversely a low variability is usually a sign of abnormal and insufficient adaptability of the ANS and it implies the presence of a physiological malfunctioning[13].

Little is known about autonomic dysfunction in patients with pulmonary sarcoidosis. The aim of this study was to evaluate HRV as a tool to assess cardiovascular ANS function in patients with pulmonary sarcoidosis patients.

MATERIALS AND METHODS

Patients

This prospective study includes the patient group diagnosed with pulmonary sarcoidosis at the clinic of chest disease with clinical and histological diagnosis. 24-h Holter monitoring, 12-channel electrocardiography (ECG), echocardiographic (ECHO) examination, blood sample analysis and baseline examination were carried out at the cardiology outpatient clinic. Patients who had preexisting medical diagnoses such as ischemic heart disease, significant valvular abnormalities, heart failure or cardiomyopathy, diabetes, renal failure, cerebrovascular disease, thyroid disease, atrio-ventricular node conduction abnormality, and cardiac pacemaker implantation history, or those who were receiving any medication that might interfere with autonomic regulation were also excluded. None of these patients had been previously diagnosed with cardiac sarcoidosis. The final patient group included 18 patients, and the control group consisted of 18 healthy volunteers. Written informed consent was obtained from each patient following a detailed explanation of the objectives and protocol. The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the Trakya University of Scientific Research Ethics Committee (protocol number: 2016/258, date: 23.11.2016).

Analysis of Heart Rate Variability

Patients underwent 24-h ECG monitoring using a three-channel DMS Holter Recorder (DM Systems Co. LTD., Beijing/China). The recording speed was 2 mm/s and the sampling rate was 300 Hz. A preliminary analysis allowed the exclusion of noise, artefacts, premature beats, or post extrasystolic pauses from further analysis. All tapes were subsequently analyzed to measure HRV using a validated CardioScan HRV program (version 11.5, DM Software Inc.). Only those ECG recordings that met the standards proposed by the task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology as acceptable for HRV interpretation were analyzed. The program calculates the mean QT interval, which is the time from the start of the Q wave to the end of the T wave. The end of the T wave was defined as the point of maximal change in the slope as the T wave merged with the baseline. QT interval was corrected for heart rate by calculating QTc. QTc was calculated with the Bazett's equation [QTc=QT interval (ms) / √(60/heart rate)]. Also, holter program calculates the mean PR interval, which is the time from the onset of the P wave to the start of the QRs complex.

Time Domain Analysis

The mean RR (mean of all normal RR intervals) duration from the whole recording and the following time domain measures

of HRV were calculated: standard deviation of all normal RR intervals (SDNN), standard deviation of the averages of RR intervals in all 5 min segments (SDANN), root-mean square of difference of successive RR intervals (RMSSD), percentage of adjacent normal RR intervals >50 ms different (pNN50).

Spectral Analysis

Spectral measures were computed using the fast-Fourier transform (FFT) method. Spectral plots allowed the identification of the total oscillatory power of 0.01 to 1.0 Hz as well as two subsets of the frequency domain: low-frequency (LF) (0.04-0.15 Hz) and high-frequency (HF) (0.15 to 0.40 Hz).

Echocardiography

Transthoracic ECHO was performed by one of the authors, who was blinded to the patient's clinical data, using a GE Vingmed ultrasound system VII (GE Healthcare, Horten, Norway) with a 2-4 MHz phased array transducer. Recordings were taken from patients positioned in standard ECHO positions, under ECG monitoring, according to the suggestions of the American Society of Echocardiography. Left ventricular ejection fraction (EF) was measured using the modified Simpson method. Left ventricle diastolic function parameters were measured by pulsed-wave Doppler-derived transmitral inflow velocities obtained in the apical 4-chamber view, with the sample volume placed at the mitral valve leaflet tips. Measurements included the trans-mitral early diastolic rapid filling (E-wave) and atrial contraction late filling (A-wave) velocities to calculate E/A ratio. The tricuspid annular plane systolic excursion (TAPSE) was obtained from the apical four-chamber view with the M mode.

Statistical Analyses

A statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software (version 17.0, SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means±standard deviation (SD) and medians (minimum-maximum). Continuous variables were compared using the independent samples t-test or Mann-Whitney U test. Correlations between ECG measures and parameters of time and spectral analysis of HRV were computed by the Spearman's correlation coefficient.

RESULTS

While 18 sarcoidosis patients studied (11 females, 7 males) had a mean age of 55.9 (±8.6 SD) years, 18 control subjects (11 females, 7 males) had a mean age of 52.3 (±14.8 SD) years. The age difference between the groups did not reach a statistical significance (p=0.367) (Table 1). The ECHO values between the patient and control groups were compared; EF% was lower in the patient group than in the control group, but not statistically significant (p>0.05). Inversion of the E/A ratio at pulsed Doppler examination of mitral flow (an index of diastolic dysfunction) was noted in 15 patients whereas it was obtained in 6 individuals of the control group (p=0.007). Although LV end-systolic diameter was greater but not statistically significant in the patient group (p>0.05), LV end-diastolic diameter was significantly greater in the same group (65.1±21.7 vs. 45.8±3.9; p=0.001). TAPSE was lower in the sarcoidosis group than in the control subjects. It was statistically significant (21.1±3.1 vs 23.2±2.9 for controls; 0.032) (Table 1).

The HRV analysis revealed a remarkable reduction in all time domain and frequency domain HRV parameters compared to the control subjects. In the time domain analyses, as SDNN, SDANN and pNN50 values were lower in the patient group than in the control group. They were not statistically significant (all p>0.05) whereas RMSDD values significantly decreased in the patient group compared to the control group (18.3±4.4 vs. 26.9±13.5 for controls; p=0.043).

In the frequency domain analyses, comparison of the LF power between sarcoidosis patients and controls demonstrated a

Table 1. Baseline demographic and echocardiographic parameters of the study population

	Patient (n=18)		Control (n=18)		p
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
Sex, M/F	7/11		7/11		1.000
Age	55.9±8.6	58.5 (42-74)	52.3±14.8	50.5 (30-79)	0.367
BMI (kg/m²)	26.0±2.4	25.9 (22.9-30.1)	26.1±4.3	26.2 (18.2-33)	0.658
EF (%)	64.2±4.8	64 (55-71)	65.6±4.2	65.5 (59-75)	0.417
LVEDD (mm)	65.1±21.7	53.5 (43-108)	45.8±3.9	45 (40-53)	0.001
LVESD (mm)	31.9±7.6	31 (20-54)	29.3±4.6	29.5 (18-41)	0.278
TAPSE (mm)	21.1±3.1	20 (15-26)	23.2±2.9	23 (17-28)	0.032
E/A, type 1 DD	15/3		6/12		0.007

M: Male, F: Female, BMI: Body mass index, EF: Ejection fraction, LVESD: Left ventricle end systolic diameter, LVEDD: Left ventricle end diastolic diameter, TAPSE: Tricuspid annular plane systolic excursion, E/A: The ratio of the early (E) to late (A) ventricular filling velocity, DD: Diastolic dysfunction, min-max: Minimum-maximum, SD: Standard deviation

statistically significant difference (18.1±5.0 vs 22.6±5.7 for controls; p=0.045). HF component in the sarcoidosis patients decreased but did not differ significantly (p>0.05). Also, the LF/HF ratio was slightly increased but there was not a statistically significant difference (p>0.05). The mean heart rate during 24-hour Holter monitorization in the patient group was lower than in the control group (p>0.05) (Table 2).

In the correlation analysis, PR duration was negatively correlated with all-time domain and frequency domain parameters. In addition, SDNN, SDANN and HF values had statistically significant differences (p=0.009, p=0.003, p=0.047 respectively). Besides, the LF/HF ratio was positively correlated with PR duration but there was no significant difference (p>0.05). QTc duration was negatively correlated with all-time domain and frequency domain parameters as well. The LF/HF ratio was positively correlated with QTc duration. All correlations with HRV and QTc duration were not statistically significant (p>0.05) (Table 3).

DISCUSSION

Non-invasive assessment of autonomic system by measuring HRV gives clinically and prognostically useful information in some cardiac and systemic diseases. Alterations in the HRV have been shown to be a strong and independent predictor of post-infarction mortality and to have prognostic significance in patients with heart failure and in patients with diabetic autonomic neuropathy[7,8,14]. Therefore, methods for assessing ANS and its modulation are very important to prevent undesired cardiovascular events in cardiac patients as well as in non-cardiac patients.

Table 2. Comparison of the heart rate variability indices between the patient and control groups

	Patient (n=18)		Control (n=18)		p
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
SDANN (ms)	101.1±25.2	96.5 (66-159)	102.2±31.4	101.5 (49-176)	0.740
SDNN (ms)	107.2±22.1	102 (77-156)	112.4±31.6	107 (62-178)	0.467
RMSDD (ms)	18.3±4.4	19 (11-25)	26.9±13.5	21.5 (12-58)	0.043
pNN50 (%)	2.1±1.4	2 (0-4)	6.0±8.3	2.5 (0-35)	0.150
LF (Hz)	18.1±5.0	18.8 (8.6-27.8)	22.6±5.7	21.43 (16.5-38.1)	0.045
HF (Hz)	6.9±5.4	5.4 (1.6-20.1)	8.3±5.8	6.5 (2.65-26.9)	0.282
LF/HF	3.9±2.9	3.5 (0.9-14)	3.7±1.9	3.5 (0.9-7.3)	0.899
Mean HR (rate/minute)	76.6±9.8	74.5 (60-94)	78.3±9.5	75 (64-93)	0.924

SDANN: Standard deviation of the averages of RR intervals in all 5 min segments, SDNN: Standard deviation of all normal RR intervals, RMSSD: Root-mean square of difference of successive RR intervals, pNN50: Percentage of adjacent normal RR intervals >50 ms different, LF: Low frequency, HF: High frequency, LF/HF: The ratio of low frequency to high frequency, HR: Heart rate, min-max: Minimum-maximum, SD: Standard deviation

Table 3. The correlation analysis between heart rate variability and electrocardiographic indices in study population

Patient (n=18)		PR duration	QTc
SDANN	r	-0,650	-0.164
	p	0.003	0.515
SDNN	r	-0,597	-0.019
	p	0.009	0.940
RMSDD	r	-0.015	-0.327
	p	0.954	0.186
pNN50	r	-0.063	-0.049
	p	0.803	0.846
LF	r	-0.278	-0.193
	p	0.265	0.444
HF	r	-0,474	-0.339
	p	0.047	0.168
LF/HF	r	0.362	0.436
	p	0.140	0.070

SDANN: Standard deviation of the averages of RR intervals in all 5 min segments, SDNN: Standard deviation of all normal RR intervals, RMSSD: Root-mean square of difference of successive RR intervals, pNN50: Percentage of adjacent normal RR intervals >50 ms different, LF: Low frequency, HF: High frequency, LF/HF: The ratio of low frequency to high frequency, HR: Heart rate, QTc: Corrected QT duration

HRV can be assessed with a number of methods. The most commonly used are frequency domain and time domain analyses. In these methods, measures are based on the analysis of the time intervals between each successive normal QRs complex which are determined from a routine 24-hour ambulatory ECG[4].

SDNN is the most commonly used time domain HRV parameter that measures the standard deviation of all normal RR (NN) intervals during a 24-hour period. SDNN is considered as all the components responsible for variability in the entire period of recording[11]. The most commonly used variables derived from differences between normal R-R intervals are RMSSD, pNN50 and NN50[15]. These measures evaluate parasympathetic modulation of normal R-R intervals driven by ventilation in the existence of normal sinus rhythm and AV-nodal function[4,11,16].

Frequency-domain methods separate to signals of the heart rate according to frequency and density. FFT or autoregressive modeling can be used to separate HRV into four main spectral bands; very LF band, LF band and HF band and ultra-LF[11].

HF is in a range from 0.15 to 0.4 Hz. The normal respiratory rate is within the HF band that reflects parasympathetic or vagal activity, and therefore, this band is frequently called the respiratory band because it corresponds to the heart rate (HR) variations related to the respiratory cycle[16]. These HR changes are known to be respiratory sinus arrhythmia[11,16].

LF power, which is modified by both the sympathetic and parasympathetic nervous systems and greatly affected by the baroreceptor system, has bandwidth from 0.04 to 0.15 Hz[4,17]. By some authors, the absolute and normalized LF powers have been considered as an index of sympathetic modulation of the heart rate and the ratio of LF to HF power has been used as an assessment of the balance between sympathetic and parasympathetic activities, which is called sympathovagal balance[14,18].

In the present study, we found that all-time domain parameters were decreased. Although they were not statistically significant except RMSSD, it might be evaluated as a deterioration of sympathovagal balance. RMSSD reflects parasympathetic modulation driven by ventilation; therefore, altered respiratory performance and reduced parasympathetic activity over the heart could cause a statistically significant decrease in RMSSD.

In the study designed by Aktop et al.[19], 31 pulmonary sarcoidosis patients were examined for daytime and night-time HRV parameters separately also during 24 hours. They found that 24-h SDNN values decreased in all time periods. In the study by Uslu et al.[20], the observed SDNN values decreased in non-cardiac sarcoidosis patients who were compared to controls. They interpreted these findings as a reduction of vagal activity with a concomitant sympathetic dominance.

Furthermore, the frequency parameters as LF and HF during 24-h, which were studied by Aktop et al.[19], were significantly lower when compared to the control group. Additionally, they observed that 24-h LF/HF ratios slightly increased but it was not statistically significant. These results were parallel when compared to our study. In our study, the patients with sarcoidosis had decreased HRV in the HF and LF components upon spectral analysis compared to healthy controls. Regarding LF, there was a statistically significant difference. It might be interpreted as reduced vagal control over the heart and shift of sympathovagal balance toward the sympathetic dominance.

Also, our results indicated 24-h LF/HF ratios that were slightly increased but not statistically significant. In the same manner, Tiran et al.[21] studied with 12 sarcoidosis patients and 12 healthy control subjects whose mean values for HRV in the HF domain were significantly reduced. This result was interpreted that the patients with sarcoidosis revealed decreased HRV in the HF component, possibly reflecting decreased parasympathetic tone and cardiac response to vagal modulation. In the same study, they found increased ratio of LF to HF power (LF/HF) in sarcoidosis patients. In the light of these findings, it could be argued that increased LF/HF ratios in sarcoidosis patients reflect an altered sympathovagal balance.

In the study of Hsiao et al.[22], fifteen AV block patients before and after temporary VVI pacemaker and 15 subjects with normal AV conduction were investigated by using an esophageal lead to detect PP intervals for the analysis of HRV with time domain as SDNN, pNN50 and RMSSD which were decreased significantly in patients with AV block. The LF/HF ratio was increased in patients with AV block and remained increased after insertion of a temporary ventricular inhibited pacemaker (VVI), whereas the time domain parameters were normalized after VVI insertion. In our study, we found that all-time domain and frequency domain parameters were negatively correlated with PR duration. SDNN and SDANN as the time domain values and HF as the frequency domain value were statistically significant. Also, the LF/HF ratio was found positively correlated in the present study. It could be assessed as decreased parasympathetic tonus and altered sympathovagal balance might delay AV conduction in sarcoidosis patients.

In the light of findings, decreased HRV may contribute to any degree of atrioventricular block, malign arrhythmia and sudden death. It may help to clinician in the course of deciding on the time and type of the therapy.

Study Limitations

Potential limitations of the present study might be the relatively small sample size, and thus the number of participating centers should be increased and the results should be confirmed with more comprehensive studies.

CONCLUSION

In conclusion, our data seem to indicate that HRV may be a noninvasive, inexpensive and efficient modality to evaluate autonomic dysfunction and also contribute to prognosis in pulmonary sarcoidosis patients.

Ethics

Ethics Committee Approval: The study were approved by the Trakya University of Scientific Research Ethics Committee (protocol number: 2016/258, date: 23.11.2016).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.M., G.T., M.A., Concept: A.M., G.T., M.A., Design: A.M., G.T., M.A., Data Collection or Processing: A.M., G.T., Analysis or Interpretation: A.M., M.A., Literature Search: A.M., G.T., M.A., Writing: A.M., G.T., M.A.

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Factors Affecting the Imaging Preference of Acute Pancreatitis Patients in the Emergency Department: A Retrospective Study on 63 Cases

Acil Serviste Akut Pankreatit Hastalarının Görüntüleme İstemlerini Etkileyen Faktörler: 63 Olguluk Retrospektif Çalışma

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ABSTRACT

Aim: Acute pancreatitis is an inflammatory disease in which the pancreas is affected at different levels. It is often reversible. The diagnosis of pancreatitis is made by evaluating the anamnesis, physical examination, laboratory and radiological examinations together. Usually ultrasonography (USG) and contrast-enhanced abdominal tomography (CT) are needed for diagnosis in emergency services. The aim of this study is to contribute to the use of imaging techniques used for the diagnosis of acute pancreatitis patients in the emergency department with the correct indications.

Materials and Methods: Our study is retrospective. All patients over the age of 18 years who were admitted to our emergency department between 01.01.2019 and 01.01.2020 and diagnosed with acute pancreatitis were included in the study. The demographic characteristics, laboratory findings, imaging procedures and imaging findings of the patients were determined by examining the files of the patients included in the study.

Results: A total of 63 patients were included in the study. The mean age of the patients was 59.69±17.33 years and 38 (60.3%) of them were women. Of these 63 patients, 54 (85.7%) had abdominal USG and 37 (58.7%) had abdominal CT imaging with contrast. The mean amylase value of the cases was 958.01±1051.69 and the mean lipase value was 1051.28±1340.92. There was no statistical relationship between Ranson score and lipase level (p=0.681). When the Ranson scores of the patients with biliary and non-biliary pancreatitis were compared, there was not a statistically significant difference (p=0.844).

Conclusion: We think that USG imaging should be used in all patients for acute pancreatitis in the emergency department, its main indication is for gallbladder and intra/extra hepatic biliary tract pathologies. In addition, we think that the indications for contrast-enhanced abdominal CT imaging should be clarified, except for the exclusion of severe acute pancreatitis and other possible emergency pathologies.

Keywords: Emergency service, acute pancreatitis, imaging, CT, USG

ÖZ

Amaç: Akut pankreatit, pankreasın farklı seviyelerde etkilendiği enflamatuvar bir durumdur. Tanısı için anamnez, fizik muayene, laboratuvar ve radyolojik tetkiklerin birlikte değerlendirilmesi gerekmektedir. Acil servislerde görüntüleme olarak sıklıkla ultrasonografi (USG) ve kontrastlı batın bilgisayarlı tomografiye (BT) ihtiyaç duyulmaktadır. Bu çalışmanın amacı acil serviste akut pankreatit hastalarının tanısı için kullanılan görüntüleme tekniklerinin doğru endikasyonlarla kullanımına katkı sağlamaktır.

Gereç ve Yöntem: Çalışmamız retrospektif bir çalışma olup çalışmaya acil servisimize 01.01.2019 ile 01.01.2020 tarihleri arasında başvuran, 18 yaşından büyük ve akut pankreatit tanısı alan tüm hastalar dahil edildi. Çalışmaya dahil edilen hastaların dosyaları incelenerek hastaların demografik özellikleri, laboratuvar bulguları, yapılan görüntüleme işlemleri ve elde edilen görüntüleme bulguları belirlendi.

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Bulgular: Çalışmaya toplam 63 hasta dahil edildi. Çalışmaya dahil edilen hastaların yaş ortalaması 59,69±17,33 yıl idi. Çalışmaya dahil edilen hastalardan 38'i (%60,3) kadındı. Bu 63 hastadan 54 (%85,7) tanesine batın USG, 37 (%58,7) tanesine kontrastlı batın BT görüntüleme yapıldı. Olguların ortalama amilaz değeri 958,01±1051,69, ortalama lipaz değeri 1051,28±1340,92 idi. Ranson skoru ve lipaz seviyesi arasında istatistiksel bir ilişki bulunamadı (p=0,681). Bilier ve non-bilier pankreatitli olguların ranson skoru karşılaştırıldığında istatistiksel olarak anlamlı bir fark bulunamadı (p=0,844).

Sonuç: Acil serviste akut pankreatit için USG görüntülemenin tüm hastalarda kullanılmasının gerekli olduğunu, bunun asıl endikasyonunun safra kesesi ve intra/ekstra hepatik safra yolu patolojilerine yönelik olduğunu, kontrastlı batın BT görüntülemede ise şiddetli akut pankreatit ve olası diğer acil patolojilerin dışlanması haricinde endikasyonlarının netleştirilmesi gerektiğini düşünmekteyiz.

Anahtar Kelimeler: Acil servis, akut pankreatit, görüntüleme, BT, USG

INTRODUCTION

Rapid hospitalization or discharge of the patients whose diagnosis is confirmed in the emergency department is important for the rapid and effective management of the crowded patient load in the emergency department. One of the biggest obstacles in front of this situation is the additional imaging tests requested by the relevant departments in the patient group whose diagnosis is confirmed. Patients with acute pancreatitis are also included in the group in which this situation is frequently experienced in emergency services.

Acute pancreatitis is an inflammatory disease in which the pancreas is directly affected by the enzymes it secretes. This inflammation can affect the pancreas as well as neighboring tissues and organs. The mortality and morbidity of acute pancreatitis is high, and this rate may increase to 25%, especially in its severe form. The clinical picture varies from mild form, which responds to medical treatment in a short time, to severe form accompanied by systemic findings, sepsis and multi-organ failure. For the diagnosis of the disease, anamnesis, physical examination, laboratory and radiological examinations should be evaluated together[1,2]. One or several of ultrasonography (USG), contrast-enhanced abdominal computed tomography (CT) or magnetic resonance cholangio-pancreatography imaging is preferred in emergency services.

Our aim in doing this study is to contribute to the use of imaging techniques with the right indications by creating awareness about the effectiveness of imaging techniques used for the diagnosis of acute pancreatitis patients in the emergency department.

MATERIALS AND METHODS

Our study is a retrospective study. Before starting the study, permission was obtained from the Non-Invasive Studies Ethics Committee of Tekirdağ Namık Kemal University Faculty of Medicine (2021.52.02.15).

All patients older than 18 years of age and clinically diagnosed with acute pancreatitis, who applied to our emergency department between 01.01.2019 and 01.01.2020, were included in the study. The files of the patients included in the study were examined and their demographic characteristics, laboratory findings, USG, CT and other imaging examinations and the findings obtained from these examinations were determined. Patients whose necessary information could not be reached were excluded from the study even if they were diagnosed with acute pancreatitis and were older than 18 years. Afterwards, all the obtained data were recorded in the database prepared in the statistical program named Statistical Package for the Social Sciences 18 and analyzed.

Statistical Analysis

Descriptive statistics for categorical variables were expressed as numbers (n) and percentage (%). The chi-square test was used to compare data between groups. The normal distribution of continuous variables was evaluated using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used for group comparisons. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 63 patients were included in the study. The mean age of the patients included in the study was 59.69±17.33 years. Of the patients included in the study, 38 (60.3%) were female. In the emergency department, 54 (85.7%) of these 63 patients underwent abdominal USG and 37 (58.7%) underwent contrast-enhanced abdominal CT imaging. Blood samples were taken from all patients for hemogram and biochemistry tests. The mean amylase value of the cases was 958.01±1051.69, and the mean lipase value was 1051.28±1340.92. In 60 (95.3%) of the subjects included in the study, the lipase value was above 60 U/L. Demographic characteristics and laboratory values of the cases included in the study are presented in Table 1.

When the cases were evaluated in terms of the Ranson criteria score at the time of first admission, it was determined that 21 (33.3%) patients scored 0, 24 (38.1%) patients 1 point, 12 (19%) patients 2 points, 6 (9.5%) patients 3 points. No statistical relationship was found between Ranson score and lipase level (p=0.681).

Gallstones were detected in 33 (61.1%) of the 54 patients who underwent USG imaging, sludge in 4 (7.4%) patients,

intrahepatic bile duct dilatation in 5 (9.3%), choledochal dilatation or normal appearance in 21 (38.9%). Information was shared for 3 (5.6%) of them about whether an evaluation could be made about the pancreas. In 48 (88.9%) patients who underwent USG, the imaging procedure was suboptimal due to intestinal gas, and it was recommended to confirm with abdominal CT if necessary (Table 2).

Thirty-three (52.4%) of the cases were evaluated as biliary pancreatitis and 30 (47.6%) as non-biliary pancreatitis. When the Ranson scores of the biliary and non-biliary pancreatitis cases were compared, no statistically significant difference was found (p=0.844).

In the official radiology reports of 37 patients who underwent contrast-enhanced abdominal CT imaging, it was determined that stones were detected in 10 (27%), gall bladder was operated in 5 (13.5%), sludge was found in 1 (2.7%), 5 (13.5%) of them had dilatation in the intrahepatic bile ducts, 5 (13.5%) had dilatation in the choledoch, pericholecystic fluid was detected in 7 (18.9%), fluid in the peripancreatic area was detected in 13 (35.1%), 14 (37.8%) had inflammation in the pancreas, and 3 (8.1%) had necrosis in the pancreas (Table 3).

Table 1. Demographic characteristics and laboratory values of the cases

	n (%) Mean±standard deviation
Age	59.69±17.33
Gender	
Female	38 (60.3%)
Male	25 (39.7%)
USG	54 (85.7%)
CT	37 (58.7%)
Biliary pancreatitis	33 (52.4%)
Amylase	958.01±1051.69
Lipase	1051.28±1340.92
AST	102.52±121.89
ALT	109.15±138.43
ALP	146.00±88.40
GGT	224.16±331.45
Hg	12.84±2.06
HTc	38.92±5.54
WBC	10.61±3.85
Plt	248.60±111.16

USG: Ultrasonography, CT: Computed tomography, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transferase, Hg: Hemoglobin, HTc: Hematocrit, WBC: White blood cell, Plt: Platelet

Table 2. Findings obtained in patients undergoing ultrasonography

Findings	n (%)
Gall bladder operated	8 (14.8%)
Gallstone	33 (61.1%)
Inside the bladder	21 (38.9%)
Bile ductus	10 (18.5%)
Choledochus	2 (3.7%)
Sludge	4 (7.4%)
Pericholecystic fluid	1 (1.9%)
Peripancreatic fluid	2 (3.7%)
Intrahepatic bile duct dilatation	5 (9.3%)
Suboptimal imaging due to intestinal gas	48 (88.9%)
Evaluation of the choledochus	21 (38.9%)
Evaluation of the pancreas	3 (5.6%)

DISCUSSION

Imaging is very important in the diagnosis and prognosis of acute pancreatitis. Considering the possibilities and conditions of the emergency services, it is still not clear in some clinical situations that which of these imagings should be done in the emergency room and which ones should be done in the relevant departments.

Gallstones and excessive alcohol use are involved in the etiology of 70-80% of acute pancreatitis cases[3]. Indeed, it is important to distinguish these etiologies due to differences in patient management. The sensitivity and specificity of USG in the detection of gallstones is over 95%[4-7]. In the review of Greenberg et al.[8], with high evidence and strong recommendation, it is stated that USG should be performed initially in all patients with acute pancreatitis to determine whether the patient has gallstones and/or stones in the common bile duct or to evaluate the biliary tract. In the study of Yardan et al.[9], it was determined that abdominal USG was performed on all patients in the emergency department and 12 (19.7%) of these patients were compatible with pancreatitis, while 29 (47.5%) were not.

Table 3. Findings obtained in patients who underwent CT

Findings	n (%)
Increase in gallbladder wall thickness	3 (8.1%)
Gall bladder operated	5 (13.5%)
Gallstone	10 (27%)
Inside the bladder	5 (13.5%)
Bile ductus	4 (10.8%)
Choledochus	1 (2.7%)
Sludge	1 (2.7%)
Intrahepatic bile duct dilatation	5 (13.5%)
Choledochus duct dilatation	5 (13.5%)
Pericholecystic fluid	7 (18.9%)
Peripancreatic fluid	13 (35.1%)
Inflammation	14 (37.8%)
Necrosis	3 (8.1%)

CT: Computed tomography

In the study conducted by Karaca and Oktay[10] it was determined that abdominal USG was performed in all cases in the emergency department. It was revealed that the USG findings were compatible with pancreatitis in 30 (25.9%) patients, not compatible with pancreatitis in 61 (52.6%) patients, and also resulted in insufficient USG interpretation due to intense intestinal gas in 25 (21.6%) patients[10]. In our study, abdominal USG imaging was performed in 54 (85.7%) of 63 patients with acute pancreatitis detected in the emergency department, and it was determined that pancreatic evaluation could be performed in 3 (5.6%) patients. However, it was also stated that imaging was suboptimal due to intestinal gas in 48 (88.9%) patients who underwent USG. The effectiveness of abdominal USG may be restricted by reasons such as intestinal gas and obesity in pancreatic imaging. In fact, it can be thought that abdominal USG request in the emergency department slows down patient management in this patient group. However, we think that abdominal USG should be applied to all patients with acute pancreatitis in the emergency department because of its contribution to the management of the patient in acute pancreatitis and its contribution to the exclusion of surgical or other causes of acute abdominal pain. In addition, we think that it should be remembered that emergency USG imaging creates a greater indication for the differentiation of biliary and non-biliary pancreatitis in these patients. USG was not performed in the emergency department for all of the cases in our study. We attribute this situation to the fact that some of the patients who applied to our emergency department were evaluated by the relevant polyclinic during the day and applied to our emergency department after the USG procedure.

The increase in the accessibility and usability of CT creates a trend for physicians to refer to this examination more frequently for research purposes. An advanced CT scan is the most effective method for diagnosing acute pancreatitis and pancreatic necrosis, with typical features on cross-sectional imaging such as pancreatic enlargement, pancreatic edema, uneven density, peripancreatic fat shift, and fluid collection[11]. In their review, Waller et al.[12] stated that CT was not sensitive for early diagnosis of pancreatitis, since CT imaging might not show findings in patients with mild acute pancreatitis. Moreover, some studies have reported that although abdominal CT can identify pancreatitis in the early phase of the disease course, it will not contribute to the diagnostic sensitivity and may be negative if performed too early[13-15]. However, it is accepted that CT imaging can be used if the possibility of necrotizing pancreatitis is suspected in severe cases[8,11,16,17]. As a result of all these, the use of CT remains limited unless there are other conditions that should be evaluated in the differential diagnosis of acute pancreatitis cases in emergency services[8]

In the study conducted by Yardan et al.[9], 52 (85.2%) of the patients with acute pancreatitis in the emergency department underwent abdominal CT, and 32 (61.5%) of the patients who were performed abdominal CT had mild clinical manifestations, 20 (38.5%) had severe. In the study conducted by Karaca and Oktay[10], it was determined that 9 (7.8%) patients had Ranson criteria score of 3 and above, and the number of patients who had abdominal CT was 38 (32.8% of all patients). Moreover, in this study, the importance of determining the indications for abdominal CT in the emergency department and the criteria for requesting tomography in the early period was emphasized.

In their study, Munoz-Bongrand et al.[18] performed contrast-enhanced abdominal CT scans of 102 patients with acute pancreatitis during their hospitalization and on the 7th day after hospitalization. They suggested that early CT in patients with a Ranson score of 2 or less was not very valuable in demonstrating acute pancreatitis, and that CT should not be routinely ordered in the late period, but should be performed to see necrosis and other complications in the occurrence of clinical and biological deterioration[10,18]. In our study, contrast-enhanced abdominal CT imaging was performed in 37 (58.7%) of 63 patients with acute pancreatitis and in patients with acute pancreatitis who underwent CT, findings related to fluid in the peripancreatic area, inflammation and necrosis in the pancreas were obtained. However, when the patients included in our study were evaluated according to the Ranson scores, it was found that the rate of patients who underwent CT was considerably higher than the severe pancreatitis group according to the scoring systems, in accordance with the literature. Causes of this condition may include exclusion of other possible causes of abdominal pain in the emergency department. However, it is a reality for all emergency services that it can also be performed upon the request of the relevant clinic when the patient is admitted to a clinic. It is known that CT has a critical importance in the staging of acute pancreatitis, evaluation of its complications and interventional treatment. Of course, we accept the necessity of performing abdominal CT in severe acute pancreatitis cases in the emergency department. In addition, it can also be preferred in the differential diagnosis to rule out other possible diagnoses. However, we think that its use in emergency services based on indications supported by strong evidence and recommendation may be more beneficial in terms of patient victimization, sustainability of emergency functioning and cost.

Study Limitations

The small sample size and retrospective nature of the study were the most important limitations. In addition, despite being detected in abdominal CTs, there was also the possibility that the findings, which were detected with USG and stated in the report, were not re-expressed in the CT reports, in order to report the CTs faster for speeding up the emergency room management in emergency conditions.

CONCLUSION

In conclusion, we think that it is necessary to use USG imaging for acute pancreatitis in the emergency department in all patients, the main indication is for gallbladder and intra/extra hepatic bile duct pathologies, and the emergency indications should be clarified in contrast-enhanced abdominal CT imaging, except for the exclusion of severe acute pancreatitis and possible other emergency pathologies.

Ethics

Ethics Committee Approval: Ethic permission was obtained from the Non-Invasive Studies Ethics Committee of Tekirdağ Namık Kemal University Faculty of Medicine (2021.52.02.15).

Informed Consent: Retrospective study.

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Risk Factors for Atrial Fibrillation Recurrence in Patients Undergoing Ablation

Ablasyon Yapılan Hastalarda Atriyal Fibrilasyon Rekürrensi için Risk Faktörleri

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ABSTRACT

Aim: The current study aimed to investigate the predictors of recurrence in patients with paroxysmal atrial fibrillation (AF) undergoing cryoballoon ablation.

Materials and Methods: This study was conducted with the participation of the patients who underwent cryoballoon ablation between October 2013 and March 2016. Patients' medical records were retrospectively evaluated. Patients were divided into two groups as those with AF recurrence and those without AF recurrence.

Results: A total of 68 patients undergoing cryoballoon ablation were included in the study. The mean age of the patients was 57.3±12 years, and 32% were male. Concomitant conditions included coronary artery disease in 25 patients (36.8%), diabetes mellitus in 9 (13.2%), hypertension in 46 (67.6%), and history of cerebrovascular event in 3 (4.4%). During the early period involving the initial three months, AF recurrence was found in 16 patients (23.5%), while 52 (76.5%) remained in the sinus rhythm during the follow-up. There were significant differences between two groups in left atrium size (38±5.3 and 44±6.6, p=0.003), left atrial appendage (LAA) flow rate [38 (24-62) cm/sec and 28 (22-55) cm/sec, p=0.001], presence of pulmonary venous anomaly [5 (9.6%) and 6 (37.5%), p=0.016], the number of antiarrhythmic drugs before the ablation (1.78±0.7 and 2.43±0.5, p=0.002), interventricular septal thickness (11±1.7 mm and 12±1.47 mm, p=0.008), left ventricular posterior wall thickness (11±0.9 mm and 12±1.3 mm, p=0.007), and left ventricular mass (195±51 g and 181±37.9 g, p=0.028).

Conclusion: According to the results, AF recurrence after ablation was found to be associated with the use of multiple antiarrhythmic drugs before the ablation, increased left atrial diameter, the reduced flow rate in the LAA, presence of a pulmonary venous anomaly, increased interventricular septal thickness, left ventricular posterior wall thickness, and left ventricular mass.

Keywords: Atrial fibrillation, cryoballoon ablation, pulmonary vein isolation, left atrium

ÖZ

Amaç: Çalışmamızda kriyobalon ablasyon uygulanan paroksismal atriyal fibrilasyon (AF) tanılı hastalarda nüksün prediktörlerinin saptanması amaçlandı.

Gereç ve Yöntem: Ekim 2013-Mart 2016 tarihleri arasında kriyobalon ablasyon uygulanan hastalar değerlendirildi. Hastaların tıbbi kayıtları retrospektif olarak incelendi. Hastalar işlem sonrası AF nüksü gelişen ve AF nüksü olmayan şeklinde iki gruba ayrıldılar.

Bulgular: Kriyobalon ablasyon uygulanan 68 hasta çalışmaya dahil edildi. Hastaların ortalama yaşı 57,3±12 yıldı ve %32'si erkekti. Eşlik eden durumlar arasında 25 hastada (%36,8) koroner arter hastalığı, 9'unda (%13,2) diabetes mellitus, 46'sında (%67,6) hipertansiyon ve 3 hastada

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serebrovasküler olay öyküsü yer almıştır (%4,4). İlk üç ayı kapsayan erken dönemde 16 hastada (%23,5) AF nüksü saptanırken, 52 hastada (%76,5) AF nüksü saptanmadı. İki grup arasında sol atriyum boyutu (38±5,3 mm ve 44±6,6 mm, p=0,003), sol atriyal apendiks (LAA) akım hızı [38 (24-62) cm/sec ve 28 (22-55) cm/sec, p=0,001], pulmoner venöz anomali varlığı [5 (%9,6) ve 6 (%37,5), p=0,016] ve işlem öncesi kullanılan antiaritmik ilaç sayısı (1,78±0,7 ve 2,43±0,5, p=0,002) açısından anlamlı farklılıklar saptandı. Sol ventrikül septum (11±1,7 mm and 12±1,47 mm, p=0,008) ve arka duvar kalınlığı (11±0,9 mm and 12±1,3 mm, p=0,007) AF rekürrensini öngörmede istatistiksel olarak anlamlı bulundu. AF nüksü olan ve olmayan hastalarda sol ventrikül kitlesi sırasıyla 195±51 g ve 181±37,9 g olarak saptandı ve fark istatistiksel olarak anlamlıydı (p=0,028).

Sonuç: Ablasyon sonrası AF nüksünün öngördürücüleri arasında işlem öncesinde öyküde çoklu antiaritmik ilaç kullanımının olması ile ekokardiyografide artmış sol atriyal çapı, azalmış LAA akış hızı, pulmoner venöz anomali saptanması, artmış interventriküler septal kalınlık, artmış sol ventrikül arka duvar kalınlığı ve artmış sol ventrikül kitlesi sayılabilir.

Anahtar Kelimeler: Atriyal fibrilasyon, kriyobalon ablasyon, pulmoner ven izolasyonu, sol atrium

INTRODUCTION

Atrial fibrillation (AF) is a supraventricular arrhythmia occurring in the atrium that is associated with irregular ventricular responses. AF is the most common type of persistent cardiac arrhythmia observed in 1 to 2% of the general population[1]. Although AF may lead to symptoms such as palpitations, fatigue, polyuria, dizziness, exertion dyspnea, chest pain, hypotension, and syncope, a significant proportion of patients with AF rhythm may be asymptomatic[2]. AF is associated with a 5-fold increased risk of stroke[3]. Cardiac and non-cardiac factors associated with AF include chronic alcohol intake, cardiac valvular disease, CAD, heart failure (HF), left ventricular hypertrophy, diabetes mellitus (DM), HT, hyperthyroidism, pulmonary embolism, chronic obstructive pulmonary disease, surgical intervention, hypertrophic or dilated cardiomyopathy or congenital cardiac diseases[1,4]. The triggering focus originates from the pulmonary veins (PV) in 90% of the cases with paroxysmal AF (PAF). Other identified foci include superior vena cava, coronary sinus, and the Marshall ligament[5,6]. The primary therapeutic method in AF ablation is based on the electrical isolation of PVs from LA. The European Society of Cardiology 2016 AF guidelines recommend catheter ablation to be performed in specialized centers by properly trained electrophysiologists for patients with symptomatic PAF recurrences during antiarrhythmic therapy, for whom the preferred therapeutic modality is rhythm control treatment[2].

In this study, the predictors of AF recurrence were investigated in 68 patients who underwent cryoablation due to symptomatic PAF.

MATERIALS AND METHODS

A retrospective file review was performed and outpatient medical records were evaluated, yielding the information of 68 patients who underwent cryoballoon ablation due to a diagnosis of symptomatic PAF between October 2013 and March 2016. Diagnoses of ischemic stroke or recurrent AF after the procedure were ascertained by telephone calls and through the review of clinical records. The first 3 months following the procedure were defined as the blind period and AF, atrial flutter, or episodes of atrial tachycardia during this period were considered as early AF recurrence. Episodes after the first 3 months were considered as recurrence.

Patients under 18 years of age and those with persistent AF, serious valvular disease, and thrombus in LA, pregnant women, and those with active neoplasm, prosthetic cardiac valve, implantable cardiac rhythm devices were excluded from the study.

In our center, procedures were performed under sedation with midazolam. The Seldinger technique was used for access via the left femoral vein and artery, and the right femoral vein. Access to the left atrium was performed under fluoroscopy with transseptal puncture with a modified Brockenborough needle accompanied by transesophageal echocardiography. The Flaxcath (metronik) brand steerable transseptal catheter was directed to the left atrium over the guide wire. Arctic front® and arctic front advance® (metronik) brand cryoablation balloon was directed through this sheath. PV circular mapping catheter through balloon the Achieve catheter was directed. Following left atrial puncture, anticoagulation was achieved using heparin with a target ACT of 300-350 seconds. After complete occlusion of PVs was ensured, a 5-minute standard cooling procedure was carried out by pumping a freezing agent (N2O) into the balloon. While ablation was performed in right PVs, continuous phrenic nerve stimulation at a low rate was performed in the superior vena cava, in conjunction with manual palpation of the contractions in the diaphragmatic area. After two freezing procedures with a minimum duration of five minutes in each PV, the procedure was terminated. One day after the cryoballoon ablation, transthoracic echocardiography was performed to rule out pericardial effusion, and patients were discharged. Treatment with oral anticoagulants and antiarrhythmic agents was planned to be continued for a minimum duration of 3 months following the cryoballoon ablation procedure, after which anticoagulant treatment was scheduled based on the CHA2DS2-VASc risk assessment.

The study was approved by the Uludağ University Local Ethics Committee for Clinical Research with decree no: 2016-5/21 and approval date: 29.11.2019.

Statistical Analysis

Statistical Package for Social Sciences for Windows 23.0 software pack was used for the statistical assessment. Descriptive statistics were expressed as mean, standard deviation, median, minimum, and maximum. Categorical variables were expressed as numbers and percentages. The Shapiro-Wilk test was used to test whether the data had a normal distribution. The t-test was employed for variables with normal distribution and the Mann-Whitney U test was used for comparisons between the two groups. Logistic regression analysis was performed to evaluate the association between variables tested and the recurrence. A p value <0.05 was considered statistically significant.

RESULTS

A total of 68 patients undergoing cryoablation due to PAF between October 2013 and March 2016 were included in the study. Patients were followed up for a mean duration of 22 months (8-37). The 68 patients included in the study were stratified into two groups as those who had AF recurrence and those who remained in sinus rhythm after the blind period of the initial three months. Of the 68 patients in the study, 32 (47.1%) were male and 36 (52.9%) were female. The mean age of the overall patient group was 57.3±12 years. With regards to cardiovascular risk factors, 25 patients (36.8%) had CAD, 9 (13.2%) had DM, 46 (67.6%) had HT, and 3 (4.4%) had a history of cerebrovascular event. Among all patients, the mean CHA2DS2-VASc score was 2.2±1.39, and the mean number of antiarrhythmic drugs the patients received was 1.94±0.7 (0-3) (Table 1).

Transthoracic echocardiography and transesophageal echocardiography performed before the procedure showed a median LA size, left ventricular ejection fraction, and LAA flow rate of 39.5±6.0 mm, 62±5.7%, and 36.5 (22-62) cm/sec, respectively. The median duration of fluoroscopy was 14±2.5 minutes. The success rate defined as successful ablation in three or PVs was 100%. PV anomaly (left or right-sided common PV) was identified in eleven patients (16.2%).

During the early period involving the initial three months, AF recurrence was found in 16 patients (23.5%), while 52 (76.5%) remained in the sinus rhythm during the follow-up. According to the evaluation of demographic characteristics of the

Table 1. Demographics and clinical characteristics of study subjects

	The study group (n=68)
Age (years)	57.3±12
Gender (male)	32 (47.1%)
BMI (kg/m^2)	29 (21-39)
BSA (m^2)	1.90±0.18
Diabetes mellitus	9 (13.2%)
Hypertension	46 (67.6%)
Hyperlipidemia	6 (8.8%)
Coronary artery disease	25 (36.8%)
Cerebrovascular event	3 (4.4%)
CHA2DS2-VASc score	2.2±1.39
Mean duration of follow up (months)	22 (8-37)
Pulmonary vein anomaly	11 (16.2%)
Number of antiarrhythmic drugs	1.94±0.7
Left ventricular ejection fraction	62±5.7
Left atrial diameter	39.5±6.0
Medical treatment	
- Beta-blocker	47 (69.1%)
- Calcium channel blocker	18 (26.5%)
- Digoxin	4 (5.8%)
- Amiodarone	26 (38.2%)
- ACEI/ARB	36 (52.9%)
- Sotalol	14 (20.6%)
- Propafenone	28 (41.2%)
- Warfarin	6 (8.8%)
- ASA	37 (54.4%)

BMI: Body mass index, BSA: Body surface area, CHA2DS2-VASc: Heart failure, hypertension, age, diabetes, history of stroke, vascular disease, female gender, ACEI: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, ASA: Acetylsalicylic acid

patients, of the 16 patients with AF recurrence, 5 (31.3%) were female and 11 (68.7%) were male, while the corresponding figures among the 52 subjects with no recurrence included 31 (59.6%) female and 21 (40.4%) male. There were no statistically significant differences between the groups with regards to gender distribution (p>0.05) (Table 2).

Again, no statistical differences between patients who had or did not have AF recurrence were observed in terms of cardiovascular risk factors such as diabetes, hypertension, hyperlipidemia, coronary artery disease, and cerebrovascular event history (p>0.05) (Table 2).

Before the procedure, the number of antiarrhythmic drugs the patients received was 2.43±0.5 (2-3) and 1.78±0.7 (0-3) in those with and without AF recurrence, respectively. The number of antiarrhythmic drugs used before the procedure was significantly higher among patients who developed AF recurrence compared to those who did not (p=0.002) (Table 2).

Of the 16 patients with AF recurrence, 37.5% (6) had an AF episode during the early period of the first three months while this percentage was 11.5% (6) among the 52 patients who had no AF episodes during the same period. An AF episode during the early period of the first three months was a significant predictor for AF recurrence (p=0.027). The number of prior cardioversions was significantly higher among those with AF recurrence than those without AF recurrence (p<0.001) (Table 2).

LA diameter in patients with and without AF recurrence was 44±6.6 mm and 38±5.3 mm, respectively. LA diameter was higher in the group with AF recurrence compared to the group without AF recurrence with a statistically significant difference (p=0.003). Septum and posterior wall thickness of the left ventricle measured in the parasternal long-axis were found to be statistically significant in predicting AF recurrence (p=0.008 and 0.007, respectively). LV mass in patients with and without AF recurrence was 195±51 g and 181±37.9 g, respectively. The difference in LV mass between the two groups was statistically significant (p=0.028). LAA flow rate determined by transesophageal echocardiography in patients with and without AF recurrence was 28 (22-55) cm/sec and 38 (24-62) cm/sec, respectively. The difference in LAA flow rate between the two groups was statistically significant (p<0.001) (Table 3).

Table 2. Demographics and clinical characteristics of groups with or without atrial fibrillation recurrence

	No AF recurrence (n=52)	AF recurrence (n=16)	p value
Age (year)	57.5±12.3	61.5±11.5	0.158
Gender (male) n (%)	21 (40.4%)	11 (68.8%)	0.084
BSA (m^2)	1.90±0.18	1.98±0.17	0.183
BMI (kg/m^2)	28.9 (21.5-39.1)	29.2 (25.5-39.8)	0.241
Duration of atrial fibrillation (month)	27.5 (6-100)	34.5 (12-96)	0.397
Diabetes mellitus n (%)	6 (11.5%)	3 (18.8%)	0.430
Hypertension n (%)	35 (67.3%)	11 (68.8%)	0.914
Hyperlipidemia n (%)	5 (9.6%)	1 (6.3%)	1.000
Coronary artery disease n (%)	16 (30.8%)	9 (56.3%)	0.65
Cerebrovascular event n (%)	2 (3.8%)	1 (6.3%)	0.559
COPD n (%)	5 (9.6%)	1 (6.3%)	1.000
Smoking n (%)	11 (21%)	7 (43%)	0.105
CHA2DS2-VASc score	2.01±1.32	2.81±1.51	0.077
Pre-procedure AF rhythm n (%)	4 (7.7%)	0	0.556
Total number of antiarrhythmic drugs before procedure	1.78±0.7	2.43±0.5	0.002
Use of drug before the procedure n (%)			
- Amiodarone	18 (34.8)	8 (50)	0.268
- Metoprolol	20 (28.4)	15 (93.7)	0.021
- Propafenone	14 (26.9)	5 (31.2)	0.453
- Sotalol	0	2 (12.5)	0.010
- Flecainide	0	1 (6)	0.022
History of cardioversion	0 (0-3)	1 (0-4)	0.001
AF episode within the first three months	6 (11.5%)	6 (37.5%)	0.027
Use of drug after the procedure n (%)			
- Amiodarone	4 (7.6)	1 (6.2)	0.321
- Metoprolol	41 (78.8)	13 (81.2)	0.411
- Propafenone	7 (13.4)	2 (12.5)	0.355

AF: Atrial fibrillation, BMI: Body mass index, BSA: Body surface area, COPD: Chronic obstructive pulmonary disease, CHA2DS2-VASc: Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, history of stroke, vascular disease, 65-74 years of age, female gender

While six patients (37.5%) had a pulmonary anomaly in the AF recurrence group, the number of corresponding figures was five (9.6%) among those without AF recurrence. Pulmonary anomalies were more common in the group with AF recurrence compared to the group without AF, with a statistically significant difference (p=0.016) (Table 4).

No statistically significant difference was found between the patients who did or did not develop AF recurrence in terms of laboratory parameters such as complete blood count, renal function tests, thyroid function tests, C-reactive protein, erythrocyte sedimentation rate, and uric acid (p>0.05) (Table 5).

DISCUSSION

PV isolation for the management of PAF is performed either by radiofrequency (RF) or cryoballoon ablation. The reported success rate for ablation in patients with persistent AF is lower compared to that in PAF patients. In a meta-analysis involving

Table 3. Distribution of echocardiographic findings across the groups

	No AF recurrence	AF recurrence	p value
LV mass (g)	181±37.9	195±51	**0.028**
LV mass index (g/m^2)	97±17.7	104±22.3	0.075
LA/BSA (cm/m^2)	21.4±3	22.1±2.6	0.515
LVEDD (mm)	46±3.5	46±4.3	0.660
Left atrium (mm)	38±5.3	44±6.6	**0.003**
Septum thickness (mm)	11±1.7	12±1.47	**0.008**
Posterior wall thickness (mm)	11±0.9	12±1.3	**0.007**
Ejection fraction (%)	62±3.96	64±9.2	0.306
Mitral annular calcification	6 (11.5%)	1 (6.3%)	1.000
sPAB (mmHg)	25 (19-45)	31 (20-39)	0.111
Left atrial appendage flow rate (cm/sec)	38 (24-62)	28 (22-55)	**<0.001**

AF: Atrial fibrillation, LV: Left ventricle, LVEDD: Left ventricular end diastolic diameter, LA: Left atrium, BSA: Body surface area, sPAB: Systemic pulmonary artery pressure

Table 4. Pulmonary vein anatomy and procedural characteristics in patients undergoing cryoablation

	No AF recurrence	AF recurrence	p value
Duration of fluoroscopy (min)	26.5±6.2	25±5.8	0.304
Total cooling time (sec)	1920 (960-3200)	1910 (960-3200)	0.836
Pulmonary vein anomaly	5 (9.6%)	6 (37.5%)	**0.016**
Upper PV freezing temperature, left -°C	48±6.9	50±7.0	0.454
Lower PV freezing temperature, left -°C	45±7.1	48±7.3	0.319
Upper PV freezing temperature, right -°C	48.±6.6	49±6.6	0.922
Lower PV freezing temperature, right -°C	41±5.6	47±6.3	0.001

AF: Atrial fibrillation, PV: Pulmonary vein

Table 5. Distribution of laboratory findings across the groups

	No AF recurrence	AF recurrence	p value
Creatinine (mg/dL)	0.73±0.24	0.70±0.1	0.919
GFR (mL/min)	109.5±33	113.5±25	0.603
Uric acid (mg/dL)	4.8±1.36	4.2±1.56	0.76
CRP (mg/dL)	0.45±1.71	0.52±0.5	0.939
ESR (mm/h)	10 (2-68)	8 (3-62)	0.467
Leukocyte count (10^3/µL)	8±3.16	6.8±3.7	0.452
Hemoglobin (g/dL)	13.2±1.61	13.6±1.52	0.670
LDL cholesterol (mg/dL)	115±43	116±27	0.836
HDL cholesterol (mg/dL)	43±13	36±6.9	0.44
Triglycerides (mg/dL)	115 (52-454)	141 (66-400)	0.517
TSH (µLU/mg)	0.7±1.09	1.56±1.06	0.228

AF: Atrial fibrillation, GFR: Glomerular filtration rate, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDL: Low-density lipoprotein, HDL: High-density lipoprotein TSH: Thyroid stimulating hormone

63 studies of RF ablation, success rates in paroxysmal and persistent AF were 70% and 14.9%, respectively[7].

Excluding the first 3 months, 76.5% of the patients with PAF in the present study were AF-free during a median follow-up of 22 months. In the STOP-AF study comparing cryoballoon ablation and antiarrhythmic medication, 69.9% of the patients in the ablation group were AF-free during the twelve months of follow-up[8]. In a prospective multi-center study by Stabile et al.[9], the success rate at one year of follow-up was 56% in the ablation group. The slightly higher success rate in the present study might have potentially resulted from the lower number of patients with structural heart disease, the relatively normal left atrium dimensions, and the small sample size.

In the above-mentioned meta-analysis of 63 studies investigating RF ablation, the reported rate of major complications was 4.9%, with PV stenosis (1.6%), pericardial effusion (0.6%), and thromboembolism (0.3%), which are the most frequent complications[7]. In another study on cryoablation, the rates of ischemic stroke, cardiac tamponade, and PV stenosis were reported as 0.3%, 0.3%, and 0.17%, respectively[10]. In the present study, none of the patients had major complications such as PV stenosis, cardiac tamponade, stroke, or death. Again, the lower complication rate in this study compared to the published data may be associated with the expertise level of our center in cryoballoon ablation for AF treatment, the limited number of patients, the inclusion of younger patients, and the lower number of comorbidities.

Pericardial effusion and phrenic nerve injury represent relatively more common complications of cryoablation. In the FIRE and ICE[11] study, phrenic nerve injury was reported in 2.3% of the cases. In the present study, 2 patients had pericardial effusion. Since none of the patients had the signs of cardiac tamponade, pericardiocentesis was not required.

Previously, an anterior-posterior LA diameter in the parasternal long-axis exceeding 45 mm was reported to be predictive for AF recurrence[12]. Aytemir et al.[13] identified LA diameter as an independent predictor for AF recurrence in their study evaluating efficacy and safety endpoints after PV isolation with cryoablation. In the present study, the mean LA diameter in patients with and without AF recurrence was 44±6.6 and 38±5.3 mm, respectively. LA dimensions were predictive for long-term AF recurrence after cryoablation. This observation supports the notion that LA dimensions should be a part of the patient selection process before cryoablation procedures.

Patients with high LAA emptying and filling rates determined by transesophageal echocardiography were found to remain in sinus rhythm for longer periods during their follow-up[14]. In a multi-center prospective study, the LAA emptying rate of less than 40 cm/sec was the single most important predictor of AF recurrence within 1 year[15]. In the current study, patients who developed recurrent AF had a 28 cm/sec (22-55) LAA flow rate determined by transesophageal echocardiography before cryoablation. A low LAA flow rate correlated with a higher likelihood of late AF recurrence. In line with the previous reports, this observation points out the role of a high LAA flow rate in maintaining the sinus rhythm.

AMIO-CAT[16] and EAST-AF[17] studies found that short-term antiarrhythmic treatment after AF ablation did not affect long-term AF recurrence although it might reduce the frequency of atrial tachyarrhythmia during the first 3 months. Lee et al.[18] found late AF recurrence among 35 of the 81 patients (43%) who developed early recurrence. Aytemir et al.[13] observed early AF recurrence in 29.1% of the patients who had AF recurrence after PV isolation with cryoablation. In the present study, 37.5% of the patients with late AF recurrence had an early AF episode, supporting the notion that early AF episodes may predict late AF recurrences.

Kubala et al.[19] performed cryoablation in 118 patients with drug-resistant PAF and found that atypical PV anatomy involving a common left PV was associated with an increased risk of AF recurrence compared to normal PV anatomy. There were 11 patients with PV anomalies in the present study. The rate was 37.5%[6] and 9.5%[5] in the group with AF recurrence and in the group with maintained sinus rhythm, respectively. The presence of a common PV was associated with AF recurrence. This observation suggests that cryoablation may be associated with lower success rates among patients with PV anomalies.

In the study by Evranos et al.[20], several biomarkers including C-reactive protein and erythrocyte sedimentation rate were found to not affect the risk of AF recurrence. Similarly, C-reactive protein and erythrocyte sedimentation rate measurements performed before cryoablation showed no association with AF recurrence in the present study.

Due to financial reasons, we could not use the three dimensional mapping system for ablation in our center. The three dimensional catheter navigation techniques can be applied to facilitate accurate catheter positioning with limited fluoroscopic exposure. The three dimensional mapping systems allow a better understanding of the anatomy and the pathophysiology of the arrhythmia[21]. In the complex patients, the combination of the three dimensional mapping system with image integration and remote magnetic navigation have been shown to be useful to facilitate ablation with very low fluoroscopy exposure. Integration of the fluoroscopy into the mapping system allows better understanding of the anatomy and might be associated with a better safety profile due to continuous catheter visualization during ablation[22].

Study Limitations

This study had several limitations. This was a retrospective analysis. Because of the sample size, future studies of larger cohorts with more statistical power were needed to validate

the findings. Some patients had a relatively short follow-up duration (8 months), and the predictive significance of the specified factors in patients with recurrent AF warrants further evaluation. Some asymptomatic AF cases may not have been included in the study.

CONCLUSION

Cryoablation is widely used for the treatment of AF worldwide. The safety and efficacy of this method have been established in several studies. However, the efficacy may vary depending on the expertise level of the operator, ablation technique, and catheter technology. Based on the results of the present study, several factors, including the occurrence of early AF episodes, history of cardioversion, use of multiple antiarrhythmic drugs before the procedure, high LA diameter, low LAA flow rate, presence of PV anomaly, increased interventricular septal thickness, left ventricular posterior wall thickness, and left ventricular mass, were predictive for AF recurrence during follow up after cryoablation We believe that consideration of these factors during patient selection may improve the success rate of this procedure.

Ethics

Ethics Committee Approval: The study was approved by the Uludağ University Local Ethics Committee for Clinical Research with decree no: 2016-5/21 and approval date: 29.11.2019.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.Ç., A.A., Concept: A.D., S.Ç., F.B., A.A., Design: E.Ç., A.A., Data Collection or Processing: E.Ç., Analysis or Interpretation: A.D., S.Ç., F.B., A.A., Literature Search: E.Ç., A.D., S.Ç., F.B., A.A., Writing: E.Ç., A.D., S.Ç., F.B., A.A.

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A Microbiology Laboratory Workflow in the COVID-19 Pandemic: Trakya University Medical Faculty

COVID-19 Pandemisinde Bir Mikrobiyoloji Laboratuvarı İş Akışı: Trakya Üniversitesi Tıp Fakültesi Deneyimi

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ABSTRACT

Aim: The Coronavirus disease-2019 (COVID-19) epidemic first started in China and spread all over the world. In our country, pandemic management is carried out under the coordination of the Ministry of Health. With the change in the case increase rate in our province within months, the needs of our hospital were fully answered as the medical microbiology laboratory. In this study, it is aimed to convey our experiences and to make a retrospective analysis of the samples that came to the coronavirus laboratory in the first seven months of the pandemic.

Materials and Methods: In order to create a safe working environment and organize the workflow during the pandemic process, some changes were made in the laboratory and it was made a guide. In addition, Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) polymerase chain reaction (PCR) and anti-SARS-CoV-2 antibody tests that came to the coronavirus laboratory between 21.03.2020 and 21.10.2020 were screened retrospectively.

Results: A total of 73,773 SARS-CoV-2 PCR tests and 1,170 anti-SARS-CoV-2 antibody tests were run in our laboratory. It was determined that total PCR positivity was 2.7% and antibody positivity was 1.9%.

Conclusion: When the PCR positivity rates were examined, a dramatic decrease was observed after the first month with the measures taken and this decrease continued until the fifth month. It is seen that PCR positivity increased again in the sixth and seventh months with the relaxation of the measures. It is thought that our experiences in the first months of the pandemic can provide valuable information for other laboratories.

Keywords: COVID-19, pandemic, microbiology, laboratory

ÖZ

Amaç: Koronavirüs hastalığı-2019 (COVID-19) salgını ilk olarak Çin'de başlamış olup tüm dünyaya yayılmıştır. Ülkemizde salgın yönetimi Sağlık Bakanlığı koordinesinde yapılmaktadır. İlimizdeki olgu artış hızının aylar içinde değişmesiyle birlikte hastanemizde oluşan ihtiyaçlara tıbbi mikrobiyoloji laboratuvarı olarak eksiksiz cevap verilmiştir. Bu çalışmada bu deneyimlerimizi aktarmak ve pandeminin ilk yedi ayında koronavirüs laboratuvarına gelen örneklerin retrospektif analizini yapmak amaçlanmıştır.

Gereç ve Yöntem: Pandemi sürecinde güvenli bir çalışma ortamı oluşturmak ve iş akışını organize etmek için laboratuvar içinde birtakım değişiklikler yapılıp rehber haline getirilmiştir. Ayrıca 21.03.2020-21.10.2020 tarihleri arasında koronavirüs laboratuvarına gelen Şiddetli akut solunum sendromu koronavirüs-2 (SARS-CoV-2) polimeraz zincir reaksiyonu (PZR) ve anti-SARS-CoV-2 antikor testleri retrospektif olarak taranmıştır.

Bulgular: Laboratuvarımızda toplam 73.773 SARS-CoV-2 PZR testi, 1.170 anti SARS-CoV-2 antikor testi çalışılmıştır. Toplam PZR pozitifliğinin %2,7, antikor pozitifliğinin ise %1,9 olduğu tespit edilmiştir.

Sonuç: PZR pozitiflik oranları incelendiğinde alınan önlemler ile ilk aydan sonra dramatik bir düşük gözlenmekte ve bu düşüş beşinci aya kadar devam etmektedir. Önlemlerin gevşetilmesi ile altıncı ve yedinci aylarda PZR pozitifliğinin tekrar yükseldiği görülmektedir. Pandeminin ilk aylarında elde ettiğimiz deneyimlerimizin diğer laboratuvarlar için değerli bilgiler sağlayabileceği düşünülmektedir.

Anahtar Kelimeler: COVID-19, pandemi, mikrobiyoloji, laboratuvar

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INTRODUCTION

In December 2019, a number of cases consistent with viral pneumonia were reported from Wuhan, China[1]. As a result of the sequence analysis of these cases, it was revealed that this disease was caused by the new Coronavirus and it was named "2019-nCoV"[1]. This name was changed as "Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)" on February 11, 2020 by the "International Virus Taxonomy Committee Coronavirus Working Group" and accepted worldwide[2]. On the same day, the World Health Organization (WHO) declared the name of this disease as "Coronavirus disease-2019 (COVID-19)"[3]. On March 11, 2020, WHO defined this outbreak as a pandemic[3].

After the declaration of the pandemic, scientific committees were established in many countries. In our country, the "Coronavirus Scientific Committee" affiliated to the Ministry of Health was established on January 10, 2020. This committee consists of scientists from different branches such as Medical Microbiology, Infectious Diseases and Clinical Microbiology, Virology, Internal Medicine and Chest Diseases[4].

SARS-CoV-2 is the seventh Coronavirus (HCoV) known to infect humans. Among these viruses, HCoV-229E, HCoV-NL63, HCoV-HKU1 and HCoV-OC43 are endemic. These four viruses are seasonal and tend to cause mild respiratory illness. The other two viruses are the more virulent zoonotic Middle east respiratory syndrome coronavirus and SARS-CoV type 1 (SARS-CoV-1). SARS-CoV-2 is most genetically similar to SARS-CoV-1, and both of these viruses belong to the Sarbecovirus subgenus within the Betacoronavirus genus[5]. The clinical manifestation of SARS-CoV-2 infection can range from asymptomatic infection to severe disease. Mortality rates vary by country[6]. Early laboratory diagnosis of SARS-CoV-2 infection can help clinical management and pandemic control. The definitive diagnosis of the disease is established by genetic tests such as polymerase chain reaction (PCR) or gene sequencing[7].

Timeline

January 10, 2020: The Coronavirus Scientific Committee was established under the coordination of the Ministry of Health[8].

January 24, 2020: With the recommendation of the Scientific Committee, flights to Wuhan were stopped, and measures such as scanning with thermal cameras for those coming from China to our country were determined. It was decided to quarantine people showing symptoms of COVID-19[9].

February 04, 2020: Scanning with thermal cameras at entry points for passengers arriving from countries where the disease was reported was begun[8].

March 5, 2020: It was underlined that everyone entering our country from other countries should pay attention to the "14 days" rule. According to this rule, it was stated that people coming from abroad should isolate themselves as much as possible for 14 days, and that they should not contact with people over the age of 65 years who were in the risk group and who had chronic diseases[10].

March 11, 2020: The first case of COVID-19 was detected in Turkey[8].

March 12, 2020: Education was suspended in primary and secondary schools and universities[8].

March 12, 2020: Public officers were prohibited from going abroad except in compulsory and urgent situations[11].

March 13, 2020: Collective events in public areas were restricted[8].

March 13, 2020: Bulgaria closed its borders to passenger entries and exits, except for trucks carrying loads, within the scope of COVID-19 measures. Although Turkey stopped the quarantine on June 11, the Bulgarian government continued the application until September 1 on the grounds that the COVID-19 epidemic continued[12].

March 16, 2020: Congregational prayers in mosques were suspended[8].

March 20, 2020: All kinds of artistic, cultural and scientific activities were postponed. On the same date, all hospitals with a tertiary adult intensive care unit with at least two specialist physicians in the branches of chest diseases, infectious diseases, clinical microbiology and internal medicine were declared as pandemic hospitals by the Ministry of Health[13].

March 21, 2020: The number of test centers detecting COVID-19 was increased to 73, and on this date, a lockdown was imposed for those over the age of 65 years and with chronic diseases. Hairdressers and beauty centers were temporarily closed. Restaurants were only allowed to provide take-out services[8].

March 22, 2020: Working hours were re-organized for public sector employees[8].

April 04, 2020: A lockdown was also imposed for those younger than 20 years old[8].

April 14, 2020: Turkish Airlines announced that it suspended international flights until May 20, 2020[14].

May 04, 2020: As part of normalization, travel restrictions were stopped for seven provinces, and it was announced that hairdressers and shopping centers would reopen on May 11[8].

May 29, 2020: Within the scope of normalization in public institutions and organizations, international travel ban and flexible working of public officers were discontinued[15].

August 26, 2020: It was decided that flexible working could be applied again at the initiative of the managers in public institutions[16].

September 7, 2020: It was made obligatory to wear masks in all areas (except residences) in 81 provinces[17].

October 2, 2020: All events organized by non-governmental organizations, public institutions, cooperatives and unions were postponed until December 1[18].

In the COVID-19 pandemic, there have been significant changes in working life with the decisions taken both in the country and in our university. In this process, different arrangements were made in the services of the medical microbiology laboratory and the distribution of personnel, and the needs related to the COVID-19 pandemic were tried to be met. In this study, it was aimed to convey the experiences of the medical microbiology laboratory during the pandemic process and to investigate the SARS-CoV-2 PCR and anti-SARS-CoV-2 antibody positivity rates in the first seven months.

MATERIALS AND METHODS

Permission was obtained from the Ministry of Health to conduct the study. In addition, the study was approved by the Scientific Research Ethics Committee of Trakya University (TUTF-BAEK 2021/70, date: 21.12.2020). Descriptive statistics for categorical variables were presented as numbers and percentages, and SPSS (ver: 21) statistical program was used for all statistical analyses.

a. Preanalytical Process

There is a molecular diagnosis laboratory in our medical microbiology laboratory. However, it was not possible to study SARS-CoV-2 PCR tests in this laboratory due to both biosafety and physical inadequacy. Instead, the tuberculosis laboratory with Biosafety level-2 (BSL-2) was modified and used. On March 21, 2020, "Trakya University Medical Faculty Coronavirus Laboratory" started to work with five technicians, three medical microbiology assistants and three academic members.

Tuberculosis tests were directed to Edirne Public Health Laboratory to be studied in this process. In addition, molecular tests, immunofluorescent antibody tests, parasitology tests and bacteriology tests were temporarily closed on April 9, 2020, as the technicians working here were working in the coronavirus laboratory (Table 1).

The coronavirus laboratory consists of three rooms. In the first room, there is a computer where the results are entered and documents. The second room is the room where the PCR device is located and the staff change their clothes. In the innermost room, the samples are opened and processed in the BGD-2 biosafety cabinet. From the date of its opening, the laboratory served 24 hours a day, 7 days a week, until October 1, 2020, with two technicians and a medical microbiology assistant. Due to the increased workload with this situation, technicians with experience of PCR in medical biology, medical genetics and Trakya University Technology Research and Development Application and Research Center PCR were requested to be assigned to our laboratory. In April, the coronavirus laboratory continued to serve with five additional personnel assigned in addition to the existing personnel and two medical microbiology assistants on standby. In June, three personnel assigned from other departments left the laboratory due to the expiry of their assignment period, and two technicians working in the medical microbiology laboratory started to work in the coronavirus laboratory. In addition, a medical microbiology assistant started to work in this process and was assigned to the coronavirus laboratory. Moreover, by talking to the head physician, it was ensured that the new technicians in our hospital were also started to work in the medical microbiology

Table 1. Change of open-closed status of laboratories according to months

Months	Labor force	Bacteriology	Tuberculosis	Parasitology	IFA	Molecular	Mycology	Serology
March	5 technicians + 3 assistants	Open	Open	Open	Open	Closed	Open	Open
April	5 technicians + 5 assistants + 5 assignments	Closed	Closed	Closed	Closed	Closed	Open	Open
May	5 technicians + 5 assistants + 5 assignments	Open	Open	Closed	Closed	Closed	Open	Open
June	7 technicians + 6 assistants + 2 assignments	Open	Open	Open	Closed	Closed	Open	Open
July	7 technicians + 6 assistants + 2 assignments	Open	Open	Open	Closed	Closed	Open	Open
August	8 technicians + 6 assistants + 2 assignments	Open	Open	Open	Closed	Open	Open	Open
September	7 technicians + 6 assistants + 2 assignments	Open	Open	Open	Open	Open	Open	Open
October	12 technicians + 6 assistants + 2 assignments	Open	Open	Open	Open	Open	Open	Open

IFA: Immunofluorescent antibody

laboratory. A total of six technicians, one in August and five in October, started to work in our laboratory, five of them were assigned to the coronavirus laboratory. On October 1, due to the decrease in the samples, two people continued the shifts. As of October 2020, the coronavirus laboratory provided uninterrupted service with 14 technicians and six medical microbiology assistants.

The COVID-19 guideline prepared by the Ministry of Health was updated five times in the first seven months of the pandemic. Except for the guideline published on April 13, 2020, the possible case definition changed in each update. The variation of the probable case definition is shown in Table 2.

Individuals suitable for the possible case definition were registered in the "Hospital Information Management System (HIMS)" and reported to e-nabız. SARS-CoV-2 PCR request was made for the diagnosis of COVID-19 via HIMS. The appropriately taken sample was delivered to the laboratory under appropriate conditions.

Collecting and Delivering Samples

Respiratory tract samples from probable or definite cases of COVID-19 were taken by healthcare personnel. The most common types of specimens taken for testing were combined swab specimens from the nasopharynx and oropharynx, which were taken together and sent in the same tube. Lower respiratory tract secretions, such as sputum and brochoalveolar lavage fluid, were also tested in patients with pneumonia.

Taking oropharyngeal swab: The inside of the mouth is illuminated so that it can be seen clearly. The tongue is pressed down with the tongue depressor and a sample is taken from the tonsils with a sterile ecuvion. During this process, strict attention is paid not to let the swab touch other points in the mouth[19].

Table 2. Change of probable case definition in COVID-19 guidelines in the first 7 months

January 2020	1	Those having *SARI that cannot be explained with another etiology and having one of the followings:
		a. Having a history of travel to China 14 days before the onset of symptoms
		b. Working in the unit where COVID-19 patients are treated
	2	Those having respiratory disease and any of the followings:
		a. Close contact with a confirmed COVID-19 patient
		b. Being in a healthcare facility in a country where hospital-associated COVID-19 has been reported
		c. Having been in China
21 February 2020		Those having respiratory disease or SARI and having any of the followings in the past 14 days
		a. Close contact with a confirmed COVID-19 patient
		b. Being in a healthcare facility in a country where hospital-associated COVID-19 has been reported
		c. Having been to China, Singapore, Iran, Thailand, Japan, Hong Kong, South Korea
		d. Working where COVID-19 patients are treated
11 March 2020	A	Having symptoms of fever and acute respiratory illness, and inability to explain the clinical picture with another condition and being abroad up to 14 days before the onset of symptoms
	B	Having symptoms of fever and acute respiratory illness, and history of contact with confirmed COVID-19 up to 14 days before symptom onset
	C	Having fever and signs of severe acute respiratory illness, and having SARI and inability to explain the clinical picture with another condition
25 March 2020	A	Having symptoms of fever and acute respiratory illness, and inability to explain the clinical picture with another condition and being abroad up to 14 days before symptom onset
	B	Having symptoms of fever and acute respiratory illness, and history of contact with confirmed COVID-19 up to 14 days before symptom onset
	C	Having symptoms of fever and acute respiratory illness, and having SARI and inability to explain the clinical picture with another condition
	D	Sudden onset of fever with cough or shortness of breath and no runny nose
29 June 2020	A	Fever, cough, shortness of breath, sore throat, muscle pain, loss of taste and smell or diarrhea, and inability to explain the clinical picture with another condition and being abroad up to 14 days before symptom onset
	B	Fever, cough, shortness of breath, sore throat, muscle pain, loss of taste and smell or diarrhea, and history of contact with confirmed COVID-19 up to 14 days before symptom onset
	C	Having symptoms of fever and severe acute respiratory illness, and having SARI and inability to explain the clinical picture with another condition
	D	Having two of symptoms including fever, cough, shortness of breath, sore throat, muscle pain, loss of taste and smell or diarrhea, and inability to explain them with another condition

*SARI: Requirement of hospitalization due to fever, cough and dyspnea, tachypnea, hypoxemia, hypotension, radiological findings and change in consciousness in a patient with acute respiratory tract infection developed in the last 14 days.

COVID-19: Coronavirus disease-2019

Taking nasopharyngeal swab: A nostril is entered with a flexible, thin-handled sterile ecuvion. Tears that appear in the eyes of the person indicate that the appropriate anatomical region is reached. After waiting for a few seconds, it is removed by turning. The process is repeated from the other nostril with the same ecuvion and placed in the appropriate transport medium[19].

The healthcare personnel taking the samples collected the samples from the patients by wearing their personal protective equipment (PPE) and following the infection prevention and control procedures. All samples taken were delivered to the laboratory by triple transport system. It was ensured that the samples were labeled correctly, the request forms were filled in correctly, and clinical information was provided. The laboratory was informed before the sample was sent.

Before the samples came to the laboratory, the barcode information (patient name-surname, date of birth, etc.), the name of the risky area visited and other necessary information (hospital name, doctor's name, etc.) together with other information including the anatomical region and location from which the sample was taken, date and time and clinical symptoms were recorded in the HIMS system by the Provincial Health Directorate.

After this registration process, the barcode of the SARS-CoV-2 PCR test request was removed and sent to our laboratory together with the relevant samples. Since the triple transport container was not opened during the delivery of the samples to the laboratory, the barcodes could not be checked at this stage. Samples were opened in the Biosafety cabinet in the third room and rejected when necessary.

b. Analytical Process

After the Ministry of Health declared it as "COVID-19 Authorized Diagnostic Laboratory (Group 1)" on March 19, 2020, all samples from Edirne, Kırklareli and Tekirdağ provinces were directed to our laboratory for SARS-CoV-2 PCR testing[20]. Since the SARS-CoV-2 PCR test was started to be studied at Tekirdağ Namık Kemal University at the beginning of April, it was continued with samples from Edirne and Kırklareli. SARS-CoV-2 PCR tests, which were carried out using the tuberculosis laboratory on March 21, 2020, were continued to be studied at the new place with the allocation of a separate laboratory on April 27, 2020. This coronavirus laboratory, like the previous one, has three rooms. With the opening of the coronavirus laboratory, tuberculosis tests began to be studied in the tuberculosis laboratory on May 13, 2020.

Polymerase Chain Reaction

When the SARS-CoV-2 PCR test was first studied, the only PCR device available in the laboratory was Montania 4896 (Anatolia Geneworks, Turkey). It was continued with a single device until August 7, 2020. On this date, two Rotor Gene Q (Qiagen, Hilden, Germany) devices were purchased for our laboratory. The Montania 4896 (Anatolia Geneworks, Turkey) device was sent to the Molecular Diagnostic Laboratory to study molecular tests such as HBV-DNA, HCV-RNA as before. With the replacement of the only PCR device in the Molecular Diagnostic Laboratory, the closed molecular test requests were reopened and samples were started to be accepted.

While Biospeedy (Bioeksen, İstanbul, Turkey) kit was used for the first six months, after the sixth month, biospeedy (Bioeksen, İstanbul, Turkey), diagnovital (RTA Laboratories, İstanbul, Turkey) and coronex (DS Bio and Nano Technology, Ankara, Turkey) kits were used alternately. While working with each kit, the manufacturer's recommendations were followed. While the kits Diagnovital (RTA Laboratories, İstanbul, Turkey) and coronex (DS Bio and Nano Technology, Ankara, Turkey) examine the ORF1ab and N gene regions, the biospeedy kits target the RdRp (RNA dependent RNA polymerase) gene region.

Serological Tests

Some time is required for the antibody response (IgM, IgA, and IgG) to occur in those infected with COVID-19. Although the first antibody response (IgM) begins after five days, detectable antibody positivity occurs 10-13 days after the onset of symptoms in most patients[21]. Whether the detected antibodies provide immunity and when it can be detected (IgG) are now unclear. The ELISA test is currently used to determine the serological response. In our laboratory, ELISA tests are performed on the roche cobas e 601 device with the roche elecsys kit.

Biosafety

It is recommended that inactivation of microorganisms be performed in a biosafety cabinet in molecular tests using the standard PCR method. National guidelines on laboratory biosafety should also be followed at all times. Testing of clinical specimens that may contain SARS-CoV-2 should be performed in appropriately equipped laboratories by personnel trained on the relevant technical and safety procedures.

However, if cell culture production of virus or neutralization tests are to be carried out, BSL-3 facilities are required at minimum[22].

The results from the first opening of the laboratory until June 26, 2020 were entered into the laboratory information management system (LIMS) one by one on the computer in the first room. In order to enter the results, the samples were first sent to the laboratory from external institution requests. The referred samples were transferred to the "waiting samples" section in the laboratory. Samples to be rejected were rejected on this page. The samples included in the study were accepted and transferred to the "not approved" page. According to the evaluations made on the device, the result of the sample was

entered into the system on this page. The results of all patients were recorded in the laboratory notebook.

c. Postanalytical Process

With the revisions made in the LIMS system in June, the "worklist" was started to be created on the computer. When the incoming samples were opened in the third room, the barcodes of the samples were read by the barcode reader on the computer there and a "worklist" was created. In this way, it was ensured that the samples fell directly into the "not approved" in the system. Thus, the "worklist" was recorded in LIMS, and the printouts of these lists were taken and the archive of these computer printouts began to be kept instead of the notebook record. Again, with the revisions made on this date, it became possible to perform collective operations while entering the results. After the positives were entered one by one to avoid confusion, negatives were entered under control. At the end of the day, work lists were prepared and added to the laboratory file. Positive samples were reported to the filiation teams by phone.

The samples studied in the postanalytical process were accepted as hazardous waste and were disposed of in accordance with BSL-2 safety precautions. After the laboratory personnel working in the third room finished their work, they went to the second room and took off their disposable PPE and threw them in the waste bin.

After all the samples were finalized, the results of the tests from our university were marked as panic values in the system. The doctors of these patients were called by phone and verbal information was given.

In order to reveal the change in the workforce in the laboratory, the number of samples coming to the bacteriology laboratory was scanned retrospectively and compared with the number of samples belonging to the same month of the previous year.

RESULTS

The total number of samples arriving at the coronavirus laboratory in the first seven months of the pandemic is 74,943. 73,773 of them are SARS-CoV-2 PCR test, 1,170 of them are anti-SARS-CoV-2 antibody test. The distribution of SARS-CoV-2 PCR test results received in our laboratory by months is given in Table 3. It is seen that the positivity rate decreases rapidly at the end of the first month and starts to rise again in the sixth and seventh months. Anti-SARS-CoV-2 antibody tests were positive at a rate of 1.9%.

Rejected SARS-CoV-2 PCR test requests are shown in Table 4. It is seen that the highest rates are in the first months, and this rate decreases in the following months.

Compared to the previous year, the change in the rates of samples coming to the bacteriology laboratory within months

Table 3. SARS-CoV-2 polymerase chain reaction test results

Province	Date	PCR (-) (n)	PCR (+) (n)	PCR (+) (%)	Total (n)
Edirne	21 March-21 April	2482	311	11.1	2793
	21 April-21 May	4062	65	1.6	4127
	21 May-21 June	6866	31	0.4	6897
	21 June-21 July	7289	96	1.3	7385
	21 July-21 August	19898	219	1.1	20117
	21 August-21 September	6624	221	3.2	6845
	21 September-21 October	4205	217	4.9	4422
Total Edirne		**51426**	**1160**	**2.2**	**52586**
Kırklareli	21 March-21 April	1945	207	9.6	2152
	21 April-21 May	4364	49	1.1	4413
	21 May-21 June	3071	35	1.1	3106
	21 June-21 July	2944	28	0.9	2972
	21 July-21 August	481	3	0.6	484
	21 August-21 September	3484	146	4.0	3630
	21 September-21 October	3602	239	6.2	3841
Total Kırklareli		**19891**	**707**	**3.4**	**20598**
Tekirdağ	**10 days**	496	93	15.8	589
General total		**71813**	**1960**	**2.7**	**73773**

SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2, PCR: Polymerase chain reaction

is quite low, especially in the first four months of the pandemic (Table 5).

DISCUSSION

In 2020, the COVID-19 pandemic has been the most important agenda item both in Turkey and in the world. In extraordinary situations such as pandemics, the society should be guided by strictly defined rules to be taken both locally and globally. Pandemic management should be carried out transparently under the control of the Ministry of Health. When we look at the timeline of the pandemic in the light of our regional data, it is seen that the positivity rates have decreased rapidly after the measures taken to prevent people from contacting each other. The rise of the positivity rate again in the sixth and seventh months of the pandemic also coincides with the period when the measures were relaxed. Considering the size of the COVID-19 pandemic and the fact that it is not known how long it will continue, we believe that the measures should not be relaxed.

PCR testing from lower respiratory tract samples is a more sensitive method than PCR testing from throat or nose swab samples[6]. However, it is not practical to take lower respiratory tract samples from everyone in every environment. For this reason, combined nose-throat swab sample has been the mostly used method in Turkey. With this method, the sample is taken with a swab and placed in viral transport medium and delivered to the laboratory. However, when placing the swab into the viral transport medium, it must be cut at the marked place. Considering that doctors from many different branches take samples in the field, we accept it normal to make mistakes at this point. Since the swab sticks sent without cutting from the appropriate place may cause scattering of the sample in the laboratory, these samples were rejected by giving feedback to the relevant doctor. Leakage of the sample, breakage of the viral transport medium and samples not delivered to the laboratory under appropriate conditions are among the other reasons for rejection. Considering the change in rejected samples within months, it is seen that these rates have decreased considerably thanks to the feedback provided and the strong communication between the laboratory and the clinician.

Medical microbiology laboratory employees have great efforts in the execution of the coronavirus laboratory. Technicians, assistants and academic members working in the medical microbiology laboratory ensured both the running of the coronavirus laboratory and the study of other microbiology tests such as bacteriology, virology, mycology, and serology. In order to work in the most efficient way with a limited workforce, rotations were made within the laboratory.

Although support was received from outside the medical microbiology laboratory in the first months of the pandemic, these assignments were terminated when new technicians appointed to our hospital started in the medical microbiology laboratory in the following months. During this seven-month period, there were significant changes in our hospital. Other departments also had some practices within themselves, such as the closure of some services, the downsizing of some, and the absence of surgery except for emergency surgeries.

Table 4. Rejected SARS-CoV-2 polymerase chain reaction test results

Date	Rejected (n)	Rejected (%)	Total specimen (n)
21 March-21 April	172	3,1	5534
21 April-21 May	396	4,6	8540
21 May-21 June	228	2,3	10003
21 June-21 July	56	0,5	10357
21 July-21 August	61	0,3	20601
21 August-21 September	2	0,0	10475
21 September-21 October	0	0,0	8263
Total	915	1,2	73773

SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2

Table 5. Change in the number of bacteriology samples compared to the previous year

	2019	2020	Difference (%)
March	3677	1276	65.3
April	3770	375	90.1
May	3141	1059	66.3
June	2438	1646	32.5
July	2152	1950	9.4
August	1878	2202	-17.3
September	2034	2033	0.0
October	2057	2092	-1.7
Total	21147	12633	40.3

Pandemic services and intensive care units were opened and started to serve only COVID-19 patients. These changes made in the hospital created significant differences in the number of samples coming to the medical microbiology laboratory when compared to the same months of the previous year. In addition, with all these changes, the needs of the hospital changed and the medical microbiology laboratory responded to this need with rotations and changes made within the laboratory.

CONCLUSION

As a result, medical microbiology laboratory is a risky unit considering the tests it performs and biosafety measures are always kept in the foreground. In addition, it is thought that the experiences about how the measures taken throughout the country and at the hospital change the work flow in a Microbiology Laboratory will contribute to other laboratory staff.

Ethics

Ethics Committee Approval: The study was approved by the Scientific Research Ethics Committee of Trakya University (TUTF-BAEK 2021/70, date: 21.12.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: İ.D., Ş.G., B.K., Design: İ.D., Ş.G., B.K., Data Collection or Processing: İ.D., Ş.G., B.K., Analysis or Interpretation: İ.D., Ş.G., B.K., Literature Search: İ.D., Ş.G., B.K., Writing: İ.D., Ş.G., B.K.

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

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CASE REPORT

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Pregnancy and Lactation-Associated Osteoporosis

Gebelik ve Emzirmeyle İlişkili Osteoporoz

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ABSTRACT

Osteoporosis in pregnancy and during lactation period is a rare clinical problem with unknown etiology and pathophysiology. Pregnancy and lactation may have significant impact on bone loss and this may result in osteoporosis and related fractures. The symptoms often occur during the first pregnancy and usually do not recur. Secondary causes of osteoporosis that may cause back pain and fractures during pregnancy should be taught in differential diagnosis. Still no guidelines exist about the accurate treatment of this rarely seen osteoporosis type, this means each case must be evaluated on an individual basis in order to decide for a treatment plan. In this case report, a 25-year-old woman, complaining of severe back pain after twenty days of giving birth, is reported.

Keywords: Pregnancy, lactation, osteoporosis

ÖZ

Gebeliğe ve emzirmeye bağlı gelişen osteoporoz etiyolojisi ve patofizyolojisi tam olarak bilinmeyen ve nadir görülen bir klinik problemdir. Gebelik ve emzirme kemik kaybı üzerinde belirgin bir rol oynayarak gebeliğe bağlı osteoporoza ve buna bağlı gelişebilecek olan kırıklara sebep olur. Semptomlar genellikle ilk gebelikten sonra olur ve tekrar etmez. Gebelik sırasında ağrı ve kırık sebebi olabilen kemik erimesinin sekonder sebepleri ayırıcı tanıda düşünülmelidir. Bu nadir görülen osteoporozun belirlenmiş bir tedavi algoritması yoktur, bu yüzden her olgu bireysel olarak ele alınmalıdır ve tedavi planı belirlenmelidir. Bu olgu sunumu ile 25 yaşında doğum yaptıktan yirmi gün sonra şiddetli bel ağrısı başlayan bir olgu rapor edilmiştir.

Anahtar Kelimeler: Gebelik, emzirme, osteoporoz

INTRODUCTION

Pregnancy and lactation associated osteoporosis (PLAO) is a very rare condition seen during the last three months of the pregnancy or at early postpartum period[1,2]. It was first defined by Nordin and Roper[3] in 1955. It is characterized by pain due to vertebral fractures. There are cases in which rarely pelvis, sacral and wrist fractures have been reported[4]. Its etiology has not been clearly defined. Risk factors associated with pregnancy-related osteoporosis include genetic factors, physical inactivity, malnutrition, low body weight, osteoporotic fracture history in family members, and secondary osteoporosis[3,4]. The high prevalence of fracture seen in female relatives of patients diagnosed with PLAO suggests an underlying genetic component[2,5,6]. Anorexia and oligomenoria history can be seen in PLAO patients[7].

CASE REPORT

Mild low back pain started in 25-year-old primigravid woman without a previously known disease or trauma in her last month of pregnancy. Twenty days after giving birth by cesarean section under spinal epidural anesthesia, a very severe low back pain suddenly occurred without trauma. There was continuous low back pain at the degree limiting daily activities. She did not benefit from the analgesic treatment which was prescribed by a physician who she visited in another center with a diagnosis

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of myalgia. Two months later after birthgiving, the patient applied to our hospital suffering from ongoing pains.

In her medical history, there was no disease or drug use that would suggest the secondary osteoporosis. The causes of secondary osteoporosis like smoking and alcohol use, menstrual irregularity, estrogen deficiency, history of fracture as a result of mild trauma, rheumatoid arthritis, infertility treatment with clomiphene, type 1 osteogenesis imperfecta, gluten enteropathy, corticosteroid or heparin usage, anorexia nervosa, chemotherapy, chronic obstructive pulmonary disease, diabetes mellitus, hypothyroidism, hyperthyroidism, chronic liver disease, and long term immobilization were all asked and none of them were positive.

Eating habits were questioned and it was detected that due to nausea and sometimes vomiting during pregnancy period, the intake of calcium with diet or supplementation was not sufficient. The patient claimed that calcium intake with diet was also low at long term before pregnancy.

Family history was normal as well. Her body mass index was 21.6 kg/m^2 (165 cm, 59 kg).

In the physical examination, there was an increase in the thoracic kyphosis, decrease in the lumbar lordosis and mildly left facing scoliosis in the thoracic region by inspection. Palpation revealed severe muscle spasms both in thoracic and lumbar paravertebral muscles. While there was pain and limited movement in all directions in the trunk, range of motion was severely compromised. No abnormality was detected in the bilateral upper and lower extremity motor and sensory examination. Deep tendon reflexes were normoactive and no pathological reflexes were detected.

The tests of complete blood count, routine biochemistry, sedimentation, C-reactive protein, *Brucella* agglutination test, parathormone, calcium excretion in urine, alkaline phosphatase, lactate dehydrogenase, and thyroid function were requested from the patient. No abnormality was detected in laboratory examinations except for phosphorus 5 mg/dL (N: 2.3-4.7 mg/dL) and 25-OH vitamin D 23.2 ng/mL (N: >30 ng/mL). Tumor markers were in normal range and no pathology was detected with mammary ultrasonography and mammography, parathyroid scintigraphy.

Bone mineral density (BMD) of the patient was measured by using the dual-energy X-ray absorptiometry method and the value were found to be low according to corresponding age group. The scores are listed in Table 1.

On plain radiographs, there was an arching at frontal T5-T12 and L1-L3 vertebrae. In the magnetic resonance imaging (MRI) of thoracic and lumbar vertebrae, it was detected that there was a widespread arch in T5-7-9-11-12, and L1-L3 vertebrae, height loss at varying grades in all of mentioned vertebrae and edematous signal changes and compression fractures in the corpuses of them (Figures 1, 2). Osteoporosis was thought to be the cause of compression fractures.

By excluding all of the reasons for the secondary osteoporosis, the patient was diagnosed as PLAO.

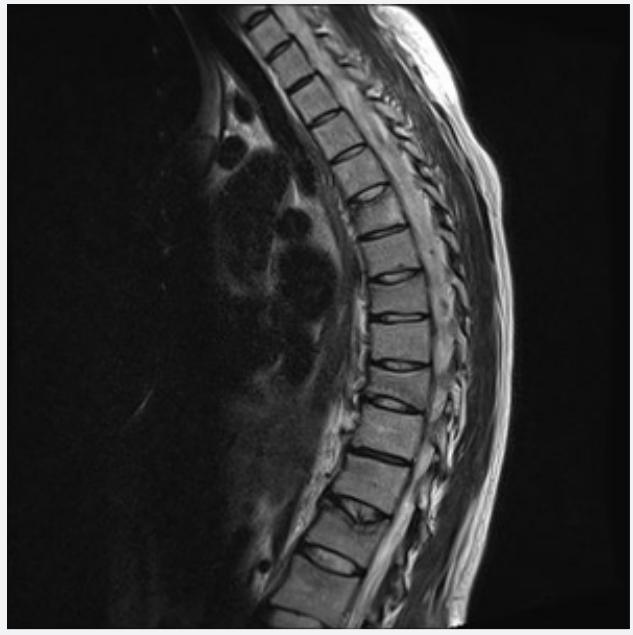

Figure 1. T1 sagittal magnetic resonance imaging at the beginning

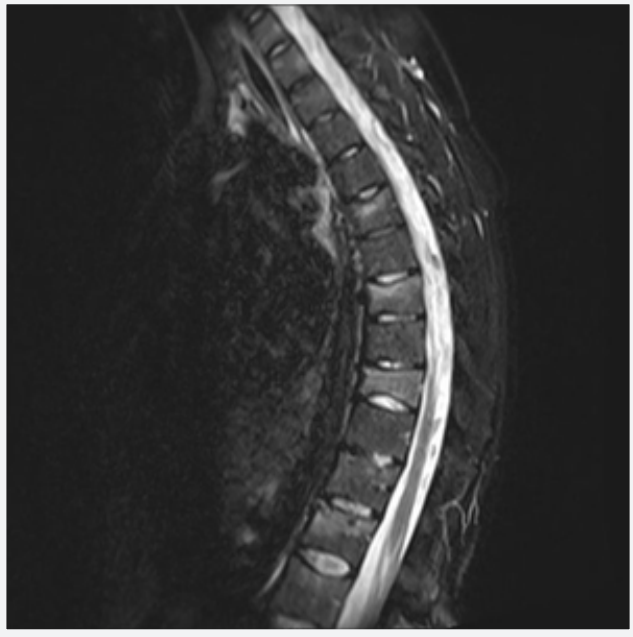

Figure 2. T2 sagittal magnetic resonance imaging at the beginning

The treatment was started by the termination of lactation since during lactation, the body would have needed twice as calcium than normal. Also, the patient was prescribed 1200 mg calcium/day, 2000 IU vitamin D3/day. As analgesic medication, non-steroidal anti-inflammatory drugs were prescribed. Alendronate 70 mg/week was added to the treatment. A dorsal splint corset was applied. Calcium rich diet was recommended to the patient. Moreover, home based exercise program, including stretching and strengthening the low back, waist extensors, strengthening isometric abdominal muscles, and 45 minutes of walking exercises were advised after consulting with the physical therapy and rehabilitation department. The patient was discharged by controls once a month for three months and then once every three months up to end of one year. The treatment regimen was continued as started for one year.

At the end of one-year follow-up, no additional fractures were observed in control X-rays and MRI. It was observed that there were improvements in BMD values in parallel with the decrease of the patient's complaints. Corset treatment was stopped. After one year, the patient came for controls once in three months up to end of two years, thereby continuing the same treatment.

At the end of two-year follow-up, it was observed that fractures were completely healed in the control X-rays and MRI (Figures 3, 4). BMD values were closer to normal at the end of two years (Table 1). It was observed that the patient's complaints completely ended at the end of two years. The treatment was ended.

DISCUSSION

Although PLAO is a rare condition, when low back pain occurs in the last trimester of pregnancy or in early postpartum period, it should be considered in differential diagnosis and not to be misdiagnosed[5-9]. PLAO may be more common than the current literature suggests[10]. Detailed examination and exclusion of the causes of secondary osteoporosis are important and should be carried out in every patient[5-9]. The risk factors for osteoporosis should be considered and if there is any reason underlying, it should be treated when detected. Evaluating the patient independently is very important for the treatment to be more effective[11]. The most important

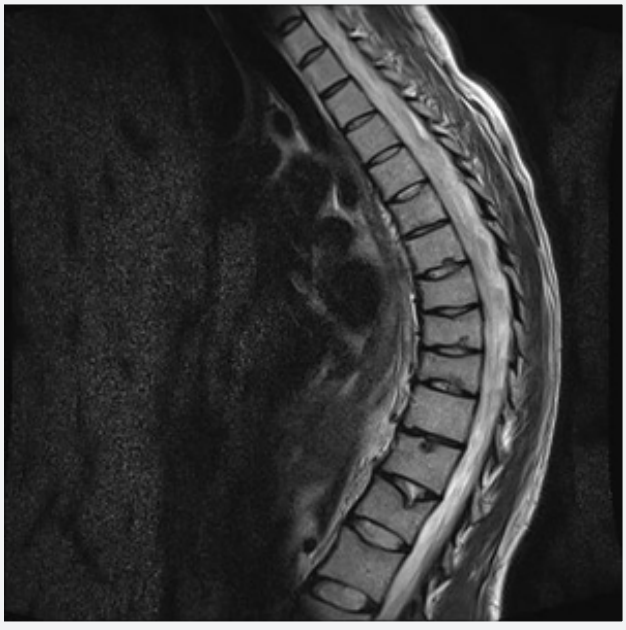

Figure 3. T1 sagittal magnetic resonance imaging at the end of two years

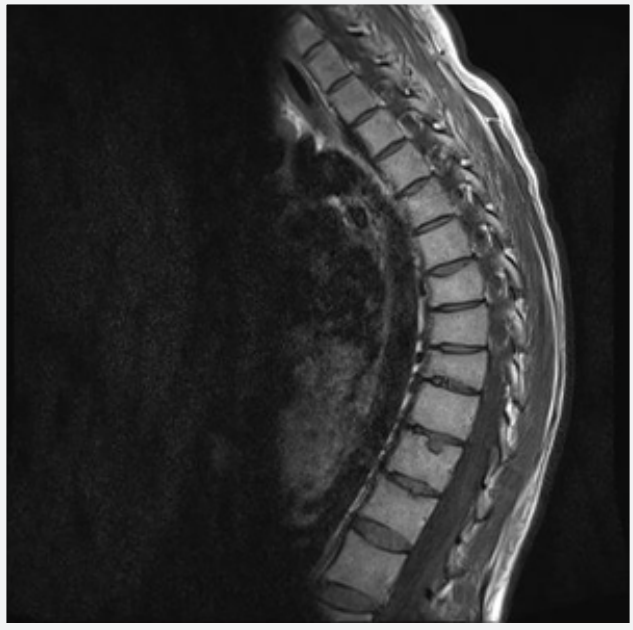

Figure 4. T2 sagittal magnetic resonance imaging at the end of two years

Table 1. BMD scores at the beginning, at one-year follow-up and at two-year follow-up

	L1-L4 T-score	L1-L4 Z-score	Femur neck T-score	Femur neck Z-score
BMD 0 day	-1.8	-2.8	-1.5	-1.8
BMD 1 year	-1.5	-2.8	-1.5	-1.8
BMD 2 years	-1.4	-1.1	1.1	-1.6

BMD: Bone mineral density

part of the treatment is not to miss other spinal fractures, so evaluation of the whole vertebral column is mandatory[12]. It is known that subsequent pregnancies are not contraindicated[5-9]. Pregnancy and lactation are not major risk factors for BMD. However, breastfeeding should be terminated because of both drug use and possible calcium deficiency[6,10]. Findings of BMD usually improve within a year. Regular calcium, vitamin D supplementation should be applied to these patients and exercises should be recommended. Bisphosphonate therapy administered soon after presentation substantially increases spinal bone density in patients with pregnancy-related osteoporosis[13].

CONCLUSION

Although PLAO is a rare entitiy, it must be kept in mind in pregnants or in new mothers who come with back pain and must not be misdiagnosed. The question which has not been answered yet is whether the recovery in these patients is spontaneous or a result of the treatment. Further investigations or case series are needed for to solve this unanswered question[14]. The most important point of the treatment is that the treatment should be specific to the patient.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

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CASE REPORT

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A Rare Hand Pain Cause, Schwannoma with Median Nerve Localisation

Nadir Bir El Ağrısı Sebebi, Median Sinir Schwannomu

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ABSTRACT

Schwannoma is a firm, properly limited, encapsulated, and slow-growing benign tumor of nerve sheaths. It can be seen at all ages, most commonly between the ages of 20 and 50 years and the ratio of female to male is 2:1. It is most commonly seen in the head and neck, but 20% of Schwannomas arise from the peripheral nerves. Peripheral nerve Schwannomas can easily be misdiagnosed as nerve entrapment syndromes because their symptoms overlap most of the times. Symptoms occur by pressing on the mass or on the surrounding tissues. There is no medical treatment of Schwannomas, but the treatment is total excision of the mass. In this case report, a 64-year-old male patient with a Schwannoma of the median nerve in the left forearm, who was misdiagnosed and misoperated as carpal tunnel syndrome, is reported.

Keywords: Schwannoma, median nerve, pain

ÖZ

Schwannom, sinir kılıflarının sert, iyi sınırlı, kapsüllü ve yavaş büyüyen iyi huylu bir tümörüdür. Her yaşta görülebilir, en sık 20-50 yaş arasında görülür ve kadın/erkek oranı 2:1'dir. En sık baş ve boyunda görülür, ancak Schwannom'ların %20'si periferik sinirlerden kaynaklanır. Periferik sinir Schwannom'ları, semptomları çoğu zaman sinir tuzaklanmaları ile örtüştüğü için kolayca yanlış teşhis edilebilirler. Semptomlar kitleye veya çevre dokulara basılarak ortaya çıkar, Schwannom'ların medikal tedavisi yoktur, tedavi kitlenin tamamen çıkarılmasıdır. Bu olgu sunumunda, karpal tünel sendromu olarak yanlış tanı konulan ve yanlışlıkla ameliyat edilen, sol ön kolda median sinir Schwannom'u olan 64 yaşında bir erkek hasta bildirilmiştir.

Anahtar Kelimeler: Schwannom, median sinir, ağrı

INTRODUCTION

Schwannoma is a firm, properly limited, encapsulated, and slow-growing benign tumor of peripheral nerve sheath[1]. It can be seen at all ages, mostly between the ages of 20 and 50 years, and the ratio of female to male is 2:1[2]. Although Schwannomas arise from the peripheral nerves by 20%, they are mostly in the head and neck[1-4]. Peripheral nerve Schwannomas symptoms may mimic nerve entrapment syndrome symptoms, so they should be differentiated carefully in the differential diagnosis. No medical treatment of Schwannomas exists, thereby it is completely surgical[5].

CASE REPORT

A 64-year-old male patient was seen with left hand pain and numbness. The patient reported no systemic complaints and stated that he had had an operation for a carpal tunnel syndrome in another institution with the same complaints a year ago; however, he did not experience any improvement.

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On physical examination, a well-healed surgical scar consistent with an open carpal tunnel release on the palmar side of the left hand was observed. The hand and wrist were normal with Phalen, Tinnel Wartenberg, and Froment tests being negative and there were no sensory impairments. However, during the palpation of the forearm, an area causing severe pain on the volar side and in the thumb of the hand was detected. The Tinel test in the same area was also significantly positive. The patient's visual analogue scale (VAS) score was 70 mm.

X rays, neurophysiological tests, and magnetic resonance imaging (MRI) of the hand, and arterial and venous doppler ultrasonography in the left upper extremity performed because of the on-going postoperative complaints were normal. However, MRI of the forearm revealed a soft tissue tumor at the volar aspect between the flexor muscles, and in the exact localization corresponding to the median nerve trace. The tumor was well-circumscribed, with the dimensions of 23x16 mm, isointense in T1-weighted and hyperintense in T2-weighted sequences, showing a homogeneous contrast enhancement after gadolinum contrast material injection, and was compatible with a Schwannoma (Figures 1A, 1B).

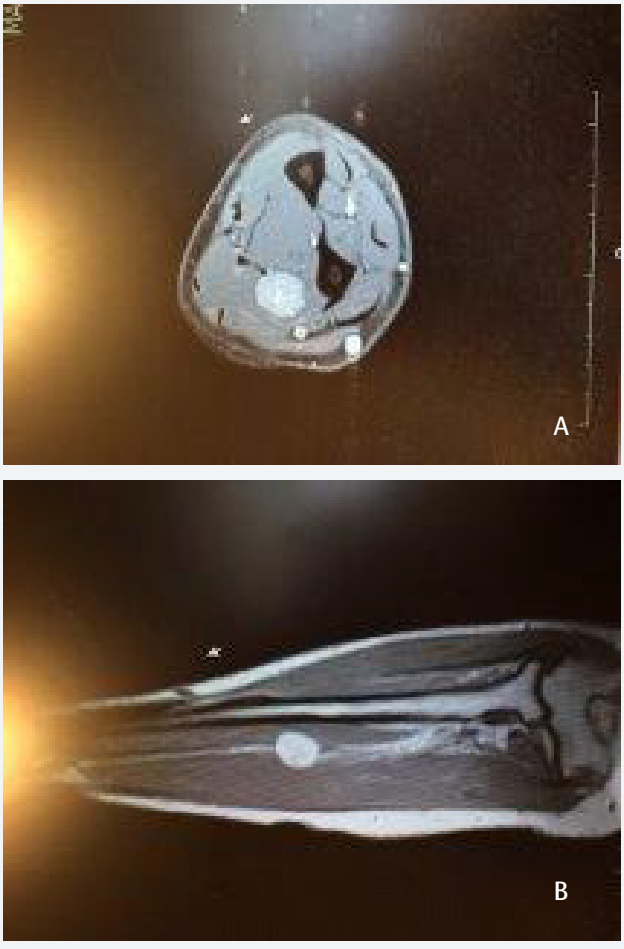

Figure 1. A) Magnetic resonance imaging revealed a 23x16 mm mass located in median nerve intermediate signal on T2-weighted axial images. B) Magnetic resonance imaging revealed a 23x16 mm mass located in median nerve intermediate signal on T1-weighted saggital images

After having written informed consent from the patient, he was operated under general anesthesia with pneumatic tourniquet control. By opening nerve sheath, the tumor was totally removed without any compromise to the nerve, leaving the nerve intact. The mass was well-circumscribed and easily distinguishable from the surrounding tissues. It was revealed that the mass had originated from the median nerve after separation from the vascular pack and surrounding tissues. It appeared to be mediumly firm, yellowish, well-circumscribed, and encapsulated. (Figure 2A, 2B, 2C, 2D).

The postoperative neurological examination was normal. The patient was discharged with full recovery on the first postoperative day. Histological result was Schwannoma with abundant spindle-cell Antoni A tissue and small-cell thick-walled veined Antoni B tissue. Immunohistochemical S-100 staining supported the diagnosis. The patient reported that all his complaints were relieved immediately. At the end of the second week, he was completely asymptomatic and returned to his daily activities. After two years of follow-up, physical examination was completely normal, and VAS score was 0 mm.

DISCUSSION

Peripheral nerve sheath tumors are benign, they originate from Schwann cells and were first described by Verocay in 1908[1]. Although it can be seen at all ages, it is most common between the ages of 20 and 50 years, and the ratio of female to male is 2:1[6]. 20% of all Schwannomas are located in the peripheral nerves[2]. Schwannomas of the median nerve make up 0.1-0.3% of all hand tumors[7,8].

Schwannomas rarely show malignant transformation and are encapsulated and well-circumscribed tumors. It shows a biphasic pattern histopathologically[3,4].

The Antoni A pattern consists of long nucleated, sequential spindle-shaped cells forming fascicles and strips. The Antoni B pattern consists of hypocellular areas that contain a small number of spindle cells with a weak myxoid matrix. Oval acellular areas surrounded by parallel nuclei known as Verocay bodies can be seen. Histopathologic examination of our case also showed Antoni A and Antoni B regions, composed of nucleated, sequential spindle-shaped cells forming fascicles and strips which are compatible with Schwannoma.

MRI is an appropriate choice of imaging thecnique for the diagnosis and the treatment plan. In T1- and T2-weighted images, high signal intensity is evident and there is a heterogeneous, sharp-edge contrast uptake. It shows the

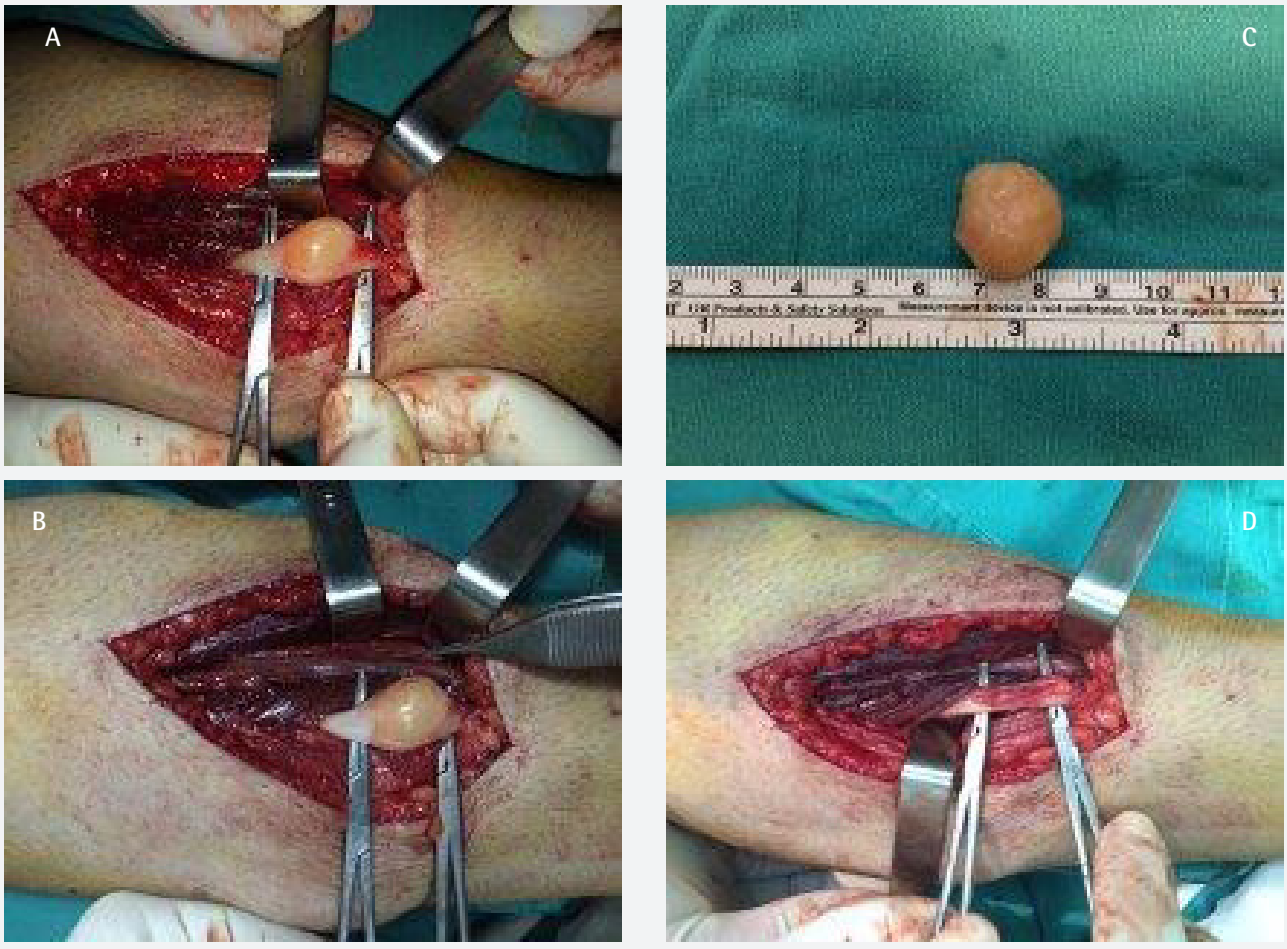

Figure 2. A) Intraoperative view of the lesion showing that the mass at the forearm was originated from the median nerve. B) Intraoperative view of the lesion showing that the mass at the forearm was originated from the median nerve. C) Intraoperative photograph showing dissection of tumour. D) Median nerve after the lesion was removed

anatomical localization of the lesion and its relation to surrounding structures. Also ultrasonography can help to differentiate a solid or cystic nature of the mass.

In the differential diagnosis of these tumors, a fine needle aspiration biopsy can reveal neurogenic source of the tumor[3,4]. Despite all these methods, the diagnosis of these tumors can usually be made after surgery[1,5].

The gold standard in the treatment is the complete excision of the tumor, preserving the nerve structure from which the tumor originated. In incomplete resections, 10% recurrence is reported[1-5]. In our case, the tumor was removed totally from the nerve by blunt dissection after dissection from the vessel-nerve pack.

CONCLUSION

Consequently, peripheral Schwannoma is a rarely seen benign tumor. The diagnosis is difficult before surgery. Schwannoma of the median nerve, a condition in which the findings can overlap one-to-one with carpal tunnel syndrome, should be considered in the differential diagnosis of atypical and lingering pain in the upper extremities, and the clinician should be careful not to misdiagnose it and perform unnecessary surgical interventions.

Ethics

Informed Consent: Consent form was filled out by a participant.

Peer-review: Externally peer-reviewed.

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